Recent Advances in the Management of Unstable Cardiac Ischemic Syndromes

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Monterey, CA
May 1, 2010

Spectrum of Acute Ischemic CAD

<table>
<thead>
<tr>
<th>No ST elevation</th>
<th>ST elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>NSTEMI</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>STEMI</td>
</tr>
</tbody>
</table>

ACUTE CORONARY SYNDROMES

~1 Million Discharges Per Year

~0.4 Million Discharges Per Year

Approach to Preventing the Consequences of a Vulnerable Plaque Rupture or Erosion

Manage the culprit lesion either invasively or conservatively based on quantifying the potential immediate and long term risk, with the primary goal of immediate (STEMI) or early (NSTEMI) restoration of maximum epicardial and microvascular coronary blood flow.

Utilize long term dual antiplatelet therapy of at least one year (whether or not a PCI was done) to minimize the potential of similar future episodes arising either from the same or other vulnerable areas.

Insure maximum long term medical management as well as appropriate lifestyle changes to pacify other potential vulnerable plaques and to arrest the generalized progression of atherothrombosis.
Kaplan-Meier mortality curves of STEMI vs NSTEMI showing all-cause mortality from the time of cardiac catheterization

Mortality

Time (years)

NSTEMI

STEMI

Management failure

n=1957

n=2399

Effect of Door-to-Balloon Time on Mortality in Patients With STEMI

Door-to-Balloon Time (min)

In-hospital Mortality, %

NRMI 3 and 4 (1999-2002)


2007 ACC/AHA STEMI Focused Update

Reperfusion Therapy for STEMI

Class I Modified Recommendations

• STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact as a systems goal (Level of Evidence: A)

• STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact should be treated with fibrinolytic therapy within 30 minutes of hospital presentation as a systems goal unless fibrinolytic therapy is contraindicated (Level of Evidence: B)

Timing of Reperfusion Therapy by Pre- versus In-Hospital ECG Utilization

<table>
<thead>
<tr>
<th>Reperfusion Times</th>
<th>Prehospital ECG (n=1941)</th>
<th>In-Hospital ECG (n=5157)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fibrinolytic agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTN time (min)≤30 min</td>
<td>19 (10, 30)</td>
<td>29 (19, 45)</td>
<td>.003</td>
</tr>
<tr>
<td><strong>Primary PCI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTB time (min)&lt;90 min</td>
<td>61 (46, 79)</td>
<td>75 (58, 95)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DTB time &lt;90 min</td>
<td>82</td>
<td>70</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>


TRANSFER-AMI

Trial design: Patients with high-risk STEMI who presented where timely Primary PCI was not feasible were randomized to a pharmacoinvasive (ASA, TNK, UFH or Enox, clopidogrel strategy with emergent transfer for PCI within 6 hours of fibrinolysis) or standard treatment after fibrinolysis.

Preliminary Results:
- Primary end point (death, MI, heart failure, severe recurrent ischemia, or shock at 30 days): 10.6% in pharmacoinvasive arm vs 16.6% in standard treatment arm (P=0.0013)
- Reinfarction: 3.3% vs 6.0% (P=0.044)
- Recurrent ischemia: 0.2% vs 2.2% (P=0.02)

Conclusions:
- Pharmacoinvasive approach safe and efficacious compared with treatment with thrombolytics and transfer for rescue PCI only. No excess in major bleeding
- Optimal window: 6 hours

NORDISTEMI Study design

Acute STEMI < 6 hours
Expected time delay to PCI ≥ 90 min ≥ 70 years

Aspirin 300 mg, Teneceplase (TNK)
Enoxaparin 30 mg iv + 1mg/kg sc, Clopidogrel 300mg

Immediate transfer for angiography/PCI
Ischemia-guided treatment in local hospitals with transfer for rescue PCI if needed

Clinical follow-up: 1, 3, 7, 12 months
SPECT: 3 months

Dierske D, et al. ESC 2009 Congress; Barcelona, Spain.
In STEMI patients undergoing PCI who are at high risk of bleeding, Bivalirudin anticoagulation is reasonable.

It is reasonable for high risk patients who receive fibrinolytic therapy as primary reperfusion therapy at a non-PCI capable facility to be transferred as soon as possible to a PCI-capable facility where PCI can be performed either when needed or as a pharmacoinvasive strategy. Consideration should be given to initiating a preparatory antithrombotic (anticoagulant plus antiplatelet) regimen before and during patient transfer to the catheterization laboratory.

It is reasonable to use an insulin-based regimen to achieve and maintain glucose levels less than 180 mg/dL while avoiding hypoglycemia for patients with STEMI with either a complicated or uncomplicated course.


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### Invasive Management of UA/NSTEMI Meta-analysis: \( \downarrow \) Death/MI at End of Follow-up (Mean 17.3 months)

<table>
<thead>
<tr>
<th>Trial (N)</th>
<th>Inv (%)</th>
<th>Cons (%)</th>
<th>Odds Ratio Death or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI IIIB (1473)</td>
<td>11.6</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>VANGWISH (920)</td>
<td>32.9</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>MATE (281)</td>
<td>14.4</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>FRISC II (2457)</td>
<td>10.4</td>
<td>14.1</td>
<td></td>
</tr>
<tr>
<td>TACTICS (2220)</td>
<td>7.3</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>VINO (131)</td>
<td>6.3</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>RITA 3 (1810)</td>
<td>10.6</td>
<td>12.9</td>
<td></td>
</tr>
<tr>
<td>Total (N = 9212)</td>
<td>12.2</td>
<td>14.4</td>
<td>OR 0.82, P&lt;0.001 2.2% abs reduction</td>
</tr>
</tbody>
</table>

Acute care patterns by early invasive management

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No early invasive care (n=9119)</th>
<th>Early invasive care (n=8027)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>87.7%</td>
<td>93.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>26.1%</td>
<td>51.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B blocker</td>
<td>71.9%</td>
<td>77.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heparin</td>
<td>73.7%</td>
<td>88.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>14.2%</td>
<td>50.9%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**TIMACS**

Trial design: 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.

- No difference in primary outcomes (death, MI, stroke) between the two arms (HR, 1.13; 95% CI, 0.78-1.64; P = .13), except in high-risk patients (GRACE risk score >140) (HR, 0.72; 95% CI, 0.51-1.03; P = .075).
- Death, MI, refractory ischemia in early invasive arm (P < 0.0001), death (P = .15), stroke (P = .74) similar.
- Major bleeding was similar (P = .53).

**Conclusions**
- An early invasive strategy (within 24 hours) is not associated with harm compared with a delayed invasive strategy (after 36 hours) in patients with NSTEMI, and may be beneficial in high-risk patients.
- Significant reduction in refractory ischemia with an early invasive strategy.

**ABOARD study design**

- **NSTE-ACS (n = 352)**
  - 2 of 3 Criteria: Ischemic symptom, ST-T change, troponin rise with TIMI score ≥3
  - IVRS RANDOMIZATION
  - Immediate cath
  - Next day cath
  - All PCIs on abciximab
  - 1-month Follow-up

**JAMA 2009;302:947-954**
Composite Ischemic Endpoints at 1 month

Optimal Timing for Pretreatment With Clopidogrel 300 mg Before PCI: CREDO Study

Pts randomize to receive study drug or placebo between 3 and 24 hours before PCI
For pretreatment ≥15 h vs placebo, P = .018; for pretreatment ≥15 h vs <15 h, P = .033;
for placebo vs pretreatment <15 h, P = .72.

ARMYDA-ACS: Design and Primary End Point

Primary end point: death, MI, or unplanned revasc. at 30 days
P<.01

In initially stabilized patients, an initially conservative (i.e., a selectively invasive) strategy may be considered as a treatment strategy for UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events, including those who are troponin positive. (Class IIb) “The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made by considering physician and patient preference.” (Class IIb)

A conservative strategy is recommended in women with low-risk features (I, B).
**Meta analysis – Death in women**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Dead / Total</th>
<th>Odds ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine</td>
<td>Selective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRISC II</td>
<td>14 / 348</td>
<td>1.25</td>
<td>0.58</td>
<td>2.70</td>
<td>0.57</td>
</tr>
<tr>
<td>RITA 3</td>
<td>18 / 350</td>
<td>2.20</td>
<td>0.94</td>
<td>5.12</td>
<td>0.07</td>
</tr>
<tr>
<td>TACTICS</td>
<td>15 / 395</td>
<td>1.06</td>
<td>0.50</td>
<td>2.26</td>
<td>0.88</td>
</tr>
<tr>
<td>OASIS 5</td>
<td>8 / 92</td>
<td>8.67</td>
<td>1.06</td>
<td>70.77</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Adjunctive Thrombectomy and Embolic Protection Devices in AMI: Meta-analysis**

* Meta-analysis of 30 randomized clinical trials with 6415 patients.


**Sites of Anticoagulant and Antiplatelet Drug Action**
ARMYDA-2 Study: Design and Primary End Point

Primary composite of death, MI, or target vessel revasc. at 30 days

- **High Loading Dose of Clopidogrel**
  - 600 mg Pre-PCI
- **Standard Loading Dose of Clopidogrel**
  - 300 mg Pre-PCI

Randomized 4-8 Hours Pre-PCI

255 patients with stable CAD or NSTEMI prior to PCI
10% received GP IIb/IIIa inhibitors
20% received drug-eluting stents


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CURRENT/OASIS-7
Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions

Patients with UA or MI planned for early invasive strategy (PCI intended as early as possible within 24 h)

- **Clopidogrel High-Dose Group**
  - Clopidogrel 600 mg loading dose day 1 followed by 75 mg from days 2 to 7
  - 75 mg from days 8 to 30

- **Clopidogrel Standard-Dose Group**
  - Clopidogrel 300 mg (+ placebo) day 1 followed by 75 mg (+ placebo) from days 2 to 7
  - 75 mg from days 8 to 30

Randomized

ASA low-dose group
- At least 300 mg day 1
- 75–100 mg from days 2 to 30

ASA high-dose group
- At least 300 mg day 1
- 300–325 mg from days 2 to 30


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Clopidogrel: Double vs Standard Dose
Primary Outcome: PCI Patients

CV Death, MI or Stroke

- **Clopidogrel Standard**
  - HR 0.85
  - 95% CI 0.74-0.99
  - RRR 15%
  - **Clopidogrel Double**

ECC Aug 30, 2009

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P=0.036

ECC Aug 30, 2009
**TRITON TIMI-38**  
**Main trial design**

**ACS (STEMI or UA/NSTEMI) and planned PCI**  
ASA  
N = 13,608  
**CLOPIDOGREL**  
300 mg LD/75 mg MD  
**PRASUGREL**  
60 mg LD/10 mg MD  
Duration of therapy: 6-15 months

1<sup>st</sup> end point: CV death, MI, stroke  
2<sup>nd</sup> end point: Stent thrombosis  
Safety end points: TIMI major bleeds, life-threatening bleeds
TRITON TIMI-38: Primary results

<table>
<thead>
<tr>
<th>End Point (%)</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>HR 1.32</th>
<th>(1.03-1.68)</th>
<th>P = 0.03</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stroke</td>
<td>12.1</td>
<td>9.9</td>
<td>1.2</td>
<td>(0.73-0.90)</td>
<td>0.0004</td>
</tr>
<tr>
<td>TIMI major</td>
<td>1.8</td>
<td>1.4</td>
<td>1.3</td>
<td>(1.03-1.68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Life threatening</td>
<td>0.9</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlife</td>
<td>0.1</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CABG</td>
<td>0.3</td>
<td>0.3</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening</td>
<td>0.9</td>
<td>1.4</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonlife</td>
<td>0.9</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CABG</td>
<td>0.1</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>0.3</td>
<td>0.3</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TRITON TIMI-38 STEMI cohort

Efficacy endpoints at 15 months

No increase in TIMI major or minor non-CABG bleeding was observed

Montalescot et al. ESC 2008

2009 ACC/AHA STEMI and PCI Guidelines Focused Updates

Thienopyridines

Class 3 New Recommendation

In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen

Pharmacogenetics of antiplatelet therapy

CYP2C19 and CVD, MI, or Stroke

CLOPIDOGREL

PRASUGREL

PLATO study design

NSTEMI ACS (moderate-to-high risk); STEMI (if primary PCI) (N=18,624)

Clopidogrel-treated or -naive; randomized <24 hours of index event

At randomization, 13,408 (72%) of patients were specified by the investigator: intent for invasive strategy

Primary endpoint: CV death + MI + Stroke

Primary safety endpoint: Total major bleeding

PCI = percutaneous coronary intervention; CV = cardiovascular; PI = principal investigator

Primary endpoint: CV death, MI or stroke

HR: 0.84 (95% CI = 0.75–0.94), p=0.0025

HR: 0.99 (95% CI = 0.89–1.10), p=0.88 for major bleeding
**Possible Relationship Between Bleeding and Mortality in ACS**

**Major Bleeding**
- Hypotension
- Cessation of ASA/Clopidogrel
- Transfusion

**Ischemia**
- Stent Thrombosis
- Inflammation

**Mortality**


**2009 ACC/AHA STEMI and PCI Guidelines Focused Updates**

**Use of GP IIb/IIIa Inhibitors in STEMI**

**Class 2b**  
*Modified Recommendation*

The usefulness of glycoprotein IIb/IIIa receptor antagonists (as part of a preparatory pharmacologic strategy for patients with STEMI prior to arrival in the cardiac catheterization laboratory for angiography) is uncertain

**1-Year Mortality (All-Cause)**

<table>
<thead>
<tr>
<th>Time in Months</th>
<th>Bivalirudin alone (n=1800)</th>
<th>Heparin + GPIIb/IIIa (n=1802)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Δ = 1.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.036</td>
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<td></td>
</tr>
</tbody>
</table>

**Immediate Pharmacotherapy for STEMI Patient Managed by Primary PCI**

**Aspirin**
- Start anticoagulant in ED
- IV Morphine as needed for analgesia
- Sublingual NTG followed by IV Drip

If enoxaparin or UFH started, switch to IV Bolus of bivalirudin once PCI begun. If procedure lasting longer than 30 minutes start bivalirudin infusion

If bivalirudin not used, consider adding a GP 2b/3a inhibitor, clopid. 600 mg or Prasugrel 60 mg after angio confirms PCI need

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

**Initial Invasive Strategy: Antiplatelet, Anticoagulant Therapy**

- Aspirin
- Initiate anticoagulant therapy as soon as possible after presentation (I, A). Regimens with established efficacy:
  - Enoxaparin or UFH (I, A)
  - Bivalirudin or fondaparinux (I, B)
- Prior to angiography, initiate one (I, A) or both (IIa, B)
  - Clopidogrel
  - IV GP IIb/IIIa inhibitor

Use both if:
- Delay to angiography
- High-risk features
- Early recurrent ischemic syndromes

Secondary Prevention: Additional Recommendations

- β-blockers
- ACE inhibitors/ARBs
- Aldosterone blockade
- Lipid management
  - Statin regardless of baseline LDL-C initiated prior to discharge
  - Goal LDL-C <100 mg/dL
  - LDL <70 mg/dL reasonable
- Treatment of triglycerides and non-HDL-C useful
  - If TG 200-499 mg/dL, non-HDL-C should be <130 mg/dL
  - TG ≥500 mg/dL, fibrate or niacin before LDL-C lowering to prevent pancreatitis
- Encouraging consumption of omega-3 fatty acids for risk reduction reasonable
  - For treatment of elevated triglycerides, higher doses may be used for risk reduction

Secondary Prevention: Additional Recommendations (cont)

- BP control
  - <140/90 mm Hg
  - <130/80 mm Hg with diabetes or CKD
- Diabetes management: HbA1c <7%
- Smoking cessation/no environmental smoke exposure
  - Education, referral programs, drug therapy
- Physical activity (30-60 min, 7 d/wk; min 5 d/wk)
- Weight management
  - BMI 18.5-24.9 kg/m²
  - Waist circumference: men, <40 in; women, <35 in
- Discharge education/referral
- Stepped-care approach to musculoskeletal pain management
- Annual influenza immunization
- HRT, antioxidant vitamin supplements (C, E, beta carotene) and folic acid not recommended