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OF BRIGHAM AND WOMEN'S HOSPITAL, BOSTON, MASSACHUSETTS

## New guidelines for the management of unstable angina and non-ST-elevation myocardial infarction

### Part I: Medical therapies

By CHRISTOPHER P. CANNON, MD

Every year, approximately 1.42 million patients are admitted to hospitals in the United States with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI).<sup>1</sup> Over the past several years, there have been numerous advances in the evaluation and management of this large patient population, including numerous effective medical therapies (eg, antiplatelet therapies, cholesterol-lowering therapy) and interventional approaches. To help improve the treatment of UA/NSTEMI, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed Guidelines for diagnosing and managing these patients.<sup>1</sup> After its initial publication in September 2000, many landmark trials were published that required the Guidelines to be updated just 2 years later.<sup>2</sup> This issue of *Cardiology Rounds* presents an overview of the new Guidelines, discusses the importance of the initial assessment of the UA/NSTEMI patient using risk stratification tools (eg, TIMI Risk Score and measurement of biomarkers), and presents a detailed update of current antiplatelet therapies. In the next issue of *Cardiology Rounds*, Part II of this topic will discuss the relative benefits of an invasive vs. a conservative approach for these patients and the importance of long-term risk factor modification.

#### Overview of the ACC/AHA Guidelines

The ACC/AHA Guidelines provide guidance in 6 major areas (Figure 1). For the evaluation of the patient, there are two steps:

1. an assessment of the likelihood that the patient's symptoms are in fact related to coronary disease, and
2. among patients with a good clinical history, applying risk stratification to identify high- vs. lower risk patients.

The goal of risk stratification is to help target therapies to appropriate patients. As discussed below, some therapies have been shown to benefit only high-risk patients, and thus, these agents can be avoided in those at lower risk. Among the therapies, there are three broad categories: anti-ischemic therapy, antithrombotic therapy (where there has been many advances), and a treatment strategy with regard to invasive vs. conservative management. Finally, the new ACC/AHA Guidelines place much more emphasis on secondary prevention, with the idea of using the time of hospital discharge following an acute coronary syndrome (ACS) as a "teachable moment" to get the patient on the optimal long-term medical regimen.



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**Figure 1: An overview of the 2002 Guideline Update**

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- Assess likelihood of CAD
- Risk stratification
- Anti-ischemic Rx
- Antithrombotic Rx\*
- Invasive vs. conservative strategy\*
- Secondary prevention/risk factor modification\*

\*New Update in 2002

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**Initial assessment**

The initial evaluation of patients with UA/NSTEMI begins with an assessment of the *likelihood* that the presenting symptoms represent ischemia (Figure 2). The clinical history is critical to this determination, with a history of typical angina being one of the most important factors indicating that the patient's symptoms are likely the result of ischemia. Several other factors associated with a high likelihood that symptoms represent an ischemic acute coronary syndrome (ACS) are shown in Figure 2. The most important are chest or left arm pain or discomfort that reproduces the patient's prior documented angina, a known history of coronary artery disease or MI, evidence of heart failure on physical examination, ST-segment or T-wave changes on ECG, or elevated cardiac biomarkers.<sup>1</sup> An intermediate likelihood can be predicted by age >70 years, male sex, and diabetes, or evidence of extra-cardiac vascular disease on physical examination, or electrocardiographic (ECG) abnormalities not documented to be new.

The approach to these patients is to admit them to hospital, initiate medical therapy, and carry out further risk stratification to determine the intensity of the medical and

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**Figure 2: Features associated with a higher likelihood of ACS**

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**High likelihood**

- Typical angina
- Known hx of CAD or MI
- CHF
- New ECG changes
- ↑troponin or CK-MB

**Intermediate likelihood**

- Probable angina
  - Age >70 years
  - Male
  - Diabetes
  - PVD, CVA
  - Old ECG abnormalities
- 

interventional approach. In contrast, a *diagnostic* approach is appropriate in patients with a lower likelihood that their symptoms are due to ischemia. This usually includes short-term observation for serial creatine kinase (CK)-MB and troponin values and ECGs. If these are negative after 6-12 hours, a stress test should be performed to evaluate for the presence of a significant coronary lesion. If negative, the patient is discharged home with advice to follow-up with his or her primary care physician for exploration of other causes of his/her symptoms.

**Risk stratification**

To determine the intensity of both medical and interventional therapies, the next assessment is for short-term risk of death or recurrent MI. Factors associated with a high risk of death or nonfatal MI are: a history of accelerating symptoms in the prior 48 hours, prolonged (>20 minutes) rest pain, evidence of congestive heart failure, age >75 years, ST-segment changes (and deep T-wave inversion), or elevated cardiac biomarkers (eg, troponin or CK-MB).<sup>1,3</sup> Low-risk patients present without rest pain,<sup>4</sup> ECG changes, or evidence of heart failure.

Antman and colleagues developed the TIMI Risk Score for patients with UA/NSTEMI as a simple, yet multifaceted tool to assess overall risk.<sup>3</sup> It was developed using multivariate analysis to predict the risk of death, MI, or recurrent ischemia requiring urgent revascularization. Seven factors were identified and the risk score is simply the number of these factors (Figure 3). An increasing number of factors correlates with an increased rate of recurrent cardiac events, as recently validated in the CURE trial (Figure 4).<sup>16</sup> Importantly, the TIMI Risk Score can identify patients who would derive greater benefits from more aggressive antithrombotic and interventional strategies.<sup>3,5,6</sup>

**Troponin**

Among all the risk factors, troponin has consistently emerged as a simple and potent factor to stratify risk.<sup>1,7-9</sup> The European Society of Cardiology (ESC)/ACC consensus

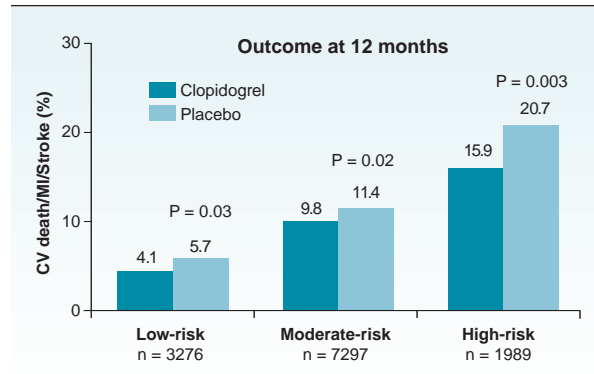
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**Figure 3: TIMI risk score for UA/NSTEMI – 7 independent predictors<sup>3</sup>**

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- Age ≥65 years
  - ≥3 CAD Risk Factors (↑ chol, FHx, HTN, DM, smoking)
  - Prior CAD (cath stenosis >50%)
  - ASA in last 7 days
  - ≥2 anginal events ≤24 hours
  - ST deviation
  - Elevated cardiac markers (CK-MB or troponin)
-

**Figure 4: CURE – Effects of clopidogrel stratified by TIMI risk score<sup>16</sup>**



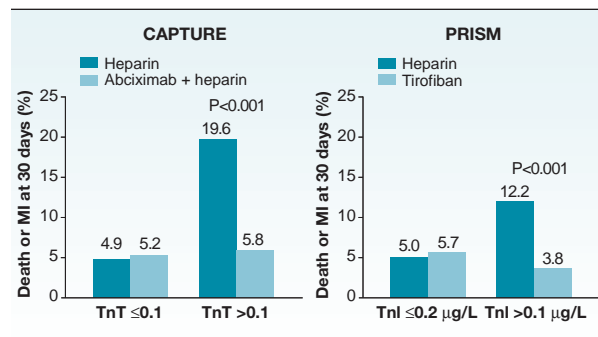
document on MI notes that any troponin elevation is a biomarker of myocyteneclerosis, and is associated with an increased adverse outcome.<sup>10</sup> An important caveat is that these data are derived from patients presenting *with a clear history of ischemic symptoms*. It should be acknowledged, however, that in patients *without* such clear clinical history, troponin elevations can sometimes be false positives,<sup>11</sup> or may be caused by congestive heart failure, pulmonary embolism, or technical problems with the assay. Thus, in patients with *unclear* symptoms of angina, low level troponin elevations may not be diagnostic of ACS, whereas higher levels and/or positive CK-MB are diagnostic of MI.

Of the numerous other emerging cardiac biomarkers, the two most clinically useful thus far are C-reactive protein<sup>12</sup> and B-type natriuretic peptide,<sup>13</sup> both of which correlate with increased mortality and recurrent cardiac events in patients presenting with ACS. Further ongoing research will determine if therapies are differentially beneficial in patients with elevation of these novel markers. A multimarker strategy is now preferred to define more fully the pathophysiologic mechanisms underlying a given patient's presentation and to provide risk stratification across the axes of myocardial necrosis, inflammation, and neurohormonal activation.<sup>14</sup>

### Risk stratification to target treatment

For clinical care, troponin elevations and the TIMI Risk Score can be used to guide antithrombotic and interventional therapies.<sup>5,8,9,15</sup> When interventions such as low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and an early invasive strategy are used in patients with a positive troponin, there is a greater benefit; whereas almost no benefit is observed with these interventions in patients with a negative troponin. For example, there was a 50% to 70% reduction in death or MI in troponin-positive patients receiving GP IIb/IIIa inhibitors (vs. not) compared with no benefit from these agents in patients without a positive troponin (Figure 5).<sup>8,15</sup> Similarly, in the TACTICS-TIMI 18

**Figure 5: Benefit of IIb/IIIa inhibitors in UA/NSTEMI by troponin levels in the CAPTURE<sup>9</sup> and PRISM<sup>15</sup> studies**



TnT = troponin T  
TnI = troponin I

study, an early invasive strategy conferred a dramatic 40% reduction in recurrent cardiac events for patients with a positive troponin, whereas no benefit was seen in patients with a negative troponin.<sup>5,9</sup> Thus, risk stratification should be a key and integral part of the initial evaluation, as well as the management of patients with ACS.

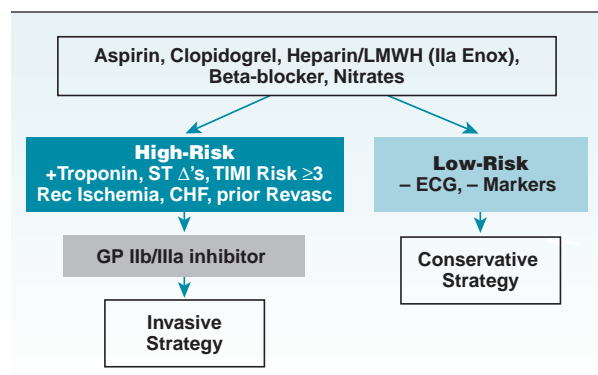
Interestingly, a very different pattern has been seen with the oral antiplatelet agents; both aspirin and clopidogrel benefit low-, intermediate-, and high-risk patients,<sup>16</sup> (Figure 4) as well as those with positive or negative cardiac markers.<sup>17,18</sup> Therefore, these agents are beneficial in all UA/NSTEMI patients, whereas the GP IIb/IIIa inhibitors and an invasive strategy can be targeted at high-risk patients who are troponin-positive or have a TIMI Risk Score ≥ 3 (Figure 6). (See also below)

### Antiplatelet treatment

#### Aspirin

Initial treatment for all suspected ACS patients should include aspirin as it reduces events by 50% to 70% as compared to placebo.<sup>19</sup> The news for aspirin is about the *dose* since its efficacy at doses as low as 75 mg per day has been clearly demonstrated in the Antithrombotic Trial-

**Figure 6: Risk stratification to target therapies in UA/NSTEMI**



ists' Collaboration.<sup>17</sup> In conjunction with this finding, new data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial found that, over 1 year of treatment, lower doses of aspirin (eg, 81 mg) are associated with a lower rate of major bleeding than doses of 300-325 mg.<sup>20</sup> For acute in-hospital management, and frequently for the first 30 days post-PCI, 160-325 mg daily is recommended; however, for long-term treatment, new data suggest that 81 mg may be safer and equally efficacious.

For patients who cannot take aspirin due to allergy or intolerance, the new Guidelines have a Class I recommendation for clopidogrel in place of aspirin. In the CAPRIE trial of over 19,000 patients, the use of clopidogrel alone was shown to have a *lower* rate of both cardiac events and major bleeding, in particular gastrointestinal bleeding.<sup>21</sup> Aspirin can cause gastric ulcers by inhibiting prostaglandins, whereas clopidogrel is only an antiplatelet agent and has no effect on prostaglandins in the gastric lining.

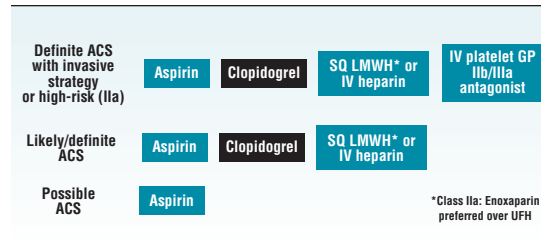
### Clopidogrel

Beyond being an effective substitute for aspirin, the 2002 Guidelines update includes new Class I recommendations for the use of clopidogrel in addition to aspirin. Clopidogrel blocks the adenosine diphosphate (ADP) pathway by blocking the P<sub>2</sub>Y<sub>12</sub> receptor, which in turn decreases platelet activation and aggregation. In the large CURE trial, clopidogrel in combination with aspirin, and on top of other standard therapies, led to a 20% relative risk reduction in cardiovascular death, MI, or stroke compared with aspirin alone.<sup>18</sup> This benefit was observed in both low- and high-risk patients with UA/NSTEMI (Figure 4).<sup>16</sup> The benefit was seen as early as 24 hours, with the Kaplan-Meier curves diverging after just 2 hours, indicating a very early antithrombotic and clinical effect.

Moreover, the benefit continued throughout the trial's one-year treatment period. This is consistent with data from the CAPRIE trial that demonstrated the benefit of clopidogrel alone versus aspirin through 3 years of follow-up in patients with prior atherothrombotic disease.<sup>21</sup> Benefit of early treatment prior to percutaneous coronary intervention (PCI) was also seen with a 31% reduction in cardiac events in patients at 30 days and 1 year.<sup>22</sup> Thus, the ACC/AHA guidelines have added clopidogrel to the Class I treatment recommendations (Figures 6 and 7).<sup>2</sup>

The CREDO trial was the second trial to study the combination of clopidogrel and aspirin in patients undergoing PCI. Most were undergoing elective PCI, but approximately 15% of patients had ACS. CREDO was the second large randomized trial to provide

**Figure 7: Recommendations for antithrombotic therapy**



evidence supporting both early and long-term use of clopidogrel in UA/NSTEMI patients. Patients undergoing planned or likely PCI were randomized to receive a loading dose of clopidogrel (300 mg) or placebo between 3 and 24 hours prior to PCI. After stenting, patients received open-label clopidogrel for 28 days post-stent as per routine practice. Then, after 28 days, patients in the pretreatment group continued on clopidogrel for 1 year, while the non-pretreated group were treated with matching placebo.

The 28-day results revealed that there was a non-significant 19% reduction in death, MI, or urgent target vessel revascularization when patients were pretreated with clopidogrel. However, in the prespecified time-to-treatment analysis, pretreatment with clopidogrel at least 6 hours prior to PCI led to a significant 38% relative risk reduction in 30-day post-PCI events. In contrast, patients pretreated with clopidogrel only 3-6 hours pre-PCI derived no added benefit beyond that of treatment with clopidogrel post-stent only. This means that for ACS patients, clopidogrel should be started as soon as possible. It was initially hoped that clopidogrel “pretreatment” could be started immediately following diagnostic catheterization and pre-PCI, but based on CREDO, it appears that this is too late to provide the added protection peri-PCI that is achieved when patients are pre-treated at least 6 hours prior to the procedure. Thus, data from PCI-CURE and CREDO emphasize the need to initiate clopidogrel as soon as possible on admission for UA/NSTEMI, prior to any planned catheterization and possible PCI. More importantly, the long-term benefit beyond 30 days was again a 38% reduction in the primary endpoint of death, MI, or stroke.

Thus, CREDO is the 3rd trial to demonstrate long-term benefit of clopidogrel, the first being CAPRIE (benefit of clopidogrel alone for up to 3 years), then CURE (the benefit of clopidogrel plus aspirin for up to 1 year), and now CREDO (a benefit in patients treated for a year). In summary, the results of the CURE, PCI-CURE, CREDO and CAPRIE trials support the long-term (at least 1 year) use of both aspirin plus clopidogrel in patients with ACS.

## Figure 8: Anti-ischemic therapy

- Bed Rest
- Oxygen
- Nitrates (sublingual then oral/topical, IV for ongoing pain).
- Morphine sulfate IV (for pain, CHF)
- $\beta$ -blocker (first dose IV if ongoing pain), then oral
- A nondihydropyridine  $\text{Ca}^{2+}$  blocker (eg, verapamil or diltiazem) if  $\beta$ -blocker is contraindicated.
- ACE inhibitor I for HTN, low LVEF or CHF, or DM.

HTN = hypertension  
LVEF = left ventricular ejection fraction  
CHF = congestive heart failure  
DM = diabetes mellitus

### GP IIb/IIIa inhibitors

Intravenous GP IIb/IIIa inhibitors have also been shown to be beneficial in treating patients with UA/NSTEMI.<sup>23</sup> For “upstream” management (ie, initiating therapy when the patient first presents to the hospital), the “small molecule” inhibitors eptifibatid and tirofiban clearly show benefit, whereas abciximab was of no benefit in an unselected UA/NSTEMI patient population<sup>24</sup> and, in fact, contraindicated in patients managed with a noninvasive strategy.<sup>2</sup> Abciximab has, however, been shown to be strongly beneficial in patients undergoing PCI.<sup>25,26</sup> As noted above, the benefit of GP IIb/IIIa inhibitors is segregated to patients at high risk and, notably, to troponin-positive patients<sup>8,15</sup> (Figure 5) whether or not they have undergone revascularization.<sup>15</sup> Because of the large benefit of GP IIb/IIIa inhibition during PCI,<sup>27</sup> the ACC/AHA guidelines emphasize using them in patients managed with an invasive strategy, and there is a Class IIa, recommendation for their use in high-risk patients in whom PCI is not planned.<sup>2</sup> However, an early invasive strategy is recommended for high-risk patients and therefore, the new ACC/AHA guidelines link together risk assessment, strategy selection, and then GP IIb/IIIa inhibition for this group of patients (Figures 6 and 7).

### Heparin and low molecular weight heparin

Unfractionated heparin (UFH) or LMWH should be added to the medical regimen for all patients with UA/NSTEMI based on a demonstrated incremental benefit over aspirin alone.<sup>28</sup> Comparative trials of enoxaparin, a LMWH, versus UFH have demonstrated its superiority in reducing recurrent cardiac

events.<sup>29,30</sup> Based on these data, the 2002 Updated ACC/AHA UA/NSTEMI Practice Guidelines have issued a Class IIA recommendation that enoxaparin is the preferred antithrombin over UFH.<sup>2</sup>

### Anti-ischemic therapy

Anti-ischemic therapy with intravenous nitrates for ongoing ischemic pain is also recommended.<sup>1</sup> Although useful for treating angina, oral nitrates have not been shown to prevent cardiac events during long-term treatment and thus can be discontinued upon successful revascularization. Beta-blockade remains a cornerstone of treatment and IV beta-blockade, followed by oral beta-blockade targeted to a heart rate of 50 to 60, is recommended for ongoing pain (Figure 8).

### Summary

To summarize the acute medical management of UA/NSTEMI, initial medical treatment should include aspirin, clopidogrel, and either heparin or LMWH, beta-blockers, or nitrates. Then, risk stratification can be applied. For high-risk patients (eg, ST-segment changes, positive troponin, TIMI Risk Score  $\geq 3$ ), the above-mentioned medications plus GP IIb/IIIa inhibition are beneficial (Figure 7). The choice of an early invasive vs. conservative strategy, and long-term medical treatments will be discussed in Part 2 of this topic in the next issue of *Cardiology Rounds*.

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**Dr. Christopher P. Cannon** is an Associate Professor of Medicine at Harvard Medical School and a member of the Cardiovascular Division at Brigham and Women's Hospital in Boston. He earned his medical degree from Columbia University College of Physicians and Surgeons in New York and, after completing his residency in internal medicine there, was a cardiovascular fellow in medicine at Brigham and Women's Hospital.

In addition to being a frequent lecturer, Dr. Cannon has published more than 300 original articles, reviews, editorials, book chapters and electronic publications in his areas of expertise. His research is published in numerous journals including *Circulation*, *Journal of the American College of Cardiology*, *American Journal of Cardiology*, *American Heart Journal*, *Journal of the American Medical Association* and the *New England Journal of Medicine*.

Dr. Cannon has received numerous awards including the Alfred Steiner Research Award, Upjohn Achievement in Research Award, and the Robert F. Loeb Award for Excellence in Clinical Medicine. He is a member of a number of professional organizations and committees and serves as Chairman of the Acute Cardiac Care Committee of the Council of Clinical Cardiology of the American Heart Association and is a Fellow of the American College of Cardiology and the American College of Chest Physicians. He is a principal investigator of several ongoing trials, including PROVE IT – TIMI 22 and CLARITY-TIMI 28, conducted by the Thrombolysis in Myocardial Infarction (TIMI) Group.

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