Acute Coronary Syndromes
for the Hospitalist

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Management of the Hospitalized Patient

• No conflicts of interest
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes

Developed in Collaboration with the Society of Thoracic Surgeons and Society for Cardiovascular Angiography and Interventions

Endorsed by the American Association for Clinical Chemistry

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Topics for today

• ACS Definition
• Management of NSTEMI
  – Invasive vs. Non-invasive strategies
  – Anti-platelet therapies
  – Anti-coagulant
  – Gp IIb/IIIa inhibitor
• STEMI
• Duration of anti-platelet therapy
• Secondary prevention measures
Hospitalizations in the U.S. Due to Acute Coronary Syndromes (ACS)

Acute Coronary Syndromes*

1.17 Million Hospital Admissions

Unstable Angina

0.43 million Admissions per year

Myocardial Infarction

0.73 million Admissions per year

Heart Disease and Stroke Statistics - 2011 Update. Circulation 2011
*Primary and secondary diagnoses.
Universal Definitions of MI

- **Type 1**: Spontaneous MI related to ischemia due to a primary coronary (e.g., plaque erosion and/or rupture)
- **Type 2**: MI from ischemia due to either \(\uparrow\) O2 demand or \(\downarrow\) supply, e.g., spasm, embolism, anemia, arrhythmias, hypertension.
- **Type 3**: Sudden unexpected death likely from MI.
- **Type 4a**: MI associated with PCI.
- **Type 4b**: MI associated with stent thrombosis
- **Type 5**: MI associated with CABG.

Timing of Release of Various Biomarkers After Acute Myocardial Infarction

- Remember, not all troponin elevations are ACS!
- History is key to diagnosis
- Recognize pattern – typical rise and fall
Incidence of MI Over Past Decade

Yeh RW et al. NEJM 2010;362:2155-2165

Decline in Mortality Following MI

Yeh RW et al. NEJM 2010;362:2155-2165
Initial Evaluation and Management of UA/NSTEMI

SYMPTOMS SUGGESTIVE OF ACS

- **Noncardiac Diagnosis**
  - Treatment as indicated by alternative diagnosis

- **Chronic Stable Angina**
  - ACC/AHA Chronic Stable Angina Guidelines

- **Possible ACS**
  - Observation ≥ 12 h from symptom onset
  - No recurrent pain; negative follow-up studies
  - Stress study to prove ischemia
    - Consider evaluation of LV function if ischemia is present (tests may be performed either prior to discharge or as outpatient)

- **Definite ACS**
  - ST and/or T wave changes
  - ST-Elevation
  - Hemodynamic abnormalities
  - Evaluate for reperfusion therapy
  - ACC/AHA STEMI Guidelines

- **Possible ACS**
  - Recurrent ischemic pain or positive follow-up studies
  - Diagnosis of ACS confirmed

- **Definite ACS**
  - Admit to hospital
  - Manage via acute ischemia pathway

Algorithm for evaluation and management of patients suspected of having ACS. Anderson JL, et al. J Am Coll Cardiol 2007;50:e1–e157, Figure 2.
Initial Steps in NSTEMI ACS Management

1. Assess Likelihood of CAD
2. Risk stratification
3. Target therapy: More aggressive Rx in higher risk patients
4. Anti-ischemic, Anti-platelet, and Antithrombotic Rx
5. Invasive vs. Conservative Strategy

Likelihood of ACS Secondary to CAD

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Likelihood Any below:</th>
<th>Intermediate Likelihood No high-likelihood features but any below:</th>
<th>Low Likelihood No high- or intermediate-likelihood features but may have:</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Typical angina Known hx of CAD, including MI</td>
<td>Probable angina Age&gt;70 years Male DMr</td>
<td>Atypical symptoms</td>
</tr>
<tr>
<td>Examination</td>
<td>CHF</td>
<td>PVD, CVA</td>
<td>Pain on palpation</td>
</tr>
<tr>
<td>ECG</td>
<td>New ECG Δs</td>
<td>Old ECG abnormalities</td>
<td>Normal ECG</td>
</tr>
<tr>
<td>Cardiac Markers</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Three Principal Presentations of UA

<table>
<thead>
<tr>
<th>Class</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest angina*</td>
<td>Angina occurring at rest and prolonged, usually greater than 20 min</td>
</tr>
<tr>
<td>New-onset angina</td>
<td>New-onset angina of at least CCS class III severity</td>
</tr>
<tr>
<td>Increasing angina</td>
<td>Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by 1 or more CCS class to at least CCS class III severity)</td>
</tr>
</tbody>
</table>


TIMI Risk Score For UA/NSTEMI

7 Independent Predictors

1. Age ≥ 65 years
2. > 3 CAD risk factors (high cholesterol, family history, hypertension, diabetes, smoking)
3. Prior coronary artery disease (stenosis > 50%)
4. ST-segment deviation on the ECG
5. ≥ 2 anginal events ≤ 24 hours
6. ASA in last 7 days
7. Elevated cardiac biomarkers (troponin or CK-MB)

TIMI Risk Score For UA/NSTEMI

UFH Group TIMI 11B (N= 1957)

\( \chi^2 \text{ trend } P < 0.001 \)

Number of Risk Factors

% Pts: 4.3 17.3 32.0 29.3 13.0 3.4


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GRACE Risk Score for In-Hospital Mortality

- Killip Class
- Blood pressure, heart rate
- Age
- Scr
- Cardiac arrest, ST deviation, ↑ biomarkers

For example, a patient has Killip class 3, SBP of 100 mm Hg, heart rate of 100 beats/min, is 65 years of age, has serum creatinine level of 1 mg/dl, and does not have a cardiac arrest at admission. The corresponding GRACE score would be (3 x 10 + 8 x 5 + 16 x 5) + (38 x 14) = 106.

Granger CB et al. Arch Intern Med 2003;163:2345-2353
GRACE Risk Score for All-Cause Mortality From Discharge to 6 Months

Eagle KA et al. JAMA 2004;291:2727-2733

Early Hospital Care
Anti-Ischemic Therapy

Class I
- Bedrest and Telemetry
- Oxygen (maintain saturation > 90%)
- Nitrates (SLx3 Oral/topical. IV for ongoing ischemia, heart failure, hypertension
- Oral β-blockers in first 24-hours if no contraindications (intravenous β-blockers class Ila indication)
- Non-dihydropyridine Ca-channel blockers for those with CI to β-blockers
- ACE inhibitors in first 24-hours for heart failure or EF<40% (class Ila for all other pts)
- ARBs for those with ACE-inhibitor intolerance
- Statin

Courtesy of Mayo Clinic
Topics for today

• ACS Definition
• Management of NSTEMI
  – Invasive vs. Non-invasive strategies
  – Anti-platelet therapies
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  – Gp IIb/IIIa inhibitor
• STEMI
• Duration of anti-platelet therapy
• Secondary prevention measures
General Considerations in Deciding Between an Early Invasive Strategy and an Initial Conservative Strategy in UA/NSTEMI

<table>
<thead>
<tr>
<th>Early Invasive Strategy Generally Preferred</th>
<th>Initial Conservative Strategy Generally Preferred or Reasonable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recurrent angina or ischemia at rest or with low level activities despite intensive medical therapy</td>
<td>• Low risk score (e.g., GRACE, TIMI)</td>
</tr>
<tr>
<td>• Elevated cardiac biomarkers (TnT or TnI)</td>
<td>• Absence of high-risk features</td>
</tr>
<tr>
<td>• New or presumably new ST-depression</td>
<td>• High risk for catheterization-related complications</td>
</tr>
<tr>
<td>• Signs or symptoms of heart failure</td>
<td>• Patient not a revascularization candidate (with either PCI or CABG)</td>
</tr>
<tr>
<td>• Hemodynamic instability</td>
<td>• Patient prefers conservative therapy</td>
</tr>
<tr>
<td>• High risk score (e.g., GRACE, TIMI)</td>
<td></td>
</tr>
<tr>
<td>• Sustained ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>• PCI within 6 mo</td>
<td></td>
</tr>
<tr>
<td>• Prior CABG</td>
<td></td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>• Mild to moderate renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>• Reduced LV function (LVEF &lt;40%)</td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk of All-Cause Mortality for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 2 y

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths, n</th>
<th>Follow-up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC-II</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>TRUCS</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>TIMI-18</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>VINO</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>RITA-3</td>
<td>102</td>
<td>60</td>
</tr>
<tr>
<td>ISAR-COOL</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ICTUS</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>

Overall RR (95% CI) 0.75 (0.60-0.90) 0.1 favors Early Invasive Therapy 1 favors Conservative Therapy

Relative Risk of Recurrent Nonfatal MI for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 2 y

<table>
<thead>
<tr>
<th>Study</th>
<th>Events, n</th>
<th>Invasive</th>
<th>Conservative</th>
<th>Follow-up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC-II</td>
<td>111</td>
<td>3</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>TRUCS</td>
<td>53</td>
<td>100</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>TIMI-18</td>
<td>2</td>
<td>100</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>VINO</td>
<td>46</td>
<td>57</td>
<td>60</td>
<td>60</td>
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<tr>
<td>RITA-3</td>
<td>12</td>
<td>21</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ISAR-COOL</td>
<td>90</td>
<td>59</td>
<td>12</td>
<td>12</td>
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</tbody>
</table>

Overall RR (95% CI) 0.83 (0.72-0.96)

Relative Risk of Recurrent UA Resulting in Rehosp for Early Invasive Therapy Compared With Conservative Therapy at a Mean Follow-Up of 13 Months

<table>
<thead>
<tr>
<th>Study</th>
<th>Events, n</th>
<th>Invasive</th>
<th>Conservative</th>
<th>Follow-up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC-II</td>
<td>547</td>
<td>796</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>TRUCS</td>
<td>13</td>
<td>17</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>TIMI-18</td>
<td>123</td>
<td>152</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>VINO</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>RITA-3</td>
<td>58</td>
<td>106</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>ICTUS</td>
<td>44</td>
<td>64</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Overall RR (95% CI) 0.69 (0.66-0.74)
TIMACS
3031 Patients with NSTE ACS
Cath w/in 24 h (median 14 h) or >36 h (median 50 h)

Mehta SR et al. NEJM 2009;360:2165-75

Timing of Intervention in ACS (TIMACS)
Early (<24hr) vs Delayed (>36)

Kaplan-Meier Cumulative Risk of the Death, MI or Stroke
Stratified by Baseline GRACE Risk Score: Low (≤140) vs High Risk (>140)

Mehta SR et al. NEJM 2009;360:2165-2175
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Coagulation Cascade and Antithrombins

Extrinsic Pathway (Tissue Factor)
  TF, FVII

Intrinsic Pathway (Contact Factor)
  FXII, FXI, FIX, FVIII, Phospholipids, Ca²⁺

Factor X → Factor Xa → Thrombin (F IIa)

Direct Factor Xa inhibitors
  ATIII Fondaparinux

ATIII LMWH

ATIII UFH

Direct thrombin inhibitors

Fibrin Formation

Prothrombin (F II)

Platelet Aggregation

ASA
  Thienopyridines
  GP IIb/IIIa inhibitors

Bivalirudin
Milestones in ACS Management

<table>
<thead>
<tr>
<th>Anti-Thrombin Rx</th>
<th>Heparin</th>
<th>LMWH</th>
<th>Bivalirudin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Platelet Rx</td>
<td>Aspirin</td>
<td>GP Ib/IIa blockers</td>
<td>Clopidogrel</td>
<td>Prasugrel/Ticagrelor</td>
</tr>
</tbody>
</table>

Treatment Strategy

Conservative

Early Invasive

- PRISM-PLUS
- REPLACE 2
- PURSUIT
- CURE
- OASIS-5
- ISAR-REACT 2
- ESSENCE
- TACTICS TIMI-18
- SYNERGY
- ACUITY

PCI ~ 5% stents


Ischemic risk

Bleeding risk

Adapted from and with the courtesy of Steven Manoukian, MD.

Platelet-mediated Thrombosis Targets

- GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = thromboxane

No currently approved antiplatelet agents specifically target Adhesion

Most approved antiplatelet agents affect different aspects of platelet Activation

GP Ib/IIa inhibitors inhibit the “final common pathway,” Aggregation

Adapted from and with the courtesy of Steven Manoukian, MD.
Platelet Activation


Platelet Activation

Oral Anti-Platelet Therapies

CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

Patient Population
Patients with ACS* presenting within 24 hours

N=12,562

Loading Dose
Clopidogrel 300 mg + ASA 75–325 mg
Placebo + ASA 75–325 mg

Maintenance Dose
Clopidogrel 75 mg + ASA 75–325 mg
Placebo + ASA 75–325 mg

Primary End Point
Composite of death from cardiovascular causes, nonfatal MI, or stroke


CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events

Primary End Point:
MI/Stroke/CV Death (N=12,562*)

Placebo + ASA¹
Clopidogrel + ASA¹

20%
RRR
P=0.00009²

The primary outcome occurred in 9.3% of patients in the clopidogrel + ASA group and 11.4% in the placebo + ASA group.

* UA/NSTEMI
² Other standard therapies were used as appropriate
³ PLAXIS Prescribing Information, sand events U.S. LLC.
RRR relative risk reduction
Benefit of PLAVIX Is Consistent Whether or Not an Intervention Was Performed in CURE

**CURE: MI, Stroke, or CV Death***

<table>
<thead>
<tr>
<th>With Intervention</th>
<th>No Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.8%</td>
<td>11.4%</td>
</tr>
<tr>
<td>18% RRR (P=0.015)</td>
<td>10.0%</td>
</tr>
<tr>
<td>8.1%</td>
<td>20% RRR (P=0.0025)</td>
</tr>
</tbody>
</table>

Patients With PTCA and/or CABG (n=4,585)

- In the composite combined end point of nonfatal MI, stroke, CV death or refractory ischemia, RRR was 18% (CI: 0.78-0.85)

Patients Without PTCA and/or CABG (n=7,977)

- In the composite combined end point of nonfatal MI, stroke, CV death or refractory ischemia, RRR was 20% (CI: 0.98-0.99)

* Only first events after randomization were counted in the composite end point.

1. PLAVIX Prescribing Information sandr-aways U.S. LLC.
2. Data on file, sandr-aways U.S. LLC.

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**Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibitor With Prasugrel (TRITON)-TIMI 38**

- ACS (UA/NSTEMI or STEMI) and Planned PCI N=13,608
- Randomized Double-blind
- Prasugrel 60-mg LD/10-mg MD + Aspirin
- Clopidogrel 300-mg LD/75-mg MD + Aspirin
- Median duration of follow up = 14.5 months

- Primary efficacy endpoint:
  - Composite CV death, nonfatal MI, or nonfatal stroke
- Safety endpoints:
  - TIMI major or minor bleeding

Administration of the clopidogrel LD in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS.


Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.
Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

1. Efficacy Full Prescribing Information.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

In the overall study, approximately 40% of MIs occurred periprocedurally and were detected solely by changes in CK-MB.


Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.
Non-CABG TIMI Major or Minor Bleeding Risk by Age and Weight

<table>
<thead>
<tr>
<th>Weight</th>
<th>Age</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 kg</td>
<td>&lt;75 years</td>
<td>4.5 (0.3)*</td>
<td>3.4 (0.1)*</td>
</tr>
<tr>
<td>≥60 kg</td>
<td>&lt;75 years</td>
<td>6.5 (0.3)*</td>
<td>6.9 (0.1)*</td>
</tr>
<tr>
<td></td>
<td>≥75 years</td>
<td>4.2 (0.3)*</td>
<td>3.8 (0.2)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.3 (0.1)*</td>
<td>2.9 (0.1)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.8 (0.2)*</td>
<td>2.9 (0.1)*</td>
</tr>
</tbody>
</table>

* Rate of fatal bleeding

Effective Full Prescribing Information.

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.

Appropriate Patient Selection

- Based on TRITON-TIMI 38 data, prasugrel appears to be most appropriate for use in patients with ACS managed with PCI who:
  - Have no history of TIA/stroke
  - Are <75 years of age
  - Weigh ≥60 kg (132 lb)

Please see Important Safety Information, including Boxed Warning, and Full Prescribing Information provided.
Ticagrelor

- Oral direct inhibitor of P2Y12 ADP receptor
- Not a pro-drug
- Faster onset and offset than clopidogrel
- PLATO study randomized 18,624 patients with ACS to clopidogrel vs. ticagrelor

NEJM 2009 Sep 10;361(11):1045-57
Secondary efficacy endpoints over time

Myocardial infarction
- Clopidogrel: 6.9%
- Ticagrelor: 5.8%

HR 0.84 (95% CI 0.75–0.95), p=0.005

Cardiovascular death
- Clopidogrel: 5.1%
- Ticagrelor: 4.0%

HR 0.79 (95% CI 0.69–0.91), p=0.001

Total major bleeding

- Ticagrelor: 11.6%
- Clopidogrel: 11.2%

- Ticagrelor: 7.9%
- Clopidogrel: 7.7%

- Ticagrelor: 8.9%
- Clopidogrel: 8.9%

- Ticagrelor: 5.8%
- Clopidogrel: 5.8%

NS: Not significant
## Adverse effects

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventricular pauses &gt; 3 sec in first week, %</strong></td>
<td>5.8</td>
<td>3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Ventricular pauses &gt; 5 sec in first week, %</td>
<td>2.0</td>
<td>1.2</td>
<td>0.10</td>
</tr>
<tr>
<td>Ventricular pauses &gt; 3 sec at 30d, %</td>
<td>2.1</td>
<td>1.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Ventricular pauses &gt; 5 sec at 30d, %</td>
<td>0.8</td>
<td>0.6</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Syncope</strong></td>
<td>1.1</td>
<td>0.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>0.9</td>
<td>0.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4.4</td>
<td>4.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart Block</td>
<td>0.7</td>
<td>0.7</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Dyspnea – any</strong></td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea with discontinuation</td>
<td>0.9</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignant neoplasms</td>
<td>1.2</td>
<td>1.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Benign neoplasms</td>
<td>0.2</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Brilinta (Ticagrelor)

**FDA boxed warning**

"aspirin doses above 100 milligrams per day decrease the effectiveness of the medication."
Algorithm for Management of Patients With Definite or Likely NSTE-ACS

**NSTE-ACS: Definite or Likely**

**Ischemia-Guided Strategy**

- **Initiate DAPT and Anticoagulant Therapy**
  1. ASA (Class I; LOE: A)
  2. P2Y12 Inhibitor (in addition to ASA) (Class IIa; LOE: B):
     - Clopidogrel or Ticagrelor
  3. Anticoagulant:
     - UFH (Class III; LOE: B) or
     - Enoxaparin (Class IIa; LOE: A) or
     - Fondaparinux (Class IIb; LOE: B)

**Early Invasive Strategy**

- **Initiate DAPT and Anticoagulant Therapy**
  1. ASA (Class I; LOE: A)
  2. P2Y12 Inhibitor (in addition to ASA) (Class I; LOE: B):
     - Clopidogrel or Ticagrelor
  3. Anticoagulant:
     - UFH (Class I; LOE: B) or
     - Enoxaparin (Class IIa; LOE: A) or
     - Fondaparinux (Class IIb; LOE: B) or
     - Bivalirudin (Class I; LOE: B)

- Can consider GPI in addition to ASA and P2Y12 inhibitor in high-risk (e.g., troponin positive) pts (Class IIb; LOE: B)
  - Epifibatide
  - Tiroliban

**Medical therapy chosen based on cath findings**

**PCIs With Stenting**

- **Initiate/continue antiplatelet and anticoagulant therapy**
  1. ASA (Class I; LOE: B)
  2. P2Y12 Inhibitor (in addition to ASA):
     - Clopidogrel (Class I; LOE: B) or
     - Prasugrel (Class I; LOE: B) or
     - Ticagrelor (Class I; LOE: B)
  3. GPI (if not treated with bivalirudin at time of PCI)
     - High-risk features, not adequately pretreated with clopidogrel (Class IIa; LOE: A)
     - High-risk features adequately pretreated with clopidogrel (Class IIb; LOE: B)
  4. Anticoagulant:
     - Enoxaparin (Class I; LOE: A) or
     - Fondaparinux (Class I; LOE: A) as the sole anticoagulant (Class IIb; Harm: LOE: B) or
     - Bivalirudin (Class I; LOE: B)

**CABG**

- **Initiate/continue ASA therapy and discontinue P2Y12 and/or GPI therapy**
  1. ASA (Class I; LOE: B)
  2. Discontinue clopidogrel/ticagrelor 5 d before and prasugrel at least 7 d before elective CABG
  3. Discontinue clopidogrel/ticagrelor up to 24 h before urgent CABG (Class I; LOE: B)
     - May perform urgent CABG<5d after clopidogrel/ticagrelor and<7 d after prasugrel discontinued
  4. Discontinue epifibatide/tirofiban at 8–12 h before, and abciximab within 1 h before CABG (Class I; LOE: B)

**Late Hospital/Posthospital Care**

- **ASA indefinitely** (Class I; LOE: A)
  2. P2Y12 Inhibitor (clopidogrel or ticagrelor), in addition to ASA, up to 12 mo if medically treated (Class I; LOE: B)
  3. P2Y12 Inhibitor (clopidogrel, prasugrel, or ticagrelor), in addition to ASA, at least 12 mo if treated with coronary stenting (Class I; LOE: B)
**Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
</table>
| In patients with NSTE-ACS, anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:  
• Enoxaparin: 1 mg/kg subcutaneous (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until PCI is performed. An initial intravenous loading dose is 30 mg. | I | A |

**Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS (cont'd)**

<table>
<thead>
<tr>
<th>Recommendations (cont'd)</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
</table>
| • Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor, provided the patient is also treated with DAPT.  
• Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed. | I | B |
| | B |
Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS (cont’d)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(cont’d)</td>
<td></td>
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</tr>
<tr>
<td>• If PCI is performed while the patient is on fondaparinux, an additional anticoagulant with anti-ⅡⅡa activity (either UFH or bivalirudin) should be administered because of the risk of catheter thrombosis.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>• UFH IV: initial loading dose of 60 IU/kg (maximum 4,000 IU) with initial infusion of 12 IU/kg per hour (maximum 1,000 IU/h) adjusted per activated partial thromboplastin time to maintain therapeutic anticoagulation according to the specific hospital protocol, continued for 48 hours or until PCI is performed.</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>In patients with NSTE-ACS (i.e., without ST elevation, true posterior MI, or left bundle-branch block not known to be old), intravenous fibrinolytic therapy should not be used.</td>
<td>III: Harm</td>
<td>A</td>
</tr>
</tbody>
</table>

Helping Cardiovascular Professionals Learn, Advance, Heal.

Early versus Delayed, Provisional Eptifibatide in ACS

Early ACS trial

The use of eptifibatide ≥12 h before angiography was not superior to the provisional use of eptifibatide after angiography, and was associated with an increased risk of non–life-threatening bleeding and need for transfusion

Initial Conservative Strategy: Antiplatelet Therapy

For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy.

Abciximab should not be administered to patients in whom PCI is not planned.

Oral Anti-Platelet Therapies

### Primary Endpoint
CV Death, MI, Stroke, Hospitalization for Ischemia, Urgent Revascularization

- **HR (95% CI):** 0.92 (0.85, 1.01)
- **P-value:** 0.072

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Placebo</th>
<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>19.9%</td>
<td>18.5%</td>
</tr>
<tr>
<td>2-4 years</td>
<td>19.7%</td>
<td>18.9%</td>
</tr>
<tr>
<td>4-6 years</td>
<td>20.2%</td>
<td>19.1%</td>
</tr>
<tr>
<td>6-24 years</td>
<td>20.8%</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

**No. at risk**
- Placebo: 6471, 5844, 5468, 5121, 3794, 2291, 795
- Vorapaxar: 6473, 5897, 5570, 5199, 3881, 2318, 832

### Bleeding Outcomes
**GUSTO Moderate/Severe**

- **HR (95% CI):** 1.35 (1.16, 1.58)
- **P-value:** <0.001

<table>
<thead>
<tr>
<th>Time Period</th>
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<th>Vorapaxar</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>5.2%</td>
<td>7.2%</td>
</tr>
<tr>
<td>2-4 years</td>
<td>5.7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>4-6 years</td>
<td>6.2%</td>
<td>7.9%</td>
</tr>
<tr>
<td>6-24 years</td>
<td>6.8%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

**No. at risk**
- Placebo: 6441, 5536, 5137, 4674, 3393, 1972, 650
- Vorapaxar: 6446, 5673, 5108, 4698, 3278, 1983, 625

---

**ICH**

- **HR (95% CI):** 3.39 (1.78, 6.45)
- **P-value:** <0.001

<table>
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<tr>
<th>Time Period</th>
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</tr>
</thead>
<tbody>
<tr>
<td>0-2 years</td>
<td>0.24%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2-4 years</td>
<td>0.7%</td>
<td>0.9%</td>
</tr>
<tr>
<td>4-6 years</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>6-24 years</td>
<td>1.2%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

**No. at risk**
- Placebo: 6441, 5973, 5281, 4823, 3511, 2038, 678
- Vorapaxar: 6446, 5694, 5272, 4760, 3411, 1965, 657

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*Duke Clinical Research Institute*
Topics for today

• ACS Definition
• Management of NSTEMI
  – Invasive vs. Non-invasive strategies
  – Anti-platelet therapies
  – Anti-coagulant
  – Gp IIb/IIIa inhibitor
• STEMI
• Duration of anti-platelet therapy
• Secondary prevention measures

**1º PCI vs Lysis**

<table>
<thead>
<tr>
<th>Event</th>
<th>Lytic (n=3720)</th>
<th>PCI (n=3717)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7.4%</td>
<td>5.3%</td>
<td>0.70 (0.58-0.85)</td>
</tr>
<tr>
<td>ReMI</td>
<td>6.8%</td>
<td>2.5%</td>
<td>0.35 (0.27-0.45)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0%</td>
<td>1.0%</td>
<td>0.46 (0.30-0.72)</td>
</tr>
<tr>
<td>D/MI/Stroke</td>
<td>14.3%</td>
<td>8.2%</td>
<td>0.53 (0.45-0.63)</td>
</tr>
<tr>
<td>ICH</td>
<td>1.1%</td>
<td>0.1%</td>
<td>0.05 (0.01-0.35)</td>
</tr>
</tbody>
</table>

Summary for STEMI

- Aspirin for everyone
- Decide early on reperfusion strategy
- If 1° PCI
  - D-to-B <90 minutes
  - Clopidogrel (600 mg) or Prasugrel (60mg) or Ticagrelor (180 mg)
  - UFH, Enox, Bival
- If Lytics
  - D-to-N <30 minutes
  - Clopidogrel
  - Enoxaparin or Fondaparinux or UFH
  - Monitor ST Resolution for reperfusion
- Beta-blockers if no signs of HF or shock
- Early ACEI/ARB for EF <40% or signs of HF

Topics for today

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- STEMI
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  - Secondary prevention measures
**Late Hospital and Posthospital Oral Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>In addition to aspirin, a P2Y₁₂ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. Options include: &lt;br&gt; a. Clopidogrel: 75 mg daily or &lt;br&gt; b. Ticagrelor*: 90 mg twice daily</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

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**Medical Regimen and Use of Medications at Discharge**

<table>
<thead>
<tr>
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<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients receiving a stent (bare-metal stent or DES) during PCI for NSTE-ACS, P2Y₁₂ inhibitor therapy should be given for at least 12 months. Options include: &lt;br&gt; a. Clopidogrel: 75 mg daily or &lt;br&gt; b. Prasugrel#: 10 mg daily or &lt;br&gt; c. Ticagrelor*: 90 mg twice daily</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation.</td>
<td>Iia</td>
<td>B</td>
</tr>
</tbody>
</table>

#Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another P2Y₁₂ receptor inhibitor.  
*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.
Topics for today

• ACS Definition
• Management of NSTEMI
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Secondary Prevention following ACS

**Medications**

- Aspirin
- ADP inhibitor
- Beta-blockers
- Statins in all – regardless of LDL
  - Fasting lipid panel within 24 hr of hospitalization
- ACE inhibitors/ARBs (low EF, HF, DM, HTN)
- Aldosterone blockade (low EF)

**Goals**

- Lipids
  - LDL-C <100 mg/dL
  - Consider LDL-C <70 mg/dL
- BP <140/90 mm Hg (<130/80 mm Hg with DM or CKD)
- No smoke exposure
- Physical activity (30 min, 7 days/week; min 5d/wk)
- Weight management
- DM care: HbA1c ~7%
- Annual influenza immunization

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; LDL-C = low-density lipoprotein cholesterol; CKD = chronic kidney disease.

Influenza

An annual influenza vaccination is recommended for patients with cardiovascular disease.

Depression

It is reasonable to consider screening UA/NSTEMI patients for depression and refer/treat when indicated.
### NSAIDs

<table>
<thead>
<tr>
<th>Level</th>
<th>I</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
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<tr>
<td>Color</td>
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</table>

NSAIDs with increasing degrees of relative COX-2 selectivity should not be administered to UA/NSTEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief.

### Hormone Therapy

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

Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after UA/NSTEMI for secondary prevention of coronary events.
Antioxidant Vitamin and Folic Acid

Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in UA/NSTEMI patients.

Folic acid, with or without B6 and B12, should not be used for secondary prevention in UA/NSTEMI patients.

Topics for today

• ACS Definition
• Management of NSTEMI
  – Invasive vs. Non-invasive strategies
  – Anti-platelet therapies
  – Anti-coagulant
  – Gp IIb/IIIa inhibitor
  – Direct Oral Factor Xa Inhibitor
• STEMI
• Duration of anti-platelet therapy
• Secondary prevention measures
THANK YOU