Unstable Angina and Non ST Elevation Acute Coronary Syndromes

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Acute coronary syndromes (ACSs) are the most common cause of hospital admission in patients with coronary artery disease (CAD). The term ACS refers to a spectrum of acute life-threatening disorders that includes: unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). The pathophysiology is similar: coronary atherosclerosis plaque rupture and subsequent thrombus formation. Such plaques usually are lesions with < 50% stenosis severity prior to ACS, but are lipid-rich soft plaques (vulnerable plaques). The clinical presentation depends on the degree of partial (UA/NSTEMI) or complete lumen obstruction of the culprit coronary artery (STEMI).

This article reviews the UA/NSTEMI ACS, since these two entities are closely related and usually, it is not possible to distinguish them upon presentation at the emergency department (ED). It presents the latest advancement on the pathophysiology, clinical presentations, diagnosis, risk stratification and management. It emphasizes on the selection of the optimal management approach which includes early invasive versus initial conservative strategies. Besides, it discusses the different approaches being used in the light of the information provided by the latest clinical trials. Although, at the present time, the optimal management approach remains unsettled, ACSs are usually managed using an early invasive strategy in tertiary care hospitals in the USA.

The application of clinical practice guidelines developed by the American College of Cardiology and the American Heart Association (ACC/AHA) has confirmed definite improvement of patient care. Part of the information presented in this article, particularly in its management, is based on these guidelines (3).

Evidence base scientific data insists upon using aggressive medical therapy (statins, anti-platelets, beta blockers [BBs], angiotensin converting enzyme inhibitors [ACE-Is], and control of coronary risk factors) as well as mechanical reperfusion, whether by percutaneous coronary intervention (PCI) or by coronary artery bypass graft (CABG). These approaches are considered complementary rather than as opposing strategies.

Key words: Acute coronary syndromes, Unstable angina, Non-ST elevation myocardial infarction, Coronary artery disease

Despite the well documented decline in cardiovascular mortality, ischemic heart disease (IHD) remains the leading cause of morbidity and mortality in both men and women worldwide. Each year in the United States (US), there are more than 5 million visits to the emergency departments (ED) for chest pain. ACS includes 3 major acute severe life-threatening entities: unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). ACS is the initial presentation of IHD in 50% of patients. Approximately, 1.7 million people are hospitalized in the US for an ACS: 39% have UA; 31% NSTEMI; and 30% STEMI. Six hundred thousand people die from acute myocardial inaction (AMI); 450,000 of these occur either before the patient can reach the hospital or in the ED, and 50% of these deaths are sudden (SCD) (1).

Coronary atherosclerosis is a chronic disease with stable and instable periods. During unstable periods, with activated inflammation in the vascular wall, patients may develop myocardial infarction (MI). MI may be a minor event in a lifelong chronic disease; it may even go undetected, but it may also be a major catastrophic event leading to SCD or severe hemodynamic deterioration. MI may be the first manifestation of CAD or it may occur repeatedly, in patients with established disease (2).

In the past 5 years numerous advances have been made in the understanding of the pathophysiology, diagnosis, risk stratification and management of these coronary artery syndromes.

The goal of this review is to summarize the current data regarding the first two (UA/NSTEMI) closely related
conditions. Their pathogenesis and clinical presentations are similar, but there is difference concerning prognosis and survival. They are considered together because it is usually difficult to distinguish between them at the patient’s first presentation when initial treatment decisions have to be made and implemented.

Having established this, the application into clinical practice of the guidelines developed by the ACC/AHA has confirmed improvement of patient outcomes. In this article part of the information, particularly regarding management, is based on these guidelines (3). Table 1 includes the format for standard classification recommendations and a level of evidence to guide management decisions (3).

Table 1. The ACC/AHA Guideline Classification of Recommendations and Level of Evidence

| Objective: To guide management decisions for the diagnosis, treatment, and prevention of specific diseases or conditions. |
| Class I: There is evidence for and/or general agreement that are beneficial, useful and effective. SHOULD be performed/administered. Benefit >> Risk |
| Class II: Conditions for which there is conflicting or a divergence of opinion about the usefulness/efficacy. |
| Class IIa: Weight of evidence favors use... Benefit > Risk |
| Class IIb: Usefulness less well established... Benefit ≥ Risk |
| Class III: Evidence and/or agreement that treatment is not effective. Contraindicated... Risk ≥ Benefit |

ACS-Clinical Presentation, Diagnosis and Stratification

At the time of presentation, patients with ACS can be indistinguishable: the spectrum of clinical presentation from UA through NSTEMI and STEMI encompass a continuum, which distinction is ultimately made on the basis of electrocardiogram (EKG) changes and presence or absence of serum cardiac markers. Damaged cardiomyocytes release several proteins in the circulation including myoglobin, creatine kinase (CK) and its MB isoenzyme (CK-MB), troponins I and T (TnI/TnT), aspartate aminotransferase, and lactate dehydrogenase. Cardiac troponins are currently the preferred biomarkers for myocardial damage because of their high sensitivity and specificity (7).

When a patient comes to the ED with ischemic chest pain lasting ≥20 min (unrelied with nitrates), frequently associated with shortness of breath, diaphoresis, nausea, weakness and fear of impending death, the operating diagnosis is an ACS. The physical examination may be unremarkable. Sinus tachycardia, pulmonary basilar rales and a fourth heart sound may be present. Patients with left ventricular dysfunction at presentation may have a third heart sound. The EKG and the cardiac serum markers are central when deciding either to segregate patients into the UA/NSTEMI or the STEMI (Table 2).

The differential diagnosis of anginal pain should include aortic dissection, pericarditis, myocarditis, acute pulmonary embolism, abdominal visceral disorders (peptic ulcer, biliary colic and pancreatitis) and musculoskeletal pain.

The EKG remains the single most useful test for diagnosing MI and for distinguishing between STEMI and NSTEMI. All patients presenting to the ED complaining of chest pain should have an EKG within 10 minutes of presentation (8). Patients with NSTEMI may present with...
ST-segments depression, T-wave inversion, or an initially normal EKG. In addition, NSTEMI patients can also have transient ST-segment elevation.

Once it has been established that no biomarkers of myocardial necrosis have been released at 6 hours apart, the patient with ACS may be considered to have experienced UA. The diagnosis of NSTEMI is established if a biomarker of myocardial necrosis (cardiac TnI and TnT, particularly) can be detected in the bloodstream hours after initial onset of ischemic chest pain.

**Echocardiography**

Preferably, patients should have an echocardiography during chest pain because the sensitivity of this test is lower when free of chest pain. Echocardiography may show wall motion abnormalities before the onset of chest pain or significant ST changes on EKG. Left ventricular function may be depressed when significant ischemia or myocardial necrosis is present. Mitral regurgitation may be present in the setting of papillary muscle dysfunction or rupture (9).

**Other Noninvasive Testing**

Patients with possible ACS, free of chest pain, a normal or non-diagnostic EKG and normal biomarkers set over 12 to 16 hours should generally have a stress test (standard exercise stress testing, nuclear perfusion scan with stress or pharmacologic stress) performed prior to ED discharge or within 72 hours of discharge. Alternatively, a multi-slide coronary computed tomography may now be considered (3). These patients should be treated with appropriate pharmacotherapy while awaiting the stress test.

**Coronary Arteriography**

Despite the deficiencies inherent to the information derived from the contrast angiogram (most plaques, particularly those responsible for ACS, are extraluminal), coronaryography during ACS has become useful due to a virtual explosion of therapies with the use of percutaneous coronary intervention (PCI). Cardiac catheterization for ACS is indicated when a subsequent revascularization procedure is likely to change the nature history of ACS or when symptoms continue despite aggressive therapy (10). Later on these aspects will be discussed in a more specific way.

**Risk Assessment and Management**

Risk assessment of patient with ACS, as previously mentioned, is a continuous process and the estimation of the short term risks of death and non-fatal cardiac ischemic events is a complex multivariable problem that cannot be fully specified. Physician must take into consideration characteristics of high risk, intermediate risk and low risk patients.

Management of UA/NSTEMI involves:
1. Pre-hospital management,
2. Early hospital care,
3. Selection of an initial treatment strategy (invasive versus conservative strategy) and
4. Post-hospital care (discharge).
This review article has taken into consideration the most recent practice guidelines of the ACC/AHA on UA/NSTEMI (3), emphasizing on class I recommendation, and in the case of another class, the recommendation will be specified.

1) Pre-hospital management

Patients with symptoms of ACS should be instructed to call 9-1-1, and should be transported to the hospital by ambulance rather than by friends or relatives. The patient should take, or Emergency Medical Services (EMS), should administer 162-325 mg of aspirin (ASA) chewed, unless contraindicated.

Patients should take, or EMS should administer, not more than 1 dose of sublingually nitroglycerin (NTG) in response to chest pain. If chest pain is unimproved 5 minutes after taking NTG, it is recommended that the patient or a family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. Patient with chronic stable angina may take up to a maximum of 3 doses, 5 minutes apart, if symptoms are significantly improved by the first dose of NTG, and call 9-1-1 if symptoms are not completely resolved.

Patients who present chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g. death or re-MI) that focuses on history, including anginal symptoms, physical findings, EKG findings, and biomarkers of cardiac injury.

2) Early hospital care

Bed/chair rest with continuous EKG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase. Supplemental oxygen should be administered to UA/NSTEMI patients with an arterial saturation less than 90%, respiratory distress, or other high risk features for hypoxemia.

Patients with UA/NSTEMI and ongoing ischemic discomfort should receive sublingual NTG (0.4mg) every 5 min for a total of 3 doses, after which assessment should be made for the need of intravenous (IV) NTG, if not contraindicated.

Antiplatelet therapy

• ASA should be administered to patients with ACS as soon as possible (unless contraindicated) and continued lifelong. Patients allergic or intolerant to ASA should receive clopidogrel.
• Clopidogrel, in addition to ASA, should be initiated in patients in whom either a conservative or an early invasive therapy is considered, but the likelihood of surgical disease requiring early coronary artery bypass grafting (CABG) is low.
• Upstream use of epifibatide or tirofiban should be considered in high-risk patients and those with troponin elevation, especially if an invasive therapy is contemplated. Abciximab should not be used unless there is no appreciable delay to PCI. Abciximab can be used safely for PCI in patients who have not received upstream GP IIb/IIIa inhibitors, and may be better than tirofiban in this population. GP IIb/IIIa inhibitors provide incremental benefit in patients with elevated troponin undergoing PCI even among those pretreated with clopidogrel.

Anticoagulation therapy

• In patient treated with conservative therapy, the preferred anticoagulation may be fondaparinux, enoxaparin (for 8 days or duration of hospitalization), or unfractionated heparin (UFH) (for 48 hours), in that order.
• In patients treated with invasive therapy, enoxaparin or UFH-based regimens have the most supporting evidence.
• For patients undergoing CABG, ASA should be continued, while clopidogrel should be stopped 5-7 days before, and low-molecular GP IIb/IIIa inhibitors stopped 4 hours before the surgery.
• Enoxaparin should be stopped 12-24 hours prior and fondaparinux stopped 24 hours prior to CABG; and UFH started.

IV NTG is indicated in the first 48 hours in patients with UA/NSTEMI for treatment of persistent ischemia, heart failure, or hypertension. Patients with hemodynamic instability or those with ongoing symptoms should be admitted to a coronary care unit, whereas others should be admitted to a step-down unit.

All patients with ACS should receive ASA, statins, BBs, and clopidogrel within 24 hours. Oral ACE-Is or ARB should be initiated in patients with abnormal left ventricular ejection fraction, hypertension, diabetes, or heart failure. Oral BBs should be instituted within the first 24 hours in absence of contraindications. Intravenous BBs should only be used for specific indications and not for routine therapy.

In UA/NSTEMI patients with continuing or frequently recurring ischemia and in those that BBs are contraindicated, a nondihydropyridine calcium channel blocker antagonist (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant left ventricular dysfunction or other contraindications.
The use of morphine for analgesic has been associated with worsening of outcome in observational studies. The guidelines (3) have downgraded it from a Class I to a Class IIa recommendation. Nonsteroidal anti-inflammatory drugs (COX-1 or COX-2 inhibitors) other than ASA should be discontinued on admission to the hospital in patients with ACS. Hormone replacement therapy (HRT) should not be started in patient with ACS. Patients on HRT suffering from ACS should be advised to discontinue it.

3) Initial conservative versus initial invasive strategies

The benefits of both PCI and thrombolysis have been well studied in patients with STEMi. If the clinical picture is consistent with acute STEMi, select and implement reperfusion therapy (PCI or fibrinolysis) as quickly as possible within 12 hours of symptoms onset. Those presenting UA/NSTEMi pose a different challenge: evidence-base experience does not support the use of fibrinolytics for UA/NSTEMi and even it may pose an excessive harm. Thrombolysis is contraindicated by the prothrombotic state that fellows thrombolytic administration (11). Therefore a clear distinction between STEMi and NSTEMi is essential because of the differences in management. To estimate the early risk of death and ischemic event at presentation in patients with UA/NSTEMi, and to provide a basis for therapeutic decision making, Antman, et al developed the TIMI (thrombolysis in myocardial infarction) risk score (12). This is a simple tool composed of 7 (1-point) risk indications rated on presentation, where 1 point given for each of the 7 variables (Table 3). Patients with a score <3 are low risk; 3-4 are intermediate; and ≥5 are considered high-risk.

Two strategies have emerged in managing patients with ACS:

A. The early invasive strategy - diagnostic angiography with intent to perform revascularization (choice of PCI versus CABG is similar to that in a patient with stable disease and should be determined by a patient’s anatomy, left ventricular function, and presence or absence of diabetes and other co-morbidities).

B. An initial conservative strategy (selective invasive) - promotes aggressive medical therapy, while reserving the angiography and intervention for high risk patients or for those with refractory symptoms.

At the present time, the optimal approach to management remains somewhat undecided. Multiple meta-analyses have examined the relative merits of both strategies in patients with ACS and have come to opposing conclusions. Thereby, current data do not support an early invasive approach over a selective conservative approach or vice versa.

### Table 3. TIMI Risk Score for UA/NSTEMI

<table>
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<th>Characteristics</th>
<th>Points</th>
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<tr>
<td>Age ≥ 65 years</td>
<td>1</td>
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<tr>
<td>At least 3 risk factors for CAD (family history, HBP, diabetes, hypercholesterolemia, current smoker)</td>
<td>1</td>
</tr>
<tr>
<td>Prior coronary stenosis of ≥ 50%</td>
<td>1</td>
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<tr>
<td>ST-segment deviation on ECG presentation</td>
<td>1</td>
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<tr>
<td>At least 2 anginal events in prior 24 hours</td>
<td>1</td>
</tr>
<tr>
<td>Use of aspirin in prior 7 days</td>
<td>1</td>
</tr>
<tr>
<td>Elevated serum cardiac biomarkers</td>
<td>1</td>
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Risk Score = Total Points (0-7)

The last meta-analyses on this question (13) include 10 clinical trials and conclude that available trial evidence is heterogeneous and insufficient for comparing routine and selective invasive strategies. Therefore, in patient with UA/NSTEMi ACS a routing invasive strategy has not been proven to reduce deaths or nonfatal MI.

To guide clinical management, the ACC/AHA guidelines on UA/NSTEMi (3) recommend:

- **Class I:**
  - An early invasive strategy is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious co-morbidities or contraindications to such procedures).
  - An early invasive strategy is indicated in initially stabilized UA/NSTEMI patients (without serious co-morbidities or contraindications to such procedures) who have an elevated risk for clinical events.
  - For low-risk patients with possible UA (e.g., without EKG changes or troponin elevation), an initially conservative strategy is appropriated and is the preferred approach in low-risk women.

- **Class IIb:**
  - In initially stabilized patients, an early conservative strategy may be considered for treatment in UA/NSTEMI patients (without serious co-morbidities or contraindications) who have an elevated risk of clinical events, including those who are troponin positive. The decision to implement an initial conservative strategy in these patients may be made considering physician and patient preference. With this strategy, an early echocardiogram should be considered to identify if significant left ventricular dysfunction is present.

ACS is recognized as a diffuse disease (evidence of a systemic inflammatory component suggests that ACS patients are at risk for plaque rupture at multiple
sites) rather than a focal stenosis whereby mainly it is directed the PCI (target vessel revascularization). Thus, late medical therapy and PCI should be considered as complementary rather than opposing strategies in the treatment and management of atherosclerosis and ACS. Statins, BBs, ACE-Is, and anti-platelet therapy decrease the incidence of death and MI (14).

4) Hospital discharge long-term medical therapy and secondary prevention

The risk of ACS progressing to MI or the development of recurrent MI or death is highest during the first 1-3 months (acute phase). Most patients then resume a clinical course similar to that in patients with chronic stable CAD. Patients who have undergone successful PCI with an uncomplicated course are usually discharged the next day, and patients who undergo uncomplicated CABG generally are discharged 4 to 7 days later.

An effort of the entire staff (physicians, nurses, dietitians, pharmacists and rehabilitation specialists) is often necessary to prepare the patient for discharge. Both the patient and family should be instructed on what course to take if ischemic symptoms occur in the future (15).

The selection of medical regimen should be individualized to the specific needs of each patient based on the in-hospital findings and events, the risk factors for CAD, drug tolerability, and recent procedural interventions. The mnemonic ABCDE (Aspirin, antianginals, and ACE-Is; BBs and blood pressure; Cholesterol and cigarettes; Diet and diabetes; Education and exercise) has been found to be useful in guiding treatment in UA/NSTEMI (16).

References


