Aspirin, Clopidogrel, Fibrinolytics, and Heparin Use for Acute Coronary Syndrome
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Objectives
- Describe the pharmacology, kinetics, indications, and monitoring parameters of the described medications
- Explain the possible implications of the Women's Health Study on primary prophylaxis with aspirin
- Explain the differences in pharmacology and kinetics of heparin to LMWH
- List the appropriate doses for heparin in different situations
- List the critical differences in between UA-NSTEMI and STEMI in how clopidogrel, LMWH, and fibrinolytics are utilized
- In a practical sense, list advantages of one lytic versus another
- Given a patient case of acute coronary syndrome, be able to outline the appropriate management of said patient accounting for co-morbidities and the literature

Aspirin
- Permanently inactivates cyclooxygenase (COX) (both 1 and 2) by acetylation of a serine on the enzyme
  - Blocks substrate entering catalytic site
- This eventually blocks thromboxane (TX)-A\(_2\) activation of platelets
  - Remember TX-A\(_2\) is produced by adhered platelets and cause activation
- Effects of aspirin are 50-100 times more potent for COX-1 than two, so only low doses needed for this effect
  - 40-81 mg is all you need!

Aspirin Kinetics
- Peak plasma levels occur 30-40 minutes after ingestion; inhibition of platelet function in 1 hour
- Enteric coated aspirin peaks in 3-4 hours
- Small doses (ie 50-100 mg) of aspirin taken daily result in nearly complete inhibition of (TX)-A\(_2\)
- 10% of platelets are turned over in 24 hours

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Aspirin-Secondary Prevention

A daily dose of aspirin (initial dose of 162 to 325 mg orally; maintenance dose of 75 to 162 mg) should be given indefinitely after UA-NSTEMI/STEMI to all patients without a true aspirin allergy.

Aspirin for Primary Prevention

- “For patients with at least moderate risk for a coronary event (based on age and cardiac risk factor profile with a 10-year risk of cardiac event of > 10%), we recommend aspirin, 75-162 mg/day, over either no antithrombotic therapy or (warfarin).”
  - Grade 2A
- The American Diabetes Association recommends aspirin for patients > 40 yo with type 1 or 2 diabetes and cardiovascular risk factors
  - Evidence better for type 2
  - Aspirin dose is 75-162 mg/day

Aspirin Differences by Sex?

- While aspirin has been shown to be clearly better for both men and women for secondary prevention of cardiac events, there is much less data for primary prevention in women
  - Benefit mainly proven in men
- Women’s Health Study randomized 39,876 healthy women 45 yo or older to aspirin 100 mg on alternate days or placebo
  - Followed 10 years
  - Primary endpoint first major cardiovascular event
    - Nonfatal MI, nonfatal stroke, or death from cardiovascular disease

Aspirin Differences by Sex?

<table>
<thead>
<tr>
<th>Event End</th>
<th>Aspirin (N=39,876)</th>
<th>Placebo (N=39,876)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular event</td>
<td>417</td>
<td>512</td>
<td>0.82 (0.80-0.85)</td>
<td>0.23</td>
</tr>
<tr>
<td>Stroke</td>
<td>232</td>
<td>266</td>
<td>0.89 (0.85-0.94)</td>
<td>0.04</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>178</td>
<td>221</td>
<td>0.86 (0.83-0.90)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>72</td>
<td>73</td>
<td>1.01 (0.93-1.09)</td>
<td>0.21</td>
</tr>
<tr>
<td>Fatal</td>
<td>23</td>
<td>22</td>
<td>1.04 (0.56-1.96)</td>
<td>0.90</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>718</td>
<td>744</td>
<td>0.98 (0.91-1.06)</td>
<td>0.62</td>
</tr>
<tr>
<td>Myocardial revascularization</td>
<td>100</td>
<td>103</td>
<td>1.02 (0.81-1.23)</td>
<td>0.82</td>
</tr>
<tr>
<td>Fracture</td>
<td>74</td>
<td>73</td>
<td>1.01 (0.86-1.19)</td>
<td>0.70</td>
</tr>
<tr>
<td>Beneficial</td>
<td>184</td>
<td>181</td>
<td>1.03 (0.81-1.34)</td>
<td>0.92</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>326</td>
<td>328</td>
<td>0.99 (0.96-1.02)</td>
<td>0.68</td>
</tr>
<tr>
<td>Death from other causes</td>
<td>166</td>
<td>153</td>
<td>1.09 (0.94-1.26)</td>
<td>0.61</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>39</td>
<td>34</td>
<td>1.14 (0.72-1.79)</td>
<td>0.81</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>694</td>
<td>642</td>
<td>0.96 (0.91-1.01)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* If the mortality data are considered, then
• Major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular cause.

Clopidogrel and Ticlopidine

- Both inhibit adenosine diphosphate (ADP)-induced platelet aggregation
- Block ADP binding sites on platelets
- It is a permanent inhibition
  - How long would you hold it for major surgery?
- Clopidogrel is often used together with aspirin for synergistic effect
**Clopidogrel Kinetics**

- Is actually a pro-drug that is rapidly converted by the liver to a short-lived active platelet inhibitor
- It requires a loading dose to get a rapid inhibition of platelet function (i.e., 300 mg, optimal dose controversial)

**Thienopyridines**

- Clopidogrel should be started when a patient has a contraindication to aspirin OR be combined with low dose aspirin and continued:
  - ≥ 1 month after bare-metal stent
  - ≥ 3 months after sirolimus-eluting stent
  - ≥ 6 months after paclitaxel-eluting stent
  - Up to 9 (NSTEMI)-12 (STEMI-PCI) months in absence of high risk for bleeding.

**Heparin: UFH and LMWHs**

- Anticoagulants of choice when a rapid anticoagulant effect is required
- UFH has pharmacokinetic limitations not shared by LMWHs and is generally restricted to the hospital setting
- When long-term anticoagulant therapy is indicated, heparin is usually switched to oral anticoagulant therapy

**Kinetic Problems of Heparin**

- Binds to a number of plasma proteins when injected in the body
- Also binds to endothelial cells and macrophages
- Very unpredictable for response and require aPTT monitoring for therapeutic use
LMWHs – method of preparation

**Unfractionated Heparin**

- Oxidative Depolymerization
- b-Eliminative Cleavage by Heparinase
- Deaminative Cleavage with Isoamyl Nitrate
- Deaminative Cleavage with Nitrous Acid
- Deaminative Cleavage by Alkaline Treatment

**LMWHs**

- Dalteparin
- Nadroparin
- Reviparin
- Enoxaparin
- Tinzaparin

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

**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>4,000-6,500</td>
<td>12,000-15,000</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>Reversal of anticoagulant effect by protamine</td>
<td>±</td>
<td>Yes</td>
</tr>
<tr>
<td>Routine Monitoring</td>
<td>No</td>
<td>Yes</td>
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**UFH Monitoring**

**Monitoring**

- The activated partial thromboplastin time (aPTT) is the most widely used assay to monitor the anticoagulant response of UFH.
- aPTT reflects the time required for a fibrin clot to form after partial thromboplastin, calcium, and an activating agent are added to the patient’s plasma.
- The goal of aPTT is generally 1.5 - 2.5 times normal (fancier way of doing this)
- aPTT measures the activity of the intrinsic coagulation system and the common pathway (factors II, V, VIII, IX, XI, XII)
**Benefits of LMWH Compared With UFH**

<table>
<thead>
<tr>
<th>Features of LMWH</th>
<th>Benefits of LMWH</th>
</tr>
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<tbody>
<tr>
<td>Enhanced anti-Xa:anti-IIa</td>
<td>Potential reason for superior efficacy and reduced bleeding 2</td>
</tr>
<tr>
<td>High bioavailability, long half-life and dose-independent clearance</td>
<td>Simple dosing 1</td>
</tr>
<tr>
<td>Predictable pharmacokinetics 1,2</td>
<td>Administration at home, save resources and ↓ cost</td>
</tr>
<tr>
<td>Potentially less immunogenic 1,2</td>
<td>Reduced need for monitoring, reduced lab costs 2</td>
</tr>
<tr>
<td>Potentially less effect on bone density</td>
<td>Associated with significantly lower incidence of HIT 3</td>
</tr>
<tr>
<td>Potential reason for superior efficacy and reduced bleeding 2</td>
<td>Reduced incidence of bone fractures 4</td>
</tr>
</tbody>
</table>


**LMWH**

**Monitoring**

- 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

**UFH/LMWH and STEMI**

Unfractionated heparin (UFH) should be given intravenously in:

- Patients undergoing PCI or surgical revascularization
- After alteplase, reteplase, tenecteplase
- After streptokinase, anistreplase, urokinase in patients at high risk for systemic emboli

Low molecular-weight heparin (LMWH) might be considered an acceptable alternative to UFH in patients less than 75 years who are receiving fibrinolytic therapy in the absence of significant renal dysfunction.

Enoxaparin used with tenecteplase is the most comprehensively studied.

**More STEMI heparin tidbits…**

- Dose of heparin with lytics is:
  - Bolus: 60 units/kg (maximum 4000 units)
  - Infusion: 12 units/kg/hr (maximum 1000 units/hr)
  - YOU MUST MEMORIZE THIS!
  - Adjusted to low intensity anticoagulation levels
  - Continued roughly 24 hours post lytic
- Heparin is discontinued after PCI when primary PCI done

**UFH/LMWH and UA/NSTEMI**

- “Anticoagulation with subcutaneous LMWH or intravenous unfractionated heparin (UFH) should be added to antplatelet therapy with ASA and/or clopidogrel (Level of Evidence: A)” (Class I recommendation)
  - Heparin typically dosed:
    - Bolus 60–70 Units/kg (maximum 5000 Units)
    - Infusion 12–15 Units/kg (maximum 1000 U/h) then titrated to a therapeutic aPTT of anti-Xa activity level
- “Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, unless CABG is planned within 24 h. (Level of Evidence: A)” (Class IIa recommendation)
In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours.

In the absence of contraindications, fibrinolytic therapy should be administered to STEMI patients with symptom onset within the prior 12 hours and new or presumably new left bundle branch block (LBBB).

Fibrinolytic therapy should not be administered to asymptomatic patients whose initial symptoms of STEMI began more than 24 hours earlier.

Fibrinolytic therapy should not be administered to patients whose 12-lead ECG shows only ST-segment depression, except if a true posterior MI is suspected.

Aspirin, clopidogrel, UFH, LMWH, and fibrinolytics all have a very important roles in the treatment of acute coronary syndromes – it is important to know the differences based on conditions and patient comorbidity!

Heparin must be dosed very carefully with fibrinolytics

Clopidogrel, LMWH, and fibrinolytics are used differently in STEMI and NSTEMI

Practical reasons usually lead to the selection of a formulary lytic for STEMI treatment, but the newer fibrin selective agents are usually chosen.
Review Questions

• What is the mechanism of aspirin? clopidogrel? Why are they synergistic? When are they used together? Separate?
• Why are LMWH more specific for Xa inhibition? Why do LMWHs have a more predictable response than heparin?
• How do you dose heparin with a lytic?
• Is clopidogrel routinely used in STEMI? If not, when?
• How long is clopidogrel usually used in UA-NSTEMI?
• Which lytic is given as a single bolus dose? Why might this be advantageous in practice?