Preventive and Therapeutic Approach to Venous Thromboembolic Disease and Pulmonary Embolism—Can Death From Pulmonary Embolism be Prevented?

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Venous thromboembolism produces chronic sequelae in the legs and occasional immediate mortality due to pulmonary embolism. Because it occurs in certain high risk situations (for example, after surgery) its prevention is a practical proposition. This has been attempted using many different approaches. Administration of low dose heparin with or without dihydroergotamine to enhance venous return has been one of the most widely tested regimens. There is little doubt that this can prevent, in many patient groups, postoperative deep venous thrombosis and fatal pulmonary embolism, with a low incidence of adverse reactions. Some particularly high risk postoperative patient groups (for example, those undergoing hip surgery) warrant more aggressive measures to prevent thrombosis. Surveys have shown that increasing use is being made of this approach, and it is hoped that all surgeons will adopt a policy that will reduce postoperative venous thrombosis and pulmonary embolism.

A reduction in the incidence of venous thromboembolism in large acute myocardial infarction is achieved by low dose heparin, although early mobilization is important. In addition, many of the patients at risk merit full dose anticoagulation to prevent intracardiac thromboembolism.

Established venous thrombosis is treated effectively by intravenous heparin, followed by warfarin to keep the prothrombin time at 1.2 to 1.5 times control, as assessed using rabbit thromboplastin; most patients need three months of treatment. Anticoagulation is warranted for pulmonary embolism, with fibrinolytic therapy reserved for patients with massive embolism and hemodynamic compromise. Embolectomy is a heroic measure, which may occasionally be lifesaving.

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Deep vein thrombosis of the legs is a common age-related phenomenon manifested by focal intravascular coagulation in which the mechanism is obscure, the clinical recognition elusive, the recurrence rate high and mortality related to pulmonary embolism unpredictable. Apart from the immediate risk to life, one must also consider the late sequelae of extensive deep vein thrombosis—swelling of the legs, varicose veins, ulceration and other trophic changes that represent an equally distressing situation.

In this review, we discuss three aspects of management: 1) the prevention of the development of deep vein thrombosis and pulmonary embolism; 2) the treatment of venous thrombosis that has already occurred, to prevent progression, embolic sequelae or recurrence; and 3) the treatment of pulmonary embolism itself.

Prevention of Venous Thrombosis and Pulmonary Embolism, Particularly in the Postoperative Period

It is often asked whether postoperative pulmonary embolism is preventable and, furthermore, whether it is worth preventing, because the mortality due to this complication is extremely low and all prophylactic measures require supervision, extra work, organization and vigilance. The data presented in this section support the argument that not only should this complication be prevented, but also several prophylactic measures now available make prevention a practical proposition. Therefore, the most rational approach would seem to be that of developing an effective method of prophylaxis if the mortality due to pulmonary embolism is to

be significantly reduced. To be adopted on a wide scale, such a method must fulfill the following criteria: it must be simple, safe and effective; it must be applicable to all types of patients at risk of developing deep vein thrombosis and it must cover the period of risk, which in surgical patients has been shown to extend from the time of operation through the first 7 to 10 postoperative days.

The efficacy of several prophylactic measures in preventing death due to postoperative pulmonary embolism has been assessed in numerous clinical trials, and in this first section, we focus on this issue. Treatments tested have included oral anticoagulants, dextran and low dose heparin. However, low dose heparin has been most extensively investigated and at present is the most commonly used prophylactic therapy for prevention of postoperative pulmonary embolism. Therefore, the data from studies using this form of prophylaxis are analyzed to answer the critical question: Can death from pulmonary embolism be prevented?

Prevention of Deep Vein Thrombosis in Surgical Patients

Low dose heparin prophylaxis. Early classical autopsy studies established the connection between emboli in the lungs and thrombi in the lower limbs. Therefore, it can be argued that prevention of such thrombi should also lead to reduction in the incidence of fatal pulmonary embolism. In the early 1970s, many studies (1–34) demonstrated the efficacy of low dose subcutaneous heparin in preventing postoperative deep vein thrombosis after nonorthopedic surgery (Table 1). These included 34 randomized clinical trials involving 6,163 patients, and deep vein thrombosis was diagnosed by means of leg scanning with iodine-125-fibrinogen uptake test. In 29 trials, there was a significant reduction in the incidence of deep vein thrombosis in patients receiving low dose heparin prophylaxis.

Few physicians would deny that venous thrombosis, although very common, is generally a benign disease. With the use of the iodine-125–fibrinogen test and phlebography, it has been shown that in surgical patients, the majority of thrombi form in the calf veins. A surprisingly high proportion of these thrombi undergo spontaneous lysis. As discussed elsewhere in this symposium (35), in about 20% of patients, these thrombi extend proximally from the calf into the popliteal, femoral and iliac veins. In this group with thrombosis extending proximally, pulmonary embolism occurs in almost 50% of patients, only a very small proportion of cases prove fatal (36). The effect of low dose heparin prophylaxis on the extension of venous thrombosis was evaluated in four of the larger studies (10,15,25,37) of patients undergoing elective abdominal surgery, which together included more than 3,000 patients (Table 2). In 1,631 control patients, thrombi were detected in 380, while extension of thrombus occurred in 99 (6%). In contrast, of 1,485 patients

receiving heparin, thrombi were detected in 95 and extension occurred in only 9 (0.6%). The difference in the frequency of extending thrombi between the two groups was statistically significant, not only in the aggregate of these four studies, but in each of the individual trials as well.

Combination of heparin and dihydroergotamine. Changes in blood coagulation and stasis in the deep veins of the lower limbs are both considered to be important factors in the pathogenesis of deep vein thrombosis. It is, therefore, logical to propose that prophylaxis might be better achieved by methods that minimize or eliminate both of these factors rather than by counteracting either factor alone.

Dihydroergotamine is a potent vasoconstrictor in humans (3). Its site of action seems to be the capacitance vessels of the limbs. Dihydroergotamine administered subcutaneously has been shown to increase the velocity of venous flow in the major veins of the legs by constricting the capacitance vessels while exerting a negligible influence on resistance vessels and capillary filtration (39). A single injection of 0.5 mg has been shown to increase the mean calf muscle blood flow significantly, an effect that persists for up to 5 hours. It has also been shown that dihydroergotamine enhances the synthesis of prostaglandins, and this may affect platelet function. Furthermore, several workers (40,41) have also shown that administration of drugs that affect vascular motility increases the release of plasminogen activator from the vein wall. Therefore, it is possible that dihydroergotamine, by producing venoconstriction through its action on alpha-adrenoreceptors of the vein wall, may enhance release of plasminogen activator and, thus, increase fibrinolytic activity.

Heparin-Dihydergot, a fixed combination of either 5,000 or 2,500 IU of heparin sodium with 0.5 mg of dihydroergotamine mesylate, is available in single dose vials as the sterile, lyophilized mixture. This preparation has been developed to overcome the physicochemical incompatibility of the available parental formulations of both sodium and calcium heparin with that of dihydroergotamine mesylate.

A number of clinical trials (42–53) of heparin-dihydroergotamine in a variety of patient populations have been reported (Table 3). The fibrinogen uptake test or venography was used for diagnosis (42,43). These trials were randomized, with one exception. In general, the addition of dihydroergotamine reduced by a further 50% the already lowered incidence of deep vein thrombosis detected when heparin alone was used. In addition, four clinical trials (44,50,54,55), in which deep vein thrombosis was detected by the iodine-125–fibrinogen test and venography performed in orthopedic patients, confirmed the superiority of the antithrombotic effect of the combination compared with heparin alone. Patients admitted to these four trials who received heparin alone had approximately a 45% incidence of deep vein thrombosis compared with 20% among those receiving the combination. There was no recognized difference in the

Table 1. Effectiveness of Low Dose Heparin in the Prevention of Postoperative Deep Vein Thrombosis*

Study Authors (reference)	Patient Population	No. of Pts.	Frequency of Thrombosis (%)		
			Controls	LD Hep.	Value
Abernethy and Hartsuck (1)	General surgery	125	5	6	NS
Ansay et al. (2)	General surgery	50	63	26	<0.05
Ballard et al. (3)	Gynecology	110	29	4	<0.01
Bergqvist and Hallbook (4)	General surgery	97	27	13	<0.05
Cerrato et al. (5)	Neurosurgery	100	34	6	<0.005
Clarke-Pearson et al. (6)	Gynecology, malignancy	185	12	15	NS
Coe et al (7)	Urology	52	25	21	NS
Covey et al. (8)	General surgery	105	10	8	NS
Gallus et al (9)	General surgery	209	15	1	<0.001
Gallus et al. (10)	General surgery	820	16	4	<0.05
Gordon-Smith et al. (11)	General surgery	150	42	14†	<0 003
				8‡	<0.001
Groote Schuur Hospital (12)	Abdominal surgery	199	27	12	<0.007
Gruber et al (13)	General surgery	194	36	13	<0.005
Hedlund and Blomback (14)	Urology	59	46	21	NS
International Multicentre Trial (15)	General surgery	1292	25	8	<0.005
Jackaman et al. (16)	Thorax surgery	183	51	28	<0.005
Joffe (17)	General surgery	120	51	9	<0.0005
Kakkar et al. (18)	General surgery	78	42	8	<0.001
Kettunen et al. (19)	General surgery	200	41	8	<0 001
Kraytman et al. (20)	General surgery	50	63	26	<0.05
Kutnowsky et al. (21)	Urology	47	36	9	<0 05
Lahnborg et al. (22)	Abdominal surgery	112	20	5	<0.05
Lawrence et al. (23)	Abdominal surgery	242	17	7	<0 05
Multi-Unit Controlled Trial (24)	General surgery	160	43	15	<0.05
	Gynecology	55	14	0	<0.05
	Thoracic surgery	38	44	15	<0.05
Nicolaides et al. (25)	General surgery	251	24	1	<0.001
Plante et al. (26)	General surgery	108	21	7	<0.05
Rem et al. (27)	General surgery, urology	178	36	13	<0.001
Rosenberg et al. (28)	General surgery	154	44	7	<0.001
Sebeseri et al. (29)	Urology	65	58	12	<0.01
Strand et al. (30)	General surgery	100	20	6	<0.05
Taberner et al. (31)	Gynecology	57	23	6	<0.05
Torngren and Forsberg (32)	Abdominal surgery	124	33	165	<0.05
Williams (33)	Abdominal surgery	44	33	0	<0.02
Wu et al. (34)	Abdominal surgery	88	14	0	<0.01

*The iodine-125–fibrinogen test was used to detect deep venous thrombosis. †In total, three doses of low dose heparin. ‡Low dose heparin for 5 days LD Hep. = low dose heparin; NS = not significant; Pts. = patients.

amount of operative or postoperative blood loss in the two treatment groups, although the heparin concentration in plasma was significantly higher in the patients who received the combined treatment (44).

Low molecular weight heparin prophylaxis. Commercially available heparin consists of a family of straight chain anionic polysaccharides, more specifically, glycosaminoglycan sulfate esters of highly variable molecular weight, averaging 9,000 to 15,000 daltons, but ranging from 3,000 to 40,00 daltons. Heparin has the ability to form a complex with antithrombin III, but only a specific portion of the heparin in clinically used preparations binds strongly to antithrombin III, as discussed by Wessler and Gitel (56) elsewhere in this symposium. With affinity chromatography

on purified matrix-bound antithrombin, heparin can be divided into one fraction (about one-third of the total amount) with a high affinity for antithrombin III and high anticoagulant activity, and one virtually inactive fraction with a low affinity for antithrombin III (57,58). According to these observations, low molecular weight heparin should possess antithrombotic properties, possibly without causing excessive bleeding.

The efficacy and safety of a low molecular weight heparin fraction in preventing postoperative venous thromboembolism was assessed in a double-blind, randomly allocated trial and in an "open" study reported together, (59). Of 395 patients included in the double-blind trial, 199 received unfractionated calcium heparin, and 196 received the low

Table 2. Effect of Low Dose Heparin on the Proximal Extension of Thrombi in the Popliteal, Femoral and Iliac Veins in Patients Undergoing Abdominal Surgery

Reference	Control Group			Heparin Group		
	No. of Pts.	DVT	No with Extension	No. of Pts.	DVT	No. with Extension
Corrigan et al. (36)	434	121	29	320	23	1
Nicolaides et al. (25)	122	29	9	128	11	0
Gallus et al. (10)	408	66	12	412	13	3
Kakkar et al. (15)	667	164	49	625	48	5
Total	1,631	380 (23.3%)	99 (6%)	1,485	95 (5.79%)	9 (0.6%)

DVT = deep vein thrombosis; Pts. = patients.

molecular weight heparin fraction. The data were analyzed on an "intention to treat" basis. The two groups were well matched for risk factors that could predispose to the development of venous thrombosis. Fifteen (7.5%) of 199 patients receiving unfractionated heparin and 5 (2.5%) of 196 patients in the low molecular weight heparin group developed deep venous thrombosis (p < 0.05). There was no significant difference between the two groups in terms of incisional or total blood loss during surgery, postoperative drainage or wound hematoma formation. Of 910 patients included in the open study who received a single injection of low molecular weight heparin every day, 30 (3.2%) died during the postoperative period; in none of the autopsy patients were pulmonary emboli detected. Thirty-one patients (3.4%) developed isotopic deep venous thrombosis; 27 (2.9%) were receiving prophylaxis at the time this was diagnosed. Thirty-six patients (3.9%) developed wound hematoma; 25 (12.4%) of these were among the 201 patients undergoing surgery for gynecologic conditions, and 11 (1.5%) were among the 709 patients having general abdominal surgery.

This difference was statistically significant (p < 0.001). Thus, the results of a double-blind trial indicate that a single daily injection of 1,850 activated partial thromboplastin time units (7,500 antifactor Xa units) of a low molecular weight heparin is efficacious in preventing postoperative deep venous thrombosis. The findings of the open study (59) suggest that this regimen also provides an effective prophylaxis against postoperative major pulmonary embolism.

Prevention of Fatal Pulmonary Embolism

Because fatal pulmonary embolism is uncommon, a large scale multicenter trial is needed to assess potential differences in mortality between treated and control patients. The most comprehensive trial of low dose heparin prophylaxis against fatal pulmonary embolism is from King's College Hospital, London, and is known as the International Multicentre Trial (15). The results of this study published in 1975 provide a foundation for current recommendations concerning postoperative prophylaxis. The study was car-

Table 3. Prophylactic Antithromboembolic Effect of Dihydroergotamine Alone or in Combination With Low Dose Heparin*

Reference	Patient Population	No. of Pts.	% With Thrombosis			
			Control	DHE	LDH	DHE-LDH
Buttermann et al. (41)	General surgery	106	35	9	—	—
Fey et al. (42)	General surgery	148	57	33	—	—
Kakkar et al. (43)	Abdominal surgery	197	—	20	4	6
	Elective surgery	100	—	—	52	20
Koppenhagen et al. (44)	General surgery Gynecologic surgery	253	—	—	14	6.5
Kunz et al. (45)	Gynecologic surgery	178	—	—	15	7
Lahnborg (46)	Hip fracture	210	39	—	20	16
Morris and Hardy (47)	Elective hip surgery	81	56	22	—	4
Muhe et al (48)	General surgery	150	44	24		
Sagar et al. (49)	Elective hip surgery	82	69	—	32	16
Schondorf and Weber (50)	Elective hip surgery	108	—	—	15	4
Sechas et al. (51)	General surgery, urologic	80	12	2	—	—
Stamatakis et al. (52)	General surgery	100	—	16	4	4

*The iodine-125-fibrinogen test was used to detect deep vein thrombosis. DHE = dihydroergotamine; LDH = low dose heparin; Pts. = patients.

ried out in 28 centers in a randomized controlled design. Eligible patients were older than 40 years of age and were scheduled to undergo elective major surgery. Those undergoing emergency surgery and those receiving anticoagulant therapy were excluded.

Patients in the treatment group received 5,000 units of subcutaneous calcium heparin 2 hours preoperatively and every 8 hours thereafter for 7 days. If a patient was still confined to bed at the end of this period, the therapeutic regimen was continued until the patient became ambulatory. Control patients did not receive any specific prophylaxis. Randomization provided treatment and control groups that were well matched for baseline characteristics. Each center's pathologist was asked to record the causes of death. Uniform criteria were established for determining that pulmonary embolism was the cause of death (that is, if necropsy revealed massive fresh emboli in the pulmonary trunk the main pulmonary artery or at least two lobar arteries and if no other possible cause of death was found).

Analysis of the results in the first 2,000 patients indicated a substantially greater benefit from heparin than had been envisaged at the planning stage. The incidence of fatal pulmonary embolism in the control group was approximately 1% rather than 0.5% as was originally thought. Entrance to the trial was, therefore, closed when 4,471 patients had been admitted. Three hundred ten patients were excluded from the analysis for several reasons, leaving 4,121 patients in whom the protocol had been correctly followed (2,076 in the control group and 2,045 in the heparin group). The two groups were well matched for age, sex, weight, blood group and other factors that could predispose to the development of venous thromboembolism. One hundred eighty patients (4.4%) died during the postoperative period, 100 in the control group and 80 in the heparin group. Of the patients who died, 72% from the control group and 66% from the heparin group underwent necropsy. Sixteen patients in the control group and two in the heparin group were found to have died as a result of acute massive pulmonary embolism (p < 0.005). In addition, emboli found at necropsy in six patients in the control group and three in the heparin group were considered either contributory to death or an incidental finding, since death in these patients was attributed to other causes. The findings were again significant (p < 0.005) when all cases of pulmonary embolism were considered together. One of the 350 patients excluded from the trial also died from pulmonary embolism. This patient had received heparin. Even when this patient was included in the analysis, the results were still highly significant (p < 0.005). In addition, 24 patients in the control group and 8 in the heparin group were treated for clinically suspected pulmonary embolism; this difference was statistically significant (p < 0.0005). Deep venous thrombosis was detected at necropsy in 24 patients in the control group and 6 in the heparin group (p < 0.005). Thirty-two

patients in the control group and 11 in the heparin group developed deep venous thrombosus that was confirmed by venography (p < 0.005). The difference in the number of patients requiring treatment for deep venous thrombosus or pulmonary embolism, or both, in the two groups was significant (p < 0.005).

No therapeutic trial has escaped some form of adverse criticism; this is true of all the trials involving an evaluation of antithrombotic agents. Of the criticisms leveled against this study, only three are considered to be pertinent to an evaluation of the accuracy of the conclusions. 1) Was the autopsy rate high enough to avoid imbalances between autopsy and nonautopsy patients? 2) To what extent did errors in pathologic interpretation influence the results? 3) To what extent could bias have influenced the results? Responses to these questions have been adequately summarized by Sherry (60). The autopsy rate of 70% is high enough to exclude imbalance as a likely source of error. As for the second question, some error in pathologic interpretation is possible, but considering the competence of the pathologists, the error must be relatively small compared with the striking differences between the groups. Finally, as to the question of bias, this is of no influence when death is used as the end point.

Subsequently, a report of Gruber et al. (61) from one of the participating centers in the International Multicentre Trial was issued. As already indicated, the major end point of the trial and fatal pulmonary embolism diagnosed at autopsy. Pulmonary embolisms was considered to have caused the patient's death if the necropsy revealed massive fresh emboli in the pulmonary trunk, the main pulmonary artery or at least two lobar arteries and if no other cause of death was found. However, Gruber et al. claimed that multiple peripheral emboli may also cause death and, hence, should be considered fatal. Using this revised criterion for fatal pulmonary embolism, they reported that in 6 of 94 patients who received heparin, the cause of death was acute pulmonary embolism. These data were inconsistent with their previous report (62) and with the study design that was returned to the multicenter trial center. Therefore, a second International Multicentre Trial was organized by these authors, using the same protocol as in the first trial. A total of 4,352 patients were admitted to this prospective randomized trial, which was designed to compare the prophylactic efficacy of dextran 70 and low dose heparin against fatal pulmonary embolism after elective operation for general, orthopedic, urologic and gynecologic diseases. The results of this study were reported in January 1980 (63). Of 3,984 patients correctly admitted to the study, 1,993 were allocated to receive dextran and 1,991 to receive low dose heparin. Of 75 patients who died within 30 days after operation, 38 had been given dextran and 37 had been given low dose heparin. Necropsy was performed in 33 and 32 of these cases, respectively. The pulmonary arteries were

dissected down to small segmental vessels. Cases of pulmonary embolism were divided into three groups: 1) those in which no other cause of death was found, 2) those in which pulmonary embolism was considered to be a contributory cause of death, and 3) those in which pulmonary embolism was regarded as incidental. Embolism found at autopsy was considered to be the sole cause of death in only 3 of 1,991 patients who had received heparin. Another three patients in the heparin group had pulmonary embolism as a contributory cause of death. Thus, the total incidence of pulmonary embolism demonstrated at autopsy was 6 of 1,991 patients. These figures are the same as reported by us in 1975 (15).

Furthermore, a statistical overview (undertaken by the Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, U.K.) of the randomized controlled trials of low dose heparin prophylaxis where mortality from pulmonary embolism was not the main end point supports the results of the original multicenter trial. Correspondence with the investigators yielded cause-specific mortality by allocated treatment for all randomized patients (Table 4). An overview of these results indicated 29 control-allocated pulmonary embolism deaths and only 6 treatment-allocated pulmonary embolism deaths (p < 0.001). In addition, nonfatal pulmonary embolism was moderately reduced, as was death from causes other than pulmonary embolism. In most of these trials, it might have been fairly obvious which patients were receiving active treatment, a factor that could have biased the assessment of nonfatal pulmonary embolism and, to a lesser extent, whether deaths were due to pulmonary embolism, although total mortality was also significantly reduced (p < 0.03).

Complications of Low Dose Heparin Prophylaxis

Hemorrhage. The risk of hemorrhage is the main limitation to the routine use of anticoagulants for the prevention

Table 4. Causes of Death in Patients With Nonfatal Pulmonary Emboli

	Control	Heparin
No. of deaths	100	80
No of necropsies	72	53
Causes of death		
Pulmonary embolus	16	2
Pneumonia	13	11
Myocardial infarction	13	7
Peritonitis	9	7
Pulmonary edema	3	5
Carcinomatosis	5	5
Septicemia	4	3
Hepatic failure	1	2
Renal failure	0	2
Hemorrhage	5	4
Others	3	5

of thromboembolic disease in surgical patients. One definite criterion for evaluating this risk is the frequency of wound hematoma formation.

Two studies (10,44) of a large number of patients reported a significant difference between the number of patients receiving heparin and the number of their control counterparts who developed wound hematoma. However, a recent double-blind study by Kiil et al. (64) failed to confirm such a difference. The reason for this discrepancy arises from the fact that in the International Multicentre Trial (15) and the study reported by Gallus et al. (10), heparin was administered every 8 hours, whereas it was administered by Kiil et al. (64) every 12 hours (64). Similar results have been reported by other workers. It seems that there is a small but definite risk of bleeding when an 8 hour regimen is used, but not when a 12 hour regimen is followed.

A much higher incidence of bleeding complications has been observed in some of the studies (65) reported in the United States. This difference could be due to several factors. Plasma heparin levels after subcutaneous administration depend not only on the molecular weight of the heparin preparation, but also on the type of heparin salt used and the standard that is used by the manufacturers for the calibration of heparin. Unfortunately, two standards are used. In the United States, heparin is calibrated according to the USP unit, which in the past has been 15% more potent than the international unit (IU) established by the World Health Organization. Most European studies have been carried out using heparin calibrated in international units. The difference between the two standards is relatively small, but together with other factors likely to affect heparin absorption, it may give rise to sufficiently higher levels to produce serious bleeding. Currently, the difference between the two units is less. The USP unit is now only 6 to 7% more potent than the international unit.

Another important factor that might have contributed to the higher incidence of bleeding complications reported from the United States relates to the concentration of heparin solution used. The use of multidose vials is inconvenient and wasteful and, at times, may lead to bleeding due to the accidental administration of large amounts of heparin. Ampules made specially for prophylactic use are now available. They contain 5,000 units of either the calcium or sodium salt of heparin in 0.2 ml aqueous solution. The widespread use of such specially prepared ampules has certainly reduced the frequency of bleeding complications.

Ecchymosis at the injection site. This complication has also been observed more frequently when the sodium salt of heparin has been used. Such differences could be due to the fact that the sodium and calcium salts of heparin behave differently when administered subcutaneously. A comparative trial (66) showed that the calcium salt caused significantly less ecchymosis at the site of injection than did the sodium salt. Of 266 subcutaneous injections (133 each of

sodium heparin and calcium heparin), sodium heparin caused local bruising greater than 0.5 cm in diameter in 7%, less than 0.5 cm in 47% and none at all in 46%, whereas calcium heparin produced local bruising over 0.5 cm in diameter in 3%, less than 0.5 cm in 22% and no bruising in 75% (p < 0.001). Pain was rarely reported. When present, it was not significantly different in patients receiving the two heparin preparations and was not related to the formation or size of hematomas.

Adoption of Low Dose Heparin Prophylaxis

Low dose heparin. The value of low-dose heparin in the prophylaxis of postoperative deep vein thrombosis can no longer be seriously disputed. For prophylactic therapy to be widely adopted, it must be easily administered, readily available, of low cost and, above all, of minimal risk. The basic question is the benefit/risk ratio. There is now good reason to believe that the potential benefits of prophylactic low dose heparin far outweigh the risk of hemorrhage. A significant reduction in the incidence of fatal pulmonary embolism, for example, can be achieved at the cost of a 2.5% increase in the incidence of postoperative bleeding, largely in the form of wound hematoma formation.

Two recent surveys suggest that low dose heparin prophylaxis is now being used more widely. All 236 clinics in Sweden dealing with general, urologic, orthopedic and gynecologic surgery were sent a questionnaire concerning their policy about prophylaxis against thromboembolism (67); 94% replied, and 76% claimed to use some kind of prophylaxis. Prophylactic methods in current use varied among the four specialties surveyed; replies were received from 87 to 100% of the clinics surveyed. Several pharmacologic agents were used as prophylaxis against postoperative venous thromboembolism. These included oral anticoagulants, low dose heparin, acetylsalicylic acid and the combination of dihydro ergotamine and heparin. Low dose heparin was used in 78% of the general surgery patients, 54% of the urologic surgery patients, only 39% of the orthopaedic surgery patients and 69% of the gynecologic surgery patients.

In a second survey (68), in the United Kingdom, 752 orthopedic and 663 general surgeons were sent a questionnaire asking how they attempted to prevent venous thromboembolism. The survey concerned prophylaxis offered routinely to elderly patients with hip fractures, patients undergoing elective hip replacement arthroplasty and patients undergoing major abdominal and thoracic operation. Approximately 70% of those questioned replied. The general surgeons returned 521 questionnaires, for an effective response rate of 78%. The orthopedic surgeons returned 605 questionnaires, and 47 surgeons did not complete that part of the questionnaire that dealt with patients who had hip fractures, either because their practice did not include such patients or because they were involved in clinical trials of

prophylactic agents. Similarly, 59 surgeons did not complete the section concerning patients undergoing elective hip replacement arthroplasty. Thus, the effective response rate was 74% for hip fractures and 73% for hip replacements. The survey showed that more general surgeons provide routine prophylaxis than do their orthopaedic colleagues. The difference was attributable mainly to the popularity of low dose heparin among general surgeons. That low dose heparin prophylaxis is effective in general surgical patients has been detailed widely, and the consensus seems to be in its favor. The safety and simplicity of the method were persuasive factors and accounted for the fact that 25% of all the general surgeons who replied use low dose heparin routinely as the sole method of prophylaxis.

Oral anticoagulants. The routine use of oral anticoagulants has been recommended for nearly 20 years for the prevention of venous thromboembolic complications. In the Netherlands, for instance, more than 60% of surgeons routinely use this form of prophylaxis. Yet in the United Kingdom, none of 515 surgeons undertaking general abdominal surgery indicated that they use oral anticoagulants compared with 128 (24.8%) who reported that they use low dose heparin routinely as the sole method of prophylaxis. This trend surely must be considered as a major breakthrough when one considers that the objective evidence of the effectiveness of this form of prophylaxis has been accumulated only during the past few years.

Reasons for not using prophylaxis: role of the clinician. The survey undertaken by Morris (68) suggests that published evidence concerning the prevention of venous thromboembolism has had only a limited influence on surgical practice in the United Kingdom, and the question has arisen as to whether the published evidence that supports the prophylaxis is convincing. To those who find it is, the inaction of the surgeons who do not employ prophylaxis may be regarded as negligence. However, those who are familiar with the published data and do not provide prophylaxis may choose not to do so for two reasons. First, there is a great discrepancy between the ubiquity of venous thromboembolism and the relative infrequency with which it causes death. Second, an individual surgeon, no matter how extensive his or her personal practice, will never recognize the success of the prophylactic action, yet will invariably be reminded of each failure. In view of such circumstances, what should be the role of the practicing clinician? The published evidence and the clinical experience with low dose heparin prophylaxis should now be used to influence the methods used by surgeons for preventing fatal pulmonary embolism occurring after operation.

Prevention of venous thromboembolism in myocardial infarction. The incidence of deep vein thrombosis in the legs in acute myocardial infarction ranges from 17 to 38% (69,70), as detected by fibrinogen uptake, which is similar to the incidence in patients after surgery, but higher

than that in patients with chest pain but no myocardial infarction. Clinically obvious pulmonary emboli occurred in 5% of patients who were not treated with anticoagulants in the Veterans Administration Cooperative Clinical Trial (71) of anticoagulants in acute myocardial infarction (0.6% of cases were fatal) and in 5% in the similar British Medical Research Council Study (72). Deep venous thrombi form early after infarction (50% or more are detectable within 3 days). The incidence is higher in patients with heart failure, shock or prolonged immobility (73) and probably in older patients.

Heparin. Full anticoagulation significantly reduces the incidence of deep venous thrombi in the legs to 6% or less and reduces the incidence of clinical pulmonary embolism from 5 to 6% to 2% (71,72). In three randomized trials (70, 74, 75) in patients with acute myocardial infarction, low dose heparin reduced the incidence of deep vein thrombosis from 23% of 145 control patients to 4% of 138 treated patients (who had no increased bleeding). Low dose heparin was started within 12 to 18 hours of the onset of symptoms of acute myocardial infarction and was continued for approximately 10 days. The low dose regimen reduced the rate of venous thrombosis even in higher risk subgroups with heart failure and reduced the propagation of thrombus to the ileofemoral veins, which is important in preventing pulmonary embolism. These studies were performed before current early mobilization schedules were practiced, and it is possible that the risk/benefit ratio is now different.

Present recommendations. The first therapeutic goal for the prevention of deep vein thrombosis and pulmonary embolism in patients with acute myocardial infarction should be early mobilization. Immediate subcutaneous administration of low dose heparin (5,000 U every 8 to 12 hours) should be reserved for the high risk patients with one or more of the following characteristics: age older than 70 years, large acute myocardial infarction, previous myocardial infarction, heart failure or shock, necessity for prolonged immobilization (>3 days), previous deep vein thrombosis or pulmonary emboli or obesity. At least some of these patients will merit full anticoagulation to prevent intracardiac thromboembolism as discussed in the review by Adams et al.(76).

Treatment of Established Deep Vein Thrombosis

Successful immediate treatment of deep vein thrombosis should prevent extension of the thrombus, prevent embolism to the lungs and restore patency to the venous circulation, while maintaining normal venous valve function and, thus, protect the patient against the postphlebitic syndrome. No controlled trial has specially addressed the use of heparin in deep vein thrombosis (77). However, its value in the prevention of deep vein thrombosis and its role in the treat-

ment of pulmonary embolism, which is almost always derived from thrombi in the deep veins of the leg and pelvis, strongly support its clinical efficacy. Heparin does not dissolve formed thrombi, although it may stimulate endogenous fibrinoloysis. In situations where an additional effect beyond the natural fibrinolytic system is necessary (that is, in the presence of threatened mechanical complications), pharmacologic fibrinolysis may be valuable, as discussed next.

Heparin. The pharmacology and administration of heparin have been dealth with elsewhere in the symposium. Two issues shoud be recapitulated here. Heparin can be given by either continuous infusion or intermittent injection. Although studies comparing the two methods of administration have given conflicting results, two of the studies (78,79) clearly indicated that a continuous infusion was associated with a considerable reduction in bleeding complications. Thus, this should be used where possible. The role of larger dose subcutaneous heparin as an alternative to infusion warrants further investigation.

Monitoring therapy. The second issue is of monitoring therapy. In animal experiments, a minimal level of heparin of 0.4 units/ml is needed to interrupt an established thrombotic process. Further support for the need for a minimal level of anticoagulation comes from a prospective study (80) in which recurrence of venous thrombosis was associated with an activated partial thromboplastin time of less than 1.5 times control. The evidence that maintaining the activated partial thromboplastin time at less than 2.5 times control will significantly reduce hemorrhage is not strong. However, this should be attempted, although often without great success, because the dose-response curve for heparin varies considerably from patient to patient.

Which patient should be treated? Patients with thrombus extending above the popliteal vein have a high incidence of postphlebitic syndrome and of pulmonary embolism (81), and anticoagulation is certainly warranted. There has been uncertainty, however, in cases where thrombosis is confined to the calf veins (82). Minor thrombi in calf veins seldom cause major pulmonary emboli, and the development of the risks of postphlebitic syndrome is low, particularly if the popliteal vein is not occluded (81). The use of anticoagulation in such cases has, therefore, been questioned. The situation has been clarified for *symptomatic* calf vein thrombosis. In a recent study (83), phlebography was used to define a population of patients in whom thrombosis was present but in whom it did not extend into the popliteal vein, although all were symptomatic. After an initial course of heparin, the patients were randomized to receive compressive stockings and warfarin for 3 months (to give a prothrombin time of 1.4 to 1.9 times control; international normalized ratio of 2.5 to 4.2) or compressive stockings alone. Recurrences, which often extended into proximal veins and were associated with pulmonary embolism in one

case, were much more common in the nonanticoagulated group. In asymptomatic cases detected by postoperative surveillance, the balance of risk and benefit remains at present unclear (77). Patients with superficial thrombophlebitis do not warrant anticoagulation; treatment with nonsteroidal anti-inflammatory agents is usually adequate. However, occasional patients with recurrent symptoms may respond to anticoagulants.

Duration of heparin therapy. Little information is available regarding the optimal duration of therapy with heparin. Although therapy with heparin is generally recommended for 7 to 10 days, this may not interrupt the thrombotic process in all patients. For example, in a study comparing low dose herapin with warfarin in the maintenance therapy of deep venous thrombosis, Hull et al (84) found that 9 of 35 patients in the low dose heparin group developed new episodes of thromboembolism after 14 days of intravenous heparin. Thus, we would recommend 7 to 10 days of therapy for most patients, less in those with a remedial thrombus-provoking factor and perhaps more for those with large thrombi or a persistent predisposing factor (for example, cancer) (85).

Warfarin. The study of Hull et al. (84) clearly showed that continued full anticoagulation is needed after heparin. Although this can be achieved with warfarin or with adjusted dose subcutaneous heparin (86), the latter   less convenient for the patient. Treatment with warfarin is adequate to prevent recurrent deep venous thrombosis if the prothrombin time is prolonged from 1.2 to 1.5 times normal (using rabbit thromboplastin; an international normalized ratio of 2.0 to 3.0). If the traditional intensity of anticoagulation is used, with a prothombin time of 1.5 to 2.0 times control, the risk of hemorrhage is unacceptably high (85). During the initiation of warfarin therapy, it can be safely overlapped with heparin, warfarin being started 4 days before heparin is to be discontinued to ensure that its anticoagulant effect is fully established (87). Warfarin can still be monitored by the prothrombin time during heparin therapy by discontinuing heparin for 6 hours before checking the patient. Indeed, if a continuous infusion of heparin is used and the activated partial thromboplastin time is within the range of 1.5 to 2.5 times control, the prothrombin time remains a reliable guide to the effect of warfarin without stopping the heparin (88).

Most authorities feel that anticoagulant treatment with warfarin should continue for at least 6 months if thrombus extends above the popliteal vein or if pulmonary embolism has occurred. If a predisposing condition (for example, immobility) has resolved, a shorter course of treatment may suffice, while a persistent thrombotic predisposition may warrant longer-term treatment (74,85), as does recurrent thrombosis. Patients with calf vein thrombosis may not need more than 12 weeks of therapy.

Fibrinolytic therapy. In patients with extensive deep vein thrombosis, it is suggested that fibrinolytic therapy is associated with a marked reduction in the incidence of the postphlebitic syndrome, particularly if treatment is given soon after the development of symptoms. The incidence of the postphlebitic syndrome in these patients with extensive thrombosis receiving streptokinase is about 10%, while it may be as high as 90% in patients treated with heparin alone (89). Furthermore it is also claimed that completely normal venograms are seen in about 60% of patients treated with streptokinase intravenously over 3 to 5 days in standard doses and in only about 11% of patients treated with heparin (90). However, recent results of long-term studies clearly demonstrate that thrombolytic therapy *does not* prevent the postphlebitic syndrome. Deciding which patients may benefit from fibrinolysis is difficult. Younger patients in whom the risk of hemorrhage is lower and those with clear evidence of proximal involvement to the thigh probably do so. Patients with a short history (< 3 days) improve the most, although treatment of longer established thrombi may be successful. It is difficult to justify the use of a fibrinolytic agent with its increased risk of hemorrhage in the absence of definitive proof of the diagnosis. Thus, venography or a similar investigation should be performed in all patients in whom fibrinolytic therapy is considered.

In summary, patients with deep venous thrombosis, including those with symptomatic calf vein thrombosis, should receive heparin for 7 to 10 days overlapped by warfarin to prolong the prothrombin time by 1.2 to 1.5 times normal. Therapy should be continued for 6 months in most patients (perhaps less in those with predisposing conditions that have resolved and probably for 12 weeks in patients with calf vein thrombosis). Fibrinolytic therapy should be considered in those patients with proximal venous obstruction who are not at risk of hemorrhage.

Treatment of Pulmonary Embolism

Heparin Therapy

Almost all pulmonary emboli arise in the deep veins of the leg or pelvis, as discussed by Hirsh et al. (91) earlier in this symposium. In many cases, the treatment for pulmonary embolism does not differ from that described for thrombosis in the deep veins (that is, immediate anticoagulation with heparin followed by maintenance therapy with warfarin. This was shown in one study (92) performed in the 1960s, in which 35 patients with pulmonary embolism were randomized to receive anticoagulants or no therapy. Five of 19 untreated patients died, while 1 of 16 in the anticoagulated group died, the cause of death being only indirectly related to pulmonary embolism. A further 38 patients received anticoagulants, with one death, not due to pulmonary embolism. This policy was examined by further studies (93,94), which although not controlled, provided confirmatory evidence of the efficacy of heparin. Furthermore, in a group of patients with pulmonary embolism in whom anticoagulant therapy was believed to be strongly contraindicated (95), the mortality was very high.

This evidence strongly supports the efficacy of heparin in the prevention of progression of disease and further embolism in venous thromboembolism (96). Its use in cases of pulmonary embolism is clearly indicated. Dose regimens will, in most cases, be similar to those used for deep vein thrombosis as outlined, but the clearance of heparin is accelerated by large pulmonary embolism (97). Thus, in this setting, larger doses of the drug are needed, in some cases up to 60,000 to 75,000 units over the first 24 hours.

Fibrinolytic Therapy

Although therapy with heparin may stimulate fibrinolysis slightly and may reverse the bronchoconstrictor response to pulmonary embolism (85), definitive therapy is needed if sufficient thrombus is present in the pulmonary circulation to embarrass significantly the patient's overall hemodynamic status. Thus, patients with massive embolism, right heart failure and hypotension have up to a 30 to 40% hospital mortality, and it is these patients who are most likely to benefit from definitive therapy, with either fibrinolytic agents or surgery.

To define the role of thrombolytic therapy, the National Heart, Lung, and Blood Institute performed two controlled trials comparing urokinase and heparin (Phase I, Urokinase Pulmonary Embolism Trial) (98) and subsequently urokinase and streptokinase (Phase II, Urokinase-Streptokinase Pulmonary Embolism Trial) (99) in the treatment of pulmonary embolism. These two trials, in which 327 patients with angiographically confirmed pulmonary embolism were studied, showed the following: 1) greater resolution of pulmonary emboli with fibrinolytic therapy than with heparin, as assessed by pulmonary angiography before and after treatment; 2) greater improvement of the abnormal hemodynamic status of the right heart and pulmonary circulation with fibrinolytic therapy than with heparin; 3) greater reperfusion of the original perfusion defects with lytic therapy than with heparin, as assessed by repeated perfusion lung scans; 4) maximal clot resolution and general improvement in patients with the largest pulmonary emboli; and 5) no difference in the relatively low, (8 to 9%) mortality rate between patients given heparin and those given thrombolytic therapy.

Although mortality was not reduced in these two studies, most deaths from pulmonary embolism occur in the first hour after symptoms, and many of the patients who die would not be included in studies of the type described. In view of the benefits noted in terms of pulmonary perfusion and cardiac output in these two studies, however, it seems likely that fibrinolytic therapy, together with intensive supportive care, may save lives.

A further potential advantage to the use of fibrinolysis is a reduction in long-term effects. Histologic changes in pulmonary arteries and arterioles occur in patients treated with heparin alone after pulmonary embolism. Lung scans 4 months after embolism reveal that normal findings return in only about 20% of patients treated with heparin over this period (100). A more recent study (101) showed better improvement in pulmonary capillary blood volume and perfusion at both 2 weeks and 1 year in a streptokinase-treated group when compared with a heparin-treated group. If fibrinolytic agents are to be used, pulmonary angiography should almost always be performed because the higher risk of bleeding with fibrinolytic therapy than with heparin (98) makes precise diagnosis mandatory. Although fibrinolytic therapy is clearly indicated when there is severe hemodynamic compromise, its value in less severe cases relatively minor for the prevention of long-term changes in pulmonary vascular resistance (101) is unclear when weighed against the inconvenience and risk of thrombolysis.

Surgical Therapy

Embolectomy. The role of surgical embolectomy is limited. The operation can be performed closed or open on cardiopulmonary bypass, the latter being preferable if adequate time is available. Occasional successes are seen, although mortality is very high. It should almost certainly be used only as a last resort, perhaps being restricted to patients with cardiac arrest (96). Percutaneous pulmonary embolectomy has been used with a special catheter (102), the tip of which consists of a suction cup with which the embolism is removed. Experience is limited with this device. Its use has generally been followed by placement of a caval occlusion device, particularly the Greenfield filter.

Inferior vena cava interruption. A few patients are seen in whom anticoagulation and particularly fibrinolytic therapy is contraindicated (for example, patients recovering from intracranial hemorrhage, neurosurgery or recent major trauma). The management of life-threatening pulmonary embolism in these patients may be aided by interruption of the vena cava to prevent further embolism. Recurrent embolism despite adequate anticoagulation is also an indication for this procedure. The inferior vena cava can be interrupted by a variety of techniques of surgical plication, while the percutaneous transvenous insertion of filters has become more popular recently. The Greenfield filter and the Mobin-Uddin umbrella are two devices in current use. Recurrent thromboembolism from such a device may occur, and sequelae in the lower body as a result of venous hypertension are not uncommon (103). Anticoagulation has been used in patients in whom the device has been placed for recurrent embolism to prevent thrombosis on the device.

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