Antithrombotic Therapy in CV Disease: Part 2

Lori A. Frank, Pharm.D., CSPI
Scientific Manager, Medical Education
Cardiovascular Scientific Team
U.S. Medical Affairs
Aventis Pharmaceuticals
lori.a.frank@aventis.com

Objectives

• Review the rationale of antiplatelet and anticoagulant therapies in specific cardiovascular disorders
• Outline the dosing, monitoring and adverse effects of the oral antiplatelet agents, namely aspirin and clopidogrel
• Differentiate unfractionated heparin (UFH) from that of low molecular weight heparin (LMWH) and be familiar with dosing, monitoring and adverse effects.
• Given patient-specific information, justify the appropriate selection of antithrombotic pharmacotherapy in various settings (e.g., NSTE ACS, STE ACS).

ACS: Tip of the Atherothrombotic “Iceberg”

ACS: acute coronary syndrome; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
Adapted from Goldstein JA. J Am Coll Cardiol. 2002;39:1464-1467.

Clinical
Subclinical

Acute Plaque Rupture ACS (UA/NSTEMI/STEMI)

Formation and Rupture of Unstable Plaque

Site of Endothelial Injury

Classes of Agents Targeted at Thrombosis

• Antiplatelet agents (aspirin, clopidogrel)
• Anticoagulants (warfarin, UFH, LMWH)
• Thrombolytic drugs (TPA, SK, TNK)

The Role of Antiplatelet Therapy in Unstable Angina and NSTEMI (NSTE ACS)

− Unstable angina/NSTEMI is one of the classic examples of the progression of atherothrombotic disease
− Platelets play a key role in thrombus formation associated with rupture of an unstable atherosclerotic plaque
− Angioscopic findings show that unstable angina is due to the formation of a platelet-rich thrombus
− Consequently, antiplatelet therapy is recognized as the foundation of long-term management

Adhesion

Role of Platelets in Atherothrombosis

1. Platelet Adhesion
2. Platelet Activation
3. Platelet Aggregation

Currently Available Oral Antiplatelet Agents in US

- Aspirin
- Clopidogrel (Plavix®)
- Ticlopidine (Ticlid®)
- Dipyridamole (Persantine®)
- ASA/Dipyridamole (Aggrenox®)

Oral Antiplatelet Agents

Different Mechanisms of Action

Aspirin: Overview

- MOA:
  - Acetylates and inactivates platelet cyclooxygenase, which inhibits thromboxane A2 synthesis, which leads to decreased platelet activation, aggregation, and vasoconstriction
  - Irreversible effect – last lifetime of platelet (~ 7 days)
- Indications:
  - Stable and unstable angina
  - Acute MI (primary & secondary prevention)
  - Stroke prevention
  - Peripheral Vascular Disease

Aspirin: Dosing

75 mg-160 mg have been shown to be effective in all indications†

NSTE ACS and STE ACS‡:

- 160-325 mg on hospital day 1
- 75-325 mg/day starting on hospital day 2 and continued indefinitely

† Grade 1A. Chest 2001:228S-252S.
‡ Class 1 Recommendation, ACC/AHA Practice Guidelines
Aspirin: Administration Considerations

Enteric Coated vs Nonenteric coated:

Adverse Effects:
- GI irritation
- Bleeding

Contradictions:
- Active Bleeding or severe bleeding risk
- Hypersensitivity

Aspirin: Monitoring

- Aspirin therapy is primarily monitored by patient tolerance and evidence of bleeding such as petechiae, bruising or blood in urine or stool.

NOTE: Many OTC products contain ASA.

Adenosine Diphosphate (ADP) Antagonists

- Irreversible effects on the platelet
- Clopidogrel is preferred to ticlopidine
  - More rapidly inhibits the platelets
  - Increased safety profile
  - Clinical data (CURE, PCI-CURE, CREDO)
- Used in patients unable to tolerate aspirin, alone and in combination with aspirin in specific settings

Clopidogrel: Administration Considerations

Dose for:

- Recent MI, recent stroke, or peripheral vascular disease:
  - 75 mg once daily

- NSTE ACS and patients undergoing PCI:
  - 300-mg loading dose on hospital day 1 followed by a maintenance dose of 75 mg starting hospital day 2
  - Administered in combination with aspirin

Clopidogrel: Administration Considerations

Duration†:
- Indefinitely in patients with an aspirin allergy
- At least 9 months in medically managed patients with NSTEMI
- At least 30 days to 1 year in patients with NSTEMI or STEMI undergoing PCI
- If possible, hold for at least 5 days in patients whom CABG is planned

Monitoring:
- No routine hematologic monitoring required

Adverse Effects:
- Bleeding
- Rash
- Diarrhea

Contradictions:
- Active Bleeding or severe bleeding risk
- Hypersensitivity

† Class 1 Recommendation, ACC/AHA Practice Guidelines, 2002.
Classes of Agents Targeted at Thrombosis

- Antiplatelet agents (aspirin, clopidogrel)
- Anticoagulants (warfarin, UFH, LMWH)
- Thrombolytic drugs (TPA, SK, TNK)

Coagulation Cascade in Thrombus Formation

Coagulation Cascade

Heparin: UFH and LMWHs

Heparin: UFH and LMWHs

Molecular Weight Distribution

Inactivation of factor IIa (Thrombin) involves the formation of a heparin-ATIII-thrombin complex
Inactivation of factor Xa only involves the binding of heparin to ATIII

![Diagram showing the interaction between heparin, Xa, and Antithrombin III]

### Properties of LMWHs vs UFH

<table>
<thead>
<tr>
<th>Property</th>
<th>LMWH</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean molecular weight</td>
<td>4,000 to 6,500 daltons</td>
<td>12,000 to 15,000 daltons</td>
</tr>
<tr>
<td>Saccharide units (means)</td>
<td>13-22</td>
<td>40-50</td>
</tr>
<tr>
<td>Plasma half-life</td>
<td>2 to 4.5 hours</td>
<td>1 to 2 hours</td>
</tr>
<tr>
<td>Anti-Xa:anti-IIa activity</td>
<td>2:1 to 4:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Inactivation of Xa on platelets</td>
<td>Strong</td>
<td>Weak</td>
</tr>
<tr>
<td>Inhibited by PF4</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of platelet function</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Property</th>
<th>LMWH</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binds to endothelium</td>
<td>No (weak)</td>
<td>Yes</td>
</tr>
<tr>
<td>Increases vascular permeability</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Augments microvascular bleeding</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Mainly hepatic</td>
<td>Mainly hepatic</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal*</td>
</tr>
<tr>
<td>Administration</td>
<td>SC, (IV-PCI)</td>
<td>IV, SC</td>
</tr>
<tr>
<td>Reversal of anticoagulant</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>effect by protamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Also via endothelial binding.
*Plasma anti-Xa monitoring may be necessary in pregnancy, in renal insufficiency, and in patients with body weight <50 kg (including pediatric patients) or obese patients.


### UFH: Indications

- Prevention of venous thrombosis
- Treatment of venous thrombosis and pulmonary embolism
- Early treatment of patients with NSTE ACS and STE ACS
- Patients undergoing cardiac surgery using cardiac bypass, vascular surgery, percutaneous coronary intervention (PCI)
- Selected patients with disseminated intravascular coagulation (DIC)

Chest 2001:64S-94S.

### UFH: Dosing

#### Prophylaxis for VTE:
5,000 units SQ q12h – q8h (q8h more effective)

#### Treatment of VTE:
- Loading dose: ~80 units/kg (or ~5,000 units)
- Maintenance dose: start at 18 units/kg/hr*
  
*Adjust based on aPTT result (target is institution-specific, but is 1.5 – 2.5 X control)

*Braunwald, 2001 ACC/AHA Practice Guidelines for UA/NSTEMI. "Ryan, 1999 ACC/AHA Practice Guidelines for AMI."
UFH: Monitoring

- The activated partial thromboplastin time (aPTT) is the most widely used assay to monitor the anticoagulant response of UFH.
- The first aPTT should be measured approximately 6 hours after the bolus dose of UFH, and the continuous infusion should be adjusted based on the results.
- The goal aPPT is generally to 1.5 - 2.5 times normal (45-75 s).
- Before starting heparin, draw baseline PT, aPTT, Plt, Hgb, Hct, UA and stool for occult blood and monitor periodically.

UFH: Adverse Effects

a) Bleeding - Risk increases with:
- Concomitant ASA or thrombolytic use
- Higher doses vs lower doses of heparin
- Longer duration of heparin therapy
- Advanced age of patient

Treatment of toxicity - Protamine Sulfate
- One mg of protamine will neutralize 100 units of heparin
- Usual dose is 10-50 mg IV at a rate of 5 mg/min (usually start with 10mg)
- Recheck aPTT in 10 - 15 minutes

UFH: Adverse Effects

b) Osteopenia - Mainly associated with long term use of heparin.

c) Thrombocytopenia - 2 types
- i) Heparin-associated thrombocytopenia (HAT)
- ii) Heparin-induced thrombocytopenia (HIT)

LMWHs – method of preparation

Unfractionated Heparin

- Oxidative Depolymerization
- Deaminative Cleavage With isourea/ Nitrate

b-Eliminative Cleavage

- By Alkaline Treatment
- By Heparinase

LMWHs – method of preparation

Pharmacology of LMWH compared to UFH

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin (Lovenox®)</th>
<th>Dalteparin (Fraxiparin®)</th>
<th>Tinzaparin (Innohep®)</th>
<th>Fondaparinux (Arixtra®)</th>
<th>Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular Weight - average (daltons)</td>
<td>4500</td>
<td>6000</td>
<td>5500-7500</td>
<td>1728</td>
<td>15000</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>100%</td>
<td>87%</td>
<td>86.7%</td>
<td>100%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Plasma half-life (hours)</td>
<td>4.5 hrs</td>
<td>7 hours</td>
<td>2.8 hrs</td>
<td>3.4hrs (4500IU)</td>
<td>3.8hrs (175 IU/kg)</td>
</tr>
</tbody>
</table>

Pharmacology of LMWH compared to UFH

Benefits of LMWH Compared With UFH

Features of LMWH | Benefits of LMWH
--- | ---
> Enhanced anti-Xa:anti-IIa | > Potential reason for superior efficacy and reduced bleeding
> High bioavailability, long half-life and dose-independent clearance | > Simple dosing
> Predictable pharmacokinetics | > Administration at home, save resources and cost
> Potentially less immunogenic | > Reduced need for monitoring, reduced lab costs
> Potentially less effect on bone density | > Associated with significantly lower incidence of HIT
> Potential reason for superior efficacy and reduced bleeding

Position Statements

US FDA  LMWHs cannot be used interchangeably.

WHO  The LMWH drugs are distinct entities.

ACC  It is important to consider each LMWH individually rather than as members of a class of interchangeable compounds.

ACCP  LMWHs may not be clinically interchangeable.

DOD  Enoxaparin and dalteparin are not sufficiently interchangeable for a closed class contract.

LMWH FDA Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dalteparin</th>
<th>Enoxaparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSTE ACS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Treatment of DVT (inpatient)</td>
<td>No controls</td>
<td>No controls</td>
<td>No controls</td>
</tr>
<tr>
<td>Treatment of DVT (outpatient)</td>
<td>No controls</td>
<td>No controls</td>
<td>No controls</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>No controls</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Extended prophylaxis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Medically ill</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

LMWH Dosing

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dalteparin</th>
<th>Enoxaparin</th>
<th>Tinzaparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient DVT</td>
<td>n/a</td>
<td>1 mg/kg q12h sc or 1.5 mg/kg qd sc as a “bridge” to warfarin</td>
<td>175 anti-Xa IU/kg qd sc as a “bridge” to warfarin</td>
</tr>
<tr>
<td>Treatment with or without PE</td>
<td>n/a</td>
<td>1 mg/kg q12h sc as a “bridge” to warfarin</td>
<td>n/a</td>
</tr>
<tr>
<td>Outpatient DVT</td>
<td>n/a</td>
<td>1 mg/kg q12h sc as a “bridge” to warfarin</td>
<td>n/a</td>
</tr>
<tr>
<td>Treatment without PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylaxis of Ischemic Complications Associated with UA/NQMI</td>
<td>120 IU/kg q12h sc for 5-8 days + aspirin</td>
<td>1 mg/kg q12h sc for 2-8 days + aspirin</td>
<td>n/a</td>
</tr>
</tbody>
</table>

LMWH Monitoring

- Baseline and periodic complete blood counts, including platelet count, and stool occult tests
- Laboratory monitoring of LMWH therapy is usually not necessary
- Anti-factor Xa monitoring may be of value in:
  - Renal insufficiency
  - Markedly obese
  - Very small patient < 40kg
  - Prolonged duration therapeutic doses of LMWH
  - Pregnant patient
  - Pediatric patient


LMWH Monitoring

- Generally, the best time to draw an anti-Xa level is 4 hours after a subcutaneous weight-adjusted dose of LMWH.

- Target Anti-factor Xa depends on patient risks
  - Therapeutic: 0.5 – 1.1 IU/ml (bid)
  - Prophylaxis: 0.1 – 0.2 IU/ml

**LMWH: Dosing in Special Patient Populations**

- **Obese:**
- **Renal Insufficiency:**
  - Anti-Xa activity t1/2 is prolonged and accumulates with decreasing renal function

**Enoxaparin Dosage Regimens for Patients with Severe Renal Impairment (Creatinine Clearance <30 ml/min)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of Ischemic Complications of UA and NQWMI†</td>
<td>1 mg/kg SC QD</td>
</tr>
<tr>
<td>Inpatient treatment of DVT, with or without PE‡</td>
<td>1 mg/kg SC QD</td>
</tr>
<tr>
<td>Outpatient treatment of DVT, without PE‡</td>
<td>1 mg/kg SC QD</td>
</tr>
</tbody>
</table>

QD=Once Daily, SC=subcutaneously, UA=Unstable Angina, NQWMI=Non-Q-Wave Myocardial Infarction, DVT=Deep Vein Thrombosis, PE=Pulmonary Embolism

† When concurrently administered with aspirin
‡ When administered in conjunction with warfarin


**Enoxaparin Dosage Regimens for Patients with Severe Renal Impairment (Creatinine Clearance <30 ml/min)**

- **Abdominal Surgery**
  - 30 mg SC QD
- **Hip or Knee Replacement**
  - 30 mg SC QD
- **Medical Patients During Acute Illness**
  - 30 mg SC QD

QD=Once Daily, SC=subcutaneously


**Xa Inhibitor: Fondaparinux (Arixtra®)**

**MOA**
- Pentasaccharide molecule binds tightly to Antithrombin III (heparin binding region) effecting ONLY Factor Xa

**Indications**
- DVT prophylaxis in high-risk surgery patients (hip/knee replacement, hip fracture)
- Additional studies in DVT treatment, Cardiology, Medical Prophylaxis

**Dosing**
- 2.5 mg SQ once daily (DVT prophylaxis only)

**Precautions**
- Renal impairment (contraindicated in Clcr<30mL/min)
- Low body weight (contraindicated in < 50 kg)
- Bleeding: MORE bleeding than heparin/LMWH
- Thrombocytopenia: LESS than heparin/LMWH
- Elderly (>65 yo): risk of bleeding increases with age

**Anticoagulation “Bridging”**

- > 1 million patients are chronically anticoagulated on warfarin
- Delayed onset/wearing off therapeutic effect of oral anticoagulant (warfarin)
  - Creates gap in therapy when starting or stopping oral anticoagulation
- “Bridging” the gap with alternate anticoagulant therapy
  - Rapid onset and wearing off

**Anticoagulation “Bridging”**

- **No chronic anticoagulation**
  - Transition from acute to chronic anticoagulation
    - Stoke or TIA
    - DVT/PE
    - Atrial fibrillation
- **Receiving chronic anticoagulation**
  - High risk patients with low INR
  - Peri-procedure bridge therapy
    - Surgery
    - Invasive procedures
Management of Oral Anticoagulation
During Invasive Procedures
ACCP Guidelines- 2C recommendations

• Low risk
  − Hold warfarin ~4d prior
  − Postop UFH prophylaxis + warfarin

• Intermediate risk
  − Hold warfarin ~4d prior
  − Begin UFH/LMWH prophylaxis 2d prior
  − Postop UFH/LMWH prophylaxis & warfarin

• High risk
  − Hold warfarin ~4d prior
  − Begin UFH/LMWH full dose ~2d prior
  − Stop UFH 5h and LMWH 12-24h prior to surgery

*No VTE >3mn or patients with AF & no history of stroke.

Management of Oral Anticoagulation
During Invasive Procedures

• Low risk of bleeding (grade 2C)
  − Continue warfarin at lower dose (4-6 d preop)
  − Operate at INR 1.3 to 1.5
  − Restart after surgery supplement with low-dose heparin 5000 U

• Dental procedures not at high bleed risk (grade 2C)
  − Continue warfarin
  − High bleed risk – D/C warfarin

• Dental procedures where local bleeding must be controlled
  (grade 2B)
  − Continue warfarin
  − Administer tranexamic acid or epsilon aminocaproic acid mouthwash


Targets for new anticoagulants

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Clinical Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>Ximelagatran (PO)</td>
<td>Prophylaxis in orthopedics</td>
</tr>
<tr>
<td>VIIa/TF</td>
<td>TFPI (IV)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Va/VIIa</td>
<td>APC (IV)</td>
<td>Prophylaxis – knee replacement</td>
</tr>
<tr>
<td>Xa</td>
<td>DX 9065A (IV)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Xa/IIa</td>
<td>Heparin (PO)</td>
<td>Unstable angina</td>
</tr>
<tr>
<td></td>
<td>TAP</td>
<td>VTE prophylaxis</td>
</tr>
</tbody>
</table>

Hirsch J, Am Heart J 2001;142:S3-8

A Call to Action

In the past 60 minutes…

170 people had an MI,
and 57 people died.