Antithrombotic Therapies: Parenteral Agents

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Evidence-Based Clinical Practice Guidelines

Chest, 2012 Feb; 141(2 suppl): 1-801

## CHEST Strength of the Recommendations Grading System

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit vs Risk and Burdens</th>
<th>Strength of Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Clear B &gt; R</td>
<td>RCTs without important limitations or exceptionally strong observational studies</td>
<td>Can apply to most patients in most circumstances; further research unlikely to change confidence in rec.</td>
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<tr>
<td>1B</td>
<td>Clear B &gt; R</td>
<td>RCTs with important limitations (inconsistent results, methodological flaws)</td>
<td>Can apply to most patients in most circumstances</td>
</tr>
<tr>
<td>1C</td>
<td>Clear B &gt; R</td>
<td>Observational studies or RCTs with serious flaws</td>
<td>Can apply to most patients in many circumstances; may change when stronger evidence is available</td>
</tr>
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Grade 1 = “strong recommendation”
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<tr>
<td>2C</td>
<td>Uncertain</td>
<td>Observational studies or RCTs with serious flaws</td>
<td>Other alternatives may be equally reasonable</td>
</tr>
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Grade 2 = “weak recommendation” (we “suggest”)

Chest 2012; Feb; 141(2 suppl):62S.
Parenteral Anticoagulants

• Indirect (potentiate antithrombin, an endogenous inhibitor of various activated clotting factors)
  – Unfractionated heparin (UFH)
  – Low molecular weight heparins (LMWHs)
  – Fondaparinux

• Direct thrombin inhibitors (DTIs)
  – Lepirudin
  – Bivalirudin
  – Argatroban
UFH and LMWHs

- Anticoagulants of choice when a rapid anticoagulant effect is required
- Administered in lower doses for primary prophylaxis
- UFH usually restricted to inpatient setting; LMWH can be administered SC w/o routine lab monitoring and therefore can be used in multiple settings
- Multiple indications
Clinical Indications: UFH

- Tx of acute venous thromboembolism (VTE) and pulmonary embolism (PE)
- Tx acute MI and unstable angina
- Prevention VTE
- Prevention thrombosis during cardiopulmonary bypass and vascular surgery
- Percutaneous coronary interventions
- Coronary stent deployment
- Selected patients with disseminated intravascular coagulation
Clinical Indications: LMWHs

- Prevention VTE following surgery
- Prevention VTE in medical patients with severely restricted mobility during acute illness
- Tx of acute venous thromboembolism (VTE) and pulmonary embolism (PE)
- Tx unstable angina and non-Q wave MI (in conjunction with ASA therapy)
- Tx of acute ST-segment elevation myocardial infarction (STEMI) managed medically or with PCI
- Tx VTE in cancer patients long-term
The Coagulation Cascade

Contact activation (intrinsic) pathway
Damaged surface

XII → XIIa

XI → Xla VIIIa

IX → IXa VIIIa

Prothrombin (II)

Active Protein C

Protein S

Protein C + thrombomodulin

Tissue factor (extrinsic) pathway

Trauma

TFPI

VIIa → VII

VIIIa → VIII

Tissue factor

Antithrombin

Common pathway

Prothrombin (IIa)

Thrombin (IIa)

Fibrinogen (I)

Fibrin (Ia)

XIIIa → XIII

Cross-linked fibrin clot
Structure / Mechanism of UFH

• Heterogeneous MW (3,000-30,000), anticoag. activity, and PK properties
  – Only 1/3 of heparin molecules contain the high-affinity pentasaccharide required for anticoagulant activity
  – HMW moieties are cleared more rapidly than LMW moieties
• Interacts with the lysine site of AT III (antithrombin) → conformational change in AT III
• Heparin/AT complex inactivates thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa
Limitations of UFH

- Pharmacokinetic
  - Poor bioavailability at low doses
  - Marked variability in anticoag. response in VTE due to binding to plasma proteins
  - Relatively short t½ (~ 60 mins) at therapeutic doses

- Biophysical
  - Inability to inactivate surface-bound thrombin and factor Xa

- Biological
  - Bleeding
  - Immune-mediated platelet activation → HIT
  - Osteoporosis
Laboratory Monitoring of UFH

- aPTT measures activities of thrombin and factor Xa
- aPTT 1.5-2.5 times the control value is the historical target
- Heparin level (protamine titration) of 0.2-0.4 international units/ml
- Chromogenic antifactor Xa heparin assay of 0.3-0.7 anti-Xa units/ml (therapeutic dose) or 0.1 – 0.3 anti-Xa units/ml (prophylactic dose)
- Activated clotting time (ACT)—used with higher doses in association with percutaneous coronary interventions or cardiopulmonary bypass surgery
# VTE Weight (TBW)-Based UFH Nomogram

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial dose</td>
<td>80 units/Kg bolus, then 18 units/Kg/h</td>
</tr>
<tr>
<td>aPTT &lt; 35s (&lt; 1.2x control)</td>
<td>80 units/Kg bolus, then increase 4 units/Kg/h</td>
</tr>
<tr>
<td>aPTT 35-45s (1.2-1.5x control)</td>
<td>40 units/Kg bolus, then increase 2 units/Kg/h</td>
</tr>
<tr>
<td>aPTT 46-70s (1.5-2.3x control)*</td>
<td>No change</td>
</tr>
<tr>
<td>aPTT 71-90s (2.3-3.0x control)</td>
<td>↓ infusion rate by 2 units/Kg/h</td>
</tr>
<tr>
<td>aPTT &gt; 90s (&gt; 3x control)</td>
<td>Hold infusion 1 h, then ↓ infusion rate by 3 units/Kg/h</td>
</tr>
</tbody>
</table>

*aPTT Measured 6 hrs after bolus dose
Institutional variations, esp. TBW caps (eg > 200 Kg)
*Corresponds to anti-Xa activity of 0.3-0.7 U/ml

UFH Dosing for Acute Coronary Syndromes

Unstable MI and non-ST-segment elevation MI
60-70 units/Kg bolus (max 5000 units); 12-15 units/Kg/h (max 1000 units/h) infusion

Acute STEMI with fibrinolytic agents
60 units/kg bolus (max 4000 units); 12 units/kg/h (max 1000 units/h) infusion

Chest 2012 Feb;141(2 suppl):e27S
Bleeding Secondary to Heparin

• Risk increases with heparin dose and concomitant use of fibrinolytic agents or glycoprotein IIb/IIIa inhibitors

• Risk increased by recent surgery, trauma, invasive procedures, hemostatic defects

• Neutralized by protamine sulfate (1 mg protamine/100 units UFH)
  – Administer protamine slowly to avoid hypotension or bradycardia
Low-Molecular-Weight Heparins

- Derived from UFH by either chemical or enzymatic depolymerization resulting in fragments of 1/3 size
- Heterogeneous MW (2,000-9,000) and anticoag. activity; mean MW 4,000-5,000 (15 saccharide units)
- Reduced binding to protein or cells
- SC administration
- $T_{1/2}$ is dose independent (3-6 hours after SC dose)
# U.S. LMWH Preparations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Method of Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin* (Lovenox)</td>
<td>Benzylation followed by alkaline depolymerization</td>
</tr>
<tr>
<td>Dalteparin (Fragmin)</td>
<td>Nitrous acid depolymerization</td>
</tr>
<tr>
<td>Tinzaparin (Innohep)</td>
<td>Enzymatic depolymerization with heparinase</td>
</tr>
</tbody>
</table>

*The FDA has approved a generic version*
# Biological Consequences of Reduced LMWH Binding to Plasma Proteins & Cells

<table>
<thead>
<tr>
<th>Target</th>
<th>Biological Effects</th>
<th>Clinical Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin</td>
<td>↓Anti-IIa to anti-Xa ratio</td>
<td>Unknown</td>
</tr>
<tr>
<td>Proteins</td>
<td>More predictable anticoag. response</td>
<td>Coag. monitoring unnecessary</td>
</tr>
<tr>
<td>Macrophages</td>
<td>Cleared renally</td>
<td>Longer t½; qd admin.</td>
</tr>
<tr>
<td>Platelets + PF4</td>
<td>↓Formation of HIT antibodies</td>
<td>↓Incidence HIT</td>
</tr>
<tr>
<td>Osteoblasts</td>
<td>↓Activation osteoclasts</td>
<td>↓risk of osteopenia</td>
</tr>
</tbody>
</table>

Chest 2012 Feb;141(2 suppl):e30S
<table>
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<tr>
<th>Indication</th>
<th>Adult Dosage</th>
<th>CrCl &lt; 30ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis-abdominal surgery</td>
<td>40mg SC qd*</td>
<td>30mg SC qd</td>
</tr>
<tr>
<td>Prophylaxis-THA or TKA</td>
<td>30mg SC q12h or 40mg SC qd*</td>
<td>30mg SC qd</td>
</tr>
<tr>
<td>Prophylaxis-acute medical patients</td>
<td>40mg SC qd</td>
<td>30mg SC qd</td>
</tr>
<tr>
<td>Unstable angina/non Q wave MI (plus ASA)</td>
<td>1mg/Kg SC q12h</td>
<td>1mg/Kg SC qd</td>
</tr>
<tr>
<td>Tx DVT with or without PE (plus warfarin) x ≥ 5 days</td>
<td>1mg/Kg SC q12h or 1.5 mg/Kg SC once a day</td>
<td>1mg/Kg SC qd</td>
</tr>
<tr>
<td>Tx acute STEMI (plus ASA)</td>
<td>30 mg IV bolus, then 1 mg/Kg SC q 12 h</td>
<td>1 mg/Kg SC qd</td>
</tr>
</tbody>
</table>

*minimum 10-14 days; may be extended up to 35 days  
SC = subcutaneous
LMWH Monitoring

- Antifactor Xa (target of 0.6-1.0 U/ml 4 hrs post dose) for twice daily enoxapirin
  - Obesity (> 150 Kg ABW)
  - Renal failure (CrCl < 30 ml/min)*
  - Lack of clinical response
  - Pregnancy
  - Pediatric patients
  - Low body weight (< 45Kg)

*UFH preferred or use 50% of the LMWH rec. dose
Heparin-Induced Thrombocytopenia (HIT)

- A prothrombotic condition that is associated with increased in vivo thrombin generation and formation of venous and arterial thromboses
- Mediated by heparin-dependent antibodies (PF4/heparin-reactive Ab)
- Timing influenced by presence or absence of prior heparin exposures (esp. within past 100 days) – typically 5-10 days after starting heparin
- Frequency:
  - Bovine UFH > porcine UFH > LMWH
  - Postsurgery > medical > pregnancy
  - Long > short exposure
  - Females > males
- Defined as platelet count < 150,000/mm³
- Consider diagnosis when
  - Platelet count decreased by 50% &/or
  - Thrombotic event between day 4-14 of initiation of UFH or LMWH
- If < 100,000/mm³, consider D/C of heparin
## HIT Incidence According to Patient Population and Type of Heparin Exposure

<table>
<thead>
<tr>
<th>PATIENT EXPOSURE (Minimum 4 Days)</th>
<th>HIT Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postoperative Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin, prophylactic dose</td>
<td>1-5</td>
</tr>
<tr>
<td>Heparin, therapeutic dose</td>
<td>1-5</td>
</tr>
<tr>
<td>Heparin, flushes</td>
<td>0.1-1</td>
</tr>
<tr>
<td>LMWH, prophylactic or therapeutic dose</td>
<td>0.1-1</td>
</tr>
<tr>
<td>Cardiac surgery patients</td>
<td>1-3</td>
</tr>
<tr>
<td><strong>Medical patients</strong></td>
<td></td>
</tr>
<tr>
<td>Patients with cancer</td>
<td>1</td>
</tr>
<tr>
<td>Heparin, prophylactic or therapeutic dose</td>
<td>0.1-1</td>
</tr>
<tr>
<td>LMWH, prophylactic or therapeutic dose</td>
<td>0.6</td>
</tr>
<tr>
<td>Intensive care patients</td>
<td>0.4</td>
</tr>
<tr>
<td>Heparin, flushes</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Obstetrics patients</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

*Chest 2012 Feb;141(2 suppl): e499S*
Sequelae Associated with HIT

- Platelet count abnormalities (> 50% fall from baseline)
- Venous thrombosis > arterial thrombosis (4:1)
- Limb-threatening thrombotic event referred to as heparin-induced thrombocytopenia with thrombosis (HITT)
- Heparin-induced skin reactions at injection site
- Miscellaneous
HIT Monitoring (UFH and LMWH)

- Platelet count at baseline and q2-3 days from Day 4 to Day 14 (or until heparin is stopped, whichever occurs first), for patients whose risk of HIT is > 1%
- If exposed to heparin within past 100 days, get baseline platelet count and repeat in 24 hours
Treatment of Suspected/Confirmed HIT

- Laboratory testing
  - Ag assays that detect presence of HIT antibodies
  - Functional assays that detect evidence of platelet activation (by HIT Ab) in presence of heparin
- 4 Ts probability score for HIT (0→8, ≥4 intermediate-high probability)
  - Thrombocytopenia
  - Timing of platelet count fall or thrombosis
  - Thrombosis (or other clinical sequelae)
  - Other cause for thrombocytopenia
- D/C all forms of heparin (flushes, regional administration for dialysis, removal of heparin-coated catheters)
- LMWH is contraindicated
- Avoid prophylactic platelet transfusions

Chest 2012 Feb; 141(2 suppl):e495S-524S.
Treatment of Suspected/Confirmed HIT

- Lepirudin (FDA approved for HIT)
- Argatroban (FDA approved for HIT) – preferred in renal insufficiency
- Bivalirudin (FDA approved for HIT)
- Fondaparinux
- Postpone warfarin until platelet count has recovered eg > 150,000/mm³; start with ≤ 5 mg

Chest 2012 Feb; 141(2 suppl):e495S-524S.
## Protamine Dose to Neutralize Anticoagulant Effects of Enoxaparin*

*No proven method for neutralizing LMWH*

<table>
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<tr>
<th>Time Elapsed Since Last Enoxaparin Dose</th>
<th>Protamine Dose</th>
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</thead>
<tbody>
<tr>
<td>≤ 8 h</td>
<td>1 mg protamine per 1 mg enoxaparin</td>
</tr>
<tr>
<td>&gt; 8 h and ≤ 12 h</td>
<td>0.5 mg protamine per 1 mg enoxaparin</td>
</tr>
<tr>
<td>&gt; 12 h</td>
<td>May not be required</td>
</tr>
</tbody>
</table>

If bleeding continues, repeat 0.5 mg protamine per 1 mg enoxaparin
Fondaparinux (Arixtra®)

- A chemically synthesized pentasaccharide with the necessary sulfate side groups to bind and promote antithrombin inhibition of procoagulant factor Xa
- Unable to promote antithrombin inhibition of thrombin, thus is a specific indirect factor Xa inhibitor
- SC once daily dosing, long plasma t½ (17 hours), renal excretion
- Contraindicated if CrCl < 30 ml/min.
- Fixed once daily doses
  - 2.5 mg for thromboprophylaxis
  - 7.5 mg for VTE in 50 – 100 Kg patients
  - 5 mg for VTE if < 50 Kg
  - 10 mg for VTE if > 100 Kg
- No interaction with platelets, monocytes, or osteoblasts
- ? Tx with recombinant factor VIIa for bleeding

Chest 2012 Feb 141(2 suppl): e33S-e34S
FDA Recs: Decreasing Risks of Spinal Column Bleeding & Paralysis in Patients on LMWH

- Epidural or spinal hematomas are a known risk of LMWH in the setting of spinal procedures
- 170 cases reported to FDA with Enoxaparin
- Preprocedure checklists advised

http://www.fda.gov/Drugs/DrugSafety/ucm373595.htm
FDA Recs: Decreasing Risks of Spinal Column Bleeding & Paralysis in Patients on LMWH

- Consider dose and t ½ of the anticoagulant
- For enoxaparin, delay placement or removal of a spinal catheter for ≥ 12 hrs after prophylactic dose.
- Consider longer delays (24 hrs) for therapeutic doses of enoxaparin (1 mg/Kg bid or 1.5 mg/Kg qd)
- Post-procedure dose ≥ 4 hrs post catheter removal

http://www.fda.gov/Drugs/DrugSafety/ucm373595.htm