Progress in Non-ST-Elevation Acute Coronary Syndromes (NSTE ACS)

Shawn Hansen, Pharm.D.
Cardiovascular Pharmacotherapy
Ministry Heart Care-St. Joseph’s Hospital
Marshfield, WI

Outline

• Defining ACS
• Contemporary Treatment Issues in NSTE ACS
  - Risk stratification: who should go to PCI?
  - Which heparin (LMWH or UFH)?
  - GP IIb/IIIa blockers?
  - Clopidogrel?

Change in U.S. Life Expectancy between 1970 and 2000


Spectrum of Acute Coronary Syndromes

Medical Stabilization and/or PCI
Thrombus formation

- Platelet
- Red cells
- Fibrin
- Plaque rupture

Spectrum of Acute Coronary Syndromes

- Acute Coronary Syndromes
  - Non-ST-segment Elevation ACS
  - ST-segment Elevation ACS (STEMI)
  - Unstable Angina
  - NSTEMI

1.8 million/yr

0.4 million/yr

6-month Mortality for ACS

- ST ↓ 8.9%
- ST ↑ MI with fibrinolytics 6.8%
- T-wave inversion 3.4%

Granger CB et al. J Am Coll Cardiol. 1998; 31:79A.

Evolution of the ACC/AHA Guidelines For NSTE ACS

- Version 1: 1994
- Version 2: Sept 2000
  - CURE
  - TACTICS-TIMI 18
  - ESPRIT
  - TARGET
  - GUSTO IV ACS
- Version 3: June 2002
  - INTERACT
  - CREDO
  - A to Z
  - GRACE

http://www.acc.org/clinical/guidelines/unstable/exec_summary/update_index.htm
Outline

• Defining ACS
• Contemporary Treatment Issues in NSTE ACS
  - Risk stratification: who should go to PCI?
  - Which heparin (LMWH or UFH)?
  - GP IIb/IIIa blockers?
  - Clopidogrel?

Patients Requiring an Early Invasive Management Strategy

<table>
<thead>
<tr>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New or presumably new ST-segment depression</td>
<td>Recurrent angina or ischemia at rest despite anti-ischemia therapy</td>
<td>Recurrent angina or ischemia at rest with CHF, S3, gallop, pulmonary edema, worsening railes, new/worsening mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>Elevated cardiac troponin</td>
<td>↓ LV function</td>
<td>Hemodynamic instability; angina at rest with BP ↓</td>
</tr>
<tr>
<td></td>
<td>Prior PCI (&lt; 6 months) or prior CABG</td>
<td>Patient with repeat ACS</td>
<td></td>
</tr>
</tbody>
</table>

TIMI Risk Score For NSTE ACS

7 Independent Predictors

• Age ≥ 65 years
• > 3 CAD risk factors (↑ chol, FHx, HTN, DM, smoking)
• Prior CAD (cath stenosis >50%)
• ASA in last 7 days
• ≥ 2 anginal events ≤ 24 hours
• ST deviation ≥0.5mm (depression or transient elevation)
• Elevated cardiac markers (CK-MB or Troponin)

TIMI Risk Score For UA/NSTEMI*

*Also known as non–Q-wave MI.

Troponin Levels Predict the Risk of Mortality in Acute Coronary Syndromes

Death, MI, Rehosp for ACS at 6 Months

TACTICS: Early Invasive Strategy Trumps Early Conservative Strategy

Download → www.acci.tv


CRUSADE: Unadjusted Mortality By Early Cath (w/in 48 Hrs)

<table>
<thead>
<tr>
<th>NO cath within 48 hours (n = 7,179)</th>
<th>YES cath within 48 hours (n = 9,462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% In-hospital Mortality</td>
<td>% In-hospital Mortality</td>
</tr>
<tr>
<td>10%</td>
<td>7.2%</td>
</tr>
<tr>
<td>9%</td>
<td>2.0%</td>
</tr>
<tr>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

A 72%↓ P < 0.0001

SIRIUS: Event-Free Survival

Outline

- Defining ACS
- Contemporary Treatment Issues in NSTE ACS
  - Risk stratification: who should go to PCI?
  - Which heparin (LMWH or UFH)?
  - GP IIb/IIIa blockers?
  - Clopidogrel?

ACS: Targeting platelets and fibrin
Enoxaparin is preferable to UFH in patients without renal failure and unless CABG is planned within 24 hours.

**Which Antithrombin in NSTE ACS?**

<table>
<thead>
<tr>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Enoxaparin is preferable to UFH in patients without renal failure and unless CABG is planned within 24 hours.

**ACS LMWH Trials**

*Composite Endpoint at Day 14*

| TRXIS (fraxiparin) | 3.9% (P=NS) |
| FRIC (dalteparin) | 0% |
| TIMI 11B (enoxaparin) | 14.5% (P=0.03) |
| ESSENCE (enoxaparin) | 16.2% (P=0.02) |

<table>
<thead>
<tr>
<th>LMWH Better</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH Better</td>
<td>0%</td>
<td>-5%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

**GrACE Registry (n=13,231)**

*Hospital Outcomes in ACS Patients on LMWH vs UFH*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>LMWH (%)</th>
<th>UFH (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3.9</td>
<td>6.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>2.1</td>
<td>4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7</td>
<td>1.2</td>
<td>0.0167</td>
</tr>
<tr>
<td>Re MI</td>
<td>1.6</td>
<td>3.0</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

**Outline**

- Defining ACS
- Contemporary Treatment Issues in NSTE ACS
  - Risk stratification: who should go to PCI?
  - Which heparin (LMWH or UFH)?
    - GP IIb/IIIa blockers?
    - Clopidogrel?

**Enoxaparin Meta-analysis**

*Triplet Composite Event Rates*

<table>
<thead>
<tr>
<th>Odds Ratio (95% CI)</th>
<th>ENOX</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A to Z (7 days)</td>
<td>8.4%</td>
<td>8.4%</td>
</tr>
<tr>
<td>INTERACT (7 days)</td>
<td>6.3%</td>
<td>8.6%</td>
</tr>
<tr>
<td>TIMI 11B (8 days)</td>
<td>12.4%</td>
<td>14.8%</td>
</tr>
<tr>
<td>ESSENCE (8 days)</td>
<td>9.2%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

**Platelet Activation**

*Smooth discoid shape of resting platelets*  
*Spiny spheroid shape of activated platelets*


Permission obtained from the Center for Biomedical Research, University of Vienna.
**Platelet Activation**

- Thrombin
- Collagen
- ADP
- Epinephrine
- Serotonin
- TXA2

**GP IIb/IIIa Blockers in NSTE ACS**

<table>
<thead>
<tr>
<th>GP IIb/IIIa</th>
<th>IIa</th>
<th>IIb/IIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- If PCI planned: Eptifibatide, Tirofiban or Abciximab (begin immediately in ED)
- High-risk patient managed medically (i.e. no PCI): Eptifibatide or Tirofiban (begin immediately in ED)
- Low risk patient managed medically: Eptifibatide or Tirofiban
- Abciximab is not recommended if PCI is not planned

**Early Initiation of GP IIb-IIIa Inhibition is Associated with Lower Mortality**

- No Early GP IIb-IIIa Inhibitor* (n = 14,892)
  - 46% RRR
  - *P < 0.0001
- Early GP IIb-IIIa Inhibitor (n = 6,761)

*Includes patients who received late GP IIb-IIIa inhibitor (> 24 hrs) therapy.
Outline

- Defining ACS
- Contemporary Treatment Issues in NSTE ACS
  - Risk stratification: who should go to PCI?
  - Which heparin (LMWH or UFH)?
  - GP IIb/IIIa blockers?
    - Clopidogrel?

CURE Study Design

- 12,562 Patients, 28 countries
- NSTE ACS
- symptom onset < 24 hours

randomize

Aspirin 75-325mg qd
Placebo

Aspirin 75-325mg qd
Clopidogrel
300mg LD, then 75mg qd

3-12 months

Death, MI or Stroke

Platelet Activation

Thrombin
Collagen
ADP
Epinephrine
Serotonin
TXA2

GPIIb/IIIa

Abciximab
Eptifibatide
Tiroliban

Oral Antiplatelet Therapies in NSTE ACS

<table>
<thead>
<tr>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Aspirin (if not contraindicated)

- Clopidogrel for at least 1 month
- Clopidogrel for up to 9 months
- Withhold clopidogrel if CABG is planned within 5-7 days


Platelet Activation

GPIIb/IIIa

Antiplatelet Drugs

Aspirin (if not contraindicated)

- Clopidogrel for at least 1 month
- Clopidogrel for up to 9 months
- Withhold clopidogrel if CABG is planned within 5-7 days


Cumulative Hazard Rates for Cardiovascular Death / MI / Stroke

No. of patients
Placebo 6303 5780 4664 3600 3644 2388
Clopidogrel 6339 5866 4779 3844 2418


Relative Risk 0.80
P<0.001

CURE

Clopidogrel in the 1st 24 Hours

CV Death, MI, Stroke, Severe Ischemia

33% RRR


Placebo + ASA

Clopidogrel + ASA

P=0.002

Hours After Randomization
### CURE Study

#### Bleeding Results

<table>
<thead>
<tr>
<th>Event</th>
<th>Clopidogrel + ASA*</th>
<th>Placebo + ASA*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding†</td>
<td>3.7%</td>
<td>2.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>2.2%</td>
<td>1.8%</td>
<td>0.13</td>
</tr>
<tr>
<td>Other major bleeding</td>
<td>1.6%</td>
<td>1.0%</td>
<td>0.005</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>5.1%</td>
<td>2.4%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Other standard therapies were used as appropriate.
†Life-threatening and other major bleeding
PLAVIX Prescribing Information.

### Potential Cumulative Effect of Four Simple Secondary-Prevention Treatments

#### The Fab Four

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk Reduction</th>
<th>2-year Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>- - -</td>
<td>8%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25%</td>
<td>6%</td>
</tr>
<tr>
<td>β-blockers</td>
<td>25%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>30%</td>
<td>3%</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Yusuf S. Lancet 2002;360:2-3

### Acute care results from CRUSADE

#### Compliance with the ACC/AHA Guidelines is Associated with Lower Mortality

CRUSADE Investigators, AHA 2002