Current Considerations in the Management of Acute Coronary Syndromes: An Update of the New ACC/AHA Guidelines for UA and Non-STEMI

ACC/AHA Guidelines at http://www.americanheart.org/
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Objectives

- Define and provide an overview of the pathophysiology and epidemiology of acute coronary syndromes (ACS) in the U.S.
- Describe specific drug related evidence for the new AHA/ACC Guidelines.
- Highlight key clinical trials supporting some the new perspectives of the guidelines for the medical management of UA/NSTEMI.

What is an Acute Coronary Syndrome?

Acute Coronary Syndromes

No ST Segment Elevation

ST Segment Elevation

Unstable Angina

NSTEMI

Myocardial Infarction

NQMI

QWMI

Spectrum of Acute Coronary Syndromes

Stable Angina

Unstable Angina

Non-Q wave MI

Q wave MI

Non ST Elevation ACS

ST Elevation MI

ECG - ST

CK-MB

Troponin

CRP

EKG - ST

ECG Changes

ST Elevation

T wave Inversion

ST Segment Depression

Electrocardiographic Waves, Intervals, and Segments

Cannon CP. 1999

2002 ACC/AHA Guidelines
**UA, NSTEMI and STEMI, What’s the difference?**

<table>
<thead>
<tr>
<th>Diagnostic Tool</th>
<th>UA</th>
<th>NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Symptoms</td>
<td>Severity and duration are similar</td>
<td>None or Depression</td>
<td>Elevation of pain is increased and ongoing</td>
</tr>
<tr>
<td>ST Segment (ECG)</td>
<td>None or Depression</td>
<td>None or Depression</td>
<td>Elevation</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Not elevated</td>
<td>Elevated troponin, and/or CK-MB</td>
<td></td>
</tr>
</tbody>
</table>


**Hospitalizations in the U.S. Due to Acute Coronary Syndromes**

1.83 Million Hospital Admissions

UA/NSTEMI

1.42 million admissions per year

STEMI

0.41 million admissions per year


**Atherothrombosis Timeline**

<table>
<thead>
<tr>
<th>From first decade</th>
<th>From third decade</th>
<th>From fourth decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelial Dysfunction</td>
<td>Fatty plaque</td>
<td>Intermediate lesion</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>Fibrous plaque</td>
<td>Complicated lesion/atheroma</td>
</tr>
</tbody>
</table>

Growth mainly by lipid accumulation and collagen thrombosis, endothelium.


**Potential Pharmacologic Interventions in ACS**

1. Downstream from thrombus: myocardial ischemia/necrosis (Beta-blockers, Nitrates etc)

2. Activation of clotting cascade - Thrombin (Heparin/LMWH)

3. Platelet adhesion/activation/aggregation/microembolization (ASA, clopidogrel, IIb/IIIa inhibitors)

4. Plaque rupture, Cholesterol content, Inflammation (hs-CRP), Infection (Statins, Antibiotics)

**Components of Coronary Thrombus**

- Platelets
- Fibrin
- Thrombin
- Antiplatelet Therapy
  - Aspirin
  - GP IIb/IIIa inhibitors
  - ADP inhibitors
- Plasminogen Activators
  - t-PA
  - r-PA
  - SK
  - TNK
- Antithrombin Therapy
  - Heparin
  - LMWH
  - Direct Antithrombin Inhibitors

Cannon, JACC v.34, no.5, 1999

**Updated ACC/AHA UA/NSTEMI Guidelines Classes of recommendations**

1. Intervention is useful and effective

2. Evidence conflicts/opinions differ but leans towards efficacy

3. Evidence conflicts/opinions differ but leans against efficacy

4. Intervention is not useful/effective and may be harmful

- A: Data derived from large multiple randomized clinical trials
- B: Limited randomized trials
- C: Expert Consensus
ACC/AHA Practice Guidelines 2002

I. Introduction
II. Initial Evaluation and Management
III. Hospital Care
   A. Anti-Ischemic Therapy
   B. Antiplatelet and Anticoagulation Therapy
   C. Risk Stratification
   D. Early Conservative Versus Invasive Strategies
IV. Coronary Revascularization
V. Hospital Discharge and Post-Hospital Discharge
VI. Special Groups

B. Recommendations for Antiplatelet and Anticoagulation Therapy

Class I
- Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely. (Level of Evidence: A)
- Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: A)
- In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of Evidence: A) and for up to 9 months (Level of Evidence: B).
- In patients for whom a PCI is planned, clopidogrel should be started and continued for at least 1 month (Level of Evidence: A) and up to 9 months in patients who are not at high risk for bleeding (Level of Evidence: B).
- In patients being discharged in whom CABG is planned, if possible the drug should be withheld for at least 9 days, and preferably for 7 days. (Level of Evidence: A)

Class IIa
- Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin or with other high-risk features in whom an invasive management strategy is not planned. (Level of Evidence: A)
- Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, unless CABG is planned within 24 hr. (Level of Evidence: A)
- A platelet GP IIb/IIIa antagonist should be administered to patients already receiving heparin, ASA, and clopidogrel in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: B)

Class IIb
- Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients without continuing ischemia who have no other high-risk features and in whom PCI is not planned. (Level of Evidence: A)

Class III
- Intravenous fibrinolytic therapy in patients without acute ST-segment elevation, a true posterior MI< or a presumed new left bundle-branch block (LBBB). (Level of Evidence: A)
- Abciximab administration in patients in whom PCI is not planned. (Level of Evidence: A)
### Medications Used for Stabilized UA/NSTEMI

<table>
<thead>
<tr>
<th>Class/Level of Evidence</th>
<th>Anti-Ischemic and Antithrombotic/Antiplatelet Agent</th>
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<th>Anti-Ischemic and Antithrombotic/Antiplatelet Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>III/ADipyridamole</td>
<td>Warfarin low intensity with or without aspirin</td>
<td>II/AM should be avoided</td>
<td>Warfarin low intensity with or without aspirin</td>
</tr>
<tr>
<td>IIb/BCalcium antagonists (short-acting dihydropyridine antagonists should be avoided)</td>
<td>Nitrates</td>
<td>II/BCalcium antagonists (short-acting dihydropyridine antagonists should be avoided)</td>
<td>Nitrates</td>
</tr>
<tr>
<td>I/C for ischemic symptoms</td>
<td>Antiplatelet/Thrombolytic</td>
<td>I/C for ischemic symptoms</td>
<td>Antiplatelet/Thrombolytic</td>
</tr>
<tr>
<td>I/A I/A ACEI (EF less than 0.40 or CHF EF greater than 0.40)</td>
<td>Beta-blockers</td>
<td>I/ABeta-blockers</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>I/A Clopidogrel* or ticlopidine</td>
<td>Warfarin low intensity with or without aspirin</td>
<td>I/AClopidogrel* or ticlopidine</td>
<td>Warfarin low intensity with or without aspirin</td>
</tr>
<tr>
<td>I/A Aspirin</td>
<td>Warfarin low intensity with or without aspirin</td>
<td>I/AAspirin</td>
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</tbody>
</table>

* Preferred to ticlopidine. 

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### Clinical Use of Antithrombotic Therapy

#### Oral Antiplatelet Therapy

- **Aspirin**
  - Initial dose of 162-325mg nonenteric formulation followed by 75-160mg/d of an enteric or a nonenteric formulation.

- **Clopidogrel (Plavix)**
  - 75mg/d; a loading dose of 4-8 tablets (300-600mg) can be used when rapid onset of action is required.

- **Ticlopidine (Ticlid)**
  - 250mg twice daily; a loading dose of 500mg can be used when rapid onset of inhibition is required; monitoring of platelet and white cell counts during treatment is required.

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### Clinical Use of Antithrombotic Therapy

#### Heparins

- **Daltaparin (Fragmin)**
  - 120IU/kg subcutaneously every 12 h (max. 10,000 IU twice daily).

- **Enoxaparin (Lovenox)**
  - 1 mg/kg subcutaneously every 12 h; the first dose may be preceded by a 30mg IV bolus.

- **Heparin (UFH)**
  - Bolus 60-70 IU/kg (max. 5000 IU IV followed by infusion of 12-15 IU/kg^-1 h^-1) (max 1000 IU/h) titrated to aPTT 1.5-2.5 times control.

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### Clinical Use of Antithrombotic Therapy

#### Intravenous Antiplatelet Therapy

- **Abciximab (ReoPro)**
  - 0.25 mg/kg bolus followed by infusion of 0.125 mcg/kg^-1 h^-1 (max 10 mcg/min) for 12 to 24 h.

- **Eptifibatide (Integrilin)**
  - 180 mcg/kg bolus followed by infusion of 2.0 mcg/kg^-1 min^-1 for 72 to 96 h*.

- **Tirofiban (Aggrastat)**
  - 0.4 mcg/kg^-1 min^-1 for 30 minutes followed by infusion of 0.1 mcg/kg^-1 min^-1 for 48 to 96 h*.

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* Different dose regimens were tested in recent clinical trials before percutaneous interventions. 

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*Quintuple Bypass* is mentioned as a procedure, which is a combination of triple bypass and balloon angioplasty. *Quadruple Bypass* refers to another surgical procedure involving four coronary arteries. *Atrial Fibrillation* is a common heart rhythm disorder.

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*David Letterman* and *John Mellencamp* are mentioned as celebrities associated with heart-related conditions such as *Dick Cheney*, *Skeeters*, and *McCall导弹*.