Prevention of Venous Thromboembolism in General Surgical Patients

Results of Meta-analysis

G. PATRICK CLAGETT, M.D. and JOAN S. REISCH, PH.D.

The results of randomized clinical trials evaluating commonly used methods of deep vein thrombosis (DVT) prophylaxis in moderate- and high-risk general surgery patients were pooled to obtain an unbiased estimate of efficacy and risks. Low-dose heparin (LDH), dextran, heparin-dihydroergotamine (HDHE), intermittant pneumatic compression (IPC), and graded elastic stockings significantly reduced the incidence of DVT; aspirin was ineffective. In contrast to other methods, elastic stockings have not been adequately studied to determine their value in reducing DVT in high-risk patients, such as those with malignancy. Only LDH and dextran were studied in numbers of patients sufficient for demonstrating a clear reduction in pulmonary embolism (PE). In comparison studies, LDH was superior to dextran in preventing DVT, but the two agents were equivalent in protecting against PE. Although HDHE was marginally better than LDH in preventing DVT, it appeared to have no advantage in preventing PE—at least in moderate-risk patients. The incidence of major hemorrhage was not increased with any of the prophylactic agents. However, wound hematomas occurred significantly more frequently with LDH, an effect noted in the pooled data from double-blind and open trials. In comparison trials with LDH, both dextran and HDHE had significantly fewer wound hematomas. LDH administered every 8 hours appeared more effective in reducing DVT than LDH administered every 12 hours; the incidence of wound hematomas was equivalent with both regimens.

A LARGE BODY OF LITERATURE has developed evaluating the benefits and risks of pharmacologic and physical agents used to prevent postoperative venous thromboembolism. Despite the convincing evidence of the efficacy of many agents, surveys conducted in the United States,[1] England[2] and Sweden[3] document wide practice variations among surgeons; approximately one half of surgeons in these countries use specific prophylaxis in less than one fifth of their patients. Skepticism of prophylaxis has, in part, been engendered by perceived variations in the actual risk of postoperative venous thromboembolism,[4–6] fear of undesirable side effects (principally bleeding),[7,8] and concerns about costs.[9,10] Much of the reluctance of surgeons to use prophylaxis, however, stems from the confusing and contradictory results of multiple clinical trials. Bewilderment is compounded by the large number of prophylactic methods advocated (over 25 were found on a recent review of the literature[11]), variations in end points used to judge efficacy and side effects, the uncertainty of the clinical relevance of end points such as calf vein thrombosis, and the lack of comparative trials evaluating methods against each other.

Recently, a new type of research, termed meta-analysis, has been developed to combine and analyze the results of randomized, controlled trials.[12] By pooling the results of several clinical trials, meta-analysis increases the statistical power for primary end points and for subgroups and helps resolve uncertainty when reports disagree. The technique is particularly appropriate when an endpoint is so rare that huge clinical trials are necessary for definitive answers. Such is the case with postoperative pulmonary embolism. While many trials demonstrate that the incidence of leg vein thrombosis is reduced by prophylactic agents, very few are large enough to show a definite reduction in pulmonary embolism. One randomized, controlled trial, the International Multicentre Trial, demonstrated a striking reduction in fatal postoperative pulmonary embolism among general surgical patients treated with low-dose heparin.[13] However, the findings were obscured by the contrary results of one of the participating centers in this trial and the ensuing controversy that played out in the medical literature.[14,15] Because uncertainties remain with regard to

From the Departments of Surgery and Academic Computing Services, The University of Texas Southwestern Medical Center at Dallas, Southwestern Medical School, Dallas, Texas

Reprint requests and correspondence: G. Patrick Clagett, M.D., The University of Texas Southwestern Medical Center at Dallas, Department of Surgery, 5323 Harry Hines Boulevard, Dallas, TX 75235-9031

Submitted for publication: January 25, 1988.

the ultimate value of perioperative low-dose heparin and other prophylactic methods in preventing venous thromboembolism,[16] and because there are a large number of published small and moderate-sized randomized trials in general surgical and related patients, the benefits and risks of prophylactic strategies are particularly well-suited to meta-analysis.

Methods

A computer search of the English language medical literature was carried out to obtain published reports of randomized trials of methods of perioperative venous thromboembolism prophylaxis in general surgery patients. The search scanned a 10-year period (up to August 1986); in order to obtain earlier and additional studies, this search was supplemented by checking the bibliographies of comprehensive references[17-20] and the bibliographies of articles obtained from the computer search. Only trials evaluating antithrombotic drugs and physical methods that are generally available and in widespread use were chosen for meta-analysis. These included low-dose heparin (LDH), dextran, low-dose heparin-dihydroergotamine (HDHE), intermittant pneumatic compression (IPC), graded compression elastic stockings, and aspirin alone or in combination with dipyridamole. For a patient to be considered for this meta-analysis, at least four randomized trials had to be available. Specifically excluded from review were newer agents (such as low molecular weight heparin), and combinations of established methods (such as LDH or dextran combined with elastic stockings or IPC), even though these prophylactic methods appear promising.[21-26] The former were not considered because they are not available for general use, and the latter were excluded because too few reported clinical trials were available for analysis. Only randomized trials of patients treated with a prophylactic method compared with control patients or compared with patients treated with another prophylactic method were selected. The trials had to be published in peer-reviewed journals; abstracts, brief reports, and unpublished trials were not included because of the possibility of unreliable data.[12]

For purposes of this review, the term "general surgery patient" is broad and refers to any patient over the age of 40 years undergoing major abdominal surgery. In most trials, the bulk of these patients had elective gastrointestinal (G.I.) surgery. In many, patients with gynecologic and urologic conditions were included, and, in a few, patients having mastectomy, pulmonary operations, or vascular procedures were also studied. Because it is not clear that the risk of perioperative venous thromboembolism is substantially different among these subgroups and because it was impossible to segregate these patients in most trials, all were considered general surgical patients. On the other hand, patients having orthopedic operations have different risks as well as different responses to prophylactic agents,[17,19] and these patients were excluded from analysis. Also excluded were trials of patients undergoing only inguinal hernia repair, vaginal hysterectomy, transurethral prostate resection, or minor operations. In some instances, these types of patients may have been included among much larger numbers of general surgery patients; in these trials, however, such patients comprised a minority.

The following end points were considered for meta-analysis: positive radioactive fibrinogen uptake test (+FUT) for deep vein thrombosis (DVT), +FUT confirmed by phlebography, above-knee deep vein thrombosis (AK DVT), all pulmonary emboli (PE) (includes nonfatal and fatal), fatal pulmonary emboli (FPE), major hemorrhage, and wound hematoma. The clinical diagnosis of PE had to be confirmed by lung scan, pulmonary angiography, or autopsy. Cases in which PE was not confirmed with objective tests were not counted. In some trials, all patients had perfusion lung scans performed after surgery. Because of the uncertain specificity of abnormal perfusion lung scans in postoperative patients having no other signs and symptoms of PE, and because of the large number of abnormal results in these trials that might skew the results, these cases were not included for meta-analysis. AK DVT was considered present when the FUT was unequivocally abnormal in the thigh or when phlebography demonstrated thrombus in the deep veins of the thigh. Major hemorrhage was defined as bleeding not due to faulty surgical technique that led to reoperation, transfusion, or death. Discontinuation of an antithrombotic drug because of perceived excessive bleeding during surgery was not considered unless another criterion for major hemorrhage was described. Although some trials used discontinuation of an antithrombotic drug because of "excessive bleeding" as an end point, this was considered too subjective and poorly defined (particularly when described in open trials where physicians knew which patients were treated) to be used for meta-analysis. Wound hematoma was defined as an abnormal collection of blood in the surgical wound. In most trials, criteria for the presence or absence of wound hematoma were not precisely defined. Descriptions varied all the way from bruising about the wound to collections of blood that led to reopening the wound or wound infection. Because investigators, in general, did not give separate accounting for these different manifestations of wound hematoma, all were counted for meta-analysis. Injection site complications (usually mild bruising) were specifically not considered wound hematomas. In at least four independent studies, the statistical analysis involved the comparison of end point or non-end point status for treated versus control groups. The Mantel-Haenszel

analysis allows the comparison across studies without the direct comparison of subjects from different studies.[27] To accomplish the analysis, the SAS package was utilized on a VAX™ 11/780 computer. As an estimate of relative risk, odds ratios were computed for treated *versus* controls, along with a 95% confidence interval for each odds ratio.[28]

The data from each trial were analyzed in two ways. First, end points in all patients randomized were counted, even if patients didn't receive the assigned treatment or were withdrawn from the study because of protocol violations (intention-to-treat method). Second, only end points occurring in patients who completed protocols (dropouts, withdrawals, and protocol violators excluded from final analysis) were counted (efficacy method). When the final data were pooled and analyzed, in no instance were the end results different, regardless of whether efficacy or intention-to-treat methods were used. Results based on efficacy are presented in Tables 1–7. Prophylactic methods are presented in descending order of frequency of the number of trials (patients) reported for a given method.

Results

Incidence of Thromboembolic End points Among Control General Surgery Patients

To assess the magnitude of the problem of venous thromboembolism among general surgery patients, the incidence of thromboembolic end points was calculated in control patients pooled from all trials of prophylactic methods (Table 1). The overall incidence of DVT (+FUT) was 25%; in trials in which the FUT was verified by phlebography, the incidence was 19.1%. The lower incidence from studies using confirmatory phlebography probably reflects the 10–20% false positive rate with the FUT[29] and is, therefore, more accurate. In 16 studies, it was possible to separate patients with malignant disease; the incidence of DVT (+FUT) was 29.1% among these patients. A discrepancy was noted in the incidence of DVT (+FUT) between trials reported from Europe and North America. The pooled results from 37 European trials documented an incidence of 29.7%. In comparison, the incidence was approximately one half this, 16.1%, from 14 North American trials.

Studies have documented that until leg vein thrombi extend into the popliteal and more proximal veins, they pose little embolic risk and are of small clinical consequence.[30,31] In assessing the more serious end point of AK DVT, data were available in control patients from 16 trials (Table 1). The incidence of AK DVT was 6.9%. The overall incidence of PE (fatal and nonfatal) was 1.6%, and the incidence of FPE was 0.87%.

Low-Dose Heparin

There were 29 trials in which over 8000 general surgery patients were randomized to LDH or control groups (Table 2). In all studies, heparin (5000 units) was given subcutaneously 2 hours before operation and after surgery, was continued every 8 or 12 hours for 7 days, until patients were fully ambulatory or discharged. The incidence of DVT (+FUT) was 8.7% among treated pa-

TABLE 1. *Venous Thromboembolism in Control General Surgery Patients*

End Point	No. Trials	References	No. Patients	Incidence	(95% CI)
DVT (+FUT)	54	13, 14, 34–56, 66–71, 82–88, 90–97, 101, 111–114, 116–118	1084/4310	25.1%	(23.9–26.5)
Confirmed DVT (+FUT, phlebogram)	20	34, 36, 39–41, 52, 56, 66–68, 83, 84, 86, 87, 95, 101, 113, 114, 116	288/1507	19.1%	(17.1–21.1)
DVT (+FUT) (Malignant disease)	16	37, 39, 42, 47, 48, 66, 67, 70, 84, 87, 90, 94, 111, 116–118	159/546	29.1%	(25.3–32.9)
DVT (+FUT) (Europe)	37	13, 14, 35–37, 42–47, 49–51, 53–55, 69–71, 82–85, 87, 88, 90–94, 96, 97, 111, 112, 114, 118	824/2775	29.7%	(28.0–31.4)
DVT (+FUT) (North America)	14	34, 39–41, 48, 52, 56, 66, 67, 95, 101, 113, 116, 117	178/1111	16.1%	(13.9–18.3)
AK DVT	16	14, 36, 39, 43, 49, 52, 66–71, 83, 91, 116, 117	83/1206	6.9%	(5.5–8.3)
A11 PE	32	13, 14, 32, 34–37, 39–42, 45, 47, 48, 52, 53, 55, 66, 67, 69–71, 82, 83, 85, 88, 91, 92, 96, 101, 116, 117	82/5091	1.6%	(1.3–1.9)
FPE	33	13, 14, 32–37, 40–42, 45, 47, 48, 52, 53, 55, 66–71, 82, 83, 85, 88, 91, 96, 101, 116, 117	48/5547	0.87%	(0.63–1.1)

TABLE 2. *Low-dose Heparin Randomized Trials*

End Point	No. Trials	References	Allocated Treatment			Allocated Control			Odds Ratio	(95% CI)	χ^2	p
			Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
DVT (+FUT)	29	13, 14, 34–37, 39–43, 45–56, 66–71	284/3265	8.7%	(7.8–9.7)	853/3382	25.2%	(23.8–26.7)	0.28	(0.25–0.32)	319.8	<0.001
Confirmed DVT (+FUT, phlebogram)	8	34, 39–41, 56, 66–68	50/831	6.0%	(4.5–7.9)	137/891	15.4%	(13.1–18.0)	0.35	(0.25–0.49)	38.9	<0.001
DVT (+FUT) (Double-blind trials)	11	36, 41, 43, 45, 46, 48, 53–56, 71	78/673	11.6%	(5.0–9.3)	129/524	24.6%	(21.0–28.6)	0.40	(0.30–0.54)	34.9	<0.001
DVT (+FUT) (Malignant disease)	10	37, 39, 42, 47, 48, 53, 55, 66, 67, 70	63/474	13.3%	(10.4–16.7)	136/445	30.6%	(26.4–35.1)	0.35	(0.25–0.48)	40.3	<0.001
AK DVT	12	13, 14, 36, 39, 43, 49, 66–71	22/1564	1.4%	(0.9–2.2)	113/1788	6.4%	(5.3–7.7)	0.21	(0.14–0.32)	53.0	<0.001
All PE	20	13, 14, 32, 35, 36, 39–42, 45, 47, 48, 52, 53, 55, 66, 67, 69, 71	22/4215	0.52%	(0.33–0.80)	52/4228	1.2%	(0.93–1.6)	0.42	(0.26–0.68)	12.2	<0.001
FPE	24	13, 14, 32–37, 39–42, 45, 47, 48, 52, 53, 55, 66–71	10/4699	0.21%	(0.11–0.40)	34/4772	0.71%	(0.50–1.0)	0.30	(0.15–0.58)	12.8	<0.001
Major hemorrhage	21	13, 14, 32, 34, 36, 37, 41–43, 45, 47, 48, 52, 54, 55, 66–69, 79, 98	14/4251	0.33%	(0.19–0.57)	14/4265	0.33%	(0.19–0.57)	1.00	(0.48–2.11)	0.00	0.99
Major hemorrhage (Double-blind trials)	4	41, 48, 54, 55	7/392	1.8%	(0.79–3.8)	2/243	0.82%	(0.14–3.3)	2.19	(0.47–10.2)	0.99	0.32
Wound hematomas	20	13, 14, 36, 39, 41, 48, 52, 54, 55, 67–69, 79, 81, 98, 99	212/3379	6.3%	(5.9–6.7)	137/3368	4.1%	(3.4–4.8)	1.56	(1.27–1.97)	16.7	<0.001
Wound hematomas (Double-blind trials)	4	36, 48, 54, 55	29/363	8.0%	(5.5–11.4)	6/216	2.3%	(1.1–6.2)	3.04	(1.29–7.16)	6.46	<0.01

tients *versus* 25.2% among controls ($p < 0.001$). In eight trials, the FUT was confirmed with phlebography. Although the overall incidence of DVT was less in treated (6%) and control (15.4%) groups, the significant ($p < 0.001$) beneficial effect of LDH remained. Eleven studies were double-blind trials in which control patients received saline placebo injections. The incidence of DVT (+FUT) was 11.6% in treated patients *versus* 24.6% in controls ($p < 0.001$). In ten trials, the effect of LDH in subgroups of patients with malignant disease was noted. Among these patients, the incidence of DVT (+FUT) was 11.6% with LDH treatment and 24.6% in controls ($p < 0.001$).

The effects of LDH on the more serious end points of AK DVT and PE were also assessed (Table 2). In 12 randomized trials, information was available for AK DVT. The incidence of AK DVT was 1.4% in LDH-treated patients *versus* 6.4% among controls ($p < 0.001$). All PE, assessed in 20 trials, was halved by LDH treatment; the incidence was 0.5% in treated patients compared to 1.2% in controls ($p < 0.001$). Even more important, LDH reduced the incidence of FPE by two thirds. The pooled data from 24 randomized trials documented a 0.2% incidence of FPE among treated patients *versus* 0.7% in controls ($p < 0.001$). The bulk of the data concerning FPE came from three studies designed for observing the effect of LDH on this end point.[13,32,33] In each of these studies, LDH significantly reduced the occurrence of FPE.

Information concerning hemorrhagic complications was available from 21 trials (Table 2). Four were double-blind studies, and the results from these were analyzed separately. The overall incidence of major hemorrhage was identical (0.33%) among LDH-treated and control patients. Although the incidence was higher in treated (1.8%) and control groups (0.8%) in double-blind trials, the difference between the groups was not significant. In contrast, wound hematomas were significantly ($p < 0.001$) more frequent with LDH-treated patients (6.3%), compared to controls (4.1%) ($p < 0.001$). This relationship was confirmed by examining data from double-blind trials in which the incidence of wound hematomas was 8.0% with LDH treatment, as compared to 2.3% among controls ($p < 0.01$).

An attempt was made to determine if there was a dosage effect of LDH in reducing DVT. Although there were no randomized studies that directly compared LDH that was administered every 12 hours with LDH administered every 8 hours, there were 34[21,22,34–65] studies in which general surgery patients were treated with the every-12-hours regimen and 15 studies[13,14,65–78] in which patients were treated with the every-8-hours regimen. These studies included controlled trials evaluating LDH, noncontrolled studies, and trials comparing LDH with other prophylactic methods. These data were not amenable to analysis with Mantel-Haenszel statistical methods. The data were simply pooled to obtain a gross proportion (incidence) with its 95% confidence interval. In general surgical patients treated with LDH every 12 hours, 289 of 2446, or 11.8% (95% CI, 10.6–13.1%), had DVT (+FUT); in patients treated with LDH every 8 hours, 153 of 2039, or 7.5% (95% CI, 6.4–8.6%), had DVT (+FUT).

A separate analysis was performed to determine if there was a difference in the frequency of hemorrhagic complications between patients administered LDH every 12 hours and those administered LDH every 8 hours. There were 18 studies* available in which the frequency of major hemorrhage was noted for patients administered LDH every 12 hours. Major hemorrhage occurred in 36 of 3839 patients for an incidence of 0.9% (95% CI, 0.6–1.2%). In eight studies[14,67,68,69,73–76] in which LDH was administered every 8 hours, 20 of 1142 patients, or 1.8% (95% CI, 1.0–2.6%), suffered major hemorrhage. Although this number is higher in comparison to that of patients who received LDH every 12 hours, the confidence intervals overlap, and it is doubtful that the difference is real. With regard to wound hematomas, the incidence was identical—with LDH administered every 12 hours,† 226 of 3272 patients, or 6.9% (95% CI, 6–7.8%), had hematomas, and with LDH administered every 8 hours,[13,14,67,68,73–76] 211 of 3048 patients, or 6.9% (95% CI, 6–7.8%), had hematomas. Thus, while there appeared to be a dosage effect with regard to the beneficial effects of LDH in reducing DVT, this was no apparent increase in hemorrhagic complications.

Dextran

Ten randomized, controlled trials of dextran, involving over 1500 general surgery patients were available for analysis (Table 3). In seven of these trials, dextran 70 (mean molecular weight, 70,000) was used;[37,47,82,83,84,85,86] in two, dextran 40 (mean molecular weight, 40,000) was used;[14,87] and in another, both preparations were evaluated.[88] Because both are probably equally efficacious[88] in preventing venous thromboembolism, the data from all ten studies were pooled. In these studies, dextran (500–1000 ml) was administered intravenously over a period that began during operation and continued for 2–6 hours afterwards. It was then infused daily (usually 500 ml) for 1–7 days.

The incidence of DVT (+FUT) was 15.6% among treated patients and 24.2% in controls ($p < 0.001$) (Table 3). In four trials, it was possible to analyze sepa-

* References 21, 22, 32, 37, 39, 41, 42, 48, 52, 54, 55, 58, 59, 61, 62, 72, 79.

† References 21, 22, 36, 39, 41, 42, 48, 52, 54, 55, 58, 59, 61, 62, 72, 78, 79, 81.

TABLE 3. *Dextran Randomized Trials*

End Point	No. Trials	References	Allocated Treatment			Allocated Control			Odds Ratio	(95% CI)	χ^2	p
			Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
DVT (+FUT)	10	14, 37, 47, 82–88	115/738	15.6%	(13.1–18.4)	193/799	24.2%	(21.3–27.3)	0.58	(0.45–0.75)	17.6	<0.001
DVT (+FUT) (Malignant disease)	4	37, 47, 84, 87	22/94	23.4%	(15.5–33.5)	38/87	43.7%	(33.2–54.7)	0.39	(0.21–0.74)	8.33	0.004
All PE	7	14, 37, 47, 82, 83, 85, 88	10/855	1.2%	(0.59–2.2)	26/926	2.8%	(1.9–4.1)	0.40	(0.20–0.82)	6.19	0.01
FPE	6	14, 37, 82, 83, 85, 88	2/737	0.27%	(0.05–0.1)	12/798	1.5%	(0.81–2.7)	0.18	(0.05–0.68)	6.44	0.01
Major hemorrhage	5	14, 37, 47, 83, 85	2/793	0.25%	(0.04–1.01)	0/861	0%	(0.01–0.55)	5.4	(0.26–113)	2.17	0.14

rately patients with malignant disease. In these patients, treatment with dextran reduced the incidence of DVT (+FUT) from 43.7% in controls to 23.4% ($p = 0.004$). There were too few trials that provided information about AK DVT to analyze this end point. However, many trials were designed to test the efficacy of dextran in preventing PE. The incidence of PE was 1.2% in patients treated with dextran and 2.8% among controls ($p < 0.01$). Dextran also prevented FPE; the incidence was 0.27% in treated patients *versus* 1.5% in controls ($p < 0.01$). In two studies, the reduction in PE with dextran prophylaxis was either significant[85] or approached significance,[14] and in one that was a double-blind trial, the reduction in autopsy-verified FPE was significant.[85] In five trials, the frequency of major hemorrhage was stated. Although the incidence was higher among dextran-treated patients (0.25%) as compared to controls (0%), this difference was not statistically significant.

Low-Dose Heparin Versus *Dextran*

Since the data from controlled trials suggest that LDH and dextran prevent PE, it is instructive to analyze data from trials in which the two antithrombotic agents are directly compared. There were five such trials involving over 4800 patients (Table 4). LDH proved superior to dextran in preventing DVT (+FUT), the incidence of which was 9.5% in LDH-treated patients *versus* 21.0% in dextran-treated patients ($p < 0.001$). Most of this difference was accounted for by the greater frequency of leg DVT among dextran-treated patients. In two trials,[14,75] AK DVT was assessed, and in neither was there a significant difference between LDH and dextran treatment. Dextran was also equivalent to LDH in preventing PE. In LDH-treated patients, the incidence of all PE and FPE was 0.82% and 0.42%, respectively, and 0.68% and 0.31%, respectively, in dextran-treated patients. These differences between agents were not significant.

Major hemorrhage was slightly more common in dextran-treated patients. The incidence was 1.8% among LDH-treated patients *versus* 2.5% in dextran-treated patients. Although this difference approached statistical significance ($p = 0.07$), most of the episodes of major hemorrhage associated with dextran came from one trial,[75] and a similar trend was not observed in the other studies. This, coupled with the information from controlled trials (which fails to document an increase in major hemorrhage with dextran treatment), suggests that dextran and LDH are equivalent in this regard. By contrast, there was a twofold increase in wound hematomas with LDH treatment (Table 4). The incidence of wound hematoma was 3.5% with dextran treatment and 7.0% with LDH treatment ($p < 0.001$). The increase in wound hematomas with LDH treatment was observed in four of the five studies.

HDHE Versus *Low-Dose Heparin*

Nine randomized trials involving over 1600 general surgery patients compared HDHE and LDH (Table 5). In seven trials,[48,64,65,72,74,78,89] the HDHE combination 5000 units of heparin plus 0.5 mg of dihydroergotamine was administered subcutaneously 2 hours before and every 12 hours after operation. In two trials, the heparin dose in HDHE was reduced to 2500 units and the combination agent administered after surgery every 8[73] or 12 hours.[78] In the groups randomized to receive LDH alone, the dose was 5000 units administered subcutaneously 2 hours before operation and every 12 hours (three studies)[48,64,65] or every 8 hours (six studies)[42–81,85–87,89–99] after operation.

HDHE was superior in reducing the frequency of leg vein thrombi; the incidence of DVT (+FUT) among patients treated with HDHE was 9.0%, as compared to 14.5% in patients treated with LDH ($p < 0.001$) (Table 5). There were not enough data from these trials for subgroup analysis to determine if there were differences between HDHE and LDH in reducing AK DVT and the incidence of DVT (+FUT) in patients with malignant disease. However, the occurrence of PE was documented in eight of these studies. There was no significant difference in the incidence of PE, which was 2.0% in patients treated with HDHE and 2.8% in patients treated with LDH ($p = 0.37$).

Of interest was an apparent difference in the frequency of hemorrhagic complications. The incidence of major hemorrhage was 0.26% in patients treated with HDHE and 1.6% in those treated with LDH ($p = 0.007$). Although this appears to be a dramatic difference, nine of the 12 cases of major hemorrhage in patients treated with LDH came from one trial[74] and when these data were excluded, the incidences were equivalent. Furthermore, the much larger body of data from randomized controlled trials demonstrates that LDH, whether administered every 12 or 8 hours, does not cause major hemorrhage. The data concerning wound hematoma are more convincing, however. There was a twofold increase in wound hematoma in patients treated with LDH (7.2%) as compared to those treated with HDHE (3.2%) ($p = 0.004$) (Table 5). This finding was consistent in that in four of the five trials that assessed this end point, wound hematomas were observed more often in patients treated with LDH. The remaining trial was the smallest and no hematomas were seen in either group.[73]

Intermittant Pneumatic Compression

There were nine randomized trials involving more than 900 general surgical patients (Table 6). Five of these trials were controlled, and four were trials in which patients treated with IPC were compared with patients

TABLE 4. *Low-dose Heparin vs. Dextran Randomized Trials*

End Point	No. Trials	References	Low-dose Heparin			Dextran			Odds Ratio	(95% CI)	χ^2	p
			Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
DVT (+FUT)	5	14, 37, 47, 61, 75	42/442	9.5%	(7.0–12.7)	95/457	21.0%	(17.2–24.9)	0.40	(0.27–0.58)	22.4	<0.001
All PE	5	14, 37, 61, 75, 80	17/2085	0.82%	(0.49–1.3)	15/2195	0.68%	(0.39–1.2)	1.19	(0.60–2.40)	0.25	0.62
FPE	5	14, 37, 47, 75, 80	9/2146	0.42%	(0.21–0.83)	7/2255	0.31%	(0.14–0.67)	1.35	(0.50–3.63)	0.36	0.55
Major hemorrhage	5	14, 37, 47, 75, 80	44/2477	1.8%	(1.3–2.4)	63/2488	2.5%	(1.9–3.2)	0.70	(0.47–1.02)	3.62	0.07
Hematoma	5	14, 37, 61, 75, 80	169/2416	7.0%	(6.0–8.1)	84/2428	3.5%	(2.8–4.3)	2.10	(1.61–2.73)	30.6	<0.001

TABLE 5. *Low-dose Heparin DHE* vs. *Low-dose Heparin Randomized Trials*

End Point	No. Trials	References	Low-dose Heparin-DHE			Low-dose Heparin			Odds Ratio	(95% CI)	χ^2	p
			Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
DVT (+FUT)	9	48, 64, 65, 72–74, 76, 78, 89	76/847	9.0%	(7.2–11.2)	121/837	14.5%	(12.2–17.1)	0.58	(0.43–0.79)	12.2	<0.001
All PE	8	48, 65, 72–74, 76, 78, 89	15/732	2.0%	(1.2–3.4)	20/723	2.8%	(1.7–4.3)	0.73	(0.37–1.44)	0.80	0.37
Major hemorrhage	8	48, 64, 65, 72–74, 76, 89	2/771	0.26%	(0.04–1.04)	12/762	1.6%	(0.85–2.8)	0.16	(0.04–0.61)	7.32	0.007
Hematoma	5	48, 72–74, 76	16/506	3.2%	(1.9–5.2)	37/517	7.2%	(5.2–9.8)	0.42	(0.24–0.76)	8.30	0.004

TABLE 6. *Intermittant Pneumatic Compression Randomized Trials*

End Point	No. Trials	References	Allocated IPC			Allocated Control			Allocated LDH			Odds Ratio	(95% CI)	χ^2	p
			Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
All (+FUT)	5	40, 90, 113, 116, 117	31/313	9.9%	(6.9–13.9)	61/300	20.3%	(16.0–25.4)	—	—	—	0.43	(0.27–0.68)	13.0	<0.001
DVT (+FUT) (Malignant disease)	4	90, 113, 116, 117	23/179	12.8%	(8.5–18.9)	37/176	21.0%	(15.4–27.9)	—	—	—	0.55	(0.32–0.97)	4.21	0.04
DVT (+FUT)	4	40, 77, 78, 100	14/190	6.9%	(3.9–11.5)	—	—	—	23/173	13.3%	(8.8–19.5)	0.48	(0.24–0.96)	4.36	0.04

receiving LDH. In the literature, there are other trials in which individual legs of patients were randomized to receive IPC (with the other leg serving as the control), but these trials are not included in our report. Although different devices were used by the investigators, all provided rhythmic external extremity compression (one compression lasting about 10 seconds per minute) with inflation pressures of 35–40 mmHg. Most devices were applied only to the legs. In two studies, the device was a sequential system that compressed the legs and thighs and was complemented by elastic stockings.[77,100] In all studies, the device was used intraoperatively and continued for 1–5 days after operation.

IPC was effective in reducing the frequency of leg DVT; the incidence of DVT (+FUT) was 9.9% in patients receiving IPC, as compared to 20.3% in control patients ($p < 0.001$) (Table 6). IPC also appeared effective in patients with malignant disease. On subgroup analysis of the pooled data from four trials, the incidence of DVT (+FUT) was 12.8% in patients with malignant disease receiving IPC, as compared to 21.0% in controls ($p < 0.04$). There were too few data available to analyze the effect of IPC on the end points of AK DVT and PE.

In the four trials in which IPC was compared with LDH, there were nonsignificant trends suggesting that IPC was more effective in reducing DVT (+FUT).[40,71,78,100] In pooling the data (Table 6), a significant difference was observed; the incidence of DVT (+FUT) was 6.9% in patients receiving IPC and 13.3% among those treated with LDH ($p < 0.04$) (Table 6). Because the number of patients in these trials was small and because the incidence of DVT in the patients receiving LDH was higher than expected (the data of Table 2, shows an incidence of 8.7%), it cannot be reliably concluded that IPC is more effective than LDH in preventing DVT (+FUT).

Elastic Stockings

The results of four randomized trials evaluating elastic stockings were pooled (Table 7). In these trials involving over 500 patients, patients wearing perioperative elastic stockings were compared to control patients not receiving specific prophylactic measures. Trials in which one of any given patient's legs were randomized to receive elastic stockings (with the unstockinged leg serving as the control) were not included. Stockings were fitted and applied 1 day before surgery and were worn throughout the operation and the postoperative period, until the patient was fully ambulatory or discharged. Except in one study where below-knee stockings were worn, the stockings were of the graded compression type and extended above the knee.[95] The overall incidence of DVT (+FUT) in patients wearing stockings was 9.3%,

TABLE 7. *Other Methods of DVT Prophylaxis*

Method	End Point	No. Trials	References	Allocated Treatment			Allocated Control			Odds Ratio	(95% CI)	χ^2	p
				Patients	Incidence	(95% CI)	Patients	Incidence	(95% CI)				
Graded compression hose	DVT (+FUT)	4	91, 95, 96, 111	28/300	9.3%	(6.4–13.3)	70/286	24.5%	(19.7–30.0)	0.32	(0.20–0.50)	24.1	<0.001
Aspirin	DVT (+FUT)	5	50, 93, 94, 101, 115	76/372	20.4%	(16.5–25)	91/390	23.3%	(19.3–27.9)	0.84	(0.60–1.19)	0.94	0.33

and 24.5% in controls ($p < 0.001$). The findings were consistent in that all four trials demonstrated a reduction in DVT (+FUT). There were too little data to assess other thromboembolic end points, and too few comparative trials to assess whether elastic stockings were equivalent to other prophylactic methods.

Aspirin

Five randomized, controlled trials of aspirin involving over 700 patients were available for analysis (Table 7). In two of these trials, aspirin was combined with dipyridamole.[50,94] The dosage of aspirin was 1.0–1.3 g daily in divided dses and was started before surgery in all but one study.[101] The incidence of DVT (+FUT) was 20.4% among aspirin-treated patients and 23.3% in controls ($p = 0.33$). There were too few data to assess other thromboembolic end points. In the two studies in which aspirin was combined with dipyridamole, a greater reduction in DVT (+FUT) was observed, and in one,[94] the reduction was significant.

Discussion

As shown in the pooled data of Table 1, venous thromboembolism is common among patients not receiving prophylaxis. It should be recognized that the incidences of thromboembolic end points among control patients from randomized trials are not applicable to all general surgery patients. In most trials, only patients over the age of 40 years having major surgery were entered. In many trials, to increase the frequency of end points for analysis, attempts were made to enter only those patients with risk factors for venous thromboembolism. In this sense, these incidences represent those expected in moderate-to high-risk general surgery patients. On the other hand, these data may cause the incidence of AK DVT and PE to be seriously underestimated. This is because all patients were followed with the FUT, so that when this test became positive, most patients were treated with anticoagulant therapy. This would have reduced proximal extension of DVT and prevented PE. Intensive surveillance with noninvasive tests is an effective, albeit expensive, strategy for preventing PE,[9] and the incidences of thromboembolic complications in control patients reflect the results expected with this method of prophylaxis. Presumably, the incidence of PE would be higher in general surgery patients receiving neither surveillance nor specific prophylaxis.

Do North American general surgery patients have a lower incidence of venous thromboembolism than their European counterparts? This question is raised by the data that demonstrate the twofold increase in incidence of DVT (+FUT) among patients from European studies (Table 1). The discrepancy has been noted by others[6,7,102] and has never been satisfactorily explained. It is unknown whether this represents selection bias in entering patients into trials (with higher risk patients entered in European trials), true regional differences in the incidence of venous thromboembolism, or differences in standards of care. Because DVT (+FUT) may be considered a marker for more clinically relevant thromboembolic end points such as PE,[103] it is possible that the risk of PE is lower in North American general surgery patients. Although this has never been documented, the assumption that the risk of venous thromboembolism is lower in this country has been a major obstacle to surgeons' acceptance of routine prophylaxis.[4]

Of the prophylactic methods evaluated, LDH has been studied the most completely. From pooled analyses (Table 2), LDH reduces significantly the incidence of DVT (+FUT), AK DVT, PE, and FPE in general surgery patients. The reliability of these conclusions is reinforced by the large number of studies using phlebography to confirm the FUT, the consistency of the results from double-blind studies, and the autopsy verification of FPE in studies assessing this end point. The data suggest that there is a dose effect in that LDH administered every 8 hours is more effective in preventing DVT (+FUT) than is LDH administered every 12 hours. Although this conclusion is not supported by randomized trials comparing LDH administered every 12 hours with LDH administered every 8 hours, it is consistent with reports demonstrating superior DVT prophylaxis with increased doses of heparin in high-risk patients.[63,104]

Despite its effectiveness, LDH causes wound hematomas. This conclusion is supported by meta-analysis of open and double-blind trials that documents a 1.5–4-fold increase in wound hematomas in patients treated with LDH (Table 2). Although this finding is neither surprising nor alarming, the potential seriousness of this complication has not received appropriate emphasis in the past. The frequency of wound hematomas is high enough that the risk:benefit ratio must be carefully considered in many general surgery patients. These would include patients with impaired hemostasis; patients in whom prosthetic material is being implanted and where a hematoma might become infected and lead to an infected prosthesis; patients undergoing procedures in which there is a high likelihood of wound infection (contaminated and clean-contaminated cases) and where a hematoma could lead to wound sepsis and impaired healing; and patients with compromised immune function (from cancer, malnutrition, or active immunosupression) who are prone to wound infection. Patients such as these comprise a large proportion of general surgery patients and, unfortunately, are frequently at high risk of perioperative venous thromboembolism.

Physicians caring for such patients must carefully consider, on an individual basis, the risks of hemorrhage *versus* the risk of DVT and PE. Alternate methods of prophylaxis that do not carry an increased risk for wound hematoma should be considered.

Because it is expensive and cumbersome to use, dextran has never been a popular antithrombotic agent for general surgery patients. This is surprising because, next to LDH, it is the most completely studied prophylactic method in randomized trials and the results of meta-analysis suggest that it is effective in preventing PE and FPE (Table 3). Paradoxically, the pooled data from comparative studies (Table 4) suggest that dextran and LDH are equivalent in preventing PE, but that dextran is significantly less effective in preventing leg DVT. These data suggest that dextran prevents growth and extension of venous thrombi but does not prevent the onset of thrombosis. Such a view is consistent with the finding that a principal action of dextran is interference with fibrin polymerization,[105,106] such that formed clots are more easily lysed.[107] By contrast, LDH is thought to inhibit thrombogenesis.[108] Although both dextran and LDH may interfere with hemostasis, wound hematomas are significantly less common with dextran prophylaxis. This advantage might offset the expense and cumbersome aspects of dextran treatment in selected patients in whom hematomas would be particularly undesirable.

HDHE is more effective than LDH in preventing leg DVT (+FUT). Does this mean that it is a superior prophylaxis of the more serious problems of AK DVT and PE? From comparative data, LDH and HDHE appear to have an equivalent effect on the incidence of PE (Table 5). Most of the patients in these studies were moderate-risk general surgery patients. HDHE has been shown to be effective in preventing DVT in some high-risk patient groups (orthopedics) where LDH alone is relatively ineffective.[73] This suggests, indirectly, that the greatest advantage of HDHE over LDH in preventing PE would be realized only in high-risk general surgery patients.

The one half reduction in wound hematomas with HDHE when compared with LDH (Table 5) is of interest. Investigators have suggested that the lower incidence observed with HDHE was due to the administration of less heparin; in most comparative trials, HDHE was administered every 12 hours (10,000 units/day), whereas LDH was administered every 8 hours (15,000 units/day).[72,74,76] However, as shown by the pooled data of LDH trials, there is no difference in the incidence of wound hematomas between the two LDH regimens. It is possible that dihydroergotamine may have a hemostatic effect, presumably by vasoconstriction, that protects against wound hematoma formation from subcutaneous heparin. In general surgery patients particularly vulnerable to wound hematomas and associated complications (wound sepsis and dehiscence), HDHE may be preferable to LDH.

IPC is a very attractive method of prophylaxis because there is no risk of hemorrhagic complications. It is not as well studied in randomized trials as LDH, dextran, and HDHE. However, according to available data, it is effective in reducing leg DVT (+FUT) in general surgery patients and in high-risk patients with malignant disease (Table 6). There is even a suggestion that IPC may be marginally superior to LDH in preventing DVT (+FUT), but this conclusion is not firm because of the small numbers of comparative trials involving small numbers of patients. It is unknown whether IPC can prevent PE in general surgery patients, but if leg DVT (+FUT) is a valid marker for PE,[103] this would be the case. IPC has also been shown to be highly effective in other high-risk patient groups (orthopedics and neurosurgery).[104,110]

Graded compression elastic stockings reduce the incidence of leg DVT (+FUT) but too few data are available to assess their protective effect on AK DVT and PE. Patients with malignant disease and other high-risk conditions have not yet been evaluated in sufficient numbers to allow any conclusion with regard to the efficacy of elastic stockings in these clinical settings. In fact, in two of the studies pooled in Table 7, some high-risk patients were specifically excluded.[111,96] Further clinical trials are needed in order for us to know if elastic stockings are effective in such patients. Because elastic stockings are free of side effects and are relatively cheap, it would also be important to know the efficacy of elastic stockings in comparison with other methods of prophylaxis.

Aspirin alone or in comparison with dipyridamole appears ineffective. While individual trials have reported variable reductions in DVT (+FUT), the aggregate data (Table 7) demonstrate no beneficial effect.

Because of limited clinical experience, new prophylactic methods that may have greater antithrombotic effectiveness and a lower incidence of hemorrhagic side effects are not included in this meta-analysis. The use of combinations of established methods (particularly attractive because the prophylactic may be summative) are also excluded. Since this analysis involves reworking of older data and ignores these newer approaches, it may be viewed as incomplete. However, the data base should provide a framework that will be helpful in evaluating newer approaches to prophylaxis in general surgery patients.

Another limitation of this report is that the conclusions reached are weakened by inherent shortcomings of meta-analysis. While these shortcomings are detailed in a recent report,[12] it is worth emphasizing that the meth-

odology, as applied here, involves a retrospective look at prospective data. As such, it can never be as scientifically sound as a well-designed, randomized prospective clinical trial of the total number of patients presented in the meta-analysis. The main shortcomings include the probability of inhomogeneity of patient populations among different studies, variations in expertize and methods of detection and reporting of end points, and the potential for bias because of inclusion of nonblinded trials. Despite these and other limitations, meta-analysis, applied properly, can provide new insights and clinically relevant information where randomized trials would be impractical or where randomized trials have been performed but have yielded inconclusive or conflicting results.

References

1. Conti S, Daschbach M. Venous thromboembolism prophylaxis. Arch Surg 1982; 117:1036–1040.
2. Morris GK. Prevention of venous thromboembolism: a survey of methods used by orthopaedic and general surgeons. Lancet 1980; ii:572–574.
3. Bergqvist D. Prevention of postoperative deep vein thrombosis in Sweden: results of a survey. World J Surg 1980; 4:489–495.
4. Bell WR, Zuidema GD. Low-dose heparin—concern and perspectives. Surgery 1979; 85:469–471.
5. Hayes AC, Baker WH. Heparin prophylaxis trials of venous thrombosis: a critical review. Semin Thromb Hemost 1985; II:222–226.
6. Strandness DE. Variations in the incidence of venous thrombosis. Presented at the NIH Consensus Development Conference on Prevention of Venous Thrombosis and Pulmonary Embolism. Bethesda, MD, 1986.
7. Pachter HL, Riles TS. Low dose heparin: bleeding and wound complications in the surgical patient. Ann Surg 1977; 186:669–674.
8. Van Ooijen B. Subcutaneous heparin and postoperative wound hematomas: a prospective, double-blind, randomized study. Arch Surg 1986; 121:937–940.
9. Salzman EW, Davies GC. Prophylaxis of venous thromboembolism: analysis of cost effectiveness. Ann Surg 1980; 207–218.
10. Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. JAMA 1987; 257:203–208.
11. Clagett GP. An overview on prophylaxis in patients in general surgery. Presented at the NIH Consensus Development Conference on Prevention of Venous Thrombosis and Pulmonary Embolism. Bethesda, MD, 1986.
12. Sacks HS, Berrier J, Reitman D, et al. Meta-analyses of randomized controlled trials. N Engl J Med 1987; 316:450–455.
13. Prevention of fatal postoperative pulmonary embolism by low doses of heparin: an international multicentre trial. Lancet 1975; ii:45–51.
14. Gruber UF, Duckert F, Fridrich R, et al. Prevention of postoperative thromboembolism by dextran 40, low doses of heparin, or xantinol nicotinate. Lancet 1977; i:207–210.
15. Prevention of fatal postoperative pulmonary embolism by low doses of heparin: reappraisal of results of international multicentre trial. Lancet 12 Mar 1977; i:567–569.
16. Ruckley CV. Protection against thrombo-embolism. Br J Surg 1985; 72:421–422.
17. Bergqvist D. Postoperative Thromboembolism: Frequency, Etiology, Prophylaxis. New York: Springer-Verlag, 1983.
18. Clagett GP, Salzman EW. Prevention of venous thromboembolism. Prog Cardiovasc Dis 1975; 17:345–366.
19. Hull RD, Raskob GE, Hirsh J. Prophylaxis of venous thromboembolism: an overview. Chest 1986; 89:374S–383S.
20. Salzman EW, Hirsh J. Prevention of venous thromboembolism, *In* Coleman RW, Hirsh J, Marder, Salzman EW, eds. Hemostasis and Thrombosis. Philadelphia: J.B. Lippincott, 1987; 1252–265.
21. Kakkar VV, Murray WJG. Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study. Br J Surg 1985; 72:786–791.
22. Torngren S, Kettunen K, Lahtinen J, et al. A randomized study of a semisynthetic heparin analogue and heparin in prophylaxis of deep vein thrombosis. Br J Surg 1984; 71:817–820.
23. Turpie AGG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med 1986; 315:925–929.
24. Bergqvist D, Lindblad B. The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70. Arch Surg 1984; 119:1329–1331.
25. Harris WH, Athanasoulis CA, Waltman AC, Salzman EW. Prophylaxis of deep-vein thrombosis after total hip replacement: dextran and external pneumatic compression compared with 1.2 or 0.3 gram of aspirin daily. J Bone Joint Surg 1985; 67-AII:57–62.
26. Wille-Jorgensen P, Thorup J, Fischer A, et al. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. Br J Surg 1985; 72:579–581.
27. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719–748.
28. Fleiss JL. Statistical Methods for Rates and Proportions, 2nd ed. New York: John Wiley and Sons, 1986; 115–116.
29. Wheeler HB, Anderson FA Jr. Diagnostic approaches for deep vein thrombosis. Chest 1986; 89:407S–412S
30. Huisman MV, Buller HR, Ten Cate JW, Vreeken J. Serial impedance plethysmography for suspected deep venous thrombosis in outpatients. The Amsterdam General Practitioner Study. N Engl J Med 1986; 314:823–8.
31. Hull RD, Hirsh J, Carter CJ, et al. Diagnostic efficacy of impedance plethysmography for clinically suspected deep-vein thrombosis: a randomized study. Ann Intern Med 1985; 102:21–28.
32. Kiil J, Kiil J, Axelsen F, Anderson D. Prophylaxis against postoperative pulmonary embolism and deep-vein thrombosis by low-dose heparin. Lancet 1978; i:1115–1116.
33. Sagar S, Massey J, Sanderson JM. Low-dose heparin prophylaxis against fatal pulmonary embolism. Br Med J 1975; 4:257–259.
34. Abernethy EA, Hartsuck JM. Postoperative pulmonary embolism: a prospective study utilizing low dose heparin. Am J Surg 1974; 128:739–742.
35. Ballard RM, Bradley-Watson PJ, Johnstone FD, et al. Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery. J Obstet Gynecol Br Commonwealth 1973; 80:469–472.
36. Belch JJF, Lowe GDO, Pollock JG, et al. Low dose heparin in the prevention of deep-vein thrombosis after aortic bifurcation graft surgery. Thromb Haemost 1979; 42:1429–1433.
37. Bergqvist D, Hallbook T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. World J Surg 1980; 4:239–243.
38. Cade JF, Andrews JT, Stubbs AE. Comparison of sodium and calcium heparin in prevention of venous thromboembolism. Aust NZ J Surg 1982; 12:501–504.
39. Clarke-Pearson DL, Coleman RE, Synan IS, et al. Venous thromboembolism prophylaxis in gynecologic oncology: a prospective, controlled trial of low-dose heparin. Am J Obstet Gynecol 1983; 145:606–613.
40. Coe NP, Collins REC, Klein LA, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. Surgery 1978; 83:230–234.
41. Covey TH, Sherman L, Baue AE. Low-dose heparin in postoper-

ative patients: a prospective, coded study. Arch Surg 1975; 110:1021–1026.
42. Gordon-Smith IC, Grundy DJ, Le Quesne LP, et al. Controlled trial of two regimens of subcutaneous heparin in prevention of postoperative deep-vein thrombosis. Lancet 1972; i:1133–1135.
43. Hedlund PO, Blomback M. The effects of low-dose heparin treatment on patients undergoing transvesical prostatectomy. Urol Res 1981; 9:147–152.
44. Jackaman FR, Perry BJ, Siddons H. Deep vein thrombosis after thoracotomy. Thorax 1978; 33:761–763.
45. Kakkar VV, Corrigan T, Spindler J, et al. Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery: a double-blind, randomized trial. Lancet 1972; ii:101–106.
46. Lahnborg G, Bergstrom, Friman L, Lagergren H. Effect of low-dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning. Lancet 1974; i:329–331.
47. Heparin *versus* dextran in the prevention of deep-vein thrombosis: a multi-unit controlled trial. Lancet 1974; ii:118–120.
48. Multicenter Trial Committee. Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis: a multicenter trial. JAMA 1984; 251:2960–2966.
49. Nicolaides AN, Dupont PA, Desai S, et al. Small doses of subcutaneous sodium heparin in preventing deep venous thrombosis after major surgery. Lancet 1972; 2:890–893.
50. Plante J, Boneu B, Vaysse C, et al. Dipyridamole-aspirin *versus* low doses of heparin in the prophylaxis of deep venous thrombosis in abdominal surgery. Thromb Res 1979; 14:399–403.
51. Sebeseri O, Kummer H, Zingg E. Controlled prevention of postoperative thrombosis in urological diseases with depot heparin. Eur Urol 1975; 1:229–230.
52. Spebar MJ, Collins GJ Jr, Rich NM, et al. Perioperative heparin prophylaxis of deep venous thrombosis in patients with peripheral vascular disease. Am J Surg 1981; 142:649–650.
53. Strand L, Bank-Mikkelsen OK, Lindewald H. Small heparin doses as prophylaxis against deep-vein thrombosis in major surgery. Acta Chir Scand 1975; 141:624–627.
54. Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin *versus* low-dose heparin in prophylaxis of deep vein thrombosis. Br Med J 1978; I:272–274.
55. Torngren S, Forsberg K. Concentrated or diluted heparin prophylaxis of postoperative deep venous thrombosis. Acta Chir Scand 1978; 144:283–288.
56. Wu TK, Tsapogas MJ, Jordan FR. Prophylaxis of deep venous thrombosis by hydroxychloroquine sulfate and heparin. Surg Gynecol Obstet 1977; 145:714–718.
57. Fasting H, Andersen K, Nielsen HK, et al. Prevention of postoperative deep venous thrombosis. Acta Chir Scand 1985; 151:245–248.
58. Kajanoja P, Forss M. Prevention of venous thrombosis by dipyridamole-naproxen and low-dose heparin in patients undergoing hysterectomy. Ann Clin Res 1981; 13:392–395.
59. Kakkar VV, Field ES, Nicholaides AN, et al. Low doses of heparin in prevention of deep-vein thrombosis. Lancet 1971; ii:669–671.
60. Loew D, Brocke P, Simma W, et al. Acetylsalicyclic acid, low dose heparin, and a combination of both substances in the prevention of postoperative thromboembolism: a double blind study. Thromb Res 1977, 11:81–86.
61. McCarthy TG, McQueen J, Johnstone FD, et al. A comparison of low-dose subcutaneous heparin and intravenous dextran 70 in the prophylaxis of deep venous thrombosis after gynaecological surgery. J Obstet Gynaecol of Br Commonwealth 1974, 81:486–491.
62. Van Vroonhoven 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; i:375–377.
63. Cade JF, Clegg EA, Westlake GW. Prophylaxis of venous thrombosis after major thoracic surgery. Aust NZ J Surg 1983, 53:301–304.
64. Veth G, Meuwissen OJ, Van Houwelingen HC, Sixma JJ. Prevention of postoperative deep vein thrombosis by a combination of subcutaneous heparin with subcutaneous dihydroergotamine or oral sulphinpyrazone. Thromb Haemost 1985, 54:570–573.
65. Wille-Jorgensen P, Kjaergaard J, Thorup J, et al. Heparin with and without dihydroergotamine in prevention of thromboembolic complications of major abdominal surgery: a randomized trial. Arch Surg 1983; 926–928.
66. Gallus AS, Hirsh J, Tuttle RJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med 1973; 288:545–551.
67. Gallus AS, Hirsh J, O'Brien SE, et al. Prevention of venous thrombosis with small, subcutaneous doses of heparin. JAMA 1976; 235:1978–1982.
68. Groote Schuur Hospital Thromboembolus Sdy Group. Failure of low-dose heparin to prevent significant thromboembolic complications in high-risk surgical patients: interim report of prospective trial. Br Med J 1979; 1:1447–14450.
69. Joffe S. Drug prevention of postoperative deep vein thrombosis: a comparative study of calcium heparinate and sodium pentosan polysulfate. Arch Surg 1976; 111:37–40.
70. Rosenberg IL, Evans M, Pollock AV. Prophylaxis of postoperative leg vein thrombosis by low dose subcutaneous heparin or peroperative calf muscle stimulation: a controlled clinical trial. Br Med J 1975; 1:649–651.
71. Vandendris M, Kutnowski M, Futeral B, et al. Prevention of postoperative deep-vein thrombosis by low-dose heparin in open prostatectomy. Urol Res 1980; 8:219–221.
72. Brucke P, Dienstl E, Vinazzer H, Simma W. Prophylaxis of postoperative thromboembolism: low dose heparin *versus* heparin plus dihydroergotamin. Thromb Res 1983; 29:377–382.
73. Kakkar VV, Stamatakis JD, Bentley PG, et al. Prophylaxis for postoperative deep-vein thrombosis: synergistic effect of heparin and dihydroergotamine. JAMA 1979; 241:3942.
74. Hohl MK, Luscher KP, Annaheim M, et al. Dihydroergotamine and heparin or heparin alone for the prevention of postoperative thromboembolism in gynecology. Arch Gynecol 1980; 230:15–19.
75. Hohl MK, Luscher KP, Tichy J, et al. Prevention of postoperative thromboembolism by dextran 70 or low-dose heparin. Obstet Gynecol 1980; 55:497–500.
76. Koppenhagen K, Wiechman A, Zuhlke HV, et al. Effectiveness and risk of thromboembolism prophylaxis in surgery: a comparison study of heparin-dihydergot and low-dose heparin. Therapiewoche 1979, 29:5920–5926.
77. Muhe E. Intermittent sequential high-pressure compression of the leg: a new method of preventing deep vein thrombosis. Am J Surg 1984; 147:781–785.
78. Moser G, Krahenbuhl B, Barroussel R, et al. Mechanical *versus* pharmacologic prevention of deep venous thrombosis.
79. Jourdan M, McColl I. The use of prophylactic subcutaneous heparin in patients undergoing hernia repairs. Br J Clin Pract 1984; 38:298–300. Surg Gynecol Obstet 1981; 152:448–450.
80. Gruber UF, Saldeen T, Brokop T, et al. Incidences of fatal postoperative pulmonary embolism after prophylaxis with dextran 70 and low-dose heparin: an international multicentre study. Br Med J 1980; 280:69–72.
81. Ribaudo JM, Hoellrich RG, McKinnon WMP, Shuler SE. Evaluation of mini-dose heparin administration as a prophylaxis against postoperative pulmonary embolism: a prospective double-blind study. Am Surg 1975; 41:289–295.
82. Becker J, Schampi B. The incidence of postoperative venous thrombosis of the legs. Acta Chir Scand 1973; 139:357–367.
83. Bonnar J, Walsh J. Prevention of thrombosis after pelvic surgery by British dextran 70. Lancet 1972; 1:614–616.
84. Carter AE, Eban R. The prevention of postoperative deep venous thrombosis with dextran 70. Br J Surg 1973; 60:681–683.
85. Kline A, Hughes LE, Campbell H, et al. Dextran 70 in prophylaxis of thromboembolic disease after surgery: a clinically ori-

ented randomized double-blind trial. Br Med J 1975; 2:109–112.
86. Stephenson CBS, Wallace JC, Vaughan JV. Dextran 70 in the prevention of post-operative deep-vein thrombosis with observations on pulmonary embolism: report on a pilot study. NZ Med J 1973; 77:302–305.
87. Lindstrom B, Holmdahl C, Johsson O, et al. Prediction and prophylaxis of postoperative thromboembolism—a comparison between peroperative calf muscle stimulation with groups of impulses and dextran 40. Br J Surg 1982; 69:633–637.
88. Bergman B, Bergqvist D, Dahlgren S. The incidence of venous thrombosis in the lower limbs following elective gallbladder surgery: a study with the ^{125}-fibrinogen test. Ups J Med Sci 1975; 80:41–45.
89. Pedersen B, Christiansen J. Thromboembolic prophylaxis with dihydroergotamine-heparin in abdominal surgery. Am J Surg 1983; 145:788–790.
90. Hills NH, Pflug JJ, Jeyasingh K, et al. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Br Med J 1972; 1:131–135.
91. Holford CP. Graded compression for preventing deep venous thrombosis. Br Med J 1976; 2:969–970.
92. Huttunen H, Mattila MAK, Alhava EM, et al. Peroperative infusion of dextran 70 and dextran 40 in the prevention of postoperative deep venous thrombosis as confirmed by the I-125-labelled fibrinogen uptake method. Ann Chir Gynaecol 1977; 66:79–81.
93. Medical Research Council. Effect of aspirin on postoperative venous thrombosis. Report of the Steering Committee. Lancet 1972; ii:441–444.
94. Renney JTG, O'Sullivan EF, Burke PF. Prevention of postoperative deep vein thrombosis with dipyridamole and aspirin. Br Med J 1976; 1:992–994.
95. Tsapogas MJ, Goussous H, Peabody RA, et al. Postoperative venous thrombosis and the effectiveness of prophylactic measures. Arch Surg 1971; 103:561–567.
96. Turner GM, Cole SE, Brooks JH. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis after major gynaecological surgery. Br J Obstet Gynaecol 1984; 91:588–591.
97. Williams HT. Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. Lancet 1971; ii:950–952.
98. Clarke-Pearson DL, DeLong ER, Synan IS, Creasman WT. Complications of low-dose heparin prophylaxis in gynecologic oncology surgery. Obstet Gynecol 1984; 64:689–694.
99. Bates T. Trial of a single low dose of heparin in the prevention of post-operative deep-vein thrombosis monitored by doppler ultrasound. Postgrad Med J 1974; 50:135–139.
100. Nicolaides AN, Miles C, Hoare M, et al. Intermittent sequential pneumatic compression of the legs and thromboembolism-deterrent stockings in the prevention of postoperative deep venous thrombosis. Surgery 1983; 94:21–25.
101. Clagett GP, Schneider P, Rosoff CB, Salzman EW. The influence of aspirin on postoperative platelet kinetics and venous thrombosis. Surgery 1975; 77:61–74.
102. Carter C, Gent M. The epidemiology of venous thrombosis, *in* Coleman RW, Hirsh J, Marder, Salzman EW, eds. Hemostasis and Thrombosis. Philadelphia: J.B. Lippincott, 1982; 805–819.
103. Consensus Conference. Prevention of venous thrombosis and pulmonary embolism. JAMA 1986; 256:744–749.
104. Leyvraz PF, Richard J, Bachmann F, et al. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. N Engl J Med 1983; 309:954–958.
105. Muzaffar TZ, Stalker AL, Bryce WAJ, Dhall DP. Dextrans and fibrin morphology. Nature 1972; 238:288–290.
106. Dhall TZ, Bryce WAJ, Dhall DP. Effects of dextran on the molecular structure and tensile behaviour of human fibrin. Thromb Haemost 1976; 35:737–745.
107. Aberg M, Bergentz SE, Hedner U. The effect of dextran on the lysability of *ex vivo* thrombi. Ann Surg 1975; 181:342–345.
108. Wessler S, Yin ET. Theory and practice of minidose heparin in surgical patients: a status report. Circulation 1973; 47:671–676.
109. Hull R, Delmore TJ, Hirsh J, et al. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. Thromb Res 1979; 16:37–45.
110. Turpie AGG, Delmore T, Hirsh J, et al. Prevention of venous thrombosis by intermittent sequential calf compression in patients with intracranial disease. Thromb Res 1979; 15:611–616.
111. Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. Br J Surg 1983; 70:172–174.
112. Flanc C, Kakkar VV, Clarke MB. Postoperative deep-vein thrombosis effect of intensive prophylaxis. Lancet 1969; i:477–478.
113. Butson ARC. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. Am J Surg 1981; 142:525–527.
114. Carter AE, Eban R. Prevention of postoperative deep venous thrombosis in legs by orally administered hydroxychloroquine sulphate. Br Med J 1974; 3:94–95.
115. Zekert F, Schemper M, Neumann K. Acetylsalicylic acid in combination with dihydroergotamine for preventing thromboembolism. Haemostasis 1982; 11:149–153.
116. Clarke-Pearson DL, Creasman WT, Coleman RE, et al. Perioperative external pneumatic calf compression as thromboembolism prophylaxis in gynecologic oncology: report of a randomized controlled trial. Gynecol Oncol 1984; 18:226–232.
117. Clarke-Pearson DL, Synan IS, Hinshaw WM, et al. Prevention of postoperative venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. Obstet Gynecol 1984; 63:92–98.
118. Browse NL, Clemenson G, Bateman NT, et al. Effect of intravenous dextran 70 and pneumatic leg compression on incidence of postoperative pulmonary embolism. Br Med J 1976; 2:1281–1284.