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Educational Objectives

This program is designed to address the following IOM competencies: provide patient-centered care and employ evidence-based practice. At the conclusion of this activity, participants should be able to:

• Adopt ischemic risk assessment stratification strategies and choose the best course of action to manage them
• Accurately diagnose and risk-stratify ACS patients who present with atypical symptoms
• Make antiplatelet treatment choices based on an understanding of the different efficacy/safety properties of available agents
• Identify institution and practice-specific lapses and inefficiencies that increase the risk of recurrent events in ACS patients
Clinical Management of Chest Pain Syndrome

Key Considerations

- Need for differential diagnosis of the spectrum of ACS
- Fundamental aspects of management of acute chest pain
  - Elements for optimal early hospital care
- The importance of risk stratification to guide practice decisions
  - Options: initial conservative or invasive strategy
    - If invasive strategy, rationale for early catheterization
- The expanded field of existing antplatelet treatment options
  - Clopidogrel, prasugrel, ticagrelor
- Emerging antiplatelet/anticoagulant therapies for ACS
  - Strong contender: very low dose rivaroxaban
- The need to balance anti-ischemic effects vs bleeding risk
- The growing importance of quality outcomes in ACS

CHEST PAIN CASE

Chest Pain Case

Initial Presentation

- 68-year-old female presents to the Emergency Department at 8:45 am
- Substernal and epigastric discomfort radiating to left shoulder for two hours; onset was with exertion but continued at rest
- ECG shows prominent ST-segment depression in the lateral precordial leads (V5, V6)
- Initial troponin-I is 0.02 mg/dL (normal, <0.04)
- CVD History: Suspected CAD with abnormal stress test, but declined catheterization one year ago; treated with beta-blockers, aspirin, prn nitroglycerin (has not used).
- Additional Medical History: Significant for positive family history, mild hypertension, and mild dyslipidemia.
Addressing Acute Chest Pain Syndrome

Program Slides

Chest Pain Case
Initial ECG

Chest Pain Case
Diagnosis, Prognosis, and Treatment Stratification Issues

• Which diagnosis: Non-cardiac? UA? NSTEMI? STEMI?
• Risk category: Low? Intermediate? High? (TIMI, GRACE)
• Choice of management strategy for next 24h depends at least in part on answers to above questions.
• Repeat troponin assay 2 hours later is positive, and patient's diagnosis is changed from UA to NSTEMI
• Invasive or conservative strategy?
• Once decided, medical therapy that supports the chosen strategy should be initiated: Anticoagulant? Which one? What dose?
  • Oral antiplatelet (beyond aspirin)? Which one? What dose?
  • GP IIb/IIIa antagonist? Small or large molecule? What dose?
  • Beta blocker? IV or PO?

Chest Pain Case
Initial Evaluation

• Plan is to take her to cath lab as first case tomorrow morning if she remains stable and pain free
• What would you choose for anticoagulation, antiplatelet, and beta-blocker therapy (patient's creatinine clearance is 45 ml/min)?
• What therapy might you add (or change) in the cath lab?
Hospitalizations in the US Due to ACS

Acute Coronary Syndromes

1.57 Million Hospital Admissions – ACS

UA/NSTEMI†

STEMI

1.24 million
Admissions per year

0.33 million
Admissions per year

*Primary and secondary diagnoses. †About 0.57 million NSTEMI and 0.67 million UA.


Acute Coronary Syndrome Spectrum
Pathophysiology and Clinical Evaluation

Presentation

Working Dx

ECG

Cardiac Biomarker

Final Dx

No ST Elevation

ST Elevation

UA

NSTEMI

Unstable Angina

Myocardial Infarction

NQMI Qw MI


Addressing Acute Chest Pain Syndrome

Program Slides

Acute Chest Pain Presentation

Classifications

Acute Coronary Syndromes

TIMI flow grade 2/3
in culprit artery

- Troponin

+ Troponin

Unstable angina
NSTEMI

TIMI flow grade 0/1
in culprit artery

+ Troponin

STEMI

Acute Coronary Syndromes

• Common Features of ACS
  – Similar pathophysiology
  – Similar presentation and early management rules

• Differentiating Features of ACS
  – Unstable Angina
    • Non-occlusive thrombus
    • No diagnostic ECG changes, but ischemic ST-T changes confer higher risk
    • Normal cardiac biomarkers
  – NSTEMI
    • Occluding thrombus sufficient to cause myocardial damage
    • No diagnostic ECG changes, but ischemic ST-T changes: higher risk
    • Elevated cardiac biomarkers
  – STEMI
    • Complete thrombus occlusion
    • ST elevation or new LBBB
    • Elevated cardiac biomarkers
    • More severe symptoms


SYMPTOMS SUGGESTIVE OF ACS

Noncardiac Diagnosis
Chronic Stable Angina
Possible ACS
Definite ACS

Treatment as indicated by alternative diagnosis

ACC/AHA Chronic Stable Angina Guidelines

No ST-Elevation
ST-Elevation
Nondiagnostic ECG
Normal initial serum cardiac biomarkers
ST and/or T wave changes
Ongoing pain
Positive cardiac biomarkers
Hemodynamic abnormalities

Evaluate for

Observe
≥ 12 h from symptom onset

Evaluate
for reperfusion therapy

ACC/AHA STEMI Guidelines

No recurrent pain; negative follow-up studies
Recurrent ischemic pain or positive follow-up studies
Diagnosis of ACS confirmed

Stress study to provoke ischemia
Consider evaluation of LV function if ischemia is present (tests may be performed either prior to discharge or as outpatient)

Negative
Potential diagnoses: nonischemic discomfort; low-risk ACS

Positive
Diagnosis of ACS confirmed or highly likely
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.
Third Universal Definition of MI

- Type I: Spontaneous MI (coronary occlusion)
- Type 2: MI due to ischemic (supply/demand) imbalance
- Type 3: MI causing death w/o biomarkers/ECGs (SCD)
- Type 4a: MI related to PCI (cTn >5 x 99%ile URL, or >20%↑ from elevated baseline, & + Sx, ECG, or angiography)
- Type 4b: MI related to stent thrombosis (detected by angio or autopsy and with cTn rise &/or fall)
- Type 5: MI related to CABG (cTn >10 x 99%ile URL from normal baseline, & + ECG, angiography, or imaging evidence of MI)


Mortality in Acute Coronary Syndromes
Death from Hospital Admission to 6 Months

RISK STRATIFICATION AND EARLY HOSPITAL CARE
“Dynamic Risk Stratification” Tools

- History and physical
- Standard ECG and non-standard ECG leads
  - 15-lead ECGs should perhaps become “standard” in all but very-low-risk patients
- Biomarkers
  - Troponin I and T, CK-MB
  - High-sensitivity troponin
  - Brain natriuretic peptide (BNP)
- Non-invasive imaging
  - Echocardiogram
  - Stress testing
  - Technetium-99m-sestamibi
- Invasive imaging
  - Cardiac computed tomography angiography (CCTA)
- Predictive indices/schemes
  - Better as research tools than for real-time clinical decision-making

Chest Pain Syndrome Suggestive of Ischemia

Immediate Assessment within 10 Minutes

<table>
<thead>
<tr>
<th>Initial Labs and Tests</th>
<th>Emergent Care</th>
<th>History &amp; Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 12 lead ECG</td>
<td>• IV access</td>
<td>• Establish diagnosis</td>
</tr>
<tr>
<td>• Obtain initial cardiac enzymes</td>
<td>• Cardiac monitoring</td>
<td>• Read ECG</td>
</tr>
<tr>
<td>• Electrolytes, CBC lipids, BUN/creatinine, glucose, coags</td>
<td>• Oxygen</td>
<td>• Identify complications</td>
</tr>
<tr>
<td>• Chest x-ray</td>
<td>• Aspirin</td>
<td>• Assess for reperfusion</td>
</tr>
<tr>
<td></td>
<td>• Nitrates</td>
<td></td>
</tr>
</tbody>
</table>

Risk Scores

<table>
<thead>
<tr>
<th>TIMI</th>
<th>GRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Age</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Heart rate</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Smoking</td>
<td>Elevated creatinine</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Family history</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>History of CAD</td>
<td>Elevated markers</td>
</tr>
<tr>
<td>Severe angiina</td>
<td>ST-segment deviation</td>
</tr>
<tr>
<td>Aspirin within 7 days</td>
<td>Elevated markers</td>
</tr>
<tr>
<td>ST-segment deviation</td>
<td>ST-segment deviation</td>
</tr>
</tbody>
</table>

GRACE = Global Registry of Acute Coronary Events; TIMI = Thrombolysis in Myocardial Infarction


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Addressing Acute Chest Pain Syndrome

**Program Slides**

**TIMI Risk Score**
All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days After Randomization

![TIMI Risk Score Diagram](image)

**Troponin Levels Predict Risk of Mortality in UA/NSTEMI**

![Troponin Levels Diagram](image)

**EARLY HOSPITAL CARE**
Optimal Upstream Management of Ischemic Risk Assessment

- Basis for assessment
  - “Pain story”
  - Background CVD risk
  - ECG
  - Troponin elevation in pertinent time frame
  - Predictive risk score
- Options
  - Antiplatelet therapy increasingly important as ischemic risk increases
  - UFH and enoxaparin established
  - Bivalirudin and fondaparinux: New options that are non-inferior

Current Medical Management of Unstable Angina and NSTEMI

<table>
<thead>
<tr>
<th>Acute Therapy</th>
<th>Maintenance Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oxygen, bed rest</td>
<td>• Antipatelet therapy</td>
</tr>
<tr>
<td>• ECG monitoring</td>
<td>• Beta blockers</td>
</tr>
<tr>
<td>• Nitroglycerin</td>
<td>• Calcium channel blockers</td>
</tr>
<tr>
<td>• Beta blockers</td>
<td>• Lipid-lowering agents</td>
</tr>
<tr>
<td>• ACE inhibitors</td>
<td>• ACE inhibitors</td>
</tr>
<tr>
<td>• Antiplatelet therapy</td>
<td>• Oral anticoagulant therapy</td>
</tr>
<tr>
<td>• Anticoagulant therapy</td>
<td></td>
</tr>
</tbody>
</table>

ACUTE CORONARY SYNDROME

Patient Management Considerations:
Initial Conservative or Invasive Strategy – Based on Risk Assessment
Addressing Acute Chest Pain Syndrome

Early Invasive vs Initial Conservative Strategy

**General Considerations in UA/NSTEMI**

**EARLY INVASIVE STRATEGY**  
**GENERALLY PREFERRED**

- Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
- Elevated cardiac biomarkers (TnT or TnI)
- Signs or symptoms of heart failure
- Hemodynamic instability
- High-risk score (e.g., GRACE, TIMI)
- PCI within 6 months
- Prior CABG
- Diabetes mellitus
- Mitral or moderate renal dysfunction
- Reduced LV function (LVEF <40%)

**INITIAL CONSERVATIVE STRATEGY**  
**GENERALLY PREFERRED OR REASONABLE**

- Low-risk score (e.g., GRACE, TIMI)
- Abnormalities of high-risk features
- High-risk for catheterization-related complications
- Patient not a revascularization candidate (with either PCI or CABG)
- Patient prefers conservative therapy
- Patient prefers conservative therapy
- Hemodynamic instability
- Low risk score (e.g., GRACE, TIMI)
- Absence of high-risk features
- Patient not a revascularization candidate (with either PCI or CABG)
- Patient prefers conservative therapy

CABG = coronary artery bypass graft surgery; GRACE = Global Registry of Acute Coronary Events; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction; TnI = troponin I; TnT = troponin T


Conservative Therapy Option for UA/NSTEMI

**Early Revascularization or PCI Not Planned**

- **Antiplatelet therapy**
  - Aspirin
  - Clopidogrel
- **MONA + BAA (enoxaparin, fondaparinux preferred over UFH)**
  - Morphine, Oxygen, Nitroglycerin, Aspirin + Beta blocker, ACEI, Anticoagulant (morphine has only Class IIa recommendation due to increased mortality risk – CRUSADE)
- **Glycoprotein IIb/IIIa inhibitors**
  - Only in certain circumstances
  - Planning PCI, elevated troponin
- **Surveillance in hospital**
  - Serial ECGs
  - Serial cardiac markers


Invasive Therapy Option for UA/NSTEMI

- **Coronary angiography and revascularization within 12 to 48 hours after presentation to ED**
- **For high-risk ACS**
  - MONA + BAA (UFH or bivalirudin or enoxaparin)
  - Morphine, Oxygen, Nitroglycerin, Aspirin + Beta blocker, ACEI, Anticoagulant (morphine has only Class IIa recommendation due to increased mortality risk – CRUSADE)
  - Antiplatelet therapy
    - Aspirin; P2Y12 inhibitor (clopidogrel or ticagrelor or prasugrel) or GPI
    - Reduction in death/MI/stent thrombosis
    - PCI + BMS: at least 1 year (may stop earlier if needed)
    - PCI + DES: at least 1 year

Addressing Acute Chest Pain Syndrome

ACCF/AHA Guidelines 2011 Focused Update
Early Invasive Strategies

High-risk patients with:
- Refractory ischemia
- Recurrent anginal ischemia
- Elevated cardiac biomarkers (T)
- New ST-segment depression
- New CHF or worsening MR
- High-risk on non-invasive testing
- LV dysfunction (EF <40%)
- Hemodynamic instability
- Sustained VT
- Diabetics with single-vessel disease
- Mild to moderate kidney disease
- PCI within 6 months, prior CABG high-risk score
- Not in low-risk women


TACTICS: Primary Endpoint
Death, MI, Rehospitalized for ACS at 6 Months


Meta-analysis: Mortality in NSTE-ACS by Strategy

Overall RR (95% CI) 0.75 (0.63-0.90)

### TIMACS

Rates of death, MI, or stroke within 6 months according to GRACE risk level and HR (95% CI), early vs delayed invasive strategy

<table>
<thead>
<tr>
<th></th>
<th>EARLY (%)</th>
<th>DELAYED (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Intermediate (n=2070)</td>
<td>7.6</td>
<td>6.7</td>
<td>1.12 (0.88–1.56)</td>
<td>0.48</td>
</tr>
<tr>
<td>High (n=981)</td>
<td>13.9</td>
<td>21.0</td>
<td>0.65 (0.48–0.89)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Low/Intermediate risk=GRACE score <140
High risk=GRACE score ≥140


### FREEDOM: PCI vs CABG in Diabetics* with MVD

<table>
<thead>
<tr>
<th></th>
<th>Death/Stroke/MI %</th>
<th>Death/Stroke/MI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>POODES</td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>Log Rank P=0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31% w/ UA</td>
<td></td>
</tr>
</tbody>
</table>

5-Year Event Rates: 25.8% vs. 18.7%


### ANTICOAGULANT THERAPY IN ACS
Addressing Acute Chest Pain Syndrome

Program Slides

Coagulation Pathways and Anticoagulant Therapy in ACS

ACC/AHA UA/NSTEMI 2011 Guidelines

Initial Anticoagulant Algorithm by Strategy

Diagnosis of UA/NSTEMI likely/definite ASA (IA); clopidogrel if ASA intolerant (IA)

SELECT MANAGEMENT STRATEGY

INVASIVE STRATEGY

Initiate anticoagulant therapy (IA)
Acceptable options: enoxaparin or UFH (IA) or bivalirudin (IB)*

CONSERVATIVE STRATEGY

Initiate anticoagulant therapy (IA)
Acceptable options: enoxaparin or UFH (IA) or fondaparinux (IB), but enoxaparin or fondaparinux are preferred (IIa:B)

*If fondaparinux is used (IB), it must be co-administered with another anticoagulant with factor IIa activity; for example, unfractionated heparin. should not be the sole anticoagulant to support PCI (IIIC).

† Timing of invasive strategy generally is assumed to be 4 to 48 hours. If immediate angiography is selected, see STEMI guidelines.

ANTIPLATELET THERAPY IN ACS
Addressing Acute Chest Pain Syndrome

Program Slides

Platelet Aggregation and Mechanisms of Action of Antiplatelet Therapies

ADP = adenosine diphosphate; TXA2 = thromboxane A2; COX = cyclooxygenase


CURE Study
Primary End Point: MI/Stroke/CV Death

Placebo + Aspirin (n=6303)

Clopidogrel + Aspirin (n=6259)

P<0.001
n=12,562

Composite Hazard Rate

Months of Follow-up


PCI-CURE
Clopidogrel for PCI after NSTE-ACS

Composite of MI or cardiovascular death from randomization to end follow-up

Placebo + ASA*

Clopidogrel + ASA*

P= 0.002
n = 2658

* In addition to other standard therapies.

CURRENT: Clopidogrel Double vs Standard Dose

Primary Outcome: PCI Patients

CV Death, MI or Stroke

15% RRR

HR 0.85
95% CI 0.74-0.99
P=0.036


CURRENT: Clopidogrel Double vs Standard Dose

Definite Stent Thrombosis

46% RRR

HR 0.54
95% CI 0.39-0.74
P=0.0001


TRITON – TIMI 38

CV Death, MI, Stroke

12.1 (781)
9.9 (643)

HR 0.81
95% CI 0.73-0.90
P=0.0004
NNT= 46

TRITON-TIMI 38 Study: Subgroups

Primary endpoint = first occurrence of CV death, MI, or stroke

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel (%)</th>
<th>Clopidogrel (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>13.6</td>
<td>20.5</td>
</tr>
<tr>
<td>Males</td>
<td>9.7</td>
<td>13.6</td>
</tr>
<tr>
<td>Age &lt;75</td>
<td>17.3</td>
<td>26.9</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>10.8</td>
<td>11.8</td>
</tr>
<tr>
<td>No Hx of DM</td>
<td>11.7</td>
<td>27.0</td>
</tr>
<tr>
<td>Hx of DM</td>
<td>12.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Age &lt;75</td>
<td>9.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>16.7</td>
<td>17.8</td>
</tr>
<tr>
<td>No Hx of DM</td>
<td>11.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Hx of DM</td>
<td>9.4</td>
<td>12.3</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>8.4</td>
<td>12.3</td>
</tr>
<tr>
<td>STEMI</td>
<td>17.0</td>
<td>12.2</td>
</tr>
<tr>
<td>BMS only</td>
<td>10.7</td>
<td>17.0</td>
</tr>
<tr>
<td>DES</td>
<td>11.3</td>
<td>13.7</td>
</tr>
<tr>
<td>CrCl ≥60</td>
<td>8.4</td>
<td>12.3</td>
</tr>
<tr>
<td>CrCl &lt;60</td>
<td>26.8</td>
<td>31.7</td>
</tr>
</tbody>
</table>


TRITON-TIMI 38

Efficacy and Safety in the Diabetic Subgroup

Risk (%) = 0.2

HR = 0.70

P < 0.001

NNT = 46


TRITON-TIMI 38

Net Clinical Benefit Bleeding Risk Subgroups

POST HOC ANALYSIS

<table>
<thead>
<tr>
<th>Risk (%)</th>
<th>Prior Stroke / TIA</th>
<th>Age ≥75</th>
<th>Age &lt;75</th>
<th>Wgt ≥50 kg</th>
<th>Wgt &lt;50 kg</th>
<th>OVERALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P = .006</td>
<td></td>
<td>-1</td>
<td>-16</td>
<td>-16</td>
<td>-13</td>
</tr>
<tr>
<td></td>
<td>P = .18</td>
<td></td>
<td>-3</td>
<td>-5</td>
<td>-5</td>
<td>-13</td>
</tr>
<tr>
<td></td>
<td>P = .36</td>
<td></td>
<td></td>
<td>-13</td>
<td>-13</td>
<td>-13</td>
</tr>
</tbody>
</table>

**Ticagrelor (AZD 6140)**

An Oral Reversible 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**
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of all circulating platelets

**PLATO:** Kaplan-Meier Estimate of Time to First Primary Efficacy Event (Composite of CV Death, MI, or Stroke)

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Days after randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>9,291</td>
<td>9,333</td>
</tr>
<tr>
<td>8,521</td>
<td>8,628</td>
</tr>
<tr>
<td>8,362</td>
<td>8,460</td>
</tr>
<tr>
<td>8,124</td>
<td>8,219</td>
</tr>
<tr>
<td>6,743</td>
<td>6,743</td>
</tr>
<tr>
<td>5,096</td>
<td>5,161</td>
</tr>
<tr>
<td>4,047</td>
<td>4,147</td>
</tr>
</tbody>
</table>

- HR = hazard ratio
- CI = confidence interval
- HR 0.84 (95% CI 0.77–0.92), P=0.0003

**Stent Thrombosis**

Evaluated in Patients with Any Stent During the Study

<table>
<thead>
<tr>
<th>Stent thrombosis, n (%)</th>
<th>Ticagrelor (n=5,640)</th>
<th>Clopidogrel (n=5,649)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>71 (1.3)</td>
<td>106 (1.5)</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>168 (2.1)</td>
<td>158 (2.4)</td>
<td>0.75 (0.69–0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, definite</td>
<td>322 (3.6)</td>
<td>202 (3.6)</td>
<td>0.77 (0.62–0.96)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Time-at-risk is calculated from first stent insertion in the study or date of randomization

Ticagrelor Interaction with Aspirin Dose
Hazard Ratio Compared with Clopidogrel

<table>
<thead>
<tr>
<th>Aspirin Dose (mg/day)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2300</td>
<td>1.45</td>
<td>1.01–2.09</td>
</tr>
<tr>
<td>&gt;100 – &lt;300</td>
<td>0.99</td>
<td>0.70–1.40</td>
</tr>
<tr>
<td>≤100</td>
<td>0.77</td>
<td>0.69–0.86</td>
</tr>
</tbody>
</table>

WARNING: ASPIRIN DOSE AND TICAGRELO EFFECTIVENESS
Maintenance doses of aspirin above 100mg reduce the effectiveness of ticagrelor and should be avoided. After any initial dose, use with aspirin 75-100 mg per day. ( FDA-approved prescribing information, July 2011)

Highlights of P2Y12 Inhibitor Trials

- **Clopidogrel**
  - Double-dose (600 mg load, 150 mg qd x 1 week) in setting of PCI decreases non-fatal MI and stent thrombosis
  - Preferred P2Y12 inhibitor in patients with h/o TIA/stroke
- **Prasugrel**
  - ↓ Ischemic events c/w clopidogrel, both early & late, cr w/clopidogrel
  - ↓ Stent thrombosis c/w clopidogrel
  - Especially large benefit in diabetics and in STEMI
  - Not superior to clopidogrel in medically managed patients
  - Contraindicated in patients with h/o TIA/stroke
- **Ticagrelor**
  - ↓ Ischemic events c/w clopidogrel, both early & late, both with invasive and conservative management, c/w clopidogrel
  - ↓ Stent thrombosis c/w clopidogrel
  - ↓ CV mortality c/w clopidogrel, including with CABG

ACC/AHA UA/NSTEMI 2012 Guidelines
Initial Antiplatelet Algorithm by Strategy

![Diagram of algorithm](Image)
**Addressing Acute Chest Pain Syndrome**

**Program Slides**

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### Oral Antiplatelet Therapy

Patients should be counseled on the need for and risk of dual antiplatelet therapy (DAPT) before placement of intracoronary stents, especially a DES, and alternative therapies should be pursued if they are unwilling or unable to comply with the recommended duration of DAPT.

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### Early Discontinuation of Antiplatelet Therapy is An Important Risk Factor for Stent Thrombosis

**Post-procedural Antiplatelet Therapy**

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**Post-procedural Antiplatelet Therapy**

*After PCI, aspirin should be continued indefinitely.*

The duration of P2Y12 inhibitor therapy after stent implantation should generally be as follows:

a) In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months. Options include: clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily.
ANTI-ISCHEMIC EFFECTS
vs BLEEDING RISK
The Delicate Balance

CRUSADE Bleeding Score in NSTEMI

- 8 predictors of in-hospital major bleeding in CRUSADE Quality Improvement Initiative: baseline Hct, CrCl, HR, sex, CHF at presentation, prior vascular disease, DM, systolic BP
- ↑ Rate major bleeding by bleeding risk score quintiles:
  - 3.1% very low risk (score ≤20)
  - 5.5% low risk (score 21-30)
  - 8.6% moderate risk (score 31-40)
  - 11.9% high risk (score 41-50)
  - 19.5% very high risk (score >50)
- CRUSADE bleeding score quantifies risk for in-hospital major bleeding; enhances risk assessment in NSTEMI care; allows improved risk/benefit analysis


Possible Relationship Between Bleeding and Mortality

- Major Bleeding
  - Hypotension
  - Cessation of ASA/Plpidogrel
  - Transfusion
  - Ischemia
  - Stent Thrombosis
  - Inflammation
  - Mortality

Addressing Acute Chest Pain Syndrome

Program Slides

**CURE: Life-threatening Bleeding**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placbo + ASA*</th>
<th>Clopidogrel + ASA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening Bleeding</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Causing 5 g/dL drop hemoglobin</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypotension requiring inotropic therapy</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Surgery required</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Causing hemorrhagic stroke</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Transfusion of 24 blood units</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Transfusion of ≥2 blood units</td>
<td>2.2</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* In combination with standard therapy


**TRITON TIMI 38**

Bleeding Events – Safety Cohort (n=13,457)

**PLATO**

Major Bleeding: Non-CABG vs CABG

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ANTIPLATELET RESPONSE VARIABILITY

Optimizing Antiplatelet Therapy
Balancing Safety and Efficacy

Variability in Antiplatelet Effect with Clopidogrel and Prasugrel

ACS = acute coronary syndrome; CKD = chronic kidney disease; DM = diabetes mellitus

IPA = inhibition of platelet aggregation
CYP2C19 Genetic Polymorphisms and Treatment with Clopidogrel

<table>
<thead>
<tr>
<th>Major Adverse CV Events (n=9684)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers vs Non-carriers</td>
<td>1.61 (1.28-2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heterozygotes vs Wildtype</td>
<td>1.50 (1.08-2.08)</td>
<td>0.016</td>
</tr>
<tr>
<td>Homozygotes vs Wildtype</td>
<td>1.81 (1.21-2.71)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Stent Thrombosis (n=5772)

| Carriers vs Non-carriers          | 2.76 (1.77-4.30)   | <0.001  |
| Heterozygotes vs Wildtype         | 2.51 (1.59-3.98)   | <0.001  |
| Homozygotes vs Wildtype           | 4.78 (2.01-11.39)  | <0.001  |

**Risk Higher With CYP2C19 Variant**

**Risk Lower With CYP2C19 Variant**


**GRAVITAS: Trial Design**

- Successful PCI with DES without major complication or GPIIb/IIIa use
- Randomized 1:1

**Results and Conclusions**

- Same rate of CV death, MI, or stent thrombosis in 2 groups (P=.98)
- GUSTO moderate or severe bleeding: 1.4% HD vs. 2.3% standard (P=.16)

**Conclusions**

- Patients with high residual platelet reactivity after PCI with DES did not benefit from high-dose clopidogrel
- High-dose clopidogrel for 6 months did not reduce the primary ischemic outcome
- GUSTO moderate or severe bleeding was not increased
- Routine testing of platelet reactivity after PCI is not warranted
Status of Platelet Function Testing (PFT) as a Guide to Therapy

- High platelet reactivity (HPR) predicts ↑ risk in most, not all studies.
- Using PFT to adjust dose ↑ did not improve outcomes in elective PCI patients (GRAVITAS, ARCTIC). Titration improved outcomes in a smaller French study enriched with ACS patients (Bonello).
- PFT most likely to benefit high-risk ACS patients receiving DES with serial guidance to both ↑ and ↓ titrate therapy, but has not been adequately tested.
- Factors other than platelets may affect atherothrombotic risk:
  - Fibrinogen
    - ↑ Fibrinogen not ↑ PRU after clopidogrel predicted ischemic risk after elective PCI (J Am Coll Cardiol. 2013;61:23)
    - Low-dose rivaroxaban added to antiplatelet Rx reduces CV events after ACS in ATLAS ACS2-TIMI51 (N Engl J Med. 2012;366:9)
  - Activated leukocytes

Platelet Function Testing For Patients Undergoing PCI

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet function testing in patients at high risk for poor clinical outcomes</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Routine clinical use of platelet function testing to screen clopidogrel-treated patients undergoing PCI</td>
<td>III – No Benefit</td>
<td>C</td>
</tr>
<tr>
<td>Treatment with an alternate P2Y12 inhibitor (e.g. prasugrel or ticagrelor) in clopidogrel-treated patients with high platelet reactivity</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

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ACC/AHA 2008 Performance Measures at Discharge for STEMI and NSTEMI

- Aspirin at discharge
- β-blocker at discharge
- Statin at discharge (changed from: lipid-lowering therapy in patients with LDL-C >100 mg/dL)
- ACEI or ARB for LVSD
- Adult smoking cessation advice/counseling
- Cardiac rehabilitation patient referral from an inpatient setting (new in 2008)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVSD = left ventricular systolic dysfunction


Quality of Care and Outcomes for Acute Coronary Syndromes

It is reasonable for clinicians and hospitals that provide care to patients with UA/NSTEMI to participate in a standardized quality-of-care data registry designed to track and measure outcomes, complications, and adherence to evidence-based processes of care and quality improvement for UA/NSTEMI.

Evidence-based Therapies on 6-month Survival GRACE Registry Cohort

<table>
<thead>
<tr>
<th>NUMBER OF THERAPIES (vs 0 or 1 therapy)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 therapies</td>
<td>0.89 (0.52-1.50)</td>
</tr>
<tr>
<td>3 therapies</td>
<td>0.74 (0.48-1.13)</td>
</tr>
<tr>
<td>4 therapies</td>
<td>0.59 (0.39-0.90)</td>
</tr>
<tr>
<td>5 therapies</td>
<td>0.51 (0.33-0.78)</td>
</tr>
<tr>
<td>6 therapies</td>
<td>0.40 (0.26-0.62)</td>
</tr>
<tr>
<td>7 therapies</td>
<td>0.27 (0.16-0.44)</td>
</tr>
<tr>
<td>8 therapies</td>
<td>0.31 (0.17-0.57)</td>
</tr>
</tbody>
</table>

OR = odds ratio

*Registry of patients with ACS
Mean 30-day Hospital Readmission Rates Following PCI: By Hospital Decile of Readmission


Hospitals
Quality of Care for Heart Attack

Data: IPRO analysis of data from CMS Hospital Compare.
Source: Commonwealth Fund Medical Scorecard on US Health System Performance, 2011.

INVESTIGATIONAL POST-DISCHARGE USE OF ADJUNCTIVE LOW-DOSE ANTICOAGULATION AFTER ACUTE CORONARY SYNDROME
RIVAROXABAN: ATLAS ACS 2 TIMI 51
Primary Efficacy Endpoint: CV Death / MI / Stroke


RIVAROXABAN: ATLAS ACS 2 TIMI 51
Efficacy Endpoints: Very Low Dose 2.5 mg BID
Patients Treated with Aspirin + Thienopyridine


RIVAROXABAN: ATLAS ACS 2 TIMI 51
Treatment Emergent Fatal Bleeds and ICH

Apixaban: APPRAISE-2 Trial
Primary Outcome: CV Death, MI, Ischemic Stroke


CONCLUSIONS
Clinical Management of Acute Chest Pain Syndrome

- Need for differential diagnosis of the spectrum of ACS
- Fundamental aspects of management of acute chest pain
  - Elements for optimal early hospital care
- The importance of risk stratification to guide practice decisions
  - Options: initial conservative or invasive strategy
    - If invasive strategy, rationale for early catheterization
- The expanded field of existing antiplatelet treatment options
  - Clopidogrel, prasugrel, ticagrelor
- Post-discharge anticoagulant therapy for ACS
  - Current contender: very low dose rivaroxaban
- The need to balance anti-ischemic effects vs bleeding risk
- The growing importance of quality outcomes in ACS