Course Title: Low-Molecular-Weight Heparin: Should I Be Using It?
Faculty: David Brown, MD, FACEP
Course #/Date: WE-197, October 17, 3:00 pm – 4:00 pm, Room 303

Course Objectives assigned:

Upon completion of this course, the participant will be able to:

- Describe the mechanism of action of LMWH.
- Discuss the differences and similarities of LMWH and unfractionated heparin.
- Discuss the indications for LMWH and the literature that supports its use.
- Explain the differences between the various LMWHs that are available.

David F. M. Brown MD, FACEP

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Introduction

Heparin sulfate (UFH) has been the mainstay of treatment for decades
LMWH used in Europe for >10 years
    Efficacious, safe, cost-effective
    Easier to administer and monitor

Coagulation Cascade

Intrinsic and Extrinsic pathways converge with Xa
    Xa and Va activate thrombin (IIa)
Thrombin converts fibrinogen to fibrin
    Fibrin is necessary for clot formation
Xa and IIa also activate platelets

Regulation of Coagulation

Antithrombin III and Protein C
    UFH main anticoagulant effect is achieved by binding to and activating ATIII
    ATIII renders thrombin and Xa inactive
        UFH makes this interaction even stronger
        UFH at high doses can directly inhibit thrombin (factor IIa)

Unfractionated Heparin

Highly sulfated large polysaccharide polymer

Molecular weight varies

Mechanism

Catalyzes the activation of ATIII

Route

SQ or IV

Advantages:

most clinicians have extensive experience with UFH

inexpensive

Disadvantages

-variable anticoagulant effect (because of interactions with plasma proteins) requires frequent monitoring (aPTT)

-sensitivity of platelet factor 4

-relative inability to inactivate platelet-bound thrombin

-potential to cause thrombocytopenia (HIT)

-rebound of clinical events after cessation of treatment

Low Molecular Weight Heparin

Produced by chemical or enzymatic depolymerization of UFH

-results in saccharide chains of variable length with mean molecular weight of ~5000 daltons

-minimum length must include the critical polysaccharide for attachment to AT III and an additional 13 saccharides that allow simultaneous attachment to thrombin

-only these sequences must be present to inhibit thrombin and Xa, so creating a mixture of short and long chain sequences leads to variable anti-thrombin:anti-Xa activity

Mechanism

All LMWHs inactivate Xa

Approximately 25%-50% also inactivate thrombin

Anti-Xa to anti-IIa ratios are 2:1 to 4:1

Reliable anticoagulant effect with no daily laboratory monitoring needed (small effect on aPTT)

If necessary, can measure anti-Xa activity

Much lower rates of thrombocytopenia

Route: SQ, IV - good bioavailability, beware of obesity, renal failure, and elderly

Excreted via the kidney

Low Molecular Weight Heparin

No two are alike!

Vary in size, mechanism of action, dosing and indications

Each preparation must be independently tested

Four approved in U.S.

Ardeparin (Normiflo®; Wyeth Ayerst) – only approved for DVT prophylaxis post-TKR

Dalteparin (Framin®; Pharmacia Upjohn)

Enoxaparin (Lovenox®; Aventis)

Tinzoparin (Innohep®; DuPont)

Another agent, nadroparin, has been tested in the NSTEMI population but is not FDA-approved for use.

Monitoring Low Molecular Weight Heparin

Baseline labs

CBC, Renal function tests

Do not need to monnitor aPTT or other coagulation tests. Should check platelets [periodically, especially in the beginning of therapy.

Bleeding Complications

LMWH measurable serum concentrations in a couple of hours after administration

T ½ is approx. 12 hrs

Minor bleeding

LMWH>UFH

Major bleeding

LMWH same or better profile than UFH

Treatment of Bleeding Complications

Give blood products if necessary

Protamine sulfate slow IVP

1 mg protamine slow IV infusion per 1 mg enoxaparin administered

May repeat ½ the dose

If enoxaparin given > 12 hrs ago, protamine may not be necessary

Low Molecular Weight Heparin Indications

DVT prophylaxis: all agents FDA approved except tinzaparin which nonetheless has good supporting data for this indication

Acute DVT±PE

Enoxaparin 1 mg/kg sq q12hrs or 1/5 mg/kg qd

Tinzaparin 175 anti-Xa IU/kg sq qd

Unstable Angina and non-Q-wave MI

Dalteparin 120 U/kg q 12 hrs (Maximum 100,000 U per dose)

Enoxaparin 1mg/kg q 12 hrs

Contradictions

Active major bleeding

Thrombocytopenia

Known hypersensitivity

Recent LP or spinal anesthesia

Warnings

History of heparin induced thrombocytopenia

Conditions with increased risk of hemorrhage

Renal insufficiency

Uncontrolled arterial hypertension

Literature for ACS

Gurfinkel, et al (nadroparin, 1995)

Single blinded study

Rest angina within the previous 24 hrs

219 pts. Randomized toone of 3 arms:

ASA 200 mg qd

UFH + ASA

Nadroparin + ASA

Treated for 5-7 days or until primary endpoint event occurred

	Composite Endpoint (recurrent angina, MI, urgent PCI or death)
ASA	43/73 (59%)
UFH + ASA	44/70 (63%)

Nadroparin + ASA 15/68 (22%)

The results are clinically and statistically significant ($p<.001$)

FRAXIS study (nadroparin, 1999)
3468 pts with UAP/NSTEMI
randomized to UFH (6d), nadrparin (6d) or nadroparin (12d)
1^0 endpoint was composite of cardiac death, MI, refractory or recurrent angina @14 days
no differences found at 14 days
increased major bleeding in the 14 day nadroparin group but not in the 6 d nadroparin group c/w UFH

FRISC I Study (dalteparin)
Fragmin during InStability in Coronary artery disease (FRISC), 1996
Placebo controlled trial
USA or non-Q-wave MI in past 72 hours
1498 patients
Placebo + ASA
Dalteparin + ASA
120 U/kg q 12 hrs for 6 days then 7,500 U/d for 35-45 days

		Composite Endpoint (Angina, MI, urgent PCI or death)
Day 6	Placebo	36/757 (4.8%)
	Dalteparin	13/741 (1.8%)
Day 40	Placebo	81/755 (10.7%)
	Dalteparin	59/738 (8%)
Day 150	Placebo	116/749 (15.5%)
	Dalteparin	102/726 (14%)

FRIC Study (dalteparin)
FRagmin In unstable Coronary artery disease (FRIC), 1997
USA in past 72 hours
Open label phase followed by double blinded phase
1482 patients
UFH IV x 48 hrs then 1000 U bid SQ x 4d + ASA
Dalteparin 120 U/kg bid + ASA
After 6 days, double blinded phase began

		Composite Endpoint (Angina, MI, urgent PCI or death)
Day 6	UFH + ASA	55/731 (7.6%)
	Dalteparin + ASA	69/751 (9.3%)

Day 45	Placebo + ASA	69/561 (12.3%)	
	Dalteparin + ASA	69/562 (12.3%)	

FRISC II Study (dalteparin, 1999)

2267 patients with UAP/STEMI

all patients received 5 d of dalteparin, then randomized to 3 mos of dalteparin vs placebo

no differences in death/ MI at 90 d (primary endpoint) or 6 mos although benefit was seen at 30d

ESSENCE Study (enoxaparin, 1997))

3,171 patients with CP and either ECG changes or h/o CAD

Randomized, double-blinded, to:

UFH + ASA

Enoxaparin 1 mg/kg bid + ASA

Treated for 2 to 8 days

		Primary Composite Endpoint (recurrent angina, MI, or death)	
Day 14	UFH + ASA	309/1,564 (19.8%)	
	Enoxaparin + ASA	266/1,607 (16.6%)	(p=0.019)
Day 30	UFH + ASA	364/1,564 (23.3%)	
	Enoxaparin + ASA	318/1,607 (19.8%)	(p=0.016)

Also found that the need for PCI within 30 d was significantly reduced in the enoxaparin arm (27% vs 32.2%, p=0.001).

No differences found in major bleeding

One Year Follow-up ESSENCE Trial

2915 of original 3171 patients

13% reduction in the number of pts requiring CABG or PTCA

15% reduction in death or MI

11% reduction in death, MI, or recurrent angina

6% reduction in death, MI, PCI

The reduction in death/MI/recurrent angina at one year was 11%

TIMI IIB Trial (Enoxaparin, 1999)

Unstable angina or non-Q-wave MI

3910 patients randomized to:

UFH for 3-8 days, then placebo for 6 wks

Enoxaparin for 6 wks

		Composite Endpoint (MI, urgent PCI, death)	
48 hrs	UFH	7.3%	
	Enoxaparin	5.5%	(p=0.026)

8 days	UFH	14.5%	
	Enoxaparin	12.4%	(p=0.046)
14 days	UFH	16.7%	
	Enoxaparin	14.2%	(p=0.029)

results maintained at 6 wks and one year

TESSMA (enoxaparin)

Meta-analysis of ESSENCE and TIMI 11B (trials were very similar)
Strengthened and confirmed the findings of each

Smaller studies

-assess efficacy and safety of LMWH when combined with GP IIb-IIIa inhibitors – results promising
-assess efficacy and safety in patients who undergo early PCI – results promising

Summary for ACS

Enoxaparin is superior to UFH for UAP/ non-Q-wave MI in the acute setting
Dalteparin appears equivalent to UFH in these same patients with non-STE ACS

Critical Review of Literature for Venous Thromboembolic Disease

Many studies have compared LMWH to UFH in the treatment of DVT. Early studies and subsequent meta-analyses have suggested the superiority of LMWH in terms of bleeding complications, prevention of further thromboembolic events, and mortality (1,2). Another meta-analysis of 16 controlled trials and more than 2000 patients found that LMWH significantly reduced thrombus extension and that there were trends toward decreased thromboembolic events, major bleeds, and mortality (3). The follow-up to this meta-analysis, with more than 3300 patients, found that LMWH was associated with statistically significant reductions in mortality, major bleeding, and clot extension, with a nonsignificant trend toward reduction in venous thromboembolic events (4). The most recent meta-analysis, published by Gould et al in 1999, reviewed 966 potentially relevant studies and ultimately pooled the results of 11 randomized trials of more than 3600 patients (5). The authors found that LMWH is at least as safe and effective as UFH, with all trends favoring LMWH. LMWH was also associated with a reduction in 3-6 month mortality (odds ratio 0.71, p=0.02) although the explanation for this was not clear as LMWH did not reduce the risk of death from major bleeding complications or documented recurrent thromboembolic events (5).

The favored choice at present is enoxaparin, which was the first FDA-approved agent. For hospitalized DVT patients, with or without pulmonary embolism, enoxaparin can be administered subcutaneously (SQ) as follows: either 1 mg/kg/bid or 1.5 mg/kg/qd. Outpatient therapy, discussed in more detail below, is limited to patients without pulmonary embolism and consists of enoxaparin 1 mg/kg SQ bid (6). More recently, tinzaparin, when administered in conjunction with warfarin, has been approved by the FDA for use in hospitalized patients with DVT with or without pulmonary embolism. The recommended dose of tinzaparin is 175 IU/kg SQ once daily for at least six days and until adequate anticoagulation with warfarin, which should generally be initiated within 1-3 days, has been achieved. The safety and efficacy of tinzaparin in outpatients has not been established as yet. Other LMWHs including dalteparin and nadroparin are likely to be approved for use in patients with DVT in the near future

Disposition of the Patient with DVT

The advent of LMWH therapy has markedly altered the disposition decisions for many patients with DVT. While patients treated with IVC filter placement, thrombolysis, or thrombectomy require inpatient care,

those who are candidates for standard anticoagulation therapy should be considered for outpatient management. The potential advantages of outpatient therapy include fewer hospital admissions with associated cost savings and increased patient comfort. Two studies have addressed this strategy and both provide evidence to support it (6,7).

In an unblinded multi-center trial, Levine et al studied 500 patients with confirmed proximal DVT who were randomized to UFH in the hospital versus LMWH (enoxaparin) primarily at home (6). Patients were transitioned to warfarin therapy over 5 days. At 90-day follow-up, there were no differences in mortality, recurrent thromboembolism, or major bleeding. Patients treated with LMWH spent a mean of 1.1 days in the hospital compared with 6.5 days for the UFH patients and nearly 50% of the LMWH patients were not hospitalized at all. Of note, 67% of screened patients were deemed ineligible for the trial; reasons included co-existing medical conditions, concurrent pulmonary embolus, inaccessibility to outpatient monitoring, and prior DVT. Of the remaining patients, 32% declined to participate. The high rates of exclusion and refusal to participate weaken the external validity of the conclusions.

Koopman et al also performed an unblinded multi-center trial of patients with confirmed proximal DVT (7). 400 patients were randomized to UFH in the hospital or LMWH (nadroparin) administered primarily at home. Both heparin strategies were continued for a mean of 6 days and warfarin was started on the first day. At 6-month follow-up, there were no differences in mortality, recurrent thromboembolism, or major bleeding. Physical activity and social functioning were better in the LMWH group. Patients assigned to LMWH therapy had a mean reduction in hospital days of 67% and 36% were never admitted at all. 31% of screened patients were excluded; the most common reasons included recent DVT, suspected pulmonary embolism, and geographic inaccessibility to outpatient monitoring. Of the remaining patients, 16% refused to participate.

Overall, in select patients, outpatient therapy with LMWH appears feasible, effective and safe. While firm guidelines await further testing and validation, a reasonable set of exclusion criteria for the present time include age <18 or >75 years, suspected pulmonary embolus, heparin allergy or history of HIT, known bleeding disorder, active bleeding, co-morbid illness with high risk of bleeding, pregnancy, renal insufficiency, geographic inaccessibility to outpatient monitoring, and a high risk of noncompliance (8). Others have recommended also excluding those with obesity or severe leg pain and swelling (9). The importance of patients' willingness and ability to participate in their own care and comply with follow up cannot be overstated. Medical centers will need to have resources for patient education available in the ED as well as committed daily outpatient follow up for monitoring of response to therapy. In some cases, it may be preferable to admit patients to ED or hospital-based observation units to allow for the initiation of therapy and more comprehensive patient teaching. It has been estimated that even with these strict guidelines in place, 22-58% of patients with proximal lower extremity DVT would be eligible for outpatient therapy (10-12). At the present time, enoxaparin is considered the drug of choice but other agents are likely to be approved for outpatient therapy in the near future. The regimen for outpatient therapy with enoxaparin is 1 mg/kg every 12 hours by SQ injection.

It is interesting to note that although SQ UFH is a reasonable treatment strategy for DVT and has been compared rigorously to intravenous UFH in hospitalized patients (13,14), there are no studies that have evaluated the feasibility, safety, and efficacy of home treatment with SQ UFH. There have also been no trials comparing outpatient LMWH with outpatient SQ UFH to compare clinical outcomes and relative cost savings. The only cost effectiveness comparisons have been made between LMWH and intravenous UFH, with the former conferring marked cost savings when as few as 8% of patients were treated entirely as outpatients or when at least 13% were eligible for early hospital discharge (15).

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General

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Venous Thromboembolic Disease

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