Attribution: Kim Eagle, M.D., 2012

License: Unless otherwise noted, this material is made available under the terms of the Creative Commons Attribution–Share Alike 3.0 License: http://creativecommons.org/licenses/by-sa/3.0/

We have reviewed this material in accordance with U.S. Copyright Law and have tried to maximize your ability to use, share, and adapt it. The citation key on the following slide provides information about how you may share and adapt this material.

Copyright holders of content included in this material should contact open.michigan@umich.edu with any questions, corrections, or clarification regarding the use of content.

For more information about how to cite these materials visit http://open.umich.edu/education/about/terms-of-use.

Any medical information in this material is intended to inform and educate and is not a tool for self-diagnosis or a replacement for medical evaluation, advice, diagnosis or treatment by a healthcare professional. Please speak to your physician if you have questions about your medical condition.

Viewer discretion is advised: Some medical content is graphic and may not be suitable for all viewers.
Attribution Key
for more information see: http://open.umich.edu/wiki/AttributionPolicy

Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government**: Works that are produced by the U.S. Government. (17 USC § 105)
- **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
Cardiovascular Sequence
Acute Coronary Syndromes (ACS)

Kim A. Eagle, M.D.
University of Michigan Cardiovascular Center

Fall 2012
Kim A. Eagle, MD

Director

University of Michigan Cardiovascular Center

Grants: NIH, Hewlett Foundation, Mardigian Foundation, Varbedian Fund, GORE

Consultant: NIH NHLBI
Acute Coronary Syndromes

Key Words: ST elevation MI, non-STE, ACS, cardiac biomarkers, treatment of ACS, mechanical complications of MI

Objectives:
1. To learn how the admission ECG dictates early therapy for ACS.
2. To learn how to use cardiac biomarkers to diagnose ACS.
3. To become familiar with strategies for treatment in ACS.
4. To become familiar with mechanical complications of ACS.
Lecture Outline

• Pathogenesis of ACS
• Clinical features of ACS
• Treatment of ACS
• Complications
• Post ACS risk stratification
Pathogenesis of ACS

• Normal hemostasis
• Endogenous antithrombotic mechanisms
• Pathogenesis of coronary thrombosis
• Nonatherosclerotic causes of ACS
Pathogenesis: ACS

- > 90% - plaque disruption with platelet aggregation → intracoronary thrombus
- Concepts of clot formation
- Continuum of ACS from unstable angina to STE MI
Pathophysiology of Acute Coronary Syndromes

1. Plaque Rupture
   Cholesterol content
   Inflammation (CRP, Mophage)

2. Platelet Adhesion
   Activation
   Aggregation

3. Activation of Clotting
   Cascade - Thrombin

4. Downstream from thrombus
   Myocardial ischemia/necrosis
The continuum of acute coronary syndromes ranges from unstable angina, through non-ST-elevation myocardial infarction (also referred to as “non-Q-wave” myocardial infarction [MI]), to ST-elevation MI (also referred to as “Q-wave” MI).
Normal Hemostasis

Vessel wall injury

• 1st defense → Platelets
  – “Primary hemostasis” → Platelet plug

• 2nd defense → Subendothelial
  – Tissue factor activates plasma
  – Coagulates proteins
  ➢ “Secondary hemostasis” → Fibrin clot
Endogenous Antithrombotic Mechanisms

Inactivation of clotting factors
- Antithrombin III
- Protein C / Protein S / thrombomodulin
- Tissue factor pathway inhibitor

Lysis of fibrin clots
- Tissue plasminogen activator

Endogenous platelet inhibition & vasodilation
- Prostacyclin
- Nitrous oxide
Endogenous Protective Mechanisms
Triggers to Plaque Rupture

- Inflammatory cytokines
- Vulnerable Plaque
- Emotional Stress
- Physical Stress
Mechanisms of Coronary Thrombosis

Atherosclerosis

- Plaque rupture
  - Intraplaque hemorrhage
  - Release of tissue factor
  - Exposure of subendothelial collagen
  - Turbulent blood flow

- Dysfunctional endothelium
  - ↓ Vasodilator effect
  - ↓ Anti-thrombotic effect

Platelet activation & aggregation
- ↓ Vessel lumen diameter
- Activation of the coagulation cascade
- Vasoconstriction

Coronary thrombosis
Consequences of Coronary Thrombosis

Coronary thrombus

- Small thrombus (non-flow-limiting)
  - No ECG changes
  - Healing and plaque enlargement

- Partially occlusive thrombus
  - ST segment depression and/or T wave inversion
    - Serum biomarkers
      - Unstable angina
    - + Serum biomarkers
      - Non-ST-segment elevation MI

- Occlusive thrombus (Prolonged ischemia)
  - ST elevation (Q waves later)
    - + Serum biomarkers
      - ST-segment elevation MI
Causes of Acute Coronary Syndromes

- Atherosclerosis with superimposed thrombus
- Vasculitic syndromes
- Coronary emboli (e.g., from endocarditis, artificial valves)
- Congenital anomalies of the coronary arteries
- Coronary trauma or aneurysm
- Severe coronary artery spasm (primary or cocaine-induced)
- Increased blood viscosity (e.g., polycythemia vera, thrombocytosis)
- Significantly increased myocardial oxygen demand (e.g., aortic stenosis)
Extent of Myocardial Injury

Determined by:

- LV mass perfused by vessel
- Magnitude/Duration of flow
- Oxygen demand of affected tissue
- Adequacy of collaterals
- Tissue response to ischemia
The continuum of acute coronary syndromes ranges from unstable angina, through non-ST-elevation myocardial infarction (also referred to as “non-Q-wave” myocardial infarction [MI]), to ST-elevation MI (also referred to as “Q-wave” MI).
Unstable Angina

• Prior stable angina ➔ ↑ in:
  – Frequency
  – Duration
  – Intensity

• Angina at rest… previously only on provocation

• New onset angina
Acute Myocardial Infarction

• History and exam
• EKG changes
• Serum markers
## Symptoms

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Pressure, Burning (hot), Chest/arms/jaw/back</td>
</tr>
<tr>
<td>Sympathetic response</td>
<td>Sweats, Tachycardia, Cool, clammy skin</td>
</tr>
<tr>
<td>Parasympathetic response</td>
<td>Nausea, Vomiting, Weak</td>
</tr>
<tr>
<td>Inflammatory response</td>
<td>Mild fever</td>
</tr>
<tr>
<td>Other</td>
<td>Dyspnea, Asymptomatic</td>
</tr>
</tbody>
</table>
Physical Findings

• Inspection

BP - often increase anterior MI
    - often decrease inferior MI

HR - often increase anterior MI
    - often decrease inferior MI

RA p° - increase in RV MI
Physical Findings

• Palpation
  - LV Bulge - dyskinetic anterior wall

• Auscultation
  - Gallop - S4-LV stiff
  - Sounds - S3-LV fatigue
  - Murmurs - Mitral regurgitation
    - VSD
Differential Diagnosis

- Cardiac

  Pericarditis
  - Sharp, pleuritic pain
  - PT prefers to sit
  - Friction rub
  - EKG diffuse STE

- Aortic Dissection
  - Instantaneous onset of severe pain
  - Pulse deficits or AI
  - Wide mediastinum (CXR)
Differential Diagnosis

• Pulmonary
  
  **Pulmonary Embolus**
  - Pleuritic pain
  - Dyspnea
  - Reason for clotting
  
  **Pneumonia**
  - Cough, sputum, fever
    - Consolidation changes

• Gastrointestinal
  
  **Esophageal Spasm**
  - Retrosternal burning (acid)
  - After meals or at night
# Diagnosis of ACS

<table>
<thead>
<tr>
<th>Typical symptoms</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crescendo, rest, or new onset severe angina</td>
<td></td>
<td>Prolonged “crushing” chest pain, more severe and wider radiation than usual angina</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serum biomarkers</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ECG initial findings</th>
<th>Unstable Angina</th>
<th>Myocardial Infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST depression and/or T wave inversion</td>
<td>ST depression and/or T wave inversion</td>
<td>ST elevation (and Q waves later)</td>
</tr>
</tbody>
</table>

**NSTEMI**, non-ST-elevation myocardial infarction (MI); **STEMI**, ST-elevation MI
Q-wave Myocardial Infarction

Normal

Acute

Hours

Day 1-2

Days later

Weeks later

- ST elevation
- \( R \) wave
- Q wave begins

- ST elevation
- T wave inversion

- T wave deeper

- ST normalizes
- T wave inverted

- ST & T normal
- Q wave persists
Non-Q-wave Myocardial Infarction

Acute

Normal

T wave inversion

or

ST & T normal

no Q waves

ST depression

Weeks later
Serum Markers of Myocardial Infarction

• Myocardial necrosis causes sarcolemma disruption
• Intracellular macromolecules are released
• Can be measured by serial blood testing
• Pattern and level of rise correlates with timing and size of MI
Cardiac-Specific Troponins

- Regulatory protein that controls interaction between actin & myosin
- 3 subunits: TnC, I, T
- Unique cardiac troponins I and T exist - absent in serum of healthy people
- Powerful marker of myocyte damage
- Rise at 3-4 hours post-MI, peak 18-36 hrs, decline slowly 10-14 days
Creatinine Kinase

- Enzyme that converts ADP to ATP
- Found in many tissues: heart, brain, skeletal muscle, kidney, etc.
- Can be elevated after injury to any of these tissues
- 3 isoenzymes:  - CK-MM
                - CK-MB
                - CK-BB
CPK-MB

- Makes up 1-3% of skeletal CK
- Makes up much higher % of cardiac CK
- Rises 4-8 hours after MI, peaks by 24 hours
- Returns to normal in 48-72 hours
Treatment of Acute Coronary Syndromes:

STE vs. Non STE
Treatment of Acute Coronary Syndromes

- **Anti-ischemic therapies**
  - B-blocker
  - Nitrates
  - +/- Calcium channel blocker

- **General measures:**
  - Pain control (morphine)
  - Supplemental O₂ if needed

- **Antithrombotic therapies**
  - **Antiplatelet agents:**
    - Aspirin
    - Clopidogrel (or prasugrel)
    - GP IIb/IIIa inhibitor (for selected high risk patients; may be deferred until PCI)

  - **Anticoagulants (use one):**
    - LMWH (enoxaparin)
    - Unfractionated intravenous heparin
    - Fondaparinux
    - Bivalirudin (should be used in ACS patient only if undergoing PCI)

- **Adjunctive therapies:**
  - Statin
  - Angiotensin converting-enzyme inhibitor
Treatment of Acute Coronary Syndromes

ST-Elevation (STEMI)
- Emergent PCI available within 90 min?
  - No
    - Fibrinolytic Therapy (e.g., tPA)
  - Yes
    - Primary PCI

Non-ST-Elevation (UA and NSTEMI)
- Risk Assessment (e.g., GRACE Score)
  - Low
    - Conservative Strategy
      (Proceed to cardiac cath only if recurrent angina or predischarge stress test is markedly positive)
  - High
    - Invasive Strategy
      (Cardiac cath leading to PCI or CABG)
1. Platelet Adhesion

Platelet

Plaque rupture

GPIIb

ASA, Clopidogrel/Ticlopidine

2. Platelet Activation

Activated Platelet

GP IIb/IIIa

3. Platelet Aggregation

GP IIb/IIIa Inhibitors
Antithrombin Rx

Factor $\text{X}$

$\text{TF} / \text{VII a}$

Factor $\text{X a}$

$\text{V}$

Ca$^{++}$

Prothrombin

Thrombin

Fibrinogen

Fibrin Clot

LMWH

UFH

Hirudin
Effect of ASA in Non-ST Elevation MI and Unstable Angina

Incidence of Death or Subsequent MI

<table>
<thead>
<tr>
<th></th>
<th>Plac.</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis et. al.</td>
<td>10.1</td>
<td>5</td>
</tr>
<tr>
<td>Cairns, et. al.</td>
<td>12.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Theroux, et.al.</td>
<td>11.9</td>
<td>3.3</td>
</tr>
<tr>
<td>RISC Group</td>
<td>17.1</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*p= 0.0005
*p= 0.012
*p= 0.008
*p<0.0001
Meta-analysis
Heparin + ASA vs. ASA alone

Summary Relative Risk
0.67 (0.44-0.1.02)

10

Heparin + ASA
55/698 = 7.9%

Deep/MI

ASAlone
68/655 = 10.4%
LMWH in Unstable Angina

RR: Triple Endpoint (Death, MI/Recurrent Ischemia*)  Day

FRIC* (dalteparine)  N=1482  6
FRAXIS (nadroparine) N=2357
ESSENCE (enox.) N=3171  (p=0.032)  14
TIMI 11B (enox.) N=3910  (p=0.029)  14

0.5  0.75  1  1.5  2.0
LMWH Better  UFH Better

*Definition of recurrent angina/urgent revasc differs between trials
Nitrates

• Reduce ischemia (not mortality)

• Venodilation: \( \downarrow \) R heart return

• Coronary vasodilation

• Usually given SL then IV
Beta Blockers

- ↓Sympathetic drive; HR & BP
- ↓O₂ demand
- ↓Shear stress
- ↓Sudden death, death, recurrent MI
Non Dihydropyridine Calcium Channel Blockers

• \(\downarrow\) Heart rate
• Vasodilate
• Relieve ischemia, not mortality
• Don’t give in patients with sx/signs of heart failure
Non - STE ACS:

Conservative vs. Early Invasive Approach
Early Invasive

- Urgent catheterization performed after initial medical Rx
- Allows rapid identification & Rx of critical CAD
- More PCI/CABG
Conservative

- Cath patients with recurrent ischemia in hospital
- Cath patients with inducible ischemia on pre-discharge stress test
Invasive vs. Conservative

- Recent clinical trials show less infarction/reinfarction & possibly death with invasive strategy

- Especially in higher risk patients:
  - ST segment deviation
  - Elevated biomarkers
  - Multiple risk factors… esp. DM
Acute Treatment: STE MI

- Reperfusion: Thrombolysis vs. PTCA
- ASA
- $O_2$
- Beta blockers
- Nitrates
- ACE inhibitors
- Morphine
- Anticoagulants
Fibrin clot

tPA → P

tPA → P*

degraded clot without systemic lytic state
Additional Rx: STE MI

- Maintain vessel patency
- Restore balance between $O_2$ supply and demand
- Relieve chest pain
- Prevent complications
Aspirin

• Reduces mortality & reinfarction
• Give immediately on presentation and daily thereafter
• If aspirin allergy, use clopidogrel
Heparin

• Give 1-2 days IV after PCI or lysis with tPA, rPA, or TNK-tPA… NOT SK

• Also if:
  – Atrial fibrillation
  – LV thrombus
  – New anterior MI with large wall motion change

• All others: SQ heparin while at bed rest to prevent DVT
β- Blockers

- ↓ Risk arrhythmia, reinfarction, rupture, death
- Give IV, then orally unless contraindication exists (asthma, hypotension, significant bradycardia)
Nitrates

- Reduce pain/ischemia
- Relieve pain
- Reduce pulmonary congestion in heart failure
ACE - Inhibitors

- Limit adverse LV remodeling
- ↓ Heart failure/death
- ↓ MI
- Benefit additive ASA, BB
- Esp. benefit anterior MI and/or LV dysfunction
Statins

• Reduce reinfarction, death

• More benefit when started early

• Give if LDL cholesterol is > 100
Acute MI: Complications

- Recurrent ischemic/reinfarction
- Arrhythmias
- Myocardial dysfunction
- Mechanical complications
- Pericarditis
- Thromboembolism
Complications of MI

Myocardial Infarction

- Ventricular thrombus
- Embolism
- Contractility
  - Electrical instability
  - Tissue necrosis
  - Pericardial inflammation
- Electrical instability
- Tissue necrosis
- Pericardial inflammation
- Ventricular septal defect
- Ventricular rupture
- Cardiac tamponade

- Papillary muscle infarction/ischemia
- Arrhythmias

- Cardiogenic shock
  - Ischemia
  - Hypotension
  - Coronary perfusion pressure

- Mitral regurgitation
- Congestive heart failure
Recurrent Ischemia

- Angina or ischemia confers increase risk for reinfarction
- Should lead to angiography and revascularization for most pts.
<table>
<thead>
<tr>
<th>Rhythm</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus Bradycardia</td>
<td>- ↑Vagal tone</td>
</tr>
<tr>
<td></td>
<td>- ↓SA nodal artery perfusion</td>
</tr>
<tr>
<td>Sinus Tachycardia</td>
<td>- CHF</td>
</tr>
<tr>
<td></td>
<td>- Volume depletion</td>
</tr>
<tr>
<td></td>
<td>- Pericarditis</td>
</tr>
<tr>
<td></td>
<td>- Chronotrophic drugs (e.g. Dopamine)</td>
</tr>
<tr>
<td>APB’s, atrial fib, VPB’s, VT, VF</td>
<td>- CHF</td>
</tr>
<tr>
<td></td>
<td>- Atrial Ischemia</td>
</tr>
<tr>
<td></td>
<td>- Ventricular ischemia</td>
</tr>
<tr>
<td></td>
<td>- CHF</td>
</tr>
<tr>
<td>AV block (1°, 2°, 3°)</td>
<td>- IMI: ↑ Vagal tone and ↓AV nodal artery flow</td>
</tr>
<tr>
<td></td>
<td>- AMI: Extensive destruction of conduction tissue</td>
</tr>
</tbody>
</table>
### Blood Supply in the Conduction System

<table>
<thead>
<tr>
<th>Conduction Pathway</th>
<th>Primary Arterial Supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA node</td>
<td>- RCA (70% of patients)</td>
</tr>
<tr>
<td>AV node</td>
<td>- RCA (85% of patients)</td>
</tr>
<tr>
<td>Bundle of His</td>
<td>- LAD (septal branches)</td>
</tr>
<tr>
<td>RBB</td>
<td>- Proximal portion by LAD</td>
</tr>
<tr>
<td>LBB</td>
<td>- Distal portion by RCA</td>
</tr>
<tr>
<td>Left anterior fascicle</td>
<td>- LAD</td>
</tr>
<tr>
<td>Left posterior fascicle</td>
<td>- LAD and PDA</td>
</tr>
</tbody>
</table>
Myocardial Dysfunction

• Congestive Heart Failure
  – Systolic or diastolic
  – Treated with vasodilators, diuretics, and Rx to reverse ischemia

• Cardiogenic Shock
  – Depressed CO
  – Hypotension
  – Poor perfusion of vital organs
  – Treatment: Look/Treat reversible cause
  – Inotropes/vasodilators/IABP
Cardiogenic Shock - MI - 1Y

Initial Medical Stabilization - n=150

Time From Randomization, mo

Proportion Alive

1.0

0.8

0.6

0.4

0.2

0.0

0

2

4

6

8

10

12

Early Revascularization - n=152

Initial Medical Stabilization - n=150

Benefit < 75 Years

Shock (JS Hochman et al.) JAMA 2001; 285:190
RV Infarction

• Common in IMI’s

• Sx/signs:
  – Hypotension
  – Increase RA Pressure

• Rx:
  – Volume, hemodynamic monitoring…PA line
Papillary Muscle Infarction

• “Common” in inferoposterior MI
• Leads to acute mitral valve regurgitation
• Left heart failure/pulmonary edema
• Rx: Coronary revascularization; IABP; valve repair
Free Wall Rupture

• More likely in elderly, HTN, women
• Usually rapidly fatal
• Occasional walls off to form pseudoaneurysm
• Urgent surgery is best chance
Ventricular Septal Defect

- Heralded by left to right shunting at ventricular level
- RV volume overload
- Loud systolic murmur over sternum
- Usually requires surgical repair
True Ventricular Aneurysm

- Occurs late
- More often in non-reperfused STE MI’s
- Complications: Clot, CHF, arrhythmias
Pericarditis

- More common in non-reperfused STE MI
- Fever, sharp pain with pleuritic tendency, friction rub
- Treatment: nonsteroidal anti-inflammatory agent; heparin relatively contraindicated
Thromboembolism

- Clot forms on infarcted akinetic myocardium
- Most common in large anterior MI
- Can cause embolic stroke
- Rx: 3-6 months anticoagulants
- If clot seen on echo or LVEF < 30% or if large anterior MI
<table>
<thead>
<tr>
<th>Predictor of Poor Outcome</th>
<th>Method to Detect</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor LVEF</td>
<td>Echocardiogram</td>
<td>ACE, BB</td>
</tr>
<tr>
<td>Residual Ischemia</td>
<td>Pre D/C ETT</td>
<td>Cath; ASA, BB</td>
</tr>
<tr>
<td></td>
<td>Max ETT later</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Monitoring/ Observation</td>
<td>Directed</td>
</tr>
</tbody>
</table>
Standard Discharge Rx

- 3 to 5 day length of stay
- ASA; clopidogrel
- Beta blocker
- ACE for CHF; LVEF ≤ 40%, perhaps all
- Warfarin as noted
- Cardiac Rehab
- PRN Nitrates
- Exercise prescription
- Low fat diet
- Smoking Cessation
- Statin if LDL cholesterol ≥ 100 mg/dl
Kaplan–Meier Cumulative Risk of the Primary Outcome, Stratified According to GRACE Risk Score at Baseline