Low molecular weight heparin for venous thromboembolic disease

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INTRODUCTION — Low molecular weight (LMW) heparin is prepared by depolymerization of unfractionated heparin using chemical methods or enzymes [1-4]. LMW heparin preparations for clinical use have been produced by several companies (table 1). They have an average molecular weight of 4000 to 6500 Daltons; by comparison, commercially available unfractionated heparin has an average molecular weight of 15,000 Daltons. Several LMW heparin preparations have been evaluated by clinical trials. The recommendations contained in this topic review are linked to the strength of the evidence from clinical trials [5]. A firm recommendation is made only when there is supporting evidence from definitive randomized clinical trials.

The current status of LMW heparin in the prevention and treatment of venous thromboembolic disease will be reviewed here. Issues relating to the general prevention of venous thromboembolic disease are discussed separately. (See "Prevention of venous thromboembolic disease in surgical patients" and "Treatment of deep vein thrombosis" and "Treatment of acute pulmonary embolism".)

USAGE GUIDELINES

Formulations — The LMW heparin preparations have different biochemical and pharmacologic properties and are not interchangeable [2,4,6,7]. Thus, each preparation must be evaluated by clinical trials measuring the outcomes of thromboembolism, bleeding, and mortality. This variability has led to the following communication from the Food and Drug Administration (FDA) in the United States [7]:

"The FDA is alerting physicians and other health professionals to important considerations in the use of LMW heparins, most particularly to the fact that LMW heparins cannot be used interchangeably, unit for unit with heparin, nor can one individual LMW heparin be used interchangeably with another."

The decision to use a LMW heparin preparation for a specific clinical indication should be based upon the available clinical trial data for that particular preparation.

Approval for the use of the various LMW heparin preparations in distinct clinical settings differs in Europe, Canada, and the United States [4]:

● In Europe, several LMW heparin preparations are licensed for the prevention and treatment of venous thromboembolism.

● In Canada, four preparations are approved by the Health Protection Branch. These are enoxaparin, tinzaparin, dalteparin, and nadroparin. The approved clinical indications differ for the individual LMW heparin preparations.

● In the United States, three preparations (enoxaparin, dalteparin, and tinzaparin) are currently

approved by the FDA for different clinical indications.

Overview — The pharmacokinetic properties of LMW heparin include a very high bioavailability after subcutaneous injection, a longer half-life than unfractionated heparin, and much less interindividual variation in the anticoagulant response to a given dose [2]. The anticoagulant response (anti-Xa activity) to a fixed dose of LMW heparin is highly correlated with the patient's body weight. These pharmacokinetic properties make it possible to give LMW heparin subcutaneously once or twice daily to patients WITHOUT the need for laboratory monitoring of the anticoagulant response or dose adjustment unless pregnancy, morbid obesity, or renal failure is present [8]. In the presence of such conditions, anti-Xa level measurement has been recommended for proper dosing.

Anti-Xa levels should be measured four hours after subcutaneous injection; the dose of LMW heparin should be titrated to achieve a level of 0.6 to 1.0 IU/mL if administered twice daily, or 1.0 to 2.0 IU/mL if administered once daily [8]. (See "Therapeutic use of heparin and low molecular weight heparin".) Some individual LMW heparin preparations have specific dosage recommendations for the very obese and those with marked renal impairment.

Severe Renal Failure — Because the pharmacokinetic response to impaired renal function may differ among LMW heparin preparations, there is no clear recommendation for the dosing of LMW heparins in patients with reduced renal function [8]. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Renal failure'.)

For the United States, in the context of patients with severe renal impairment (creatinine clearance <30 mL/minute), if enoxaparin is to be used, a reduced dose of 30 mg should be administered subcutaneously once daily for prophylaxis in medical patients during acute illness, abdominal surgery, or hip or knee replacement surgery. In the treatment of acute deep vein thrombosis in outpatients without pulmonary embolism or inpatients with or without pulmonary embolism a reduced dose of enoxaparin (1 mg/kg) should be administered subcutaneously once daily along with warfarin sodium [9,10].

For Canada, the clinician is referred to the Compendium of Pharmaceuticals and Specialties for additional guidance [11].

Obese Patients — For the United States, using tinzaparin for treatment of deep-vein thrombosis, dosage in obese patients should be based on actual body weight [9]. For Canada and the United Kingdom, when using dalteparin for the treatment of acute deep vein thrombosis in obese patients, the single daily dose should not exceed 18,000 units [11]. (See "Therapeutic use of heparin and low molecular weight heparin", section on 'Obese patients'.)

Cost effectiveness — A number of studies have compared the cost effectiveness of the LMW heparin enoxaparin with either unfractionated heparin or warfarin for the prevention of venous thrombosis after hip replacement surgery [12-15]. However, there has been no randomized trial directly comparing enoxaparin with warfarin in patients undergoing knee replacement.

The reported cost-effectiveness analyses are based upon comparisons of thrombosis rates across separate trials evaluating prophylaxis with either warfarin or enoxaparin. As a result, the differences in thrombosis rates reported based upon comparison across trials may be due to features other than the intervention, such as differences in the patients or center variability [16]. A valid cost-effectiveness comparison of LMW heparin and warfarin prophylaxis must therefore be based on data from randomized trials directly comparing these alternate approaches.

A cost-effectiveness analysis comparing warfarin sodium and LMW heparin prophylaxis with tinzaparin has been reported [17] and is based upon a randomized trial of 1436 hip or knee arthroplasty patients which directly compared these treatment regimens [16]. The study found that the decision to

use LMW heparin or warfarin prophylaxis in patients having major joint replacement surgery is a trade-off based upon finely varying points. LMW heparin was found to be as effective or even more effective than the more complex prophylaxis with warfarin. This conclusion is sensitive to parameters which may influence the comparative cost-effectiveness, including the cost of the drug, INR monitoring, and the cost associated with major bleeding [17].

The analysis also demonstrated that the results are health-care system dependent (Canada versus the United States) since:

- In Canada, LMW heparin (tinzaparin) is less costly than warfarin
- In the United States, the drug cost for LMW heparin will likely be the principal determinant of relative cost-effectiveness

Several economic evaluations compared the cost-effectiveness of LMW heparin and intravenous unfractionated heparin for the initial treatment of patients with proximal deep vein thrombosis [15,18-20]. The results indicate that LMW heparin treatment is at least as effective and safe as well as less costly than intravenous unfractionated heparin treatment. It is important to caution that the findings may not apply to different LMW heparin fractions because these fractions intrinsically differ, and their cost may vary substantially. However, the potential for outpatient therapy in 30 to 40 percent of patients treated with LMW heparin, along with a lower hospital readmission rate for VTE recurrence noted in one study [20], would substantially augment the cost savings.

PREVENTION OF VTE — LMW heparin has been extensively evaluated for the prevention of venous thromboembolism (VTE) by clinical trials performed in Europe and North America [2,16,21-27]. The clinical indications for prophylaxis that have been studied include general abdominothoracic surgery, hip or knee replacement, surgery for fractured hip, stroke, spinal cord injury, lower leg immobilization, and medical illness [2,21,28,29].

General abdominothoracic surgery — In patients having general abdominothoracic surgery, LMW heparin is effective and safe [21]. The ultimate clinical role of LMW heparin in this context will depend upon its relative cost-effectiveness by comparison to low-dose unfractionated heparin or intermittent pneumatic leg compression.

Hip fracture surgery — In patients having surgery for hip fracture, LMW heparin is effective and safe. The role of LMW heparin in this setting depends upon its relative cost-effectiveness by comparison to other recommended treatments, such as fondaparinux, adjusted dose vitamin K antagonists, and low dose unfractionated heparin [21].

Neurosurgery — One double-blind trial randomly assigned 307 patients undergoing elective neurosurgery to postoperative treatment with compression stockings alone or with 40 mg of enoxaparin, administered once daily [30]. Patients who received enoxaparin had a significantly lower rate of venous thromboembolism (17 versus 32 percent) and an equivalent rate of major hemorrhage.

Major trauma — The LMW heparin enoxaparin has been shown to be more effective than low-dose unfractionated heparin for preventing venous thromboembolism in patients who have had major trauma [31]. In this randomized trial, LMW heparin was associated with a lower incidence of proximal vein thrombosis confirmed by venography (6 versus 15 percent), a lower incidence of calf-vein thrombosis (31 versus 44 percent), but a higher incidence of major bleeding (2.9 versus 0.6 percent) than was low-dose unfractionated heparin.

Elective hip and knee surgery — Many of the clinical trials in North America have been performed in patients undergoing either hip or knee replacement [16,24-27]. This section on prevention will therefore emphasize these patient groups. The focus is also on the relative effectiveness and safety of LMW heparin and warfarin sodium, since warfarin has been the most widely used pharmacologic prophylaxis in

arthroplasty surgery in North America. By comparison, warfarin is less commonly used in Europe; most European trials in hip replacement have therefore compared LMW heparin with either unfractionated heparin or intravenous dextran [2,21,22].

This review of clinical trials of patients undergoing hip or knee replacement surgery is confined to studies that used routine venography to measure the presence or absence of venous thrombosis, since the noninvasive tests (including B-mode or duplex ultrasound and impedance plethysmography) are insensitive for detecting calf-vein and proximal-vein thrombosis (popliteal, femoral, or iliac vein thrombosis) in the setting of hip or knee replacement. Venography provides a valid measure of the thrombosis rates, and should be bilateral since up to 20 percent of the thrombi are detected only in the nonoperated leg [16].

The clinical trials performed to date include both double-blind and open-label designs. If feasible, a double-blind design is preferable because it provides a more valid assessment of the relative safety of LMW heparin (eg, bleeding rates) in comparison with other clinical approaches.

LMW heparin is effective and produces marked risk reductions of 70 to 80 percent in the frequency of thrombosis after hip replacement compared with the use of no prophylaxis [21]. The key issue, however, is the relative efficacy and safety of LMW heparin compared with the prophylactic approaches currently used in clinical practice (eg, fondaparinux, adjusted dose vitamin K antagonists).

In North American, a number of randomized trials have compared the LMW heparins tinzaparin and enoxaparin with warfarin in the setting of knee replacement [16,27,32]. In addition, LMW heparin was compared with acenocoumarol in a European trial [23]. The results of these trials are summarized in the table (table 2). In each of these studies, LMW heparin was more effective than warfarin; however, the absolute rates of thrombosis remained high. The rates of major bleeding were low for both warfarin and LMW heparin.

In the largest trial, the findings of the predefined pooled analysis for hip and knee arthroplasty patients showed that the reduction in the incidence of venous thrombosis with LMW heparin (31.4 versus 37.4 percent with warfarin) was offset by a small but statistically significant increase (2.8 versus 1.2 percent) in major bleeding [16]. Separate analysis of the 517 patients undergoing knee surgery revealed a statistically significant decrease for all deep vein thrombosis with LMW heparin (45 versus 55 percent with warfarin) and a nonsignificant reduction in proximal deep vein thrombosis (7.8 versus 12.3 percent).

LMW heparin versus unfractionated heparin — Several clinical trials have compared LMW heparin with low-dose unfractionated heparin (5000 units subcutaneously every eight hours) in patients undergoing hip replacement [21]. LMW heparin is more effective and as safe as conventional low-dose unfractionated heparin prophylaxis in this setting [21].

LMW heparin (enoxaparin, 30 mg subcutaneously every 12 hours) has also been compared with unfractionated heparin (given as a regimen of 7500 units every 12 hours) in 521 patients [26]. Both regimens were begun 12 to 24 hours postoperatively. The overall deep vein thrombosis rates were similar in the LMW heparin and unfractionated heparin groups (19 versus 23 percent, respectively). A significantly lower frequency of bleeding complications (combined major and minor bleeding) was noted in the patients given LMW heparin (5.1 versus 9.3 percent). It is uncertain, however, whether the lower bleeding rate was due to an intrinsic safety advantage of LMW heparin or to the regimen of unfractionated heparin used, which is not a standard regimen. It is possible that a different unfractionated heparin regimen, such as 6500 units every 12 hours, would have been equally effective but without the increased bleeding observed with the higher dose.

LMW heparin versus warfarin — In North America, there have been a number of randomized trials comparing the LMW heparins dalteparin and tinzaparin with oral warfarin in patients having hip replacement [16,21,25,33,34]. Furthermore, a European trial has also compared the LMW

heparin nadroparin with the oral anticoagulant acenocoumarol in patients undergoing hip replacement [23]. The results of these trials are summarized in the table (table 3). LMW heparin prophylaxis in a high risk dose begun postoperatively is as effective as oral anticoagulants adjusted to maintain the International Normalized Ratio (INR) between 2.0 and 3.0.

Major bleeding complications occurred with low frequency in both the LMW heparin and warfarin groups. LMW heparin begun six to eight hours postoperatively using a modified dalteparin regimen was more effective than warfarin (table 3) [33]. This regimen of LMW heparin administered in close proximity to surgery was also safe, with major bleeding occurring infrequently. The superiority of the close proximity regimen may in the future render the 12 to 24 hour postoperative administration of LMW heparin obsolete.

LMW heparin versus IV dextran — LMW heparin (enoxaparin, 40 mg subcutaneously once daily) has been compared with intravenous (IV) dextran [22]. Enoxaparin was more effective.

Conclusions — In patients having hip replacement surgery, several LMW heparin regimens have been shown by clinical trials to be effective and associated with a low risk of major bleeding. The specific LMW heparins include enoxaparin, tinzaparin, dalteparin, and nadroparin.

A modified dalteparin regimen administered post-operatively provided superior efficacy versus warfarin without significantly increasing overt bleeding [33]. LMW heparin is simpler to use because it does not require laboratory monitoring of the anticoagulant effect and dose adjustment.

In patients having knee replacement, four LMW heparin regimens (tinzaparin, ardeparin, enoxaparin, and nadroparin) have been shown to be more effective than oral anticoagulant prophylaxis with warfarin or acenocoumarol. However, the absolute thrombosis rates remain high (table 2).

TIMING AND DURATION OF PROPHYLAXIS

Timing — An important issue is whether prophylaxis should be begun pre- or post-operatively. Many of the European clinical trials have evaluated regimens begun preoperatively, whereas the North American clinical trials have tested prophylaxis begun postoperatively. It is possible that LMW heparin begun preoperatively may be more effective than prophylaxis begun postoperatively, without an increased risk of major bleeding. This issue is now clearer because of a randomized trial published in 2000 [21,33,35].

The optimal interval for beginning the administration of LMW heparin for thromboprophylaxis is between two hours preoperatively and six to eight hours postoperatively, with the postoperative regimen appearing to cause slightly less major bleeding. Pre-operative administration of LMW heparin in close proximity to surgery is less desirable due to increased major bleeding [33]. A modified dalteparin regimen administered post-operatively provided superior efficacy versus warfarin without significantly increased overt bleeding [33]. Accordingly, administering the modified LMW heparin regimen post-operatively is preferred [33].

Duration — The appropriate duration of prophylaxis with LMW heparin after hip or knee replacement remains the subject of ongoing research, since the period of risk for the development of deep vein thrombosis may extend beyond the period of some prophylactic treatment regimens [36-38]. One study, for example, demonstrated that in patients undergoing hip replacement, in whom venography is negative at 13 to 15 days postoperatively, there is a significant incidence of deep vein thrombosis developing over the following three to four weeks (19 and 8 percent for calf and proximal deep vein thrombosis, respectively) [39].

Two randomized trials demonstrated that continuing prophylaxis for one month, rather than only during the hospitalization phase of 10 to 14 days, results in a reduced incidence of deep vein thrombosis at one month [39,40]. The LMW heparin regimen evaluated in both studies was enoxaparin (40 mg given once

daily). One of these studies, for example, demonstrated that enoxaparin reduced the incidence of proximal vein thrombosis at one month (7 versus 24 percent for placebo) [40]. A different North American randomized trial has confirmed the benefit of post-discharge thromboprophylaxis using dalteparin for a total of 35 days [41].

Additional randomized trials of out-of-hospital low molecular weight heparin versus placebo have supported these findings. Indeed, extended LMW heparin prophylaxis showed consistent effectiveness and safety in the trials for venographic deep venous thrombosis and symptomatic venous thromboembolism, regardless of study variations in clinical practice and length of hospital stay. The aggregate findings support the need for extended out-of-hospital prophylaxis in patients undergoing hip arthroplasty surgery (table 4) [42]. Based upon these data, prophylaxis with LMW heparin should be considered for at least one month following hip replacement [21,42,43].

Oral anticoagulant prophylaxis may be less preferred out-of-hospital. In one study, a significantly higher benefit-risk ratio was observed for patients undergoing elective hip replacement who received extended out-of-hospital prophylaxis with LMW heparin versus use of the vitamin K antagonist acenocoumarol. LMW heparin prophylaxis was at least as effective as oral anticoagulants, but with a marked improvement in safety [44]. (See "Prevention of venous thromboembolic disease in surgical patients", section on 'Extended prophylaxis'.)

Similar clinical trials need to be performed in patients undergoing knee replacement in order to determine the optimal duration of thromboprophylaxis in this patient group.

Medical patients — The efficacy and safety of thromboprophylaxis using LMW heparin in patients with acute medical illnesses who may be at risk for venous thromboembolism has been determined by two major randomized trials (table 5) [45,46].

TREATMENT OF VTE — Numerous studies have documented the safety and efficacy of LMW heparin in the treatment of established venous thrombosis and thromboembolism [47,48]. The clinical trials to date indicate that the simplified therapy provided by LMW heparin may allow patients with uncomplicated proximal vein thrombosis to be treated safely in an outpatient setting [49,50].

LMWH has shown similar effectiveness to the usual care vitamin K antagonist treatment for preventing recurrence of venous thromboembolism in a broad-spectrum of patients, enhancing the clinician's therapeutic options for patients with proximal vein thrombosis. Accordingly, LMW heparin may also be suitable for long-term use in patients with venous thromboembolism who cannot tolerate warfarin [51,52], in the elderly [53], and in patients with cancer [54]. (See "Treatment of deep vein thrombosis", section on 'Use in special population groups'.)

Deep venous thrombosis — LMW heparin has been evaluated for the initial treatment of deep venous thrombosis (DVT) by several clinical trials both in Europe and in North America [40,49,55-60]. Two outcome measures have been used to assess the effectiveness of treatment: repeat venography after several days of treatment to assess thrombus size, and clinical outcome on long-term follow-up to determine the incidence of recurrent venous thromboembolism (VTE) documented by objective testing. The latter outcome provides more useful data for the practicing clinician. The results of studies using long-term follow-up to document the clinical outcomes of recurrent VTE and mortality are summarized here. The findings of trials using repeat venography to assess effectiveness have been reviewed elsewhere [55,56]. (See "Treatment of deep vein thrombosis", section on 'Low molecular weight heparin'.)

A number of randomized trials have incorporated long-term follow-up [49,50,57-60]. The LMW heparins evaluated were nadroparin, tinzaparin, enoxaparin, and dalteparin. Three of these trials were performed in Europe [57,59,60], two were performed in North America [49,58], and one trial was performed in Europe, Australia, and New Zealand [50]. A meta-analysis of 11 randomized trials also has been

published [61]. With a high degree of consistency, LMW heparin given in a fixed dose per kilogram subcutaneously either once or twice daily [62] was as effective as continuous intravenous unfractionated heparin for the initial treatment of patients with proximal vein thrombosis (table 6).

The lack of required laboratory monitoring or manipulation of infusion pumps makes the outpatient treatment of DVT with LMW heparin feasible; initial trials and a Cochrane review indicate that this approach is safe, effective, and associated with a high level of patient satisfaction [63,64].

Existing malignancy — In patients with cancer and acute VTE, LMW heparin has been more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding. This subject is discussed in detail separately. (See "Hypercoagulable disorders associated with malignancy", section on 'Treatment of VTE'.)

Pulmonary embolism — Several trials have examined the use of LMW heparin in the treatment of pulmonary embolism. One study randomly assigned 1021 patients with symptomatic deep venous thrombosis, pulmonary embolism, or both to treatment with fixed dose, twice daily, subcutaneous reviparin, or adjusted dose, unfractionated, intravenous heparin [65]. Pulmonary embolism was present in approximately one-third of patients, and all patients started therapy with an oral coumarin derivative on the first hospital day. No significant differences in recurrent thromboembolic events, major bleeding, or mortality were found between the two treatment groups. (See "Treatment of acute pulmonary embolism", section on 'Anticoagulant therapy'.)

A second trial randomly assigned 612 patients with pulmonary embolism not requiring thrombolytic therapy or embolectomy to initial treatment with either once daily, fixed dose, subcutaneous tinzaparin, or adjusted dose, intravenous unfractionated heparin [66]. No significant differences in death, symptomatic recurrent thromboembolism, or major bleeding occurred on days 8 or 90.

A third trial randomly assigned 200 patients to receive once daily fixed-dose tinzaparin or dose-adjusted continuous intravenous unfractionated heparin [67]. Significantly fewer patients treated with tinzaparin suffered recurrent thromboembolism (zero versus 7 percent), and rates of bleeding were equivalent among the two treatment groups.

The hypothesis has been advanced that LMW heparin may in fact be superior to unfractionated heparin. As examples, one subgroup analysis of a randomized trial found a significantly lower rate of recurrent venous thromboembolism among patients treated with tinzaparin (zero versus 7 percent) [67], while a meta-analysis suggested a mortality benefit of LMW heparin, although rates of recurrent venous thromboembolism did not differ significantly between LMW and unfractionated heparin groups [48]. However, no superiority of LMW heparin with regard to mortality or recurrent thromboembolism has yet been demonstrated in prospective randomized trials.

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GRAPHICS

Low molecular weight heparins

Generic name	Trade name	Manufacturer
Enoxaparin	Lovenox	Sanofi-Aventis
Dalteparin	Fragmin	Pfizer
Tinzaparin*	Innohep	Leo Pharma
Nadroparin•	Fraxiparine	Glaxo Smith-Kline
Certoparin	Sandoparin	Sandoz Pharmaceuticals
Reviparin	Clivarin	Abbott
Parnaparin	Fluxum	Opocrin

* Prepared by heparinase digestion. All others prepared by chemical depolymerization.
• Ca salt. All others are sodium salt.

Clinical trials comparing low molecular weight heparin with oral anticoagulants in knee replacement

Study	Design	Regimens	All DVT, n/n (percent)	Proximal DVT*, n/n (percent)	Occurrence of major bleeding, n/n (percent)
N Engl J Med 1993; 329:1370	Randomized double-blind; Bilateral venogram	Tinzaparin 75 Xa U/kg sc once daily vs	116/258 (45)*	20/258 (8)	9/317 (2.8)
		Warfarin sodium (INR 2.0-3.0)	152/277 (55)	34/277 (12)	3/324 (0.9)
Ann Intern Med 1996; 124:619	Randomized double-blind; Bilateral venogram	Enoxaparin 30 mg sc bid vs	76/206 (37)*	24/206 (12)	7/336 (2)
		Warfarin sodium (INR 2.0-3.0)	109/211 (52)	22/211 (10)	6/334 (2)
Thromb Haemost 1994; 74:1428	Randomized single-blind; Bilateral venogram	Nadroparin 60 Xa U/kg sc once daily vs	16/65 (25)*	5/65 (8)	2/65 (3)
		Acenocoumarol (INR 2.0-3.0)	23/61 (38)	6/61 (10)	1/61 (1)
Bone Joint Surg Am 2001; 83:900	Randomized single-blind; Unilateral venography⚫	Enoxaparin 30 mg SC once daily vs	44/173 (25)	3/173 (2)	9/173 (5)
		Warfarin sodium (INR 2.0-3.0)	80/176 (46)*	20/176 (11)	4/176 (2)

DVT: deep vein thrombosis; INR: international normalized ratio; sc: subcutaneously.
* (P<0.05).
⚫ Contrast venography or ultrasonography of the contra-lateral extremity bid: twice daily.

Clinical trials comparing low molecular weight heparin with oral anticoagulants in hip replacement

Study	Design	Regimens	All DVT, n/n (percent)	Proximal DVT*, n/n (percent)	Occurrence of major bleeding, n/n (percent)
N Engl J Med 1993; 329:1370	Randomized double-blind; Bilateral venogram	Tinzaparin 75 Xa U/kg sc once daily vs	69/332 (21)	16/332 (5)	11/398 (2.8)
		Warfarin sodium (INR 2.0-3.0)	79/340 (23)	13/340 (4)	6/397 (1.5)
Thromb Haemost 1995; 74:1428	Randomized single-blind; Bilateral venogram	Nadroparin 60 Xa U/kg sc once daily vs	27/195 (14)	12/195 (6)	3/195 (1)
		Acenocoumarol (INR 2.0-3.0)	27/196 (14)	9/196 (5)	7/196 (3.6)
J Bone Joint Surg Am 1997; 79:1365	Randomized single-blind; Bilateral venography	Dalteparin 2500 IU pre- and post surgery then 5000 IU sc once daily vs	28/192 (15)	10/192 (5)	6/271 (2)
		Warfarin sodium (INR 2.5) begun pre-surgery	49/190 (26)	16/190 (8)	4/279 (1)
Arch Intern Med 2000; 160:2199	Randomized double-blind; Bilateral venography	Dalteparin 2500 IU pre- and post surgery, then 5000 IU qd vs	37/337 (11)	3/354 (0.8)	10/496 (2)
		Dalteparin 2500 IU post- surgery, then 5000 IU qd vs	44/336 (13)	3/358 (0.8)	5/487 (1)
		Warfarin sodium (INR 2.0-3.0) begun post-surgery	81/338 (3)	11/363 (3)	8/489 (1.6)

DVT: deep vein thrombosis; INR: international normalized ratio; sc: subcutaneously
* Popliteal, femoral, or iliac vein thrombosis.

Relative risk for all episodes of deep venous thrombosis after elective hip arthroplasty during the out-of-hospital time interval

Study	Patients with events, n/n (percent)		Relative risk (95% CI)
	LMW Heparin	Placebo	
N Engl J Med 1996; 335:696	21/117 (17.9)	45/116 (38.8)	0.46 (0.30-0.73)
Lancet 1996; 348: 224	6/85 (7.1)	17/88 (19.3)	0.37 (0.15-0.88)
Thromb Haemost 1997; 77:26	11/93 (11.8)	23/89 (25.8)	0.46 (0.24-0.88)
Thromb Res 1998; 89:281	5/113 (4.4)	12/102 (11.8)	0.38 (0.14-1.03)
Arch Int Med 2000; 160:2208	14/291 (4.8)	14/133 (10.5)	0.46 (0.22-0.93)
J Bone Joint Surg 2001; 83-A: 336	15/152 (9.9)	39/138 (28.2)	0.35 (0.20-0.60)
Total	72/911 (7.9)	150/666 (22.5)	0.41 (0.32-0.54)

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Clinical trials of low molecular weight heparin in medical patients

Study	Design	Regimens	Incidence of VTE n/n (percent)	Occurrence of major bleeding, n/n (percent)
N Engl J Med 1999; 341:793	Randomized double-blind	Enoxaparin 40 mg once daily	16/291 (5.5)	6/360 (1.7)
		vs		
		Enoxaparin 20 mg once daily	43/287 (15.0)	1/351 (0.3)
		vs		
		Placebo	43/288 (14.9)	4/362 (1.1)
Circulation 2004; 110:874	Randomized double-blind	Dalteparin 5000 IU sc daily	42/1518 (2.8)*	9/1848 (0.5)
		vs		
		Placebo	73/1473 (5.0)*	3/1833 (0.2)

VTE: venous thromboembolism.
* Includes VTE and sudden death VTE: venous thromboembolism.

Clinical outcome of trials of low molecular weight heparin for the treatment of venous thrombosis

Study	Design	Regimens	Recurrence of VTE, n/n (%)	Occurrence of major bleeding, n/n (%)	Death, n/n (%)
N Engl J Med 1992; 326:975	Randomized, double blind	Tinzaparin 175 Xa U/kg sc once daily **vs**	6/213 (3)	1/213 (0.5)*	10/213 (5)*
		IV heparin aPTT 1.5-2.5	15/219 (7)	11/219 (5.0)	21/219 (10)
Thromb Haemost 1994; 72:186	Randomized, open, home treatment	Dalteparin 200 Xa U/kg sc once daily **vs**	5/101 (5)	0	2 (2)
		IV heparin aPTT 1.5-3.0	3/103 (3)	0	2 (2)
N Engl J Med 1996: 334:677	Randomized, open, home treatment	Enoxaparin 1 mg/kg sc bid **vs**	13/247 (5)	5/247 (2)	11/247 (4)
		IV heparin aPTT 60-85 s	17/253 (7)	3/253 (1)	17/253 (7)
N Engl J Med 1996; 334:682	Randomized open, home treatment	Nadroparin sc bid ☀ **vs**	14/202 (7)	1/202 (0.5)	14/202 (7)
		IV heparin aPTT 1.5-2.0	17/198 (9)	4/198 (2)	16/198 (8)
Ann Int Med 2001; 134:191	Randomized single blind	Revaparin sc bid ☀ **vs**	9/312 (3)	4/312 (1)	7/312 (2)
		Reviparin sc once/day **vs**	13/298 (4)	5/298 (2)	11/298 (4)
		IV heparin aPTT 1.5-2.5	12/290 (4)	6/290 (2)	9/290 (3)
N Engl J Med 2001; 344:626	Randomized single blind	Reviparin sc bid ⊿ **vs**	24/375 (6)	27/388 (7)	9/388 (2)
		Reviparin sc once/day **vs**	13/374 (4)	26/374 (7)	15/374 (4)
		IV heparin aPTT 1.5-2.5	24/375 (6)	28/375 (8)	11/375 (3)
N Engl J Med 2003;349:146	Randomized single blind	Dalteparin 200 IU/kg once daily for 5-7 days and coumarin for 6 months (INR 2.5) **vs**	27/336 (8)◊	19/338 (6)	130/336 (39)
		Dalteparin 200 IU/kg once daily for 1 month followed by dalteparin	53/336 (16)	12/335 (4)	136/336 (41)

		150 IU/kg for 5 months			

aPTT: activated partial thromboplastin time; bid: twice daily; sc: subcutaneously; VTE: venous thromboembolism

* P<0.05 by comparison to intravenous (IV) heparin group.

■ Total daily doses were: 8,200 I Xa U for patients weighing less than 50 kg, 12,300 I Xa U for patients between 50 and 70 kg, and 18,400 I Xa U for patients weighing more than 70 kg; patients were treated at home if they did not require hospital for management of other conditions; about 40 to 50 percent of patients were treated without ever being admitted to the hospital, and in the remaining patients, the hospital stay was significantly reduced.

⚐ Total daily doses were 7,000 anti-Xa U for patients weighing 35-45 kg, 8,400 anti-Xa U for patients between 46 and 60 kg, and 12,600 U for patients weighing over 60 kg.

⚑ p=0.002