Case Study

- A 54-year-old woman is evaluated in the emergency department for jaw and shoulder pain that has occurred intermittently for the past week. The symptoms occur with activity and are relieved by rest. Medical and family history are unremarkable. She is not taking any medications.

- Physical examination shows a blood pressure of 130/68 mm Hg and a pulse of 90/min. There is no jugular venous distention and carotid upstrokes are normal. There are no cardiac murmurs and the lung fields are clear. Extremities show no edema and peripheral pulses are normal bilaterally.
Case Study con’t

- Laboratory studies:
  - Hematocrit 42%
  - Platelet count 220,000/µL (200 × 10^9/L)
  - Troponin I 9.0 ng/mL (9.0 µg/L)
  - Creatinine 1.0 mg/dL (76.3 µmol/L)
  - Electrocardiogram shows 1.0-mm ST-segment depression in leads V1 through V4 with T-wave inversions.

- The patient is given aspirin, intravenous nitroglycerin, low-molecular-weight heparin, metoprolol, and atorvastatin. The pain subsides after approximately 20 minutes, and she is admitted to the coronary care unit. One hour later, she has recurrent jaw and shoulder pain. She denies chest pain. A repeat electrocardiogram is unchanged.
Question

What is the next best step?

- A: Stop metoprolol and start verapamil
- B: Stop low-molecular weight heparin and start unfractionated heparin
- C: Start enalapril
- D: Start a glycoprotein IIb/IIIa inhibitor
Acute coronary syndrome

Definition: “any constellation of symptoms consistent with acute coronary ischemia”
Definitions--STEMI

...clinical syndrome characterized by coronary ischemia and characteristics ECG changes, with subsequent release of biomarkers.
Pathophysiology of ACS/MI
Underlying Pathophysiology is Similar

- Not progressive obstructive disease
- Plaque rupture/erosion
- Occlusive vs. Non-occlusive thrombus (Correlation with ECG)

Image from NEJM 2000; 342: 101-114.
Approach to ACS: Assessing Risk

Are symptoms due to cardiac ischemia?  
What is the risk to the patient?

Greater risk of disease: 
  justifies more intense therapy

Less risk of disease: 
  more intense therapy unjustified, puts patient at more risk of harm than is justified.
Four Tools to Risk Stratification

- History
- Physical exam
- ECG
- Biomarkers
History & Physical Exam

**Typical history:** vague, diffuse, visceral discomfort, explained as a pressure, heaviness, tightness under the sternum, favoring the left chest, with possible radiation to jaw, neck, or left arm/shoulder. Frequent associated symptoms are nausea, dyspnea, fatigue.

**Compatible history:**
- Exclusively dyspnea, nausea, or fatigue
- Abdominal pain
- Rarely exclusively back/neck/shoulder pain

**Physical exam:** Often normal (does not exclude). Look for evidence of HF, valvular disease, non-cardiac disease.
<table>
<thead>
<tr>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nature of angina</strong></td>
<td><strong>Nature of angina</strong></td>
</tr>
<tr>
<td>- Ongoing</td>
<td>- Increasing pattern of prior stable angina</td>
</tr>
<tr>
<td>- Prolonged, rest pain</td>
<td>- New onset angina beginning &gt; 2 weeks ago</td>
</tr>
<tr>
<td>- Accelerated tempo over 48 hrs</td>
<td></td>
</tr>
<tr>
<td><strong>Age &gt; 75</strong></td>
<td><strong>Age &lt; 75</strong></td>
</tr>
<tr>
<td><strong>Exam: HF, new MR, hypotension</strong></td>
<td><strong>Exam: normal</strong></td>
</tr>
<tr>
<td><strong>ECG: &gt; 0.5 ST changes, VT, new BBB</strong></td>
<td><strong>ECG: normal, nonspecific findings</strong></td>
</tr>
<tr>
<td><strong>Biomarkers: positive</strong></td>
<td><strong>Biomarkers: negative</strong></td>
</tr>
</tbody>
</table>
ECG Changes

- ST elevation
- ST depression
  - Downsloping > horizontal > upsloping
  - Magnitude + number of leads
- T wave inversions
- Any different/changing ST portion
- Normal
<table>
<thead>
<tr>
<th>Feature</th>
<th>High Risk (At least 1 of the following features must be present)</th>
<th>Intermediate Risk (No high-risk feature but must have 1 of the following features)</th>
<th>Low Risk (No high- or intermediate-risk feature but may have any of the following features)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Accelerating tempo of ischemic symptoms in preceding 48 hrs</td>
<td>Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use</td>
<td>New-onset CCS Class III or IV angina in the past 2 wk with moderate or high likelihood of CAD</td>
</tr>
<tr>
<td>Character of pain</td>
<td>Prolonged ongoing (&gt;20 min) rest pain</td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rest angina (&lt;20 min or relieved with rest or sublingual NTG)</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Pulmonary edema, most likely related to ischemia</td>
<td>Age &gt;70 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>New or worsening MR murmur</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S3 or new/worsening rales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension, bradycardia, tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age &gt;75 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG findings</td>
<td>Angina at rest with transient ST-segment changes &gt;0.05 mV</td>
<td>T-wave inversions &gt;0.2 mV</td>
<td>Normal or unchanged ECG during an episode of chest discomfort</td>
</tr>
<tr>
<td></td>
<td>Bundle-branch block, new or presumed new</td>
<td>Pathological Q waves</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sustained ventricular tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Markedly elevated (eg, TnT or TnI &gt;0.1 ng/mL)</td>
<td>Slightly elevated (eg, TnT &gt;0.01 but &lt;0.1 ng/mL)</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Approach to ACS: Assessing Risk

History, exam, & ECG

- ST elevation → Emergent reperfusion therapy
  PPCI, Fibrinolytics

- No ST elevation

Biomarkers

- Medium-High risk → Urgent/early coronary angiography,
  revascularization as indicated

Other Risk Assessment

- Low risk

Observe/Med Rx

Stress testing, RF modification

Other test (as indicated)

Recurrent symptoms, High risk findings
Coronary Angiography: For whom?

Conservative Approach

Early Invasive

Urgent Angiography

Immediate Reperfusion

Low risk ACS

Med/High Risk ACS
Refractory/ongoing angina
Hemodynamic instability
Electrical instability

- - - - - - - - - - - - - - - - - -

Low risk, (Doc or patient preference)

STEMI
### Interventional Strategy:
**“To cath or not to cath”**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable angina</td>
<td>Reduces angina</td>
</tr>
<tr>
<td>Unstable angina/NSTEMI</td>
<td>Reduces MI (+/- mortality)</td>
</tr>
<tr>
<td></td>
<td>Reduces angina</td>
</tr>
<tr>
<td>STEMI</td>
<td>Reduces mortality</td>
</tr>
<tr>
<td></td>
<td>Reduces recurrent MI</td>
</tr>
<tr>
<td></td>
<td>Reduces angina</td>
</tr>
</tbody>
</table>
TACTICS-TIMI 18 Study Design

UA/NSTEMI

Early Invasive

CATH/ PCI/ CABG

Early Conservative

PCI/ CABG

Medical Rx

Angio

Endpoints

Baseline Troponin

ASA, Hep, Tirofiban

UA/NSTEMI

ETT

Medical Rx

+ischemia

Cath/ PCI/ CABG
Primary Endpoint

Death, MI, Rehosp for ACS at 6 Months

TACTICS-TIMI 18

% Patients

0 1 2 3 4 5 6
Time (months)

0 4 8 12 16 20

CONS

INV

O.R 0.78
95% CI (0.62, 0.97)
p=0.025

19.4%
15.9%
## Cardiac Events at 6 Months

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CONS (%)</th>
<th>INV (%)</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1º Endpoint</td>
<td>19.4</td>
<td>15.9</td>
<td>0.78</td>
<td>0.025</td>
</tr>
<tr>
<td>Death/MI</td>
<td>9.5</td>
<td>7.3</td>
<td>0.74</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Death</td>
<td>3.5</td>
<td>3.3</td>
<td>0.93</td>
<td>0.74</td>
</tr>
<tr>
<td>MI</td>
<td>6.9</td>
<td>4.8</td>
<td>0.67</td>
<td>0.029</td>
</tr>
<tr>
<td>Rehosp ACS</td>
<td>13.7</td>
<td>11.0</td>
<td>0.78</td>
<td>0.054</td>
</tr>
</tbody>
</table>

No. Pts

<table>
<thead>
<tr>
<th>No. Pts</th>
<th>1106</th>
<th>1114</th>
</tr>
</thead>
</table>

TACTICS-TIMI 18
What determines high risk?

- TIMI Risk Score
  - Age, RFs, CAD, ASA use, angina w/i 24 hrs, TnI, ST depression

- GRACE Risk score
  - Age, Killip class, systolic BP, cardiac arrest, ST changes, Cr, TnI, HR

- “TIM” Risk score
Risk Stratification  

**TIM Risk Score**

“TIM” Risk Score: 0 or 1

---

**Prognostic Power of TnI**

---

*Graph showing troponin I levels to predict the risk of mortality in acute coronary syndromes.*

- **Cardiac Troponin I (ng/ml):**
  - 0 to <0.4: 1.0 (831 patients)
  - 0.4 to <1.0: 1.7 (174 patients)
  - 1.0 to <2.0: 3.4 (148 patients)
  - 2.0 to <5.0: 3.7 (134 patients)
  - 5.0 to <9.0: 6.0 (50 patients)
  - ≥9.0: 7.5 (67 patients)

**Mortality at 42 Days (% of patients):**

- 1.0
- 1.7
- 3.4
- 3.7
- 6.0
- 7.5

**Risk Ratio and 95% Confidence Interval:**

- 1.0
- 1.8 (0.5–6.7)
- 3.5 (1.2–10.6)
- 3.9 (1.3–11.7)
- 6.2 (1.7–22.3)
- 7.8 (2.6–23.0)
Troponin T: 1°EP at 6 months

Death, MI, Rehosp ACS at 6 Mo

TnT cut point = 0.01 ng/ml
(54% of Pts TnT +)

OR=0.52
*p<0.001
Interaction
P<0.001

N=414
14.5
p=NS

N=396
16.9

N=463
24.2

N=495
14.3

TnT -

TnT +

TnT cut point = 0.01 ng/ml
(54% of Pts TnT +)
**Approach to ACS: Assessing Risk**

- **History, exam, & ECG**
- **Biomarkers**
- **Other Risk Assessment**

**ST elevation**
- **Emergent reperfusion therapy**
  - PPCI, Fibrinolytics

**No ST elevation**
- **Medium-High risk**
  - **Urgent/early coronary angiography**
  - Revascularization as indicated

**Low risk**
- **Observe/Med Rx**
- **Stress testing, RF modification**
- **Other test (as indicated)**

**Recurrent symptoms, High risk findings**
Reperfusion in STEMI

- All communities should create/maintain a regional STEMI system that incorporates EMS/ED/hosp
- Primary percutaneous coronary intervention (PPCI) is preferred method
  - < 90 minutes, qualified center & operators
- Fibrinolytics indicated if PCI not readily available
  - Check contraindication
  - Not as effective if symptoms > 3 hours
  - Consider if delay to PPCI > 90 mins (time to balloon - time to drug >60 mins), esp if early presentation
PCI vs Fibrinolysis for STEMI: Short Term Clinical Outcomes

N = 7739

Approach to ACS: Assessing Risk

- **History, exam, & ECG**
  - **ST elevation**: Immediate reperfusion therapy (PPCI, Fibrinolytics)
  - **No ST elevation**
    - **Biomarkers**
    - **Medium-High risk**: Coronary angiography, revascularization as indicated
    - **Low risk**: Observe, Stress testing, RF modification, Other test (as indicated)
    - **Observe**

- **Recurrent symptoms, High risk findings**
Unstable angina/NSTEMI
What is “urgent/early” angiography?

- **ISAR-COOL**
  - 2000-2002, 2.6 hrs vs. 86 hrs
  - Early angiography superior

- **TIMACS**
  - 2009, 14 hrs. vs 50 hrs
  - No difference in primary outcomes, trends favoring early angio, esp in high risk patients

- **ABOARD**
  - 2009, 70 min vs. 21 hrs
  - No trends suggesting any difference
Unstable angina/NSTEMI
What is “urgent/early” angiography?

“Taken together…provide support for a strategy of early angiography and intervention to reduce ischemic complications in patients who have been selected for an initial invasive strategy, particularly among those at high risk, whereas a more delayed approach is reasonable in low to intermediate risk patients.

“Early” is considered to be within the first 24 hours after hospital presentation, although there is no evidence that incremental benefit is derived by angiography…performed within the first few hours of hospital admission.
Unstable angina/NSTEMI

What is “urgent/early” angiography?

Take Home:
1. Reasonably early (24-48 hrs) for patients assigned to early invasive approach
2. Tend toward earlier treatment among high risk patients
3. No real proof that a “cooling off” period is helpful.
Treatment of (Medium-High Risk) ACS

- Admit, telemetry, defibrillation capability
- Serial cardiac troponin
- Aspirin
- Beta blockers
- Statins
- Assess LV function
- Antiplatelets
- Anticoagulants
### Antiplatelets / Anticoagulants

#### COX Inhibitor
- Aspirin

#### Thienopyridine
- Clopidogrel
- Prasugrel (Effient)
- Ticagrelor (Brilinta)

#### Platelet IIb/IIIa antagonist
- Eptifibatide (Integrin)
- Abciximab (Reopro)
- Tirofiban (Aggrastat)

#### Unfractionated heparin

#### Low molecular weight heparin
- Enoxaparin (Lovenox)

#### Direct Xa inhibitor (parenteral)
- Fondaparinux (Arixtra)

#### Direct thrombin inhibitor (parenteral)
- Bivalirudin (Angiomax)
Antiplatelets

- All patients: Aspirin ASAP, 325 mg loading dose, then 81-162 mg/day indefinitely

- Invasive strategy planned:
  - Aspirin (as above), plus one of either:
    1. Clopidogrel 300-600 mg po load, then 75/day, or
    2. IV IIb/IIIa antagonist (eptifibatide or tirofiban)

  At time of presentation
  1. Prasugrel or ticagrelor may be substituted for clopidogrel
  2. Abciximab could also be used for IIb/IIIa antagonist

In cath lab
Antiplatelet Therapy

Diagnosis of UA/NSTEMI (Likely or Definite)

Aspirin

Select Management Strategy

Initial Conservative

Initiate Anticoagulation

Initiate clopidogrel or ticagrelor

Invasive Strategy

Initiate Anticoagulation

Precath: add a second antiplatelet clopidogrel or ticagrelor, or IIb/IIIa antagonist

Next step per triage at angiography

CABG
Maintenance ASA

PCI
clopidogrel or ticagrelor, or prasugrel, or IIb/IIIa antagonist

Medical Therapy
D/C IIb/IIIa antagonist
Clopidogrel or ticagrelor

Anticoagulation
1. Conservative approach: UFH, enoxaparin, fondaparinux
2. Invasive approach UFH, enoxaparin, bivalirudin
Antiplatelets

- **Non-invasive strategy planned:**
  - Aspirin (as above), plus
  - Clopidogrel 300-600 mg po load, then 75/day or,
  - Ticagrelor\(^1\) 180 mg po load, then 90 mg po BID

- **Non-invasive strategy fails (recurrent ischemia)**
  - Angiography
  - If not already in use, add (Class I)
    - clopidogrel or ticagrelor, or
    - IIb/IIIa antagonist,
  - Add the third agent (Class IIa)

1. Anytime ticagrelor is used, aspirin dose should be reduced to 81 mg/day
Antiplatelets

Miscellaneous

- If high risk of bleeding, consider PPI or H2 blocker
  - Prior UGIB
  - Concomitant steroid, NSAID, or warfarin use
  - Advanced age
  - *H. pylori* infection

- Duration of thienopyridine
  - If present with ACS—1 year
  - If receive DES—1 year
  - If stable angina + BMS—1 month
In Hospital Care

- Initiate aspirin, thienopyridine, anticoagulation (UFH x 48 hrs, enoxaparin/fondaparinux up to entire hospital course)
- *Oral* beta blockers
- Evaluate LV function
  - ACE-I or ARB if LV systolic dysfunction
- Initiate statin in-house
- Smoking cessation counseling
- Recommend cardiac rehab
- Diabetes: reasonable control (< 180 mg/dl)
- CKD: measure CrCl and adjust doses accordingly
Does everyone have to be admitted?

Admit to hospital
1. STEMI
2. Mod-high risk ACS (regardless of invasive or conservative strategy)

Outpatient evaluation acceptable
1. Noncardiac chest pain
2. Chronic stable angina
3. Low risk ACS
   - Nondiagnostic ECG
   - Negative biomarkers
   - No recurrent sx/instability
   - Observe 6-12 hours after onset of pain
1. Aspirin on arrival
2. Aspirin on discharge
3. ACE-I for LV dysfunction
4. Oral beta blocker at discharge
5. Median time to fibrinolysis
6. Fibrinolytic Therapy ≤ 30 mins
7. Median time to PCI
8. PPCI ≤ 90 mins
9. Statin at discharge
Metrics & Public Reporting

1. Aspirin on arrival
2. Aspirin on discharge
3. ACE-I/ARB for LV dysfunction
4. Oral beta blocker at discharge
5. Statin at discharge
6. Evaluation of LV systolic function
7. Cardiac rehab
8. Smoking cessation counseling

STEMI Patients
1. Reperfusion Therapy
2. Time to Fibrinolytics
3. Time to PCI
Summary

- First assess risk by history, exam, and ECG
  - STEMI: immediate reperfusion
- Add biomarker data to complete risk assessment
- Medium-high risk patients
  - ASA, thienopyridine (or IIb/IIIa antagonist)
  - Anticoagulants
  - Angiography
- Low risk patients
  - Aspirin, anticoagulation, clopidogrel or ticagrelor x 1 year, stress test
  - If symptoms recur, or high risk findings emerge → angiography
Case Study

- A 54-year-old woman is evaluated in the emergency department for jaw and shoulder pain that has occurred intermittently for the past week. The symptoms occur with activity and are relieved by rest. Medical and family history are unremarkable. She is not taking any medications.
- Physical examination shows a blood pressure of 130/68 mm Hg and a pulse of 90/min. There is no jugular venous distention and carotid upstrokes are normal. There are no cardiac murmurs and the lung fields are clear. Extremities show no edema and peripheral pulses are normal bilaterally.
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Question

What is the next best step?

- A: Stop metoprolol and start verapamil
- B: Stop low-molecular weight heparin and start unfractionated heparin
- C: Start enalapril
- D: Start a glycoprotein IIb/IIIa inhibitor
Answer

D: Start a glycoprotein IIb/IIIa inhibitor

Why?
Recommendations for patients with ACS include anticoagulation, aspirin, and a second antiplatelet agent. Since she is not immediately going to the cath lab, acceptable choices would include clopidogrel or ticagrelor, or IIb/IIIa antagonist such as eptifibatide (Integrilin) or tirofiban (Aggrastat). Beta blockers are class 1. Both LMWH and UFH are class 1 recommendations.
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THE END

Questions?