Chapter-8
Bibliography
Where is the evidence?

Literature Cited


Selected Abstracts on Prevention of Deep Vein Thrombosis

Cost-Effectiveness


BACKGROUND: Postoperative venous thrombosis and pulmonary embolism present a major clinical threat to patients undergoing total hip or knee arthroplasty. We performed an economic evaluation of warfarin sodium and subcutaneous low-molecular-weight heparin sodium prophylaxis comparing cost and effectiveness. METHODS: A consecutive series of 1436 patients who underwent hip or knee arthroplasty comparing these 2 regimens in a randomized trial with objective documentation of outcomes provided the opportunity to perform economic evaluations for Canada and the United States. RESULTS: Deep vein thrombosis was documented in 231 (37.4%) of 617 patients given warfarin and in 185 (31.4%) of 590 patients given low-molecular-weight heparin (P = .03). In Canada, warfarin and low-molecular-weight heparin (tinzaparin sodium) incurred costs per 100 patients of $11,598 and $9,197, respectively, providing a cost savings of $2,401 for the low-molecular-weight heparin group. The drug cost of low-molecular-weight heparin (tinzaparin) was $6 per day and for warfarin was $0.32 per day. Sensitivity analysis showed that low-molecular-weight heparin is more costly if drug costs are increased by 1.5-fold (ie, the cost of tinzaparin is increased from $6 per day to $8.82 per day or more). In the United States, the analysis was also not definitive; low-molecular-weight heparin was more costly than warfarin at drug costs of $15 and $2.01 per day, respectively. CONCLUSIONS: Our findings indicate that the decision to use low-molecular-weight heparin or warfarin prophylaxis in patients undergoing major joint replacement surgery is a finely tuned trade-off. Prophylaxis with low-molecular-weight heparin is equally or more effective than the more complex prophylaxis with warfarin. Major bleeding is uncommon but less frequent with warfarin use. The most significant parameters that influence the comparative cost-effectiveness are the cost of the drug, the cost of international normalized ratio monitoring, and the costs associated with major bleeding. The analysis also demonstrates that the results are health care system dependent (Canada vs US). In Canada, low-molecular-weight heparin (tinzaparin) is less costly because it avoids the need for international normalized ratio monitoring. In the United States, the drug cost for low-molecular-weight heparin will likely be the principal determinant of relative cost-effectiveness.


BACKGROUND: Enoxaparin sodium, a low-molecular-weight heparin, was recently approved for use in the United States to prevent deep-vein thrombosis after total hip replacement surgery. Its cost-effectiveness relative to prophylaxis with low-dose warfarin sodium is unknown. METHODS: A decision-analytic model was developed to compare two strategies of prophylaxis for deep-vein thrombosis with a strategy of not using prophylaxis in a hypothetical cohort of 10,000 patients undergoing total hip replacement surgery. For each of these strategies, we estimated the expected number of cases of confirmed deep-vein thrombosis or pulmonary embolism, the expected number of thromboembolic deaths, and the expected costs of venous thromboembolic care, including prophylaxis, diagnosis, and treatment. Data were drawn primarily from the published literature. RESULTS: Compared with no prophylaxis, the use of low-dose warfarin would
be expected to reduce the number of cases of confirmed deep-vein thrombosis from about 1000 (per 10,000 patients) to 420 and the number of thromboembolic deaths from about 250 to 110. Expected costs of care related to deep-vein thrombosis also would be reduced from approximately $530 to $330 per patient. Prophylaxis with enoxaparin would be expected to reduce further the number of cases of confirmed deep-vein thrombosis and the number of thromboembolic deaths (to 250 and 70, respectively) but increase costs of care by approximately $50 per patient. The cost-effectiveness of enoxaparin (relative to low-dose warfarin) is estimated to be approximately $12,000 per death averted. CONCLUSION: Although enoxaparin is more costly than low-dose warfarin, its cost-effectiveness in total hip replacement compares favorably with that of other generally accepted medical interventions.

Cost-effectiveness of prophylaxis in total hip replacement.

Paiement GD, Wessinger SJ, Harris WH
Division of Orthopedics, University of Montreal Medical School, Quebec, Canada.

A theoretical analysis was performed regarding the cost-effectiveness in terms of lives saved (reduction of fatal pulmonary embolism [PE]) and in terms of money (dollars spent for prevention and treatment) of seven strategies in the management of venous thromboembolic disease in patients over 39 years of age undergoing elective total hip replacement (THR). Strikingly, this theoretical analysis suggests that low-dose warfarin combined with clinical surveillance of deep vein thrombosis would reduce the incidence of fatal PE from 20 per 1,000 patients to 4 per 1,000 patients and simultaneously reduce the charges for venous thromboembolic disease from $550,000 to about $400,000 per 1,000 patients. Based on this analysis, we strongly recommend this measure on a routine basis. Adding venography or duplex sonography routinely to this prophylactic regimen would, in this theoretical analysis, reduce the incidence of fatal PE from 4 per 1,000 patients to 0.15 per 1,000, but adds charges of $200,000 per extra life saved in the case of routine venography and $50,000 in the case of routine sonography. Low-dose warfarin prophylaxis combined with routine sonography does not generate more charges than no prophylaxis with no screening while drastically reducing the incidence of fatal PE from 20 to 0.3 per 1,000 patients. Where duplex sonography is not easily available, a 12-week postoperative course of low-dose warfarin for every patient with no routine screening will be efficacious in reducing fatal PE and as cost-effective.

Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement.

O’Brien BJ, Anderson DR, Goeree R
Can Med Assoc J 1994 Apr 1;150(7):1083-1090
Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ont.

OBJECTIVE: To compare the efficacy and cost-effectiveness of enoxaparin, a low-molecular-weight heparin derivative, with that of low-dose warfarin in the prevention of deep-vein thrombosis (DVT) after total hip replacement. DATA SOURCES: English-language articles on enoxaparin and warfarin prophylaxis is patients undergoing total hip replacement published from January 1982 to December 1992. STUDY SELECTION: Four trials of enoxaparin (involving 567 patients) and six trials of warfarin (involving 630) met the following criteria: randomized controlled trial, prophylaxis started no later than 24 hours after surgery and continued for at least 7 days, warfarin dose monitored and adjusted appropriately, enoxaparin dosage 30 mg twice daily, and DVT confirmed by bilateral venography. DATA EXTRACTION: Rates of DVT, cost of prophylaxis, diagnosis and treatment per patient, rate of pulmonary embolism (PE), number of deaths and incremental cost-effectiveness (cost per life-year gained). DATA SYNTHESIS: The pooled rate of DVT was 13.6% with enoxaparin (95% confidence interval [CI] 10.9% to 16.3%) and 20.6% with warfarin (95% CI 17.4% to 23.8%). At a cost of $19.55 per day for enoxaparin the total cost per patient, including prophylaxis and management of DVT, exceeded that per
patient receiving warfarin by about $121. For every 10,000 patients treated the use of enoxaparin will prevent 47 cases of DVT, 3 cases of PE and 4 deaths. Thus, the estimated incremental cost-effectiveness of enoxaparin is $29 120 per life-year gained. CONCLUSION: On the basis of current Canadian cost-effectiveness guidelines the results of this study would be considered moderate to strong evidence to adopt enoxaparin prophylaxis against DVT after total hip replacement. However, because of the limited data the estimates are uncertain. Future trials should compare enoxaparin and warfarin and incorporate a prospective economic appraisal.

Efficacy and cost of low-molecular-weight heparin compared with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty.

Anderson DR, O’Brien BJ, Levine MN, Roberts R, Wells PS, Hirsh J
McMaster University Medical Centre, Hamilton, Ontario, Canada.

PURPOSE: To compare the efficacy, safety, and cost-effectiveness of low-molecular-weight heparin with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. DATA IDENTIFICATION: Studies were identified by MEDLINE search and review of bibliographies of retrieved articles. Hospital resources used in treating deep vein thrombosis and bleeding complications after total hip arthroplasty were estimated using retrospectively collected data from 447 patients who participated in a recently completed randomized controlled deep vein thrombosis prophylaxis trial at our center. STUDY SELECTION: Randomized controlled trials directly comparing a low-molecular-weight heparin preparation with standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty were potentially eligible for the meta-analysis. DATA EXTRACTION: Data from eligible studies were extracted independently by two of the authors. Multiple regression analysis of data from the patient cohort was used to estimate the effect of deep vein thrombosis and bleeding on length of hospital stay. A hypothetical North American price for low-molecular-weight heparin was determined based on the ratio between low-molecular-weight heparin and standard heparin in France. Costs were based on weighted per-diem hospital expenditures and physician fees for procedures and reported in 1992 U.S. dollars. RESULTS OF DATA SYNTHESIS: Meta-analysis of six eligible trials determined that low-molecular-weight heparin was significantly more effective than standard heparin at preventing deep vein thrombosis after total hip arthroplasty (common odds ratio, 0.72; 95% CI, 0.53 to 0.95). However, this benefit was restricted to the prevention of proximal deep vein thrombosis (common odds ratio, 0.40; CI, 0.28 to 0.59). No significant differences were found in the rates of distal deep vein thrombosis or total, major, or minor bleeding between the two groups. Based on a 2.6 to 1 price ratio between low-molecular-weight heparin and standard heparin, use of low-molecular-weight heparin would save the health care system about $50,000 per 1000 patients treated. Sensitivity analysis shows that if the low-molecular-weight heparin/standard heparin price ratio exceeds 3.7 (the threshold value lies between 0.8 and 5.5 based on the extremes of the 95% CI of the common odds ratios for deep vein thrombosis and bleeding complications), use of low-molecular-weight heparin is more expensive. At a price ratio of 10, it would cost more than $250,000 to treat 1000 patients with low-molecular-weight heparin compared with standard heparin or about $5000 for each additional deep vein thrombosis prevented with low-molecular-weight heparin. CONCLUSIONS: Low-molecular-weight heparin is more effective and is at least as safe as standard heparin for the prevention of deep vein thrombosis after total hip arthroplasty. Based on the current French price ratio of low-molecular-weight heparin to standard heparin, the use of low-molecular-weight heparin in North America would result in overall savings in cost; however, the relative cost-effectiveness is critically dependent on the price ratio between the two drugs. Further research is needed to compare the cost-effectiveness of low-molecular-weight heparin with other prophylactic regimens and postoperative deep vein thrombosis management strategies.
Prevention of deep-vein thrombosis following total hip replacement surgery with enoxaparin versus unfractionated heparin: a pharmacoeconomic evaluation.

Menzin J, Richner R, Huse D, Colditz GA, Oster G
Department of Medicine, Brigham and Women’s Hospital, Boston, MA.

OBJECTIVE: To compare the use of healthcare services in patients receiving enoxaparin, a low molecular weight heparin versus those receiving unfractionated heparin as prophylaxis against deep-vein thrombosis (DVT) following total hip replacement surgery. DESIGN: Economic evaluation undertaken in conjunction with a randomized, open-label, parallel group, Phase III clinical trial. SETTING: 32 US acute-care hospitals. PATIENTS: 607 patients undergoing elective total hip replacement. INTERVENTIONS: Enoxaparin 30 mg q12h, enoxaparin 40 mg qd, or unfractionated heparin 5000 units q8h started within 24 hours following surgery and continued for 7 days. MAIN OUTCOME MEASURES: (1) Use of selected tests and treatments for DVT; (2) use of selected tests and treatments related to postoperative bleeding; (3) length of stay in hospital; and (4) readmissions to hospital within 14 days. RESULTS: Although the use of selected tests and treatments related to DVT or postoperative bleeding did not differ significantly between the three treatment groups, mean length of stay in the hospital (following the start of study therapy) was shorter among patients receiving enoxaparin 30 mg (9.5 days; p = 0.01) or 40 mg (9.9 days; p < 0.05) than those receiving unfractionated heparin (11.3 days). There was also a trend toward fewer hospital readmissions in both of the enoxaparin groups. CONCLUSIONS: Compared with unfractionated heparin, use of enoxaparin following total hip replacement may decrease the risk of DVT and length of hospital stay.

Orthopaedic Surgery - General Papers


The efficacy and safety of low molecular weight heparin (LMWH), unfractionated heparin (UFH) and warfarin for prophylaxis of thrombo-embolism in orthopaedic surgery were compared using meta-analysis techniques. Twenty-two studies were included, 2 of which compared LMWH to warfarin. The mean probabilities to develop deep-vein thrombosis (DVT), pulmonary embolism and major and minor bleeding using UFH were: 0.21 (95% confidence interval, CI: 0.18-0.24); 0.01 (95% CI: 0.01-0.02); 0.05 (95% CI: 0.03-0.07), and 0.19 (95% CI: 0.17-0.22), respectively. The relative risk (RR) of DVT for LMWH vs. UFH was 0.76 (95% CI: 0.60-0.91), p < 0.05 and for LMWH vs. warfarin 0.78 (95% CI: 0.69-0.87), p < 0.05. The RR of minor bleeding for LMWH vs. UFH was 0.76 (95% CI: 0.64-0.92), p < 0.05. The RR of minor bleeding for LMWH vs. warfarin was 3.28 (95% CI: 2.21-4.70), p < 0.05. Conclusion: in orthopaedic surgery, LMWH is significantly superior to both UFH and warfarin in the prevention of DVT and results in significantly less minor bleeding complications when compared to UFH, but significantly more minor bleeding when compared to warfarin.

The risk of venous thromboembolism in the orthopedic patient: epidemiological and physiological data.

Paiement GD, Mendelsohn C Orthopedics 1997 Feb;20 Suppl:7-9 University of California at San Francisco, USA.

Venous thromboembolism is responsible for 500,000 deaths annually in industrialized countries. It is probably the most common preventable cause of death in elective orthopedic surgery patients. Rates of deep vein thrombosis (DVT) and fatal pulmonary embolism (PE) in unprotected orthopedic patient populations are high. The overall DVT rate is >
40% in patients undergoing hip or knee arthroplasty or suffering from multiple injuries. The proximal DVT rate for these patients is $> 15\%$, and the fatal PE rate is $> 1\%$. Risk factors associated with venous thromboembolism are related to the vascular injury, activation of blood coagulation, and venous stasis. Lower extremity orthopedic procedures carry a risk greater than that of surgery itself. Thus, orthopedic patients are at high risk for venous thromboembolic conditions. A systematic assessment of this risk should be performed in every patient, and an appropriate management plan should be implemented.

**Efficacy and safety of low molecular weight heparin, unfractionated heparin and warfarin for thrombo-embolism prophylaxis in orthopaedic surgery: a meta-analysis of randomised clinical trials.**

Haemostasis 1997 Mar;27(2):75-84
Institute for Medical Informatics and Biostatistics, Riehen, Switzerland.

The efficacy and safety of low molecular weight heparin (LMWH), unfractionated heparin (UFH) and warfarin for prophylaxis of thrombo-embolism in orthopaedic surgery were compared using meta-analysis techniques. Twenty-two studies were included, 2 of which compared LMWH to warfarin. The mean probabilities to develop deep-vein thrombosis (DVT), pulmonary embolism and major and minor bleeding using UFH were: 0.21 (95% confidence interval, CI: 0.18-0.24); 0.01 (95% CI: 0.01-0.02); 0.05 (95% CI: 0.03-0.07), and 0.19 (95% CI: 0.17-0.22), respectively. The relative risk (RR) of DVT for LMWH vs. UFH was 0.76 (95% CI: 0.60-0.91), p < 0.05 and for LMWH vs. warfarin 0.78 (95% CI: 0.69-0.87), p < 0.05. The RR of minor bleeding for LMWH vs. UFH was 0.76 (95% CI: 0.64-0.92), p < 0.05. The RR of minor bleeding for LMWH vs. warfarin was 3.28 (95% CI: 2.21-4.70), p < 0.05. Conclusion: in orthopaedic surgery, LMWH is significantly superior to both UFH and warfarin in the prevention of DVT and results in significantly less minor bleeding complications when compared to UFH, but significantly more minor bleeding when compared to warfarin.

**Low-molecular-weight heparin: from the bench to the orthopedic patient.**

Turpie AG
Orthopedics 1997 Feb;20 Suppl:10-13
Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Standard heparin is widely used for the prevention and treatment of venous thromboembolism; however, it has several limitations including variable dose response, dose-dependent clearance and inhibition of platelet function. To overcome these disadvantages, standard heparin, which is composed of glycosaminoglycans of various molecular weights, has been fractionated into its low-molecular-weight component. Low-molecular-weight heparin (LMWH) exhibits less binding to plasma proteins and endothelial cells than standard heparin resulting in a more predictable dose response profile, a dose-independent mechanism of clearance and a longer plasma half-life. LMWH also has a lower binding affinity for platelets and produces less microvascular bleeding. Evidence from randomized clinical trials demonstrates that LMWH is effective in the prevention of deep vein thrombosis (DVT) in high-risk orthopedic patients. There is also considerable evidence of its efficacy and safety in the initial treatment of proximal DVT. Recent studies have demonstrated the feasibility of home treatment with LMWH, which offers the advantage of greater clinical utility compared with current antithrombotic regimens and hence the possibility of cost savings.
RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty.

RD Heparin Arthroplasty Group.  

The efficacy and safety of RD heparin, a low-molecular-weight heparin, for the prevention of venous thromboembolic disease among patients managed with an elective total hip or total knee arthroplasty were compared with the efficacy and safety of warfarin in an open-label prospective, multicenter trial. Patients were randomized to receive either a fixed dose of fifty anti-factor-Xa units of RD heparin per kilogram of body weight, administered subcutaneously twice daily, beginning postoperatively; a fixed dose of ninety anti-factor-Xa units of RD heparin per kilogram of body weight, administered subcutaneously once daily, beginning postoperatively; or five milligrams of warfarin, administered orally preoperatively, followed by a daily adjusted dose of warfarin to prolong the prothrombin time ratio to 1.2 to 1.5. The primary measure of efficacy was contrast venography of the treated limb, performed by local radiologists blinded to the type of treatment that had been assigned. Nine hundred and sixty-nine patients had a complete assessment for the presence of deep-vein thrombosis. The over-all rates of venous thromboembolic disease were 16 percent (95 percent confidence interval, 13 to 21 percent) (fifty-three) for the 328 patients who received RD heparin twice daily, 21 percent (95 percent confidence interval, 17 to 26 percent) (sixty-eight) for the 320 patients who received RD heparin once daily, and 27 percent (95 percent confidence interval, 22 to 32 percent) (eighty-seven) for the 321 patients who received warfarin (p < 0.001 for RD heparin administered twice daily compared with warfarin; p = 0.13 for RD heparin administered once daily compared with warfarin). Compared with warfarin, RD heparin administered twice daily and RD heparin administered once daily reduced the risk of venous thromboembolic disease by 41 percent (95 percent confidence interval, 20 to 56 percent) and 18 percent (95 percent confidence interval, 16 to 37 percent), respectively. The rates of venous thromboembolic disease after 523 total hip arthroplasties were 8, 14, and 14 percent for the patients who received RD heparin twice daily, those who received it once daily, and those who received warfarin (p = 0.07 for RD heparin administered twice daily compared with warfarin; p = 0.82 for RD heparin administered once daily compared with warfarin).

Post-discharge prevention of deep vein thrombosis following total joint replacement.

Fitzgerald RH Jr  
Orthopedics 1996 Aug;19 Suppl:15-18

Recent prospective studies demonstrate that the peak incidence of deep vein thrombosis (DVT) occurs on the fifth postoperative day. If the patient is to be discharged from an acute care facility on day 3 through 6, then the patient will be removed from direct supervision by professionals-frequently observing the patient in an acute care hospital during the high-risk period for the development of DVT or pulmonary embolism. In addition, the period of vulnerability for the development of thromboembolic disease in this group of patients appears to occur for an extended period of time, eg, 3 months. This change in practice has altered the surgeon’s approach to the selection of agents for the prevention of thromboembolic complications. Most surgeons wish to administer an agent in the acute care setting that can be continued after the patient is discharged to the rehabilitation facility, subacute care facility, or home. This information reflects the belief of most orthopedic surgeons that prophylactic therapy should be continued beyond the time frame in which the patient is confined to the acute care facility. Although progress has been made in identifying effective prophylactic agents, questions remain as to the appropriate duration of prophylaxis. Based upon available data, it would appear that prophylaxis against thromboembolic disorders should be continued until the patient is spending the majority of his or her day ambulating with or without external aides.
Graded compression stockings for prevention of deep-vein thrombosis after hip and knee replacement.

Hui AC, Heras-Palou C, Dunn I, Triffitt PD, Crozier A, Imeson J, Gregg PJ
The Glenfield Hospital NHS Trust, Leicester, UK.

We performed a prospective, randomised controlled trial in 177 patients who were having either total hip or knee replacement, to evaluate the use of both above- and below-knee graded compression stockings in the prevention of deep-vein thrombosis (DVT). With above-knee stockings, we found no significant reduction of the overall, proximal or major calf (> 5 cm) DVT rates. With below-knee stockings, the overall thrombosis rate was similar to that of the control group but the stockings appeared to have altered the pattern of thrombosis. Patients who had total hip replacement and wore below-knee stockings had a significantly higher rate of proximal or major calf DVT (p = 0.03). This pattern was reversed in patients with total knee replacement who developed a significantly lower rate of proximal or major calf DVT with below-knee stockings (p < 0.05). Our results showed that, with the exception of below-knee stockings in knee replacement patients, graded compression stockings were ineffective in preventing DVT after hip or knee replacement surgery.

Incidence of venographically proved deep vein thrombosis after knee arthroscopy.


BACKGROUND: Deep vein thrombosis is a common, important complication of major orthopedic surgery, particularly knee arthroplasty. Knee arthroscopy is performed more frequently and in younger patients than knee arthroplasty. However, the true risk of deep vein thrombosis in patients who undergo this procedure is unknown. OBJECTIVE: To determine the incidence of deep vein thrombosis after knee arthroscopy in a large cohort of patients. METHODS: Consecutive patients scheduled for knee arthroscopy were eligible for the study. Enrolled study patients received no thromboprophylaxis. They were discharged home the day of surgery and underwent unilateral contrast venography approximately 1 week after their operation. The primary outcome measure was the incidence of venous thromboembolism. Risk factors for deep vein thrombosis were evaluated. RESULTS: Among the 184 patients who had adequate venography, deep vein thrombosis was detected in 33 (17.9%; 95% confidence interval, 12.7%-24.3%). Of these, 9 were proximal (4.9%; 95% confidence interval, 2.3%-9.1%). No patient died and no patient presented with clinically suspected pulmonary embolism. Of 33 patients, only 20 (60.6%) with deep vein thrombosis had symptoms while 13 (39.4%) were asymptomatic. The risk of deep vein thrombosis was significantly higher among patients who had a tourniquet applied for more than 60 minutes. CONCLUSIONS: The results of our study demonstrate that 17.9% of patients develop deep vein thrombosis after knee arthroscopy (most being either proximal or extensive). It is reasonable to perform a randomized trial to determine whether the incidence of deep vein thrombosis can be safely reduced in patients undergoing knee arthroscopy.

Screening for deep-venous thrombosis after hip and knee replacement without prophylaxis.


We performed routine venography after operation in a consecutive series of 252 patients with total joint arthroplasties in whom no form of routine chemical or mechanical prophylaxis had been used. The prevalence of deep-vein thrombosis (DVT) was 32% (16% distal, 16% proximal) after total hip replacement and 66% (50% distal, 16% proximal) after total knee replacement (p < 0.001). We did not treat distal DVT. There were only two readmissions within three months of surgery because of thromboembolic disease. There were two deaths within this period, neither of which was due to pulmonary embolism.
Orthopaedic Surgery - Total Knee Arthroplasty

Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardeparin Arthroplasty Study Group.

Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, Lyons R
Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN 55905, USA.

We performed a double-blind, randomized clinical trial to compare the efficacy and safety of three different subcutaneous (s.c.) low molecular weight heparin doses (ardeparin sodium 25, 35, or 50 anti-Xa U/kg twice daily [BID]) to adjusted-dose warfarin (international normalized ratio [INR] = 2.0 to 3.0), as venous thromboembolism prophylaxis after total knee replacement surgery. The primary endpoint was total venous thromboembolism prevalence, defined as deep vein thrombosis discovered at postoperative venography of the operated leg, or symptomatic, objectively-documented pulmonary embolism. Of 860 patients randomized, 680 (79%) had an evaluable venogram or pulmonary embolism. The total venous thromboembolism prevalence was significantly greater among patients prophylaxed with warfarin compared to ardeparin 50 BID (38% vs 27%, p = 0.019); the prevalence among ardeparin 25 BID (37%) and 35 BID (28%) patients was similar to warfarin and ardeparin 50 BID patients, respectively. Overt bleeding occurred in 22 (7.9%) ardeparin 50 BID patients compared to 12 (4.4%) warfarin patients (p = 0.08), and in seven ardeparin 25 and 35 BID patients each (5.2% and 5.0%, respectively). Compared to the warfarin group, blood loss was significantly greater in the ardeparin 50 and 25 BID groups, and not different in the ardeparin 35 BID group. CONCLUSIONS: Postoperative, unmonitored, fixed-dose ardeparin 50 anti-Xa U/kg s.c. BID is significantly more effective than adjusted-dose warfarin for this indication. Although overt bleeding among warfarin and ardeparin 50 BID patients did not differ significantly, ardeparin 50 BID patients had significantly greater blood loss. Ardeparin 35 anti-Xa U/kg s.c.BID may provide efficacy similar to ardeparin 50 anti-Xa U/kg s.c. BID but with reduced bleeding.

Comparison of two warfarin regimens in the prevention of venous thrombosis following total knee replacement.

Francis CW, Pellegrini VD Jr, Leibert KM, Totterman S, Azodo MV, Harris CM, Cox C, Marder VJ
Thromb Haemost 1996 May;75(5):706-711
Department of Medicine, University of Rochester School of Medicine and Dentistry, NY, USA.

A prospective, randomized trial was conducted to compare the effectiveness and safety of warfarin given in two regimens in prevention of venous thrombosis after total knee replacement. Adult patients scheduled for primary or revision total knee replacement were randomly assigned to receive either a “two-step” warfarin regimen beginning 10-14 days pre-operatively or, alternatively, to begin warfarin the night before surgery. Post-operatively, the dose was adjusted in both groups to achieve a target International Normalized Ratio (INR) of 2.2 and prophylaxis was continued until venography on post-operative days five through nine. Bleeding was assessed by surgical blood loss, transfusion requirements, changes in hematocrit, and clinically identified bleeding complications. The occurrence of deep vein thrombosis was nearly the same in the two treatment groups, 39% in patients randomized to the two-step regimen as compared to 38% in those beginning the night before surgery. The occurrence of proximal vein thrombosis was also similar, 5% versus 7% (p = NS). Patients in the two-step group received 1.33 +/- 1.26 transfusions compared to 0.95 +/- 1.22 in the night before group (p < 0.05) and also had a lower nadir post-operative hematocrit of 26.7 +/- 3.1 as compared to 28.5 +/- 3.2 (p < 0.0001). Major bleeding complications were associated with excessively prolonged INRs and occurred in five patients in the two-step group and two in the night before group. Patients in both groups who developed thrombosis had a significantly lower INR on post-operative days two and three compared to those without thrombosis. We conclude that a prophylactic warfarin regimen for prevention of deep vein thrombosis after total knee replacement
beginning the night before surgery is more convenient and may be associated with less bleeding than a regimen beginning warfarin 10-14 days pre-operatively. Careful control of anticoagulant intensity is needed to achieve maximum effectiveness and avoidance of bleeding complications.

**Prevention of deep vein thrombosis after major knee surgery—a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo.**


Thromb Haemost 1992 Apr 2;67(4):417-423

Department of Medicine, Montreal General Hospital, McGill University, Canada.

Consecutive patients undergoing knee arthroplasty or tibial osteotomy at four participating hospitals received either enoxaparin, 30 mg subcutaneously every 12 h (n = 66) or an identical-appearing placebo (n = 65). All study medications started the morning after the operation and were continued up to a maximum of 14 days. Patients underwent surveillance with 125I-fibrinogen leg scanning and impedance plethysmography. Bilateral contrast venography was performed routinely at Day 14 or at time of discharge, if sooner. Deep vein thrombosis was detected by venography in 35 of 54 patients (65%) in the placebo group and in 8 of 41 patients in the enoxaparin group (19%), a risk reduction of 71%, P less than 0.0001. For the entire study group, deep vein thrombosis was detected by either venography of non-invasive tests in 37 of 64 patients (58%) in the placebo group and in 11 of 65 patients (17%) in the enoxaparin group, a risk reduction of 71%, P less than 0.0001. Proximal vein thrombosis was found in 19% of the placebo patients and in none of the enoxaparin patients, a risk reduction of 100%, P less than 0.001. Bleeding complications occurred in 5 of 65 patients (8%) in the placebo group and in 4 of 66 patients (6%) in the enoxaparin group, P = 0.71. There were no differences in the amount of blood loss, minimum hemoglobin levels and number of units of packed red cells given between the two treatment groups. We conclude that a fixed dose regimen of enoxaparin, started post-operatively, is an effective and safe regimen for reducing the frequency of deep vein thrombosis after major knee surgery.

**Ardeparin (low-molecular-weight heparin) vs graduated compression stockings for the prevention of venous thromboembolism. A randomized trial in patients undergoing knee surgery.**


Arch Intern Med 1996 Apr 22;156(8):851-856

Department of Medicine, McMaster University, Hamilton, Ontario.

BACKGROUND: Deep vein thrombosis is common in patients undergoing major knee surgery. Static graduated compression stockings effectively prevent venous thrombosis in general surgery. Because of the demonstrated prophylactic efficacy of pneumatic compression in knee surgery, the similar efficacy of static graduated compression and pneumatic compression in neurosurgery, and the easier use of static graduated compression in knee surgery, graduated static compression stockings were used as the control arm in our clinical trial. Although low-molecular-weight heparin had been shown to be effective in general surgery and hip replacement, its efficacy was unproved in knee surgery. METHODS: A double-blind, randomized trial compared the combination of low-molecular-weight heparin and graduated compression stockings with graduated compression stockings alone in patients undergoing major knee surgery. Patients received either ardeparin (Normiflo) (low-molecular-weight heparin), 0.005 mL/kg (50 anti-Xa U/Kg), or placebo. Both were administered subcutaneously twice daily commencing 12 to 24 hours after surgery and continued for 14 days or until discharge, if sooner. Both study groups wore graduated compression stockings. Bilateral venography was performed on day 14, or sooner if the patient was ready for discharge. RESULTS: One hundred twenty-two patients were allocated to receive ardeparin and 124 received placebo. Ninety-six patients in the ardeparin group and 103 in the placebo group had evaluable venograms. Deep vein
thrombosis was detected in 28 patients in the ardeparin group and in 60 in the placebo group. Proximal deep vein thrombosis was detected in two patients who received ardeparin and 16 who received placebo. One patient in each group, both of whom did not have venography, experienced pulmonary embolism. Thus, deep vein thrombosis or pulmonary embolism was detected in 29 (29.9%) of the 97 patients in the ardeparin group and in 61 (58.7%) of the 104 patients in the placebo group, a relative risk reduction of 49% (P< 0.01). The rate of major bleeding in the ardeparin group was 2.5%, compared with 2.4% in the placebo group. CONCLUSION: Ardeparin administered postoperatively twice daily is effective and safe for the prevention of venous thrombosis in patients undergoing major knee surgery. Whereas graduated compression stockings have been shown to be effective prophylactic agents in general surgery and neurosurgery, they have little effect in knee surgery.

**Orthopaedic Surgery - Total Hip Arthroplasty**

Efficacy of a postoperative regimen of enoxaparin in deep vein thrombosis prophylaxis.

Turpie AG
McMaster University Department of Medicine, Hamilton, Ontario, Canada.

Venous thromboembolism is a common complication in patients undergoing elective hip replacement, in whom the incidence of calf vein thrombosis is 40% to 60%; proximal vein thrombosis, 20%; and fatal pulmonary embolism, 1% to 2% when prophylaxis is not used. A double-blind, randomized trial comparing low-molecular-weight heparin (enoxaparin) with placebo for the prevention of venous thrombosis in patients undergoing elective hip surgery was carried out. Prophylactic treatment with a fixed dose was begun postoperatively and continued for 14 days. Fifty patients in each treatment group underwent surveillance with 125I-fibrinogen leg scanning and impedance plethysmography. In the first 24 patients, venography was performed only if their surveillance test was positive. Venography was requested in the remaining 76 patients even if the screening tests were negative; in this latter group, venous thrombosis occurred in 4 patients (10.8%) given enoxaparin and 20 patients (51.3%) given placebo (p = 0.0002). The corresponding rates for proximal vein thrombosis were 5.4% and 23.1%, respectively (p = 0.029). In the entire group of 100 patients, venous thrombosis occurred in 12% of those given enoxaparin and 42% of those given placebo (p = 0.0007). The corresponding rates for proximal vein thrombi were 4% and 20%, respectively (p = 0.014). The observed hemorrhagic rate was 5% in each treatment group. The results of this study show that prophylaxis with fixed-dose enoxaparin is effective and safe for patients undergoing elective hip replacement.

Prevention of fatal pulmonary embolism with warfarin after total hip replacement.

Suomalainen O, Makela AE, Harju A, Jaroma H
Int Orthop 1996;20(2):75-79
Department of Surgery, Kuopio University Hospital, Finland.

We studied retrospectively the efficacy of low-dose warfarin for the prevention of fatal pulmonary embolism in 1140 patients (1280 hips) undergoing total hip replacement between 1972 and 1989. The first dose, 10-20 mg, was given the night before operation and the regime was continued for 2 weeks after the procedure. Anticoagulation was aimed at achieving a therapeutic level in 4 to 5 days. All the patients were followed for 3 months. Seven died during this period and autopsy showed that 2 (0.16%) died from pulmonary embolism, one at 3 days and the other 10 days after operation. Pulmonary embolism causing symptoms, but which was not fatal, occurred in 32 patients (2.5%). Symptomatic deep vein thrombosis was present in 45 patients (3.5%). There were 14 (1.1%) massive postoperative haematoma, and 7 needed operative treatment. Low-dose warfarin can be recommended as a safe and efficient method of achieving an acceptably low incidence of postoperative thrombo-embolic complications after total hip replacement.

Ann Intern Med 1991 Apr 1;114(7):545-551
McMaster University, Hamilton, Ontario.

OBJECTIVE: To determine the relative efficacy and safety of low molecular weight (LMW) heparin (Enoxaparin) compared with standard calcium heparin for the prevention of postoperative deep vein thrombosis in patients undergoing elective hip surgery. DESIGN: A double-blind, randomized, controlled trial. PATIENTS: Six hundred sixty-five consecutive patients undergoing hip replacement at five participating hospitals. INTERVENTIONS: Patients received either fixed-dose LMW heparin, 30 mg subcutaneously twice daily, or fixed-dose standard calcium heparin, 7500 units subcutaneously twice daily; both regimens were started 12 to 24 hours after surgery and continued for 14 days or until discharge if sooner. MEASUREMENTS: All patients had postoperative I-125-fibrinogen leg scanning and impedance plethysmography. If results of one or both tests were positive, then venography was done. Otherwise, venography was done between day 10 and day 14, or sooner if the patient was ready for discharge. RESULTS: Evaluable venograms were obtained in 258 of the 333 patients randomly assigned to receive LMW heparin and in 263 of the 332 patients assigned to receive calcium heparin. For patients with evaluable venograms, thrombosis was detected in 50 patients (19.4%) who received LMW heparin compared with 61 patients (23.2%) who received standard heparin (difference, -3.8%; 95% CI, -11.1% to 3.6%) (P greater than 0.2). Proximal deep vein thrombosis was detected in 5.4% of the patients receiving LMW heparin and in 6.5% of the patients receiving standard heparin (difference, -1.1%; CI, -5.2% to 3.3%) (P greater than 0.2). For the entire group of 665 patients, venous thrombosis occurred in 17.1% given LMW heparin and in 19.0% given standard heparin. Hemorrhagic complications occurred in 31 patients (9.3%) given standard heparin and in 17 patients (5.1%) given LMW heparin (difference, 4.2%; CI, 0.3% to 8.2%) (P = 0.035). The relative risk reduction was 45%. The rate of major bleeding in the standard heparin group was 5.7% compared with 3.3% in the LMW heparin group (difference, 2.4%; CI, -1.0% to 5.4%) (P = 0.13). The relative risk reduction was 42%. CONCLUSION: Low molecular weight heparin is significantly less hemorrhagic than standard unfractionated heparin; the difference in the rate of deep vein thrombosis, although not statistically significant (P greater than 0.2), favors the use of LMW heparin.


Hamulyak K, Lensing AW, van der Meer J, Smid WM, van Ooy A, Hoek JA
Thromb Haemost 1995 Dec;74(6):1428-1431
Department of Haematology, University Hospital of Maastricht, The Netherlands.

OBJECTIVE: To compare efficacy, safety, and feasibility of adjusted-dose oral anticoagulants (OAC) versus fixed-dose subcutaneous low molecular weight heparin (LMWH) for the prevention of deep venous thrombosis (DVT) in patients who have undergone elective hip or knee replacement. DESIGN: Multicentre, single blind randomised trial. OAC (acenocoumarol, target International Normalised Ratio, 2.0-3.0) and LMWH (nadroparine, 60 aXa IU/kg once daily) were started preoperatively and continued for 10 days. All outcome measures were adjudicated by an independent committee unaware of treatment allocation. SUBJECTS: 672 consecutive patients scheduled for elective hip or knee replacement surgery. All patients wore bilateral graduated compression stockings. MAIN OUTCOME MEASURES: The endpoint for the assessment of efficacy was venography confirmed DVT or confirmed symptomatic pulmonary embolism. The endpoint for the assessment of safety was clinically important bleeding during study treatment or within 48 h of the end of treatment. RESULTS: Among the 517 patients with interpretable venograms, 391 had a hip replacement and 126 had a knee implant. DVT was demonstrated in 50 (20%) of 257 patients allocated to OAC and 43 (17%) of 260 patients allocated to nadroparine (p = 0.45), for an absolute difference in DVT incidence of 2.9% in
favour of nadroparine (95% CI, -3.7-9.5). Clinically important bleeding occurred in eight (2.3%) of the 342 oral anticoagulant treated patients and in five (1.5%) of the 330 nadroparine treated patients (p = 0.62), for an absolute difference in favour of nadroparine of 0.8% (95% CI, -1.3-2.9). Conclusion: Patients who undergo major orthopaedic operations have a high risk of venous thromboembolism. Once daily fixed-dose subcutaneous nadroparine is at least as efficacious and safe as daily adjusted OAC for prophylaxis against DVT after hip or knee implantation but is more simple to administer.

**Efficacy and safety of enoxaparin to prevent deep vein thrombosis after hip arthroplasty.**

Colwell CW Jr, Spiro TE
Scripps Clinic and Research Foundation, La Jolla, CA 92037, USA.

Four clinical studies were conducted in the United States and Canada to compare the efficacy and safety of Enoxaparin, a low molecular weight heparin, with low dose unfractionated heparin and placebo for the prevention of deep venous thrombosis after hip arthroplasty. In each study, patients were randomized consecutively into treatment groups of placebo, unfractionated heparin (5000 IU 3 times daily or 7500 IU twice daily), or Enoxaparin (30 mg twice daily, 40 mg once daily, or 10 mg once daily), with treatment started postoperatively. All patients had noninvasive studies and bilateral lower extremity radiocontrast venography at the end of study treatment or on discharge from the hospital (not applicable to the first 24 patients enrolled in the Canada-1 study). One thousand nine hundred forty patients were treated, and 1937 patients were included in efficacy analysis. The incidence of total deep venous thrombosis was as follows: placebo group, 46% (22 of 50 patients); heparin group, 16% (87 of 539 patients); Enoxaparin group, 30 mg twice daily 12% (93 of 785 patients); Enoxaparin 40 mg daily group, 14% (14 of 402 patients); and Enoxaparin 10 mg daily group, 25% (40 of 161 patients). Incidence of proximal deep venous thrombosis was 22%, 5%, 4%, 4%, and 11%, respectively. Major bleeding events were reported in 4% of the placebo group, 2% to 4% in the Enoxaparin group, and 6% in the unfractionated heparin group. In these clinical studies, Enoxaparin, 30 mg twice daily, was shown to be as effective and safe as low dose unfractionated heparin to prevent deep venous thrombosis after hip arthroplasty.

**A prospective study on intermittent pneumatic compression in the prevention of deep vein thrombosis in patients undergoing total hip or total knee replacement.**

Pidala MJ, Donovan DL, Kepley RF
Department of Surgery, Akron City Hospital, Ohio 44309.

Three hundred and forty-six consecutive patients undergoing total hip or total knee replacement were prospectively studied to evaluate the effectiveness of intermittent pneumatic compression of the legs for the prevention of postoperative deep vein thrombosis. All patients were serially studied using impedance plethysmography and duplex ultrasound with color flow preoperatively and on the fourth and seventh postoperative day. The incidence of postoperative deep vein thrombosis in this series was 4 percent. Each patient with a postoperative duplex ultrasound had positive impedance plethysmography. Of the 14 patients who had postoperative deep vein thrombosis, seven had positive test results on postoperative day four and seven had positive tests on postoperative day seven. No patients were symptomatic. The results suggest that the high incidence of postoperative deep vein thrombosis after extensive orthopedic operation is significantly lowered by the use of intermittent pneumatic compression. Intermittent pneumatic compression, therefore, may be the preferred approach in prophylaxis of postoperative deep vein thrombosis.
Orthopaedic Surgery - Hip Fracture

Low-molecular-weight heparinoid orgaran is more effective than aspirin in the prevention of venous thromboembolism after surgery for hip fracture.

Circulation 1996 Jan 1;93(1):80-84
Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada.

BACKGROUND: The study objective was to determine the relative efficacy and safety of a low-molecular-weight heparinoid (Orgaran) compared with aspirin for the prevention of postoperative venous thromboembolism in patients undergoing surgery for fractured hips. A double-blind, randomized, controlled trial was used to study 251 consecutive eligible and consenting patients undergoing surgery for hip fracture in seven participating hospitals. METHODS AND RESULTS: Patients received either fixed-dose Orgaran by subcutaneous injection every 12 hours in a dose of 750 anti-Factor Xa units or aspirin 100 mg orally twice daily; both regimens were started 12 to 24 hours after surgery and continued for 14 days or until discharge, if sooner. All patients had postoperative 125I-fibrinogen leg scanning and impedance plethysmography. If the results of one or both tests were positive, then venography was performed. Otherwise, venography was done at day 14, or sooner if the patient was ready for discharge. Pulmonary embolism in symptomatic patients was diagnosed on the basis of a high probability perfusion/ventilation lung scan, a positive angiogram, or a clinically significant embolism detected at autopsy. Evaluable venograms were obtained in 90 of the 125 patients randomly assigned to receive Orgaran and in 87 of the 126 patients assigned to receive aspirin. Venous thromboembolism was detected in 25 (27.8%) patients in the Orgaran group and in 39 (44.3%) patients in the aspirin group. Thus, there was a relative risk reduction of 37% with Orgaran (P=.028; 95% confidence interval, 3.7% to 59.7%). Six (6.8%) of 88 patients in the Orgaran group and 12 (14.3%) of 84 patients in the aspirin group developed proximal deep vein thrombosis or pulmonary embolism, a relative risk reduction of 52% with Orgaran (P=.137; 95% confidence interval, -30.7% to 84.6%). Hemorrhagic complications occurred in 2 (1.6%) patients given Orgaran and 8 (6.4%) patients given aspirin (P=.10). There was one major bleed in the Orgaran group compared with four in the aspirin group. CONCLUSIONS: This study demonstrates that Orgaran is significantly more efficacious than aspirin in preventing postoperative venous thromboembolism in patients undergoing surgery for fractured hips, with no evidence of any increase in hemorrhagic complications.

Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis.

Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ
Department of Orthopaedics, University of British Columbia, Vancouver, Canada.

A prospective, randomized clinical trial in 304 orthopaedic trauma patients with hip and pelvic fractures was conducted to investigated the effectiveness of pneumatic sequential leg compression devices (PSLCDs) for the prevention of thromboembolic disease. The control group received no specific form of prophylaxis. Patients were followed by venous Doppler, duplex can, and ventilation perfusion lung scans. The study end-point was documented pulmonary embolism and/or deep vein thrombosis. The incidence of a venous thromboembolic event in the control group was 11% and in the experimental group 4%. This difference was statistically significant (p = 0.02). These patients were also stratified into hip and pelvic fracture groups. In the hip fracture patients, the control group had a thromboembolic event incidence of 12% and the experimental group 4%. This difference was also statistically significant (p = 0.03). In the pelvic fracture group there was a thromboembolic incidence of 11% in the controls, demonstrating this patient population to be at significant risk. In this group, the PSLCDs were not statistically shown
to be effective. Pneumatic leg compression devices are effective in reducing the incidence of thromboembolic events in patients with hip fractures.

**Prevention of deep vein thrombosis and pulmonary embolism in acetabular and pelvic fracture surgery.**

Fishmann AJ, Greeno RA, Brooks LR, Matta JM  
Clin Orthop 1994 Aug;305:133-137  
Department of Medicine, Hospital of the Good Samaritan, Los Angeles, CA.

In a prospective nonrandomized study, a protocol was examined for prophylaxis of deep venous thrombosis and pulmonary embolism in patients with operative treatment of acetabular and pelvic fractures. There were 197 patients in the study with 203 fractures, including 148 acetabular and 55 pelvic fractures. There were 2 cases of bilateral acetabular fractures and 4 cases with both acetabular and pelvic fractures. The protocol involved preoperative noninvasive screening of the lower extremities, intraoperative and postoperative use of mechanical antithrombotic devices, and chemical prophylaxis with warfarin for 3 weeks following removal of surgical drains. There were 11 cases (6%) of preoperative deep venous thrombosis detected. There were 6 cases of postoperative deep venous thrombosis and 2 cases of pulmonary embolism. The incidence of postoperative venous thrombosis and pulmonary embolism was 3% and 1%, respectively. The protocol was found to be effective for preoperative detection of venous thrombosis and prevention of deep venous thrombosis and pulmonary embolism in trauma patients with minimal bleeding complications and no morbidity from embolic disease.

**Low-molecular-weight heparinoid compared with warfarin for prophylaxis of deep-vein thrombosis in patients who are operated on for fracture of the hip. A prospective, randomized trial.**

Gerhart TN, Yett HS, Robertson LK, Lee MA, Smith M, Salzman EW  
Department of Orthopaedic Surgery, Beth Israel Hospital, Boston, Massachusetts 02115.

In a randomized, prospective trial, a low-molecular-weight heparinoid (Org 10172 [Lomoparan]) was compared with warfarin for efficacy and safety in preventing deep-vein thrombosis in 263 patients who had an operatively treated fracture of the hip. One group of patients received Org 10172 in a dose of 750 units subcutaneously every twelve hours until the ninth postoperative day; on the seventh postoperative day, warfarin was added to the regimen. The other group received only warfarin. Both drugs were begun preoperatively, immediately after the admission evaluation. In the patients who received warfarin, the desired prothrombin time was one and one-half times the control level. Deep-vein thrombosis was detected by 125I-fibrinogen scanning and impedance plethysmography and was confirmed by phlebography and compression ultrasonography. Deep-vein thrombosis was found in nine (7 per cent) of the 132 patients who received Org 10172 and in twenty-eight (21 per cent) of the 131 patients who received warfarin (p less than 0.001). Adverse reactions were not significantly different in the two groups. Major bleeding complications occurred in eight patients in the Org-10172 group, only four of whom were receiving the drug at the time of bleeding, and in five patients who were receiving warfarin (not significant). There was no difference in intraoperative loss of blood or in requirements for transfusion. We concluded that the low-molecular-weight heparinoid Org 10172 is a safe, convenient, effective antithrombotic agent for the prevention of venous thrombosis after an operation for fracture of the hip.
Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a fracture of the neck of the femur.

Barsotti J, Gruel Y, Rosset P, Favard L, Dabo B, Andreu J, Delahousse B, Leroy J
Clinique Traumatologique et Orthopedique, CHU Trousseau, Tours, France.

A randomized double-blind study comparing the efficacy and safety of two different dosage regimens of a low-MW heparin, Enoxaparin (Lovenox) 20 mg twice (group A) or 40 mg once (group B), was carried out in 103 elderly patients with a fracture of the neck of the femur. Distal and proximal thrombosis occurred in 18.3% of patients in group A and in 10.4% in group B. No major hemorrhagic complication was observed, except for two hematomas in each group. This trial suggests that a total daily dose of 40 mg of Enoxaparin can be effective in the prevention of deep vein thrombosis in elderly surgically treated patients and does not involve a major risk of bleeding.

General Surgery

Low molecular weight heparin and unfractionated heparin for prevention of thromboembolism in general surgery: a meta-analysis of randomised clinical trials.

Institute for Medical Informatics and Biostatistics, Riehen, Switzerland.

Low molecular weight heparin (LMWH), unfractionated heparin (UFH) and warfarin were compared with respect to efficacy and safety in the prevention of thromboembolism in general surgery. Meta-analysis (MA) with a priori definition of the MA protocol was used to combine the results from randomised trials with patients who underwent general surgery and deep-vein thrombosis (DVT) prophylaxis with LMWH, UFH or warfarin. Forty-four studies were identified for assessment and 33 were included, however, none for warfarin. For efficacy (DVT and pulmonary embolism) and major bleeding, no significant difference between the LMWH- and UFH-treated groups was demonstrated. The relative risk of minor bleedings for LMWH versus UFH was 0.75 (0.64-0.88; 95% confidence interval) and is significant (p < 0.05). Within the limitations of the MA, LMWH and UFH did not differ significantly in terms of prevention of thromboembolism, but LMWH had a significantly better safety profile. On this basis, LMWH may be preferable to UFH in the prevention of thromboembolism in general surgery.

A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery.

Centre for Hemostasis, Thrombosis, Atherosclerosis and Inflammation Research, Academic Medical Centre, Amsterdam, Netherlands.

BACKGROUND: Various studies have been performed in general surgery patients comparing low molecular weight heparin (LMWH) with standard heparin (SH) for the prevention of postoperative deep vein thrombosis (DVT), revealing contradicting results. Therefore, we have compared the efficacy and safety of a LMWH for the prevention of DVT after major general surgery. PATIENTS AND METHODS: Patients received either 20 mg LMWH (enoxaparin) once daily, or 5,000 IU SH TID, starting preoperatively in a prospective, randomized, double-blind international multicenter trial. DVT was diagnosed using fibrinogen I 125 leg scanning. Major and minor bleeding were assessed clinically. RESULTS: A total of 718 patients were randomized to LMWH, and 709 patients to SH. DVT was detected in 58 LMWH-treated patients (8.1%, 95% confidence interval [CI] 6.2% to 10.3%) and in 45 patients allocated to SH (6.3%, 95% CI 4.7% to 8.4%, P > 0.05). Major bleeding complications occurred in 11 LMWH-treated patients (1.5%, 95% CI 0.8% to
2.7%) and in 18 patients to whom standard heparin was administered (2.5%, 95% CI 1.5% to 3.9%, P > 0.05). Four LMWH-treated patients (0.6%) required reoperation for bleeding as compared to 13 patients in the SH group (1.8%, P = 0.03). CONCLUSION: This LMWH appeared as effective and safe as SH. In view of its more convenient way of administration, this LMWH might be preferred for thromboprophylaxis.

**Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery.**

Thromb Haemost 1992 Jun 1;67(6):627-630
Koppenhagen K, Adolf J, Matthes M, Troster E, Roder JD, Hass S, Fritsche HM, Wolf H
Department of Nuclear Medicine, Universitatsklinikum Steglitz, Berlin, Germany.

In a prospective, double-blind, randomized multicenter trial the efficacy and safety of low molecular weight heparin and unfractionated heparin were compared for the prevention of postoperative deep vein thrombosis in patients undergoing abdominal surgery. Six hundred and seventy-three patients were randomly allocated to the two prophylaxis groups; 20 of these, however, did not undergo surgery and did not receive any prophylaxis. Of the remaining 653 patients 323 received one subcutaneous injection of 3,000 anti-Xa units of low molecular weight heparin and 330 received subcutaneously 5,000 U heparin three times a day. Treatment was initiated 2 h preoperatively and continued for 7 to 10 days. The occurrence of DVT was determined by the 125I-labelled fibrinogen uptake test and phlebography. Venous thrombosis was diagnosed in 24 of 323 patients (7.4%) treated with low molecular weight heparin and in 26 of 330 patients (7.9%) treated with low-dose heparin. DVT of proximal veins was detected in four patients of the low molecular weight heparin group and in three patients of the low-dose heparin group. During the observation period three pulmonary emboli - one fatal and two non-fatal - occurred in patients receiving prophylaxis with low-dose heparin. No pulmonary embolism was found in patients treated with low molecular weight heparin. Both prophylactic schemes were well tolerated. Intra- and postoperative blood loss, incidence of wound hematoma, frequency and volume of intra- and postoperative blood transfusion were similar in both groups with a slight advantage for the low molecular weight heparin group.

**Comparison of a low molecular weight heparin and unfractionated heparin for the prevention of deep vein thrombosis in patients undergoing abdominal surgery.**

The European Fraxiparin Study (EFS) Group.

In a prospective, randomized multicentre trial the efficacy and safety of the low molecular weight heparin (LMWH) fraction Fraxiparin and unfractionated calcium heparin (Calciparin) were compared for the prevention of postoperative deep vein thrombosis. Of 1909 patients included in the trial 1896 underwent abdominal surgery and received either one daily subcutaneous injection of 7500 anti-Xa units Fraxiparin or 5000 units calcium heparin three times a day subcutaneously. Elastic compression stockings were worn by both groups of patients in the postoperative period. Before randomization the patients were stratified in two subgroups with or without malignant disease. To assess the rate of deep vein thrombosis (DVT), 125I-labelled fibrinogen leg scanning was performed daily for 7 postoperative days. Positive results were confirmed by phlebography whenever possible. Venous thrombosis occurred in 27 of 960 patients (2.8 per cent) given Fraxiparin and in 42 of 936 patients (4.5 per cent) given calcium heparin (P = 0.034). The rates of proximal vein thrombosis were 0.4 per cent (4 patients) and 1.4 per cent (13 patients) respectively (P less than 0.05). Pulmonary embolism occurred in 2 of 960 patients (0.2 per cent) treated with Fraxiparin and in 5 of 936 patients (0.5 per cent) treated with calcium heparin. The two treatments were equally well tolerated. Intra- and postoperative blood loss, the number of wound haematomas as well as frequency and volume of transfusions were similar in both groups. The present trial demonstrates that a single daily subcutaneous injection of Fraxiparin is more effective than the established low dose subcutaneous heparin prophylaxis with 5000 units three times per day in preventing postoperative DVT after abdominal surgery in patients wearing compression stockings.
Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group.

Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK, Maher KT, Sanderson RM, Ward VP, Kakkar S
Lancet 1993 Jan 30;341(8840):259-265
Thrombosis Research Institute, London, UK.

Low-molecular-weight heparin (LMWH) is effective in the prevention of postoperative venous thromboembolism but does it have the safety advantages over standard heparin (SH) that have been claimed? In a multicentre randomised trial in 3809 patients undergoing major abdominal surgery (1894 LMWH, 1915 SH) heparin was given preoperatively and continued for at least 5 postoperative days. Patients were assessed in the postoperative period and were followed up for at least 4 weeks, the emphasis being on safety. Major bleeding events occurred in 69 (3.6%) patients in the LMWH group and 91 (4.8%) patients in the SH group (relative risk 0.77, 95% confidence interval 0.56-1.04; p = 0.10). 93 indices of major bleeding were observed in the 69 LMWH patients and 141 in the SH patients. (p = 0.058). Severe bleeding was less frequent in the LMWH group (1.0% vs 1.9%; p = 0.02), as was wound haematoma (1.4% vs 2.7%; p = 0.007). Bleeding episodes with LMWH were less likely to lead to further surgery to evacuate a haematoma or to control bleeding, and injection site bruising was also less common in the LMWH group. No significant differences were found in the efficacy of the two agents. Perioperative death rates were 3.3% in the LMWH group and 2.5% in the SH group; pulmonary emboli were detected in 0.7% and 0.7%; and deep-vein thrombosis was diagnosed in 0.6% of patients in each group. Follow-up was done on 91% of 3699 evaluable patients. There were 19 further deaths (10 LMWH, 9 SH group) and 25 patients with thromboembolic complications (15 and 10). Of the 3 patients with fatal pulmonary emboli during follow-up 2 had received LMWH and 1 SH. The two drugs were of similar efficacy. The primary end point, the frequency of major bleeding, showed a 23% reduction in the LMWH group, but this difference was not significant. The secondary safety end points revealed that LMWH was significantly better than SH. Fatal pulmonary embolism occurs rarely (0.09%) following discharge from hospital so the cost benefit ratio would not justify prolonged prophylaxis in this setting.

Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis.

Clagett GP, Reisch JS
Department of Surgery, University of Texas Southwestern Medical Center, Southwestern Medical School, Dallas 75235-9031.

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), intermittent 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.
Thigh length versus knee length stockings in the prevention of deep vein thrombosis.

Porteous MJ, Nicholson EA, Morris LT, James R, Negus D
United Medical School, Guy’s Hospital, London, UK.

Above-knee graduated compression stockings are effective in preventing postoperative deep vein thrombosis, but are more expensive and less acceptable than below-knee stockings. One hundred and fourteen patients undergoing major abdominal surgery were randomly allocated to wear above-knee or below-knee graduated compression stockings. Deep vein thromboses were diagnosed by isotope uptake in three of 56 patients (5.4 per cent) in the above-knee group and one of 58 patients (1.7 per cent) in the below-knee group. These differences are not statistically significant. Results suggest that below-knee stockings are as effective as above-knee in the prevention of postoperative deep vein thrombosis.

Prevention of venous thromboembolism in high risk patients.

Agnelli G, Sonaglia F Haematologica 1997 Jul;82(4):496-502 Istituto di Medicina Interna e Medicina Vascolare, Universita di Perugia, Italy. medvasc@unipg.it

BACKGROUND AND OBJECTIVE: Venous thromboembolism includes two closely related clinical manifestations: deep vein thrombosis (DVT), more commonly of the lower limbs, and pulmonary embolism. Pulmonary embolism is the most common cause of preventable death in hospitalized patients. The definition of the risk factors for venous thromboembolism should allow to adopt the most suitable prophylactic regimen. Determinants for the risk of venous thromboembolism are patient risk factors, both clinical and molecular, and the clinical setting. In this article the prophylactic regimens most widely employed in the prevention of venous thromboembolism in high-risk clinical settings will be reviewed. Then, the available guidelines for the management of thrombophilic patients will be given. INFORMATION SOURCES: The authors have been working in this field contributing original papers. In addition, the material examined in this review article includes papers published in the journals covered by the Science Citation Index and Medline. STATE OF ART AND PERSPECTIVES: Pharmacological prophylaxis is an effective approach for reducing morbidity and mortality from venous thromboembolism. Nevertheless, prophylaxis for venous thromboembolism is under employed because the incidence of venous thromboembolism is underestimated and there is fear of bleeding side effects. Adopting the proper prophylactic strategy for venous thromboembolism requires defining the patient risk factor. Determinants for the risk of venous thromboembolism are patient risk factors, both clinical and molecular, and the clinical setting. The risk connected with the clinical setting is the only risk defined by properly performed epidemiological studies. High-risk clinical settings are major orthopedic surgery, elective neurosurgery, spinal cord injury, cancer surgery and multiple trauma. The most effective anticoagulant regimens in the prevention of venous thromboembolism in high-risk patients are adjusted-dose unfractionated heparin, low molecular weight heparins (LMWHs) and oral anticoagulants. LMWHs are as effective and safe as the other two agents, but they do not require laboratory monitoring. On the other hand, LMWHs are more expensive than unfractionated heparin and warfarin. The use of effective agents still leaves the patients with a high prevalence of venous thromboembolism. Hence the search for more effective agents such as selective thrombin inhibitors like hirudin and its analogues. In patients undergoing elective hip surgery, hirudin has been recently shown to be more effective than low-dose unfractionated heparin and the LMWH enoxaparin.
Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature.

Department of Surgery, University Hospital, Uppsala, Sweden.

The purpose of this study was to quantify the risk of thromboembolic complications after laparoscopic cholecystectomy by a survey of the literature. We reviewed 60 laparoscopic cholecystectomy series consisting of 153,832 patients. The average mortality was 0.08%. The average rate of fatal pulmonary embolism was 0.02% and total pulmonary embolism 0.06%. The average rate of reported deep vein thrombosis was 0.03%. We conclude that laparoscopic cholecystectomy is a safe procedure, and the rate of clinically evident postoperative thromboembolic complications is probably lower than after conventional cholecystectomy. A lingering bias due to the overrepresentation of young and healthy patients early in the era of laparoscopic cholecystectomy could, however, still affect these figures. An underreporting of the lesser complications is likely. The risk is not negligible, though, and some authors have recommended thromboembolism prophylaxis, although further studies are necessary to find the optimal prophylaxis strategy. The true incidence is possible to establish only by using objective diagnostic methods for surveillance.

Trauma

Prevention of venous thromboembolism in trauma patients.

Knudson MM, Lewis FR, Clinton A, Atkinson K, Megerman J
J Trauma 1994 Sep;37(3):480-487
University of California, San Francisco.

Trauma patients are at risk for thromboembolic complications, but effective methods of prophylaxis have not been established for this heterogeneous population. In this prospective trial, 400 trauma patients were assigned to one of three groups, depending upon their injuries, and randomized within each group to a treatment mode: Group I: sequential gradient pneumatic leg compression (SCD), low-dose subcutaneous heparin (H), or control (C); Group II: H or C; Group III: SCD or C. Venous duplex ultrasound examinations were performed on admission and weekly thereafter. Of the 251 patients who completed the study, 15 (6%) developed lower extremity venous thrombosis and two additional patients developed pulmonary embolism (one fatal). Significant risk factors associated with the development of thromboembolism included immobilization > 3 days, age 30 years or older, and the presence of pelvic or lower extremity fractures. In patients with neurotrauma who cannot receive heparin (Group III), the SCD was more effective than control in preventing DVT (p = 0.057). Neither H nor SCD appeared to offer protection for the other groups of trauma patients, but surveillance with ultrasound examinations allowed for prompt recognition and treatment of occult deep vein thrombosis.
A prospective study of venous thromboembolism after major trauma.

Geerts WH, Code KI, Jay RM, Chen E, Szalai JP
Department of Medicine, Sunnybrook Health Science Centre, University of Toronto, ON, Canada.

BACKGROUND: Although deep-vein thrombosis and pulmonary embolism are considered common complications after major trauma, their frequency and the associated risk factors have not been carefully quantified. METHODS. We performed serial impedance plethysmography and lower-extremity contrast venography to detect deep-vein thrombosis in a cohort of 716 patients admitted to a regional trauma unit. Prophylaxis against thromboembolism was not used. RESULTS. Deep-vein thrombosis in the lower extremities was found in 201 of the 349 patients (58 percent) with adequate venographic studies, and proximal-vein thrombosis was found in 63 (18 percent). Three patients died of massive pulmonary embolism before venography could be performed. Before venography, only three of the patients with deep-vein thrombosis had clinical features suggestive of the condition. Deep-vein thrombosis was found in 65 of the 129 patients with major injuries involving the face, chest, or abdomen (50 percent); in 49 of the 91 patients with major head injuries (53.8 percent); in 41 of the 66 with spinal injuries (62 percent); and in 126 of the 182 with lower-extremity orthopedic injuries (69 percent). Thrombi were detected in 61 of the 100 patients with pelvic fractures (61 percent), in 59 of the 74 with femoral fractures (80 percent), and in 66 of the 86 with tibial fractures (77 percent). A multivariate analysis identified five independent risk factors for deep-vein thrombosis: older age (odds ratio, 1.05 per year of age; 95 percent confidence interval, 1.03 to 1.06), blood transfusion (odds ratio, 1.74; 95 percent confidence interval, 1.03 to 2.93), surgery (odds ratio, 2.30; 95 percent confidence interval, 1.08 to 4.89), fracture of the femur or tibia (odds ratio, 4.82; 95 percent confidence interval, 2.79 to 8.33), and spinal cord injury (odds ratio, 8.59; 95 percent confidence interval, 2.92 to 25.28). CONCLUSIONS. Venous thromboembolism is a common complication in patients with major trauma, and effective, safe prophylactic regimens are needed.

A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma.

Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA
N Engl J Med 1996 Sep 5;335(10):701-707
Department of Medicine, Sunnybrook Health Science Centre, University of Toronto, ON, Canada.

BACKGROUND: Patients who have had major trauma are at very high risk for venous thromboembolism if they do not receive thromboprophylaxis. We compared low-dose heparin and a low-molecular-weight heparin with regard to efficacy and safety in a randomized clinical trial in patients with trauma. METHODS: Consecutive adult patients admitted to a trauma center who had Injury Severity Scores of at least 9 and no intracranial bleeding were randomly assigned to heparin (5000 units) or enoxaparin (30 mg), each given subcutaneously every 12 hours in a double-blind manner, beginning within 36 hours after the injury. The primary outcome was deep-vein thrombosis as assessed by contrast venography performed on or before day 14 after randomization. RESULTS: Among 344 randomized patients, 136 who received heparin and 129 who received enoxaparin had venograms adequate for analysis. Sixty patients given heparin (44 percent) and 40 patients given enoxaparin (31 percent) had deep-vein thrombosis (P= 0.014). The rates of proximal-vein thrombosis were 15 percent and 6 percent, respectively (P= 0.012). The reductions in risk with enoxaparin as compared with heparin were 30 percent (95 percent confidence interval, 4 to 50 percent) for all deep-vein thrombosis and 58 percent (95 percent confidence interval, 12 to 87 percent) for proximal-vein thrombosis. Only six patients (1.7 percent) had major bleeding (one in the heparin group and five in the enoxaparin group, P= 0.12). Conclusions: Low-molecular-weight heparin was more effective than low-dose heparin in preventing venous thromboembolism after major trauma. Both interventions were safe.
Screening for major deep vein thrombosis in seriously injured patients: a prospective study.

The purpose of the study is to determine the prevalence of acute deep venous thrombosis (DVT) in severely injured trauma patients, to investigate the cost effectiveness of a noninvasive surveillance program, and to assess the merit of current methods of prophylaxis against DVT. One hundred and forty-eight patients (295 limbs) with a mean age of 36.5 years, mean trauma score of 13.3, mean injury severity score of 22.4 with predominantly blunt injuries (88.5%), were part of the study. The mean length of stay was 17.6 days. Venous duplex scans (VDS) were performed on inpatients on days 2-5, day 11, and day 30 following admission. Sequential compression device and/or subcutaneous heparin was used in 99% of patients with compliance being monitored by trauma nurse clinicians. A total of 272 VDS were performed with total charges of $111,520. DVT was found by VDS or venography in eight limbs (2.7%) of six patients (4%), our of the limbs being symptomatic. Two additional patients had pulmonary embolism, both with normal VDS. Routine serial VDS in severely injured patients who undergo aggressive prophylaxis against DVT is not cost effective and therefore not justified.

Spinal Cord Injury

Enoxaparin for thromboembolism prophylaxis in spinal injury: preliminary report on experience with 105 patients.

Venous thromboembolism continues to be a major cause of morbidity and mortality in patients with spinal injury (SI). Recently, we reported on the effectiveness and safety of a low molecular weight heparin (LMWH), tinzaparin, in preventing deep vein thrombosis in motor-complete SI patients. Recently, another LMWH, enoxaparin, was approved by the United States Food and Drug Administration for prevention of thromboembolism in hip and knee replacement surgery. Since its approval, we have used 30 mg of enoxaparin subcutaneously every 12 h as routine prophylaxis in all hospitalized SI patients. In this retrospective study, we present an analysis of safety and efficacy of the first six months experience, during which 105 patients received the drug. No patient developed clinical evidence of thromboembolism, and none of the 60 venous ultrasound examinations showed a deep vein thrombus. Eleven patients had evidence of hemorrhage, but the LMWH was considered to have contributed to the bleeding in only three. This additional experience with enoxaparin reinforces our previous conclusion that LMWHs are safe and effective thromboprophylactic agents in SI patients.

Etiology, incidence, and prevention of deep vein thrombosis in acute spinal cord injury.
Merli GJ, Crabbe S, Paluzzi RG, Fritz D Arch Phys Med Rehabil 1993 Nov;74(11):1199-1205 Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA 19107.

This article provides a critical review of the literature on the etiology, incidence, and prevention of deep-vein thrombosis in acute spinal cord injured patients. Stasis and hypercoagulability are the two major factors contributing to the development of thrombosis in this patient population. This has been supported by studies that demonstrate an impaired venous return from the lower extremities and abnormal coagulation factors, which predispose to thrombogenesis. The incidence of deep vein thrombosis secondary to the above etiologies varies from 49% to 100% in the first 12 weeks with the first 2 weeks having the highest rate following acute injury. This high rate of complication has led to numerous studies to identify the most effective regimens of prophylaxis. Studies
using noninvasive testing and venography in acute spinal cord injury have supported two approaches for preventing deep-vein thrombosis. Single agent pharmacologic therapy with adjusted dose heparin is effective but does carry some risk of bleeding. Combination therapy with external pneumatic compression sleeves plus either aspirin/dipyridamole or low-dose heparin and electrical stimulation plus low-dose heparin have significantly reduced the incidence of deep vein thrombosis. The duration of prophylaxis with the above modalities has varied between 8 and 12 weeks following acute injury. Further large scale studies are required in this high-risk population to better delineate the incidence of deep vein thrombosis and pulmonary embolism, to identify the best modalities, and to define the duration of treatment for the prevention of these complications.


Arch Phys Med Rehabil 1994 Mar;75(3):290-292
Department of Medicine, Northwestern Memorial Hospital, Northwestern University Medical School, Chicago, IL.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are major causes of morbidity and mortality in patients with acute spinal cord injury. Our preliminary studies indicated that low molecular weight heparin (LMWH) was significantly more effective than standard heparin in preventing these complications. We have now extended these studies by screening an additional 122 patients and treating 60 who met predefined criteria with LMWH in a dose of 3,500 anti-Xa U given subcutaneously once daily for 8 weeks. All patients were examined daily at bedside and had regularly scheduled venous ultrasonography; those with abnormalities had confirmatory venography and lung scans. Postmortem examinations were conducted in those who died. Forty completed the trial without incident; 6 had DVT (4 proximal and 2 distal), 1 had a fatal PE, 1 had postoperative bleeding requiring discontinuation of the LMWH, 10 were transferred or discharged, and 2 died of respiratory failure. The percentage of patients free of thrombosis or bleeding after 8 weeks of treatment was 85.9 +/- 5.0% standard error of mean (SEM). Thirty-three patients entered a follow-up observation period of 4 weeks without thromboprophylaxis; 2 weeks into this period 1 had a proximal DVT and 1 had a fatal PE; the course of the remainder was uneventful. We conclude that LMWH compares favorably with standard heparin in preventing venous thromboembolism, and is associated with significantly less bleeding. Eight weeks of prophylaxis seems adequate for most patients.

Practice Guidelines and Outcome Studies

Implementation of guidelines for prevention of deep vein thrombosis in a managed care environment.

Brox WT
Orthopedics 1996 Aug;19 Suppl:12-14

Implementation strategies are key factors in determining the overall success of clinical guidelines. They are important for changing physician practices and expected to result in clinical improvement or cost savings. Within an organization, the method of implementation should be a major component of the development of the guideline itself. In a group practice system, clinical guidelines must be clear and provide numeric thresholds or explicit criteria for decision points and subsequent action. Assessing the overall impact of a clinical practice guideline provides excellent feedback in determining whether goals are being met and provides guidance for fine-tuning strategic approaches. With regard to the prevention of deep vein thrombosis (DVT) monitoring, the overall results of a clinical practice guideline would assess guideline compliance, complications of the guideline interventions, as well as the incidence of DVT, pulmonary embolism, hospital readmissions, and mortality.
Physician practices in the prevention of deep vein thrombosis: the MassPRO DVT Study.

Anderson FA Jr, Audet AM
Orthopedics 1996 Aug;19 Suppl:9-11

Numerous well-designed clinical trials have demonstrated that prophylaxis reduces the incidence of acute deep vein thrombosis (DVT) in high-risk surgical patients by two-thirds, with a corresponding reduction in mortality from pulmonary embolism. However, studies of clinical practices suggest that DVT prophylaxis is underused—for example, only 39% of high-risk surgical patients in 16 central Massachusetts hospitals were administered DVT prophylaxis in 1986. Subsequently, an intensive educational initiative was launched to improve utilization of DVT prophylaxis. Although some improvement was reported, the level of use was not optimal. The Massachusetts Peer Review Organization (MassPRO) DVT study was designed to gather data on recent practice patterns among Massachusetts surgeons and determine the need for additional educational and quality assurance efforts. The results indicate that there is broad compliance among orthopedic surgeons with consensus recommendations for the use of DVT prophylaxis. Nearly all patients who undergo total hip replacement in Massachusetts are protected from DVT by one or more methods of prophylaxis. These data suggest that the ongoing efforts to improve the use of DVT prophylaxis in Massachusetts since 1986 have come to fruition, at least with respect to total hip replacement.

Optimizing the flow of care for prevention and treatment of deep vein thrombosis and pulmonary embolism.

Ecklund MM

Critically ill patients have multiple risk factors for deep vein thrombosis and pulmonary embolism. The majority of patients with pulmonary embolism have a lower extremity deep vein thrombosis as a source of origin. Pulmonary embolism causes a high mortality rate in the hemodynamically compromised individual. Awareness of risk factors relative to the development of deep vein thrombosis and pulmonary embolism is important for the critical care nurse. Understanding the pathophysiology can help guide prophylaxis and treatment plans. The therapies, from invasive to mechanical, all carry risks and benefits, and are weighed for each patient. The advanced practice nurse, whether in the direct or indirect role, has an opportunity to impact the care of the high risk patient. Options range from teaching the nurse who is new to critical care, to teaching patients and families. Development of multidisciplinary protocols and clinical pathways are ways to impact the standard of care. Improved delivery of care methods can optimize the care rendered in an ever changing field of critical care.

Nursing care for the prevention of deep vein thrombosis.

Morris BA
Today's OR Nurse 1995 Sep;17(5):4-8

1. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are major health problems that often result in significant postsurgical morbidity and mortality. 2. To prevent DVT, patient care includes graduated compression stockings or the use of a pneumatic compression device, and administration of the correct dose of anticoagulation agent (heparin or LMWH). 3. Taken together, the various drug therapies and physical interventions can clearly prevent DVT. Careful evaluation of the patient’s risk factors, along with a monitored postoperative therapy can minimize the morbidity and mortality of this “unseen” condition.
**Cardiovascular Surgery**

**Prevention of venous thrombosis after coronary artery bypass surgery (a randomized trial comparing two mechanical prophylaxis strategies).**

Goldhaber SZ, Hirsch DR, MacDougall RC, Polak JF, Creager MA, Cohn LH
Am J Cardiol 1995 Nov 15;76(14):993-996
Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Although venous thrombosis may occur often after coronary artery bypass grafting, prophylaxis with low-dose heparin is rarely used due to the risk of bleeding. Therefore, we compared the efficacy of 2 mechanical regimens of prophylaxis against deep vein thrombosis (DVT). Consecutive patients undergoing coronary artery bypass without concomitant valve surgery or coronary endarterectomy were randomized to either a more intensive regimen of intermittent pneumatic compression (IPC) plus graduated compression stockings (GCS) versus standard compression stockings alone. Of 611 patients screened, 184 were excluded due to peripheral vascular disease, postoperative intraaortic balloon support, or immediate postoperative anticoagulation. An additional 83 patients refused consent, leaving 172 in each prophylaxis group. The primary study end point was DVT diagnosed by a predischarge leg ultrasound examination performed on postoperative days 4 to 6. Of 344 patients enrolled, 330 (96%) underwent predischarge ultrasonography. DVT was detected in 19% of patients assigned to IPC plus stockings versus 22% assigned to GCS alone (95% confidence interval for the difference, -11% to 6%, p = 0.62). The addition of IPC did not add significant incremental benefit to GCS alone for DVT prophylaxis among patients undergoing coronary artery bypass surgery.

**A randomised controlled trial of a low-molecular-weight heparin (Enoxaparin) to prevent deep vein thrombosis in patients undergoing vascular surgery.**

Farkas JC, Chapuis C, Combe S, Silsiguen M, Marzelle J, Laurian C, Cormier JM

The incidence of postoperative deep vein thrombosis (PDVT) after aortic surgery and lower limb revascularisation has not been assessed by a large prospective study. In a prospective randomised trial the effect of a low-molecular-weight heparin fragment, Enoxaparin (ENX) 4200 anti factor Xa IU once daily was compared to that of unfractionated heparin (UFH) 7500 IU twice daily. Two hundred and thirty-three consecutive patients were classified into three groups, aortic or aortoiliac and aneurysmectomy (n = 75), aorto-femoral bypass for atherosclerotic disease (n = 71), and femoropopliteal or femorodistal bypass (n = 87). Patients were analysed for development of deep vein thrombosis by Duplex scanning and, if positive, by venography between the seventh and tenth postoperative day. PDVT was present in 10 patients in the ENX group and in four patients in the UFH group (8.2 and 3.6% respectively, NS). The incidence of PDVT was 8% after aortic or aortoiliac aneurysmectomy, 7% after aortofemoral revascularisation, and 3.4% after femoropopliteal or femorodistal bypass. The overall incidence of PDVT after aortic surgery was 7.5% (95% CI 5.4-9.7). There was no pulmonary embolism. Intraoperative blood loss and postoperative bleeding events did not differ significantly between the ENX and UFH groups. After 1 month follow-up, no clinical event or death could be related to PDVT or pulmonary embolism. In conclusion, in vascular surgery ENX is as safe and effective in the prevention of PDVT as is UFH.
Medical Patients

Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer.

Lancet 1994 Apr 9;343(8902):886-889
Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Patients receiving chemotherapy for metastatic breast cancer are at high risk of thromboembolic disease. Long-term oral anticoagulant therapy is needed but increases the risk of haemorrhagic complications. We have assessed the safety and efficacy of warfarin in very low doses as prophylaxis. Women receiving chemotherapy for metastatic breast cancer were randomly assigned either very-low-dose warfarin (152 patients) or placebo (159). The warfarin dose was 1 mg daily for 6 weeks and was then adjusted to maintain the prothrombin time at an international normalised ratio (INR) of 1.3 to 1.9. Study treatment continued until 1 week after the end of chemotherapy. The average daily dose from initiation of titration was 2.6 (SD 1.2) mg for the warfarin group and the mean INR was 1.52. The mean time at risk of thrombosis was 199 (126) days for warfarin-treated patients and 188 (137) days for placebo recipients (p = 0.45). There were 7 thromboembolic events (6 deep-vein thrombosis, 1 pulmonary embolism) in the placebo group and 1 (pulmonary embolism) in the warfarin group, a relative risk reduction of about 85% (p = 0.031). Major bleeding occurred in 2 placebo recipients and 1 warfarin-treated patient. There was no detectable difference in survival between the treatment groups. Very-low-dose warfarin is a safe and effective method for prevention of thromboembolism in patients with metastatic breast cancer who are receiving chemotherapy.


Harenberg J, Roebruck P, Heene DL
Haemostasis 1996 May;26(3):127-139
1st Department of Medicine, Faculty for Clinical Medicine Mannheim, University of Heidelberg, Germany.

In a multicenter, double-blind clinical trial in 1,968 inpatients 1 daily subcutaneous administration of LMW heparin plus 2 placebo injections or 3 x 5,000 IU unfractionated (UF) heparin was given for 10 (8-11) days. The primary end point was the incidence of proximal deep-vein thrombosis or pulmonary embolism. Patients were assessed during the study period for development of proximal deep-vein thrombosis by compression sonography at days 1 and 10 and for pulmonary embolism by scintigraphy in symptomatic patients. Aim of the study was to demonstrate the equivalence of both treatment regimens. A total of 1,968 patients were randomized to receive UF or LMW heparin. Of these, 378 patients were excluded during the study period, so that 780 patients on UF and 810 on LMW heparin were included in the efficacy analysis. Four primary end points were observed with UF and 6 with LMW heparin, demonstrating the equivalence of treatments (p = 0.012). Additionally, pulmonary embolism was suspected as the cause of death in 6 patients who died during the study (3 per treatment group). A higher frequency of death (n = 32) was observed in the LMW-heparin group (p = 0.02) particularly documented in a part of the centers. Safety analysis showed a higher frequency of local pruritus, local erythema and subcutaneous hematoma, a higher increase in plasma levels of triglycerides, total cholesterol, alanine aminotransferase and aspartate aminotransferase, and a decrease of antithrombin III in patients receiving UF heparin. A decrease in platelet count (values ranging between 40,000 and 80,000/microliter) was observed in 4 patients with UF and in none with LMW heparin. No severe thrombocytopenia was observed. Subcutaneous LMW heparin is as effective as UF heparin for prophylaxis of thromboembolism in bedridden, hospitalized medical patients.
Prevalence of deep venous thrombosis among patients in medical intensive care.

Hirsch DR, Ingenito EP, Goldhaber SZ
JAMA 1995 Jul 26;274(4):335-337
Department of Medicine, Brigham and Women’s Hospital, Boston, MA

OBJECTIVE—To determine the frequency of deep venous thrombosis (DVT) in medical intensive care unit (MICU) patients. DESIGN—Prospective ultrasound case series. SETTING—An MICU in a large tertiary care hospital in Boston, Mass. SUBJECTS—Patients older than 18 years of age admitted to the MICU with an anticipated stay of more than 48 hours. MAIN OUTCOME MEASURE—Deep venous thrombosis as detected by ultrasonography with color Doppler imaging performed twice weekly in the MICU and once within 1 week of discharge from the MICU. RESULTS—Deep venous thrombosis was detected in 33% (95% confidence interval, 24% to 43%) of 100 eligible patients during the 8-month study period. Forty-eight percent (16/33) were proximal lower extremity DVT, and 15% (5/33) were upper extremity DVT associated with central venous catheters, with one patient having both upper and proximal lower extremity DVT. Ultrasound examination results led to inferior vena cava filter placement in three patients, initiation of full-dose anticoagulation in four patients, initiation or continuation of low-dose subcutaneous heparin in 10 patients, follow-up ultrasound studies in three patients, central line removal in one patient, and no intervention in 10 patients due to active bleeding, prior filter, or heparin-induced thrombocytopenia. Two patients remained anticoagulated for other reasons. In this series, there was no difference in age, gender, body mass index, diagnosis of cancer, recent surgery, duration of hospitalization prior to DVT detection, and DVT prophylaxis between patients with DVT and those without. CONCLUSIONS—An unexpectedly high rate of DVT was detected by ultrasound in these MICU patients despite prophylaxis in 61%. Traditionally recognized DVT risk factors failed to identify patients who developed DVT. Routine ultrasound surveillance or more intensive prophylaxis regimens may be warranted in this patient population if these DVT rates are confirmed in other settings.

Neurosurgery

Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery.

Thromb Haemost 1996 Feb;75(2):233-238
Center for Hemostasis, Thrombosis, Atherosclerosis and Inflammation Research, Academic Medical Center, Amsterdam.

Perioperative anticoagulant prophylaxis for postoperative venous thromboembolism (VTE) in neurosurgical patients has not gained wide acceptance due to the fear of intracranial bleeding. Physical methods give a worthwhile reduction of postoperative VTE but there still remains a substantial residual incidence. In other clinical indications, low molecular weight heparins have proven to be effective for prophylaxis of VTE when administered postoperatively, with the advantage of no bleeding enhancement during surgery. Therefore, we performed a multicentre, randomized, double-blind trial in neurosurgical patients to investigate the efficacy and safety of adding a low molecular weight heparin (LMWH), nadroparin, initiated postoperatively, to graduated compression stockings in the prevention of VTE. Deep-vein thrombosis was detected by mandatory venography. Bleeding was determined according to pre-defined objective criteria for major and minor episodes. An adequate bilateral venogram was obtained in 166 of 241 LMWH patients (68.9%) and 179 of 244 control patients (73.4%). A total of 31 of 166 LMWH patients (18.7%) and 47 of 179 controls patients (26.3) had VTE up to Day 10 postoperatively (p = 0.047). The relative risk reduction (RRR) was 28.9%. The rates for proximal deep-vein thrombosis/pulmonary embolism were 6.9% and 11.5% for the two groups, respectively (RRR: 40.2%; p = 0.065). Secondary analyses involved all VTE up to day 56 post-surgery which was detected in 33 patients of 241 in the LMWH group (13.7%) and 51 of 244 control patients (20.9%; RRR 34.5%; p = 0.018). The corresponding percentages
for proximal deep-vein thrombosis/pulmonary embolism were 5.8% and 10.2% for the two groups, respectively, giving a RRR of 43.3%; p = 0.36. Major bleeding complications, during the treatment period, occurred in six low molecular weight heparin treated patients (2.5%) and in two control patients (0.8%); p = 0.87. A higher mortality was observed in the low molecular weight heparin group over the 56-day follow-up period (22 versus 10; p = 0.026). However, none of these deaths was judged by a blinded adjudication committee to be related to the study drug. In conclusion, this study demonstrates that the low molecular weight heparin, nadroparin, added to graduated compression stockings results in a clinically significant decrease in VTE without inducing any significant increase of major bleeding.

**Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control.**

Turpie AG, Hirsh J, Gent M, Julian D, Johnson J
Arch Intern Med 1989 Mar;149(3):679-681
Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

In a randomized trial of neurosurgical patients, groups wearing graduated compression stockings alone (group 1) or graduated compression stockings plus intermittent pneumatic compression (IPC) (group 2) were compared with an untreated control group in the prevention of deep vein thrombosis (DVT). In both active treatment groups, the graduated compression stockings were continued for 14 days or until hospital discharge, if earlier. In group 2, IPC was continued for seven days. All patients underwent DVT surveillance with iodine 125-labeled fibrinogen leg scanning and impedance plethysmography. Venography was carried out if either test became abnormal. Deep vein thrombosis occurred in seven (8.8%) of 80 patients in group 1, in seven (9.0%) of 78 patients in group 2, and in 16 (19.8%) of 81 patients in the control group. The observed differences among these rates are statistically significant. The results of this study indicate that graduated compression stockings alone or in combination with IPC are effective methods of preventing DVT in neurosurgical patients.

**Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study.**


A prospective study of a series of 77 patients on adjuvant radiochemotherapy following surgery for high-grade gliomas was conducted to evaluate the risk of deep vein thrombosis and identify risk factors. We found a 20.8% risk of deep vein thrombosis at 12 months (standard error = 4.8%) and a 31.7% risk (standard error = 7.4%) at 24 months (Kaplan-Meier method). Twenty patients (26%) developed deep vein thrombosis with a maximum incidence within the first 7 months after surgery when chemotherapy was still being administered, often with corticosteroids. The risk factors identified were histology (glioblastoma versus anaplastic astrocytoma, P = 0.032, log rank test; 0.0485 L-ratio) and the presence of paresis (P = 0.010, log rank test; 0.0161 L-ratio). A borderline tendency was found for an association between the deep vein thrombosis site and the side of paresis (P = 0.103, Fisher’s exact test). Four patients (5%) had massive pulmonary embolism, which was fatal in 3 (4%).
Prophylaxis of venous thromboembolism in stroke patients.

Turpie AG Semin Thromb Hemost 1997;23(2):155-157 Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

Venous thromboembolism is a common complication in patients with acute thrombotic stroke. Estimates of the frequency of deep vein thrombosis (DVT) in untreated patients range from 20 to 75%. This wide range reported depends on the methods used to detect DVT and, importantly, on the degree of lower limb paralysis. Most thrombi occur in the paralyzed limbs in which the frequency ranges from 60 to 75%. Of these thrombi, 25% occur in the proximal segment and present a high risk for pulmonary embolism. Indeed, pulmonary embolism is the third most common cause of death in stroke patients and occurs in 1 to 2% of patients who do not receive prophylaxis. A number of methods of preventing DVT have been shown to be safe and effective in stroke patients. These include low-dose heparin, low-molecular-weight heparin, and a heparinoid. Of these, the data with the heparinoid danaparoid provide the most solid evidence for efficacy, and in comparative trials it has been shown to be more effective than heparin.


Ann Intern Med 1992 Sep 1;117(5):353-357
McMaster University, Hamilton, Ontario, Canada.

OBJECTIVE: To compare the relative safety and efficacy of a low-molecular-weight heparinoid (ORG 10172) with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke. DESIGN: Double-blind randomized trial. SETTING: Seven Canadian university-affiliated hospitals. PARTICIPANTS: Eighty-seven patients with acute ischemic stroke resulting in lower-limb paresis. INTERVENTION: Patients received either low-molecular-weight heparinoid, 750 anti-factor Xa units twice daily, or unfractionated heparin, 5000 units subcutaneously twice daily. Treatment was continued for 14 days or until hospital discharge if sooner. MEASUREMENTS: Deep vein thrombosis was diagnosed using 125I-labeled fibrinogen leg scanning and impedance plethysmography. Venography was indicated if either test was positive. Overt hemorrhage, major or minor, was assessed clinically. RESULTS: Venous thrombosis occurred in four patients (9%) given low-molecular-weight heparinoid and in 13 patients (31%) given heparin (relative risk reduction, 71%; 95% CI, 16% to 93%). The corresponding rates for proximal vein thrombosis were 4% and 12%, respectively (relative risk reduction, 63%; P greater than 0.2). The incidence of hemorrhage was 2% in both groups. CONCLUSION: Low-molecular-weight heparinoid, given in a fixed dose of 750 anti-factor Xa units subcutaneously twice daily, is more effective than subcutaneous low-dose heparin for the prevention of deep vein thrombosis in patients with acute ischemic stroke.

A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke.

Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U
Semin Thromb Hemost 1990 Oct;16 Suppl:25-33
Department of Medicine, Aker University Hospital, Oslo, Norway.

The effect of LMW heparin (Kabi 2165, Fragmin) was compared with placebo for the prevention of DVT in 103 patients with acute ischemic stroke using a prospective, double-blind, randomized trial design. Treatment was started within 72 hours, and LMW heparin was administered subcutaneously once daily according to body weight classes, which corresponded to about 55 to 65 Factor-Xa inhibitory U/kg, for 14 days, or until discharge...
Deep vein thrombosis: prevention in stroke patients during rehabilitation.

Pambianco G, Orchard T, Landau P
Department of Epidemiology, University of Pittsburgh, PA

Deep vein thrombosis (DVT) and subsequent pulmonary embolism (PE) is a major source of mortality and morbidity in stroke patients. This study was designed to determine the effectiveness of different prophylactic treatments in the prevention of DVT after a stroke in patients undergoing rehabilitation. An additional objective was the identification of risk factors for DVT in stroke patients during rehabilitation. Three hundred and sixty patients, over a 3-year period, were randomly assigned to one of four groups: adjusted dose heparin, intermittent pneumatic compression (IPC), functional electrical stimulation (FES), or control. There was no significant difference in the development of DVT by treatment group. Patients with DVT on admission (prevalent, n = 61) were compared with the study patients (n = 360). Time interval (from stroke to admission) and lactic dehydrogenase (LDH) concentration were significant risk factors, as well as predictors, for development of DVT (p < .000). These results suggest that the longer a patient remains without DVT prophylaxis after a stroke, the greater the risk of developing DVT and this supports early prophylaxis before rehabilitation.

Obstetrics and Gynecology

Prevention of venous thromboembolism in gynecologic surgery patients.

Clarke-Pearson DL
Department of Obstetrics and Gynecology, Duke University Medical Center

To reduce the morbidity and mortality of postoperative deep vein thrombosis and pulmonary embolism, effective prophylactic methods must be used. An assessment of the individual patient’s risk is essential in deciding the most appropriate method. In general, women over 40 years of age and all women with other risk factors benefit from some form of prophylaxis. For patients with benign gynecologic conditions, low-dose heparin (every 12 hours) and perioperative intermittent pneumatic calf compression have been shown to be of benefit. Patients at higher risk, such as gynecologic oncology patients, should receive more intense prophylaxis with either low-dose heparin (every 8 hours) or prolonged (5 days) intermittent pneumatic calf compression. Of the two methods, the latter has no significant complications and is therefore our method of choice.
Low molecular weight heparins and their use in obstetrics and gynecology.

Fejin MD, Lourwood DL

A low molecular weight (LMW) heparin, has recently been approved for clinical use in the prevention of deep vein thrombosis in patients undergoing hip surgery. This product is enoxaprin (Lovenox, Rhone-Poulenc Rorer Pharmaceuticals, Paris, France). The purpose of this review is to examine the possible use of LMW heparin in obstetrics and gynecology. LMW heparins are fragments of standard heparin and show a similar anticoagulant effect. The risk of bleeding complications and thrombocytopenia is reduced with the use of these agents. This may be due to their lesser effects on factor II and platelet factor 4. The enhanced bioavailability of these drugs, in conjunction with their prolonged half-life, makes subcutaneous therapy, in one to two daily doses, possible. A review of the published experience of the utilization of LMW heparins in Obstetrics and Gynecology revealed that 1) LMW heparins are effective and safe in the prevention of thromboembolic complications in gynecologic surgery. 2) LMW heparins do not cross the placenta in any trimester. 3) There is no evidence of any mutagenic and teratogenic effect of these drugs. 4) The clinical experience, although limited, suggests their safety and effectiveness in thromboprophylaxis and treatment during pregnancy.

Activated protein C resistance (factor V Leiden) associated with thrombosis in pregnancy.


OBJECTIVE: Our purpose was to evaluate activated protein C resistance phenotype and genotype among patients with thrombosis during pregnancy and the puerperium. STUDY DESIGN: This observational study was conducted prospectively during a 2-year period (July 1993 to June 1995) in a preselected population. All patients admitted to our high-risk pregnancy unit with a diagnosis of deep vein thrombosis, pulmonary emboli, transient ischemic attack, and cerebrovascular accident during pregnancy and the puerperium were included. Prothrombin time, partial thromboplastin time, fibrinogen levels, protein C, protein S, antithrombin III, functional test for activated protein C resistance, and factor V Leiden mutation by polymerase chain reaction were performed on each patient. RESULTS: Fifteen patients were included. Seven (46.6%) patients were positive for activated protein C resistance (factor V Leiden). All other coagulation studies were negative for all patients. All patients with activated protein C resistance had a venous thrombotic event, deep vein thrombosis, or pulmonary emboli, and only one had a cerebrovascular accident on the basis of sagittal sinus thrombosis. Only two of the activated protein C resistance-negative patients had venous thrombosis (pulmonary emboli). The remaining six patients had transient ischemic attacks or cerebrovascular accidents. For the subgroup with venous thrombosis during pregnancy and the puerperium, the incidence of activated protein C resistance (factor V Leiden) was 78%. CONCLUSION: This study demonstrates the incidence of factor V Leiden in a selected population in whom thrombotic events developed during pregnancy and the puerperium. This small-scale study provides justification for a large cohort study that will identify women with factor V Leiden and determine their risk for thrombosis during pregnancy and the puerperium. We believe that factor V Leiden should be evaluated in conjunction with thrombotic events in the pregnant woman.
Duration of Prophylaxis

Prolonged prophylaxis in postoperative medicine.

Bergqvist D Semin Thromb Hemost 1997;23(2):149-154
University Hospital, Department of Surgery, Uppsala, Sweden.

Major surgical procedures, especially orthopedic surgeries, such as elective hip or knee replacement, are associated with a high incidence of postoperative deep vein thrombosis (DVT) and potentially fatal pulmonary embolism (PE). Although most surgeons exercise thromboprophylaxis, the length of time of prophylactic measures is at this time uncertain. With increasing shortening of in-hospital stays and thus shorter times of prophylaxis, increasing numbers of “late” PE are being recognized. These observations have raised the issue of postdischarge continuation of prophylaxis. This problem was recently addressed by four studies involving hip arthroplasty patients. In all trials prophylaxis was performed with low-molecular-weight heparins (LMWH). Two studies used enoxaparin, two used dalteparin. Duration of in-hospital treatment lasted from 7 to 15 days. The length of postdischarge prophylaxis ranged from 21 to 28 days. DVT was diagnosed by bilateral venography. In all instances there was a significant reduction in DVT in the treated patient group, compared with those who were not treated after discharge. It is assumed that this reduction also impacts the frequency of potentially fatal PE. The trials suggest that thrombosis prophylaxis should be continued in patients following discharge from hospital after major surgical procedures, especially when risk factors persist.

The post-hospital discharge venous thrombosis risk of the orthopedic patient.

Planes A, Vochelle N
Orthopedics 1997 Feb;20 Suppl:18-21
Clinique Radio-Chirurgicale du Mail, La Rochelle, France.

A prospective, randomized, double-blind trial was performed in total hip replacement patients to document the risk of deep vein thrombosis (DVT) after hospital discharge, and to assess the efficacy of sustained antithrombotic prophylaxis. In a total of 179 patients receiving enoxaparin 40 mg/day during hospitalization, those without venogram-proven DVT at discharge were randomly assigned to continue prophylaxis with enoxaparin (N = 90) or receive placebo (N = 89). At the end of 21 days’ treatment, intention-to-treat analysis in 173 evaluable patients demonstrated a significantly lower incidence (P = 0.018) of DVT in the enoxaparin group (7.1%; N = 6) compared with the placebo group (19.3%; N = 17). These findings were confirmed by perprotocol analysis in 155 patients. Minor bleeding episodes occurred in three patients in the enoxaparin group and one in the placebo group. Thus, total hip replacement patients have a significant risk of developing DVT after hospital discharge. Continued prophylaxis with enoxaparin is effective in reducing this risk.

Treatment of DVT

Subcutaneous heparin compared with continuous intravenous heparin administration in the initial treatment of deep vein thrombosis. A meta-analysis.

Hommes DW, Bura A, Mazzolai L, Buller HR, ten Cate JW
Academic Medical Center, Amsterdam, The Netherlands.

OBJECTIVE: To quantitatively assess the efficacy and safety of published randomized trials comparing subcutaneous heparin with continuous intravenous heparin for the initial treatment of deep vein thrombosis. DATA IDENTIFICATION: Studies published between January 1986 and April 1991 were identified through computer searches of the MEDLINE database and through reviews of the Science Citation Index, Current Contents, proceedings and abstract books, and references cited in the identified articles. Complete manuscripts were obtained from the authors if only abstracts were available. STUDY SELECTION: Eight clinical trials were identified that compared subcutaneous with intravenous
heparin administration in patients with venographically confirmed deep vein thrombosis. DATA EXTRACTION: Each study was independently analyzed for the percentage distribution of thrombosis, the method of outcome measurement, and the heparin dose. The methodologic strength of each study was assessed using predefined standards for the proper evaluation of a therapeutic intervention with particular emphasis on the type of patient allocation and objective measurements. RESULTS OF DATA ANALYSIS: The overall relative risk for efficacy (defined as prevention of extension and recurrence of venous thromboembolism) of subcutaneous compared with intravenous heparin treatment was 0.62 (95% CI, 0.39 to 0.98), whereas for safety (defined as major hemorrhage) it was 0.79 (CI, 0.42 to 1.48). CONCLUSIONS: The results of our meta-analysis indicated that heparin administered subcutaneously twice daily in the initial treatment of deep vein thrombosis is more effective and at least as safe as continuous intravenous heparin administration. Administration of heparin subcutaneously may simplify patient treatment and could facilitate home treatment.

Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis.

Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, Lerner RG, Hall J, Sparling T, Brettell HR, et al
Division of General Internal Medicine, University of Calgary, Alberta,

BACKGROUND. Low-molecular-weight heparin has a high bioavailability and a prolonged half-life in comparison with conventional unfractionated heparin. Limited data are available for low-molecular-weight heparin as compared with unfractionated heparin for the treatment of deep-vein thrombosis. METHODS. In a multicenter, double-blind clinical trial, we compared fixed-dose subcutaneous low-molecular-weight heparin given once daily with adjusted-dose intravenous heparin given by continuous infusion for the initial treatment of patients with proximal-vein thrombosis, using objective documentation of clinical outcomes. RESULTS. Six of 213 patients who received low-molecular-weight heparin (2.8 percent) and 15 of 219 patients who received intravenous heparin (6.9 percent) had new episodes of venous thromboembolism (P = 0.07; 95 percent confidence interval for the difference, 0.02 percent to 8.1 percent). Major bleeding associated with initial therapy occurred in 1 patient receiving low-molecular-weight heparin (0.5 percent) and in 11 patients receiving intravenous heparin (5.0 percent), a reduction in risk of 91 percent (P = 0.006). This apparent protection against major bleeding was lost during long-term therapy. Minor hemorrhagic complications were infrequent. Ten patients receiving low-molecular-weight heparin (4.7 percent) died, as compared with 21 patients receiving intravenous heparin (9.6 percent), a risk reduction of 51 percent (P = 0.049). CONCLUSIONS. Low-molecular-weight heparin is at least as effective and as safe as classic intravenous heparin therapy under the conditions of this study and more convenient to administer. The simplified therapy provided by low-molecular-weight heparin may allow patients with uncomplicated proximal deep-vein thrombosis to be cared for in an outpatient setting.

A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis.

McMaster University, Hamilton, Ont., Canada.

BACKGROUND. Patients with acute proximal deep-vein thrombosis are usually treated first in the hospital with intravenous standard (unfractionated) heparin. However, the longer plasma half-life, better bioavailability after subcutaneous administration, and more predictable anticoagulant response of low-molecular-weight heparins make them attractive for possible home use. We compared these two approaches. METHODS. Patients with
acute proximal deep-vein thrombosis were randomly assigned to receive either intravenous standard heparin in the hospital (253 patients) or low-molecular-weight heparin (1 mg of enoxaparin per kilogram of body weight subcutaneously twice daily) administered primarily at home (247 patients). The study design allowed outpatients taking low-molecular-weight heparin to go home immediately and hospitalized patients taking low-molecular-weight heparin to be discharged early. All the patients received warfarin starting on the second day.

RESULTS. Thirteen of the 247 patients receiving low-molecular-weight heparin (5.3 percent) had recurrent thromboembolism, as compared with 17 of the 253 patients receiving standard heparin (6.7 percent; P=0.57; absolute difference, 1.4 percentage points; 95 percent confidence interval, -3.0 to 5.7). Five patients receiving low-molecular-weight heparin had major bleeding, as compared with three patients receiving standard heparin. After randomization, the patients who received low-molecular-weight heparin spent a mean of 1.1 days in the hospital, as compared with 6.5 days for the standard-heparin group; 120 patients in the low-molecular-weight- heparin group did not need to be hospitalized at all.

CONCLUSIONS. Low-molecular-weight heparin can be used safely and effectively to treat patients with proximal deep-vein thrombosis at home.

Treatment of Venous Thrombosis with Intravenous Unfractionated Heparin Administered in the Hospital as Compared with Subcutaneous Low-Molecular-Weight Heparin Administered at Home.

Academic Medical Center, University of Amsterdam.

Background: An intravenous course of standard (unfractionated) heparin with the dose adjusted to prolong the activated partial-thromboplastin time to a desired length is the standard initial in-hospital treatment for patients with deep-vein thrombosis, but fixed-dose subcutaneous low-molecular-weight heparin appears to be as effective and safe. Because the latter treatment can be given on an outpatient basis, we compared the two treatments in symptomatic outpatients with proximal-vein thrombosis but no signs of pulmonary embolism. Methods: We randomly assigned patients to adjusted-dose intravenous standard heparin administered in the hospital (198 patients) or fixed-dose subcutaneous low-molecular-weight heparin administered at home, when feasible (202 patients). We compared the treatments with respect to recurrent venous thromboembolism, major bleeding, quality of life, and costs. Results: Seventeen of the 198 patients who received standard heparin (8.6 percent) and 14 of the 202 patients who received low-molecular-weight heparin (6.9 percent) had recurrent thromboembolism (difference, 1.7 percentage points; 95 percent confidence interval, -3.6 to 6.9). Major bleeding occurred in four patients assigned to standard heparin (2.0 percent) and one patient assigned to low-molecular-weight heparin (0.5 percent; difference, 1.5 percentage points; 95 percent confidence interval, -0.7 to 2.7). Quality of life improved in both groups. Physical activity and social functioning were better in the patients assigned to low-molecular-weight heparin. Among the patients in that group, 36 percent were never admitted to the hospital at all, and 40 percent were discharged early. This treatment was associated with a mean reduction in hospital days of 67 percent, ranging from 29 percent to 86 percent in the various study centers. Conclusions: In patients with proximal-vein thrombosis, treatment with low-molecular-weight heparin at home is feasible, effective, and safe.
A Clinical Trial of Vena Caval Filters in the Prevention of Pulmonary Embolism in Patients with Proximal Deep-Vein Thrombosis.


Background: The efficacy and safety of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis are still a matter of debate.

Methods: Using a two-by-two factorial design, we randomly assigned 400 patients with proximal deep-vein thrombosis who were at risk for pulmonary embolism to receive a vena caval filter (200 patients) or no filter (200 patients), and to receive low-molecular-weight heparin (enoxaparin, 195 patients) or unfractionated heparin (205 patients). The rates of recurrent venous thromboembolism, death, and major bleeding were analyzed at day 12 and at two years.

Results: At day 12, two patients assigned to receive filters (1.1 percent), as compared with nine patients assigned to receive no filters (4.8 percent), had had symptomatic or asymptomatic pulmonary embolism (odds ratio, 0.22; 95 percent confidence interval, 0.05 to 0.90). At two years, 37 patients assigned to the filter group (20.8 percent), as compared with 21 patients assigned to the no-filter group (11.6 percent), had had recurrent deep-vein thrombosis (odds ratio, 1.87; 95 percent confidence interval, 1.10 to 3.20). There were no significant differences in mortality or the other outcomes.

Conclusions: In high-risk patients with proximal deep-vein thrombosis, the initial beneficial effect of vena caval filters for the prevention of pulmonary embolism was counterbalanced by an excess of recurrent deep-vein thrombosis, without any difference in mortality. Our data also confirmed that low-molecular-weight heparin was as effective and safe as unfractionated heparin for the prevention of pulmonary embolism.

The effect of mobilisation of patients during treatment of thromboembolic disorders with low-molecular-weight heparin.


OBJECTIVE: To elucidate the risk of pulmonary embolism (PE) in patients with deep vein thrombosis (DVT) who are kept walking with compression bandages.

EXPERIMENTAL DESIGN: Perfusion/ventilation scanning of the lungs was performed at admission and after 10 days of treatment.

SETTING: General community hospital.

PATIENTS: A total of 631 consecutive patients were studied (upper limit of the thrombi: iliofemoral vein, n=212; femoral or popliteal vein, n=302; lower leg, n=117).

The patients received different dose regimens of low-molecular-weight heparin (dalteparin) subcutaneously.

RESULTS: The study revealed that the prevalence of PE at baseline was between 45.1% and 51% (95% CI 38.2-55.2 and 45.2-56.8% respectively) in patients with proximal DVT, and 31.9% (95% CI 23.6-41.2%) in those with DVT restricted to the lower leg. The majority of these cases of PE were completely asymptomatic. The incidence of a new PE, revealed by a second lung scan on day 10 after admission, was 7.0% (95% CI 3.9-11.4%) in patients with iliofemoral DVT, 5.5% (95% CI 3.2-8.7%) in those with femoropopliteal DVT and 2.7% (95% CI 0.6-7.6%) in those with lower-leg DVT. These incidence rates for new PEs were significantly lower than the rates previously reported (p<0.01). The fatality rate was also lower compared with the literature: one patient suffered a fatal PE (0.2%; 95% CI 0-0.9%), four patients died from malignant tumours, and one from pneumonia. The frequency of malignant tumours was greater in this study than in the literature (23% in patients with iliofemoral DVT, 14% in those with femoropopliteal DVT and 9% in those with DVT of the lower leg).

CONCLUSION: Mobile patients with DVT do not need bed-rest. Low-molecular-weight heparin s.c., compression bandages and walking exercises make home-treatment of DVT feasible.
Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators.


BACKGROUND: Low-molecular-weight heparin is known to be safe and effective for the initial treatment of patients with proximal deep-vein thrombosis. However, its application to pulmonary embolism or previous episodes of thromboembolism has not been studied.

METHODS: We randomly assigned 1021 patients with symptomatic venous thromboembolism to fixed-dose, subcutaneous low-molecular-weight heparin (reviparin sodium) or adjusted-dose, intravenous unfractionated heparin. Oral anticoagulant therapy with a coumarin derivative was started concomitantly and continued for 12 weeks. Approximately one third of the patients had associated pulmonary embolism. The outcome events studied over the 12 weeks were symptomatic recurrent venous thromboembolism, major bleeding, and death. We sought to determine whether low-molecular-weight heparin is at least equivalent to unfractionated heparin in patients with venous thromboembolism.

RESULTS: Twenty-seven of the 510 patients assigned to low-molecular-weight heparin (5.3 percent) had recurrent thromboembolic events, as compared with 25 of the 511 patients assigned to unfractionated heparin (4.9 percent). The difference of 0.4 percentage point indicates that the two therapies have equivalent value according to our predetermined definition of equivalence. Sixteen patients assigned to low-molecular-weight heparin (3.1 percent) and 12 patients assigned to unfractionated heparin (2.3 percent) had episodes of major bleeding (P=0.63), and the mortality rates in the two groups were 7.1 percent and 7.6 percent, respectively (P=0.89). CONCLUSIONS: Fixed-dose, subcutaneous low-molecular-weight heparin is as effective and safe as adjusted-dose, intravenous unfractionated heparin for the initial management of venous thromboembolism, regardless of whether the patient has pulmonary embolism or a history of venous thromboembolism.

A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group.


BACKGROUND: Low-molecular-weight heparin appears to be at least as effective and safe as standard, unfractionated heparin for the treatment of deep-vein thrombosis, but only limited data are available on the use of low-molecular-weight heparin to treat acute symptomatic pulmonary embolism. METHODS: We randomly assigned 612 patients with symptomatic pulmonary embolism who did not require thrombolytic therapy or embolectomy to either subcutaneous low-molecular-weight heparin (tinzaparin) given once daily in a fixed dose or adjusted-dose, intravenous unfractionated heparin. Oral anticoagulant therapy was begun between the first and the third day and was given for at least three months. We compared the treatments at day 8 and day 90 with respect to a combined end point of recurrent thromboembolism, major bleeding, and death. RESULTS: In the first eight days of treatment, 9 of 308 patients assigned to receive unfractionated heparin (2.9 percent) reached at least one of the end points, as compared with 9 of 304 patients assigned to low-molecular-weight heparin (3.0 percent; absolute difference, 0.1 percentage point; 95 percent confidence interval, -0.2 to 0.4). By day 90, 22 patients assigned to unfractionated heparin (7.1 percent) and 18 patients assigned to low-molecular-weight heparin (5.9 percent) had reached at least one end point (P=0.54; absolute difference, 1.2 percentage points; 95 percent confidence interval, -0.7 to 3.1). The risk of major bleeding was similar in the two treatment groups throughout the study. CONCLUSIONS: Under the conditions of this study, initial subcutaneous therapy with the low-molecular-weight heparin tinzaparin appeared to be as effective and safe as intravenous unfractionated heparin in patients with acute pulmonary embolism.
Prevention of Recurrent DVT

Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomized trial.

Das SK, Cohen AT, Edmondson RA, Melissari E, Kakkar VV
Thrombosis Research Institute, Chelsea, London, UK.

A group of 105 consecutive patients with venographically proved major acute deep vein thrombosis (DVT) were randomized in an open prospective study to evaluate the comparative efficacy and safety of a fixed dose of subcutaneous low-molecular-weight heparin (LMWH) and warfarin for the prevention of recurrent venous thromboembolism. Four patients developed venographically proved recurrent DVT during the 3 months of treatment: three in the LMWH group and one in the warfarin group. Nonfatal pulmonary embolism occurred in two patients in the LMWH group and in one in the warfarin group. Five of the 55 patients (10%) in the warfarin group and none of the 50 patients in the LMWH developed bleeding complications (two-tailed Fisher exact test, p = 0.06). A preliminary assessment of the costs indicated that treatment with LMWH was less expensive by Pounds 900 per patient than warfarin. In conclusion, the fixed daily dose of LMWH and the adjusted dose of warfarin therapy were of similar efficacy in preventing recurrence of DVT. However, warfarin therapy, despite strict laboratory control, is associated with more frequent side effects and is expensive. Another study with a higher dose of LMWH is recommended.

Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis.

Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, Tagliaferri A, Dettori AG
Divisione Medica e Centro Emostasi, Ospedale Maggiore, Parma, Italy.

To evaluate the role of low-molecular weight heparin (LMWH) as an alternative to oral anticoagulants in the prevention of recurrent venous thromboembolism, we compared in a randomized trial conventional warfarin treatment with a three-month course of enoxaparin 4000 anti-Xa units once a day subcutaneously. 187 patients with symptomatic deep-vein thrombosis (DVT), diagnosed by strain-gauge plethysmography plus D-dimer latex assay and confirmed by venography in most cases, were treated with full-dose subcutaneous heparin for ten days and then randomized to secondary prophylaxis. During the 3-month treatment period, 6 of the 93 patients who received LMWH (6%) and 4 of the 94 patients on warfarin (4%) had symptomatic recurrence of venous thromboembolism confirmed by objective testing (p = 0.5; 95% confidence interval [CI] for the difference, -3% to 7%). Four patients in the LMWH group had bleeding complications as compared with 12 in the warfarin group (p = 0.04; 95% CI for the difference, 4% to 14%). In the 9-month follow-up period, during which 34 patients on warfarin prolonged treatment for other 3 months and 14 up to one year, 10 patients in the enoxaparin group and 4 patients in the warfarin group suffered a documented recurrence of venous thromboembolism. Of these 14 late recurrences, just one occurred in patients with postoperative DVT. After one year there were 16 recurrences (17%) in the LMWH group and 8 (9%) in the warfarin group (p = 0.07; 95% CI for the difference, 1% to 16%).

The risk of recurrent venous thromboembolism in patients with and without factor V Leiden.

Department of Internal Medicine I, University of Vienna, Austria.

Thromboprophylaxis with oral anticoagulants up to six months is established in patients after a first venous thromboembolic event (VTE). The risk of recurrent VTE is still considerable thereafter, and it is uncertain whether some patients might benefit from extended
anti-coagulation. We performed a prospective, multicenter trial (4 thrombosis centers) and evaluated in 380 patients with a first or recurrent VTE (patients with a deficiency of antithrombin, protein C, protein S or plasminogen; cancer; or an antiphospholipid antibody syndrome were excluded) the risk of recurrence after discontinuation of secondary thromboprophylaxis with oral anticoagulants. It was the aim of the study to evaluate whether patients, with factor V Leiden are at an increased risk of recurrent VTE. 112 (29.5%) patients were carriers of factor V Leiden (26.9% heterozygous, 2.6% homozygous). After a median observation time of 19.3 months the overall recurrence rate of VTE was 9.9%. Recurrent deep vein thrombosis and/or pulmonary embolism occurred in 26 of 268 patients without factor V Leiden (9.7%) and in 10 of 112 patients with factor V Leiden (8.9%). The probability of recurrent VTE two years after discontinuation of oral anticoagulants was 12.4% (95% CI 7.8-17) in patients without factor V Leiden and was 10.6% (95% CI 3.8-17.4) in carriers of the mutation. This difference was statistically not significant. Patients with factor V Leiden are not at a higher risk of recurrent VTE within two years after discontinuation of oral anticoagulants than patients without factor V Leiden. Balancing the risk of recurrent VTE and bleeding from oral anticoagulants, patients with factor V Leiden are not likely to benefit from oral anticoagulant therapy extended beyond six months.

The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group.


BACKGROUND: A consensus has not been reached about the optimal duration of oral anticoagulant therapy after a second episode of venous thromboembolism. METHODS: In a multicenter trial, we compared six months of oral anticoagulant therapy with anticoagulant therapy continued indefinitely in patients who had had a second episode of venous thromboembolism. Of 227 patients enrolled, 111 were randomly assigned to six months of anticoagulation and 116 were assigned to receive anticoagulant therapy indefinitely; for both groups, the target international normalized ratio was 2.0 to 2.85. The initial episodes of deep-vein thrombosis (n = 193) and pulmonary embolism (n = 34), as well as recurrent episodes, were all objectively confirmed. RESULTS: After four years of follow-up, there were 26 recurrences of venous thromboembolism that fulfilled the diagnostic criteria, 23 in the group assigned to six months of therapy (20.7 percent) and 3 in the group assigned to continuing therapy (2.6 percent). The relative risk of recurrence in the group assigned to six months of therapy, as compared with the group assigned to therapy of indefinite duration, was 8.0 (95 percent confidence interval, 2.5 to 25.9). There were 13 major hemorrhages, 3 in the six-month group, (2.7 percent) and 10 in the infinite-treatment group (8.6 percent). The relative risk of major hemorrhage in the six-month group, as compared with the infinite-treatment group was 0.3 (95 percent confidence interval, 0.1 to 1.1). There was no difference in mortality between the two groups. CONCLUSIONS: Prophylactic oral anticoagulation that was continued for an indefinite period after a second episode of venous thromboembolism was associated with a much lower rate of recurrence during four years of follow-up than treatment for six months. However, there was a trend toward a higher risk of major hemorrhage when anticoagulation was continued indefinitely.
Miscellaneous Topics

Advances in antithrombotic therapy: novel agents.

Most of the clinical evaluation of the direct thrombin inhibitors has been in coronary artery disease. The recent clinical reports suggest that there is a narrower window of safety with recombinant hirudin than initially thought particularly when it is used in conjunction with thrombolytic agents and aspirin in acute myocardial infarction. The efficacy data, however, indicate that the direct thrombin inhibitors have great potential particularly in the initial management of patients with acute unstable angina and non-Q-wave infarction. There is much to learn regarding the mechanism of action, optimal dose, and optimal concomitant therapy in the use of direct thrombin inhibitors in the management of acute coronary ischaemia; and since hirudin and other direct thrombin inhibitors have so much potential in the management of acute coronary ischaemia, it is critical that dose-finding studies be performed to determine safe regimens of these agents to allow their evaluation in large-scale trials with important clinical outcomes. The direct thrombin inhibitors have also shown to have promise in the prevention of deep vein thrombosis in high-risk surgical patients. There is limited clinical data on the other novel anticoagulants which are currently being developed.

Deep vein thrombosis prophylaxis in the outpatient setting: preventing complications following hospital discharge.
Turpie AG
Orthopedics 1995 Jul;18 Suppl:15-17
McMaster University, Hamilton, Ontario, Canada.

Venous thromboembolism is an important complication in patients undergoing major orthopedic surgery. Without prophylaxis, there is a 50% to 60% incidence of deep vein thrombosis (DVT), a 10% to 30% incidence of proximal vein thrombosis, and a 1% to 2% rate of fatal pulmonary embolism after total hip replacement. The incidence of DVT after knee arthroplasty is even higher, ranging from 55% to 70% and, although there are no accurate figures on the incidence of fatal pulmonary embolism, it is likely to be similar to that following hip arthroplasty. Low molecular weight heparins (LMWHs) have been shown to be effective and safe in the prevention of venous thromboembolism in patients undergoing major orthopedic procedures. In comparative studies, LMWHs are more effective than adjusted dose heparin or warfarin without increased risk of bleeding.

Comparison of biological activities of two low molecular weight heparins in 10 healthy volunteers.
Azizi M, Veyssier-Belot C, Alhenc-Gelas M, Chatellier G, Billaud-Mesguish E, Fiessinger JN, Aiach M

1. Low molecular weight heparins (LMWHs) are produced by different depolymerization processes and may therefore differ with respect to their pharmacokinetic properties. 2. We designed a single dose, randomized cross-over study in 10 healthy volunteers to compare the 24 h pharmacokinetics of two LMWHs, reviparin and enoxaparin, which have been previously shown to be clinically equivalent in terms of post-operative deep vein thrombosis prevention, despite significant differences in their in vivo biological activity. The two LMWHs were subcutaneously administered at the same dosages that are used in clinical studies: 4250 anti-Xa iu for reviparin and 40 mg for enoxaparin which have similar in vitro anti-Xa activities. 3. The overall 24 h profiles of the plasma anti-Xa and anti-thrombin activities were similar for reviparin and enoxaparin. The Amax and the AUC(0, 24h) of plasma anti-Xa activity after reviparin administration were both slightly but significantly lower than those observed after enoxaparin administration (difference
Comparison of the pharmacokinetic profiles of three low molecular mass heparins—dalteparin, enoxaparin and nadroparin—administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism).

Rhone-Poulenc Rorer S.A., Department of Biodynamics, Antony, France.

The present trial was designed to comparatively investigate the pharmacokinetic profile and evaluate the apparent bioavailability pattern of three already marketed low molecular mass heparins (LMMHs): dalteparin (Fragmin), nadroparin (Fraxiparin), and enoxaparin (Lovenox) given by subcutaneous route. The study was carried out in 20 healthy young volunteers given, according to a cross over design, a single subcutaneous injection of the doses recommended for the prophylaxis of deep vein thrombosis (commercial preparations, prefilled syringes): dalteparin 2,500 IU (= 2,500 IU anti-Xa), nadroparin 7,500 ICU (= 3,075 IU anti-Xa), enoxaparin 20 mg (= 2,000 IU anti-Xa) and enoxaparin 40 mg (= 4,000 IU anti-Xa). Of the markers used, activated partial thromboplastin time (APTT),
thrombin clotting time (TCT), Heptest, anti-thrombin (aIIa) activity and anti-Xa (aXa) activity, the most pertinent parameter (from a biodynamic viewpoint) is plasma aXa activity. We demonstrated that dalteparin, nadroparin and enoxaparin exhibit statistically significantly different pharmacokinetic and overall disposition patterns. Normalized to the same injected dose (1,000 IU aXa), the relative actual amount of plasma anti-Xa activity generated by enoxaparin is 1.48 times greater ($p < 0.001$) than that of nadroparin and 2.28 times greater ($p < 0.001$) than that of dalteparin while the plasma amount induced by nadroparin is 1.54 times greater ($p < 0.001$) than that of dalteparin. The apparent total body clearance of enoxaparin doses ($CL/F = 16.7 +/- 5.5$ and $13.8 +/- 3.2$ ml/min) is significantly smaller than those of nadroparin ($CL/F = 21.4 +/- 7.0$ ml/min; $p < 0.01$) and dalteparin ($CL/F = 33.3 +/- 11.8$ ml/min; $p < 0.001$) while dalteparin apparent clearance is about 1.5-fold greater ($p < 0.001$) than that of nadroparin. These LMMHs also differ by their renal excretion pattern: more fragments exhibiting an anti-Xa activity are recovered in urine following enoxaparin doses (6.4 and 8.7% of the dose, respectively) than following nadroparin (3.9%) and dalteparin (3.4%) injection. These differences in the disposition profiles explain why the apparent elimination half life $t_{1/2}$ values of the LMMHs compared here are different: dalteparin: 2.8 h; nadroparin: 3.7 h; and enoxaparin: 4.1 h. Whether or not these differences may contribute to explain the different safety/efficacy balance of each of these antithrombotic medications remains to be discussed and needs further studies.

Low molecular weight heparins.
Cosmi B, Hirsh J
Curr Opin Cardiol 1994 Sep;9(5):612-618
Hamilton Civic Hospitals Research Centre, Ontario, Canada.

Low molecular weight heparins are derived from unfractionated heparin by chemical or enzymatic depolymerization; as a result, the mean molecular weight of unfractionated heparin is reduced by about one third and its biochemical and pharmacologic properties are improved. Demonstrated advantages of low molecular weight heparins over unfractionated heparin are the greater bioavailability at low doses, the longer half-life, and the more predictable dose response, which allows for fixed doses to be administered without laboratory monitoring; a potential advantage is the reduced hemorrhagic-to-thrombotic ratio observed in experimental animals. Clinical studies in the prevention of venous thromboembolism have shown that whereas the advantages offered by low molecular weight heparin over unfractionated heparin are modest in general surgery, they are substantial when compared with these and other agents in orthopedic surgery. In addition, low molecular weight heparins are at least as safe and effective as unfractionated heparin in the treatment of established deep vein thrombosis, but have the advantage that they can be administered once or twice daily without laboratory monitoring and can be used to treat uncomplicated deep venous thrombosis on outpatient basis.

Low molecular weight heparin therapy: is monitoring needed?
Boneu B
Laboratoire de Recherche sur l’Hemostase et la Thrombose, Toulouse, France.

Recent meta-analyses indicate that low molecular weight heparins (LMWH) are more effective than unfractionated heparin (UH) in preventing and treating deep vein thrombosis. This article presents the arguments for and against the need for laboratory monitoring. At the present time, the only tests currently available for monitoring LMWH therapy are those which measure the anti-Xa activity in the plasma. Due to lower binding to plasma proteins and to cell surfaces, the plasma anti-Xa activity generated by a given dose of LMWH is more predictable than for UH. Some clinical trials suggest that LMWH delivered at the recommended dose expose the patient to less bleeding risk than UH. Several meta-analyses indicate comparable risk while any overdose unacceptably increases the haemorrhagic risk. The lowest dose of LMWH still effective in treating established DVT is presently unknown; some reports indicate that inadequate doses of LMWH are associated
with a lack of efficacy for prevention. An overview of the published clinical trials indicates that the LMWH dose has never been monitored for prevention of DVT. In the treatment of established DVT, several trials have been performed without any monitoring, while in others the dose was adapted to target a given anti Xa activity. These considerations suggest that in prevention of DVT, monitoring the dose is not required.

Fatal pulmonary embolism in an unselected series: the possible role of caval filters in prevention.
Thomsen MB, Lindblad B, Bergqvist D
Department of Surgery, County Hospital, Kristianstad, Sweden.

OBJECTIVE: To evaluate the possible benefit of inserting a caval filter for the prevention of pulmonary embolism (PE) in an unselected group of patients admitted to hospital. DESIGN: Analysis of clinical data collected prospectively. SETTING: University hospital, Sweden. SUBJECTS: 1391 patients who presented during 1987 435 with deep vein thrombosis (DVT), thrombus in the right atrium or the right ventricle or PE at necropsy; 366 patients shown to have DVT on phlebography; 44 shown to have PE on pulmonary scintigraphy; and 546 patients operated on for hip fractures. OUTCOME MEASURES: Clinical description of patients and groups of patients who died of PE who could possibly have benefitted from insertion of a filter. RESULTS: Of the 435 patients with DVT or PE or both, 141 had DVT in the femoral or iliac veins or in the inferior vena cava together with PE which contributed to the cause of death. Only 11 of these had been suspected clinically of having DVT in or below the inferior vena cava and only 1 of these was less than 80 years old and did not have malignant disease with distant metastases. Of the 366 patients with phlebographically confirmed DVT 8 died with PE that had contributed to the cause of death; 6 had incurable cancer and the remaining two were over 85 years. Of the 44 patients with scintigraphically confirmed PE 2 patients (aged 78 and 89) died of PE that had already been diagnosed clinically and none would have benefited from insertion of a filter after diagnosis. There were 9 PE deaths related to PE among 546 patients operated on for hip fractures, and all but one had potentially lethal coexisting disease or were over 80 years old. CONCLUSION: In this epidemiological survey only a few patients would have benefited from insertion of a caval filter. The results call for a restricted use of caval filters until benefit has been confirmed by prospective studies.

Prophylaxis of postoperative thromboembolism with low molecular weight heparins.
Jorgensen LN, Wille-Jorgensen P, Hauch O
Department of Surgical Gastroenterology, Hvidovre Hospital, University of Copenhagen, Denmark.

To evaluate the thromboprophylactic use of low molecular weight heparins (LMWHs), publications from 27 orthopaedic trials and 35 studies of patients undergoing general or gynaecological surgery were scrutinized and subjected to a partial meta-analysis. In orthopaedic surgery, LMWHs were superior to placebo or dextran and at least as efficient as unfractionated heparin in the prevention of deep vein thrombosis (DVT). Compared with unfractionated heparin, one of the LMWH preparations significantly reduced the total incidence of DVT. The rate of non-fatal pulmonary embolism was 0.49 per cent in patients receiving LMWH and 1.22 per cent in controls. Seven orthopaedic patients (0.15 per cent) died from pulmonary embolism, none of whom received LMWH. In general surgery, the LMWHs were at least as efficient as unfractionated heparin, with a trend towards a lower risk of pulmonary embolism with the former. Compared with unfractionated heparin, LMWHs did not reduce the postoperative mortality rate, nor did they cause haemorrhage. LMWHs provide safe and efficient prophylaxis by administration once daily.
Pre-surgical identification of the patient at risk for developing venous thromboembolism post-operatively.

Brandjes DP, ten Cate JW, Buller HR
Academic Medical Centre, Amsterdam, The Netherlands.

The pre-surgery identification of patients at risk for the development of post-operative venous thromboembolism has not yet been achieved. It is a well recognized fact that major surgery without prophylaxis encompasses a high risk for thrombosis, in particular orthopaedic operations (hip/knee surgery approximately 50%) and abdominal surgery (approximately 20%). Other well-defined risk factors, though rarely occurring, are deficiencies of the major inhibitors of blood coagulation (i.e. protein C, protein S and antithrombin III). Less well-defined risk factors are a history of previous thrombosis, obesity, varicosis, cancer etc. In an attempt to identify patients at risk for thrombosis prior to surgery, several investigators have developed complicated risk predictors, i.e. formulae comprising combinations of coagulation test results and physical characteristics such as body weight. However, the clinical usefulness has only been demonstrated in two small studies evaluating gynaecological surgery patients. These prognostic indices have not, however, found general acceptance and are not used routinely. The importance of all these risk factors for patient management with regard to thrombosis prevention is relatively small. Irrespective of the absence or presence of identified risk factors, currently the majority of patients will receive some formal thrombosis prophylaxis. The major problem at present is the development of proximal vein thrombosis despite the best possible thrombosis prophylaxis (approximately 10% after hip surgery). Identification of these patients pre-operatively or in an early stage in the post-operative phase by single screening tests should be a major research issue. Furthermore, the development of a prophylactic regimen which eliminates proximal deep vein thrombosis is still desperately needed.