Update in the Management of Acute Coronary Syndromes

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Objectives

At the conclusion of this activity, participants will be able to:

- Recognize the pathophysiology and presentation of acute coronary syndrome (ACS)
- Differentiate current subtypes of ACS
- Discuss appropriate initial treatment algorithm for different subtypes of ACS

Chest pain

-Differential Diagnosis-

- Angina/infarction
- Aortic stenosis
- HOCM
- Severe HTN
- Severe anemia
- Aortic insufficiency
- Aortic dissection
- Pericarditis
- Mitral Valve Prolapse
- Esophageal spasm
- Psychogenic
- Thoracic outlet syndrome
- Costochondritis
- Herpes Zoster
- Pulmonary embolus
- Pneumonia
- Pleurisy
What is Acute Coronary Syndrome?

- Any array of clinical symptoms resulting from underlying acute myocardial ischemia

- Almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related coronary artery.

Progression of Coronary Disease

<table>
<thead>
<tr>
<th>Chronic Ischemic Heart Disease</th>
<th>ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic CAD</td>
<td>Unstable Angina</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>NSTEMI</td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
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</tbody>
</table>

NSTEMI

STEMI

WARNING: Nothing you can eat can cure heart disease.
Atherosclerosis

Plaque rupture

Dysfunctional endothelium

Platelet activation

Coagulation Cascade activation

Decreased Vasodilator effect

Antithrombotic effect

Coronary Thrombosis

Endothelial cells activated

Extracellular lipids form in intima

Macrophages become lipid laden foam cells

Lesion grows

Fibrous cap weakens and ruptures

Coagulation & platelet aggregation

Coronary Thrombosis

Partial occlusion = decreased blood flow in the artery distal to the partial occlusion = decreased O2 to myocardium /ischemia

Complete Occlusion = cessation of blood flow & O2 to the entire portion of myocardium supplied by that artery = ischemia
Partial Occlusion Angiogram

Right coronary artery Following revascularization

Total Occlusion Angiogram

Right coronary artery Following revascularization

Myocardial Ischemia

Transmural—ischemia spans the entire thickness of the myocardium
Most often due to occlusion
Subendocardial—ischemia involves the innermost layers of myocardium
Most often due to partial occlusion
If ischemia is prolonged, it may result in myocyte death and tissue necrosis – i.e. myocardial infarction
Diagnosis of ACS

- Clinical history and symptoms
- ECG evaluation
- Serum biomarkers

Myocardial Ischemia: Clinical Symptoms

<table>
<thead>
<tr>
<th>Angina -- chest pain / pressure / tightness or its equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable -- present when there is increased demand for myocardial oxygen in a reproducible fashion</td>
</tr>
<tr>
<td>Unstable -- increase in duration, intensity or frequency</td>
</tr>
<tr>
<td>-- less provocative</td>
</tr>
<tr>
<td>-- new onset</td>
</tr>
</tbody>
</table>

Symptoms

<table>
<thead>
<tr>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
</tr>
<tr>
<td>Burning (hot)</td>
</tr>
<tr>
<td>Chest/arms/jaw/back</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sympathetic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweats</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Cool, clammy skin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parasympathetic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Weak</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inflammatory response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild fever</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>
ECG Changes of Ischemia

**SUBENDOCARDIAL ISCHEMIA:**
ST vector is directed toward inner layer of affected ventricle (away from overlying leads) → ST DEPRESSION

**TRANSMURAL ISCHEMIA:**
ST vector is directed outward (toward overlying leads) → ST ELEVATION

ST Elevation MI—ECG Progression

NSTEMI ECG…or UA with Symptoms
ECG

• First point of entry into ACS algorithm
• Neither 100% sensitive or 100% specific for AMI
• Single ECG for AMI – sensitivity of 60%, specificity 90%
• Represents single point in time – needs to be read in context
• Normal ECG does not exclude ACS – 1-6% proven to have AMI, 4% unstable angina

ECG Guidelines

• Initial 12 lead ECG – goal door to ECG time 10min, read by experienced doctor (Class 1 B)
• If ECG not diagnostic/high suspicion of ACS – serial ECGs initially 15 -30 min intervals (Class 1 B)
• ECG adjuncts – leads V7 –V9, RV 4 (Class 2a B)
• Continuous 12 lead ECG monitoring reasonable alternative to serial ECGs (Class 2a B)

Serum Markers of Myocardial Infarction

• Myocardial necrosis causes sarcolemma disruption
• Intracellular macromolecules are released
• Can be measured by serial blood testing
BIOCHEMICAL MARKERS

IDEAL MARKER:
High concentration in myocardium
Myocardium specific
Released early in injury
Proportionate to injury
Non expensive testing

Troponins
CKMB
Myoglobin
Other markers

Serum Markers of Myocardial Infarction

Troponin I and Troponin T

--Both equivalent in diagnostic and prognostic ability (except in renal failure, Troponin T less sensitive)
--Very sensitive and specific for myocardium
--Begin to rise 3-4 hours after onset of pain
--Peak at 18-36 hours
--Decline slowly over 10-14 days

Troponin Level: Prognostic Indicator

% mortality at 42 days as function of trop level
Serum Markers of Myocardial Infarction

Creatine Kinase – MB isoenzyme
--Not as specific for myocardium as troponin
--Begins to rise 3-8 hours after onset of pain
--Peaks at 24 hours
--Returns to normal in 48-72 hours
--Used in conjunction with troponin
--Useful in diagnosing reinfarction

Myoglobin
--Not cardiac specific
--Rapid release within 2 hours
--Rule out rather than rule in NSTEMI

Serum Markers: “Other”

BNP
• Released from heart muscle in response to increased ventricular wall stress.
• Studies – BNP not a specific marker but a strong predictor of ACS especially in patients with chest pain, no ECG changes, non diagnostic troponins.
• Also positive in heart failure, PE, atrial arrhythmias, renal failure

Cardiac Biomarkers: Guidelines

I
• Cardiac biomarkers measured in all patients with suspicion of ACS
• If troponin negative within 6 hours of onset, repeat 8-12 hours later

II
• Remeasuring of positive biomarkers to determine infarct size/necrosis
• Patients presenting within 6 hours of symptom onset – myoglobin in conjunction with troponin measured
• 2hr delta CKMB/delta troponin considered in <6hr presentation
• BNP level – for global risk assessment

III
• Class 3 – AST/LDH/CK without CKMB
What is ACS?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical symptoms</td>
<td>escalating, rest, new onset angina</td>
<td>Prolonged chest pain, more severe than usual angina</td>
</tr>
<tr>
<td>Pathophysiology / vessel occlusion</td>
<td>Partial</td>
<td>Partial</td>
</tr>
<tr>
<td>Serum biomarkers</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ECG initial findings</td>
<td>ST dep/ elev*</td>
<td>ST dep</td>
</tr>
</tbody>
</table>

*ST elevation when pain-free, could look normal

ACS Goals of Treatment

- Relief of ischemic pain + Anti-platelet and anticoagulant therapy to prevent further thrombosis
- Initiate reperfusion therapy with percutaneous angioplasty/intervention or thrombolysis* if appropriate
- Continuously assess hemodynamic state
- Secondary prevention

*STEMI only
Anti-Ischemic Therapy Class I recommendations

- Bedrest with telemetry
- Supplemental oxygen (keep sats>90%)
- Nitrates for persistent ischemia (SL x 3; consider transition to IV for HTN, HF) — caution with suspected RV infarction or hypotension
- Statin: high intensity
- Oral beta blocker in first 24 hours if no contraindication (signs of HF, low output state, risk of cardiogenic shock, heart block).
- Non-dihydropiridine CCB if contraindications to beta blocker
- ACE-I in first 24 hours if pulmonary congestion, EF < 40%
- ARB in those intolerant of ACE-I

Class III Recommendations Anti-ischemic Therapy

- Nitrates with BP<90, HR <50 or >100 in absence of symptomatic HF or in RV infarct
- Nitrates within 24 h of sildenafil or 48 h of tadalafil
- IV ACE-I (risk of hypotension)
- ß blocker use in the contraindications mentioned
- NSAIDS/ COX-2 (increased mortality, reinfarct, hypertension, HF, myocardial rupture)

ACS Goals of Treatment

- Relief of ischemic pain + Anti-platelet and anticoagulant therapy to prevent further thrombosis
- Initiate reperfusion therapy with percutaneous angioplasty or thrombolysis if appropriate
- Continuously assess hemodynamic state
- Secondary prevention
Antiplatelet Therapy

Moses Receiving the Tablets from God
Aspirin

- Reduces mortality & reinfarction
- Give immediately on presentation (325 mg) and daily (81mg) thereafter
- If aspirin allergy, use clopidogrel

Anti-platelet Therapy: Class I Recommendations

- ASA 162-325 mg
- Choice of second antiplatelet therapy to be added to ASA:
  
<table>
<thead>
<tr>
<th>Drug</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading Dose</td>
<td>600, 300 mg</td>
<td>60 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Peak effect</td>
<td>6 hours</td>
<td>2 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Maintenance Dose</td>
<td>75 mg</td>
<td>10 (5) mg</td>
<td>90 mg BID</td>
</tr>
</tbody>
</table>

**Only if proceeding to cath lab**

Oral Antiplatelet Agents: P2Y12 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>No (active)</td>
</tr>
<tr>
<td>Reversibility</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (CYP2C19)</td>
<td>Hepatic (CYP3A4 &amp; CYP2C19)</td>
<td>Hepatic (CYP3A4)</td>
</tr>
<tr>
<td>Loading Dose</td>
<td>600, 300 mg</td>
<td>60 mg</td>
<td>100 mg</td>
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<td>75 mg</td>
<td>10 (5) mg</td>
<td>90 mg BID</td>
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**Degree of platelet inhibition: Prasugrel > Ticagrelor > Clopidogrel**

**Risk of bleeding: Prasugrel > Ticagrelor > Clopidogrel**
### Caveats: Prasugrel, Ticagrelor, Clopidogrel

- **Prasugrel:**
  - is contraindicated in those with previous TIA or stroke
  - degree of benefit is questionable in those over age 75 or under 60kg
  - is not recommended prior to definition of coronary anatomy or med mg.

- **Ticagrelor:**
  - is contraindicated in those with previous intracranial hemorrhage
  - benefit or harm is uncertain in those with previous TIA or stroke
  - requires BID dosing
  - ASA 81 mg should be used in conjunction with Ticagrelor
  - may be associated with increased dyspnea, creat/UA levels or ventricular pauses

- **Clopidogrel:**
  - genetic variations / loss of CYP2C19 alleles may lead to decreased efficacy
  - offers slower onset of action and apparent decreased clinical efficacy
  - offers a generic
  - less bleeding compared to prasugrel or ticagrelor

### Anti-platelet Therapy Class III Recommendations

- Abciximab if PCI is not planned
- Upstream IIb/IIIa in low risk patients or high risk bleeding if already receiving ASA and P2Y12 inhibitor
- Prasugrel in patients with prior history of TIA and/or stroke
- Ticagrelor in patients with history of ICH

### Anticoagulants: Class I Recommendations

- UFH and enoxaparin (Level of Evidence A)
- Bivalirudin and Fondaparinux (Level of Evidence B)
## Treatment of ACS

<table>
<thead>
<tr>
<th>Antiplatelet agent</th>
<th>Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASPIRIN</strong></td>
<td>Choice of one:</td>
</tr>
<tr>
<td>+</td>
<td>Unfractionated heparin,</td>
</tr>
<tr>
<td></td>
<td>enoxaparin</td>
</tr>
</tbody>
</table>

*Choice of P2Y12 inhibitor: Clopidogrel, (Prasugrel) or Ticagrelor*. 
If proceeding to catheterization or high risk, consider addition of Glycoprotein IIa/IIIb inhibitor: Eptifibatide, (Abciximab).

## Treatment of ACS--STEMI

- **STEMI**: 
  - **Open the Artery!**
  - *Can the artery be opened within 120 min of FMC?*
  - *If yes → Primary PCI, otherwise give fibrinolytic and transfer.*
  - **Reduce myocardial oxygen demand**

- **Time** = **Muscle**
- **Beta blocker?**
- **Nitrates?**

## Brief Word on Fibrinolytics

- **Preparations**: streptokinase, alteplase, reteplase, tenecteplase
- **Mechanism**: activate plasminogen → degrades fibrin (“clot busting”)
- Many contraindications – approx 30% not eligible
- PCI leads to lower bleeding, greater survival and less reinfarction
Treatment of ACS--STEMI

Initial Angiography

Following Intervention

Treatment of ACS—UA/NSTEMI

UA / NSTEMI

Halt the propagation of clot

+ 

Reduce myocardial oxygen demand

beta blockers, nitrates

Invasive vs. Conservative Strategy

Treatment Strategy

• Invasive: diagnostic angiography with intent to perform revascularization (without prior noninvasive stress testing)

• Conservative / selectively invasive: proceeding with invasive evaluation only for those who fail medical therapy (i.e. angina at rest or with minimal activity) or objective evidence for ischemia (dynamic ECG changes or high risk stress test)

How do we decide which strategy is best?
Invasive Strategy = Better Outcome with Higher Risk Patients

What Constitutes a High Risk Patient?

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Status</th>
<th>Patient Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization performed</td>
<td>Recurrent angina or instability at rest or with limited activity despite intense medical therapy</td>
<td></td>
</tr>
<tr>
<td>New or presumably new ST segment depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs or symptoms of HP or new or worsening heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk findings from noninvasive testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemo-dynamic instability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilator unresponsive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTO &lt; 10 mEq/L, Na</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI/CHF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk score (e.g., TIMI, GRACE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI/heart failure renal dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced left ventricular function (LVEF &lt; 40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>Generally preferred</td>
<td>Low-risk score (e.g., TIMI, GRACE)</td>
</tr>
<tr>
<td></td>
<td>Patient or physician preference in the absence of high-risk features</td>
<td></td>
</tr>
</tbody>
</table>

Risk Stratification Models

TIMI Risk Score (≥ 3 = high risk)

- Age ≥ 75 yrs
- Total cholesterol ≥ 240 mg/dL
- Prior MI
- Prior CABG
- Prior stroke
- Prior severe peripheral vascular disease
- Recent angina
- Cardiac marker
- ST depression ≥ 0.2 mV
Management Strategies—NSTEMI

Definite or possible ACS

- Early Invasive Strategy
  - Recurrent angina
  - Medical instability
  - New ST depression
  - High-risk stress test
  - Hemodynamic instability
  - Secondary ST changes
  - Prior CABG

- Definite ACS
  - Stable recurrent symptoms
  - High-risk score
  - Hemodynamic instability

Conservative Strategy
- Low risk score (TIMI, GRACE)
- Stable, physician preference

- Recurrent symptoms
- Serious arrhythmia
- Hemodynamic instability
- Persistent symptoms

Non-invasive Testing Risk Stratification

High risk
- Rest LV dysfunction <35%
- Acute risk factors
- Exercise stress test +
- Multivessel moderate stress defects

Intermediate risk
- Rest LV dysfunction 35-49%
- Intermediate risk factors
- Moderate stress defects
- Multivessel moderate stress defects

Low risk
- Rest LV dysfunction <35%
- Normal at rest
- Normal stress test
- No change on stress echo

Invasive Strategy

Initiate Anticoagulant Therapy
- Ticagrelor, UFH (IA)
- Enoxaparin, Fondaparinux (IB)

Precath: Add Second Antiplatelet Agent
- Clopidogrel or Ticagrelor (IB)
- IV Hb/Na – nadir, heparin (IA)

Med Management
- dt: Hb/Na
- Give Clopidogrel, or Ticagrelor per conservative strategy

- LABS
- Maintain ASA, UFH
Conservative Therapy

- **Anticoagulation Therapy:**
  - Enoxaparin, UFH (IA), or Fondaparinux (IB) but Enox or Fondaparinux preferred (IA)
  
  - Initiate Clopidogrel or Ticagrelor (IB)

- **Medical Therapy and Discharge:**
  - ASA
  - Clopidogrel or Ticagrelor 1-12 mos (IIb/IIIa)
  - UFH for 48 h; enoxaparin or fondaparinux for duration of hospitalization (max 8 d)

Summary

- ACS is unstable angina, NSTEMI or STEMI
- Treatment includes relief of ischemia, anticoagulation and antithrombotic therapy
- Invasive or conservative management of NSTEMI depends on risk
- High risk patients benefit from invasive vs. conservative therapy