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A Guide to Therapeutic Decision-Making in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes

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Recent clinical trial evidence supports an inflammatory etiology in acute ischemic heart disease. When a segment of coronary artery becomes inflamed, important cytokines, such as tissue factor, are released, facilitating thrombosis. Serum inflammatory markers are elevated in most acute coronary syndrome patients at presentation. Mortality risk has been shown to be associated with increased levels of high-sensitivity C-reactive protein (CRP), interleukin 6, and serum vascular cell adhesion molecule. Platelets, which are rich in inflammatory mediators (CD40 and its ligand thrombospondin, and phospholipase A2), also supply important triggers for the inflammatory cascade. In addition, more than 35 platelet-associated messenger ribonucleic acid mediators involved in arterial injury and inflammation have been found. The use of biomarkers of inflammation, such as CRP, and of the sequelae of embolization, such as troponin, provide a window into the underlying pathophysiology of acute ischemic heart disease. New agents from three distinct drug classes have recently flooded the therapeutic armamentarium. Decision-making is further complicated by the choice of an invasive (aggressive) or a medical (conservative) strategy of management with respect to coronary revascularization. For patients at highest risk, aspirin, beta-blockers, nitrates, and a statin should be given, and clopidogrel, enoxaparin, a glycoprotein (GP) IIb/IIIa inhibitor, plus an invasive strategy should be considered. For intermediate- and low-risk patients, a "sliding-scale" approach may be best. Decisions about the three classes of antithrombotics—low-molecular-weight heparins, GP IIb/IIIa inhibitors, and thienopyridines—along with whether to adopt an early invasive strategy, should be made on an individual basis. (J Am Coll Cardiol 2003;41:123S–129S) © 2003 by the American College of Cardiology Foundation

Evidence from recent clinical trials and mechanistic studies underline the importance of an inflammatory etiology in acute ischemic heart disease. While there are many acknowledged risk factors (hypercholesterolemia, smoking, obesity, diabetes, homocysteinemia, and many others), their final common pathway appears to involve the inducement of an arterial inflammatory state. Arterial plaques that are low in collagen but rich in matrix metalloproteinases and mononuclear cells are particularly vulnerable. When a segment of coronary artery becomes inflamed, important cytokines, such as tissue factor, are released, and thrombosis is greatly facilitated.

While the inflammation hypothesis for the pathogenesis of acute ischemic heart disease is not new (1), its acceptance has grown substantially. At the same time, the availability of multiple new agents from three distinct drug classes has virtually flooded the therapeutic armamentarium. The decision whether coronary revascularization should be performed, and when, is further complicated by the need to choose an invasive/aggressive or a medical/conservative strategy of management. In a sense, this has transformed the therapeutic landscape of acute coronary syndrome (ACS) into an "acute confusional state," given the wide variety of choices for clinicians and the minimal evidence for rational and integrated use of the entire array of therapeutic approaches.

This review will highlight the key principles that we have come to accept regarding the underlying pathophysiology of ACS, and attempt to link these principles with particular therapeutic options. In so doing, the goal will be to create a framework for a unifying approach to treatment.

Inflammation and embolization. Multiple sites of the coronary arteries may be involved in a smoldering, chronic inflammatory state (Fig. 1). There appears to be considerable interpatient and interlesion variability with respect to the extent of the inflammatory atherosclerotic process. Serum inflammatory markers, however, are elevated in most ACS patients at presentation. The risk of subsequent fatality has been shown to be associated with increased levels of high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), and serum vascular cell adhesion molecule (VCAM) (2–4).

Although we commonly consider white blood cells to be the principal mediators of inflammation, the pivotal role of platelets has recently been demonstrated (5,6). Despite being enucleated, platelets are rich in inflammatory mediators, including the CD40 receptor and CD40 ligand thrombospondin and phospholipase A2 (5,6). Recent work by Lindemann et al. (6) has demonstrated the important

Please refer to the Trial Appendix at the back of this supplement for the complete list of Clinical Trials.

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
ACUTE = Antithrombotic Combination Using Tirofiban and Enoxaparin trial
CRP = C-reactive protein
GP = glycoprotein
hs-CRP = high-sensitivity C-reactive protein
IL = interleukin
LMWH = low-molecular-weight heparin
MI = myocardial infarction
mRNA = messenger ribonucleic acid
VCAM = vascular cell adhesion molecule

contribution of platelet-derived messenger ribonucleic acid (mRNA); more than 35 platelet-associated mRNA mediators involved in arterial injury and inflammation have been found (6). Originally, the CD40 receptor and ligand were believed to be predominantly T-cell lymphocyte-derived, but data from recent studies indicate that at least 90% of CD40 ligand in the body is derived from platelets. Furthermore, the CD40 receptor and ligand are among the most important triggers of the cascade of inflammatory cytokines and adhesion molecules, with rapid induction of the expression of VCAM, intercellular adhesion molecules, and multiple potent inflammatory mediators (7).

Along with our enhanced understanding of the expanded role of platelets, we have also learned about the propensity of atherosclerotic plaque to embolize. This occurs spontaneously, as evidenced by the occurrence of circulating endothelial cells (8), but also when the artery is directly manipulated via balloon angioplasty, stenting, or other endovascular therapeutic techniques. The embolization is apt to be comprised of microparticulate atheromatous material, as has been routinely demonstrated through the use of emboli capture devices (9). The embolus may or may not contain platelet thrombus. However, a key response to the showering of debris into the microvasculature will be platelet activation and aggregation (10). Microvascular obstruction leads to ischemic cell death and the development of troponin positivity. Thus, the use of biomarkers of inflammation such as CRP, and of the sequelae of embolization such as troponin, provides a window into the underlying pathophysiology of acute ischemic heart disease.

Using troponin to guide therapy. It is clear that clinical and electrocardiographic criteria are insufficient to determine risk in patients with ACS. For example, using data from a large cohort of over 290,000 patients, Welch et al. (11) found a 5.7% death rate by day 7 in patients with a normal electrocardiogram on presentation (Fig. 2). There is now abundant evidence linking elevated levels of the important cardiovascular biomarker troponin (specifically troponin I or T) with adverse major cardiovascular events, including an overall fourfold increased risk of fatality in an aggregate of 13 series (12) (Fig. 3). Beyond elevated risk, several studies have confirmed the specific value of low-molecular-weight heparin (LMWH) (13,14) or small molecule platelet glycoprotein (GP) IIb/IIIa inhibitors (15,16) in troponin-positive patients (Fig. 4). Recently, the use of invasive strategies, specifically angiography and coronary revascularization, was also shown to be particularly appro-

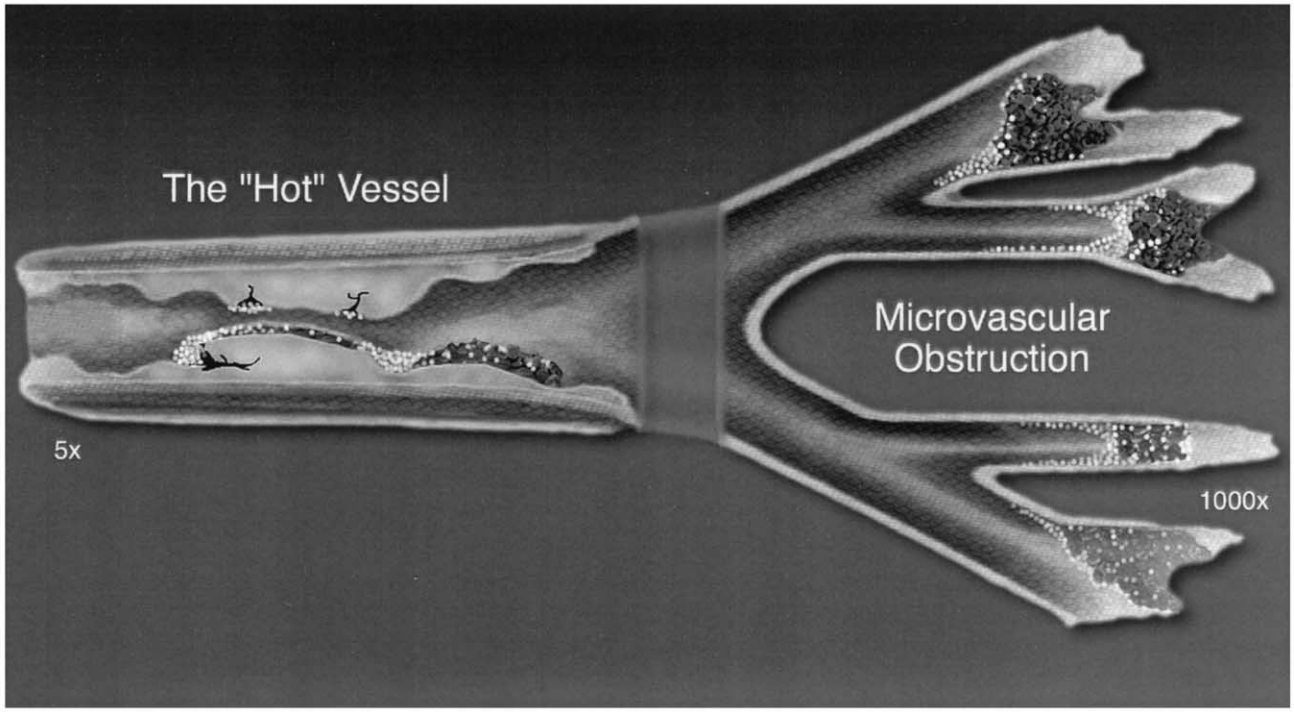

Figure 1. Schematic depiction in sagittal view of inflammation and embolization.

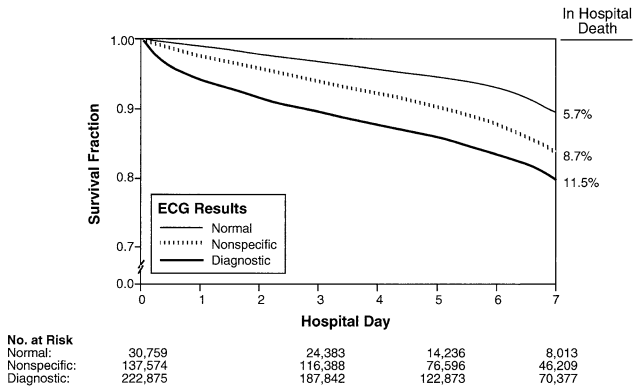

Figure 2. The survival distribution function curves represent the unadjusted fraction of survivors as a function of remaining hospitalized patients at the given time (patients at risk). ECG = electrocardiogram. With permission from Welch RD, et al. JAMA 2001;286:1977–84, ©2002, American Medical Association.

priate in patients with an abnormal troponin elevation on admission (17) with GP IIb/IIIa inhibitor therapy as background therapy. In contrast, clopidogrel did not afford preferential benefit in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial. In this case the approximate 20% reduction in death or nonfatal myocardial infarction (MI) was similar in both groups, regardless of troponin measurement (18). Of note, abciximab failed to provide benefit in troponin-positive patients in the Global Use of Strategies To Open occluded arteries in acute coronary syndromes (GUSTO)-4 trial. In fact, the observed trend of detrimental outcome demonstrates an unexpected adverse effect of long (48-h) infusions of abciximab in medically treated patients (19).

Based on the current evidence, platelet GP IIb/IIIa inhibitors (tirofiban and lamifiban) and LMWHs (enoxaparin or dalteparin), combined with an invasive strategy, have been shown to be beneficial in patients with elevated troponin. Therefore, it is vital to measure this biomarker on admission in patients who present with clinical and electrocardiographic evidence of a non–ST-segment elevation ACS. Although the combined beneficial impact of an invasive strategy plus LMWH or an invasive strategy plus

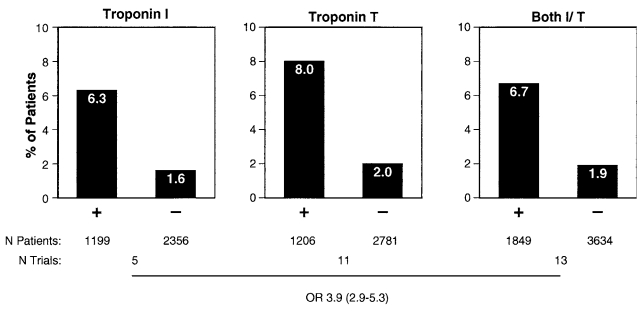

Figure 3. Risk of mortality in acute coronary syndrome studies. I/T = troponin I/troponin T; OR = odds ratio. Adapted from data contained in Heidenreich PA, et al. J Am Coll Cardiol 2001;38:478–85.

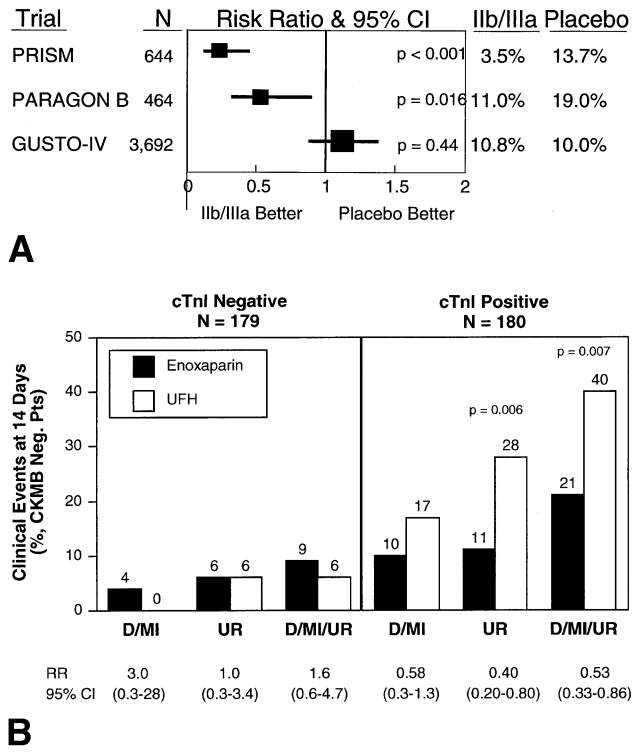

Figure 4. (A) Comparison of glycoprotein IIb/IIIa receptor inhibition trials in patients testing troponin-positive demonstrates marked homogeneity. $p < 0.001$ Breslow-Day homogeneity. **(B)** Clinical outcomes at 14 days for patients treated with enoxaparin versus unfractionated heparin (UFH) stratified by 0 to 24 h cardiac troponin I (cTnI) results. CI = confidence interval; CKMB Neg. Pts = creatine kinase-myocardial band-negative patients; D/MI/UR = death, MI, or urgent revascularization; GUSTO = Global Use of Strategies To Open occluded arteries in acute coronary syndromes trial; IIb/IIIa = glycoprotein IIb/IIIa receptor inhibitor; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome Global Organization trial; PRISM = Platelet Receptor Inhibition for Ischemic Syndrome Management trial; RR = relative risk of the outcome for patients treated with enoxaparin versus unfractionated heparin. Reprinted with permission from the American College of Cardiology (J Am Coll Cardiol 2000;36:1812–7).

small molecule GP IIb/IIIa inhibitor has been fully validated in two large-scale trials (17,20), there has not yet been a trial combining all three of these components—GP IIb/IIIa inhibitor, LMWH, and an invasive strategy.

Combination of LMWH and GP IIb/IIIa inhibitor. There are ongoing large-scale trials designed to evaluate these agents in combination. These include the Superior Yield of the New strategy of Enoxaparin, Revascularization, and GlYcoprotein IIb/IIIa inhibitors (SYNERGY), which compares enoxaparin versus unfractionated heparin, with or without GP IIb/IIIa inhibitor, and the A to Z trial, which compares the combination of tirofiban plus unfractionated heparin versus tirofiban plus enoxaparin. The early data, which appear encouraging, consist of two randomized pilot trials: the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE) I and II, and a subgroup analysis of the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome Global Organization Network

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(PARAGON)-B trial, which allowed the use of LMWH (21–23). In ACUTE I, an additive effect on antiplatelet inhibition was demonstrated when enoxaparin and tirofiban were combined (21). This was extended in ACUTE II for 525 patients randomly assigned to tirofiban plus enoxaparin, compared with tirofiban plus unfractionated heparin. No significant or numerical excess in major bleeding or transfusions was associated with the tirofiban/enoxaparin combination (22). In the PARAGON-B trial, almost 600 patients received LMWH rather than unfractionated heparin. Subjects treated with both lamifiban and LMWH had the lowest death or nonfatal MI rate and no evidence of an increase in major bleeding (23).

Added to these recent trials are the results of the Enoxaparin plus TNK-tPA wIth/without GP IIb/IIIa as REperfusion for STEMI-Thrombolysis In Myocardial Infarction (ENTIRE-TIMI)-23, which combined enoxaparin and abciximab with tenecteplase for acute MI reperfusion therapy (24). Of note, even with fibrinolytic background therapy, the combination of the LMWH and GP IIb/IIIa inhibitor was associated with less bleeding than combinations using unfractionated heparin.

Definitive judgments must await the completion of trials such as the SYNERGY and A to Z, but high-risk patients such as those with troponin positivity, diabetes, prior MI, and other risk factors may warrant consideration for the use of both classes of agents. The original concerns about bleeding have largely been mitigated, and the only remaining issue is to establish definitive proof of enhanced efficacy to justify the higher cost of therapy. The issue of safety for very low incidence adverse events, such as intracerebral hemorrhage, will be firmly established only when the data from ongoing large-scale trials become available.

The importance of diabetes mellitus in decision-making. Roffi et al. (25) recently performed a pooled analysis of data from all diabetic patients ($n > 6,750$) enrolled in intravenous platelet GP IIb/IIIa inhibitor trials and found an important reduction in mortality from 6.2% (placebo group) to 4.6% in the GP IIb/IIIa inhibitor-assigned patients (Fig. 5). This 26% reduction in mortality ($p = 0.007$) was also demonstrated to be a highly significant treatment by diabetic subgroup interaction (25). The precise mechanism for this particular benefit among diabetics is not known. Indeed, the frank survival benefit is distinct from that in troponin-positive patients associated with reduced MI incidence. Whether this benefit is related to increased platelet activation in diabetics, other evidence of heightened inflammation, or more diffuse atherosclerosis with a propensity for microvascular obstruction needs further exploration. Even without definition of the mechanism, the data are convincing enough that the use of GP IIb/IIIa inhibitors should be strongly considered for diabetic patients presenting with ACS.

The importance of inflammatory markers. Beyond routine testing for troponin, the additive value of tracking inflammation has been definitively established. Morrow et al. (26) demonstrated this in the TIMI IIA trial that indexed prognosis for 14-day mortality to the rapid troponin-T assay and C-reactive protein (CRP) level (Fig. 6A). In the FRagmin during InStability in Coronary artery disease (FRISC) trial, Lindahl et al. (27) measured the incidence of cardiac death at one year and found that the risk ranged from 0% to 16% among patients who had elevated troponin and CRP levels (Fig. 6B). A host of other studies have supported the prognostic value of other inflammatory markers, including a simple white blood cell count, measurement of VCAM, or pregnancy-associated plasma protein A (28). For patient prognosis, and particularly for risk of late (one year as opposed to seven days) death, hs-CRP is the most economical, widely available, and validated test to date.

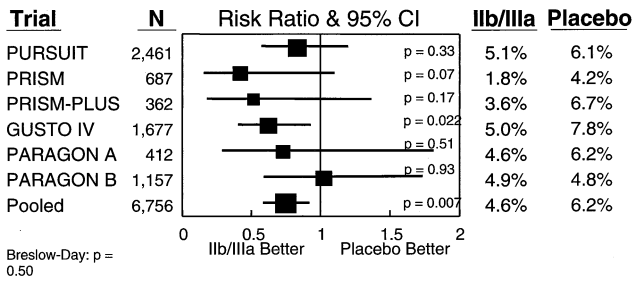

Figure 5. Odds ratio with 95% confidence intervals (CI) and corresponding p values for treatment effect on 30-day mortality among diabetic patients with acute coronary syndromes. **Values to the left of 1.0** indicate survival benefit of platelet glycoprotein IIb/IIIa inhibition. GUSTO = Global Use of STrategies to Open occluded arteries in acute coronary syndromes trial; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome Global Organization Network trial; PRISM-PLUS = Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms trial; PURSUIT = Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy trial. Roffi M, Chew DP, Mukherjee D, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non–ST-segment elevation acute coronary syndromes. Circulation 2001;104:2767–71. Reproduced with permission from Lippincott, Williams and Wilkins.

Recently, CRP and IL-6 have been shown to be useful guides to therapy because of their ability to predict which patients would benefit from an invasive strategy (29). Glycoprotein IIb/IIIa inhibitors and LMWHs have not yet been shown to be indexed to CRP levels. However, enoxaparin's anti-inflammatory effect may be based on its capability to lower plasma levels of von Willebrand factor (30,31). The GP IIb/IIIa inhibitors have been shown to suppress CRP and other inflammatory markers (32), but their particular use in patients with an elevated CRP has not yet been addressed. An important strategy that awaits testing is the use of medications to lower the CRP level before coronary revascularization is performed.

The role of thienopyridines to reduce inflammation. Chew et al. (33) recently demonstrated that clopidogrel treatment before percutaneous coronary intervention was effective in reducing the level of hs-CRP. This effect does not seem to occur with low dose aspirin (34), but there

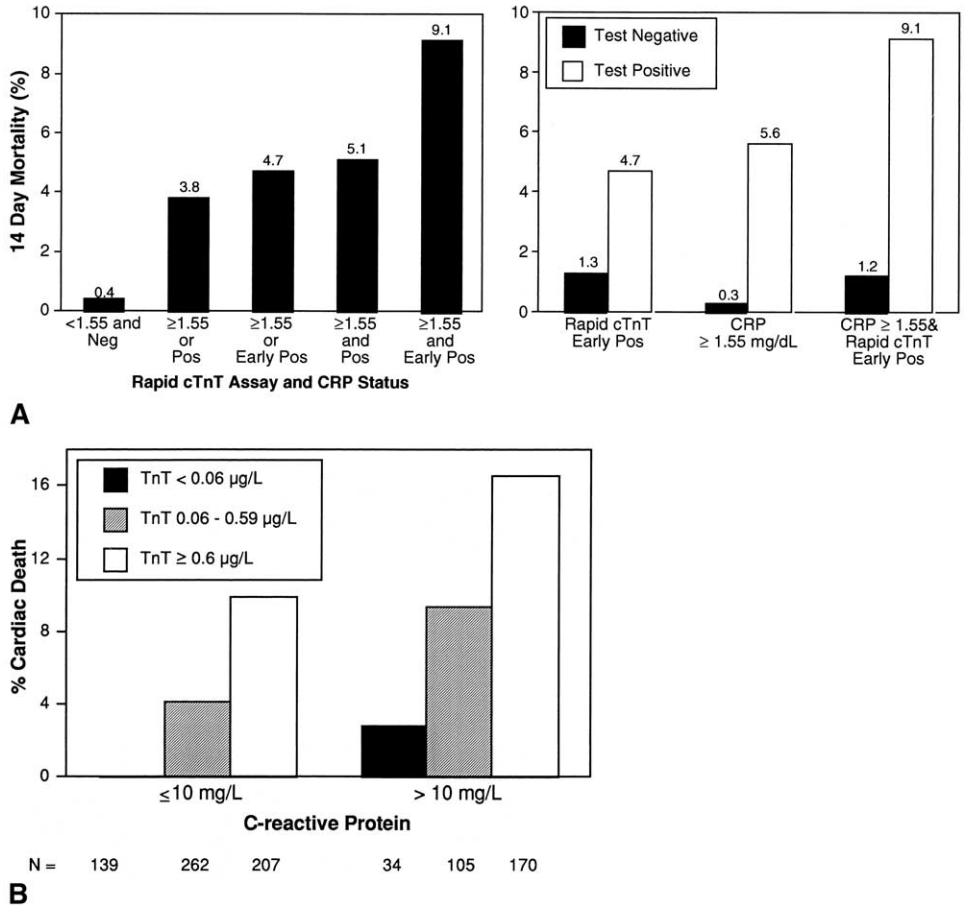

Figure 6. (A) (Left) Risk stratification by C-reactive protein (CRP) (mg/dl) and rapid cardiac troponin T (cTnT) assay status expressed as 14-day mortality rate by CRP and rapid cTnT result. Early positive rapid cTnT assays are those that could be read positive by ≤10 min. Trend evaluated by chi-squared test. **(Right)** Mortality rate at 14 days by CRP and rapid cTnT assay status. Early positive rapid assays for cTnT are those for which the red line appeared by ≤10 min, with a "negative" test in this category including both negative and late positive rapid cTnT results. C-reactive protein ≥1.55 mg/dl is considered a positive test. "Test Positive" in the category "CRP ≥1.55 mg/dl and Rapid cTnT early positive" requires both tests to be positive, with a "negative" test in this category representing all other combinations. With permission from Morrow DA et al. J Am Coll Cardiol 1998;31:1460–5. **(B)** Incidence of death from cardiac causes at two years in the FRagmin during InStability in Coronary artery disease trial (FRISC) according to the presence or absence of ST-segment depression on the admission electrocardiogram and the maximal troponin T (TnT) levels during the first 24 h after enrollment and to the CRP levels and the maximal TnT levels. Neg = negative; Pos = positive. With permission from Lindahl B, et al. N Engl J Med 2000;343:1139–47.

are synerism effects with the combination of aspirin and clopidogrel on markers of platelet activation, such as P-selectin (a proxy for a heightened state of inflammation) (35). With the recent CURE trial (18) validating the use of combined clopidogrel and aspirin in patients with non–ST-segment elevation acute ischemic heart disease, there is now mechanistic support for the significant benefit documented in that trial.

Recommendations based on a clinical and pathophysiologic approach. As we await data from ongoing trials and mechanistic studies, it seems reasonable to assay both troponin and hs-CRP in all patients with ACS. If the hs-CRP assay is unavailable, a white blood count, at least, is recommended. The clinical risk profile should be established, noting a history of diabetes, age, prior history of heart failure or stroke, renal impairment, and ST depression on the electrocardiogram on presentation or at repeat assessment. Prior use of aspirin appears to be another important risk feature (36,37).

For patients at highest risk—those with elevated troponin and CRP levels, an ST depression on the electrocardiogram, and diabetes—the "maximum" therapy is warranted. Aspirin, beta-blockers, nitrates, and a statin should be given, and clopidogrel, enoxaparin, a GP IIb/IIIa inhibitor, plus an invasive strategy should be considered. The timing of the first dose of clopidogrel (loading, 300 mg) needs to be determined on the basis of whether the patient is likely to undergo emergency coronary artery bypass surgery. The risk of significant bleeding is at least 60% higher among patients who have received both clopidogrel and aspirin compared with those given aspirin alone at the time of bypass surgery when the surgery is performed within five days of clopidogrel dosing (18). Accordingly, clopidogrel can be initiated in the emergency room setting, if early coronary artery

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bypass graft surgery is not anticipated, or deferred until an angiogram rules out surgical anatomy.

The decision to implement a GP IIb/IIIa inhibitor for such high-risk patients is simply a matter of "when" and not "if," unless there is a bleeding diathesis or if the coronary anatomy demonstrates lack of suitability for percutaneous coronary revascularization. In high-risk patients, starting a small molecule GP IIb/IIIa inhibitor in the emergency room (either tirofiban or eptifibatide) is a reasonable strategy with early angiography performed the following morning. Alternatively, the patient can undergo acute angiography, and the GP IIb/IIIa inhibitor abciximab can be reserved for the patient who proves to be suitable for percutaneous coronary revascularization. This agent has been shown to be superior to tirofiban, especially in ACS patients undergoing stenting, at the doses tested in the comparative large-scale do Tirofiban And Reopro Give similar Efficacy Trial (TARGET) (38). There are no definitive data comparing eptifibatide with abciximab. Until data become available from trials of tirofiban at increased doses, or eptifibatide in head-to-head trials, abciximab should be considered the agent of choice in patients with ACS undergoing percutaneous coronary intervention.

The only LMWH proven to be superior to unfractionated heparin in the setting of ACS is enoxaparin. The sole remaining issue for large-scale application of this agent has been its use during percutaneous coronary revascularization procedures, as there has been concern regarding the inability to monitor the level of anticoagulation during the procedure. This concern appears to be addressed by recent studies using an empiric approach based on the timing of the last dose of enoxaparin to the performance of the coronary intervention. More data will be forthcoming from trials such as SYNERGY and A to Z. In high-risk patients presenting at hospitals without emergency cardiac catheterization facilities, the use of enoxaparin to replace unfractionated heparin is supported by the results of two trials (39,40).

For intermediate- and low-risk patients, a "sliding-scale" approach may be best. Decisions about the three classes of antithrombotics—LMWHs, GP IIb/IIIa inhibitors, and the thienopyridines—along with whether to adopt an early invasive strategy, should be made on an individual basis.

There will undoubtedly be continued refinement of our approach, both with respect to optimal use of biomarkers and the implementation of the various pharmacologic and revascularization approaches. It is indeed striking, however, that our increased insight about the propensity for inflammation and embolization has already markedly affected our routine approach to patients with ACS.

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