Risk Stratifying the Acute Coronary Syndrome Patient: A Focus on Treatable Risk

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Providing the optimal treatment for patients who present to the emergency room with chest pains or suspected acute coronary syndrome (ACS) remains a dilemma for many practitioners due to subjectivity, delayed diagnoses, and widely variable mechanisms with similar clinical presentations. In treating patients with chest pain but no obvious electrocardiogram changes, practitioners frequently utilize the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines. The guidelines group possible ACS patients together as unstable angina/non–ST-segment elevation myocardial infarction (NSTEMI) and recommend that treatment be based on level of risk. The challenge for practitioners is discriminating between "risk" and "treatable risk." Evaluation of troponin levels can help identify patients with possible ACS who are at high risk of death and MI, and guide early decision making. Available data indicate that in the troponin-negative patient, routine interventions such as unfractionated heparin, glycoprotein IIb/IIIa receptor antagonists, and invasive approaches have no benefit in terms of reducing death and MI. Although the ACC/AHA Guidelines combine patients with unstable angina and NSTEMI, it is essential to evaluate troponin status in order to optimize patient outcomes and safety in the treatment of suspected ACS.

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Over 6 million patients present to emergency rooms throughout the United States every year with chest pain or other symptoms suggestive of a diagnosis of an acute coronary syndrome (ACS).[1] During a similar time period, the number of patients discharged from the hospital with a primary diagnosis of an acute myocardial infarction (MI) is approximately 767,000.[2] Therefore, of all the patients presenting to the emergency room for

the evaluation of chest pain, fewer than 1 in 6 are diagnosed with MI. The remaining patients are diagnosed with either unstable angina or some variation of "non-cardiac chest pain." However, there are substantial limitations to these diagnoses. First, they are very subjective; one physician's interpretation of a "classic" history for unstable angina may be thought of as atypical chest pain by another provider. Secondly, these diagnoses are frequently made retrospectively only after the results of serial blood tests, electrocardiograms (ECGs), stress testing, and even angiography are available. Finally, the pathophysiologic processes underlying the presenting symptoms can vary remarkably, from gastroesophageal reflux to spinal nerve compression or coronary artery plaque rupture. These issues of subjectivity, delayed diagnoses, and widely variable mechanisms with similar clinical presentations lead to treatment decisions that can prove to be either life saving or possibly life threatening.

Therein lies the dilemma of how to best treat patients at the time of presentation and then throughout their hospitalization when diagnoses are clear in only a small percentage of patients at presentation and over the ensuing several hours. In treating patients who present to the emergency room with chest pain but without obvious ECG changes, practitioners frequently and appropriately turn to the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines to help guide their initial therapeutic decisions.[3] In the guidelines, which group possible ACS patients together as unstable angina/non–ST-segment elevation MI (NSTEMI), it is recommended that patients be treated based on their level of risk. The challenge that has not been well addressed in the literature is discriminating between *risk* and *treatable risk*. For example, based on the guidelines, a patient older than 75 years of age is placed into a high-risk category. This seems reasonable if one considers a 75-year-old and a 40-year-old presenting with identical symptoms and identical cardiac anatomy; irrespective of the treatment received by both patients, the 75-year-old is going to have a significantly higher risk of dying over the next year compared with the 40-year-old. On the other hand, even if the 75-year-old had previous bypass surgery and at present has chest discomfort but no ST-segment changes or troponin elevations, the risk of an MI over the next several weeks is substantially lower for this patient than for the 40-year-old with no prior cardiac history but presenting with chest pain, troponin elevations, and ST-segment depressions. So, although both patients are considered "high-risk," it is only the latter patient who has objective evidence of a cardiac etiology for his/her symptoms. This article will focus on clinical trial evidence that shows how aggressive pharmacological interventions and invasive procedures impact that level of cardiac risk.

The challenge that has not been well addressed in the literature is discriminating between risk *and* treatable risk.

Although multiple excellent risk scores such as Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), Global Registry of Acute Cardiac Events (GRACE), and Thrombolysis in Myocardial Infarction (TIMI) have been developed that can discriminate the short- and long-term risks of patients presenting with a possible non–ST-segment elevation ACS,[4] their ability to guide therapeutic interventions are less well described. This article will evaluate the role of troponin in identifying patients at high risk for death and MI and, in particular, emphasize the role of troponin as a powerful discriminator to guide the vast majority of early (ie, in-hospital) decision making in the treatment of patients with chest pain and possible ACS.

Evaluation of the Patient With Suspected ACS

When a patient presents with complaints of chest discomfort, immediate tools for triage typically include an ECG, primarily to rule out an ST-segment elevation MI (STEMI), as well as ST and T wave changes consistent with NSTEMI. At the same time, biomarkers such as serum troponin are determined to assess for myocardial necrosis. In looking at all patients presenting with chest pain to the emergency room, an ECG is diagnostic in only a relatively small percentage of patients and STEMI is diagnosed in only approximately 11%. Approximately 50% of individuals have ST-segment depressions, T-wave changes, or conduction abnormalities, which may or may not be new, and the remaining patients have no abnormal ECG findings.[5] Similarly, among patients presenting to the emergency room with chest discomfort suggestive of ACS, only approximately 20% are found to have abnormally elevated troponins.[6] Therefore, only a minority of patients presenting with chest pain syndromes to the emergency room have objective evidence of myocardial ischemia, dynamic ECG changes, or troponin elevations.

Elevations of cardiac troponins, both I and T, are unique as markers of cardiac risk. This contrasts with other biological markers such as creatine kinase (CK) and its MB isoenzyme (CKMB), as well as ECG abnormalities. Any elevation in myocardial troponin levels is specific for myocardial necrosis or possibly severe coronary ischemia and, therefore, never normal.[7]

The clinical benefit of determining troponin levels was highlighted in a series of early trials evaluating the diagnostic and prognostic implications of troponin elevation. In one such trial involving 106 chest pain patients, investigators found that in patients with normal levels of CKMB, an abnormally elevated troponin level was associated with almost 6 times the incidence of subsequent MI or death compared with patients with normal troponin levels.[8] It was these relatively dramatic findings that solidified the place of troponin evaluation in all patients presenting to emergency rooms with suspected ACS. Troponin levels were also measured in several placebo-controlled and other trials identifying the optimal treatment in patients with ACS. It is through these trials that we are able to gain guidance as to how troponin elevations can be used to help optimize the treatment of patients presenting to emergency rooms with suspected ACS.

Troponin-Based Treatment of Patients

Aspirin

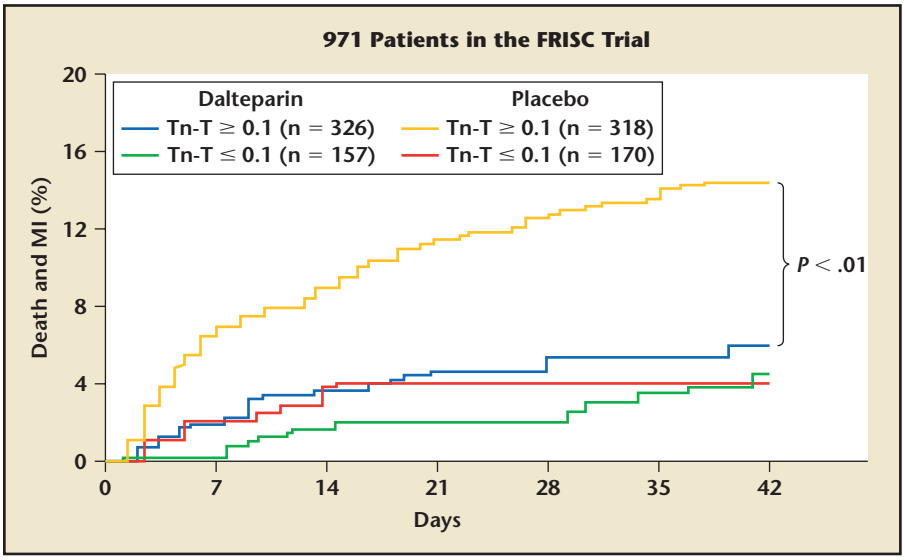
There are no troponin studies available in early placebo-controlled trials of aspirin in patients with suspected non–ST-segment elevation ACS. In these early trials, aspirin was associated with a greater than 50% relative risk reduction in the incidence of recurrent MI and death and, therefore, remains a mainstay of initial therapy in all patients with chest pain, irrespective of risk.[9] Current guidelines recommend that aspirin be administered immediately to any patient with chest pain even remotely suggestive of myocardial ischemia.

Heparin

Following aspirin, the next decision often made for patients with chest pain and suspected ACS is the initiation of an anticoagulant. For a long period of time the mainstay of therapy was unfractionated heparin (UFH). There have been several placebo-controlled trials of UFH in ACS. Most individual trials did not show a significant impact on death and MI; even a meta-analysis of the placebo-controlled trials only showed a very strong trend toward benefit in those patients randomized to UFH versus placebo.[10] However, none of these trials were conducted in the era of troponin testing. More recently, there have been several placebo-controlled and active-controlled trials of low-molecular weight-heparins. One of these early placebo-controlled trials was the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, which randomized patients with suspected non–ST-segment elevation ACS to either dalteparin or placebo.[11] A substudy of this trial evaluated the prognostic impact of troponin status, as well as the interaction between randomized treatment, baseline troponin, and outcomes.[12] Interestingly, only those patients who were troponin positive received any benefit by randomization to the anticoagulant dalteparin compared with placebo. In patients who were troponin negative, irrespective of randomization arm, the risk for recurrent MI or death was low and unchanged by randomized therapy. In patients who were troponin positive, however, randomization to dalteparin decreased event rates to those of patients who were troponin negative (Figure 1).

As subsequent studies have found dalteparin to be equivalent to UFH, based on the results of the FRISC trial it seems fair to conclude that if a patient is troponin negative, then

Figure 1. *Outcomes from the Fragmin during Instability in Coronary Artery Disease (FRISC) trial based on troponin status and randomized therapy. MI, myocardial infarction; Tn-T, troponin-T. Reprinted with permission from Lindahl B et al.*[12]



receiving an anticoagulant in addition to aspirin, whether it be UFH or low-molecular-weight heparin, offers no additional benefit to aspirin alone.

Glycoprotein IIb/IIIa Receptor Antagonists

What might be considered one of the better success stories in combining novel technologies with pharmacotherapies are the results of several placebo-controlled trials of the glycoprotein (GP) IIb/IIIa receptor antagonist in patients with suspected non–ST-segment elevation ACS and the interaction with troponin status. Troponin levels were studied in the following 3 placebo-controlled trials of GP IIb/IIIa receptor antagonists in an ACS population: c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-B. In all 3 of these trials, patients who were troponin negative experienced overall low event rates, and randomization to a GP IIb/IIIa receptor antagonist had no impact on patient outcome.[13] Conversely, in patients who were troponin positive, randomization to a GP IIb/IIIa receptor antagonist led to a significant and dramatic reduction in death and MI, whereas patients randomized to the control arm, which included aspirin and typically UFH, experienced the highest event rates (Figure 2).

The results of an active-controlled trial also supported utilizing GP IIb/IIIa receptor antagonists only for the treatment of patients who have abnormally elevated troponins. In the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT)-2, only patients with objective evidence of ACS as manifest by anginal symptoms at rest or with minimal exertion accompanied by an elevated troponin-T or a new ST-segment deviation or bundle branch block were enrolled.[14] All patients received a 600-mg clopidogrel loading dose and were randomized to an abciximab bolus and infusion or matching placebo at the time of their percutaneous coronary intervention. Just over half of the 2022 patients had elevated troponins. Overall, randomization to abciximab was associated with a significant 25% relative risk reduction in the 30-day combined endpoint of death, MI, or urgent target vessel revascularization. However, this benefit was confined to the 1049 patients with elevated troponin levels in whom abciximab decreased the occurrence of the primary endpoint by 29%. Troponin-negative patients experienced substantially lower and almost identical event rates irrespective of randomized therapy.

Therefore, based on these 4 trials it is difficult to justify the use of a GP IIb/IIIa receptor antagonist in patients with a suspected ACS who are troponin negative.

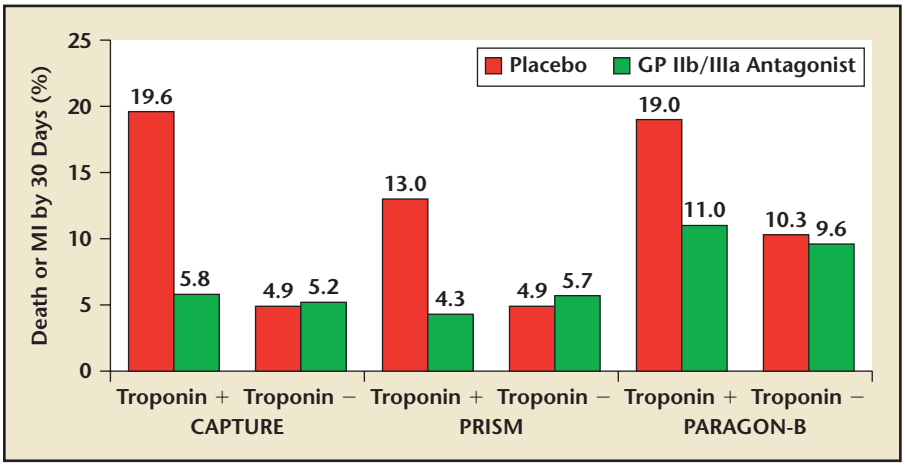
Clopidogrel

The data on adding clopidogrel to treatment are much more limited. In the 1 placebo-controlled trial of clopidogrel in the setting of ACS, the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, no data have been presented regarding troponin status.[15] One of the subgroups evaluated in the initial manuscript was based on positive or negative biomarker status. Interestingly, at least in terms of the 1-year outcome of cardiovascular death, MI, or stroke, randomization to clopidogrel seemed to be equally beneficial irrespective of biomarker status.

Invasive Therapies

There have been 2 recent studies comparing an invasive versus conservative approach in patients with suspected non–ST-segment elevation ACS. In both the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC-2)[16] and Treat Angina with Aggrastat and Determine Cost of Therapy with an

Figure 2. *Incidence of 30-day death and myocardial infarction in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE), Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON)-B trials based on randomized therapy and troponin status. GP, glycoprotein; MI, myocardial infarction. Reprinted with permission from Steinhubl SR.*[13]



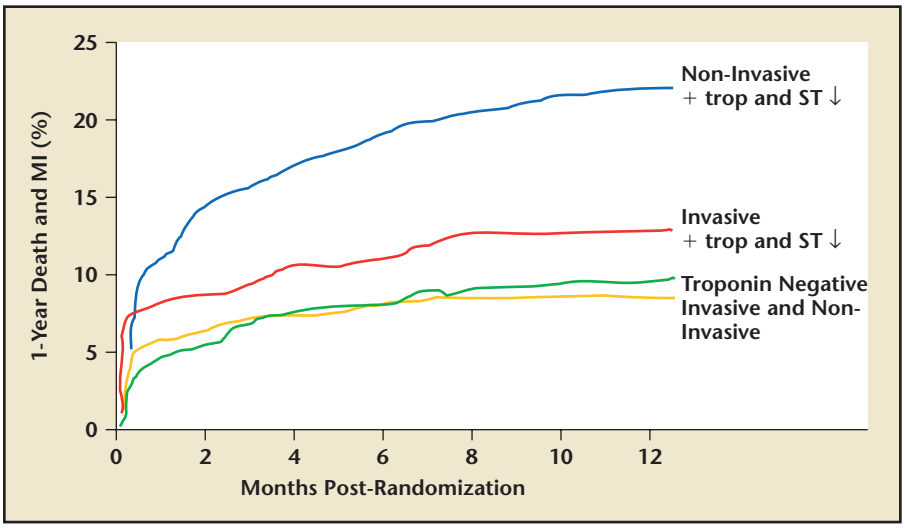


Figure 3. *One-year incidence of death and myocardial infarction (MI) among acute coronary syndrome patients randomized to an initial invasive or conservative management strategy based on baseline troponin status and electrocardiogram changes from the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC)-2 trial. Reprinted with permission from Diderholm E et al.*[18]

Invasive or Conservative Strategy (TACTICS)[17] trials, troponin status was measured at baseline. In both of these studies, an invasive approach was found to be beneficial only in those patients with objective criteria for myocardial ischemia. In the FRISC-2 trial, an invasive approach was associated with improved outcomes only in patients who were troponin positive with ST-segment depressions at the time of presentation (Figure 3).[18]

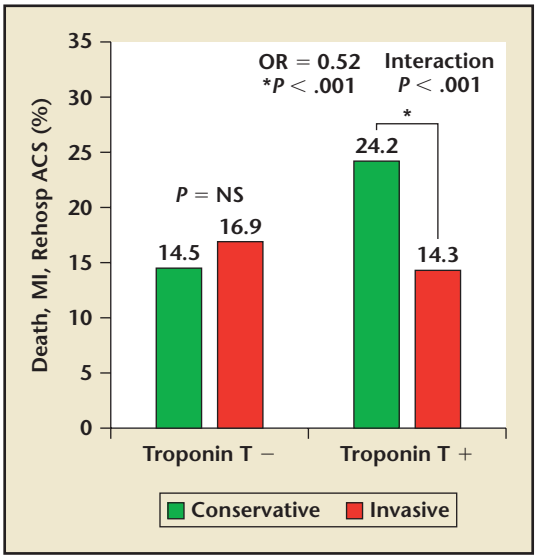
In the TACTICS trial based on troponin status, an invasive strategy demonstrated a marked reduction in recurrent MI or death compared with a conservative approach, whereas in troponin-negative patients there was not even a trend toward benefit (Figure 4).[19]

Summary

The optimal treatment for the patient presenting with suspected ACS remains a dilemma for many practitioners due to the heterogeneous nature of the population. Potential etiologies include gastroesophageal, musculoskeletal, psychiatric, pulmonary, or cardiac. Obviously, identifying those patients who will benefit the most from the large armamentarium of pharmacological and procedural interventions available to the cardiologist is critical in optimizing patient outcomes and safety. Currently, available data highlight that routine interventions such as UFH, GP IIb/IIIa receptor antagonists, and invasive approaches have no benefit in terms of reducing death and MI in the troponin-negative patient. Although patients who are troponin negative still experience events, it is important to realize that no good data presently exists to suggest that what practitioners do impacts the rate of those events. Also, it is important to highlight that these data focus on the reduction of death and MI, which is our primary goal when patients present with suspected ACS. However, symptom relief is also important. In some situations, therapy such as angiography and possible revascularization may be beneficial to the patient in terms of symptom relief. Still, a less aggressive antithrombotic regimen appears to be warranted in these patients.

Although the ACC/AHA Guidelines continue to group together patients with unstable angina and NSTEMI, it is important to recognize that the data do not suggest that these patients, as distinguished by their troponin status, represent a similar group of patients with similar responses to therapy. ■

Figure 4. *Incidence of the primary endpoint from the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial based on randomization to an initial conservative or invasive treatment strategy, based on troponin status. ACS, acute coronary syndrome; MI, myocardial infarction. Reprinted with permission from Morrow D et al.*[19]



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Main Points

- Over 6 million patients present to emergency rooms throughout the United States every year with chest pain or other symptoms suggestive of a diagnosis of an acute coronary syndrome (ACS). However, diagnoses are clear in only a small percentage of patients.
- The evaluation of troponin levels can identify patients at high risk for death and myocardial infarction (MI) and guide the vast majority of early (ie, in-hospital) decision making in the treatment of patients with chest pain and possible ACS.
- In a clinical trial investigating the diagnostic and prognostic implications of troponin elevation, investigators found that an abnormally elevated troponin level was associated with almost 6 times the incidence of subsequent MI or death compared with patients with normal troponin levels.
- In early placebo-controlled trials of aspirin in patients with suspected non–ST-segment elevation ACS, aspirin was associated with a greater than 50% relative risk reduction in the incidence of recurrent MI and death and remains a mainstay of initial therapy in all patients with chest pain, irrespective of risk.
- In several clinical trials, only patients who were troponin positive received benefit from unfractionated heparin, glycoprotein IIb/IIIa receptor antagonists, and invasive therapies in terms of reducing death and MI.
- Although the American College of Cardiology/American Heart Association Guidelines continue to group possible ACS patients with unstable angina and non–ST-segment elevation MI together, it is important to recognize that the data do not suggest that these patients, as distinguished by their troponin status, represent a similar group of patients with similar responses to therapy.