Acute Coronary Syndrome Management

HMS & BWH
Intensive Review of Internal Medicine
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Scientific Advisory Boards: Amgen, Joint Venture, GlaxoSmithKline, Merck, Pfizer, Sanofi-Aventis

STEMI: Immediate Reperfusion Therapy

When to do it:
• Within 12 hrs of sx onset, or
• 12-24 hrs after sx onset if clin/ECG evidence of ongoing ischemia

How to do it:
• Fibrinolysis (tenecteplase, reteplase, IPA, or SK) w/in 30 mins
• Primary percutaneous coronary intervention (PCI) w/in 90 mins
• Primary PCI preferred to fibrinolysis if:
  • Experienced team w/in 90 min of 1st med contact (120 min if presenting to non-PCI capable hospital)
  • High-risk STEMI (shock, congestive heart failure)
  • Late presentation (eg, >3 hrs from sx onset)
  • Contraindication to fibrinolytic
    o Absolute: prior ICH; intracranial neoplasm, aneurysm, or AVM; stroke or head trauma w/in 3 mos; active internal bleeding or diathesis; suspected AoD
    o Relative: severe HTN; stroke; prolonged CPR; recent bleed, surgery or trauma; noncompressible vasc puncture; pregnancy; current use of anticoagulants

What To Do after Fibrinolysis?
• If it fails (persistent STE <50% resolution) or sx, development of shock, evidence of infarct-related artery reocclusion): PCI
• If it succeeds:
  • Non-invasive ischemia testing (ie, stress test), OR
  • Transfer high-risk pts w/in 3-24 hrs for elective PCI
    (high-risk = anterior MI, inferior MI w/ low EF or RV infarct, extensive STE or LBBB, HF, hypotension or tachycardia)

  • 1059 high-risk STEMI
    Pts Rx’d with lytic
    • Rand. to immed transfer w/ PCI w/in 6 h or rec for cath w/in 2 wks (earlier if needed)

NSTEMI Management Strategy: Invasive vs. Conservative

INVASIVE (12-24 hrs)
PCI / CABG

CONSERVATIVE (Select invasive)
Stress test
Ischemia
Stress Rx

Med Rx

Med Rx
Invasive vs. Conservative Strategy

**INVASIVE**
Routine angiography and revascularization as indicated, within 12-24 hours if high-risk, within 48 hours if low-risk.

1. Refractory angina
2. Hemodynamic or electrical instability
3. ↑ risk of ischemic events
   a. Recurrent angina, angina at rest, or with low-level activity
   b. High-risk features on stress test
   c. Troponin
   d. ST depressions
   e. ↑ TIMI or GRACE risk score
   f. Heart failure, low EF, or worsening MR
   g. PCI in past 6 months, prior CABG

**CONSERVATIVE**
Coronary angiography and revascularization only if significant stress-test induced ischemia or recurrent spontaneous ischemia.

1. Low TIMI or GRACE Risk score
2. Patient or physician preference in absence of high-risk features

**INV vs. CONS Meta-Analysis**

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.8 (1.14-2.50)</td>
<td>0.007</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>3.7 (1.94-6.37)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Mehta et al., JAMA 2005; 293: 2908

**TIMACS**
3031 Patients with NSTEMI
Cath within 24 hours (median 14 hours) or >36 hours (median 50 hours)

**Determinants of Myocardial O2 Supply & Demand**

- Supply: Oxygen carrying capacity, coronary blood flow
- Demand: Wall stress (P<2/h), heart rate, contractility

↓ Myocardial O2 Demand

- Wall stress
- Blood pressure
- Coronary vasospasm

- β-BLOCKERS
  - ↓ HR
  - ↓ contractility
  - ↓ BP
  - ↓ arrhythmias

- CALCIUM CHANNEL BLOCKERS
  - agent specific
  - ↓ HR
  - ↓ contractility
  - ↓ BP
  - venodilation

**COMMIT: Effects of METOPROLOL on Death**

45,852 Patients p/w AMI within 24 hrs; ASA; lytic therapy (~1/2)
Randomized to metoprolol (5 mg IV q 5 min x 3, 50 mg PO q 6 hr x 4, then 200 mg XL qd) or placebo

<table>
<thead>
<tr>
<th>Cause(s)</th>
<th>Metoprolol (22,929)</th>
<th>Placebo (22,923)</th>
<th>Odds ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANY DEATH</td>
<td>1774 (7.7%)</td>
<td>1797 (7.8%)</td>
<td>1.1 (0.95-1.26)</td>
</tr>
<tr>
<td>Shock</td>
<td>406 (2.2%)</td>
<td>384 (1.7%)</td>
<td>1.2 (0.94-1.54)</td>
</tr>
<tr>
<td>Other causes</td>
<td>890 (3.9%)</td>
<td>915 (4.5%)</td>
<td>0.9 (0.74-1.13)</td>
</tr>
<tr>
<td>Metop. better</td>
<td>43% SE 4</td>
<td>46% SE 4</td>
<td></td>
</tr>
<tr>
<td>Placebo better</td>
<td>39% SE 4</td>
<td>40% SE 4</td>
<td></td>
</tr>
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Beta-Blockers in ACS

Class I
Oral βB should be initiated in the first 24 hrs if w/o any of following:
1) heart failure,
2) low output state,
3) ↑ risk for cardiogenic shock, or
4) other relative contraindications

Class IIA
IV βB at time of presentation if HTN and w/o any of following:
1) heart failure,
2) low output state,
3) ↑ risk for cardiogenic shock, or
4) other relative contraindications

Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk) are age >70 yrs, SBP <120 mm Hg, HR >110 bpm or <60 bpm, and T time since onset of symptoms.

Antithrombotics

- Antiplatelet drugs
  - COX Inhibitors: aspirin
  - P2Y<sub>12</sub> ADP Receptor Blockers: clopidogrel, prasugrel, ticagrelor
  - Glycoprotein IIb/IIIa Inhibitors: abciximab, eptifibatide, tirofiban

- Anticoagulants
  - Unfractionated heparin (UFH)
  - Low-molecular-weight heparins: enoxaparin, dalteparin
  - Pentasaccharide blockers: fondaparinux
  - Direct thrombin inhibitors: bivalirudin

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Clopidogrel Variability & Recommendations

- Platelet function testing & genetic testing
  - Evidence base insufficient to recommend routine use
  - May be considered in high-risk pt if would change Rx
- PPI
  - Recommended if h/o UGIB
  - Appropriate if risk factors for GIB (advanced age, concurrent use of a/c, steroids, or NSAIDs, H pylori)
  - Routine use not recommended if low risk
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (1,2,5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2,3,5,1)
- Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole, (5,1)

JACC 2010;16:3051-66; Plavix Label 3/12/2016

Prasugrel vs. Clopidogrel: Speed of Onset and Non-responders

Prasugrel: more potent than clopidogrel, fewer "non-responders", irreversible (dic 7 days before surgery)

F DA

JACC 2010;16:3051-66; Plavix Label 3/12/2016
Ticagrelor Pharmacodynamics


Ticagrelor: more potent than clopidogrel, fewer "non-responders", reversible

Prasugrel
Clopidogrel

13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)

CV Death / MI / Stroke
TIMI Major
Non-CABG Bleeds

Risk (%)

HR 0.84
(95% CI 0.77-0.92)
P=0.003

Prasugrel
Clopidogrel

HR 1.32
(1.03-1.68)
P=0.03

Greater benefit in patients with high bleeding risk:

Prasugrel
Clopidogrel

Major bleeding
(95% CI) 0.75-1.03
P=0.18

PLATO major bleeding
TIMI major bleeding
Non-CABG major bleeding
Red cell transfusion
PLATO major
TIMI bleeding
Fast bleeding

Risk (%)

0.3 0.3

0.2 0.2

7.3 7.2

8.9 8.9

=0.025

Glycoprotein IIb/IIIa Inhibitors

- Potent intravenous antiplatelet drugs
- Typically consider giving at time of PCI
- UA/NSTEMI
  - INV Strategy: give at time of PCI; upstream use (ie, prior to angiography) w/o clear efficacy and increases risk of bleeding
  - CONS Strategy: usually no role unless Pt goes for PCI
- STEMI
  - Primary PCI: give at time of PCI (not before)
  - Fibrinolysis: CONTRAINDICATED
Search for Better Anticoagulants

**Anticoagulants in UA/NSTEMI**

- **INVASIVE STRATEGY**
  - UFH
  - Enoxaparin (LMWH)
  - Bivalirudin
  - Fondaparinux
  - **Discontinue after uncomplicated PCI**

- **CONSERVATIVE STRATEGY**
  - UFH (Rx for 48 hrs)
  - Enoxaparin (LMWH) (Rx until end of hosp, up to 8d)
  - Fondaparinux
  - [NOT Bivalirudin]

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**Enoxaparin vs. UFH Summary**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ENOX</th>
<th>UFH</th>
<th>ARR</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/MI at 30 d in all 6 RCTs</td>
<td>10.1</td>
<td>11.0</td>
<td>0.91</td>
<td>(0.83-0.99)</td>
</tr>
<tr>
<td>All patients</td>
<td>6.0</td>
<td>9.4</td>
<td>1.4</td>
<td>(0.70-0.94)</td>
</tr>
<tr>
<td>No PreRx</td>
<td>8.8</td>
<td>8.5</td>
<td>-0.3</td>
<td>(0.77-1.40)</td>
</tr>
<tr>
<td>D/MI/RI at 7 d in A to Z (TIMI 21)</td>
<td>7.7</td>
<td>10.6</td>
<td>2.9</td>
<td>(0.51-0.98)</td>
</tr>
<tr>
<td>Invasive</td>
<td>4.7</td>
<td>4.5</td>
<td>-0.2</td>
<td>(0.89-1.30)</td>
</tr>
<tr>
<td>Conservative</td>
<td>7.5</td>
<td>5.3</td>
<td>-2.2</td>
<td>(1.03-2.05)</td>
</tr>
</tbody>
</table>

**Bivalirudin in NSTEMI ACS**

- **Primary End Point (ITT)**
  - Death or Nonfatal MI

- **Relative Risk**
  - UFH: 0.83 (0.77 to 0.90)
  - Enoxaparin: 0.99 (0.95 to 1.03)

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**Recommendations**

- **C**
  - UFH x 48 hrs

- **B**
  - Enoxaparin (adj for age & CrCl) x dur of hosp or 8 days
  - Fondaparinux x duration of hosp or 8 days
Recommendation
Anticoagulant Therapy w/ PCI

- UFH
- Bivalirudin

If at high risk of bleeding, bivalirudin is reasonable

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Bivalirudin vs. UFH + GPI for 1° PCI

Stone GW et al. for the HORIZONS-AMI Investigators. NEJM 2008;358:2218-28

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Beta-Blockers: Clinical Data

1884 Patients 1-4 weeks after acute MI
Randomized to β-blocker vs. placebo

- 48% risk reduction P=0.0001
- 28% risk reduction P=0.0006


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PROVE IT – TIMI 22

4162 patients hospitalized w/in prior 10 d for ACS

- Pravastatin 40 mg (avg achieved LDL = 95 mg/dl)
- Atorvastatin 80 mg (avg achieved LDL = 62 mg/dl)
- 16% RR (P = 0.005)

Cannon et al. NEJM 2003; 350: 1495

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ACE Inhibitors Post-MI with EF <40% but asx

- 19% Reduction in Mortality P = 0.019


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ACE Inhibitors in All Acute MI

Greater apparent benefit in anterior STEMI than in inferior STEMI or NSTEACS

**Aldosterone Antagonists**

6632 patients with recent MI, heart failure, and ejection fraction <40%

**Discharge Checklist**

**Risk Factor Modification**
1. Low chol (<200 mg/dl) and low fat (<7% saturated) diet
2. LDL goal <70 mg/dl
3. HDL >40 mg/dl
4. BP <140/90, <130/80 if DM or CKD
5. Smoking cessation
6. If DM, HbA1c <7%
7. Exercise (≥30 min 3-4 x per wk)
8. BMI goal 18.5-24.9 kg/m²

**Medical Therapy**
1. Aspirin 81-162 mg/d for life
2. ADP Receptor blocker for 12 mos
3. β-Blocker
4. Statin high-intensity lipid-lowering (eg, atorva 80 mg qd)
5. ACEI if CHF, EF<0.40, HTN, DM; 4-6 wks or at least until hosp d/c in all STEMI; 7 in all CAD
6. Aldo antag if EF <40% & CHF
7. Nitrates standing if sx, prn for all

**Question #1**

A 62 year old man presents approximately 2 hours after the onset of severe substernal chest pain. A 12-lead ECG reveals ST-elevation V1-V4. The hospital does not have ready access to a cardiac catheterization laboratory, so fibrinolytic Rx is chosen.

In addition to tenecteplase and aspirin, you should also:

a. UFH and low-level stress test before discharge
b. Fondaparinux and transfer for immediate cath
c. Clopidogrel 300 mg load, then 75 mg daily + enoxaparin and transfer for cath
d. Clopidogrel 600 mg load + bivalirudin and low-level stress test before discharge
e. Abciximab + unfractionated heparin and transfer for cath

**Question #2**

A 67 year old diabetic woman presents with substernal chest pain at rest for 15 minutes that, after beta-blocker and nitrates, has partially but not completely resolved. A 12-lead ECG reveals inferior ST-segment depressions. Cardiac troponin is elevated.

In addition to ASA, the most appropriate treatment strategy would be:

a. UFH, GP 2b/3a inhibitor, stress test in 24-48 hrs
b. Clopidogrel, bivalirudin, stress test in 24-48 hrs
c. Clopidogrel, fondaparinux, cardiac catheterization that day
d. Enoxaparin, cardiac catheterization in 48 hrs
e. UFH, cardiac cath w/in 12-24 h, prasugrel ± GP 2b/3a if PCI
Key References

- Wright et al. *Circulation* 2011;123:2022-60