Acute Coronary Syndromes (ACS)

Liane Horiuchi, Pharm.D.
PGY-1 Pharmacy Resident
Memorial Hospital Miramar
March 13, 2016

www.fshp.org

Objectives

- Pharmacist:
  - Distinguish between unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI)
  - Review treatment modalities in ACS
  - Describe different reperfusion therapies and their roles
- Technician:
  - Define ACS and its associated risk factors
  - Review what drugs are used to treat ACS
  - Explain the significance of timely treatment of ACS

Disclosures

- Nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject of this presentation

Acute Coronary Syndrome (ACS)

- Definition: Clinical syndromes compatible with acute myocardial ischemia and/or infarction due to an abrupt reduction in coronary blood flow.
Risk Factors

Non-Modifiable
- Age
- Gender
- Ethnicity
- Family history

Modifiable
- Hypertension
- Hyperlipidemia
- Diabetes mellitus
- Smoking
- Overweight/Obesity
- Physical inactivity

Coronary Artery Disease
- Average age at first MI is 65 years for men and 71.8 years for women.
- Each year, 635,000 Americans suffer a new coronary event, and ~300,000 will suffer a recurrent attack.
- Approximately every 43 seconds, an American will have an MI.
- Causes 1 out of every 7 deaths in the U.S.

Diagnosis

Combination of Diagnostic Criteria

4 Differential Diagnosis

Non-Cardiac

Chronic Stable Angina

Possible ACS

Definite ACS

NSTE (NSTEMI/UA)

STEMI

NSTE: Non-ST-Segment Elevation

ACS Pathophysiology and Characteristics
Goals of Therapy

- UA/NSTEMI goals
  - Prevent total occlusion
    - Antiplatelets (ASA, P2Y12, +/- GPs) + antithrombotic
  - Control chest pain and associated symptoms
- STEMI goals
  - Restore patency
    - Door-to-needle < 30 min (Fibrinolytics)
    - Door-to-balloon < 90 min (PCI)
    - If >120 min to PCI, fibrinolysis unless CI
  - Prevent complications
  - Control chest pain and associated symptoms

Immediate Management

- 12 Lead ECG (done by EMS & ED)
- History & Physical Examination
  1. Nature of the anginal symptoms
  2. Prior history of CAD
  3. Sex (Male)
  4. Older age (Most important in CHD)
  5. Increasing number of traditional risk factors
- Cardiac Biomarkers (Troponin)
- TIMI and GRACE risk scores

Initial Management of NSTE-ACS (UA/NSTEMI)

Echocardiogram (ECG)

- EMS & w/in 10 min at ED, then q15-30min if not initially diagnostic
- ST-changes developing at rest strongly suggest acute ischemia:
  - ST ↑↑ ↑↑ = STEMI
  - ST ↓↓ ↓↓ = NSTEMI
  - ↔↔↔↔ = UA (?)
- Inverted T waves may also indicate UA/NSTEMI
- Q waves suggesting prior MI indicate a high likelihood of CAD
- ST elevation in posterior leads V7-V9 qualifies the patient for reperfusion therapy as a STEMI
- Normal ECG ≠ no NSTEMI or UA
Timing of Release of Biomarkers After Acute Myocardial Infarction

- Serial cardiac troponins at presentation and 3-6 hours after symptom onset

Risk Assessment Tools

- **TIMI**: Thrombolysis in Myocardial Infarction
  - Percent risk of all-cause mortality at 14 days in NSTE-ACS and at 30 days in STEMI-ACS
  - Risk score determined by sum of presence of 7 variables at admission (1 point each)

- **GRACE**: Global Registry of Acute Coronary Events
  - Predicts in-hospital and 6 month mortality across ACS patients

**TIMI Risk Assessment for NSTE-ACS**

- Percent risk of all-cause mortality at 14 days in NSTE-ACS and at 30 days in STEMI-ACS
- Risk score determined by sum of presence of 7 variables at admission (1 point each)

**GRACE Risk Assessment**

- Predicts in-hospital and 6 month mortality across ACS patients
TIMI Risk Assessment for STEMI

Deciding between Early Invasive vs. Conservative Strategies

Definitive/Likely ACS
- Initiate ASA, BB, Nitrates, Anticoagulants, Telemetry

Early Invasive Strategy
- TIMI Risk Score >3
- GRACE>140
- New ST segment depression
- Positive biomarkers
- High risk features

Ischemia Driven Strategy
- TIMI Risk Score 0-1 (Esp. Women)
- GRACE<109
- No ST segment deviation
- Negative Biomarkers

Coronary angiography
- Recurrent Signs/Symptoms
- Heart failure
- Arrhythmias

Remaining Stable
- Assess EF and/or Stress Testing
- EF<40% OR Positive stress
- Go to Angiography

AHA/ACC Guideline Classification of Recommendations and Level of Evidence

Management of ACS

Anti-ischemic Therapy
- Oxygen
- Nitroglycerin
- β-blocker
- Morphine

Antiplatelet Therapy
- Aspirin
- P2Y12 inhibitor
- GP IIb/IIIa inhibitor

Anticoagulant Therapy
- UFH
- Enoxaparin
- Fondaparinux
- Bivalirudin

Disease modifying therapy
- Statin
- ACE inhibitor

Adapted from Morrow DA. Circulation 2000.
Initial Management of ACS: MONA + β-blocker

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1-5mg IV q5min if sx not relieved by NTG or recur</td>
<td></td>
</tr>
<tr>
<td>Oxygen</td>
<td>If SaO₂&lt;90% or high-risk features or hypoxia</td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin (NTG)</td>
<td>0.4mg spray or SL q5min x 3 doses</td>
<td>Call 911 if unresponsive to 1st dose</td>
</tr>
<tr>
<td></td>
<td>5-10mg/min IV, intrate to CP relief or 200mg/min</td>
<td></td>
</tr>
<tr>
<td>Aspirin (ASA)</td>
<td>Chew and swallow non-enteric coated 162-325mg x 1</td>
<td>Reduces mortality</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>PO/IV initiated within 24 hours if eligible</td>
<td>Reduces mortality; 若有心绞痛及心源性休克，可使用。</td>
</tr>
</tbody>
</table>

Oxygen: If SaO₂<90% or high-risk features or hypoxia

Nitroglycerin (NTG): 0.4mg spray or SL q5min x 3 doses. If unresponsive to 1st dose, call 911.

Aspirin (ASA): Chew and swallow non-enteric coated 162-325mg x 1 to reduce mortality.

Management of NSTE-ACS: Dual Antiplatelet Therapy (DAPT)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose (PO)</th>
<th>Maintenance Dose (PO)</th>
<th>LOE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>162-325mg non-enteric coated</td>
<td>81-162mg daily</td>
<td>I A</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>300mg ischemia-guided</td>
<td>75mg daily</td>
<td>I B</td>
<td>Best if patient cannot drink full class of water</td>
</tr>
<tr>
<td>Ticagrelor* (Brilinta)</td>
<td>100mg</td>
<td>90mg BID</td>
<td>I B</td>
<td>CI, ICH, severe hepatic disease</td>
</tr>
<tr>
<td>Prasugrel (Effient)</td>
<td>60mg</td>
<td>10mg daily</td>
<td>IIa</td>
<td>Option for PCI/w/stenting; avoid in Hx of TI or stroke, &gt;75y, or &lt;60kg</td>
</tr>
</tbody>
</table>

*Reasonable to use in preference to clopidogrel in NSTE-ACS. (IIa, B)
*Recommended maintenance dose of aspirin is 81 mg daily.

PGY₁₂ Antagonists

- **Agents**
  - Collagen
  - Thromboxane A₂
  - ADP
  - Thrombosis
  - Antiplatelet

- **Targets for antithrombotics**
  - Platelet aggregation
  - Thrombin activation
  - Factor Xa inhibition

- **Drug/Disease Interactions**
  - PPIs inhibit CYP2C19
  - Limit ASA <100mg

- **Clinical Trials**
  - CREDO, CURE, PCI-CURE, CLARITY, COMMIT
  - TRITON-TIMI 38
  - PLATO*

Adapted from Finks SW. Acute Coronary Syndromes. ACCP Updates in Therapeutics 2015.
Management of NSTE-ACS: Anticoagulant

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th>Comments</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>60 IU/kg IVB over ≥ 3 min (Max 4000 IU)</td>
<td>12 IU/kg/hr (max 1000 IU/hr) x 4th or until PCI performed</td>
<td>aPTT goal: 50-75s I B</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td><strong>Enoxaparin (Lovenox)</strong></td>
<td>30mg IVB</td>
<td>1mg/kg SQ Q12h x 24-48h CrCl&lt;30: Q24h</td>
<td>Highest bleeding risk of 4 agents I A</td>
<td>1</td>
<td>A</td>
</tr>
<tr>
<td><strong>Fondaparinux (Arixtra)</strong></td>
<td>-</td>
<td>2.5mg SQ daily CrCl&lt;30: Avoid</td>
<td>Best for those with high risk of bleed I B</td>
<td>1</td>
<td>B</td>
</tr>
<tr>
<td><strong>Bivalirudin (Angiomax)</strong></td>
<td>0.1mg/kg IB 0.25mg/kg/hr IV if planned invasive surgery</td>
<td>Only in early invasive strategy or be of HIT</td>
<td></td>
<td>1</td>
<td>B</td>
</tr>
</tbody>
</table>

AHA/ACC Guideline for the management NSTEMI ACS. Circulation 2014.

Management of NSTE-ACS: GP IIb/IIIa inhibitor

- Intermediate/High risk: GP IIb/IIIa inhibitor may be considered as part of initial tx in early invasive strategy.

<table>
<thead>
<tr>
<th>GP IIb/IIIa inhibitor</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th>Comments</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epifibatide (Integrilin)</strong></td>
<td>180mcg/kg IVB over 1-2 min (Max 22.6 mg)</td>
<td>2mcg/kg/min IV infusion x 12-72h (Max 15 mg/hr) CrCl&lt;50: 1 mcg/kg/min (Max 7.5 mg/hr)</td>
<td>Continue until discharge, CABG initiation, or 72h Ccr&lt;10ml/min • CE dialysis pts I B B</td>
<td>1b</td>
<td>B</td>
</tr>
<tr>
<td><strong>Tirofiban (Aggrastat)</strong></td>
<td>25mcg/kg IVB</td>
<td>0.15mcg/kg/min for up to 18h CrCl&lt;60: 0.075 mcg/kg/min</td>
<td></td>
<td>1b</td>
<td>B</td>
</tr>
</tbody>
</table>

AHA/ACC Guideline for the management NSTEMI ACS. Circulation 2014.

Other Early Hospital Therapies

- **Nitrates:** Topical or Oral
- **ACE-Inhibitors:**
  - CHF, EF≤40%, HTN, DM, stable CKD (ARB if intolerant)
- **Aldosterone antagonist:**
  - On ACE-I and β-blocker with EF≤40%, Sx HF or DM and if CrCl<30 ml/min and K≤5.0 mEq/L
- **Calcium Channel Blocker:**
  - For ischemic symptoms when β-blocker not successful, CI or intolerant
- **Statins:** High-intensity
- **Nonsteroidal anti-inflammatory drugs (NSAIDs):**
  - (Except aspirin) Should not be initiated and should be discontinued during hospitalization

Immediate Invasive Strategy

- <90 minutes from presentation
- Refractory angina
- Sx of HF or new/worsening mitral regurgitation
- Hemodynamic/electrical instability
- Recurrent angina or ischemia despite intensive medication treatment
- Severe VT or VF
- Severe comorbidities
Initial Management of STEMI

STEMI Treatment: Reperfusion Therapy

Percutaneous Coronary Intervention (PCI)
- Balloon angioplasty alone
- Balloon angioplasty with stents
  - Bare metal stents (BMS)
  - Drug-eluting stent (DES)
    - Anti-proliferative agents: Sacrolimus, Paclitaxel, Everolimus, Zotarolimus

Pharmacologic: Fibrinolytic

Management of STEMI: Reperfusion Therapy


DIDO = door-in-door-out

*Patients with cardiogenic shock or severe HF initially seen at non-PCI-capable hospital should be transferred for cardiac catheterization and revascularization as soon as possible, irrespective of time delay from MI onset (I, B)
STEMI Management

- Reperfusion therapy for all eligible patients with STEMI with symptom onset ≤ 12 hrs
  - Reperfusion therapy options: Percutaneous Coronary Intervention (PCI) or fibrinolytic therapy
  - First line: Primary PCI
    - PCI-capable hospital (90 min) vs. non-PCI capable hospital (120 min)
  - Second line: Fibrinolytic therapy
    - If time is > 120 min to get to PCI hospital

STEMI Management

- Reperfusion therapy reasonable for patients with STEMI with symptom onset in prior 12-24 hours if:
  - Clinical and/or ECG evidence of ongoing ischemia
  - First line: Primary PCI

- PCI also first line if:
  - STEMI + cardiogenic shock, acute severe HF, or CI to fibrinolytics

Management of STEMI: DAPT with Primary PCI

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Loading Dose</th>
<th>Follow-Up Dose</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>162 – 325mg</td>
<td>81 - 325mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>prior to procedure</td>
<td>Indefinitely (LA)</td>
<td>B (LD)</td>
<td></td>
</tr>
</tbody>
</table>

P2Y12 inhibitors

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Loading Dose</th>
<th>Follow-Up Dose</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>600mg</td>
<td>75mg daily</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>60mg</td>
<td>10mg daily</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>180mg</td>
<td>90mg BID*</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Management of STEMI undergoing PCI: GP IIb/IIIa inhibitor

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>60U/kg IVB (Max 4000 U)</td>
<td>12 U/kg/h (Max 1000U/h)</td>
<td>1</td>
<td>C</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>≤75y: 30mg IVB, &gt;75y: omit bolus</td>
<td>≤75y: 1mg/kg SQ q12h, &gt;75y: 0.75mg/kg SQ q12h, CI&gt;30: 1mg/kg SQ q24h, index hospitalization, up to 8d or until revascularization</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5mg IVB</td>
<td>2.5mg SQ daily for index hosp up to 8d or until revascularization, CI&lt;50: Cl</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

Reperfusion choice: Fibrinolytic

<table>
<thead>
<tr>
<th>Fibrinolytic Agent</th>
<th>Dose</th>
<th>Patency rate</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteplase (t-PA, Activase)</td>
<td>15mg IVP, then 0.75 mg/kg over 30 min (max 50mg), then 0.5mg/kg (max 35 mg) over next 60 min (total dose ≤ 100 mg)</td>
<td>73-84%</td>
<td>Stroke, ICH</td>
</tr>
<tr>
<td>Reteplase (r-PA, Retavase)</td>
<td>10 units IV; repeat dose in 30 min</td>
<td>84%</td>
<td>Reperfusion arrhythmias, anemia</td>
</tr>
<tr>
<td>Tenecteplase (TNK-tPA, TNKase)</td>
<td>Single IV dose: Weight ≤ 60 kg: 30mg, Weight 60-69 kg: 35mg, Weight 70-79 kg: 40mg, Weight 80-89 kg: 45mg, Weight ≥90 kg: 50mg</td>
<td>85%</td>
<td>Minor bleeding, reperfusion arrhythmias</td>
</tr>
</tbody>
</table>

Reperfusion choice: Fibrinolytics

<table>
<thead>
<tr>
<th>Relative contraindications</th>
<th>Table 6: Contraindications and Coordinators for Fibrinolytic Therapy in STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>History of stroke, heart attack, severe heart failure, unstable angina, or claudication</td>
</tr>
<tr>
<td>Asthma</td>
<td>Significant coronary artery disease</td>
</tr>
</tbody>
</table>
STEMI: Reperfusion therapy routes

1. PCI
   (Recommended)

2. Fibrinolytic therapy

3. Fibrinolytic, then PCI

Adapted from Calil M, Perrin D. Acute Coronary Syndromes.

STEMI: Reperfusion therapy routes

1. PCI
   (Recommended)

2. Fibrinolytic therapy

3. Fibrinolytic, then PCI

Adapted from Calil M, Perrin D. Acute Coronary Syndromes.
2. Reperfusion choice: Fibrinolytic
Timeline of Antithrombotic therapy

Before Fibrinolytic:
- ASA 162-325 mg LD
- Clopidogrel as only P2Y₁₂ inhibitor
  - Age ≤ 75 y: 300 mg LD
  - Age > 75 y: No LD, give 75 mg

With Fibrinolytic:
1. UFH: 60 U/kg IV bolus, then 12 U/kg/h infusion adjusted for aPTT 1.5-2x control (~50-70s for 48h or until revascularization)
2. Enoxaparin:
  - Age < 75 y: 30 mg IV bolus, then 1 mg/kg SQ q12h
  - Age > 75 y: no bolus; 0.75 mg/kg SQ q12h
3. Fondaparinux:
  2.5 mg IV, then 2.5 mg SQ daily in 24h

Duration for both: Up to 8 days, or until revascularization

After Fibrinolytic: See dosing table

---

PCI after fibrinolytic therapy

| Immediate transfer for cardiogenic shock or severe acute HF irrespective of delay from MI onset | I | B |
| Urgent transfer for failed reperfusion or reocclusion | IIa | B |
| As part of invasive strategy in stable* patients with PCI between 3-24h after successful fibrinolysis | IIa | B |

*absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or supraventricular tachyarrhythmias, and spontaneous recurrent ischemia

---

STEMI: Reperfusion therapy routes

1. PCI
2. Fibrinolytic therapy
3. Fibrinolytic, then PCI

---

3. Reperfusion Choice: PCI after fibrinolytic therapy
Timeline of Antithrombotic therapy

Before PCI:
- If PCI ≤ 24h after fibrinolytic:
  - Clopidogrel 300 mg LD
- If PCI > 24h after fibrinolytic:
  - Clopidogrel 600 mg LD or Prasugrel 60 mg

With PCI:
- Enoxaparin
  - If last dose ≤ 9h, no additional drug
  - If last dose > 9h, give 0.3 mg/kg IV bolus

After PCI:
- Aspirin indefinitely and P2Y₁₂ inhibitor x 1 year (DES) or for 30 days – 1 year (BMS)

---
Coronary Artery Bypass Graft (CABG)

- Limited role
- Indications:
  - STEMI w/coronary anatomy not amenable to PCI + ongoing ischemia, cardiogenic shock, severe HF
  - STEMI at time of operative repair of mechanical defects

Anti-thrombotic therapy:
- Give aspirin before CABG surgery
- Discontinue clopidogrel or ticagrelor ≥ 24h before “on-pump” CABG
- Discontinue short acting IV GP Ib/IIa antagonists ≥ 2-4h before urgent CABG
- Discontinue abciximab ≥ 12h before urgent CABG

Late Hospital/Post-hospital Care

- Anti-ischemia Management
  - Nitroglycerin
  - Statins: High intensity if no CI
  - Beta Blockers
  - ACE inhibitors
  - Aldosterone antagonists
- Oral Antiplalet Therapy
  - Aspirin
  - P2Y12 inhibitor + ASA ≥ 12 months
    - Clopidogrel
    - Ticagrelor
    - Prasugrel (option for BMS or DES)

References