

Overview of Enoxaparin in the Treatment of Deep Vein Thrombosis

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Presentation Summary

Standard medical treatment for patients with acute venous thrombosis is antithrombotic therapy. Following a historical overview of the evolution of heparin therapy to include low-molecular weight heparin (LMWH), the pharmacokinetic properties of enoxaparin are described. Therapeutic advantages of LMWH over unfractionated heparin (UFH) are also discussed, including once- or twice-daily subcutaneous dosing, reduced hospital

stays, elimination of therapeutic monitoring for most patients, and possibly less bone density loss. Studies have demonstrated that enoxaparin is at least equivalent to UFH with regard to efficacy and safety. Opportunities for future study include evaluation of enoxaparin's efficacy for the prevention of deep vein thrombosis within high-risk groups and for the treatment of thrombosis in such conditions as pregnancy, cancer, obesity, and renal insufficiency, and in children.

The magnitude of the clinical thrombosis problem in the United States can be, in part, expressed by comparing thrombosis with cancer, a more widely appreciated medical condition. Although cancer is widely perceived as the most prevalent life-threatening disease, the incidence of serious thrombosis and resulting deaths in the United States far exceeds that of cancer, with 1498 serious venous and arterial thrombotic events per 100,000 people per year. This represents nearly 4 million cases a year and nearly 2 million deaths.¹ The number of cases of serious thrombosis is nearly triple the incidence of cancer in the United States. Venous thrombosis alone, including deep vein thrombosis (DVT) and pulmonary embolism (PE), accounts for

more than 600,000 cases in the United States each year. The magnitude of the problem of thrombosis justifies significant attention to thrombosis prevention and treatment.

Evolution of DVT Management

Several highlights in the evolution of DVT management warrant mention (Figure). These highlights reflect advances that form the basis for current management strategies. In the early part of the 20th century, medical literature was replete with case reports of patients presenting to the hospital with a swollen limb and then unexplainably dying 1 to 2 days later. After heparin was introduced for clinical use in 1937—21 years after its discovery—the number of reported deaths in such cases dropped dramati-

ically. Thus it was felt that using an antithrombotic agent for swollen legs, or DVT, would have a great impact not only on alleviating patients' leg symptoms but in extending their overall survival rate.

Despite anecdotal reports of the benefits of heparin, the first randomized prospective trial of heparin therapy for acute venous thromboembolic disease didn't appear until 1960 when a pivotal study by Barritt and Jordan appeared in the *Lancet*.² This small study (35 patients) compared antithrombotic therapy, including heparin, with placebo in patients with acute PE. Death from PE and nonfatal recurrent PE were seen only in the placebo group. As a result, it has become standard medical practice to treat patients with acute venous thrombosis with antithrombotic therapy.

In the 1970s, low-molecular weight heparin (LMWH) was appreciated as a distinct subfraction of unfractionated heparin (UFH) that still had antithrombotic properties, despite the fact it did not have the same anticoagulant properties as standard heparin. The first randomized, prospective, controlled trial comparing an LMWH with UFH for DVT treatment was published in 1985.³ Other highlights in the evolution of DVT treatment include an appreciation for the importance of treatment intensity and for rapidity in achieving therapeutic intensity anticoagulation.⁴ Subsequently, Raschke et al demonstrated the ability of weight-based UFH dosing to accelerate the achievement of the target intensity activated partial-thromboplastin time (aPTT), within 24 hours of presentation.⁵ The evolution culminated in weight-based subcutaneous enoxaparin sodium receiving Food and Drug Administration approval in December of 1998 for the inpatient and outpatient treatment of acute DVT.

Composition and Mechanism of Action of UFH

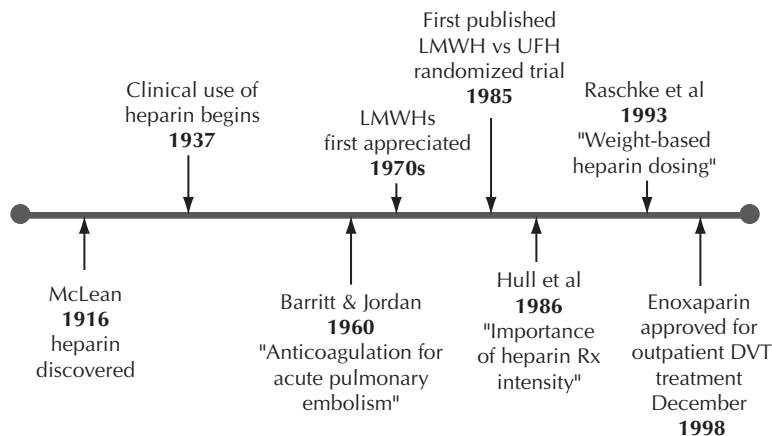
UFH is a heterogeneous mixture of polysaccharide (sugar) chains ranging

in molecular weight from 3000 to 30,000 Daltons with a mean molecular weight of 15,000 Daltons. A randomly distributed unique pentasaccharide sequence in heparin is responsible for binding to the natural anticoagulant protein called antithrombin. This binding leads to a conformational change in antithrombin that accelerates its ability to inactivate 2 very key coagulation enzymes, thrombin and factor Xa, by about 1000 times.⁶ Most pentasaccharide-containing heparin chains are at least 18 sugar units long and able to equally inactivate thrombin and factor Xa. Further enhancing the antifactor Xa activity of heparin is its ability to promote the release of tissue factor pathway inhibitor from endothelial cells.⁷

Enoxaparin Sodium Composition and Mechanism of Action

Enoxaparin sodium a LMWH is composed of fragments of UFH produced by benzoylation and alkaline depolymerization, yielding chains with a mean molecular weight of

Figure. Evolution of DVT Management



DVT = deep vein thrombosis; LMWH = low-molecular weight heparin; UFH = unfractionated heparin.

approximately 4500 Daltons, significantly less than the 15,000 Daltons mean molecular weight of UFH. Enoxaparin, too, exerts its antithrombotic activity by activating antithrombin, but fewer than half of the pentasaccharide-containing chains are of sufficient length to bind both antithrombin and thrombin. As a result, LMWH has preferential activity against factor Xa, with an anti-Xa to anti-IIa ratio of 2.7:1.⁸ This is in contrast to the anti-Xa to anti-IIa ratio of UFH which is 1:1. Enoxaparin sodium also promotes the release of tissue factor pathway inhibitor from endothelial cells, which enhances its antifactor Xa activity. Some data suggest that tissue factor pathway inhibitor release is more pronounced and sustained following enoxaparin administration than following UFH.

Pharmacokinetic Properties of Heparin Versus LMWH

As seen in Table 1, some very notable pharmacokinetic differences exist between heparin and LMWH. At low dose, UFH bioavailability is only 30% versus 90% for

enoxaparin.⁹ UFH has a propensity to nonspecifically bind to cells such as platelets, endothelial cells, and reticulo-endothelial cells, as well as to acute-phase proteins. This binding results in a saturable cellular uptake that limits its biological availability. Renal elimination is responsible for the remainder of UFH clearance.

LMWH, on the other hand, lacks this nonspecific cellular uptake and has essentially a nonsaturable, almost exclusively renal elimination. As a result, the bioavailability and antithrombotic efficacy of the 2 drugs at low doses differ significantly—30% for UFH versus 90% for LMWH. At a higher dose (>17,500 units of UFH), bioavailability of the 2 tends to equalize.¹⁰

In summary, both UFH and LMWH are able to accomplish several key goals of venous thrombosis therapy, namely to prevent thrombus extension, thrombus embolization, and early and late recurrence. Advantages of LMWH over UFH include less binding to plasma proteins and proteins released from activated platelets and endothelial

Table 1. Comparison of Pharmacokinetic Properties of UFH and LMWH

	UFH	LMWH
Bioavailability (low doses)	30%	90%
Bioavailability (high doses)	90%	90%
Elimination (low doses)	Renal elimination	Renal elimination
Elimination (high doses)	Cellular uptake (saturable)	Renal elimination (nonsaturable)
Plasma half-life	Dose dependent (0.5 to 4 hours)	Dose independent (3 to 6 hours SC)

LMWH = low-molecular weight heparin; SC = subcutaneous; UFH = unfractionated heparin.

cells, a more predictable anticoagulant response, better bioavailability at low doses, a dose-independent clearance mechanism, and longer half-life. These advantages can also be described as practical therapeutic advantages, including:

- Once- or twice-daily subcutaneous weight-based dosing
- Elimination of therapeutic monitoring for most patients
- Less heparin-induced thrombocytopenia, a syndrome of paradoxical thrombosis associated with heparin
- Less osteoclast activation and bone density loss, especially significant for patients being treated in the setting of cancer and pregnancy¹¹

Meta-Analyses Comparing LMWH with UFH in DVT Treatment

The numerous early randomized trials comparing LMWH with UFH lacked sufficient power to adequately address the issue of efficacy and safe

ty equivalency. This issue was initially addressed in the form of a meta-analysis. Conclusions drawn from several meta-analyses were that LMWH, in general, are superior in efficacy and safety compared with UFH (Table 2). Besides the obvious limitations of meta-analysis, these particular analyses included individual studies using several different LMWHs in varying doses and varying schedules. Of particular interest are the meta-analyses published by Lensing et al¹³ and Siragusa et al.¹⁴ In these reports, a subgroup analysis of cancer patients with acute thrombosis revealed mortality rates approximately 50% lower for those patients treated with LMWH initially. These findings have stimulated a recent interest in the use of LMWH as a means of modifying the natural history of malignancy.

Randomized Trial Comparing Enoxaparin with UFH in DVT Treatment

In the first major published randomized trial comparing enoxaparin

Table 2. Meta-Analyses: Subcutaneous LMWHs Versus IV Unfractionated Heparin for Initial DVT Therapy

Study	n	VTE Recurrence	Major Bleed	Overall Mortality	Mortality in Cancer Patients
Leizorovicz et al ¹² (10-day to 23-month follow up)	2034 (All)	2.82% vs 4.63% RR 0.66 (0.41-1.07) P = 0.09	2.43% vs 4.04% RR 0.65 (0.36-1.16) P = 0.15	3.30% vs 4.83% RR 0.72 (0.46-1.40) P = 0.16	N/A
Lensing et al ¹³ (3- to 6-month follow up)	1086 (VTE) 1512 (Bleed) 1086 (Mortality)	3.1% vs 6.6% RR 0.47 (0.27-0.82) P < 0.01	0.8% vs 2.8% RR 0.32 (0.15-0.69) P < 0.005	3.9% vs 7.1% RR 0.53 (0.31-0.90) P < 0.04	12% vs 28% RR 0.44 (0.17-0.76) P < 0.01
Siragusa et al ¹⁴ (90-day follow up)	1228 (VTE) 1694 (Bleed) 1733 (Mortality)	2.5% vs 4.5% RR 0.5 (0.3-0.9) P = 0.2	2.2% vs 4.7% RR 0.44 (0.20-0.70) P = 0.04	3.3% vs 5.9% RR 0.51 (0.2-0.9) P = 0.01	14% vs 28% RR 0.33 (0.1-0.8) P = 0.01

134 patients in each meta-analysis were treated with enoxaparin. DVT = deep vein thrombosis; IV = intravenous; LMWH = low-molecular weight heparin; RR = relative risk; VTE = venous thromboembolism.

Table 3. Treatment of Proximal DVT

Condition Measured	Number of Patients	
	Enoxaparin, 1 mg/kg SC q12h (n=67)	UFH, Adjusted Dose IV (n=67)
Thrombus size**		
Increase	1	5
No change	24	34
Decrease	35	18
Recurrent VTE**	1 (1.5%)	7 (10.4%)
Major bleeding*	0	0

*Days 1 through 10; †P < 0.002
DVT = deep vein thrombosis; IV = intravenous; q12h = every 12 hours; SC = subcutaneous;
UFH = unfractionated heparin; VTE = venous thromboembolism.
Source: Reference 15.

Table 4. Design and Studied Endpoints of Trial Performed by Levine et al

- DVT patients were randomly assigned to receive adjusted-dose IV unfractionated heparin in the hospital or enoxaparin sodium (1 mg/kg SC twice daily) primarily at home
- Oral warfarin therapy was begun on the second day of therapy in all patients
- Clinical endpoints included symptomatic recurrent venous thromboembolism within 90 days of randomization and bleeding during study medication use within 48 hours after its discontinuation

DVT = deep vein thrombosis; IV = intravenous; SC = subcutaneous.
Source: Reference 16.

Table 5. Clinical Outcomes of Enoxaparin Clinical Trials Group Study Comparing SC Enoxaparin with IV Unfractionated Heparin for the Initial Treatment of DVT

Recurrent condition	Number of Patients Experiencing Recurrent Condition		
	UFH (n = 290)	Enoxaparin, once daily (n = 298)	Enoxaparin, twice daily (n = 312)
Proximal DVT	7	7	7
Distal DVT	3	1	0
PE alone	1	1	2
PE and DVT	3	1	0

DVT = deep vein thrombosis; IV = intravenous; PE = pulmonary embolism; SC = subcutaneous;
UFH = unfractionated heparin.
Source: Reference 17.

with UFH, researchers evaluated thrombus size, venous thromboembolic event (VTE) recurrence, and major bleeding during the first 10 days following DVT diagnosis.¹⁵ The investigators found that among 67 patients randomized in each arm of the trial, an increase in thrombus size was experienced by 1 enoxaparin patient versus 5 UFH patients; no notable change was reported in 24 enoxaparin patients versus 34 UFH patients; and a reduction in size at day 10 was reported in 35 enoxaparin patients versus 18 UFH patients. With regard to recurrence, 1.5% of patients treated with enoxaparin demonstrated evidence of recurrence at day 10 versus 10.4% in those treated with UFH ($P < 0.002$). No significant difference in bleeding between the 2 groups was reported at day 10 (Table 3).

Trials Comparing Subcutaneous Enoxaparin with IV UFH for Initial DVT Treatment

In a trial performed by Levine et al,¹⁶ 247 DVT patients were randomly assigned to receive subcutaneous enoxaparin 1.0 mg/kg administered twice a day primarily at home. Adjusted-dose UFH was administered intravenously to 253 patients. Oral warfarin therapy was begun by the second day of therapy in all patients in both groups (Table 4).

At 90 days, 5.3% of the enoxaparin group experienced recurrence of thromboses versus 6.7% of the UFH patients. No significant difference in major bleeding was reported between the groups. Thus, enoxaparin and UFH were equivalent with regard to safety and efficacy. The most dramatic difference between treatment arms was reflected in hospital length of stay. The mean length of stay for patients treated with enoxaparin was 1.1 days versus 6.5 days for UFH patients. In fact, 48% (120) of the enoxaparin patients were able to be treated entirely on an outpatient

basis. Those enoxaparin patients, who were initially admitted, had an average length of stay of only 2.2 days. These data suggest that

[In a trial performed by Levine et al,] enoxaparin and UFH were equivalent with regard to safety and efficacy. The most dramatic difference between treatment arms was reflected in hospital length of stay.

many patients with acute proximal DVT can be simply and effectively treated in the outpatient setting with weight-based dosing of subcutaneous enoxaparin. Outpatient DVT therapy is well tolerated and convenient and may have the added benefit of substantially reducing healthcare costs.

As a result of this trial, in December 1998, indications for enoxaparin treatment were granted for inpatient treatment of acute DVT with and without PE when administered in conjunction with warfarin, and for outpatient treatment of acute DVT without PE when administered in conjunction with warfarin.

In a subsequent study conducted by the Enoxaparin Clinical Trials Group,¹⁷ the efficacy and safety of subcutaneous enoxaparin once and twice daily were compared to continuous intravenous infusions of UFH in the treatment of DVT patients with or without PE. This randomized, partially blind, parallel-group clinical trial consisted of 3 treatment arms: enoxaparin 1.5 mg/kg once daily; enoxaparin 1.0 mg/kg twice daily; and UFH weight-based bolus and infusion with therapeutic monitoring based on the aPTT. Clinical outcome was assessed over 3 months with the finding that there

was no significant difference in efficacy with regard to the recurrence of proximal DVT, distal DVT, PE alone, and PE with DVT (Table 5). No statistically significant difference was reported in major bleeding outcomes or death. Based on these findings, subcutaneous enoxaparin administered once or twice daily for treatment of DVT is equivalent to UFH.

Opportunities for future study include evaluation of enoxaparin's efficacy for the prevention of DVT within high-risk groups and for treating thrombosis in patients with conditions such as pregnancy, cancer, obesity, or renal insufficiency, and within the pediatric age group. Thrombosis does not exclude these individuals, and more data and information pertaining to these groups is needed. Moreover, barriers to outpatient treatment of DVT must be removed to allow LMWH to become the standard of care.

Conclusion

Many cases of acute proximal DVT can be simply and effectively treated in the outpatient setting with weight-based dosing of subcutaneous enoxaparin. Outpatient DVT therapy is well tolerated and convenient, and may also substantially reduce healthcare system costs. Moreover, subcutaneous enoxaparin administered once or twice daily as treatment for DVT is as safe as continuous infusion UFH, based on the incidence of major hemorrhage and death.

... REFERENCES ...

1. Bick RL, Kaplan H. Syndromes of thrombosis and hypercoagulability. Congenital and acquired causes of thrombosis. *Med Clin North Am* 1998;82:409-448.
2. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism: A controlled trial. *Lancet* 1960;i:1309-1312.
3. Bratt G, Tornebohm E, Granqvist S, et al. A comparison between low molecular weight heparin (KABI 2165) and standard heparin in the intravenous treatment of deep venous thrombosis. *Thromb Haemost* 1985;54:813-817.
4. Hull RD, Raskob GE, Hirsh J, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal vein thrombosis. *N Engl J Med* 1986;315:1109-1114.
5. Raschke RA, Reilly BM, Guidry JR, et al. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med* 1993;119:874-881.
6. Weitz JI. Low molecular weight heparins. *N Engl J Med* 1997;337:688-698.
7. Broze GJ Jr. Tissue factor pathway inhibitor. *Thromb Haemost* 1995;74:90-93.
8. Hirsh J, Levine MN. Low molecular weight heparin. *Blood* 1992;79:1-17.
9. Barrowcliffe TW. Low molecular weight heparin(s). *Br J Haematol* 1995;90:1-7.
10. Pini M, Pattocini C, Quintavalla R, et al. Subcutaneous vs. intravenous heparin in the treatment of deep venous thrombosis—a randomized clinical trial. *Thromb Haemost* 1990;64:222-226.
11. Monreal M, Lafoz E, Olive A, et al. Comparison of subcutaneous unfractionated heparin with a LMWH (Fragmin) in patients with venous thromboembolism and contraindications to coumadin. *Thromb Haemost* 1994;71:7-11.
12. Leizorovicz A, Simonneau G, Decousus H, et al. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: A meta-analysis. *BMJ* 1994;309:299-304.
13. Lensing AW, Prins MH, Davidson BL, et al. Treatment of deep venous thrombosis with low molecular weight heparins and unfractionated heparin in initial treatment of venous thrombosis: A meta-analysis. *Arch Intern Med* 1995;155:601-607.
14. Siragusa S, Cosmi B, Piovella F, et al. Low molecular weight heparins and unfractionated heparins in the treatment of patients with acute venous thromboembolism: Results of a meta-analysis. *Am J Med* 1996;100:269-277.

15. Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low molecular weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med* 1993;13:1541-1546.

16. Levine M, Gent M, Hirsh J, et al. A com

parison of low molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. *N Engl J Med* 1996;11:677-681.

17. Data on file. Aventis Pharmaceuticals, Inc., Parsippany, New Jersey.