Low Molecular Weight Heparin

Smaller is Better!

Guna Raj, M.D.

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Guna Raj, M.D.

Assistant Professor
Department of Internal Medicine
University of Texas Southwestern Medical Center

Section of General Internal Medicine
Veterans Affairs Medical Center, Dallas

Interests
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Primary Care

Introduction

Heparin was discovered in 1916 by Jay McLean, who as a medical student was assigned the task of isolating thromboplastic substances from the liver. He found that one of the substances, heparphosphatid did not promote coagulation, but in fact showed marked power to inhibit coagulation (1). This was later named heparin, by Howell, (in whose laboratory McLean made the initial discovery) because of its natural abundance in animal livers or "hepars". Its potential as an antithrombotic agent was recognized, and heparin was developed as a drug by research groups headed by Charles H. Best in Toronto and Erik Jorpes in Stockholm. (2)

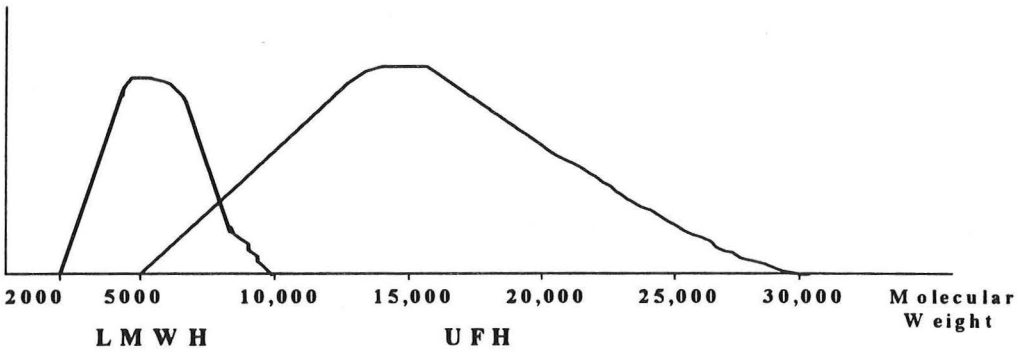
Unfractionated Heparin

Heparin is a highly sulfated glycosaminoglycan (GAG) that is present naturally in mast cells of animal tissues including lung, liver and intestines. The commercial sources for this substance are bovine or porcine lung and intestine. Standard or unfractionated heparin (UFH) is a heterogeneous mixture of polysaccharides with molecular weights ranging between 5000-30,000 daltons (average MW of 12000-15,000 daltons) (3,4). The different components of heparin have different affinity for endogenous modulators of their function, which will be discussed later. The therapeutic anticoagulant action of heparin represents a cumulative effect of its interaction with all of these modulators (5).

Low Molecular Weight Heparin

Low molecular weight heparins (LMWH) are fractions or fragments of UFH with a mean molecular weight of 4000 to 6500 daltons, and are obtained by gel filtration or solvent extraction. LMWH differs from UFH in molecular weight distribution (Fig 1), pharmacologic activity and pharmacokinetics (5-8).

Fig 1. MW distribution of UFH and LMWH

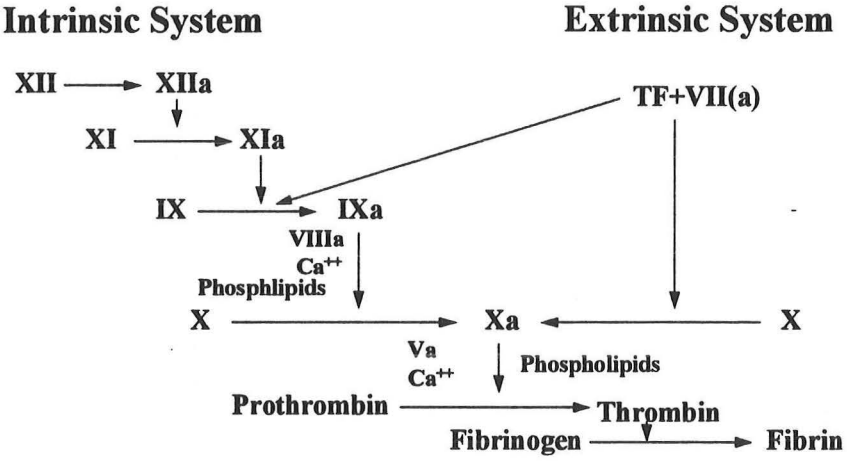


Mechanism of action of Heparin:

The Coagulation Cascade

Figs 2 and 3 show a simplified view of the coagulation cascade to provide a perspective for understanding the mechanism of action of heparin (9,10). Coagulation process is the sequential activation of precursors of coagulation factors (zymogens) to their derivative enzymes by limited proteolysis, with factors V and VIII serving as cofactors in their active form.

Fig 2. Coagulation Cascade



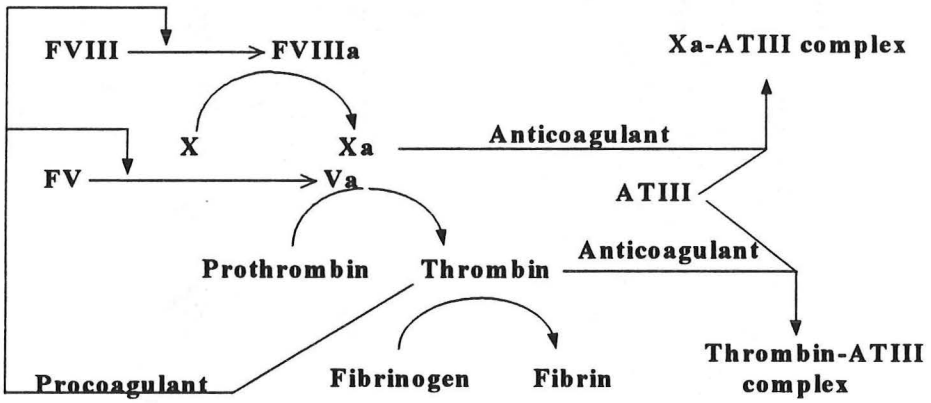
By convention the inactive precursors or zymogens are designated by the Roman numeral and the active form by the Roman numeral with the subscript "a". e.g. factor X and Xa. Factor VII is thought to have some enzymatic activity in its native form, and therefore, the zymogen and the enzyme are together referred to as factor VII(a). The dominant pathway of coagulation is initiated by the interaction of factor VII(a) with tissue factor (TF), a specific protein present on the plasma membrane of many cells. When tissues are injured, this protein is exposed to, and comes in contact with factor VII(a). The physical association of VII(a) with TF converts it into a two-chain serine proteinase and results in the initiation of the extrinsic pathway of coagulation, leading to the conversion of X to Xa. The tissue factor pathway also converts factor IX to IXa and results in the activation of X indirectly (11,12). Both the intrinsic pathway, beginning with factors XIIa and continuing with XIa and IXa, and the extrinsic pathway culminate in the activation of factor X to Xa, and the formation of the ***prothrombinase complex*** comprising of Xa (an enzyme), Va (a cofactor), Ca^{++} and phospholipids, on the platelet membrane. The prothrombinase complex converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin and leads to clot formation. Thrombin also leads to the activation of factors V and VIII, and platelets, and thus plays a central role in the coagulation process. Concomitant with the

initiation of coagulation and the generation of thrombin, the two principal anticoagulants, i.e., antithrombin III (ATIII) (Fig 3) and protein C are also activated to regulate the activity of the proteinases.

Heparin-Antithrombin III Interaction

In 1939 Brinkhous et al demonstrated that the anticoagulant action of heparin required a plasma cofactor which they called heparin cofactor, and was subsequently renamed antithrombin III by Abildgaard (13). The major anticoagulant effect of heparin is through its interaction with ATIII, whereby thrombin and the other serine proteinases (IXa, Xa, XIa and XIIa) of the intrinsic coagulant pathway are inhibited. Of these, inhibition of thrombin and Factor Xa is physiologically the most significant reaction (Fig 3).

Fig 3. Antithrombin III Mediated Regulation of Coagulation



Heparin binds to lysine sites on ATIII and produces a conformational change in its arginine reactive center. This transforms ATIII from a progressive, slow inhibitor of serine proteinase to a very rapid inhibitor. After inactivation of a serine proteinase, heparin dissociates from the complex and can be reutilized. Of the serine proteinases, thrombin is the most sensitive to inhibition by heparin for two reasons; ATIII inhibits thrombin more rapidly than factor Xa, and factor Xa, when bound to platelet membrane phospholipid in the prothrombinase complex is protected from inhibition by the heparin-ATIII complex(13,14).

The AT III binding property, and hence the anticoagulant activity of heparin resides in a unique pentasaccharide sequence that is randomly distributed along the heparin molecule (15-17) (Fig 4). Only about one third of the standard heparin molecules contain this pentasaccharide sequence and participate in ATIII mediated anticoagulation. The main difference between unfractionated heparin and LMWH is in their interaction with factor Xa and thrombin as shown in Fig 5 (14,18,19).

Fig 4. Pentasaccharide Sequence

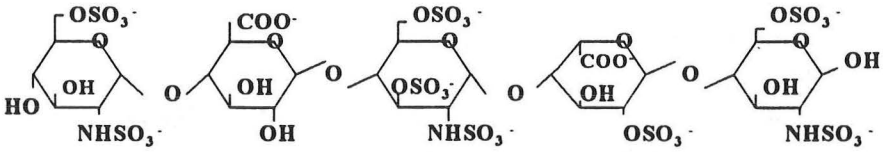
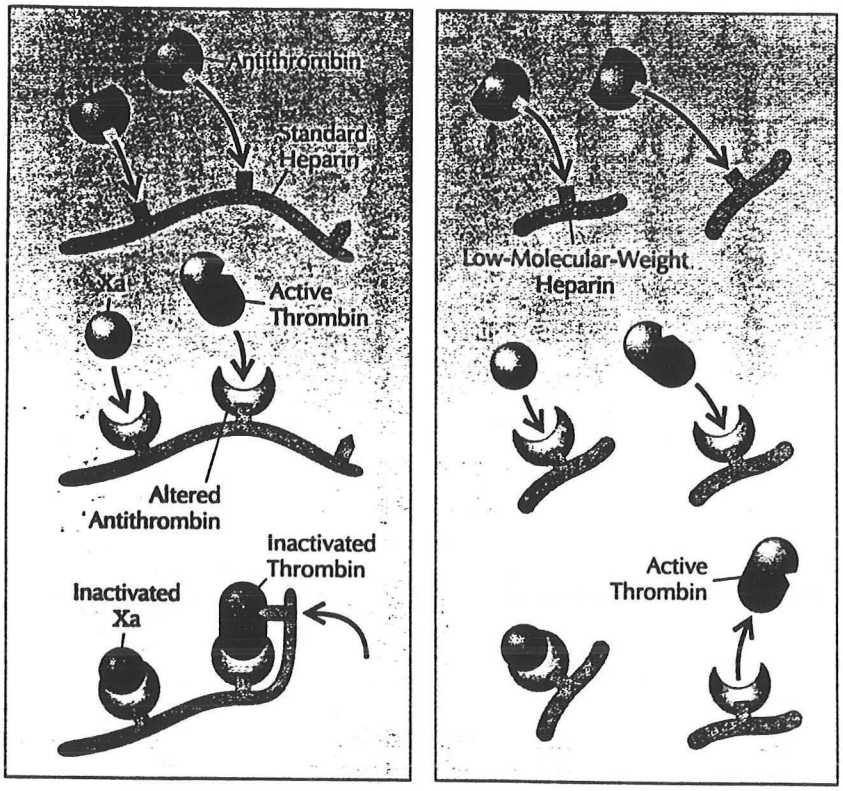


Fig 5. Heparin-ATIII Mediated Inhibition of Xa and Iia



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The glycosaminoglycans potentiate the inactivation of thrombin by serving as a template to which both ATIII and thrombin bind to form a ternary complex. This requires a minimum chain length of 18 saccharide units, the pentasaccharide unit for binding to ATIII and an additional 13 saccharide unit for binding to thrombin. UFH, with a mean molecular weight of 12000-15000 daltons and a mean chain length of 40-50 saccharide units can bind to ATIII and thrombin simultaneously. LMWH molecules with less than 18 saccharide units (MW <5,400) cannot bind

to thrombin and ATIII simultaneously and, therefore cannot accelerate the inactivation of thrombin. On the other hand, inactivation of Xa requires only the minimum pentasaccharide sequence for binding to ATIII, which in turn binds to Xa. Virtually all the molecules of UFH contain at least 18 saccharide units, where as only 25-50% of the different low molecular weight heparins contain fragments with 18 or more saccharide units. Therefore, the ratio of anti-Xa to anti-IIa activity of UFH is approximately 1:1, but varies from 4:1 to 2:1 among the different LMWHs.

Antithrombotic and Anticoagulant Effects of Glycosaminoglycans

The antithrombotic effect of a drug is its ability to prevent the formation of a thrombus or to inhibit its propagation, and is a desirable therapeutic effect. The anticoagulant effect is its ability to inhibit hemostasis, which is responsible for the undesirable side effect of bleeding. These properties are assayed in experimental animals in vivo, using variations of the Wessler model of venous thrombosis, where thrombus formation is induced in isolated jugular veins of animals by a combination of stasis and administration of procoagulants. The antithrombotic effect of different preparations are then compared by measuring the relative inhibition of accretion of labeled fibrinogen onto preformed thrombi, and expressed in terms of heparin level by protamine titration units or as anti-Xa or anti-IIa units/ml. Anticoagulant effects are measured directly by quantitating blood loss from a standardized injury to the microvasculature or indirectly by global clotting tests such as the activated partial thromboplastin time (APTT) or the thrombin time (TT) (20-21).

UFH produces marked inhibition of fibrinogen accretion (<10% of control accretion) at an APTT value of between 75 and 80 seconds (control 34 sec) and at a level of heparin activity of 0.4-0.5 U/ml by protamine titration (22). In comparative studies, at equivalent doses, LMWH produced greater inhibition of fibrinogen accretion (approximately 20 fold, compared to about ten fold inhibition with UFH) with a significantly smaller increment in the mean APTT and TT (Table 1) (23).

Table 1. Antithrombotic and Anticoagulant Effects of UFH and LMWH

Experiment	Mean Total Heparin Dose	Fibrinogen Accretion	Mean ΔAPTT (± 1 SD)
Saline		156.1 ugms	-
UFH	425 USP/Kg	16.7 ugms	83 ± 15.7
LMWH	403 USP/Kg	5.9 ugms	30 ± 19.6

From Ref. 23

Although both UFH and different LMWHs prevented venous thrombosis at anti-Xa levels of 0.1-0.2 U/ml, for a similar antithrombotic effect, LMWHs produced significantly less bleeding than UFH (24). It is important to note that LMWH does affect clotting tests, but not to the same extent as UFH. What determines this superior efficacy to safety ratio of LMWHs?

Other Effects of Heparin on Hemostasis

Besides potentiating the activity of AT III, UFH has other properties that can influence its hemostatic effect. UFH is capable of inactivating thrombin through interaction with heparin cofactor II (HC II), another serine proteinase inhibitor highly homologous with ATIII. This effect is specific for thrombin, does not require the unique pentasaccharide sequence, and requires a minimum chain length of 24 saccharide units (MW approx. 7,200). However, this action of heparin does not appear to be significant at doses used clinically (14). By inhibiting thrombin, and preventing the generation of thrombin, heparin can prevent the thrombin mediated activation of factors V and VIII. Heparin binds to platelets in vitro and can either induce or inhibit platelet function depending on the experimental conditions (27,28). Heparin also interacts with endothelial cells and causes increased vascular permeability. These interactions of heparin with platelets and endothelial cells may contribute to heparin induced bleeding by mechanisms that are independent of its antithrombotic properties. Furthermore, heparin binds nonspecifically to several plasma and matrix proteins, including von Willebrand Factor (vWF), platelet factor 4 (PF4), histidine-rich glycoprotein (HRGP), fibronectin (Fn) and vitronectin (Vn) (Table 2).

Table 2. Effect of Heparin on Hemostasis

ATIII dependent effect	Inactivates IIa, Xa, IXa, XIIa
HCII dependent effect	Inactivates IIa
Platelet interaction#	Inhibits Platelet aggregation*
Endothelial cell interaction#	Increases vascular permeability
Nonspecific Protein binding vWF, PF4, HRGP, Fibronectin, Vitronectin	Decreased bioavailability, HIT

*can also promote aggregation under certain conditions

accounts for the increased hemorrhagic potential in experimental animals

PF4 and HRGP inhibit or neutralize the effect of heparin, whereas binding to the other proteins results in complicated pharmacokinetics and decreased bioavailability of UFH.

Properties of LMWH

Chemical or enzymatic depolymerization is used to obtain LMWH from UFH for commercial purposes. The molecular composition, and hence the molecular weight and biologic activity of the different LMWH preparations vary depending on the manufacturing process used. Several products have been marketed after undergoing clinical trials and new ones are being evaluated. An International Standard (IS) for low molecular weight heparin was established in 1986 to compare and standardize the different LMWHs. This first IS LMWH preparation has an anti-Xa

activity of 168 IU/mg, anti-IIa activity of 67 IU/mg and anti-Xa:anti-IIa ratio of 2.5 (25,26). All LMWHs are assigned specific activity units by the manufacturers after assay of those products against the IS. Table 3 lists the activity of the IS LMWH and some LMWH brands along with UFH for comparison.

Table 3. Anticoagulant activities of LMWHs

	Anti-Xa (IU/mg)	Anti-IIa (IU/mg)	Ratio
UFH (4th IS)	193	193	1.0
LMWH (Ist IS)	168	67	2.5
Fragmin	130	58	2.2
Logiparin	79	53	1.5
Fraxiparine	95	27	3.5
Clexane	98	25	3.9

Ref. 26

Is LMWH better than UFH?

Although on a molar basis, UFH appears to have more antithrombotic potency, there are several factors that make it less effective in vivo, compared to LMWH; 1) Platelet Factor 4 that is released during coagulation is a powerful inhibitor of UFH but not of LMWHs, 2) UFH binds to HRGP and is inhibited by it (29), 3)UFH is also less effective in potentiating the inactivation of Xa in the prothrombinase complex (Xa bound to phospholipids on the platelet membrane) than LMWH (30). LMWH can inhibit fibrin bound thrombin more effectively than UFH. The decreased hemorrhagic potential of LMWH has been observed in animal experiments and has been demonstrated in some recent clinical studies, particularly in the treatment of established thrombosis.

Table 4. Comparison of UFH and LMWHs

	Unfractionated Heparin	**LMWHs**
Mean MW	12,000-15,000	4,000-6,500
Mean Saccharide units	40-50	13-22
Anti-Xa : Anti-IIa activity	1:1	2:1 to 4:1
Neutralization by Platelet factor 4	Yes	No
Binding to Endothelium	Yes	Weak to none
Inactivation of platelet bound Xa	Weak	Strong
Inhibition of Platelet Function	++++	++
Induction of thrombocytopenia	not rare	very rare
Nonspecific protein binding	Vn, Fn, HRGP, vWF, PF4	Vn
Bioavailability after SC administration	≈30 %	>90%
Dose response	Poor	Fair
Increase in vascular permeability	Yes	No

Ref. 2,14

In addition, LMWH has several advantages over UFH, including less platelet interaction, less nonspecific protein binding and endothelial binding, all of which result in superior bioavailibilty and decreased side effects such as thrombocytopenia and experimental bleeding. In comparative studies, the bioavailability, after subcutaneous (SC) administration is about 30% for UFH and >90% for LMWH. There are other differences between UFH and LMWH as well, some that are clearly significant (Table 4), while the significance of the others is unknown at this time.

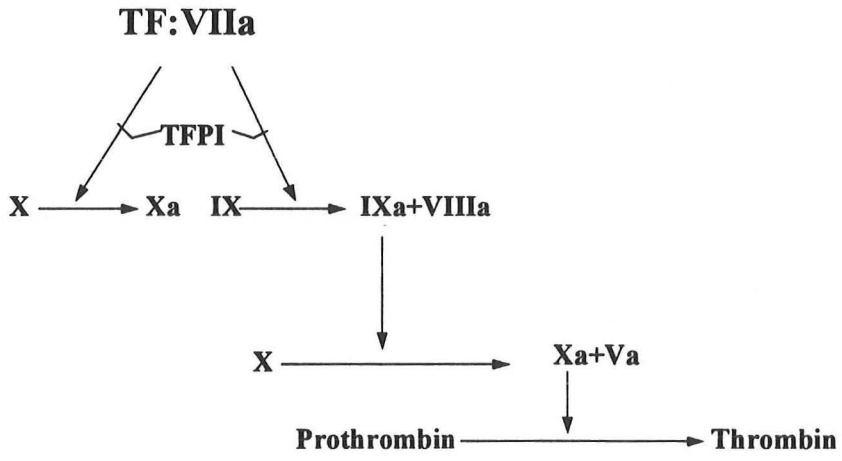
Effect of Heparin on the Extrinsic (Tissue Factor) Pathway of Coagulation

Until recently, it was believed that heparin exercised its anticoagulant effect mainly by inhibiting the serine proteinases of the intrinsic and the common pathways of coagulation. There is now evidence that heparin also affects the tissue factor pathway.

Tissue Factor Pathway Inhibitor

Regulation of the extrinsic pathway requires the presence of an inhibitor, Lipoprotein-Associated Coagulation Inhibitor (LACI), present in the lipoprotein fraction of plasma. This protein is now referred to as Extrinsic Pathway Inhibitor (EPI) or Tissue Factor Pathway Inhibitor (TFPI) (31). TFPI mediated regulation of extrinsic coagulation requires the presence of VII(a)-TF complex, Xa, Ca^{++} and TFPI. Thus, factor Xa that is generated by tissue factor pathway binds to TFPI and causes feedback inhibition of TF-VII(a) by binding to TF-VII(a) in the presence of Ca^{++} and forming an inert TF/VII(a)/Xa/Ca^{++}/TFPI complex (Fig 6). What, if any, is the role of heparin in this process?

Fig 6. Tissue Factor Pathway Inhibitor



With the availability of recombinant TFPI and anti-TFPI antibodies, it is now possible to study the effect of TFPI in normal plasma, plasma depleted of TFPI by immunoadsorption with anti-TFPI IgG, and plasma to which exogenous TFPI is added. Table 5 shows the effect of increasing dilutions of TF on the PT of normal and TFPI depleted plasma. Prothrombin time (PT) is increasingly prolonged with decreasing levels of TF. At dilutions of TF of 1:10 to 1:1000, the

difference in PT between normal and TFPI depleted plasma is very little, but becomes more substantial at 1:10,000. Similar results were obtained by adding exogenous TFPI to depleted plasma suggesting that TFPI has a modest effect on the extrinsic pathway of coagulation at high dilutions of TF(32). However, addition of heparin changes this dramatically (Fig 7).

Table 5. Effect of TFPI on the Prothrombin Time of Normal Plasma

	PT (seconds)	
TF dilution	**Plasma+ Nonspecific Ig (TFPI intact)**	**Plasma + Anti TFPI-Ig (TFPI depleted)**
1:10	27.1	25.5
1:100	44.6	42.7
1:1,000	86.1	75.5
1:10,000	175.7	129.1

Modified from Ref. 32.

In TFPI-depleted plasma, increasing concentrations of heparin (0-0.6U/ml plasma) progressively prolong the PT in a linear fashion. With intact TFPI, and TF at 1:1000 and 1:100 dilution, plasma becomes fully anticoagulated (remains unclotted for more than 1 hour) at heparin concentrations of 0.5U/ml and 2U/ml respectively, suggesting that heparin is a cofactor for TFPI. At TF dilutions of 1:10, heparin induced prolongation is much less, suggesting that heparin potentiates the effect of TFPI at lower concentrations of TF. Several different antithrombotic agents, including UFH, LMWH and other related polysaccharides such as pentosan polysulfate, dermatan sulfate and heparan sulfate are capable of enhancing the anticoagulant effect of TFPI. LMWH appears to potentiate TFPI activity at a lower concentration than any of the other polysaccharides (Fig 8) (32).

Fig 7. Effect of Heparin on TFPI and PT

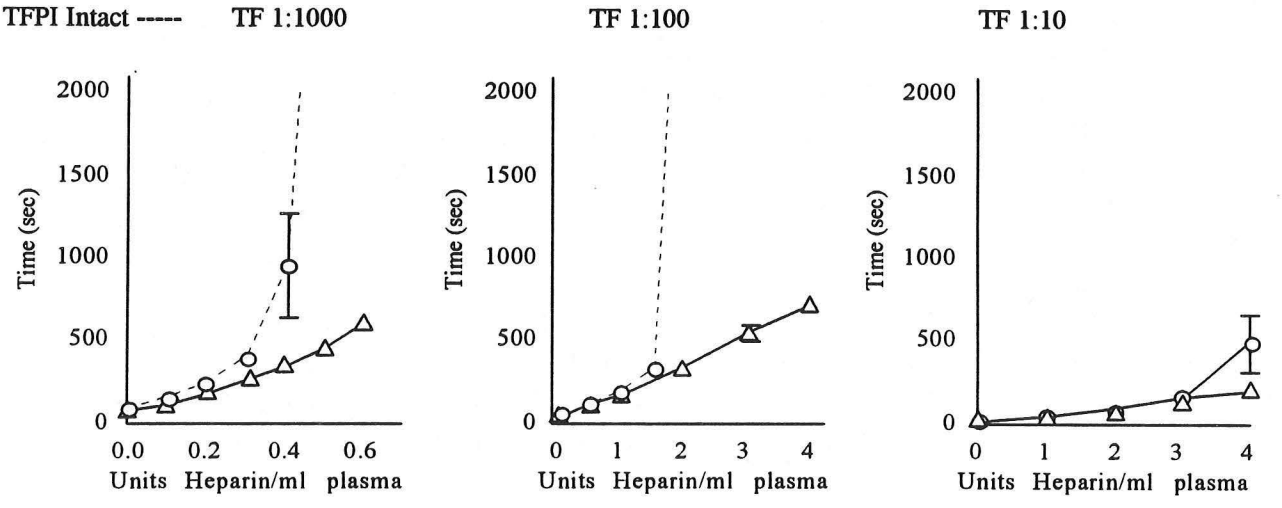
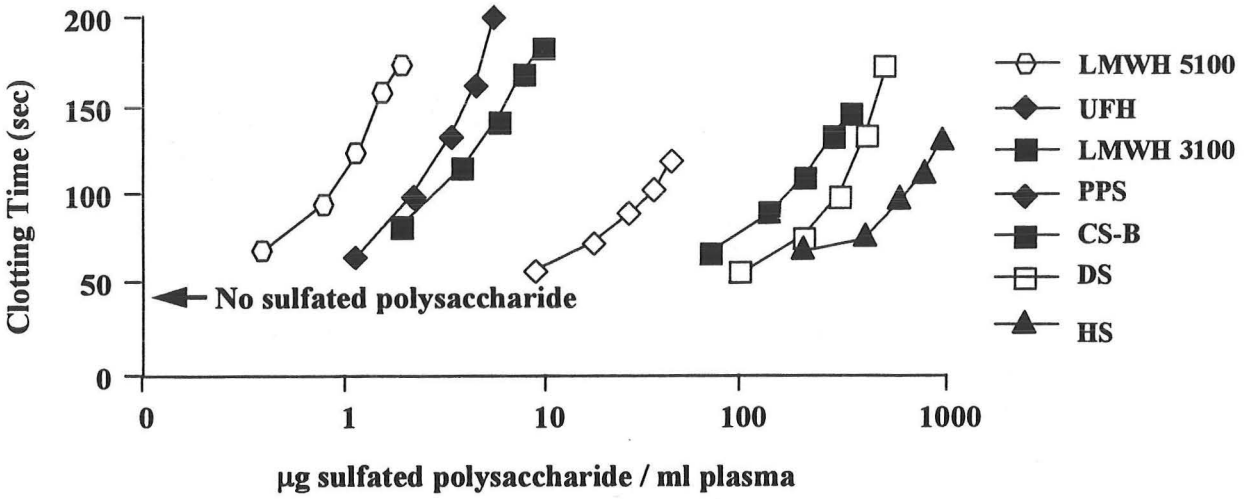


Fig 8. Effect of Different Sulfated Polysaccharides on PT of Normal Plasma

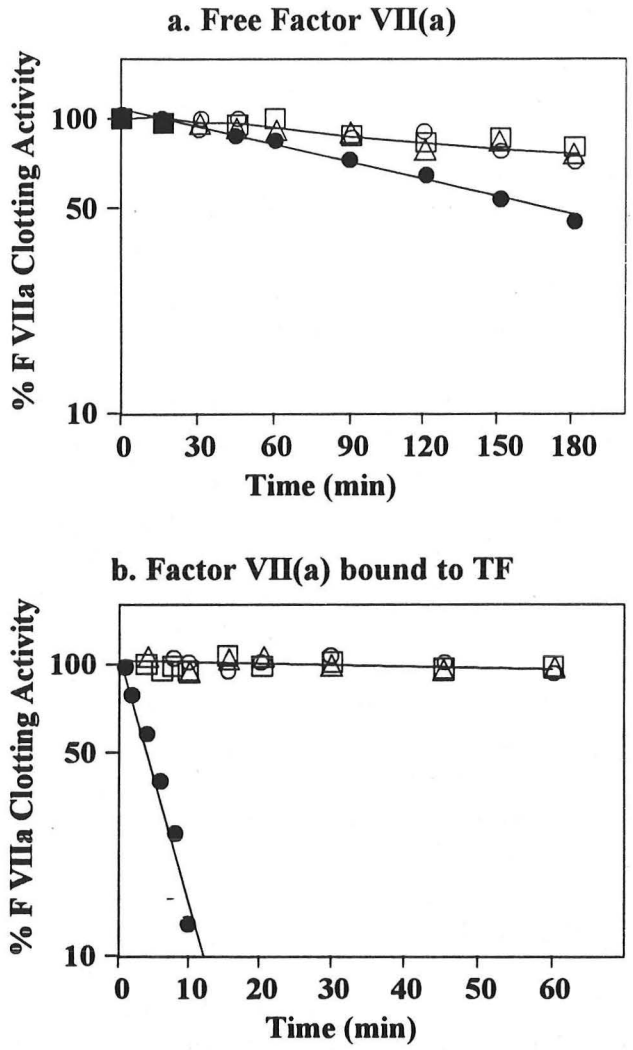


In addition, studies in human volunteers and in patients receiving prophylaxis for deep vein thrombosis (DVT) after general and orthopedic surgery have shown that both UFH and LMWH stimulate the release of TFPI from endothelial cells (33-35).

Effect of Heparin-Antithrombin III on the Extrinsic Pathway

It has been known for some time that, in the presence of heparin, ATIII also inhibits Factor VII(a). However, the rate of inhibition is so slow that ATIII was not thought to be a physiologic regulator of the extrinsic pathway of coagulation. There is now evidence that this effect of ATIII may be significant as well, and the mechanism of this interaction has been elucidated. Fig 9a and 9b show the effect of incubating free factor VII(a) and VII(a) bound to TF at 37°C in different solutions containing 1)buffer, 2)ATIII, 3)heparin, and 4)ATIII plus heparin. ATIII, in the presence of heparin, rapidly inactivates VII(a) bound to TF, but not free factor VII(a), as measured by residual VII(a) activity in the mixture. The rate of inactivation increases with increasing concentrations of heparin (36). This suggests that factor VII(a), when bound to TF, is inactivated by ATIII, and that this reaction is potentiated by heparin. When ATIII binds to VIIa-TF complex, it leads to the dissociation of VIIa from TF. The resulting VIIa-ATIII complex is incapable of binding to any more TF (36-38). The same ATIII-binding pentasaccharide sequence of heparin that is involved in inactivating factor Xa and thrombin appears to be involved in the inactivation of factor VII(a) as well (39).

Fig 9 a-b. Time Course of Inactivation of VII(a) by Antithrombin III



(O) buffer (Δ) 100 ug/ml ATIII (□) 1 U/ml heparin (•) 100 ug/ml ATIII plus 1 U/ml heparin

It has been proposed that when coagulation is activated through the intrinsic pathway, ATIII is the primary regulator. Heparin at low concentrations (<0.6 U/ml) progressively prolongs the clotting time, and at higher concentrations (>0.8 U/ml) effectively shuts down the intrinsic cascade. When coagulation is activated through the extrinsic pathway, TFPI and ATIII are both key regulators. Heparin inactivates factor VII(a) by enhancing the action of TFPI and forming an inert TF/VIIa/Xa/TFPI/Ca^{++} complex and by causing dissociation of VII(a) from TF by ATIII mediated effect, *and* catalyzes the inhibition of downstream proteinases by ATIII.

Attractive as this hypothesis is, the physiological significance of the interaction of heparin with ATIII and TFPI in the regulation of the extrinsic pathway has not been evaluated in clinical studies. The relative effects of UFH and LMWH in this system are also not known.

Effect of heparin on platelets

Non-idiosyncratic Effect

The effect of heparin on platelets is complex. It binds to platelets, and depending on the experimental conditions, may either inhibit or induce platelet aggregation. This could be due to the heterogeneity of commercially available heparin and the presence of various plasma proteins. In citrated, platelet-rich plasma, heparin induces and enhances platelet aggregation and promotes serotonin release in response to other agonists. This effect is blocked by EDTA and substances that increase cyclic AMP content of platelets, but not by inhibitors of platelet cyclooxygenase. The effect on platelets also depends on the molecular weight of heparin. Among high molecular weight fractions, fractions with high as well as low affinity to ATIII are capable of inducing platelet aggregation, whereas, with low molecular weight fractions, there is an inverse relationship between platelet reactivity and ATIII affinity. In ATIII depleted plasma, both high and low molecular weight fractions, regardless of their ATIII affinity cause platelet aggregation, suggesting that formation of heparin-ATIII complex protects platelets from heparin induced aggregation (27,28). Thus, low molecular weight fractions with high ATIII affinity react the least with platelets. This type of nonidiosyncratic heparin-platelet interaction often results in a transient, moderate drop in platelet count and appears to be entirely benign. In one study of 665 patients treated with unfractionated or low molecular weight heparin for DVT prophylaxis, there was no difference in the frequency of early thrombocytopenia in the two groups. Ninety three of 332 patients (28%, 95% CI 23,33.2) receiving unfractionated heparin and 96 of 333 patients receiving LMWH (28.8%, 95% CI 24,34%; p 0.86) developed early thrombocytopenia. In 188 of the 199 patients (99.5%), this early thrombocytopenia resolved without sequelae in about three days despite continuation of heparin therapy (40).

Heparin-induced Thrombocytopenia

Unlike the transient thrombocytopenia alluded to above, heparin induced thrombocytopenia (HIT) is an idiosyncratic reaction induced by heparin that occurs in 1-3% of patients who receive the drug for 7-14 days. It is progressive, and is complicated by paradoxical thrombosis, with substantial morbidity and mortality. This is an immune mediated phenomenon that typically occurs after 7-10 days of therapy but can appear earlier in patients previously exposed to heparin. The target antigen recognized by patients' immunoglobulin has been identified as heparin-Platelet Factor 4 complex (41-43).

The proposed mechanism for the pathogenesis of this syndrome is illustrated in Figure 10 (44). Heparin reacts with PF4 that is normally present on the surface of endothelial cells or released in small quantities from circulating platelets. This can elicit an immune reaction in some patients and specific IgG antibodies are formed against the PF4-heparin complex. The resulting immune complex binds to the Fc receptors on circulating platelets and leads to Fc mediated platelet activation and release of more PF4 from alpha granules. Newly released PF4 binds to additional heparin with formation of more immune complexes and a cycle of platelet activation is established. Excess PF4 binds to heparin like molecules on the surface of endothelial cells, which

is also recognized by the antibody. This leads to immune complex mediated endothelial cell injury, which may then lead to thrombosis.

The seriousness of this disorder is highlighted by two recent studies (40,45). In a retrospective study of 127 patients with serologically confirmed HIT, new venous and arterial thrombotic events occurred in 78 and 18 patients respectively. (ratio of venous to arterial thrombosis of 4:1) (Table 7). A complicating thrombotic event had occurred before the diagnosis of HIT was made in half the patients. Of the remaining 62 patients in whom HIT was diagnosed by the onset of thrombocytopenia alone, the subsequent 30 day risk of thrombosis was 52.8%. Thrombotic complications occurred despite discontinuation of heparin in 36, and initiation of warfarin in 21 patients (45). In a prospective study, 9 of 332 (2.7) patients who received unfractionated heparin developed HIT, with 8 of the 9 (88.9%) developing one or more thrombotic events (7 venous and 1 arterial). Of the 656 patients without HIT, 117 (17.8%) developed a new thrombotic event. The odds ratio (OR) for developing a thrombotic event with HIT was 36. (40)

Fig 10. Pathogenesis of HIT and Complicating Thrombosis

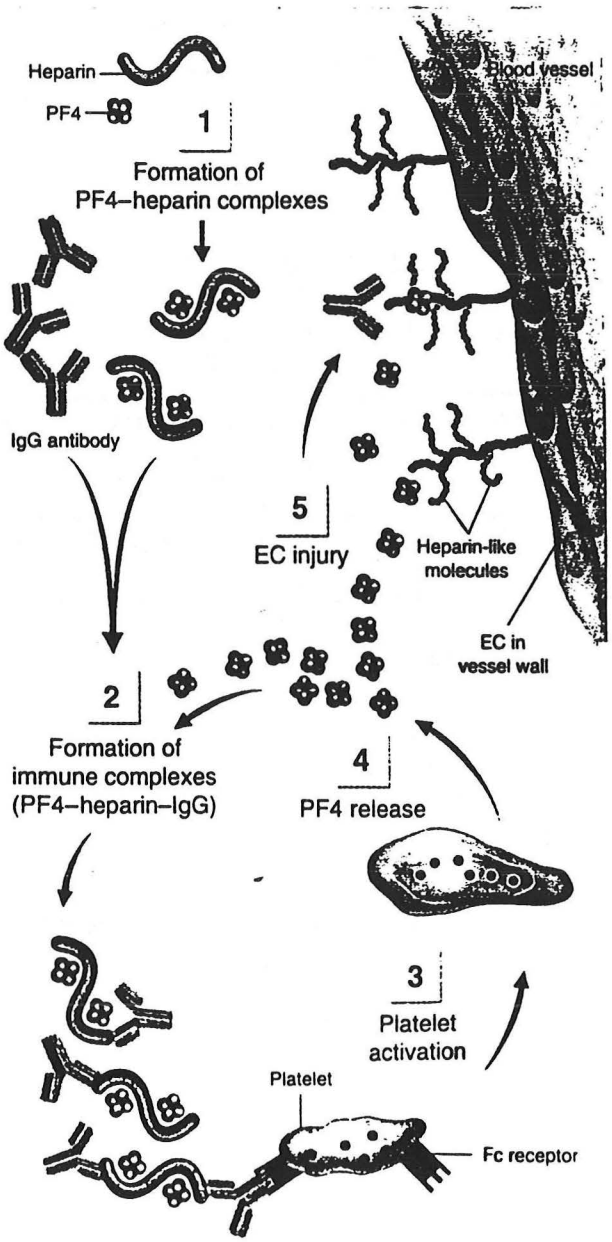


Table 7. Heparin-induced Thrombocytopenia (n-127)

	Presenting with thrombosis (n-65)	Presenting with isolated thrombocytopenia (n-62)
Surgical	51	33
Medical	14	29
Venous thrombosis	54(83%)	24(80%)
Arterial thrombosis	12	6
No thrombosis	NA	30 (48%)

Ref. 45

Thus HIT is a serious disorder, and although older reports emphasized the predominance of arterial thrombosis, recent evidence suggests that venous thrombosis is more common. However, arterial thrombosis with myocardial infarction, cerebrovascular accidents, limb infarction and disseminated intravascular coagulation have all been reported with this entity.

The incidence of Heparin-induced Thrombocytopenia and associated thrombotic events appear to be less common with LMWH. This was prospectively evaluated in a randomized study comparing LMWH (enoxaparin) with UFH for the prevention of DVT after elective hip surgery (Table 8) (40). Daily platelet counts were obtained (Table 8) (40) in all and serial testing was done for the presence of heparin-dependent antibody in a subset of 387 patients drawn from both groups .

Table 8. HIT in patients treated with LMWH vs. UFH

Frequency of HIT - Entire Cohort		
LMWH n-333	**UFH n-332**	**p**
0 (0 %)	9 (2.7 %)	0.0018
Frequency of Heparin-dependent Antibodies - Subset of 387		
LMWH n-182	**UFH n-205**	**p**
4 (2.2)	16 (7.8)	0.02
Thrombotic Complications - Entire Cohort		
With HIT n-9	**Without HIT n-656**	OR
8 (88.9%)	117 (17.8%)	36.9

Warkentin et al. N Engl J Med 1995

In this study, HIT was defined as a decrease in platelet count below 150,000/mm^3 that began five or more days after the start of heparin therapy, and a positive test for heparin-dependent IgG antibodies. HIT occurred in 9 of the 332 patients who received UFH and in none of the 333 patients who received LMWH (2.7% vs 0%; p 0.0018) (Table 8). Eight of the 9 patients who developed HIT had one or more thrombotic complications, as compared with 117 of 656 patients without HIT (88.9% vs. 17.8%; OR, 36.9: $p<0.001$) While none of the patients treated with LMWH developed HIT, routine testing revealed the presence of heparin-dependent antibodies in 2.2% of patients in the LMWH group, compared to 7.8% in the UFH group (p0.02).

Management of HIT

Continuing treatment with other anticoagulants is the mainstay of therapy in patients with HIT. Early experience seemed to suggest that patients who developed HIT could be successfully switched to LMWH for continued anticoagulation.(46- 48). However, there are anecdotal reports of HIT with thrombotic events in patients treated with LMWH for different indications (49-51), as well as reports of development of heparin-dependent antibodies as discussed above. Although LMWH is less immunogenic, there is significant cross-reactivity between LMWHs and heparin-dependent antibodies from patients treated with UFH. Therefore LMWH is not indicated for the treatment of HIT despite previous reports of its safety for this indication. Although there are reports of safe use of LMWH in patients with HIT after ruling out cross-reactivity, the clinical applicability of this strategy is not clear. There is universal agreement on the early use of oral anticoagulants, but there is an inherent delay in the onset of full anticoagulation (3-5 days) with oral anticoagulants. There is no consensus on the modality of antithrombotic treatment during this interval. Danaparoid (Org 10172, a heparinoid containing low molecular weight sulfated glycosaminoglycuronans comprising ~84% heparan sulfate, ~12% dermatan sulfate, and ~4% chondroitin sulfate), has been used successfully in some patients, although, this agent contains heparan sulfate, and there is some risk of cross reactivity with this drug also (52-54). Besides low molecular weight heparinoid, the defibrinogenating snake venom ancrod (Arvin) has been used for initial anticoagulation. Dosage regimens for these two agents are available in the literature (55), although these drugs are not available for use in this country. Hirudin, a direct thrombin inhibitor, appears to be another good candidate, and its use for this condition is under investigation.

Pharmacokinetics

Disappearance of the anticoagulant activity of UFH follows both zero order and first order kinetics, resulting in a dose-response relationship that is non linear (56). Over the range of heparin doses used clinically, the anticoagulant response increases disproportionately in intensity and duration as the dose increases (Table 9) (57,58).

Table 9. Dose of heparin and biological half-life

Study	Dose (IV bolus)	Half-life (min)
Olson et al	100 U/Kg	56
(Ref. 57)	400 U/Kg	152
Bjornsson et al	25 U/Kg	30
(Ref. 58)	75 U/Kg	60

In the treatment of acute venous thromboembolism, failure to rapidly achieve minimum therapeutic concentration of heparin increases the risk of recurrent thromboembolism (59,60). The complicated pharmacokinetics and poor bioavailability make this a difficult goal to achieve despite frequent monitoring and dose adjustment. Several dosing nomograms have been published with the goal of achieving therapeutic threshold as quickly as possible. Table 10 gives

an example of a weight based nomogram for heparin dosing that is easy to use (61). This does not eliminate the need for frequent monitoring.

Table 10: Weight-based Heparin Dosing Nomogram

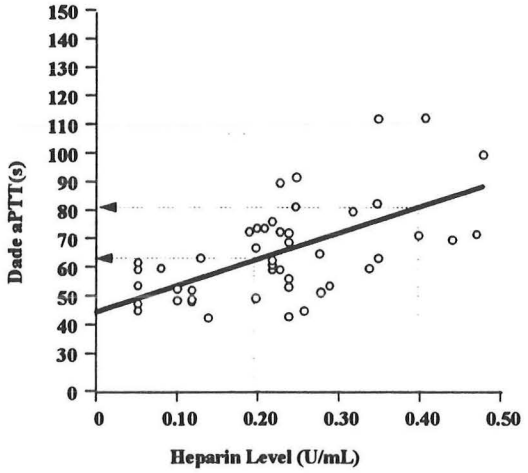
Initial Dose	80 U/Kg bolus, then 18 U/Kg/hr
APTT <35 s (<1.2 x control)	80 U/Kg bolus, then ↑ by 4 U/Kg/hr
APTT 35-45 s (1.2-1.5 x control)	40 U/Kg bolus, then ↑ by 2 U/Kg/hr
APTT 46-70 s (1.5-2.3 x control)	No Change
APTT 71-90 s (2.3-3 x control)	↓ infusion rate by 2 U/Kg/hr
APTT >90 s (>3 x control)	Hold infusion 1 hour, then ↓ by 3 U/Kg/hr

Ref. 61

Laboratory monitoring - Unfractionated Heparin

As there are no tests to measure heparin levels directly, therapeutic efficacy is monitored indirectly. Therapy can be monitored by means of a clotting test, anti-Xa or anti-IIa activity, or heparin level by protamine titration. Heparin level of 0.2-0.4 U/ml by protamine titration assay has been shown to correlate with clinical efficacy in experimental venous thrombosis. Assays of anti-Xa activity and protamine titration are expensive and cumbersome, and not suitable for clinical use. Clotting tests such as APTT measurements are easy to perform and widely available and can be used to monitor therapy and to maintain patients within a therapeutic range. Traditionally, the goal of therapy has been to maintain patients' APTT ratios between 1.5-2.5 as this range was shown to inhibit clot propagation and correspond to a heparin level of 0.2-0.4 U/ml by protamine titration in some early studies (22). While this is true for APTT assays performed with some thromboplastin reagents, it is not true for all APTT reagents (Fig 11 a,b).

Fig 11a Therapeutic APTT with Dade Reagent



This is reminiscent of the problems in monitoring oral anticoagulant therapy using prothrombin time ratios (PTR), where the variable responsiveness of different thromboplastin reagents can

give different PTR for equivalent degree of anticoagulation. This was overcome by standardizing the thromboplastin reagents and adapting the international normalized ratio (INR) system of reporting. Unfortunately, there is no such standardization for APTT reagents.

Fig 11b Therapeutic APTT with Ortho Reagent

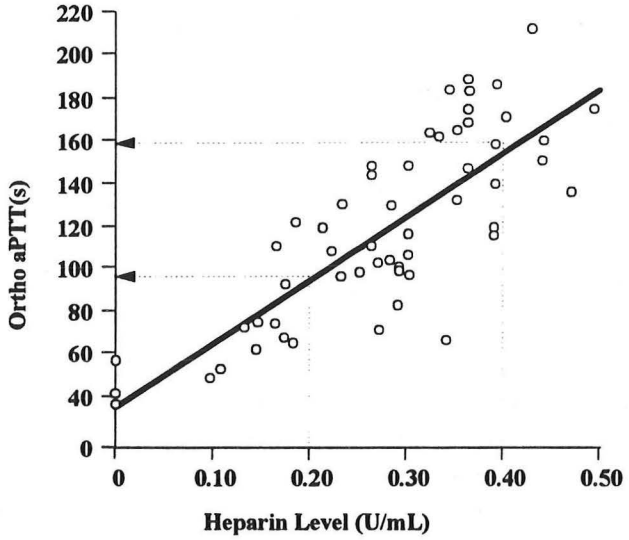


Table 11 highlights the problem with using an arbitrary range to monitor therapy(62). In this study, simultaneous APTT and heparin levels were measured using different APTT reagents in a group of patients on heparin infusion to demonstrate the variability in APTT results with different reagents. It can be seen that when therapeutic APTT ranges are established utilizing APTT ratios of 1.5-2.5, the corresponding heparin levels are subtherapeutic and would result in inadequate treatment. The APTT in seconds, and the APTT ratios that correspond to therapeutic heparin levels of 0.2-0.4 U/ml are clearly higher for all the reagents tested in this study, with therapeutic APTT ratios varying from 2.1-3.3 to 2.6-4.2. Adapting a rigid ratio of 1.5-2.5 without taking into account the reagent used would result in undertreatment for most patients.

Table 11 : Comparison of different APTT reagents

Reagent	Mean APTT	Therapeutic Range of APTT (1.5-2.5 X control)	Corresponding Heparin level	Therapeutic Range of APTT (0.2-0.4U/ml)	Corresponding APTT ratios
Units	s	s	U/ml	s	
Ortho	38	57-95	0.09-0.18	100-160	2.6-4.2
Organon	37	55-93	0.08-0.22	85-130	2.3-3.5
IL	35	53-88	0.08-0.23	80-120	2.3-3.4
Biotrack	31	47-78	0.09-0.24	65-100	2.1-3.3

modified from Ref. 62.

For clinical purposes, it s recommended that each laboratory establish therapeutic APTT range corresponding to heparin levels of 0.2-0.4 U/ml by protamine titration or (0.3-0.7 anti-Xa U/ml) for the APTT reagent used locally. Clinicians can then use the APTT for daily monitoring, with the goal of maintaining patients' APTT within the therapeutic range instead of using APTT ratios.

Laboratory Monitoring - LMWH

LMWH has >90% bioavailability and a very predictable dose-response effect even with subcutaneous administration. Therefore, **routine laboratory monitoring is not necessary with the use of LMWH.** Although LMWHs can increase the in vitro clotting time slightly, tests such as the APTT and TT are not sensitive enough for use with LMWH. Assays for anti-Xa activity are neither required nor recommended for routine clinical use except when dealing with patients with extreme body weights or renal failure, or with occurrence of bleeding complications or thrombosis during its use (63).

Relative Importance of anti-Xa and anti-IIa activity

Although LMWHs possess more anti-Xa activity than anti-IIa activity, the relative importance of anti-Xa activity for in-vivo antithrombotic effect is a subject of ongoing controversy. In the overall scheme of regulation of coagulation, the inhibition of thrombin mediated activation of factors V and VIII may be the most important role played by the ATIII-heparin complex. There is experimental evidence that 1)fractions of heparin with high anti-Xa activity but low anti-IIa activity are poor inhibitors of thrombin generation, and thus thrombus formation and 2) antithrombotic effect achieved by inhibiting factor-Xa is limited and that better antithrombotic effects are achieved by heparin or heparin-like substances capable of influencing both the inactivation and the generation of thrombin (21,64,65)
Using more sensitive assays of anti-IIa activity (Plasma Thrombin Neutralization Assay: PTNA), Agnelli et al have demonstrated high and sustained plasma antithrombin activity in healthy volunteers administered therapeutic doses of two different LMWH preparations, with only a moderate prolongation of the APTT (Table 12) (66).

Table 12. Peak Plasma anti-Xa and anti IIa activity and t1/2 with LMWH

	Nadroparin		Enoxaparin	
	10,000 ICU	**450 ICU/Kg**	**40 mg**	**2 mg/kg**
A_{max} U/ml Anti-Xa activity	0.63±0.15 0.48-0.78	1.55±0.22 1.32-1.78	0.58±0.15 0.43-0.73	2.02±0.54 1.45-2.58
t1/2, h	4.50±1.96 2.73-6.27	4.38±1.50 2.52-6.24	4.32±1.66 2.58-6.06	5.35±1.75 3.52-7.17
A_{max} U/ml Anti-IIa activity*	0.37±0.08 0.26-0.48	0.87±0.21 0.64-1.10	0.25±0.14 0.11-0.39	0.91±0.18 0.69-1.13
t1/2, h	.....	4.28±2.33 1.84-6.72	.....	3.90±0.75 3.11-4.68
A_{max} U/ml - PTNA Anti-II activity	0.28±0.10 0.18-0.38	0.72±0.09 0.63-0.81	0.29±0.07 0.21-0.37	0.81±0.27 0.53-1.09
t 1/2, h	5.85±2.11 2.67-19.03	5.60±0.46 5.02-6.17	6.62±1.77 3.82-9.42	7.40±1.39 5.93-8.86
Amax APTT ratio		1.58±0.10		1.67± 0.13

A_{max}- peak activity. *Chromogenic assay **modified from Ref. 66**
PTNA - Plasma thrombin Neutralization Assay **Values are mean±SD and 95% CI**

After single subcutaneous injections of the drug in doses recommended for the prevention of DVT in moderate-risk and high-risk patients, and for treatment of established DVT in twice-daily and once-daily regimen, they showed that there was a dose dependent peak activity (A_{max}) of anti-Xa and anti-IIa. With the more sensitive assay, mean half-life for anti-IIa activity was 6.36 hours and mean half-life for anti-Xa activity was 4.6 hours. After administration of the highest doses of Nadroparin and Enoxaparin, anti-Xa activity was detectable for up to 19 and 20 hours respectively and PTNA measured anti-IIa activity was detectable up to 18 and 17 hours respectively. This was accompanied with only a moderate prolongation of the APTT.

Different LMWH Preparations

There are several different LMWH preparations in use or under investigation (Table 13). It is important to recognize that because of the differences in manufacturing process, molecular weight, anti-Xa and anti-IIa activity/mg, and half-life, the different LMWH preparations must be considered to be different drugs The clinical efficacy of one agent can not be extrapolated to another agent.

Table 13. Properties of Different LMWHs

Product	Synonym	MW (Saccharide units)	Anti-Xa: Anti-IIa	Plasma t1/2 (min)	Dose	
					Prevention	Treatment
Enoxaparin	Lovenox Clexane	4500 (10-27)	2.7:1	129-180	3200 U qd 2400 U bid	5600 U bid
Dalteparin	Fragmin	5000 (7-30)	2:1	119-139	5000 U qd 2500 U bid	8400 U bid (70 kg b/w)
CY216	Fraxiparin	4500 (7-27)	3.2:1	132-162		31,500 U/IC* qd
Novo LMWH	Logiparin	4500 (10-20)	1.9:1	111	50 U/Kg qd	12,250 U/Kg (70 Kg b/w)
RD Heparin	Ardeparin	6000 (7-50)	2:1	200	50 U/Kg bid	
Sandoz LMWH	Sandoparin	6300				
OP2123	Fluxum					
Knoll LMWH	Reviparin Clivarin					
ORG10172[$]	Orgaran Lomoparin	6500	20:1	1110	750 U bid	

***U/IC** (Istitut Choay Unit). 3 U/IC = 1 IU

[$] ORG10172 is a heparinoid containing low molecular weight sulfated glycosaminoglycuronans comprising heparan sulfate (~84%), dermatan sulfate (~12%), and chondroitin sulfate (~4%) and not a low molecular weight heparin, although listed under LMWH by many.

Table 14. Optimum Range of Anti-Xa Activity for LMWH

Indication for Treatment	Anti-Xa activity (IU/ml)
Prophylaxis for Moderate Risk	0.10-0.25
Prophylaxis for High Risk	0.20-0.50
Treatment of Established DVT	0.50-1 (or 1.2)

Modified from Ref. 63

Antagonization with Protamine Sulfate

The bleeding effect of unfractionated heparin, as well as the effect on global clotting assays is completely neutralized by equimolar doses of protamine sulfate. While the use of LMWH is associated with less hemorrhagic complications, acute reversal of the anticoagulant effect of LMWH may sometimes become necessary, especially when using these drugs in high doses, e.g. during surgery with extracorporeal circulation or during hemodialysis. Protamine sulfate has proven to be effective in neutralizing LMWH induced bleeding in both animal experiments and in humans, although the anti-Xa activity and anti-IIa activity may be only partially reversed (67-70). (For the exact dose of protamine sulfate to be administered with different brands of LMWH, it is prudent to refer to the manufacturer's recommendation).

Bioequivalence of LMWHs

There is very limited data on the comparative clinical efficacy of the different LMWH preparations. Bioequivalence is used to establish if different preparations or formulations of the same ingredients have the same pharmacokinetic properties by measuring Cmax (maximum activity measured), tmax (time for appearance of Cmax), and AUC (area under the plasma activity vs time curve). Eriksson et al have reported on the bioequivalence of three LMWH; Clexane® (Enoxaparin), Fragmin® (Dalteparin), Logiparin® (Tinzaparin) and UFH by administering the drugs subcutaneously in a cross-over technique in 12 healthy volunteers. The anti-Xa peak activity (Cmax) and the AUC were highest for Enoxaparin and Dalteparin and lower for Tinzaparin and UFH. Enoxaparin and dalteparin were considered bioequivalent for anti-Xa activity. No bioequivalence was found between the products regarding anti-IIa activity. Dalteparin was clearly different from the other products regarding anti-IIa activity, with Cmax and AUC approximately twice as high as the other drugs. This data reflects the limited comparative efficacy of the above brands of these particular LMWH only (71). Whether the differences in anti-Xa and anti-IIa activities are of any clinical significance remains to be established.

Clinical Trials of Low Molecular Weight Heparins

Venous Thromboembolism

Venous thromboembolism (VTE) accounts for approximately 300,000 hospitalizations per year in the United States and, annually, as many as 50,000 deaths are attributed to pulmonary embolism

(PE). Most fatal emboli arise from thrombosis in the deep veins of the lower extremities (72). Although anticoagulants arrest the thromboembolic process in those who survive PE, their scope for reducing mortality from this disease is limited for two reasons; 1) 70% of deaths after massive PE occur within 1-2 hours of onset, with little time for intervention, 2) studies have shown that in most patients with fatal pulmonary emboli, the preceding thromboembolic events were clinically unsuspected (73). Venous thromboembolism also increases the cost of health care and results in long term post phlebitic complications. The most effective way to prevent fatal and nonfatal venous thromboembolism is by the systematic use of effective prophylactic measures to prevent DVT in patients at risk for these events. Risk factors for VTE and the incidence of DVT and PE in the different risk groups are listed in Tables 15-18 (75,76).

Table 15. Risk Factors for Venous Thromboembolism

Patient Factors	Disease or Surgical Procedure
Age	Trauma or Surgery
Obesity	Malignancy, Cancer Chemotherapy
Varicose Veins	Congestive Heart Failure
Prolonged Immobilization	Recent Myocardial Infarction
Pregnancy & Puerperium	Paralysis of Lower Limbs
Oral Contraceptive Use	Infection
Previous h/o DVT/PE	Inflammatory Bowel Disease
Deficiency of ATIII, Protein C or S	Nephrotic Syndrome
Antiphospholipid Antibody	Polycythemia
	Paroxysmal Nocturnal Hemoglobinuria
	Bechet's disease
	Homocystinemia

Modified from THRIFT Study Group (75).

Table 16. Overall Risk of Perioperative Venous Thromboembolism

Group	Incidence
General Surgery	About 25%
Gynecology	10-30%
Trauma	10-40%
Orthopedic Surgery	40-70%

Modified from Med Clinics North America 78; 733-743: May 1994 (Ref. 76)

The Thromboembolic Risk Factors Consensus Group (THRIFT) has defined three groups of patients at risk for VTE based on the medical or surgical risk/condition (Table 17) (75).

Table 17. Venous Thromboembolism Risk Categories

Low Risk Groups	Minor Surgery (<30 min), no risk factors besides age Major Surgery (>30 min); age <40, no other risk factors* Minor trauma or medical illness
Moderate Risk Groups	Major general, urologic, gynecological, cardiothoracic, vascular or neurological surgery; age >40, or other risks Major medical illness: heart or lung disease, cancer, Inflammatory bowel disease Major trauma or burns Minor surgery, trauma or illness in patients with previous VTE or thrombophilia
High Risk Groups	Fracture or major orthopedic surgery of pelvis, hip or lower limb Major pelvic or abdominal surgery for cancer Major surgery, trauma or illness in patients with previous VTE or thrombophilia Lower limb paralysis Major lower limb amputation

Thromboembolism risk factors (THRIFT) consensus group BMJ 1992;305:567-574
*** See table x for risk factors**

18. Incidence of Venous Thromboembolism without Prophylaxis

Group	DVT	Proximal DVT	Fatal PE
Low Risk	<10%	<1%	0.01%
Moderate Risk	10-40%	1-10%	0.1-1%
High Risk	40-80%	10-30%	1-10%

modified from THRIFT Consensus Group

Several consensus groups have published recommendations for the prevention of VTE in the different risk groups (74,75). Low molecular weight heparins have been investigated in all these risk groups for both efficacy and safety. Recent studies where the incidence of DVT was evaluated objectively in all patients at the end of treatment are reviewed here. Ascending venography is considered the test of choice for evaluating DVT in asymptomatic patients after major orthopedic surgery on the lower extremity, where as fibrinogen uptake test (FUT) is considered an appropriate test in other settings. These studies were carried out before labeled fibrinogen became unavailable. In most of the studies, a bleeding event was generally defined as major if it met one of the following criteria; resulted in a significant fall in hemoglobin, required blood transfusion, resulted in hospitalization or prolongation of hospital stay, was intracranial or retroperitoneal in location or resulted in death.

LMWH for Prophylaxis of Venous Thromboembolism after Major Orthopedic Surgery

Total Knee Arthroplasty

Four randomized trials have compared three different LMWH preparations with other antithrombotic agents for VTE prophylaxis after total knee arthroplasty (TKA). Three of the trials compared LMWH with warfarin given to maintain the INR between 2 and 3 (77-79), one study compared LMWH with UFH (80). A fifth study compared LMWH with placebo (81). In all the studies LMWH was given in a fixed dose without monitoring. Warfarin therapy was monitored with daily PT. Bilateral ascending venography was performed before discharge in three trials. Routine venography was performed only on the operated limb in the RD Heparin Arthroplasty Trial, unless subjects had symptoms in the unoperated limb. Tables 19 and 20 summarize the results of these trials with regard to efficacy and safety.

Table 19. LMWH for Venous Thromboembolism Prophylaxis in TKA: efficacy

Author/Ref.	Drug	Dose	Venogram (n)	Total DVT(%)	Prox DVT(%)
Leclerc et al (81)	Enoxaparin Placebo	30 mg BID	41 54	8(19) 35 (65) p <0.02	0 11(20) p <0.02
Leclerc et al (77)	Enoxaparin Warfarin	30 mg BID **INR 2-3**	206 211	76(36.9) 109(51.7) p 0.0003	24(11.7) 22(10.4) p NS
RD Heparin Arthroplasty Group (78)	Ardeparin Ardeparin Warfarin	50 U/Kg BID 90 U/Kg QD **PTR 1.2-1.5**	150* 149* 147*	37(25)# 41(28) 60(41) # p 0.0004	9(6) 7(5) 15(10) p NS
Hull et al (79)	Logiparin Warfarin	75 U/Kg QD INR 2-3	258 277	116(45) 152(54) p <0.02	20(7.8) 34(5) p NS
Fauno et al (80)	Enoxaparin UFH	40 mg QD 5000 U TID	92 93	21(23) 25(27)	3(3) 5(5)

* unilateral venogram

Table 20. LMWH for VTE Prophylaxis in TKA: safety

Study	Drug	Major Bleeding %	p
Leclerc et al (77)	Enoxaparin Warfarin	2.1 1.8	>0.2
RD Heparin Arthroplasty GP (78)	Ardeparin BID Ardeparin QD Warfarin	4 4 4	NS
Hull et al (79)	Logiparin Warfarin	2.8 1.2	0.04

It appears that in patients undergoing TKA, LMWH administered subcutaneously in a fixed dose is superior to placebo in preventing total and proximal DVT, and more effective than warfarin in preventing total DVT. Enoxaparin given once a day was as effective as UFH given three times daily. This suggests that enoxaparin may not be as effective when given once a day. The number of episodes of PE was too low to make any definite statement. There was no significant difference in major bleeding or clinically significant bleeding compared to warfarin in two of three studies. In one study, LMWH therapy was associated with a slight increase in major bleeding. It should also be noted that in all the studies, the risk of DVT remained substantial (20-45%) despite therapy, although the majority of these were calf vein thrombosis and there were very few episodes of symptomatic PE .

In summary, fixed dose subcutaneous LMWH was effective and safe in preventing DVT in patients undergoing TKA and was superior to warfarin and placebo. In one study it was as effective as UFH given three times a day.

Total Hip Arthroplasty

Several studies have compared LMWH with placebo or other antithrombotic agents in the prevention of VTE after total hip arthroplasty (THA). Table 21 highlights the results of nine studies where DVT was evaluated by means of ascending venography before discharge (78,79,82-88). All included bilateral venograms with the exception of the RD Heparin Study Group trial where routine venogram was obtained only on the operated limb unless patients had symptoms in the opposite limb. Three of the studies were double blind (GHAT, Hull and Eriksson), and the rest were open labeled. Review of venograms was performed by blinded adjudicators in all the studies. Eriksson et al included routine V/Q scan in the study.

LMWH was superior to placebo in preventing both total and proximal DVT after hip arthroplasty with risk reduction of 79% and 31% respectively. . LMWH was superior to UFH in preventing proximal DVT in 2 out of 4 studies, and in preventing total DVT in 1 out of 4 studies. LMWH was superior to adjusted dose UFH in preventing proximal DVT and was as effective as warfarin in preventing total and proximal DVT. LMWH was superior to Dextran in preventing total DVT, but the total number of proximal DVT was too small to make any conclusions in this study.

Routine V/Q scans performed in patients treated with Fragmin or UFH in the study by Eriksson showed a significant difference in the incidence of asymptomatic PE in the LMWH group. Eight (12.3 %) patients in the Fragmin group compared to 19 (30%) in the UFH group had positive V/Q scans with only 3 of the 27 patients showing clinical symptoms. In this study, LMWH decreased the incidence of proximal DVT and PE compared to UFH (85).

Only one study has compared two different LMWH preparations after THA (89). In this double blind trial, 247 patients received Reviparin® at a dose of 4200 anti-Xa units subcutaneously and 251 received enoxaparin at a dose of 4200 anti-Xa units sc. Bilateral ascending venography was done between 10 and 13 days postoperatively. There was no difference in the rate of total or proximal DVT in the two groups. There were 18 DVT (9%) in the enoxaparin group, of which 13 (6%) were proximal, and 21 (10%) DVT in the Reviparin® group, of which 12(6%) were

proximal. Major bleeding rate was 2% in each group. Thus, Reviparin® and enoxaparin were equivalent in efficacy and safety after total hip arthroplasty.

Table 21. LMWH for VTE Prophylaxis after THA: efficacy

Study	Drug	Dose	Venogram (n)	DVT (%)	Prox DVT (%)
Turpie et al (DB) (82)	Enoxaparin Placebo	30 mg BID Saline BID	37 39	4(10.8) 20(51.3) **p 0.0002**	2(5.4) 96(23) **p 0.029**
Levine et al (83)	Enoxaparin UFH	30 mg BID 7500 U BID	258 263	50(19.4) 61(23.2)	14(5.4) 17(6.5)
Eriksson et al (DB) (84)	Fragmin UFH	5000 U QD 5000 U TID	63 59	19(30.2) 25(42.4)	6(9.5) 18(30.5) **p 0.011**
GHAT (DB) (85)	Fraxiparin UFH	48 mg QD 5000 U TID	136 137	45(33) 47(34)	14(10) 26(19) **p 0.04**
Enoxaparin Clinical Trial Group (86)	Enoxaparin Enoxaparin UFH	30 mg BID 40 mg QD 5000 U TID	136 136 142	8(6)* 28(21)* 21(15) ***p<0.0003**	4(3) 8(6) 10(7)
Leyvraz et al (87)	Fraxiparin ADH	41-62U/Kg QD[$] **APTT 2-5 s >C**	174 175	22 (12.6) 28 (16)	5 (2.9) 23 (13.1) **p <0.001**
Hull et al (DB) (79)	Logiparin Warfarin	75U/Kg QD INR 2-3	332 340	69(20.8) 79(23.2)	16(4.8) 13(3.8)
RD Heparin Group (78)	Ardeparin Ardeparin Warfarin	50 U/Kg BID 90 U/Kg QD PTR 1.2-1.5	178 171 171	14(8) 24(14) 24(14)	5(3) 12(7) 11(6)
Danish Enoxaparin Study Gp (88)	Enoxaparin Dextran	30 mg BID Std regimen	108 111	7(6.5) 24(21.6) **p 0.0013**	2(1.8) 6(6.5)

[$] lower dose preop to postop day 3.
ADH Adjusted Dose unfractionated Heparin
Unless specified, p values are >0.5 (NS)

Table 22 summarizes the incidence of hemorrhagic complications from three of the above studies (79,82,88). In all the other studies of THA, hemorrhagic complication rate was reported to be similar between LMWH and the other agent with which it was compared. In the study comparing LMWH with dextran there was an increase in transfusion requirement in the dextran group (83).

Table 22. LMWH for DVT Prophylaxis after THA: safety

Study	Drug	Major bleeding %	p
Enoxaparin Clinical Trial Group (88)	Enoxaparin 30 mg BID Enoxaparin 40 mg QD UFH 5000 U TID	4 1* 6*	*p0.02
Hull et al (79)	Logiparin 75U/Kg QD Warfarin INR 2-3	2.8 1.5	p<0.05
Turpie et al (82)	Enoxaparin 30 mg BID Placebo	2 4	NS

Table 23 summarizes the results of a meta-analysis of randomized studies of DVT prophylaxis in elective total hip and knee arthroplasty in which investigators compared currently recommended doses of LMWHs and used adequate screening techniques for DVT (90). LMWH was more effective than UFH in reducing the incidence of DVT and PE, and was safe. The authors concluded that LMWHs are preferable to UFH for orthopedic surgery patients, in view of the large absolute risk reduction for venous thrombosis.

Table 23. LMWH for VTE Prophylaxis in Orthopedic Surgery: Meta-analysis

Outcome	Number Evaluated LMWH	UFH	N with Outcome LMWH	UFH	RR (95% CI)	Risk Reduction
DVT	672	622	93	132	0.68 (0.54-0.86)	32%
PE*	590	582	10	24	0.43 (0.22-0.82)	57%
Major Bleeding	672	622	8	8	0.75 (0.26-2.14)	

* includes fatal and nonfatal PE

Nurmohammed et al. Lancet 1992;340:152-56 (90)

LMWH administered in a fixed dose once or twice daily appears to be superior to placebo, Dextran, and UFH given three times a day. It is as effective as warfarin administered to maintain INR between 2-3 in preventing DVT after total hip arthroplasty.

Hip Fractures

In the absence of prophylaxis, prevalence of DVT and PE in patients who undergo surgery for fracture of the hip is in the range of 43-91% and 4.3 -24% respectively (74). LMWH has been compared with dextran and UFH for the prevention of VTE. In addition, investigators have compared two different doses of LMWH (Table 24) (91-93).

In the subset of patients evaluated with venogram, **Enoxaparin 30 mg QD was superior to Enoxaparin 15 mg BID in preventing proximal DVT, Sandoparin was superior to Dextran in preventing total DVT, but Fragmin used in doses of 5000U QD was less effective than UFH in preventing total DVT.**

Table 24. LMWH for VTE Prophylaxis after hip fracture

Study	Drug	Dose	Venogram(n)	DVT (%)	Prox DVT
Barsotti et al (91)	Enoxaparin Enoxaparin	30 mg QD 15 mg BID	48 49	5 (10.4) 9 (18.3)	2 (4.2) 6 (12.2) p<0.05
Monreal et al (92)	Fragmin UFH	5000 U QD 5000 U TID	32 30	14 (43.7) 6 (20) p<0.05	12 (37.5) 5 (16.7)
Oertli et al (93)	Sandoparin Dextran	3000 U QD Std dose	34 46	16 (15.5) 31 (32.6) p<0.005	2 (6) 1 (3)

Major Trauma

Enoxaparin 30 mg BID was compared with UFH 5000 units BID in a double blind study of 344 trauma patients without intracranial bleeding. In 265 evaluable patients with adequate bilateral venography performed at or after 14 days, 44% in the UFH group and 31% in the LMWH group developed DVT (p0.014). The corresponding numbers for proximal vein thrombosis was 15 and 6% (p0.012, RRR 30%). Major bleeding occurred at a rate of less than 2% and was not different in the two groups (94).

Enoxaparin was superior to UFH in preventing DVT in trauma patients and did not increase the risk of bleeding.

General Surgery

UFH given perioperatively in doses of 5000 units sc two or three times a day decreases the incidence of DVT after general surgery by about 70%, with an increase in the risk of hemorrhagic complications (mainly wound hematoma or injection site hematoma) from 3.8% to 5.9% (95). Table 25 lists the studies of VTE prophylaxis in general surgery where the efficacy of LMWH was evaluated objectively using FUT (96-100).

LMWH was superior to placebo and equivalent to UFH in preventing DVT after general surgery. Similar results were obtained in subgroup analysis of patients with and without malignancy (99,100). With the proven efficacy of low dose unfractionated heparin given two or three times a day, routine use of LMWH cannot be recommended, although the once daily or twice daily dosing is an advantage.

Table 25. VTE Prophylaxis in General Surgery

Study	Drug	Dose	FUT	DVT %
Ockelford et al (96)	Fragmin Placebo	2500 U QD Saline QD	95 88	4.2 15.9 p0.008
Caen JP (97)	Fragmin UFH	2500 U QD 5000 U BID	195 190	3.1 3.7
Nurmohammed et al (98)	Enoxaparin UFH	20 mg QD 5000 U TID	718 709	8.1 6.3
Limmer et al (99)	LMWH 21-23 UFH	2500 U QD 5000 U TID	103 100	3.9 5
Bergquist et al (100)	Fragmin Fragmin	2500 U QD 5000 U QD	976 981	12.7 6.6 <0.001

unless specified, p - >0.5

Table 26 summarizes the results of a meta-analysis of randomized studies of DVT prophylaxis in general surgical patients in which investigators compared currently recommended doses of LMWHs and used adequate screening techniques for DVT (90).

Table 26. LMWH for VTE Prophylaxis in General surgery: Meta-analysis

Outcome	Number Evaluated		Number with Outcome		RR (95% CI)
	LMWH	UFH	LMWH	UFH	
DVT	3467	3411	184 (5.3%)	230 (6.7%)	0.79 (0.65-0.95)
PE	2888	2843	9 (0.31%)	20 (0.7%)	0.44 (0.21-0.95)
Major Bleeding	1977	1966	52 (2.6%)	51 (2.6%)	1.01 (0.70-1.48)

* includes fatal and nonfatal PE

Nurmohammed et al. Lancet 1992;340:152-56 (90)

The authors concluded that there was no convincing evidence that in general surgical patients, LMWHs, compared with standard heparin, generate a clinically important benefit to risk ratio.

Spinal Cord Injury

Table 27. VTE Prophylaxis in Spinal Cord Injury

Treatment	Number	DVT+PE	Bleeding
UFH	79	16	9
LMWH	68	7	1

From Ref. 104

About 16% of patients with acute spinal cord injury develop clinically evident deep vein thrombosis (101). With objective testing, the rate increases to 79%. The risk is highest in the

early phase when patients have flaccid paralysis, and are invariably immobilized following the acute injury, and VTE prophylaxis is recommended during this acute phase. Fixed, low dose UFH is not very effective in this setting and adjusted dose heparin treatment was associated with a high incidence of bleeding complications in one study (102). In a group of 41 patients randomized to 5000 units of UFH every 8 hours or 3500 a-Xa units of Logiparin once daily for 8 weeks and followed with impedance plethysmography and duplex ultrasound, 3 of 21 in the UFH group had evidence of DVT and 2 additional patients died of massive pulmonary embolism confirmed at autopsy (103). None of the 20 in the LMWH group had a thromboembolic event during the 8 week period. Two patients in the UFH group had major hemorrhagic complications, giving a total event rate (thrombosis+hemorrhage) of 34.% in the UFH group and 0 in the LMWH group. An additional 40 patients were treated with LMWH by the same investgators. Seven developed thrombotic events and one patient had a major hemorrhage. In this single institution study, a total of 68 patients received LMWH; 7 developed thrombosis and one had a bleeding complication. Seventy nine were treated with UFH (50 with fixed dose, 29 with adjusted dose) of which 16 developed thrombosis and 9 developed major bleeding (Table 27). **This limited data suggests that LMWH may be more effective and safer in preventing VTE in patients with acute spinal cord injury** (104).

Medical Patients

Patients admitted with medical illnesses, particularly myocardial infarction and cerebrovascular accidents, have a high risk of venous thromboembolic events. In the absence of prophylaxis, reported incidence of VTE by fibrinogen uptake test has ranged from 24% in patients hospitalized for acute myocardial infarction to 42% in those hospitalized for acute cerebrovascular accident (74). Low molecular weight heparin has been compared against placebo and low dose UFH in hospitalized, bedridden patients with a variety of medical illnesses, including congestive heart failure, malignancy, ischemic stroke, respiratory disease and infection. In a placebo controlled study, LMWH decreased the rate of DVT diagnosed by routine FUT from 9.1% (12 of 131) to 3% (4 of 132), which was statistically significant (105). In another study involving 423 patients, Enoxaparin 20 mg once a day was equivalent in efficacy to UFH 5000 units twice a day (VTE rate of 4.8% versus 4.6%). Major bleeding occurred in 0.9% of patients on LMWH and 1.8% on UFH (106). **LMWH is superior to placebo and as effective and safe as UFH in preventing DVT in patients admitted with acute medial illnesses**. However, considering the efficacy of UFH in this setting, it is unlikely that LMWH will replace UFH, despite the convenience of once daily dosing (107).

Treatment of Acute Venous Thromboembolism

Treatment of acute venous thromboembolism with anticoagulants reduces mortality and morbidity from pulmonary embolism and recurrence of DVT and PE. Patients are usually treated with 5 to 10 days of intravenous unfractionated heparin, followed by oral anticoagulants for a minimum of three months. Management of this disease has always necessitated hospitalization and intensive laboratory monitoring to ensure therapeutic anticoagulation to minimize the high risk of recurrent VTE and bleeding complications. Administration of oral anticoagulants on the first day of heparin therapy and discontinuation of heparin after the prothrombin time remains therapeutic for

at least 24 hours has resulted in shorter hospital stay without compromising efficacy or safety, but this still requires 5-7 days of inpatient treatment.

LMWH has been evaluated for the initial treatment of acute DVT in several randomized trials. Many of the trials included patients with abnormal V/Q scans in addition to DVT. LMWH was administered subcutaneously in a fixed dose once or twice daily without monitoring, while UFH was given as an intravenous bolus followed by continuous infusion with monitoring by APTT. Primary endpoints assessed were venographic improvement at the end of heparin treatment or symptomatic recurrence of VTE (confirmed objectively) over the following 3 to 6 months, and bleeding during heparin treatment. Warfarin was started on the first day in all except one study (111) where it was started on day 7. Data from some of the more recently published randomized studies evaluating the efficacy and safety of LMWH for the treatment of DVT in an inpatient setting are reviewed below (Table 28) (108-113).

Table 28. LMWH for Initial Treatment of Acute Venous Thromboembolism:

Author (ref.)	Drug (Number of patients)	Dose	Venographic Improvement	Symptomatic Recurrence (%)	Major Bleeding
Prandoni (108)	Fragmin (85) UFH (85)	Wt based APTT 1.5-2.5		6 (7) 12(14)	1(1) 3(4) **p<0.02**
Hull (109)	Logiparin (213) UFH (219)	175 U/Kg QD APTT 1.5-2.5		6 (2.8) 15(6.9 **p0.07**	1(0.5) 11(5) **p0.006**
Simonneau (110)	Enoxaparin(60) UFH (57)	1 mg/Kg BID APTT 1.5-2.5	43% 27% **p0.007**		0 0
Lopaciuk (111)	Fraxiparine (68) UFH (66)	92U/Kg BID APTT 1.5-2.5	66% 32%		0 1
Holmstrom (112)	Fragmin (50) Fragmin (51)	200 U/Kg QD 100U/Kg BID	-1.8±2.5 -1.8±3.1	0 1	
Fiessinger (113)	Fragmin (96) UFH (103)	200U/Kg QD APTT 1.5-3	67% 60%	(4) (2)	0 2

Unless specified, p >0.5 for rates between groups

These studies showed that LMWH given subcutaneously without monitoring was as effective and safe as intravenous unfractionated heparin in the initial treatment of DVT. In another study, mortality at 6 months in the subgroup of patients with cancer was significantly lower in the LMWH treated group than in the group that received UFH (108).

In a meta-analysis of ten studies of LMWH in the initial treatment of acute VTE that met rigorous methodological criteria (randomization, objective confirmation of index and recurrent DVT, maintaining optimum range of heparin therapy, independent outcome assessment), the risk reduction for symptomatic recurrence of VTE, clinically significant bleeding and mortality were all statistically significantly in favor of LMWH (Table 26) (114).

Table 26. Treatment of DVT with LMWH: A Meta-analysis

	LMWH-n (%)	UFH-n(%)	p
Rec VTE @ 6 mths	17/540 (3.1)	36/546 (6.6)	<0.01
Risk Reduction	53% (95% CI 18-73)		
Significant Bleeding	6/753 (0.8)	21/259 (2.8)	<0.005
Risk Reduction	68% (95% CI 31-85)		
Mortality (RRR)	47% (95% CI 10-69)		

Lensing et al. Arch Intern Med 1995;155:601-607 (114)

Another meta-analysis evaluated the efficacy of LMWH versus UFH, and mortality during different treatment phases; the initial heparin phase (days 1-15), subsequent oral anticoagulant phase (days 16-90), and the entire anticoagulant treatment phase (days 1-90). Bleeding complications were analyzed for the initial phase only (Table 27) (115) .

Table 27. LMWH for acute DVT: A Meta-analysis

		Day 1-15	Day 16-90	Day 1-90
Recurrent VTE	**LMWH**	5/615 (0.8%)	10/608 (1.6%)	15/606 (2.5%)
	UFH	15/613 (2.4%)	12/605 (2%)	27/605 (4.5%)
	p	0.02	0.8	0.02
Relative Risk (95%CI)		0.32(0.1-0.9)	0.84(0.3-1.9)	0.5(0.3-0.9)
Risk Reduction		68%	26%	50%
Mortality*	**LMWH**	5/848 (0.59%)	16/641 (2.5%)	21/641 (3.3%)
	UFH	9/875 (1%)	29/640 (4.5%)	38/640 (5.9%)
	p	0.3	0.03	0.01
Relative Risk (95%CI)		0.61 (0.21-0.8)	0.48 (0.2-0.8)	0.51 (0.2-0.9)
risk Reduction		39%	52%	49%
Bleeding	**LMWH**	19/850 (2.2%)		
	UFH	39/834 (4.7%)		
	p	0.04		
Relative Risk		0.44 (0.2-0.7)		
Risk Reduction		66%		

* morality similar for subgroup with cancer

Siragusa S et al. Am J Med 1996;100:269-77 (115)

Studies were classified as level 1 if outcome assessment was blinded, and level 2 if this was not assured. Analysis for efficacy and safety were not significantly different when level 1 and 2 studies were considered separately and together. The authors reviewed 3 level 1 studies and 3 level 2 studies for efficacy and 3 level 1 studies and 7 level 2 studies for safety.

Relative risk of recurrent DVT was significantly lower in the LMWH group during the initial treatment phase, with a risk reduction of 68%. Bleeding was also significantly lower in the LMWH group during this phase, with a risk reduction of 66%. Similar benefit was noted in the analysis of the entire treatment period, with risk reduction of 50% for recurrent VTE in the

LMWH group. There was no difference in the rate of recurrent VTE during treatment with warfarin between the two groups.

Two more studies published within the last year have evaluated the safety of home treatment with LMWH compared with continuous intravenous UFH in the initial management of patients with acute DVT (116,117). In the study by Koopman et al comparing subcutaneous Fraxiparin (weight based regimen; b/w <50 Kg-8200 anti-Xa U/Kg, 50 to 70 Kg-12,300 anti-Xa U/Kg, and >70 Kg-18,400 anti-Xa U/Kg total daily dose) twice daily with intravenous UFH, 36% of the 202 patients randomized to the Fraxiparin group were not admitted to the hospital. Mean reduction in hospital stay for the LMWH group was 67%. There was no difference in the incidence of symptomatic recurrence or bleeding complications (116). In the study by Levine et al, 120 of the 247 (48%) patients randomized to receive enoxaparin at a dose of 1 mg/Kg q12 hours were not hospitalized at all. Warfarin was started on the second day in both groups, and heparin was discontinued after INR was therapeutic, but not before day 5. There was no difference in the rate of symptomatic recurrence of VTE or bleeding episodes in the two groups. The mean length of hospital stay in the LMWH group and the UFH group was 1.1±2.9 days and 6.5±3.4 days respectively (117).

Long Term Treatment of Acute DVT

One study evaluated LMWH for the long term treatment of acute DVT. After initial treatment with intravenous UFH, Das et al randomized patients to either LMWH in a fixed dose (5000 units Fragmin once a day subcutaneously) or warfarin adjusted to maintain INR between 2-3, for three months. Compliance in the LMWH group was monitored by periodic anti-Xa levels. There was no difference in the rate of recurrent VTE or major bleeding between the two groups, but the rate of minor bleeding was significantly higher in the warfarin group (118).

Thus, LMWH appears to be a safe and effective alternative to UFH in the initial treatment of acute DVT without the need for laboratory monitoring, and in selected patients, without the need for hospitalization. If its safety and efficacy in the long term treatment of DVT is validated in other studies, we may soon be able to send selected patients with acute DVT home with a three to six month prescription of a LMWH preparation without any hospitalization!

Cost Effectiveness of LMWH

A recent cost analysis study of LMWH versus UFH in the initial treatment of acute DVT showed that LMWH was not only safe and effective, but less costly than intravenous heparin (119). In this study, 432 patients with proximal DVT were treated in the hospital with either a fixed, once daily dose of LMWH administered subcutaneously or UFH administered by continuous intravenous infusion. The cost per 100 patients in the LMWH group was $335,687 (US), and the cost per 100 patients in the UFH group was $375,836 (US), providing a cost saving of $40,149 with LMWH. As the cost of this treatment is entirely dependent on the price of the LMWH, multiple sensitivity analyses were performed varying the price of the drug by a range of 40% to 300%, and the resulting cost savings ranged from $23,337 to $45,193. The authors concluded that with the potential for outpatient therapy in up to 37% of patients receiving

LMWH, the feasibility of which has since been confirmed in other studies (116,117), the cost savings would be further augmented.

LMWH has also proved to be more cost effective than UFH for the prevention of DVT in patients undergoing total hip arthroplasty in Europe (120). In a study comparing the cost effectiveness of LMWH versus warfarin for the prevention of DVT after hip or knee arthroplasty, in the United States, warfarin use provided a cost savings of US$4718 per 100 patients ($20,876 vs $25,594) in favor of warfarin. The results were very sensitive to the cost of the LMWH (121).

Other Indications for LMWH

Pregnancy

Like UFH, LMWH does not cross the placenta, does not have mutagenic or teratogenic effect and appeared to be safe and effective for VTE prophylaxis during pregnancy in several small, descriptive studies (122,123).

Arterial Thrombosis

Although LMWHs are effective in reducing thrombus formation in the venous system, in porcine models of deep arterial injury, these agents were less effective than UFH in reducing the deposition of platelet thrombi (124). Nevertheless, these agents have been investigated in small clinical studies of arterial thrombosis as well. LMWH combined with aspirin was superior to aspirin alone, and a combination of aspirin and UFH, in decreasing the rate of recurrent angina, non-fatal myocardial infarction and need for urgent revascularization in patients with unstable angina (125). In patients undergoing peripheral vascular reconstructive surgery, LMWH was superior to UFH in one study (126) and comparable to UFH in another (127) in preventing arterial thrombosis. In patients with peripheral vascular disease, LMWH once daily for 6 months was superior to placebo in increasing time to claudication and pain free interval (128).

Miscellaneous Indications

LMWH was effective in improving neurological outcomes in patients with acute ischemic stroke (129). LMWH has been used as an anticoagulant instead of citrate or UFH during hemodialysis (130,131), and for prophylaxis and treatment of disseminated intravascular coagulation in acute promyelocytic leukemia (132), but there are no comparative studies of LMWH with UFH for these indications.

Heparinoid

The low molecular weight heparinoid Org 10172 has a plasma half-life of approximately 1,100 minutes and anti-Xa to anti-IIa ratio of 20:1 to 28:1 and a mean molecular weight of 6,555 daltons. Although reviews of LMWH frequently include Org 10172, this agent is not a true LMWH. Only 4% of the heparan sulfate contains the ATIII binding pentasaccharide sequence. It has been evaluated for DVT prophylaxis during THA, after hip fracture, in patients with acute

ischemic stroke, and for treatment of acute venous thromboembolism, and appears to be safe and effective for all these indications (133-135). It has also been used for continued anticoagulation in patients developing heparin induced thrombocytopenia (53). However, cross reactivity between LMW heparinoid and LMWH has been reported and this agent may not be entirely safe for this indication (54).

Summary

LMWHs differ from UFH in molecular weight distribution, pharmacological activity and pharmacokinetics. They have a more favorable antithrombotic and anticoagulant profile, are less immunogenic, and associated with a lower incidence of HIT. Greater bioavailability, longer half-life and more predictable dose response allow once daily or twice daily subcutaneous administration of these agents without the need for laboratory monitoring, for both prophylaxis and treatment of DVT. Different preparations of LMWH with different anti-Xa activity and half-life are available.

Enoxaparin, Fragmin, Fraxiparin, Logiparin and Ardeparin have been evaluated for prevention of DVT after major orthopedic surgery. LMWH was superior to warfarin after total knee arthroplasty. LMWH was superior to placebo, dextran and UFH given three times a day and as effective as warfarin after total hip arthroplasty. It is superior to UFH in trauma patients and may be superior to UFH after acute spinal cord injury. It is as effective as low dose UFH in preventing DVT after general surgery and in patients hospitalized with acute medical illnesses.

Enoxaparin, Fraxiparin, Logiparin and Fragmin have been evaluated for the treatment of acute DVT in several recent studies. LMWH was as effective and safe as intravenous UFH for the initial treatment of acute DVT. In meta-analyses, LMWH was safer and more effective than intravenous UFH for the treatment of acute DVT. It was also more cost effective than UFH for the treatment of DVT. Use of LMWH may obviate the need for initial hospitalization in selected patients with acute DVT

The role of LMWH in maintaining arterial patency after coronary angioplasty and as an anticoagulant during extracorporeal perfusion (both hemodialysis and cardiopulmonary bypass) is still under investigation.

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