2010 Perspectives on Evidence-Based Therapy for Acute Coronary Syndromes

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ACS: Scope of the Problem

• Single Largest Cause of Death
  – CVD claims more lives each year than the next 5 leading causes of death combined
  – 1 in every 5 deaths
  – CVD #1 cause of death worldwide by 2020

• Incidence
  – 1,100,000 Americans will have a new or recurrent coronary attack each year
  – Demographic trends suggest that hospital admissions for UA/NSTEMI will grow dramatically over the next decade as baby boomers age

AHA 2002 Heart and Stroke Statistical Update.

On the Verge of an Epidemic Growth of NSTEMI Diagnoses

Data from National Registry of Myocardial Infarction (NRMI) 2 and 3 (N=748,949) ¹


1
Demographics of PCI Patients
ACC/NCDR Data Base
N=158,367

<table>
<thead>
<tr>
<th>Presentation</th>
<th>% Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>38.4%</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>14.6%</td>
</tr>
<tr>
<td>STEMI</td>
<td>13.9%</td>
</tr>
<tr>
<td>Total ACS cases</td>
<td>66.9%</td>
</tr>
</tbody>
</table>

ACS Treatment Strategies

Reperfusion/Revascularization Therapy
- PCI (with/without stenting)
- CABG
- Medical therapy

Antithrombotic Coltherapy
- UFH
- ASA
- LMWH
- GPI IIb/IIIa
- DTI
- ADP antagonists
- Penta.

Acute and Long-Term Medical Therapy
- Miracles
- BBs
- ACEIs
- ARBs
- CCBs
- Statins
- APT

TIMI Risk Score For UA/NSTEMI

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>% Popn: 0.3</th>
<th>17.3</th>
<th>32.0</th>
<th>29.3</th>
<th>13.0</th>
<th>3.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/1</td>
<td>4.7</td>
<td>8.3</td>
<td>13.2</td>
<td>19.9</td>
<td>26.2</td>
<td>40.9</td>
</tr>
</tbody>
</table>

TIMI = thrombolysis; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; ASA = aspirin; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; GPI = glycoprotein IIb/IIIa inhibitors; DTI = direct thrombin inhibitors; GP IIb/IIIa = glycoprotein IIb/IIIa inhibitors; Penta. = pentasaccharide; ARMs = angiotensin receptor blockers; CCBs = calcium channel blockers; APT = antithrombotic therapy.

TIMI Risk Score Assessment

GRACE Risk Score Assessment

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>GRACE Scores</th>
<th>Probability of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1-80</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Medium</td>
<td>89-118</td>
<td>3-8%</td>
</tr>
<tr>
<td>High</td>
<td>119-263</td>
<td>&gt;8%</td>
</tr>
</tbody>
</table>


Cardiac Markers: The Future in ACS

Markers of Hemostasis
- vWF
- D-dimer
- Fibrinogen
- Anti-Xa, Anti-IIa

Markers of Inflammation
- CRP
- SAA
- IL-6
- TNFα, MCP-1, MMPs

Markers of Necrosis
- cTnT and cTnl
- CKMB and isoforms
- Myoglobin

Markers of Platelet Function
- P-Selectin
- GIIb/IIIa occupancy

Markers of Hemodynamic Stress
- Myoglobin
- BNP

Multimarker Approach:
- cTnI, CRP, & BNP

Early Invasive Approach for UA/NSTEMI and Mortality Reduction

Study
- FRISC II
- TRITAC
- TIMI-18
- VINO
- RITA-3
- ISAR-COOL
- ICTUS

Deaths (n) Follow up (months)
- Invasive
- Conservative

Favors Early Invasive Therapy

Benefit of Invasive Strategy by Troponin and ST Changes

Death, MI, Rehosp ACS at 6 Months

Conservative
- TnT -
- TnT +

Invasive
- No ST change
- ST change

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

Benefit of Invasive Strategy
- NNH = 28
- NNT = 12

Early Invasive Approach for UA/NSTEMI and Mortality Reduction

Meta-analysis of Recent Trials (N=8375)

Deaths (n) Follow up (months)

Favors Early Invasive Therapy

Conservative

Benefit of Invasive Strategy by Troponin and ST Changes

Death, MI, Rehosp ACS at 6 Months

Conservative
- TnT -
- TnT +

Invasive
- No ST change
- ST change

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

Benefit of Invasive Strategy
- NNH = 28
- NNT = 12
**Trial design:** 3031 Patients with NSTEMI were randomized to an early (within 24 hours) or delayed (after 36 hours) invasive strategy. Clinical outcomes were compared at 6 months.

**TIMACS**

**TIMACS Trial: Primary End Point Results in High- Versus Low-Risk Patients**

High Risk=Grace Score > 140


**“Vulnerable” Plaque and “Stable” Plaque**

Initial Presentation of Acute Coronary Syndromes: Disruption of “Culprit” Plaque with Thrombus

Fibrous Cap Disruption
Thrombus

(from M. Davies)

Technologies to predict “vulnerable” plaque

- Higher resolution IVUS
- Optical coherence tomography
- Infrared Spectroscopy
- Thermal imaging
- Endovascular MRI
- Raman spectroscopy
- Pulse laser irradiation
- Fluorescence-mediated tomography (FMT)

80% of ACS Patients Have >1 Plaque Rupture

3-Vessel IVUS Study (N=24)


Plaque Cap Synthesis and Breakdown

Vasculoprotective effects of lipid lowering with statins

- Endothelial normalization
- Strengthening of fibrous cap
- Inhibition of platelet thrombus formation and deposition
- Anti-inflammatory effects

PROVE IT: Is Aggressive LDL-C Lowering More Effective in Reducing Clinical Events?

All-Cause Death or Major CV Events

<table>
<thead>
<tr>
<th>Months of Follow-up</th>
<th>Pravastatin 40mg (26.3%)</th>
<th>Atorvastatin 80mg (22.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>9</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td>12</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>15</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>18</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>21</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>24</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>27</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>30</td>
<td>0.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

LDL (106) fell to 95 vs 62 mg/dl
CRP (12.3) fell to 2.1 vs 1.3

Ridker PM et al, NEJM 2005;352:20-28

Clinical Relevance of Achieved LDL and Achieved CRP After Treatment with Statin Therapy

Thrombosis on a disrupted atheroma, the cause of most acute coronary syndromes, results from:

- Weakening of the fibrous cap
- Thrombogenicity of the lipid core
USA/Non-ST Elevation ACS

- Generally caused by partially occlusive, platelet-rich thrombus

Sites of anti-thrombotic drug action

- Tissue factor
- Plasma clotting cascade
- Prothrombin
- Thrombin (Factor II)
- Fibrinogen
- Fibrin
- Thrombolytics
- Platelet aggregation
- Conformational activation of GPIIb/IIIa
- Thromboxane A2
- ADP
- Aspirin
- Ticlopidine
- Clopidogrel
- Prasugrel
- GPIIb/IIIa inhibitors
- Bivalirudin
- Hirudin
- Argatroban
- Factor Xa
- LMWH
- Heparin
- Thrombolytics
- Fondaparinux
- AT

ASA in UA/NSTEMI

Efficacy of Heparin + ASA vs ASA Alone in Reducing MI and Death: Meta-analysis
Outcomes with Aspirin Plus Heparin for NSTE ACS
Clinical Outcomes at 30 Days in Standard Care Arm

Risk of Death or MI

<table>
<thead>
<tr>
<th>Time (Days)</th>
<th>Enoxaparin</th>
<th>UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>8.8%</td>
<td>7.7%</td>
</tr>
<tr>
<td>44</td>
<td>5.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td>40</td>
<td>8.0%</td>
<td>9.1%</td>
</tr>
<tr>
<td>30</td>
<td>11.5%</td>
<td>11.9%</td>
</tr>
<tr>
<td>28</td>
<td>15.7%</td>
<td></td>
</tr>
</tbody>
</table>

TIMI IIb: Primary outcome at 43 days

Enoxaparin vs Unfractionated Heparin in UA/NSTEMI: A Systematic Overview (N=21,946)
Death or MI at 30 Days (ITT*)

<table>
<thead>
<tr>
<th>Trial</th>
<th>OR (95% CI)</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESSENCE</td>
<td>0.76 (0.58 – 1.01)</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>0.89 (0.70 – 1.11)</td>
<td></td>
</tr>
<tr>
<td>ACUTE II</td>
<td>0.97 (0.51 – 1.83)</td>
<td>UFH</td>
</tr>
<tr>
<td>INTERACT</td>
<td>0.54 (0.30 – 0.98)</td>
<td></td>
</tr>
<tr>
<td>A to Z</td>
<td>0.94 (0.73 – 1.20)</td>
<td></td>
</tr>
<tr>
<td>SYNERGY</td>
<td>0.96 (0.86 – 1.07)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.91 (0.83 – 0.99)</td>
<td></td>
</tr>
</tbody>
</table>

*ITT = Intent-to-Treat population.
No significant difference found in blood transfusion or minor bleeding at 7 days after randomization in overall safety population or in population of patients receiving no prerandomization antithrombin therapy.
**ACUITY: Study design—First randomization**

*Acute Catheterization and Urgent Intervention Triage Strategy*

N = 13,819 with ACS undergoing invasive strategy

**ACUITY: Treatment effects on primary outcomes—All patients**

<table>
<thead>
<tr>
<th></th>
<th>30-day rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH/ENOX + GP IIb/IIIa</td>
<td>7.3</td>
</tr>
<tr>
<td>Bivalirudin + GP IIb/IIIa</td>
<td>7.7</td>
</tr>
<tr>
<td>Bivalirudin alone*</td>
<td>11.7</td>
</tr>
</tbody>
</table>

*Stratified by pre-angiography conditions for abciximab monotherapy
†All patients received ASA and clopidogrel; ENOX = enoxaparin, UFH = unfractionated heparin

**ACUITY: Major bleeding predicts mortality—All patients**

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Patients at risk</th>
<th>With major bleeding</th>
<th>Without major bleeding</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>644</td>
<td>11,168</td>
<td>12,809</td>
<td>12.07%</td>
</tr>
<tr>
<td>2-14</td>
<td>623</td>
<td>12,151</td>
<td>12,715</td>
<td>11.51%</td>
</tr>
<tr>
<td>14-28</td>
<td>614</td>
<td>12,482</td>
<td>13,007</td>
<td>11.61%</td>
</tr>
<tr>
<td>28-35</td>
<td>609</td>
<td>12,761</td>
<td>13,234</td>
<td>11.65%</td>
</tr>
<tr>
<td>Over 35</td>
<td>600</td>
<td>12,803</td>
<td>13,369</td>
<td>12.05%</td>
</tr>
</tbody>
</table>

**ACUITY: Medical management**

- PCI
- CABG

**ACUITY: Risk stratification—PCI**

- UFH or ENOX + GP IIb/IIIa inhibitor†
- Bivalirudin + GP IIb/IIIa inhibitor†
- Bivalirudin alone†


**Acute Catheterization and Urgent Intervention Triage Strategy**

N = 13,819 with ACS undergoing invasive strategy

**Medical management**

- PCI
- CABG

*Stratified by pre-angiography conditions for abciximab monotherapy
†All patients received ASA and clopidogrel; ENOX = enoxaparin, UFH = unfractionated heparin

**Ischemic composite**

- Death, MI, unplanned revascularization for ischemia
- Non-CABG


**Mortality**

- OR 7.58 (4.68-12.18)
- Log rank P = 0.00001∗

*Unadjusted
†Stratified
ACUITY: Impact of MI and Major Bleeding (non-CABG) in the First 30 Days on Risk of Death Over 1 Year

- Both MI and Major Bleed (N = 546): 12.5%
- Major Bleed only (without MI) (N = 551): 12.2%
- MI only (without Major Bleed) (N = 611): 8.6%
- No MI or Major Bleed (N = 2,557): 3.4%

1-year Estimate: 28.9%

Days From Randomization

Mortality (%) vs. Days From Randomization


Potential Relationship Between Bleeding and Mortality

- Major Bleeding
- Hypotension
- Cessation of ASA/Clopidogrel
- Anti-thrombotics
- Transfusion
- Ischemia
- Stent thrombosis
- Inflammation
- Mortality


Patients with NSTE ACS, Chest discomfort < 24 hours
2 of 3: Age > 60, ST Segment Δ, ↑ cardiac markers

OASIS-V: Study Design:
Randomized, Double Blind

- UFH
- Direct Antithrombin
- LMWH
- Pentasaccharide

- Patients with NSTE ACS: Chest discomfort < 24 hours
  2 of 3: Age > 60, ST Segment Δ, ↑ cardiac markers

- Randomize
- ASA, Clop, GP IIb/IIIa, planned Cath/PCI as per local practice
- Fondaparinux 2.5 mg sc once daily
  PCI < 6 h: IV Fonda 2.5 mg without UFH, 5 with UFH
  PCI > 6 h: IV Fonda 2.5 mg with and 5.0 mg without UFH
- Enoxaparin 1 mg/kg sc twice daily
  PCI < 6 h: No additional UFH
  PCI > 6 h: 1 mg UFH

- N=20,000

- Outcomes:
  - Death, MI, refractory ischemia at 9 days
  - Major bleeding at 9 days
  - Death, MI, refractory ischemia, major bleeds at 9 days
  - Above & each component separately at day 30 & 6 months
  - First test non-inferiority, then test superiority

Anticoagulation in UA/NSTEMI

- 4 classes of anticoagulants are available
  - Unfractionated heparin (UFH)
  - Low-molecular-weight heparins (LMWH)
  - Direct thrombin inhibitors
  - Factor Xa inhibitors

- Current guidelines support use of UFH and LMWH, with enoxaparin preferred over UFH (Class IIa)

- Recent studies suggest direct thrombin inhibitors (bivalirudin) and factor Xa inhibitors (fondaparinux) may be appropriate new options for anticoagulation
  - Effective, lower risk of bleeding
ASA in UA/NSTEMI

Death or MI

<table>
<thead>
<tr>
<th>ASA dose</th>
<th>% odds reduction</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg daily</td>
<td>10.1 (P = 0.005)</td>
<td></td>
</tr>
<tr>
<td>325 mg daily</td>
<td>12.9 (P = 0.012)</td>
<td></td>
</tr>
<tr>
<td>150 mg daily</td>
<td>11.9 (P = 0.008)</td>
<td></td>
</tr>
<tr>
<td>&lt; 75 mg daily</td>
<td>17.1</td>
<td></td>
</tr>
</tbody>
</table>

Any ASA dose 23% ± 2 (p < 0.0001)

ATC: Efficacy of Aspirin at Various Doses in Reducing Vascular Events* in High-Risk Patients: What Dose is Best?

ASA dose % odds reduction

<table>
<thead>
<tr>
<th>ASA dose</th>
<th>CURE: ASA Group Bleds</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–1500 mg daily</td>
<td>&gt; 200 mg: 4.02%</td>
</tr>
<tr>
<td>160–325 mg daily</td>
<td>100–200 mg: 2.27%</td>
</tr>
<tr>
<td>75–150 mg daily</td>
<td>&lt; 100 mg: 2.03%</td>
</tr>
<tr>
<td>&lt; 75 mg daily</td>
<td></td>
</tr>
</tbody>
</table>

Any ASA dose 23% ± 2 (p < 0.0001)

*Vascular events included nonfatal MI, nonfatal stroke, and death from vascular causes.

Targets for antiplatelet therapies

Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events

CURE: Clopidogrel 75 mg q.d. + ASA 75-325 mg q.d.* (6259 patients)

CURE Study: Event-free Survival

CV Death, MI, or Stroke First 30 Days

- Clopidogrel: 6259
- Placebo: 6303

RRR: 21% 95% CI, 0.67–0.92  P=0.003

CV Death, MI, or Stroke >30 Days–1 Year

- Clopidogrel: 6259
- Placebo: 6303

RRR: 18% 95% CI, 0.70–0.85  P=0.009

CURE: Efficacy of Very Early Clopidogrel Therapy in ACS Patients

CV Death, MI, Stroke, Severe Ischemia Within First 24 Hours

- Placebo + Aspirin (n=6303)
- Clopidogrel + Aspirin (n=6259)

Relative Risk Reduction: 34%

CURE: Major/Life-Threatening Bleeds within 7 Days of CABG

<table>
<thead>
<tr>
<th></th>
<th>Plac</th>
<th>Clop</th>
<th>RR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stopped ≤ 5 days prior to CABG</td>
<td>N = 476</td>
<td>N = 436</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with Maj/LT Bleeds</td>
<td>6.3%</td>
<td>9.6%</td>
<td>1.53</td>
<td>0.06</td>
</tr>
<tr>
<td>Stopped &gt; 5 days prior to CABG</td>
<td>N = 454</td>
<td>N = 456</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with Maj/LT Bleeds</td>
<td>5.3%</td>
<td>4.4%</td>
<td>0.83</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Variability in Platelet Responsiveness to Clopidogrel Among 544 Individuals

Distribution of Adjusted to Baseline Response in Subjects After Clopidogrel
**Clopidogrel Resistance and Increased Risk of Ischemic Events**

*N = 60 Prim PCI for STEMI*

- **Quartiles of Response:**
  - Q1: 30%
  - Q2: 60%
  - Q3: 90%
  - Q4: 100%

- **5μM ADP Induced Plt Agg: Clop Resist**
  - Q1: 40%
  - Q2: 30%
  - Q3: 20%
  - Q4: 10%

- **Death/ACS/CVA by 6 m Days:**
  - Q1: 0%
  - Q2: 10%
  - Q3: 20%
  - Q4: 30%

- **P=0.007**

*Matetzky, Circulation 2004:109:3171*

**Clinical Relevance of Clopidogrel Nonresponsiveness as Measured by Multiplate Analyzer**

- **Clop Resist: 40%**
- **P=0.007**


**Can platelet function testing guide clopidogrel treatment?**

- **N = 162 undergoing PCI, randomized to single clopidogrel 600 mg loading dose (control) or up to 4 doses until VASP index <50%**

- **Major CV events:**
  - VASP-guided: 34%
  - Control: 38%

- **Bleeding events:**
  - VASP-guided: Major bleeding 1%, Minor bleeding 4%
  - Control: Major bleeding 1%, Minor bleeding 3%

- **CV event-free survival (%):**

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Control</th>
<th>VASP-guided</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>10</td>
<td>85%</td>
<td>85%</td>
</tr>
<tr>
<td>15</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>20</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>25</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>30</td>
<td>65%</td>
<td>65%</td>
</tr>
</tbody>
</table>


**POPULAR Study**

- **Survival free from Primary Endpoint:**

  | Composite of death, non-fatal myocardial infarction, definite stent thrombosis and stroke |
  |------------------|------------------|------------------|------------------|
  | Fibrinogen (mg/dL) | Urokinase (U/kg) | Clopidogrel (mg) | Primary endpoint |
  | 300               | 400              | 600              | 80%              |
  | 400               | 500              | 800              | 90%              |

*Presented at the AHA Scientific Meetings, Orlando, 2009*
Genetic Variations and Clinical Outcomes in Patients Taking Clopidogrel

**1st Efficacy Outcome**
- Carriers of CYP2C19 reduced-function allele:
  - CV death, MI or stroke (%): 12.1
  - Days Since Randomization: [Graph showing data points and trend]
- Non-carriers of CYP2C19 reduced-function allele:
  - CV death, MI or stroke (%): [Data points and trend]

**Stent Thrombosis**
- Carriers of CYP2C19 reduced-function allele:
  - Definite or Probable Stent Thrombosis (%): 2.6
  - Days Since Randomization: [Graph showing data points and trend]
- Non-carriers of CYP2C19 reduced-function allele:
  - Definite or Probable Stent Thrombosis (%): [Data points and trend]

CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel. Optimal dose regimen for poor metabolizers has yet to be determined.

**Clopidogrel Response Variability (300 mg vs 600 mg, n=194)**

- 300 mg Clopidogrel:
  - Resistance = 28% (300 mg)
- 600 mg Clopidogrel:
  - Resistance = 8%

**Visual Aid 1:**
- **Title:** Genetic Variations and Clinical Outcomes in Patients Taking Clopidogrel
- **Graphs:**
  - 1st Efficacy Outcome
  - Stent Thrombosis

**Visual Aid 2:**
- **Title:** Clopidogrel Response Variability (300 mg vs 600 mg, n=194)
- **Graphs:**
  - Resistance at 24 hours

**Visual Aid 3:**
- **Title:** Successful PCI with DES without major complication or GPIb/IIIa use
- **Graphs:**
  - VerifyNow P2Y12 Assay 12-24 hours post-PCI

**Visual Aid 4:**
- **Title:** Genetic Variations and Clinical Outcomes in Patients Taking Clopidogrel
- **Graphs:**
  - Efficacy Outcome
  - Stent Thrombosis
**Clopidogrel 600 mg vs 300 mg loading dose**

Meta-analysis, N = 1567; Primary endpoint: Cardiac death or MI at 1 month

<table>
<thead>
<tr>
<th>Trial</th>
<th>Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALBION</td>
<td>1.03 (0.09-11.5)</td>
</tr>
<tr>
<td>ARMYDA-2</td>
<td>0.35 (0.14-0.87)</td>
</tr>
<tr>
<td>CLEAR PLATELETS</td>
<td>0.36 (0.05-2.61)</td>
</tr>
<tr>
<td>Cuisset et al</td>
<td>0.46 (0.19-1.09)</td>
</tr>
<tr>
<td>Gurbel et al*</td>
<td>1.28 (0.44-3.74)</td>
</tr>
<tr>
<td>ISAR-CHOICE*</td>
<td>0.42 (0.23-0.75)</td>
</tr>
<tr>
<td>Muller et al*</td>
<td>0.54 (0.32-0.90)</td>
</tr>
<tr>
<td>Non-randomized studies</td>
<td>1.28 (0.44-3.74)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.59 (0.32-0.90)</td>
</tr>
</tbody>
</table>

No events in either group

*Peto fixed-effect method

---

**CURRENT-OASIS 7: Study Design**

**2x2 Factorial**

- **Clopidogrel 300 mg Days 1-7 75 mg**
- **ASA ≥ 300 mg Day 1**
- **Clopidogrel 75 mg daily**

- **Clopidogrel 600 mg Days 1-7 150 mg**
- **ASA ≥ 300 mg Day 1**
- **Clopidogrel 75 mg daily**

N=25,087

ACS (NSTE-ACS or STEMI) patients planned for early PCI within 24 hours (ischemic ECG changes or Troponin biomarker)

---

**Cumulative Hazard Ratios for the Primary Outcome at 30 Days, According to Treatment Group**

---

**Hazard Ratios for the Primary Outcome in the Clopidogrel and Aspirin Dose Groups According to the Factorial Design**

---

ASA = acetylsalicylic acid; ECG = electrocardiogram; PCI = percutaneous coronary intervention; STEMI = ST segment elevation myocardial infarction.

Hazard Ratios for the Primary Outcome According to the Clopidogrel Dose in Selected Subgroups


CURRENT - Clopidogrel: Double Versus Standard Dose Sub-Group of PCI Patients (N=17,232)

CV Death, MI or Stroke

CURRENT/OASIS 7: Bleeding Events by 30 Days (PCI Population)

0 2

0 0.5 1.1 1.6 0.8 1.1 0.2 0.1 0.04 0.05

Standard Double

Bleeds

Major

Severe

ARD, 0.5%

HR, 1.44

P=0.006

ARD, 0.3%

HR, 1.39

P=0.034

ICH

ARD, 0.01%

P=0.69

Fatals

ARD, -0.1%

P=0.13

ARD=absolute risk difference; HR=hazard ratio; ICH=intracerebral hemorrhage; PCI=percutaneous coronary intervention; TIMI= thrombolysis in myocardial infarction.

Mehta SR. Presented at: Annual Meeting of the European Society of Cardiology; August 29-September 2, 2009; Barcelona, Spain.
Active Metabolite Formation

**Prasugrel**

**Sankyo Ann Report 51:** 1999

**Pro-drug**

Oxidation (Cytochrome P450)

**HOO**

**CHO**

**O**

**O**

**F**

**Prasugrel**

**HS**

**HS**

**NN**

**O**

**O**

**F**

**OO**

**F**

**OO**

**Cl**

**Cl**

**OCH**

**OCH**

**HH**

**HH**

**Cl**

**Cl**

**OCH**

**OCH**

**HH**

**HH**

**Active Metabolite**

**HOO**

**CHO**

**O**

**O**

**F**

**Prasugrel**

**HS**

**HS**

**NN**

**O**

**O**

**F**

**OO**

**F**

**OO**

**Cl**

**Cl**

**OCH**

**OCH**

**HH**

**HH**

**Cl**

**Cl**

**OCH**

**OCH**

**HH**

**HH**

**Active Metabolite**

---

**PRINCIPLE-TIMI 44: Inhibition of Platelet Aggregation With Prasugrel**

- Irreversible inhibitor of P2Y12
- Pathway of activation differs from clopidogrel
- Rapid onset (< 2 h)
- More potent than clopidogrel
- Less variable than clopidogrel

---

**Inhibition of Platelet Aggregation (IPA) at 24 Hours, Clopidogrel vs. Prasugrel**

- Clopidogrel responder
- Clopidogrel non-responder

---

**TRITON TIMI-38: Treatment effects on primary efficacy and key safety endpoints**

- N=15,600 ACS Patients With Planned PCI
- **Cardiovascular Death, MI, Stroke**
- **TIMI Major Non-CABG Bleeds**
- **CABG=coronary artery bypass surgery; HR=hazard ratio; MI=myocardial infarction; TIMI=thrombolysis in myocardial infarction.**

---

BMS = bare-metal stent; DES = drug-eluting stent; HR = hazard ratio.


TRITON TIMI-38: Definite/Probable Stent Thrombosis: Any Stent (N=12,844)

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
<th>400</th>
<th>450</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clot</td>
<td>2.5</td>
<td>2</td>
<td>1.5</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>2.35%</td>
<td>2%</td>
<td>1.5%</td>
<td>1.0%</td>
<td>0.5%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Significant reductions both with BMS, DES

HR, 0.48 (0.36-0.65) P=0.0001

P<0.0001

2.35%

1.13%

52%

TRITON-TIMI 38 post hoc analysis: Net clinical benefit in subgroups at increased bleeding risk

<table>
<thead>
<tr>
<th>Prior stroke/TIA</th>
<th>Prasugrel better</th>
<th>Clopidogrel better</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (n = 509; 4%)</td>
<td>1.76% (0.97-3.22)</td>
<td>2.35% (1.44-3.80)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>No (n = 12,340; 95%)</td>
<td>2.13% (1.36-3.34)</td>
<td>1.22% (0.73-2.02)</td>
<td>P=0.18</td>
</tr>
</tbody>
</table>

Age

| <75 y (n = 11,072; 87%) | 1.30% (0.82-2.03) | 0.86% (0.52-1.41) | -16 |
| ≥75 yrs (n = 1785; 13%) | 1.91% (1.16-3.18) | 1.22% (0.73-2.02) | -10 |

Weight

| <60 kg (n = 684; 5%) | 1.13% (0.57-2.22) | 0.90% (0.44-1.81) | +3 |
| ≥60 kg (n = 12,160; 95%) | 2.25% (1.70-3.06) | 1.49% (1.08-2.08) | -14 |

Overall

| No (n = 12,948; 95%) | 2.13% (1.36-3.34) | 1.34% (0.87-2.08) | -13 |
| Yes (n = 509; 4%) | 1.76% (0.97-3.22) | 1.30% (0.82-2.03) | +4 |

This information concerns a use that has not been approved by the US Food and Drug Administration.


Ticagrelor

- First reversible oral ADP antagonist
- New class of P2Y12 inhibitors
  - Not a thienopyridine or ATP antagonist
  - Direct-acting (not a pro-drug)
- Rapid onset (<2 hours)
- Plasma t1/2 ~7-8 hours
- Greater and more consistent inhibition of ADP-induced platelet activation than clopidogrel

PLATO

Can PLATElet Inhibition be Optimized to Prevent Vascular Events?

18,624 patients within 24 h of an index ACS (clopidogrel treated or naïve) (STEMI for primary PCI or NSTEMI)

Primary end point:
Time to first occurrence of the composite of CV death, MI, or stroke

Primary safety end point:
Major bleeding

ASA 75-100 mg QD

180 mg Ticagrelor BID

Clopidogrel 75 mg QD

Double-blind, double-dummy
6-12 months exposure

At least 2 inclusion criteria:
1. ST segment changes
2. 1 or more of:
   - ≥60 years old
   - Previous MI/CABG
   - Known >1V CAD
   - DM
   - PAD
   - Renal dysfunction

Ticagrelor load: Additional 300 mg allowed pre-PCI

CAD=coronary artery disease; CABG=coronary artery bypass surgery; CV=cardiovascular; DM=diabetes mellitus; STEMI=ST segment elevation myocardial infarction; MI=myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; PAD=peripheral arterial disease; ASA=aspirin; QD=every day; BID=twice daily; CV=cardiovascular; MI=myocardial infarction; STEMI=ST segment elevation myocardial infarction; NSTEMI=non-ST segment elevation myocardial infarction; PCI=percutaneous coronary intervention; DM=diabetes mellitus.
PLATO: Primary Efficacy Analysis
Cardiovascular Death, MI, or Stroke

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N at risk</td>
<td>9,291</td>
<td>9,333</td>
<td>8,521</td>
<td>8,628</td>
<td>8,362</td>
</tr>
<tr>
<td>Days After Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Incidence (%)

- Clopidogrel: 12
- Ticagrelor: 11

HR, 0.84 (95% CI, 0.77-0.92)

P <0.001

---

PLATO: 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 (1.9)</td>
<td>0.67 (0.50-0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>118 (2.1)</td>
<td>158 (2.8)</td>
<td>0.75 (0.59-0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, definite</td>
<td>155 (2.8)</td>
<td>202 (3.6)</td>
<td>0.77 (0.62-0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

---

PLATO: Bleeding and Safety Events

- TIMI Major Bleeds
- Non-CABG TIMI Major Bleeds
- Non-CABG Major TIMI bleed
- Other Safety: Pauses ≥3 sec, P=0.01
- Dyspnea, ARD, ICH

---

PLATO: Effect of CYP2C19 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes. Landmark analysis from day 31

---

Source: The Lancet Wallentin (DOI:10.1016/S0140-6736(10)61274-3)
PLATO: Effect of CYP2C19 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes

Source: The Lancet
Wallentin (DOI:10.1016/S0140-6736(10)61274-3)

PLATO: Effect of CYP2C19 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes

30-Day Death or Nonfatal MI
Risk Ratio and 95% CI

Placebo Better
GP IIb/IIIa Inhibitor Better

Trial
Pooled

PRISM 11.5%

10.7% 29,855

0.92 (0.86, 0.995)
P = .037

PRISM-PLUS 11.9%

10.2% 1,915

PARAGON A 15.7%

14.2% 9,461

PARAGON B 11.4%

10.5% 5,165

GUSTO-IV ACS 8.0%

7.1% 7,800

0.92 (0.86, 0.995) P = .037

ISAR-REACT 2 Trial: Study Design

2022 patients with an episode of angina within the preceding 48 hours and an elevated troponin T level or new ST-segment depression of ≥0.1 mV or transient (<20 minutes) ST-segment elevation of ≥0.1 mV or new or presumed new bundle-branch block, significant angiographic lesions in a native coronary vessel or bypass graft amenable to and requiring a PCI.

Placebo-Controlled. Randomized. Blinded.
24% female, mean age 66 years, mean follow-up 30 days

Abciximab (usual bolus or infusion dose) n=1012
Placebo n=1010

Pretreatment with high-dose (600 mg) clopidogrel at least 2 hours preprocedure


Adapted with permission from www.clinicaltrialresults.org.

ISAR-REACT 2: High-Risk ACS Patients Undergoing PCI, Pretreated With ASA, Clopidogrel 600 mg, and UFH

Troponin >0.03 µg/L Log-Rank P=0.02

ISAR-REACT 2, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2.

### Summary

- Risk stratification (incorporating risk scores, initial and serial ECGs, and biomarker findings) is an integral prerequisite to decision making in ACS.
- Whether an early invasive or early conservative strategy is selected, antiplatelet and anticoagulant therapy should be initiated as soon as possible after presentation.
- Clopidogrel use includes higher loading-dose options, brief higher maintenance doses; consideration of Prasugrel.
- Bivalirudin and fondaparinux are new anticoagulant treatment alternatives to enoxaparin and UFH.
- More aggressive long-term antiplatelet and statin therapy, and secondary prevention measures are recommended.

---

#### 2007 ACC/AHA UA/NSTEMI Guideline Revision

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INITIAL MID Tx</th>
<th>DURING PCI</th>
<th>AFTER PCI</th>
<th>DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>325-650 mg topical, orally or chewed</td>
<td>No additional treatment</td>
<td>100-325 mg daily</td>
<td>Max 12-4 months after death, 6 months after PCI, and 1 month after PES, followed by daily therapy, or 75 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dalteparin</strong></td>
<td>150-300 mg daily</td>
<td>No additional treatment</td>
<td>150-400 mg daily</td>
<td>Max 10-12 months after death, 6 months after PCI, and 1 month after PES, followed by daily therapy, or 75 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bivalirudin</strong></td>
<td>0.25 mg/kg/h infusion</td>
<td>No additional treatment</td>
<td>0.25-0.75 mg/kg bolus</td>
<td>Max 6 months after death, 6 months after PCI, and 1 month after PES, followed by daily therapy, or 75 mg every other day</td>
</tr>
<tr>
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#### 2007 ACC/AHA UA/NSTEMI Guideline Revision (cont.)

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<th>DRUG</th>
<th>INITIAL MID Tx</th>
<th>DURING PCI</th>
<th>AFTER PCI</th>
<th>DISCHARGE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clopidogrel</strong></td>
<td>60 mg SC every 12 h</td>
<td>No additional treatment</td>
<td>60-325 mg</td>
<td>Max 12-4 months after death, 6 months after PCI, and 1 month after PES, followed by daily therapy, or 75 mg every other day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unfractionated Heparin</strong></td>
<td>4000-8000 U IV bolus</td>
<td>No treatment</td>
<td>70-100 U/kg bolus</td>
<td>Max 12-4 months after death, 6 months after PCI, and 1 month after PES, followed by daily therapy, or 75 mg every other day</td>
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<td>No additional treatment</td>
<td>150-400 mg daily</td>
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#### 2007 ACC/AHA UA/NSTEMI Guideline Revision (cont.)

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</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>DRUG</th>
<th>INITIAL MED TREAT</th>
<th>DURING PCI</th>
<th>AFTER PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Continue MD infusion for 12 h</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>LD of IV bolus of 180 mcg/kg MD of IV infusion of 0.1 mcg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance &lt;30 mL/min</td>
<td>Continue infusion</td>
<td>Continue MD infusion for 12 h</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>LD of IV infusion of 0.4 mcg per kg per min for 30 min MD of IV infusion of 0.1 mcg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance &lt;60 mL/min</td>
<td>Continue infusion</td>
<td>Continue MD infusion for 12 h</td>
</tr>
</tbody>
</table>