Prophylaxis of Venous Thromboembolism

Analysis of Cost Effectiveness

EDWIN W. SALZMAN, M.D., GERALD C. DAVIES, M.B., B.S., F.R.C.S.*

The rapidly expanding literature regarding prevention of venous thromboembolism is confusing and contradictory, but, when analysed in the aggregate, the collective experience permits a judgment about the relative efficacy of different prophylactic regimens in specific patient populations, who vary in the risk factors predisposing them to thromboembolism. The dollar cost of the several approaches to prevention and their consequences should also be a matter of concern. Efficacy and dollar cost together determine cost effectiveness, which provides a practical guide to selection of the prophylactic approach appropriate to an individual patient.

From the Department of Surgery, Harvard Medical School and Beth Israel Hospital, Boston Massachusetts

THE RAPIDLY EXPANDING literature on techniques for prevention of venous thromboembolism contains many contradictions and competing claims of efficacy. Conflicting recommendations have become a source of confusion for the practitioner. Several physical methods and a number of antithrombotic drugs appear to prevent venous thrombosis, but each has its drawbacks. A preventive program suitable for one type of patient may be inappropriate or ineffective for another. Undesirable side effects of prophylactic agents are often overlooked by their zealous advocates, and the dollar cost of therapeutic interventions and diagnostic procedures is usually ignored.

Understanding is further complicated by problems in the translation of data derived from clinical trials into practice. For example, in a trial of the ability of a drug to prevent venous thrombosis, detected by the labelled fibrinogen scan, one is not likely to get clear information about the influence of the drug on pulmonary embolism (PE). The use of the fibrinogen scan will provide earlier diagnosis of deep vein thrombosis (DVT) than is to be expected if clinical detection alone is used. This will result in earlier treatment of thrombi and fewer pulmonary emboli. This reduction in the frequency of pulmonary embolism will be an expression not only of the efficacy of the drug in question but also of the method of surveillance used. Since sensitive diagnostic methods are not routinely applied in clinical practice, a different outcome may be expected in this situation from that seen in investigative trials conducted with sophisticated diagnostic aids.

In an effort to bring some order to these questions, we have examined the options available to patients at risk of venous thromboembolism in terms of what the clinician can expect to encounter in a real life situation. We have analyzed the possible approaches in terms of their cost to patients as well as their effectiveness. Insofar as possible, the analyses are based on data from prospective controlled trials. There is, however, a problem with the use of different criteria for diagnosis in different reports. In the pages that follow, reference will be made to the frequency of DVT and PE diagnosed by conventional clinical appraisal of symptoms and signs as distinguished from the frequency of these conditions as they truly exist, largely silent and undiagnosed except when sensitive objective diagnostic techniques are employed in an entire population. The true rate of DVT is readily accessible in the large literature based on labelled fibrinogen scanning of the legs or phlebography, but the true frequency of pulmonary embolism is more difficult to discern at present and may not be possible to determine with present day methods. Robin has argued that even studies in which every patient has been examined by the most specific technique available, pulmonary arteriography, may not provide this

* Present address: Department of Surgery, Guy's Hospital, London, England.

Reprint requests: Edwin W. Salzman, M.D., Department of Surgery, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

Supported by grant #HL 13754 from the N.H.L.B.I.

Submitted for publication: May 11, 1979.

0003-4932/80/0200/0207 $01.10

information because of limited sensitivity and that lung scanning alone surely gives an inflated estimate of the occurrence rate of PE because of inadequate specificity.[98] The literature contains no studies of pulmonary arteriography in asymptomatic patients, and none are likely to be performed, so the argument is a frustrating one. Fortunately, there are data available on the mortality due to pulmonary embolism in various clinical situations, which permit one to calculate cost-effectiveness without recourse to disputable information derived from lung scanning.

In the analyses that follow, the data have been grouped for consideration when patient populations in different studies appeared comparable. This technique is equivalent to computing a weighted mean value for a series of studies, each of which is assigned a weight corresponding to the number of patients considered. The limitations of such an approach should be kept in mind. Uniformity of patient groups in different studies is difficult to prove, and interpretations based on a compilation of data from several reports must be considered provisional, especially if they run counter to the results of even a single well designed randomized prospective controlled clinical trial that includes large numbers of patients. Therefore, when a particular trial appeared to be of satisfactory design and involved such a large number of patients that its figures dominated the tabulation, its results have been specifically cited.

Despite the above qualifications, experience is sufficiently extensive to identify a high risk group of patients and to provide at least a tentative selection from among the many techniques available for prophylaxis. Patients undergoing surgical operations are known to constitute a high risk group, as are patients sustaining trauma to the lower extremities or pelvis, those taking oral contraceptives, those with malignant disease, those with a history of prior thromboembolism, and those with obesity, advanced age, and prolonged bedrest.[21,70]

It is convenient to acquire perspective regarding the question of prophylaxis by first considering the expected course of events in patients undergoing general surgical operations and then examining the important differences in certain other patient groups.

Approaches to Prophylaxis in General Surgical Patients

Natural History of Venous Thromboembolism

If no particular precautions are taken, approximately 3.5% of patients undergoing general surgical operations will, on clinical grounds, be labelled as having deep vein thrombosis (385/10904)[5,13,17,32,54,61,64,67,68,78,81,86,92,109,111] In studies of over 100 patients, the range is 1–15%. Surveys employing sensitive diagnostic techniques, such as labeled fibrinogen scanning, have indicated the true rate of deep vein thrombosis in such patients to be closer to 27% (1173/4373).[5,11,14,15,19,22,24,31,32,36–39,41,42,54,55,65,67–69,75,77,86,88,100,110,115,117,120,124,127] The figures range from 10 to 47% in individual reports. The majority of these thrombi are clinically silent and will therefore be undetected and untreated in a population not surveyed by these techniques. Clinical evidence of pulmonary embolism will be noted in 1.8% of patients (149/8120),[5,13,14,17,67,70,72,85,92,104] most of whom will not have been recognized as having DVT. About one third of those with a clinical diagnosis of PE (0.6% of all patients) will die from this cause.[26] The true rate of pulmonary embolism is very likely much higher; the majority of these are silent and will escape diagnosis. Estimates of the frequency of silent pulmonary embolism have varied from 14 to 45%,[1,3,31,77] but the validity of the figures is questionable. Either they are confounded because they are derived from studies of labelled fibrinogen scanned patients and because of early treatment are therefore lower than in a population without surveillance, or they are based on scintigraphic lung scans, which may include many false positives.[82,87,98]

Patients with clinically diagnosed venous thrombosis or pulmonary embolism should have objective confirmation of the diagnosis and then will receive treatment, usually full doses of anticoagulants, and will suffer recurrent thromboembolism at an average rate of 2.4% during treatment.[40] Since the fatality rate in anticoagulated patients who experience recurrent pulmonary embolism is about 6%,[8,9,71,91,118] this group can be expected to contribute an additional 0.1% to the total mortality.

No data are available on the rate of recurrence of pulmonary emboli in patients with undiagnosed (and therefore untreated) silent thromboembolism. The total mortality from pulmonary embolism is about 1% in patients receiving no prophylaxis,[5,67,81,104] so 0.3% of the deaths remain to be accounted for and can reasonably be attributed to this group.

The rate of major bleeding complications in fully anticoagulated patients varies from 1 to 20%,[91,107] depending on the route and schedule of administration. The mortality from bleeding in patients who receive heparin in full anticoagulant dosage for treatment of venous thromboembolism varies from 0 to 1.9% and averages 0.3%.[2]

In general surgical patients studied by labelled fibrinogen scanning one will encounter about 25% with thrombosis confined to veins of the calf.[67,89] Major pulmonary embolism from these small distal thrombi is reputed to be unlikely, and some authors have

recommended withholding treatment from such patients. Unfortunately, there are no conclusive data to support this advice. It is claimed from studies employing ventilation/perfusion lung scanning that embolization occurs in half the patients with fibrinogen scan-diagnosed thrombi confined to the calf.[14] Although many of these events probably are of no moment, it is not at present possible to decide which patients will have progression of their thrombus and a major embolus and which will have spontaneous lysis. Rapid proximal progression of thrombosis is known to occur,[30] and major, even fatal, pulmonary embolism has been encountered in this setting. If facilities are available for fibrinogen scanning and impedance plethysmography, an argument might be made for continued surveillance after diagnosis of calf thrombi, treatment being instituted for evidence of proximal extension of the thrombus. However, this gives no protection against progression and embolization occurring overnight between examinations or against these complications after surveillance has been discontinued. In patients in whom only clinical diagnosis is employed, safe practice would appear to indicate that all deep venous thrombi, thigh and calf, should be treated.

One will also encounter patients with venous thromboembolism unsuitable for treatment with anticoagulants and therefore candidates for surgical interruption of the vena cava, with a mortality of 5–40%,[4,76] depending on selection of cases. Insertion of an intracaval umbrella or other device may offer a lower fatality rate.[84]

Prophylactic Measures

The effectiveness of low dose subcutaneous heparin, dextran, and physical measures, including external pneumatic compression of the legs and electrical stimulation of the calf muscles, has been tested by controlled prospective trials in general surgical patients. Warfarin has also been studied and found highly effective, but its use leads to bleeding complications more commonly than do other methods. It should probably be reserved for patients at very high risk, such as those having a history of previous thromboembolism or undergoing orthopedic operations (see below). Aspirin appears to be effective in orthopedic patients; there is argument concerning its efficacy in general surgical patients, and the data are not conclusive. Several other drugs and physical methods, such as the use of elastic stockings, have received limited trial, but the data available about these are too few for consideration here.

Low-dose heparin. Among patients undergoing elective general surgical operations who receive subcutaneous heparin in doses of 5,000 units every eight or 12 hours, clinically evident deep vein thrombosis can be expected to occur in about 1.8% (39/2155).[5,92,127] The true rate as determined by fibrinogen scanning is higher, around 6% (168/2590; range 0.8–13.5%),[5,22,24,39,41,42,65,69,77,88,92,99,110,115,119,120,127] but in clinical practice prophylaxis will usually be employed without surveillance, so the 4% of patients with silent DVT will not be recognized. Pulmonary embolism will be clinically evident in about 0.6% (3/499) of patients.[1,41,42,65,88,92,115] The true frequency will of course be higher: a study with perfusion lung scans found a 16% rate in patients receiving low dose heparin, about ⅓ the rate in controls in that study.[120] In the Multicentre Trial of Kakkar and associates,[5] PE was judged the cause of death in 22% of autopsied control patients, which, when extrapolated to include deaths without postmortem examination, indicated an overall death rate of 1.1% from PE. Corresponding figures among patients who received low-dose heparin were 4% of autopsies and 0.16% overall mortality from PE.

One can anticipate that under 3% of patients on low-dose heparin will require full dose anticoagulant therapy for overt thromboembolism. Few patients will have major hemorrhages, and only 0.2% of those given low-dose heparin will die from this cause. In the Multicentre trial, heparin was discontinued in 2.6% of patients because of bleeding, and 0.2% died of hemorrhage, the same number as in the control group.

Dextran. Controlled prospective trials have, for the most part, shown that dextran of molecular weight 70,000 or 40,000 is effective for prevention of venous thromboembolism in general surgical patients, but there are disclaimers. The two preparations appear to be approximately equal in effectiveness. In the aggregate, the studies reported indicate that clinically evident DVT occurred in 6% of patients who received dextran (89/1459),[12,53,59,61,62,73,84,99,109,111,119] but a figure lower than this can probably be expected with a larger experience. The published studies with dextran are somewhat anomalous, since the average DVT rate among control patients in dextran trials was 10% (compared with 3.5% in the larger accumulated control group cited above). The total rate of DVT was 20% (135/688) in studies employing sensitive diagnotic methods,[10,19,43,73,110,114,120] and thus the frequency of silent DVT was 13%. These results are inferior to those obtained with low-dose heparin.

From the literature one would predict that clinically recognized pulmonary embolism will occur in 1.2% of dextran-treated patients (18/1451);[10,12,18,53,59,62,73,79,109–111] this may be an overestimate, since eight of the 18 pulmonary emboli in the collected material (11 studies) occurred in a single trial with a 9% rate

of embolization.[12] The total frequency of pulmonary embolism, including silent cases, is stated to be 20%.[114] The mortality from PE in general surgical patients receiving dextran is reported, in the aggregate, as 0.6%.[43,59,62,73,74,79,102,112] The frequency of major bleeding on dextran is 0.6% (5/775);[12,62,73] a higher rate can be expected in association with surgery of greater magnitude. Other side effects of dextran, such as pulmonary edema secondary to fluid overload, are not rare. Anaphylactoid reactions occur occasionally and are said to be 10 times more frequent with the 70,000 Dalton preparations than with the product of 40,000 average molecular weight (94).

External pneumatic compression. Physical methods available for prevention of venous thromboembolism include electrical stimulation of calf muscles, elastic stockings, and external pneumatic compression (EPC) of the calves with inflatable boots or leggings. The last of these has the largest body of literature to support its use. The development of deep vein thrombosis can be expected in about 8% (25/270) of patients who receive external pneumatic compression.[20,55,96,97,103,116] The results are comparable to those of low-dose heparin. It is likely that 1–2% will be symptomatic. The rate of clinically diagnosed pulmonary embolism in collected reports is 0.9% and in our own experience is 0.7% (1/180), but the total number of patients studied is small. Additional large clinical trials are needed to establish the influence of EPC on the rate of pulmonary embolism. If the data available are representative, over 90% of patients receiving EPC will be free of thrombotic complications, a figure similar to that with low-dose heparin. No bleeding is encountered with external pneumatic compression of the legs, and other reported complications have been trivial. The principal drawback to the system is that it is somewhat cumbersome, and patient acceptance can be a problem because of discomfort.

Surveillance

In an effort to avoid the hemorrhagic side effects of administration of antithrombotic drugs, surveillance of high risk patients with sensitive diagnostic tests has been advocated to allow the early detection of venous thrombi in the legs at a time when prompt treatment will prevent the subsequent development of pulmonary embolism. In general surgical patients the labelled fibrinogen scanning technique is adequate for surveillance. With surgery or trauma to the hip or pelvis, there are frequent proximal thrombi not detected by labelled fibrinogen scanning,[50,58] and some method sensitive to iliofemoral thrombi (*e.g.*, impedance plethysmography) is also needed, but in general surgical patients isolated proximal thrombi are uncommon.[90] In patients followed by fibrinogen scanning and receiving no specific prophylactic measures, a positive scan will be found in about 27% (1173/4373).[5,11,14,15,17,19,22,24,31,32,36–39,41,42,54,55,65,67–69,75,77,86,88,100,110,115,117,120,124,127] A false negative examination is expected in 6% of those with thrombi (*i.e.*, 2% of all patients); it will be accompanied by false positive tracings in a further 2%.[56] Thus, 25% of patients will have a positive scan associated with deep vein thrombosis, and 2% more will have DVT which is not detected. Pulmonary embolism will be clinically evident in only 1.2% of patients under surveillance (16/1373),[31,41,42,65,67,88,100,115,124] and silent emboli will also be infrequent. Surveillance appears to be particularly effective in preventing fatal PE: in the nine studies cited, there were no deaths from PE among the 1373 patients. Patients with positive fibrinogen scans will receive treatment with full doses of anticoagulants, for the most part, with an expected rate of recurrent thromboembolism of about 2%.[40] Patients with negative leg scans will have few pulmonary emboli; by lung scan, Browse[14] found evidence of embolization in only one of 29 patients with negative ^{125}I-fibrinogen leg scans.

Bleeding complications are not encountered with surveillance methods, but since 28% of the population under surveillance will be recognized as having thromboembolism (27% DVT and 1% pulmonary embolism) and will therefore require full anticoagulation, the number of patients exposed to the bleeding complications of full anticoagulant therapy will be higher than if the patients had been given low-dose heparin without surveillance (3%).[1]

Cost-effectiveness

One can calculate a dollar cost for the various approaches to prevention of venous thromboembolism by adding the cost of the drugs, labor, apparatus, and laboratory tests employed in prophylaxis (Tables 1 and 2) to the estimated costs accrued as a result of the various possible outcomes (Table 3), taking into account the probabilities of each. As an indicator of costs to the patient or his insurer, the figures shown in Tables 1 to 3 are based on actual charges at an urban teaching hospital in New England and may have to be adjusted up or down for other institutions. The relative costs or charges are probably generally applicable. A period of seven days is arbitrarily used for the calculations, but it is important to note that the length of time a patient is at risk of thromboembolism will vary with the circumstances, and the duration of prophylactic measures should be decided accordingly.

It should be noted that for calculation of cost-effectiveness, the important factors are the mortality from pulmonary embolism and the frequencies of clinically diagnosed venous thrombosis and pulmonary embolism rather than the true rates of occurrence of these complications. The latter are of course crucial in determining outcome, but the dollar cost of treatment is dictated by the clinician's perception of what is wrong with the patient, and silent thromboembolism is, by definition, not perceived. The uncertainty that attends any estimate of the true frequency of pulmonary embolism, discussed earlier, does not therefore interfere with analysis of cost/effectiveness.

Table 4 presents a synthesis of the foregoing applied to 1,000 patients undergoing general surgical operations. The dollar costs and probabilities illustrated in Tables 1 to 3 and described in the text have been combined in a formulation that considers the mortality from pulmonary embolism or from bleeding as a complication of prophylaxis or treatment but makes no attempt to assign a dollar value to the loss incurred by death. Efforts to calculate such a cost have been published and can be applied to these figures if the reader is inclined, as can estimates of the dollar value of relief of suffering and years of life saved, but the determination of cost-effectiveness can be accomplished without the introduction of these issues.[16,35,123]

Certain conclusions to be derived from Table 4 deserve emphasis.

1) Failure to take any effective precautions in 1,000 general surgical patients will result in at least 10 deaths from pulmonary embolism. This figure is higher than expected with any of the prophylactic programs listed, including intensive surveillance.

2) The dollar cost of prophylaxis using low-dose heparin or external pneumatic compression of the legs is somewhat higher than that of simply treating thromboembolic events as they arise, but the additional expense seems well justified by the saving of at least six lives. The marginal cost for the use of heparin prophylaxis relative to taking no precautions would be $870 per death averted and for EPC, $620 per death averted. If larger clinical trials of EPC confirm the present impression of the method's effectiveness against pulmonary embolism, it should prove to be an acceptable alternative to low-dose heparin and preferable in patients with a special hazard of hemorrhage, such as neurosurgical patients or those undergoing operation on the prostate.

3) Since in general surgical patients dextran appears to be less effective than either low-dose

TABLE 1. *Cost of Prophylaxis (7 Days)*

Heparin		
5,000 u b.i.d. @ $4.50/day	$31.50	
baseline PT, PTT, platelets	20.00	
	$51.50	
Dextran		
MW 40,000 $15/500 ml	$30.00	if 1 L in OR only;
(MW 70,000 $9/500 ml)	$75.00	if 500 ml × 3, then qod
External pneumatic compression		
compressor $1,000.00 (5 year expected life; $50 annual maintenance; 52 uses/yr)	$ 4.80	
inflatable boots and stockinette	18.75	
technician time	18.10	
	$41.65	
Warfarin		
50 mg	$ 1.34	
baseline PT, PTT, platelets	20.00	
daily PT	48.00	
	$69.34	
Aspirin		
1.2 g/day	No charge	

The cost of prophylaxis with a drug will vary according to the schedule of its administration. In the example shown, heparin is given by subcutaneous injection twice daily. A few simple laboratory screening tests are recommended for assurance of hemostatic competence before heparin prophylaxis is initiated. Dextran has been given according to many different regimens, most often as either a single infusion of 1,000 ml in the operating room or by administration of 500 ml daily for three days and then every other day for the balance of the period of immobilization. The cost of external pneumatic compression of the legs varies, depending on the manufacturer of the apparatus. In this example, the compressor is arbitrarily depreciated over a five-year period. Figures for warfarin and aspirin are shown for comparison.

TABLE 2. *Cost of Surveillance*

^{125}I-Fibrinogen scan	
γ-detector and rate meter $1,400 (7 year expected life; 16 scan/day × 5 d/wk × 50 wk/yr)	$ 0.35
NaI 100 mg/day @ 0.30 × 10	3.00
^{125}I-Fibrinogen 100 μCi	61.25
nurse/technician time ($7.74/hr.)	27.09
professional fee and hospital service charge	30.00
	$121.69/7 days
Impedance plethysmography	
IPG #200 machine $5,100 (10 year expected life; 8 exams/day × 5 d/wk × 50 wk/yr)	$ 0.25
nurse/technician time ($7.74/hr.)	7.74
professional fee and hospital service charge	30.00
	$37.99/exam

The cost of surveillance is calculated assuming daily scanning of the legs for labelled fibrin. Less frequent examinations would be less expensive but would also offer less security against embolization before detection of the venous thrombus. Surveillance by methods sensitive to iliofemoral thrombi, such as impedance plethysmography, is probably not indicated in general surgical patients, unless there is a particular predisposition to thrombosis of the proximal veins (*e.g.*, pelvic lymph node dissection). The method is time-consuming and therefore expensive, so it is usually not employed daily. In the example, note that the charge is for each examination rather than for a seven day period.

TABLE 3. *Cost of Complications*

Typical Costs		Optional Costs	
	DVT		
Heparin 5000 u, then 1000 u/hr		Phlebogram	
7 days	$ 23.04	1 leg: 329.00 + prof. fee	
-daily PTT × 7	56.00	+ 125.00 contrast injection	$ 484.00
warfarin 3 months	18.00	^{125}I-fibrinogen scan (2 days)	102.09
-daily PT × 7, then 1/wk	144.00	impedance plethysmography	37.99
7 hospital days @ $172.00	1,204.00	streptokinase (72 hr course)	575.00
	$1,445.00		
	Pulmonary Embolism		
chest Xray	$ 49.00	ventilation lung scan	$ 166.00
perfusion lung scan (98.00 + 55.00 prof. fee)	153.00	pulmonary angiography (492.00 including catheter + 60.00 prof. fee + 200.00 contrast injection)	752.00
electrocardiogram	51.00		
blood gases	19.00	intensive care unit	460.00/day
enzymes	20.00	streptokinase (72 hr course)	575.00
anticoagulant therapy	241.04	pulmonary embolectomy	5,214.00
7 hospital days @ $172.00	1,204.00		
	$1,737.04		

In these examples, the items for which costs are indicated in the left-hand column are probably a minimum list of expenses which the patient will incur in the course of diagnosis and treatment. The items listed in the right-hand column are additional options, whose applicability will vary from patient to patient. The figure shown for pulmonary embolectomy includes operating room, anesthesia, recovery room, and professional charges.

TABLE 4. *Cost Analysis in 1,000 General Surgical Patients**

Costs		Outcome
No precautions		
35 clinical DVT	$50,575	52 anticoagulated patients (1–10 major bleeds)
18 clinical PE	31,267	6 deaths from clinical PE
	$81,842	4 deaths from silent PE
		10 deaths total
Surveillance		
cost	$121,690	276 anticoagulated patients (3–55 major bleeds)
270 DVT by scan (including 20 false positive)	390,150	1 death from bleeding
6 clinical PE	10,422	?0 deaths from PE
	$522,262	1 death total
Prophylaxis		
Heparin		
cost	$51,500	23 fully anticoagulated patients (1–5 major bleeds)
18 clinical DVT	26,010	26 major bleeds from low-dose heparin
6 clinical PE	10,422	2 deaths from bleeding
	$87,932	1 death from PE
		3 deaths total
Dextran		
cost	$30,000–$75,000	70 anticoagulated patients (1–15 major bleeds)
60 clinical DVT	86,700	6 bleeds from dextran
12 clinical PE	20,844	6 deaths from PE
	$137,544–$182,544	6 deaths total
External pneumatic compression		
cost	$41,650	29 anticoagulated patients (1–6 major bleeds)
20 clinical DVT	28,900	3 deaths from PE†
9 clinical PE	15,633	3 deaths total
	$86,183	

* 7 days.

† Estimated as ⅓ of the total frequency of recognized pulmonary embolism. Published data are too few for a definite statement.

Figures for the number of fully anticoagulated patients are derived from the expected total number of DVT and PE episodes minus the number of patients in whom the event would be recurrent and who would therefore already be receiving full anticoagulent therapy. No attempt has been made to cost-account the bleeding complications of anticoagulant therapy.

heparin or calf compression, it is not recommended for routine administration. Its high cost reinforces this conclusion. In high risk patients, there may be indications for its use (see below).

4) Although highly effective in preventing fatal PE, surveillance is not a cost-effective alternative to active prophylactic measures in general surgical patients (marginal cost $48,935 per death averted). If there were sensitive and specific predictive techniques that permitted more selective application of surveillance by identification of a population most at risk, this conclusion might require reassessment. The situation would also be altered by better understanding of the natural history of venous thrombosis, which might enable the physician to distinguish calf vein thrombi that could be safely managed without full anticoagulant therapy.

Approaches to Prophylaxis in High Risk Patients

Venous thromboembolism occurs so often as a complication of certain conditions that they constitute an especially high risk group. In such patients, including those with fractures or reconstructive surgery of the hip, increasing evidence suggests that low dose subcutaneous heparin is inadequate for protection.[108] Other prophylactic measures, on the other hand, appear to be effective, and the frequency of thromboembolism in this very high risk population jutifies their use despite, in some cases, undesirable side effects. The group most thoroughly studied by modern diagnostic methods consists of patients undergoing total hip replacement.

Natural History of Venous Thromboembolism (Table 5)

Without special prophylactic measures, total hip replacement is followed by a hospital mortality of over 2%, virtually all from pulmonary embolism.[23,66,108] Clinical evidence of DVT is recognized in 12% (52/419)[47,80] and of PE in 11% (221/2005).[23,27,28,33,47,52,58,66,80,101,105,106,121,126] At least 35% more will have silent DVT as judged by phlebography,[33,52,113] and half the deaths will occur in this group. Many reports have employed labelled fibrinogen scanning as the sole diagnostic method, although this technique is insensitive to thrombi above midthigh. These occur as isolated findings without accompanying calf thrombi in at least 10% of patients with total hip replacement[52,97] and are particularly prone to give rise to major pulmonary embolization. Bleeding among the many patients who require anticoagulant therapy will make an additional contribution to the mortality. The dollar cost of these complications is summarized in Table 6.

TABLE 5. *Total Hip Replacement*

	Clinical DVT	Silent DVT	Clinical PE	Silent PE	Fatal PE
No precautions	12%	35%	11%	?	1.7%*
Low-dose heparin	7%	14.6%†	5.3%	14%	1.2%
Warfarin	4.4%	18.0%	1.1%	?	0.4%
Aspirin	7.8%	23%	2%	?	0
Dextran	3.2%	16.6%	6.1%	21.9%	0.8%

* This figure is drawn from the same sources as for clinical PE plus references 6 and 57.

† This figure may be too low, as it is based on trials employing fibrinogen scanning as the sole diagnostic method. All other figures in this column are derived from phlebographic studies.

Prophylactic Measures

Table 5 summarizes the most instructive experience with the four antithrombotic drugs that have received thorough evaluation in total hip replacement.

Low-dose heparin is probably not without an effect on DVT and may lower the mortality from PE. The literature on this subject is in disagreement. Apparently well designed trials have led to discordant results. On the evidence available at present, low-dose heparin appears inferior to other agents and not the preferred drug in this application. Clinically obvious DVT may be found in 7% (12/170) of high risk patients on low-dose heparin.[80,95] An additional 14% may have silent thrombi as detected by ^{125}I-fibrinogen scanning and even more if studied by phlebography.[7,29,34,39,44,49,69,80,89,95,105,121] Five per cent (18/337) will have clinical signs of pulmonary emboli[7,49,58,95] with a mortality of 1.2%. The total rate of embolization appears not to be reduced by low-dose heparin.[125] Bleeding complications have been unusual in some series but in other studies have occurred frequently, with one study being abandoned because of bleeding.[49,66]

Warfarin has the advantage of being given in therapeutic dosage when employed for prophylaxis, so it is suitable for administration to patients who may enter the hospital with a pre-existing thrombus: a frequent problem with fractures of the hip, for example. If used prophylactically in association with hip reconstruction, warfarin reduces the rate of deep vein thrombosis as judged phlebographically to 23.4% from the 47.3% seen in patients not receiving prophylaxis[49,51] and lowers the frequency of fatal PE to 0.4%[7,27,47–49,51,66,95,106] or even less (see below). Unfortunately, bleeding is a frequent complication of oral anticoagulation. Fatal hemorrhage has been reported in 1.8% of patients on warfarin,[40] but this figure is probably unrealistically high, since it is derived from patients treated for degenerative arterial diseases rather than for prevention of venous thromboembolism. Compilation of data from studies of hip

TABLE 6. *Cost Analysis in 1,000 Total Hip Replacements**

Costs			Outcome
No precautions			
clinical DVT	120	$173,400	224 anticoagulated patients (2–45 major bleeds)
clinical PE	110	191,074	1 death from bleeding
		$364,474	17 deaths from PE
			18 deaths total
Prophylaxis			
Heparin			
cost		$ 51,500	120 fully anticoagulated patients (2–26 major bleeds)
clinical DVT	70	101,150	26 bleeds from low-dose heparin
clinical PE	53	92,063	2 deaths from bleeding
		$244,713	12 deaths from PE
			14 deaths total
Warfarin			
cost		$ 69,340	1,000 anticoagulated patients (54 with heparin)
clinical DVT	44	63,580	(50–70 major bleeds)
clinical PE	11	19,107	3 deaths from bleeding
		$152,027	4 deaths from PE
			7 deaths total
Aspirin			
cost		$ 0	96 anticoagulated patients (1–20 major bleeds)
clinical DVT	78	112,710	?0 deaths from PE
clinical PE	20	34,741	?0 deaths total
		$147,451	
Dextran			
cost		$30,000–$75,000	91 anticoagulated patients (1–18 major bleeds)
clinical DVT	32	46,240	8 deaths from PE
clinical PE	61	105,960	8 deaths total
		$182,200–$227,200	

* 7 days.

replacement in which warfarin was the sole prophylactic agent[48,57,106] yields a figure of 0.3% fatal bleeding.

Aspirin has been proved effective in male patients. Studies at different dosages are now in progress in women, but the data so far published support the use of aspirin only in men. The only randomized double blind study to date[52] showed the rate of phlebographically confirmed DVT in aspirin treated patients to be 25% (18% in males), compared with 45% in controls. The fatality rate due to PE in patients receiving aspirin is not known. In the studies by Salzman,[106] Harris[59,52] and Jennings,[63] there were no deaths among 665 patients of either sex who received such prophylaxis.

Dextran apparently is similar to warfarin in its effectiveness in orthopedic patients, as shown by controlled studies using phlebography as the diagnostic endpoint.[28,33,49] Its bleeding complications appear to be less frequent[7,49,66,83] although in one study they occurred as often.[48] Warfarin, aspirin and dextran prophylaxis all reduce the rate of clinical pulmonary emboli and decrease the number of embolic deaths. The fatality rates cited in Tables 5 and 6 may actually be too high, since in 3800 consecutive hip reconstructions at the Massachusetts General Hospital in patients receiving warfarin, aspirin, or dextran, there have been no fatal pulmonary emboli (W. H. Harris, personal communication).

External pneumatic compression of the legs has been studied only in patients with a history of prior thromboembolism. The procedure was as effective as warfarin in patients whose preoperative phlebogram were normal but was significantly inferior to warfarin if the phlebogram before hip replacement showed residual abnormalities from a previous episode of thrombosis.[51] Although the method shows promise as a prophylactic measure in high risk patients, we have omitted EPC from the analysis in Tables 5 and 6 because of insufficient data.

The dollar cost of prophylaxis employing these drugs is calculated in Table 6. There is a reduction in mortality as well as cost with all four agents considered.

Surveillance

The alternative approach of surveillance with selective treatment of early DVT, presumably before pulmonary embolization has occurred, has also been pro-

posed for patients undergoing total hip replacement.[58] Since labelled fibrinogen scanning is insufficient as the sole diagnostic measure after hip operations, because of the confusing effects of the perioperative thigh hematoma and the frequency of isolated thigh thrombi,[50] an additional technique sensitive to more proximal thrombi is required. Of those available, impedance plethysmography seems the most objective and is of reasonable sensitivity in the thigh, although the method fails to detect most calf thrombi and occasional nonocclusive thigh thrombi. Both fibrinogen scanning and impedance plethysmography have large blind spots, and even the combination misses about 15% of thrombi after hip replacement.[50] Experience with this approach is too limited to permit analysis of cost/effectiveness.

Other High Risk Patients

For high risk patients other than those with operations on the hip, there are few satisfactory trials to offer guidance. A history of prior thromboembolism is an important risk factor, especially if documented by objective diagnostic tests. In patients who have suffered major trauma, thromboembolism is a serious threat, but there are few data on such patients. One must decide on an approach to prophylaxis by extrapolation from studies of other conditions, a perilous undertaking. The dollar cost of preventive measures is not great, and the potential gain seems sufficient to warrant prophylaxis. A reasonable approach might be external pneumatic compression or dextran in the immediate postinjury period and warfarin later, when the hazard of hemorrhage has abated. Such a recommendation may be overturned at any time by information derived from prospective controlled trials.

In nonoperative patients, the cost/effectiveness of prophylactic techniques will depend on the frequency of thromboembolism in the absence of preventive measures. Data are available only after myocardial infarction and in congestive heart failure, where the rate of DVT and PE seems to justify prophylaxis with low-dose heparin.[25,39,45,46,60,122] Warfarin is also effective, and the hazard of bleeding is less than in surgical patients. The possible efficacy of external pneumatic compression or antiplatelet drugs has not been assessed.

Concluding Recommendations

Many questions remain unanswered, but therapeutic decisions must be made daily in spite of incomplete understanding. Even though there are many gaps in the data, the foregoing analysis can provide guidance to clinicians, provided one is mindful of the many exceptions and special cases discussed in the previous text. Table 7 presents a tentative scheme based on the cost-effectiveness of prophylactic methods in several types of patients. The recommendations are of course provisional and subject to revision whenever the results of well designed clinical trials make new information available.

TABLE 7. *Recommended Prophylaxis in Various Patient Groups*

	Warfarin	Miniheparin	Antiplatelet agents	EPC
Highest risk	+	0	0	0
General surgery				
< 40 yrs.*	0	0	0	0
> 40 yrs.	0	+	±	+
Orthopedic	+	0	+	±
Trauma	+	0	±	±
Nonoperative	+	+	±	±

+ cost/effective method of prophylaxis
± method of prophylaxis with some support, but data are equivocal or insufficient
0 not recommended

* Unless some additional risk factor is present.

Acknowledgments

We thank colleagues too numerous to cite who reviewed this manuscript before publication, Ms. Janet Ploetz for assistance in the compilation of these data, and Ms. Kaylene Graham for aid in preparation of the manuscript.

References

1. Abernethy EA, Hartsuck JM. Postoperative pulmonary embolism. A prospective study utilising low dose heparin. Am J Surg 1974; 128:739.
2. Aggeler PM, Kosmin M. Anticoagulant prophylaxis and treatment of venous thromboembolic disease. *In* Edited by Sherry, S, Brinkhous KM, Genton E, et al., Thrombosis, Washington DC, Nat Acad Sci, 1969, pp 639–689.
3. Allgood RJ, Cook JH, Weedn RJ, et al. Prospective analysis of pulmonary embolism in the postoperative patient. Surgery 1970; 68:116.
4. Amador E, Li TK, Crane C: Ligation of inferior vena cava for thromboembolism. JAMA 1968; 206:1758.
5. An international multicentre trial. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. Lancet 1975; 1:45.
6. Askey JM. Hemorrhage during long-term anticoagulant drug therapy. Calif Med 1966; 104:6.
7. Barber HM, Feil EJ, Galasko CSB, et al. A comparative study of dextran 70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. Postgrad Med 1977; 53:130.
8. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet 1960; 1: 1309.
9. Bauer C. Clinical experiences of a surgeon in the use of heparin. Am J Cardiol 1964; 14:29.
10. Becker J, Schampi B. The incidence of postoperative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. Acta Chir Scand 1973; 139:357.
11. Bolton JP, Hoffman VJ. Incidence of early post-operative iliofemoral thrombosis. Br Med J 1975; 1:247.

12. Brisman R, Parks LC, Haller JA, Jr. Dextran prophylaxis in surgery. Ann Surg 1971; 174:137.
13. Browse NL, Hall JH. Effect of Dipyridamole on the incidence of clinically detectable deep-vein thrombosis. Lancet 1969; 2:718.
14. Browse NL, Clemenson G, Croft DN. Fibrinogen-detectable thrombosis in the legs and pulmonary embolism. Br Med J 1974; 1:603.
15. Browse NL, Clemenson G, Bateman NT, et al. Effect of intravenous dextran 70 and pneumatic leg compression on incidence of postoperative pulmonary embolism. Brit Med J 1976; 2:1281.
16. Bunker JP, Barnes BA, Mosteller F (eds). Costs, Risks and Benefits of Surgery. New York, Oxford University Press, 1977.
17. Carter AE, Eban R, Perrett RD. Prevention of postoperative deep venous thrombosis and pulmonary embolism. Br Med J 1971; 1:312.
18. Carter AE, Eban R. The prevention of postoperative deep venous thrombosis with dextran 70. Br J Surg 1973; 60:681.
19. Carter AE, Eban R. Prevention of postoperative deep vein thrombosis in legs by orally administered hydroxychloroquine sulphate. Br Med J 1974; 3:94.
20. Clark WB, Prescott RJ, MacGregor AB, et al. Pneumatic compression of the calf and postoperative deep vein thrombosis. Lancet 1974; 2:5.
21. Coon WW. Epidemiology of venous thromboembolism. Ann Surg 1977; 186:149.
22. Corrigan TP, Kakkar VV, Fossard DP. Low-dose subcutaneous heparinoptimal dose regimen. Br J Surg 1974; 61:320.
23. Coventry MB, Nolan DR, Beckenbaugh RD. "Delayed" prophylactic anticoagulation. A study of results and complications in 2,012 total hip arthroplasties. J Bone Joint Surg 1973; 55A:1487.
24. Covey TH, Sherman L, Baue AE. Low-dose heparin in postoperative patients. Arch Surg 1975; 110:1021.
25. Crawford WJ, Hillman F, Charnley J. A clinical trial of prophylactic anticoagulant therapy in elective hip surgery. Internal publication No 14, Centre for Hip Surgery, Wrightington Hospital, London, 1968.
26. Dalen JE, Alpert JS. Natural history of pulmonary embolism. *In*. Sasahara AA, Sonnenblick EH, Lesch M, (eds.) Pulmonary Emboli. New York, Grune and Stratton. 1974. pp. 77–88.
27. D'Ambrosia RD, Lipscomb PR, McClain EJ, et al. Prophylactic anticoagulation in total hip replacement. Surg Gynecol Obstet 1975; 140:523.
28. Darke SG. Ilio-femoral venous thrombosis after operations on the hip. A prospective controlled trial using Dextran 70. J Bone Joint Surg 1972; 54B:615.
29. Dechavanne M, Ville D, Viala JJ, et al. Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. Haemostasis 1975; 4:94.
30. Doig RI, Browse NL. Rapid propagation of thrombus in deep vein thrombosis. Br Med J 1971; 4:210.
31. Douss TW. The clinical significance of venous thrombosis of the calf. Br J Surg 1976; 63:377.
32. Effect of aspirin on postoperative venous thrombosis. Report of the Steering Committee of a trial sponsored by the Medical Research Council. Lancet 1972; 2:441.
33. Evarts CE, Feil EJ. Prevention of thromboembolic disease after elective surgery of the hip. J Bone Joint Surg 1971; 53A: 1271–1280.
34. Evarts CE, Alfidi RJ.Thromboembolism after total hip reconstruction. Failure of low doses of heparin in prevention. JAMA 1973; 225:515.
35. Fein R. On measuring economic benefits of health programmes. *In* McLachlan G, McKeown T, (eds.) Medical History and Medical Care. London, Oxford University Press for the Nuffield Provincial Hospitals Trust. 1971. pp 181–217.
36. Flanc C, Kakkar VV, Clarke MB. The detection of venous thrombosis of the legs using ^{125}I-labelled fibrinogen. Br J Surg 1968; 55:742.
37. Flanc C, Kakkar VV, Clarke MB. Postoperative deep-vein thrombosis. Effect of intensive prophylaxis. Lancet 1969; 1:477.
38. Gallus AS, Hirsh J, Gent M. Relevance of preoperative and postoperative blood tests to postoperative leg vein thrombosis. Lancet 1973; 2:805.
39. Gallus AS, Hirsh J, Tuttle RJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med 1973; 288:545.
40. Gallus AS, Hirsh J. Treatment of venous thromboembolic disease. Semin Thromb Hemostas 1976; 2:291.
41. Gallus AS, Hirsh J, O'Brien SE, et al. Prevention of venous thrombosis with small, subcutaneous doses of heparin. JAMA 1976; 235:1980.
42. Gordon-Smith IC, Grundy DJ, LeQuesne LP, et al. Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. Lancet 1972; 1:1133.
43. Gruber UF, Fridrich R, Duckert F et al. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. Lancet 1977; 1:207.
44. Hampson WGJ, Harris FC, Lucas HK, et al. Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. Lancet 1974; 2:795.
45. Handley AJ. Low-dose heparin after myocardial infarction. Lancet 1972; 2:623.
46. Handley AJ, Emerson PA, Fleming PR. Heparin in the prevention of deep vein thrombosis after myocardial infarction. Br Med J 1972; 2:436.
47. Harris WH, Salzman EW, DeSanctis RW. The prevention of thromboembolic disease by prophylactic anticoagulation. A controlled study in elective hip surgery. J Bone Joint Surg 1967; 49A:81.
48. Harris WH, Salzman EW, De Sanctis RW, et al. Prevention of venous thromboembolism following total hip replacement. Warfarin vs Dextran 40. JAMA 1972; 220:1319.
49. Harris WH, Salzman EW, Athanasoulis C, et al. Comparison of warfarin, low-molecular-weight dextran, aspirin, and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. J Bone Joint Surg 1974; 56A: 1552.
50. Harris WH, Athanasoulis C, Waltman AC, et al. Cuff-impedance phlebography and ^{125}I fibrinogen scanning versus roentgenographic phlebography for diagnosis of thrombophlebitis following hip surgery. J Bone Joint Surg 1976; 58A: 939.
51. Harris, WH, Raines JK, Athanasoulis C, et al. External pneumatic compression versus warfarin in reducing thrombosis in high risk hip patients. *In* Madden JL, Hume M (eds.) Venous Thromboembolism. Prevention and Treatment. New York, Appleton-Century-Crofts. 1976. pp 51–60.
52. Harris WH, Salzman EW, Athanasoulis CA, et al. Aspirin prophylais of venous thromboembolism after total hip replacement. N Engl J Med 1977; 297:1246.
53. Hartshorn JWS, Teale SN, Faiz M. Dextran 75 and postoperative phlebitis. Evaluation of Dextran 75 in the prophylaxis of postoperative thrombophlebitis, pulmonary embolism and myocardial infarction. Arch Surg 1969; 98:694.
54. Hartsuck JM, Greenfield LJ. Postoperative thromboembolism. A clinical study with ^{125}I fibrinogen and pulmonary scanning. Arch Surg 1973; 107:733.
55. Hills NH, Pflug JJ, Jeyasingh K, et al. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Br Med J 1972; 1:131.
56. Hirsh J, Gallus AS. ^{125}I labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. JAMA 1975; 233:970.
57. Hume M, Kuriakose TX, Zuch L, et al. ^{125}I fibrinogen and the prevention of venous thrombosis. Arch Surg 1973; 107:803.

58. Hume M, Turner RD, Kuriakose TX, et al. Venous thrombosis after total hip replacement. Combined monitoring as a guide for prophylaxis and treatment. J Bone Joint Surg 1976; 58A:933.
59. Huttunen HJ, Matilla MAK, Hakalehto J, et al. Single infusion of Dextran 70 in the prophylaxis of postoperative deep vein thrombosis. Ann Chir Gynaecol Fenn 1971; 60:119.
60. Ivins JC, Bickel WH, Nelson JW. Arthroplasty of the hip for idiopathic degenerative joint disease. Surg Gynecol Obstet 1967; 125:1281.
61. Jansen H. Dextran as a prophylaxis against thromboembolism in general surgery. Acta Chir Scand Suppl 1968; 387:86.
62. Jansen H. Postoperative thromboembolism and its prevention with 500 ml dextran given during operation. Acta Chir Scand Suppl 1972; 427:1.
63. Jennings JJ, Harris WH, Sariento A. A clinical evaluation of aspirin prophylaxis of thromboembolic disease after total hip arthroplasty. J Bone Joint Surg 1976; 58A:926.
64. Joffe SN. The incidence of postoperative deep vein thrombosis. Thromb Res 1975; 7:141.
65. Joffe S. Drug prevention of postoperative deep vein thrombosis. A comparative study of calcium heparinate and sodium pentosan polysulfate. Arch Surg 1976; 111:37.
66. Johnson R, Green JR, Charnley J. Pulmonary embolism and its prophylaxis following the Charnley Total Hip Replacement. Clin Orthop 1977; 127:123.
67. Kakkar VV, Flanc C, Howe CT, et al. Natural history of postoperative deep-vein thrombosis. Lancet 1969; 2:230.
68. Kakkar VV. the Diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. Arch Surg 1972; 104:152.
69. Kakkar VV, Corrigan T, Spindler J, et al. Efficacy of low doses of heparin in prevention of deep vein thrombosis after major surgery. Lancet 1972; 2:101.
70. Kakkar VV, Howe Ct, Nicolaides AN, et al. Deep vein thrombosis of the leg. Is there a "high risk" group? Am J Surg 1972; 120:527.
71. Kernohan RJ, Todd C. Heparin therapy in thromboembolic disease. Lancet 1966; 1:621.
72. Kiil J, Kiil J, Axelsen F, et al. Prophylaxis against postoperative pulmonary embolism and deep-vein thrombosis by low-dose heparin. Lancet 1978; 1:115.
73. Kline A, Hughes LE, Campbell H, et al. Dextran 70 in prophylaxis of thromboembolic disease after surgery. A clinically orientated randomized double-blind trial. Br Med J 1975; 2:109.
74. Koekenberg LJL. Experimental use of Macrodex as a prophylaxis against post-operative thromboembolism. Bull Soc Int Chir 1962; 21:501.
75. Knight MTN, Dawson R. Effect of intermittent compression of the arms on deep venous thrombosis in the legs. Lancet 1976; 2:1265.
76. Krause RJ, Cranley JJ, Hallaba MAS, et al. Caval ligation in thromboembolic disease. Arch Surg 1963; 87:184.
77. Lahnborg G, Bergstrom K, Friman L, et al. Effect of low-dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning. Lancet 1974; 1:329.
78. Loew D, Wellmer HK, Bauer U, et al. Postoperative thromboembolie-prophylaxe mit acetylsalicylsaure. Dtsch Med Wochenschr 1974; 99:565.
79. London D, Crosfill ML. The effect of dextran '70' on postoperative deep venous thrombosis. Br J Clin Pract 1969; 23:158.
80. Mannucci PM, Citterio LE, Panajotopoulos N. Low-dose heparin and deep-vein thrombosis after total hip replacement. Thromb Haemostas 1976; 36:157.
81. Matis P. Results of alternating anticoagulant prophylaxis in surgery. *In* Greep JM, Loeliger EA, Roos J, (eds.) Proceedings of the Dijkzigt Conference on the Prevention of Thromboembolism in Surgery. Amsterdam, Excerpta Medica Foundation. 1961. pp 22–25.
82. McNeil BJ. A diagnostic strategy using ventilation-perfusion studies in patients suspect for pulmonary embolism. J Nucl Med 1976; 17:613.
83. Mendes DG: Prophylactic treatment with dextran 70 in total hip replacement. Clin Orthop 1973; 90:110.
84. Mobin-Uddin K, Utley JR, Bryant LR. The inferior vena cava umbrella filter. Prog Cardiovasc Dis 1975; 17:391.
85. Moloney GE, Morrell MT, Fell RH. The effect of electrical stimulation of the legs on postoperative thrombosis. Br J Surg 1972; 59:66.
86. Negus D, Pinto DJ, LeQuesne LP, et al. ^{125}I-labelled fibrinogen in the diagnosis of deep vein thrombosis and its correlation with phlebography. Br J Surg 1968; 55:835.
87. Nichols AB, Cochavi S, Hales CA, et al. Scintigraphic detection of pulmonary emboli by serial position imaging of inhales ^{15}O-labeled carbon dioxide. N Engl J Med 1978; 299:279.
88. Nicolaides AN, DuPont PA, Desai S, et al. Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. Lancet 1972; 2:890.
89. Nicolaides NA, DuPont P, Parsons D, et al. Small dose subcutaneous heparin in preventing deep venous thrombosis after elective hip surgery. Br J Surg 1974; 61:320.
90. Nicolaides AN, O'Connell JD. Origin and distribution of thrombi in patients presenting with clinical deep vein thrombosis. *In* Edited Nicolaides AN, (ed.) Thromboembolism Baltimore, University Park Press. 1975. pp 167–180.
91. O'Sullivan EF, Hirsh J, McCarthy RA, et al. Heparin in the treatment of venous thromboembolic disease: administration control and results. Med J Aust 1968; 2:153.
92. Pachter HL, Riles TS. Low dose heparin: bleeding and wound complications in the surgical patient. A prospective randomised study. Ann Surg 1977; 186:669.
93. Pinto DJ. Controlled trial of an anticoagulant (warfarin sodium) in the prevention of venous thrombosis following hip surgery. Br J Surg 1970; 57:349.
94. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet 1977; 1:466.
95. Ritter MA, Hamilton CW. A comparative analysis of warfarin and low-dose heparin as thromboembolism prophylaxis in total hip replacement patients. Ann Surg 1975; 181:896.
96. Roberts VC, Cotton LT. Prevention of postoperative deep vein thrombosis in patients with malignant disease. Br Med J 1974; 1:358.
97. Roberts VC, Cotton LT. Failure of low-dose heparin to improve efficacy of preoperative intermittent calf compression in preventing postoperative deep vein thrombosis. Br Med J 1975; 3: 458.
98. Robin ED. Overdiagnosis and overtreatment of pulmonary embolism: the emperor may have no clothes. Ann Int Med 1977; 87:775.
99. Rosenberg IL, Pollock AV. A comparison of mechanical and chemical methods of prevention of postoperative venous thrombosis. Br J Surg 1974; 61:924.
100. Rosenberg IL, Evans M, Pollock AV. Prophylaxis of postoperative leg vein thrombosis by low dose subcutaneous heparin or preoperative calf muscle stimulation. A controlled clinical trial. Br Med J 1975; 1:649.
101. Rothermel JE, Wessinger JB, Stinchfield FE. Dextran 40 and thromboembolism in total hip replacement surgery. Arch Surg 1973; 106:135.
102. Ruckley CV. Heparin versus dextran in the prevention of deep-vein thrombosis. A multi-unit controlled trial. Lancet 1974; 2:118.
103. Sabri S, Roberts VC, Cotton LT. Prevention of early postoperative deep vein thrombosis by intermittent compression of the leg during surgery. Br Med J 1971; 4:394.
104. Sagar S, Massey J, Sanderson JM. Low dose heparin prophylaxis against fatal pulmonary embolism. Br Med J 1975; 4:257.
105. Sagar S, Nairn D, Stamatakis JD, et al. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis

in patients undergoing total hip replacement. Lancet 1976; 1:1151.
106. Salzman EW, Harris WH, DeSanctis RW. Reduction in venous thromboembolism by agents affecting platelet function. N Engl J Med 1971; 284:1287.
107. Salzman EW, Deykin D, Shapiro RM, et al. Management of heparin therapy. N Engl J Med 1975; 292:1046.
108. Salzman EW, Harris WH. Prevention of venous thromboembolism in orthopaedic patients. J Bone Joint Surg 1976; 58A:903.
109. Sawyer RW. Clinical experience with dextran treatment. Acta Chir Scand Suppl 1968; 387:58.
110. Scottish study. Heparin versus dextran in the prevention of deep vein thrombosis. A multiunit controlled trial. Lancet 1974; 2:118.
111. Stadil F. Macrodex prophylaxis in postoperative thrombosis. A preliminary communication. Acta Chir Scand Suppl 1968; 387:88.
112. Stadil F. Prevention of venous thrombosis. Lancet 1974; 2:50.
113. Stamatakis JD, Kakkar VV, Sagar S, et al. Femoral vein thrombosis and total hip replacement. Brit Med J 1977; 2:223.
114. Stephenson CBS, Wallace JC, Vaughan JV. Dextran 70 in the prevention of postoperative deep-vein thrombosis with observations on pulmonary embolism: Report on a pilot study. N Z Med J 1973; 77:302.
115. Strand L, Bank-Mikkelse OK, Lindewald M. Small heparin doses as prophylaxis against deep-vein thrombosis in major surgery. Acta Chir Scand 1975; 141:624.
116. Taylor DF. Cited by Collins REC: Physical methods of prophylaxis against deep vein thrombosis. *In* Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism. Edited by J Fratantoni, S Wessler (DHEW Publication No (NIH) 79-866). Washington DC, Government Printing Office, 1975, pp 158–172.
117. Tsapogas MJ, Miller R, Peabody RA, et al. Detection of postoperative venous thrombosis and effectiveness of prophylactic measures. Studies with the fibrinogen ^{125}I technique. Arch Surg 1970; 101:149.
118. Urokinase pulmonary embolism trial. Phase 1 results. A cooperative study. JAMA 1970; 214:2163.
119. VanVroonhoven TJMV, Van Zijl J, Muller H. Low-dose subcutaneous heparin versus oral anticoagulants in the prevention of postoperative deep-venous thrombosis. A controlled clinical trial. Lancet 1974; 1:375.
120. Vasilescu C. A multiunit trial of dextran and heparin in the prophylaxis of deep vein thrombosis. Br J Surg 1974; 61:320.
121. Venous Thrombosis Clinical Study Group. Small doses of subcutaneous sodium heparin in the prevention of deep venous thrombosis after elective hip operations. Br J Surg 1975; 62:348.
122. Warlow C, Terry G, Kenmure ACF, et al. A double-blind trial of low-doses of subcutaneous heparin in the prevention of deep vein thrombosis after myocardial infarction. Lancet 1973; 2:934.
123. Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977; 296:716.
124. Williams HT. Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. Lancet 1971; 2:950.
125. Williams JW, Eikman EA, Greenberg SH, et al. Low-dose heparin fails to prevent pulmonary embolism after hip surgery or above knee amputation. Ann Surg 1978; 188:468.
126. Wilson PD, Amstutz HC, Czerniecki A, et al. Total hip replacement with fixation by acrylic cement. A preliminary study of 100 consecutive McKeefarrar prosthetic replacements. J Bone Joint Surg 1972; 54A:207.
127. Wu TK, Tsapogas MJ, Jordan FR. Prophylaxis of deep vein thrombosis by hydroxychloroquine sulfate and heparin. Surg Gynecol Obstet 1977; 145:714.