Acute Coronary Syndromes

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Conflicts of Interest

- Consultant: Medicure in 2014

Objectives

- Describe a Comprehensive Algorithm for ACS
  - Based on the ACC/AHA Guidelines

- Discuss the Management
  - STEMI
  - NSTE-ACS

What do you need to know about ACS for the IM Boards?

ACC/AHA Guidelines

- Class I
  - Benefit >>> Risk
  - Procedure/Treatment SHOULD be performed/administered

- Class IIa
  - Benefit >> Risk
  - Additional studies with focused objectives needed
  - IT IS REASONABLE to perform procedure/administration

- Class IIb
  - Benefit ≥ Risk
  - Additional studies with broad objectives needed; Additional registry data would be helpful
  - Procedure/Treatment MAY BE CONSIDERED

- Class III
  - Risk ≥ Benefit
  - No additional studies needed
  - Procedure/Treatment SHOULD NOT be performed/administered
  - SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL

Clinical Vignette

- 64 year old male
- History of Dyslipidemia and arthritis
- Severe chest pain after bike ride

EMS EKG
Protocols Use Risk Stratification

**ACUTE CORONARY SYNDROME PROTOCOL**

- **STEMI on ECG?**
  - Yes: Activate STEMI Protocol
  - No: 
    1. ASA 120 mg x 1 x 1? Yes: Admit to CABG Unit and Activate CD/CP Protocol
    2. Troponin T x 1:90 or cTnT x 0.07? Yes: Admit to CABG Unit and Activate CD/CP Protocol
    3. Ruptured plaque with occlusive thrombus

**Diagnosis: EKG Early Risk Stratification**

- 12-lead ECG within 10 min of arrival

**Protocols Use Risk Stratification**

- If the initial ECG is not diagnostic but remains symptomatic, serial ECGs should be performed

**STEMI: Pathophysiology**

- RCA
  - Ruptured plaque with occlusive thrombus
**STEMI Protocol**

1. ASA 325 mg PO once
2. Clopidogrel 600 mg PO, Ticagrelor 180 mg, or Prasugrel 60 mg PO once
3. Heparin 60 Units/Kg (max 5,000 units) IV bolus
4. Direct transfer to cardiac cath lab for Primary PCI

**Clinical Vignette**

**Coronary Angiography**

ASA 325mg, Clopidogrel 600mg, UFH 60 U/kg Upstream

**Occluded Right Coronary**

**Radial Access Reduces Mortality in STEMI**

Meta-analysis 5,055 patients with STEMI

**Protocols Use Risk Stratification**

**ACUTE CORONARY SYNDROME PROTOCOL**

1. Positive Troponin cTnT or cTnI > 0.01 mg/L if not admitted emergently
2. PCI if patient has 3 vessels disease
3. Cardiogenic shock or heart failure or extreme/isolated ST elevation

**STEMI 3 Randomized Trials of PCI vs. Lysis**

<table>
<thead>
<tr>
<th>Event Rate</th>
<th>PCI</th>
<th>Lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7.0%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>6.8%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>1.0%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

**Keeley, Grines, Lancet 2003;361:13-20**
Protocols Use Risk Stratification

**ACUTE CORONARY SYNDROME PROTOCOL**

1. STEMI on ECG, non-STEMI, or serial report ECG?
   - Yes: Activate STEMI Protocol
   - No: Admit to observation Unit and Activate CD Protocol

   **Nitroglycerin** (NTG 0.4 mg every 5 min for a total of 3 doses)
   - Dilates coronary vessels—increases blood flow
   - Reduces systemic vascular resistance and preload
   - Careful with hypotension or RV infarction

   Protocols Use Risk Stratification

**Aspirin in ACS**

- **n=54,089**
- **Category of trial**
  - **MI, Stroke, or Vascular Death**
  - **Odds ratio & CI (Antiplatlet: Controls)**
  - **% odds reduction (SD)**

<table>
<thead>
<tr>
<th>Category</th>
<th>N of trials</th>
<th>MI, Stroke, or Vascular Death</th>
<th>Antiplatlet: Controls</th>
<th>% odds reduction (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI</td>
<td>11360/6677 (13.7%)</td>
<td>1693/1614 (17.1%)</td>
<td>11.5% (1.2%)</td>
<td>25%</td>
</tr>
<tr>
<td>Acute MI</td>
<td>9320/3838 (10.6%)</td>
<td>1348/3635 (14.4%)</td>
<td>11.9% (1.2%)</td>
<td>29%</td>
</tr>
<tr>
<td>Prior Stroke/TIA</td>
<td>1065/5837 (18.4%)</td>
<td>301/5870 (22.2%)</td>
<td>11.6% (1.2%)</td>
<td>45%</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>1823/1567 (9.1%)</td>
<td>285/2027 (14.1%)</td>
<td>11.6% (1.2%)</td>
<td>45%</td>
</tr>
</tbody>
</table>

**ACS Initial Acute Therapy**

- **Nitroglycerin** (NTG 0.4 mg every 5 min)
  - Dilates coronary vessels—increases blood flow
  - Reduces systemic vascular resistance and preload
  - Careful with hypotension or RV infarction

Protocols Use Risk Stratification
A 75 year old woman with a past medical history significant for hypertension, dyslipidemia, and diabetes presents to the ED 4 hours after the onset of stuttering, severe substernal chest pain with radiation to the left arm and jaw, associated with diaphoresis. After 2 SL NTG, the patient is chest pain free. The initial troponin is 8ng/mL. There are no significant EKG changes. There are no contraindications to anticoagulation. The patient is treated with ASA, oral blocker, and high dose statin therapy.

What is the best management strategy?
A. Start enoxaprin and initiate a conservative management strategy.
B. Start enoxaparin and proceed with immediate coronary angiography.
C. Start prasugrel, abciximab, and unfractionated heparin and proceed with coronary angiography in 24-48 hours.
D. Start unfractionated heparin and clopidogrel and proceed with coronary angiography in 24-48 hours.
Anticoagulant Therapy

Unfractionated Heparin can be administered for patients with NSTE-ACS in whom either an early invasive or physiology guided strategy is selected.

What about Low Molecular Weight Heparins?

- Shortened polysaccharide sequence
- Better bioavailability
- Longer half-life
- Anti-thrombin effect through Anti-Xa and small anti-II activity
- Requires dose adjustment in renal failure

Outcomes Similar with LMWH & UFH

9% RRR in MACE vs. UFH in ACS (NNT=107)

ACS: NSTE-ACS Protocol

- Admit to CCU
- Start of Dual Anti-platelet Therapy: NOC
- Non-invasive Stress Testing
- Admission to Invasive Unit
- Outcomes related to ischemia or shock
- Left heart catheterization within 72 hours
- No
- No
- Yes

Formation of Thrombus

1. Adhesion
2. Activation
3. Aggregation
4. Platelet Plug

ACC/AHA NSTE-ACS Guidelines: Initial Invasive or Conservative Strategy

In addition to ASA, dual anti-platelet therapy should be administered as soon as possible after admission and ideally up to 1 year with either:

- Clopidogrel
- Ticagrelor
ACC/AHA NSTE-ACS Guidelines: Initial Invasive or Conservative Strategy

In addition to ASA, dual anti-platelet therapy should be administered as soon as possible after admission and ideally up to 1 year with either:

- Clopidogrel
- Ticagrelor

Accrual data >> ASA

Metabolic Syndrome

ACC/AHA NSTE-ACS Guidelines: Initial Invasive or Conservative Strategy

ACC/AHA NSTE-ACS Guidelines: Initial Invasive or Conservative Strategy

Meta-Analysis of Clopidogrel Pretreatment

Pretreatment Reduces MACE

N=37,814 patients from 6 RCT and 9 observational studies

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>No Pretreatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>9.8%</td>
<td>12.3%</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.6%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

ACS benefit more than elective PCI

Pretreatment Reduces MACE

Bellemain-Appaix. JAMA 2012; 308 (23):2507-2516

What about “upstream” GPIs in ACS?

Upstream GPIs Omitted

1. Unstable angina—EPIC with Gensini score (1-3) followed by weight-based protocol
2. Clopidogrel or Ticagrelor loading dose followed by daily maintenance dose
3. Holter monitor data (inhouse arrhythmias) over 24 hours
4. NSTEMI: Loading dose followed by clopidogrel 75 mg/day
5. Candidate for PCI with high-risk features

Routine Upstream GPI vs. Deferred GPI at PCI

No Benefit to Upstream GPI: EARLY ACS Trial

Routine Upstream GPI vs. Deferred GPI at PCI

10,500 patients with high-risk NSTEMI

No Benefit to Upstream GPI: EARLY ACS Trial

Routine Upstream GPI vs. Deferred GPI at PCI

10,500 patients with high-risk NSTEMI

Death, MI, uTVR TBO (%)
Antiplatelet therapy with both clopidogrel and an upstream GPI may be considered for those with high risk.

High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use.

NO MORPHINE!!!
Troponin Only Serial Testing

- Troponin ONLY at 0, 3, and 6 hours

Goal
- Earlier Detection of AMI
- Earlier “rule out” of AMI
- Earlier directed therapy and hospital discharge
- Reduce Costs

Troponin is Superior to Other Biomarkers in the Early Diagnosis of AMI

1,818 patients with suspected AMI

ROC Curves

Keller. NEJM. 2009; 361: 868-77

Troponin at 3 and 6 Hours Identifies 100% of AMI

1,818 patients with suspected AMI

Keller. NEJM. 2009; 361: 868-77

Does CK-MB Add Anything?

- Cost
- Confusion
- Quality Control issues
- Machine-to-machine variability

ACS: NSTE-ACS Protocol

Amsterdam. JACC 2014; 64: 139-228
Immediate Invasive Strategy in NSTE-ACS

Immediate (within 2 hours) invasive strategy is indicated in patients with ongoing angina or hemodynamic or electrically instability.

NO MORPHINE!!!
An early invasive PCI strategy is indicated in initially stabilized patients with NSTE-ACS who have an elevated risk for clinical events.

Recurrent MI
Early Invasive Compared With Conservative Therapy
Mean Follow-Up of 2 yr

Mortality
Early Invasive Compared With Conservative Therapy
Mean Follow-Up of 5 yr

P2Y₁₂ Inhibitor Therapy for ACS
2011 ACC/AHA PCI Guidelines

Which Patients with ACS should get the “Second Generation” P2Y₁₂ Antagonists: Prasugrel or Ticagrelor?
Prasugrel

**PY**₁₂, Inhibitor

Following oral administration, ≥79% of the dose is absorbed, with peak plasma concentrations of the active metabolite occurring approximately 30 minutes after dosing.

**Prasugrel in ACS**

TRITON-TIMI 38

13,608 patients with moderate-to-high risk ACS undergoing PCI

Randomized after Angiography


Full dose prasugrel is contraindicated for all of the following patients except:

A. History of stroke/TIA
B. Creatine Clearance<30 ml/min
C. Age >75 years
D. Weight<60kg

No Benefit to Prasugrel with High Bleeding Risk

Real world registry data from 27,533 patients receiving prasugrel from NCDR PINNACLE registry found 18.4% received prasugrel with these contraindications


All of the following are true about Ticagrelor except:

A. Ticagrelor does not require metabolic activation

B. Results in greater inhibition of platelet aggregation than clopidogrel

C. Has greater efficacy with higher doses of aspirin

Ticagrelor
P2Y₁₂ Antagonist

- Direct acting
  Not a prodrug; does not require metabolic activation
  Rapid onset of inhibitory effect on the P2Y₁₂ receptor
  Greater inhibition of platelet aggregation than clopidogrel

- Reversibly bound
  Faster offset of effect than clopidogrel

CV death, MI or Stroke:
PLATO TRIAL

Wallentin. NEJM. 2009

Major Bleeding

Wallentin. NEJM. 2009
### No Benefit to Ticagrelor in North America

**CV Death, MI, Stroke**

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Total patients</th>
<th>KM at month 12</th>
<th>Clop</th>
<th>Tic</th>
<th>HR (95% CI)</th>
<th>Interaction p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia / Australia</td>
<td>1714</td>
<td>11.4</td>
<td>14.8</td>
<td>0.80</td>
<td>(0.61, 1.04)</td>
<td>0.045</td>
</tr>
<tr>
<td>Central America / South America</td>
<td>1237</td>
<td>15.2</td>
<td>17.9</td>
<td>0.86</td>
<td>(0.65, 1.13)</td>
<td>0.01</td>
</tr>
<tr>
<td>Europe / Middle East / Africa</td>
<td>13859</td>
<td>8.8</td>
<td>11.0</td>
<td>0.80</td>
<td>(0.72, 0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>North America</td>
<td>1814</td>
<td>11.9</td>
<td>9.6</td>
<td>1.25</td>
<td>(0.93, 1.67)</td>
<td></td>
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Clopidogrel better

**Interaction p-values**

<table>
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<tr>
<th>HR (95% CI)</th>
<th>0.80 (0.61, 1.04)</th>
<th>0.86 (0.65, 1.13)</th>
<th>0.80 (0.72, 0.90)</th>
<th>1.25 (0.93, 1.67)</th>
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</thead>
</table>

### Thank You

**Wallentin, NEJM. 2009**

**WARNING**: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).