Introduction to “Optimizing Management of Non–ST-Segment Elevation Acute Coronary Syndromes”
Harmonizing Advances in Mechanical and Pharmacologic Intervention

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Advances in the management of patients with acute coronary syndromes (ACS) have evolved dramatically over the past decade and, in many respects, represent a rapidly moving target for the cardiologist or internist who seeks to integrate these recent developments into contemporary clinical practice (1,2). Traditionally, the approach to treating ACS patients has predominantly involved the rapid initiation of intensive medical management, followed by noninvasive risk stratification to identify those who need urgent catheterization and possible revascularization versus continued medical therapy alone (3–5).

Patients with unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) comprise a growing subgroup of patients with ACS, producing a major public health problem worldwide, especially in Western countries, despite significant improvements and refinements in management over the past 20 years. In the U.S. alone, over 2.4 million people present with ACS each year, with more than six million individuals undergoing in-hospital vascular and cardiac surgery and related procedures (6). Consequently, much attention has been directed toward optimizing the diagnosis and management of such patients, particularly in light of the continued evolution of catheter-based interventions and newer pharmacologic strategies that afford more complete platelet and thrombin inhibition. When used together, these approaches appear to have an important synergistic effect in reducing prognostically important ischemic events (7–12).

Various randomized, controlled clinical trials have established the scientific foundation upon which evidence-based treatment strategies have emerged and become increasingly refined. Against this backdrop, the clinician is frequently confronted with a panoply of choices that can create uncertainty or confusion regarding “optimal management.” The debate about the ideal approach to the management of NSTE ACS (i.e., routine “early invasive strategy” versus an “ischemia-guided” or “conservative” strategy) has been ongoing for over a decade (3–5,7–9). Recently, compelling evidence from randomized clinical trials has demonstrated that intermediate- and high-risk ACS patients derive significant reductions in both morbidity and mortality with mechanical or surgical intervention, especially when revascularization is coupled with aggressive, multifaceted (anti-platelet, antithrombin, anti-ischemic and antiatherogenic) medical therapy (10–12).

When one considers the various pharmacologic options available (low molecular-weight heparins [LMWHs], unfractionated heparin [UFH], glycoprotein (GP) IIb/IIIa inhibitors, thienopyridines, plus the more “time-honored” treatments of aspirin, intravenous (IV) nitroglycerin, beta-blockers, statins and other dyslipidemic agents, and angiotensin-converting enzyme [ACE] inhibitors), the myriad possible drug combinations, and the important role of establishing prompt coronary reperfusion with either catheter-based intervention or surgical revascularization, it is easy to understand how complex and difficult the decision-making process has become for cardiologists, emergency medicine physicians, intensivists, and hospital pharmacists.

For these reasons, it seems especially timely and appropriate to undertake a comprehensive review of the latest advances in the management of NSTE ACS, mindful of the fact that even this noble effort to synthesize and integrate a prodigious amount of scientific information and cardiovascular therapeutics is destined to evolve still further as our full-scale assault on optimizing clinical outcomes by harmonizing the advances in mechanical and pharmacologic interventions continues unabated.

In this unique supplement to the Journal of the American College of Cardiology, we have assembled a distinguished international faculty of 16 clinical scientists, trialists, subject-matter experts, and opinion leaders. Their superlative contributions have shaped and honed the many diag-

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nastic and therapeutic facets of this challenging and increasingly common clinical syndrome.

Dr. Valentin Fuster provides an important and lucid introduction to the Pathogenetic Concepts of Acute Coronary Syndromes. In his report he describes the role of plaque disruption as a major determinant of future ischemic events, and the interdependent atherosclerotic and thrombotic processes that are becoming increasingly integrated under the term “atherothrombosis.” Inflammation, as a major determinant of both plaque vulnerability and thrombogenicity upon plaque disruption, and the pivotal role that the endothelium plays in vascular homeostasis and hemostasis, are both reviewed in considerable detail.

Dr. Prediman K. Shah then discusses the Mechanisms of Plaque Vulnerability and Rupture. In this elegant contribution, Dr. Shah reviews the role of coronary thrombosis in the genesis of acute ischemic syndromes leading to acute MI, UA, and sudden cardiac death. He describes the constituents of the so-called vulnerable plaque: thin fibrous cap, upstream propagation of thrombus from the site of cap rupture, and the roles of lipid and inflammation in mediating the development and progression of atherosclerotic plaques. He also discusses the effects produced by reducing lipids and inflammation in atherosclerotic plaques for decreasing the risk of plaque rupture and subsequent thrombosis.

Next, Dr. Carl J. Pepine discusses the exciting concept of Pharmacologic Plaque Passivation for the Reduction of Recurrent Cardiac Events in Acute Coronary Syndromes. Passivation of vulnerable plaque represents an essential therapeutic strategy that can prevent or limit the magnitude of a new rupture to reduce the recurrence or severity of events. The author has explored the use of pharmacological agents targeting plaque vulnerability and passivation, including lipid-modifying agents (e.g., statins), antiplatelet agents (acetysalicylic acid, thienopyridines, GP IIb/IIIa inhibitors), and antithrombotic agents (UFH and LMWH), and has examined their potential role in reducing the occurrence of acute coronary events in ACS patients.

Dr. E. Magnus Ohman then reviews the vital role of Troponin: An Important Prognostic Marker and Risk Stratification Tool in Non–ST-Segment Elevation Acute Coronary Syndromes. In recent years, the development of highly sensitive and cardiac-specific troponin assays has resulted in a consensus change in the definition of MI, placing increased emphasis on cardiac marker testing with troponins as the new “gold standard.” Perhaps more importantly, Dr. Ohman has described the establishment of the troponins as superior markers of subsequent cardiac risk in ACS patients and the role these markers play in identifying patients with ACS who may derive particular benefit from potent antithrombotic and antiplatelet therapy or early invasive treatment strategies.

It has, however, become increasingly clear that biomarkers alone do not provide the only basis for delineating subsets of ACS patients at high risk for developing recurrent events. Dr. Paul Ridker reviews the increasingly important role of C-Reactive Protein and Other Inflammatory Risk Markers in Acute Coronary Syndromes. In his report, Dr. Ridker highlights the fact that many ACS patients without evidence of myocyte necrosis are at high risk for recurrent ischemic events. Given the role of inflammatory processes in determining plaque stability, recent work has focused on whether plasma markers of inflammation may help improve risk stratification. Of these markers, C-reactive protein (CRP) has been the most widely studied. There is evidence that CRP is a strong predictor of cardiovascular risk among apparently healthy individuals, patients undergoing elective revascularization procedures, and patients presenting with ACS. Initial evidence suggests that the benefits of lifestyle modification and drug therapy with aspirin or statins may be greatest among those with elevated CRP levels.

Dr. Christopher Cannon then shifts to a discussion of Small Molecule Glycoprotein IIb/IIIa Receptor Inhibitors as Upstream Therapy in Acute Coronary Syndromes, focusing on the results of the TACTICS TIMI-18 trial. Several large trials have shown GP IIb/IIIa inhibition to be beneficial in UA/NSTEMI either in patients treated predominantly with medical management, early interventional management, or both. These agents appear to be of greatest benefit in patients at higher risk—for example, those with a positive troponin at baseline, those with diabetes or ST-segment depression, recent angina, prior aspirin use, or a Thrombolyis in Myocardial Infarction (TIMI) risk score ≥4. These results provide evidence to physicians that early GP IIb/IIIa inhibition in combination with a prompt invasive approach should be utilized more widely in UA/NSTEMI patients, particularly those at high risk.

To complete the discussion of the role of GP IIb/IIIa agents in ACS patients, Dr. David Moliterno discusses the data in support of using Glycoprotein IIb/IIIa Inhibition in Early Intent-to-Stent Treatment of Acute Coronary Syndromes: EPISTENT, ADMIRAL, CADILLAC, and TARGET. The ACSs, with or without ST-segment elevation, share a common pathophysiology of activated platelets and thrombin generation stimulated by plaque erosion and rupture. Both mechanical and pharmacologic treatment strategies have evolved in an attempt to improve reperfusion at the myocardial tissue level. When used with intracoronary stents, potent platelet inhibition from IV GP IIb/IIIa antagonists has reduced the rate of periprocedural MI and late mortality. In particular, abciximab has well-established clinical benefits in percutaneous revascularization trials, and several recent landmark studies have evaluated the efficacy of concomitant abciximab during mechanical reperfusion therapy in the setting of ACS. These trials are reviewed and an overall perspective is provided.

Dr. Marc Cohen provides an important commentary and perspective on the emerging Role of Low–Molecular–Weight Heparin in the Management of Acute Coronary Syndromes. Several studies have consistently demonstrated that LMWH compounds are effective and safe alternative anti-
coagulants to UFH and improve clinical outcomes in ACS patients. Of the several LMWH agents that have been studied in large clinical trials, including enoxaparin, dalteparin, and nadroparin, not all have shown better efficacy than UFH. Enoxaparin is the only LMWH compound to have demonstrated sustained clinical and economic benefits in comparison with UFH in the management of UA/NSTEMI. Enoxaparin may also be a reliable and effective antithrombotic treatment as adjunctive therapy in patients undergoing percutaneous coronary intervention (PCI). The most recent modifications to the American College of Cardiologists/American Heart Association (ACC/AHA) Management Guidelines for patients with NSTE ACS now advocate enoxaparin as a Class I indication for antithrombin therapy.

Dr. Sonia Anand provides an important overview of a therapeutic approach utilizing Oral Anticoagulants in Patients With Coronary Artery Disease, a class of drugs not often regarded by clinicians as efficacious for ACS patients. In her report, Dr. Anand undertakes a systematic review of the role of oral anticoagulants, with and without antiplatelet therapy, in patients with established coronary artery disease. The results revealed that high-intensity oral anticoagulation with an international normalized ratio (INR) target of >2.8 significantly reduced cardiovascular complications but increased bleeding compared to controls. Low-intensity oral anticoagulation (INR <2), in the presence of aspirin, did not reduce cardiovascular complications, but increased bleeding compared to aspirin alone. Moderate-intensity oral anticoagulation (INR 2–3) was found to reduce cardiovascular complications compared to controls. The combination of aspirin plus moderate-intensity oral anticoagulation proved to be more effective and just as safe as aspirin alone. Moderate-intensity oral anticoagulation, therefore, used together with aspirin, reduces recurrent cardiovascular events and is relatively safe compared to aspirin alone when used in patients with established coronary artery disease.

Next, Dr. John Eikelboom highlights The Evolving Role of Direct Thrombin Inhibitors in Acute Coronary Syndromes. Thrombin plays a central role in the initiation and propagation of intravascular thrombus, providing a strong rationale for using direct thrombin inhibitors in ACS patients. Whereas the heparins block only circulating thrombin, direct thrombin inhibitors block both circulating and clot-bound thrombin. The Direct Thrombin Inhibitor Trialists’ Collaboration meta-analysis confirmed the superiority of direct thrombin inhibitors, particularlyhirudin and bivalirudin, over UFH for the prevention of death or MI during treatment of ACS patients. These results were due to primarily a reduction in MI (odds ratio, 0.80; 95% confidence interval, 0.70 to 0.91) with little impact on death. These and other preliminary data support the potential benefit of bivalirudin over heparin for the prevention of death or MI at 30 days, but further studies in ACS are warranted.

Drs. Salim Yusuf and Shamir Mehta discuss the expanding role of Short- and Long-Term Oral Antiplatelet Therapy in Acute Coronary Syndromes and Percutaneous Coronary Intervention. The investigators highlight the central role played by platelets in both the acute and long-term manifestations of atherosclerosis, especially in ACS where there is a steep early rise in cardiovascular events, followed by a long-term incremental increase in events. The Antiplatelet Trialists Collaboration found a 46% reduction in vascular events with antiplatelet therapy (mostly aspirin), but despite treatment with aspirin and proven therapies, recurrent events remain high. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated the significant short- and long-term benefits (up to one year) of aspirin plus clopidogrel in reducing major cardiovascular events (cardiovascular death, MI, and stroke reduced by 20%, p = 0.00009) in a broad range of ACS patients. The benefits emerged very rapidly (within 2 h) after a 300 mg loading dose, and they were likewise observed in the large number of patients undergoing PCI in CURE. Here, the benefit was observed regardless of whether intervention was performed early or late. Because of the broad-based benefits associated with clopidogrel in all subgroups of ACS patients, the revised ACC/AHA Treatment Guidelines have been updated in 2002 to include clopidogrel as a Class I indication in all ACS patients.

Drs. Elliott Antman and Marc Sabatine review the utility and clinical application of The Thrombolysis In Myocardial Infarction Risk Score in Unstable Angina/Non–ST-Segment Elevation Myocardial Infarction. Certainly, risk stratification in ACS is important in quantifying an estimate of a patient’s prognosis and as a guide to optimizing clinical choices. The TIMI risk score for NSTE ACS represents an integrated approach using baseline variables that are part of the routine medical evaluation to identify patients at high risk for death and other major cardiac ischemic events. Employing multivariable logistic regression of seven independent predictor variables, a weighted risk score can be constructed as the simple arithmetic sum of the number of predictors. The rate of death, MI, or urgent revascularization significantly increased as the TIMI risk score increased, ranging from <5% for patients with a risk score of 0 or 1 to >40% for patients with a risk score of 6 or 7. Thus, the TIMI risk score provides a clinically meaningful tool to define a gradient of benefit for specific treatments such as LMWH, GP IIb/IIIa inhibitors, and an early invasive strategy.

Which approach—an interventional, anatomically driven one or a functional, biologically driven one—is preferable for managing patients with NSTE ACS? Dr. Raymond McKay and Dr. Steven Nissen address this ongoing controversy in a lucid “point-counterpoint” discussion of these differing management strategies. In his report, “Ischemia-Guided Versus Early invasive Strategies in the Management of Acute Coronary Syndrome/Non–ST-Segment Elevation Myocardial Infarction: The Interventionalist’s Perspective,” Dr. McKay summarizes the key findings of more recent studies.
Figure 1. Strategies for mechanical and pharmacologic intervention in acute coronary syndrome (ACS) patients. ACE = angiotensin-converting enzyme; ASA = acetylsalicylic acid; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCU = Cardiac Care Unit; CHF = congestive heart failure; ECG = electrocardiogram; GP = glycoprotein; inflammation; IV = intravenous; LBBB = left bundle branch block; LMWH = low molecular-weight heparin; MI = myocardial infarction; MPI = myocardial perfusion imaging; NTC = nitroglycerin; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

* Consider also inflammatory markers: Brain Natriuretic Peptide (BNP), CHF, deep T-wave inversions on ECG, etc.
Improved clinical outcomes have been demonstrated with the use of an “early invasive” approach, employing routine coronary angiography early in the patient’s hospital course, followed by PCI or bypass surgery. The emerging role for the combined use of GP IIb/IIIa inhibitors and intracoronary stenting, which may reduce the potential early hazard of an invasive approach by specifically decreasing the incidence of death and nonfatal MI associated with PCI, is also discussed. In this overview, Dr. McKay highlights the importance of PCI to treat “culprit” lesions as part of a broader treatment strategy employing a combination of aggressive medical therapy to treat the widespread coronary atherosclerosis commonly seen in ACS patients.

In his related report, Dr. Nissen endorses the opposing view that Pathobiology, Not Angiography, Should Guide Management in Acute Coronary Syndrome/Non–ST-Segment Elevation Myocardial Infarction: The Non–Interventionist’s Perspective. In this provocative essay, Dr. Nissen concedes that, while an “early invasive” strategy (angiography and PCI) is the convention in ACS/NSTEMI management in the United States, a conservative pharmacologic approach is common in other countries. Identification of hemodynamically significant stenoses may be confounded by coronary “remodeling” and most plaques, particularly those responsible for acute events, are “extraluminal.” Assessment of the luminal diameter of a lesion, which requires comparison with a “normal” reference segment, may be impossible because of the diffuse nature of the disease, and PCI following plaque rupture may itself cause embolization and “no-reflow” phenomena leading to severe complications. The inability of angiography to depict the true extent of atherosclerosis is supported by necropsy and transplant donor studies. Statins, beta-blockers, and ACE inhibitors decrease the incidence of death and MI by stabilizing atherosclerotic plaques throughout the coronary bed, reducing inflammation, collagen degradation, tissue factor expression, and vasomotor tone.

Dr. William Boden reviews the continuing controversy regarding the “Routine Invasive” versus “Selective Invasive” Approaches to Non–ST-Segment Elevation Acute Coronary Syndromes Management in the Post–Stent/Platelet Inhibition Era. Dr. Boden poses an important question: Does a “routine invasive” or “selective invasive” strategy constitute the best management approach for patients who present with NSTE ACS? Two trials, the second Fragmin and fast Revascularization during Instability in Coronary artery disease (FRISC-II) and the Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS TIMI-18), have demonstrated significant reductions in death, recurrent MI, or hospitalization for biomarker-positive ACS during 6- to 12-month follow-up when myocardial revascularization was undertaken two to six days after symptom onset. Importantly, while FRISC-II and TACTICS TIMI-18 indicated benefit for patients with ST-depression and/or elevated serum levels of biomarkers (troponin or creatine kinase) who received the early interventional approach, patients who did not have these characteristics benefited equally from an invasive or conservative approach.

More recent results from the third Randomized Intervention Trial of unstable Angina (RITA-3) also found a significant reduction in the combined risk of death, nonfatal MI, or refractory angina with early intervention, mainly attributable to a decrease in angina. Subjects enrolled in RITA-3 tended to be at lower risk (younger, more female subjects, fewer or no diseased vessels) than those in FRISC-II or TACTICS TIMI-18. The benefits of early intervention in RITA-3 were strongly gender-linked, with significant reductions in the composite of death and MI limited to men. Trends to an increased hazard with early intervention were revealed in female subjects. Thus, management that incorporates both invasive and conservative strategies—and one that, ultimately, tailors therapy to the level of risk—is both appropriate and evidence-based.

Finally, in the concluding report of these 16 invited papers, Dr. Eric Topol offers a practical synthesis in A Guide to Therapeutic Decision-Making in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes. In this summary, Dr. Topol highlights recent clinical trial evidence supporting both an inflammatory and atherothrombotic etiology in acute ischemic heart disease. For example, when a segment of coronary artery becomes inflamed, important cytokines, such as tissue factor, are released, facilitating thrombosis; as a consequence, serum inflammatory markers are elevated in most ACS patients at presentation. Importantly, mortality risk has been shown to be associated with increased levels of high-sensitivity CRP, interleukin-6, and serum vascular cell adhesion molecule while platelets, which are rich in inflammatory mediators (CD40 and its ligand, thrombospondin, and phospholipase A2), also supply important triggers for the inflammatory cascade.

Regardless of whether an “invasive” or “conservative” strategy is employed, clinicians must now weigh the role of new agents from three distinct drug classes—GP IIb/IIIa inhibitors, LMWHs, and clopidogrel, which have recently flooded the therapeutic armamentarium together with more traditional secondary prevention strategies (aspirin, beta-blockers, nitrates, and statins). To this end, a schema depicting the strategies of mechanical and pharmacologic intervention is provided to guide therapeutic decision making in the comprehensive management of ACS patients (Fig. 1). In summary, we believe that this substantive Journal supplement will provide clinicians with a relevant and timely review of a common syndrome that beckons us to pause and reflect upon achievements gained and challenges that will confront us in the years to come. We hope you will find this collection of 16 papers by a cadre of world-renowned subject-matter experts and opinion leaders a valuable resource to facilitate and optimize both the management and, more importantly, clinical outcomes of all patients with NSTE ACS.
REFERENCES


