Chapter

14

Low Molecular Weight Heparin Current Status

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McLean, 90 years ago, discovered that heparin has antithrombotic properties. Brinkhous and associates demonstrated that heparin is an indirect anticoagulant, requiring plasma cofactor. This plasma cofactor was subsequently named Antithrombin (AT) III by a Abildgard in 1968. The main anticoagulant action of heparin is mediated by heparin / AT interaction. Heparin binds to AT through a unique glucosamine unit, A.T. that is contained within pentasacharide sequence.

The development of Low Molecular Weight Heparin (LMWH) in 1980 introduced the concept that the ability of heparin molecules to inactivate thrombin and other activated coagulation factors are chain length-dependent, whereas the inactivation of factor Xa only require the presence of the high–affinity pentasaccharide.

Low molecular weight heparins are derived from unfractionated heparin (UFH) by chemical or enzymetic depolymerization.

The low molecular weight heparins have following advantages:

1. They can be given subcutaneously once or twice daily.
2. Their pharmacokinetics are so predictable that APTT monitoring is not necessary.
3. They are less immunogenic and less likely to cause thrombocytopenia.
4. They have reduced antifactor IIa activity relative to antifactor Xa activity.
5. Animal studies showed that LMWHs have more favourable benefit / risk ratio.
6. LMWH causes less osteoporosis on chronic administration than UFH.

LMWHs are polysulfated glycosaminoglycans and 1/3 of molecular weight of UFH.

LMWH has mean molecular weight of 4000 to 5000 d with range of 2000 to 9000 d.

Table 1: Development of heparin and related compounds

1st Generation	Unfractionated heparins (bovine, porcine, ovine)
	Various salts
2nd Generation	Low molecular weight heparins
	Medium molecular weight heparins
3rd Generation	Chemically modified heparins
	Heparin derivatives
	Heparin formulation
4th Generation	Synthetic heparins
	Biotechnology derived heparins

Table 2: Structural changes in heparin inflicted by the depolymerization process

Process	*Chemical changes*
Nitrous acid depolymerization	Formation of anhydromannose ring
Isoamyl nitrite depolymerization	Formation of anhydromannose ring
Benzylation followed by alkaline hydrolysis	Introduction of double bond at the end grouping
Peroxidative cleavage	Generation of labile glycosidic bonds
Heparinase digestion	Introduction of double bond at the end grouping

The various LMWHs are prepared by different methods of depolymerization. Therefore, they differ in pharmacokinetic properties and anticoagulant profile and are not clinically interchangeable. Depolymerization of heparin gives low molecular weight fragments with reduced binding to proteins or cells. Therefore

compared to heparin, LMWHs, have reduced ability to inactivate thrombin. The bridging between AT and factor Xa is less critical for antifactor χα activity. This reduced biding to plasma proteins is responsible for the more predictable dose-response relationship of LMWH. Lower incidence of binding to cell (macrophages and endothelial cells) increases the plasma half life of LMWH. This reduced binding to platelets and PF4 can explain the lower incidence of thrombocytopenia osteoblasts results. Also, reduced binding of LMWH to osteoblasts results in low incidence of activation of osteoclast and lower bone loss.

LMWH produce their major anticoagulant effect by activating antithrombin, this interaction with AT is mediated by pentasacchride sequence which is found on 1/3 LMWH molecules.

Heparin has an antifactor Xa/IIa ratio of 1:1, while LMWHs have different antifactor Xa/AT II 2:1 and 4:1 depending on their molecular size distribution.

Table 3: The different low molecular weight heparins

Agents	*Xa : IIa*	*Mol Wt (d)*
Enoxaparin	3.8:1	4,200
Dalteparin	2.7:1	6,000
Ardeparin	1.9:1	6,000
Nadroparin	3.6:1	4,500
Reviparin	3.5:1	4,000
Tinzaparin	1.9:1	4,500

When chain is shorter, the heparin molecule is not able to bind to both thrombin and antithrombin, and it can easily accommodate antithrombin bound to factor Xa. Thus, antithrombin Xa activity is more predominant than the anti IIa activity.

In 1980 various studies reported that LMWH had superior pharmacokinetics than UFH. LMWH after subcutaneous injection bioavailability nearly 100% at low doses. The peak anti Xa activity occur in 3 to 5 hours. After subcutaneous injections, with a more predictable dose response. However, elimination of half life LMWH was longer 3 to 6 hours and is not dose dependent. LMWH is cleared by kidney hence use of LMWH in renal failure is not recommended, because renal insufficiency has been reported to increase the risk of bleeding in therapeutic doses of LMWH.

The different LMWH cannot be considered interchangeable because pharmacologically active material varies from product to product. They have varied physical and chemical compositions originating in the manufacturing process, which translate into biological different actions.

The clinical trials for specific indications are performed at optimum doses of that product. US-FDA has classified as distinct drug and cannot be interchangeable.

Different LMWHs have different doses, protocols and they are different compounds and all of them are at least as effective as UFH. The specific indication, type of patients and clinical evidence will have to decide use particular LMWH. Dalteparin and enoxaparin have comparable efficacy in the prevention of death or MI in patients with UA/MI.

The International Cardiology Forum (ICF-2000) gave the guidelines that "Although LMWH are similar in many respects, the differences in molecular structure result in differences in relative antixa and anti IIa and in pharmokinetic properties. These compounds should therefore be considered to be distinct therapeutic agents."

Table 4: Advantages of LMWHs over UFH

- Administration is subcutaneous once or twice day.
- No need for monitoring of activity by apt
- Incidence of HIT is lower than UFH
- Less binding to plasma proteins and endothelial cells than UFH
- Less stimulation of platelets than UFH
- Longer half-life than UFH
- More reproducible and sustained anticoagulation than UFH
- Superior efficacy in reducing cardiac events and revascularization in UA

LMWH in UA / NSTEMI

The aim of antithrombotic therapy in UA/NSTEMI is to prevent the progression of intracoronary thrombus and promote stabilization of the atheromotous plaque which reduces myocardial ischemia and prevent further CV evens. Aspirine remains mainstay of therapy. Inspite of aspirine there is risk of recurrent ischemic events in UA/NSTEMI at 5 to 150 days in 5 to 40% cases. This is because of unregulated thrombin generations which produces recurrent ischemia. Aspirine not completely blocks the thrombin mediated plate activation. LMWH or UFH is used to inhibit thrombin generation and block thrombin activity. But UFH has short duration of action, poor bioavailability, unpredictable anticoagulant response and there is risk of heparin induced thrombocytopenia and reactivation of problem of disease. LMWH has smaller molecular weight, biological activity of heparin is encoded in pentasaccharide segment and retain antithrombin qualities of parent molecule with

better pharmacokinetic and pharmacodynamic properties.

LMWH has clear clinical advantages over UFH, i.e. it is less binding to proteins and endothelial cells, longer half life and better dose dependent clearance. LMWH can be given subcutaneous twice daily. Monitoring is not required in UA / NSTEMI.

Table 5: Recommendations for use of LMWHs in high risk UA / NSTEMI

- Benefits of treatment with LMWH are more in high-risk patients with raised troponin levels and ST-segment deviation.
- Geriatric (elderly) patients benefit as much as the younger patients with LMWH.
- Enoxaparin is not inferior to UFH in high-risk patients as revealed in SYNERGY trial. Sub-analysis showed "switching" causes more bleeding problems.

Table 6: Recommendations for use of LMWHs in coronary intervention in UA / NSTEMI

- LMWH is a safe procedural anticoagulant though it carries minimal increased risk of bleeding when used with Gp llb llb receptor inhibitors.
- Lower than conventional dosage (75% enoxaparin, 50% dalteparin) have been used in conjunction with Gp llb/lllb receptor inhibitor.
- Efficacy wise, LMWHs are not inferior to UFH in patients undergoing PCI.
- Only enoxaparin and dalteparin are studies in patients with UA/ NSTEMI undergoing coronary intervention/PCI and enoxaparin has been studied more extensively.

Table 7: Recommendation for use of LMWHs in STEMI

- Low – molecular – weight heparin might be considered an acceptable alternative to UFH as anallary therapy of patients with STEMI aged less than 75 years who are receiving fibrinolytic therapy, provided that significant renal dysfunction (serum creatinine greater than 205 mg dL in men or 2.5 mg/dL in women) is not present.
- There is definite but minor increase in the risk of bleeding complications following the use of LMWH in STEMI especially in patients with renal dysfunction and age? 75 years. Dosage reduction in such situations helps to reduce the risk of bleeding complications.
- Dalteparin, enoxaparin in combination with rtPA and reviparin combinations with STEMI. Reviparin has been studied most extensively among the group. Delteparin has been studied in patients with STEMI not receiving fibrinolytic therapy.
- LMWH (Reviparin) is superior to placebo in terms of reduction in MACE at 30 days after ancillary usage in patients with STEMI.

Clinical trials in patients with UA / ASTEMI (FRIC and FRAXIS) demonstrated that there is difference between dalteparin and nadroparin compared to UFH. Patients in whom revascularization is delayed for any reason may benefit from medical stabilization with LMWH.

LMWH in ST segment elevation myocardial infarction might be considered as alternative to UFH. Because it has inhibitory effect in coagulation predominantly related to inhibition or factor Xa activity and reduced thrombin generation.

LMWH in medical thromboprophylaxis. Epidemiological studies showed that various thromboembolism (VTE) is major cause of morbidity and mortality in hsopitalised patients. Autopsy studies confirmed the high number of deaths due to or associated with pulmonary embolism (PE) in hospitalized patients. Because of various reason hospitalized patients are at higher risk of developing VTE i.e., advanced age, prolonged bed rest, CCF, past history of VTE and chronicity of disease.

Table 8: Risk factors for VTE

Acute Medical Illness	
Stroke	
Myocardial infarction	
Illness requiring ICU	
Other acute illness requiring immobilization for at least 3 days	
Clinical Risk Factors	
Previous PE or DVT	Collagen vascular disorders
Cancer	Internal cardiac defibrillator
Congestive heart failure	Stroke with limb paresis
Chronic obstructive pulmonary disease	Nursing home confinement, current of repeated hospital admission
Diabetes mellitus	Varicose veins
Inflammatory bowel disease	Hormone replacement therapy
Antipsychotic drug use	Obesity
Chronic in-dwelling central venous catheter	Cancer chemotherapy
Permanent pacemaker	
Thrombophilia	
Factor V Leiden mutation	
Prothrombin gene mutation	
Hyperhomocysteinemia (including mutation in methylene tetrahydrofolate reductase)	
Antiphospholipid antibody syndrome	
Deficiency of antithrombin ill, protein C, or protein S	
High concentrations of factor VIII, IX, or XI	
Increased lipoprotein(a)	

ICU, intensive care unit; PE, pulmonary embolism.

A meta-analysis of smaller trials designed to evaluate the prevention of asymptomate DVT, concluded that treatment with LMWH compared with placebo reduced the rate of DVT and symptomatic PE.

Table 9: Thromboprophylaxis for acutely ill medical patients

STEP 1: Systematically assess all cases	
Hospitalized patients with acute medical illness Projected immobilization of 3 or more days	
Step 2: Consider thromboprophylaxis in particular if reason for admission and/or risk factors are among the following lists	
Reason for administration	Risk factors
Congestive heart failure NYHA class III/IV	Age 60 years
Acute lung disease	Cancer
Acute infectious disease	Previous VTE
Inflammatory disease	Obesity
	Previous VTE
	Obesity
	Varicose veins
	Chronic heart disease
	Chronic pulmonary disease
	Hormone therapy
	Thrombophilia
Step 3: Give thromboprophylaxis for 2 weeks (if no contraindications)	
Enoxaparin 40 mg daily or dalteparin 5000 U daily or UFH 5000 U 3 X daily	
Graduated compression stockings or intermittent pneumatic compression devices for patients with contraindications to anticoagulation	
Combined LMWH or UFH plus graduated compression stockings or intermittent pneumatic compression devices for patient at very high risk.	

Meta-analysis of all studies comparing UFH and LMWH included 9 trials for total number of patients included 4665. There was a trend in favour of LMWH for the reduction of DVT and PE. Major bleeding was marginally less frequent in LMWH group. Patients with few days immobilization, hormonal therapy (estrogen), elderly patients, patients with CCF or respiratory failure, benefit from thromboprophylaxis.

Patients who are receiving full doses of UFH, LMWH or oral anticoagulants are obviously not eligible for low doses of UFH / LMWH, unless their original treatment is stopped during hospitalization.

Treatment with UFH / LMWH should not exceed 2 weeks. Through risk stratification and timely identifying high risk patients and giving thromboprophylaxis with UFH / LMWH will greatly reduce VTE in hospitalized patients.

Patients with idiopathic DVT or PE have high risk of recurrent events of thromboembolism. Various trials have shown indefinite–duration anticoagulation therapy as effective and safe in most of the patients.

In majority of patients undergoing surgery (Orthopedic, Gynecological, General Surgery, Urologic Surgery and Vascular Surgery), the risk for VTE has been adequately evaluated and benefit of thromboprophylaxis established.

When pharmacological prophylaxis is used properly, the risk of bleeding complications is low. Mechanical method is preferred in patients of high risk of bleeding complications. It is cost effective for many surgical patients and should be implemented in all clinical settings where its effectiveness and safety has been established.

Table 10: Thromboembolism risk with different types of surgeries

Risk Level	*Calf DVT*	*Proximal*	*Clinical PE*	*Fatal PE*
Low risk	2%	0.4%	0.2%	< 0.01%
Minor surgery in patients aged < 40 yr with no additional risk factors				
Moderate risk	10%-20%	2%-4%	1%-2%	0.1%-0.4%
Minor surgery in patients with additional risk factors				
Surgery in patients aged 40-60 yr or with no additional risk factors				
High risk	20%-40%	4%-8%	2%-4%	0.4%-1.0%
Surgery in Patients > 60 yr or with additional risk factors (eg, prior VTE, cancer)				
Highest risk	40%-80%	10%-20%	4%-10%	0.2%-5%
Surgery in patients with multiple risk factors (age > 40 yr, cancer, prior VTE)				
Hip or knee arthroplasty, hip fracture surgery				

Adapted from Geerts WH, Helt JA, Clagett GP, et al. Chest 2001;119 (suppl 1) : 132S-175S

Table 11: VTE prevalence after major orthopedic surgery in absence of prophylaxis

Procedure	*DVT*		*PE*	
	Total	*Proximal*	*Total*	*Fatal*
HIP arthroplasty	14% - 57%	18% - 36%	0.9% - 28%	0.1% - 2.0%
Knee arthroplasty	41% - 85%	5% - 22%	1.5% - 10%	0.1% - 1.7%
Hip fracture surgery	46% - 60%	23% - 30%	3% - 11%	2.5% - 7.5%

Adapted from Geerts WH, Helt JA, Clagett GP, et al, Chest 2001;119(suppl 1):132S-175S

Till today the cost of LMWH is more than UFH or other anticoagulants. But cost-effectiveness of a particular medication is not fixed or permanent. It varies with patients in whom it is used, or the nature of the underlying disease for which they require therapy. The health care system must be aggressively perused to provide the most appropriate (cost effective) anticoagulant care to the largest number of patients for prevention of VTE and PE.

CONCLUSION

Enoxaparin, dalteparin and nadroparin are studied in various clinical trials which show that these drugs have different dose protocols, and they are different compounds, and all of them are least as effective as UFH.

Choice of LMWH should reflect the level of clinical evidence-in particular, the indication and type of patients. Dalteparin and enoxaparin have comparable efficacy in the prevention of death or MI in patients with unstable angina / myocardial infarction.

Dalteparin has highest anti Xa and optimal anti IIa activity. Bleeding index is highest with enoxaparin.

LMWHs are useful in medical and surgical high risk patients VTE, IHD, OVA, PVD, knee and hip replacement surgery, gynecological surgery and vascular surgery for prophylaxis and treatment.

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