Supplement on Acute Coronary Syndromes: Introduction

Robert M. Califf, MD

As a student of therapeutics for acute coronary syndromes (ACS) for more than 20 years, I have been gratified to see the remarkable changes that have benefited patients with these syndromes, which represent the leading cause of death and disability in technologically developed countries. In the course of my career, mortality rates among reperfusion-eligible patients with ST-elevation myocardial infarction (STEMI) have plummeted, and the outcomes of patients with non-ST-elevation (NSTEMI) myocardial infarction or unstable angina (collectively, NSTE ACS) have improved at an accelerated pace. To a large extent, the visible improvements in patient outcomes reflect the work of the authors of this supplement and the tremendous teamwork of similarly energetic investigators and clinicians around the globe, who take scientific discoveries and translate them into therapies backed by definitive and compelling outcome data, dictating widespread use.

The timing of this supplement falls at a fascinating point in the history of therapeutics. Just as we are consolidating dramatic gains in clinical outcomes in ACS, we have an onslaught of new technologies that threaten to oustrip anything we have done before: cell-replacement therapy, mechanical heart replacements, and therapy tailored to the genes and proteins of individual patients. At the same time, we have major societal reminders that the quality of health care delivery can be measured and systematically improved, and early measures show that our pragmatic delivery falls far behind our technological capability. This gap is threatened even further by the crisis over payment for increasingly expensive and effective health care. All of the proposed approaches to therapeutics must be judged by the 6 attributes of quality defined by the Institute of Medicine: effectiveness, safety, timeliness, patient-centricity, efficiency, and equity.1

For patients with STEMI, Topol2 points out that percutaneous coronary intervention (PCI) has triumphed over fibrinolytic therapy, provided that the procedure can be done promptly by a competent team. The question now is whether societies can muster the resources and discipline to develop an organized approach to reperfusion similar to the national trauma systems. The only rational argument against such a system, which would bring quality, efficiency, and access to patients, is that it would disrupt the financing of some hospitals and physicians.3 Meanwhile, questions remain about the best fibrinolytic and antithrombotic regimens when primary PCI is unavailable. Topol makes the case that the combination of a fibrinolytic agent and a platelet glycoprotein (GP) IIb/IIIa inhibitor may yet be superior for particular groups of patients, such as those with previous bypass grafting and young patients with large infarctions. He touches on the clinical-trial forays into improved antithrombotic therapy, concluding that enoxaparin appears to be superior to unfractionated heparin and that direct thrombin inhibitors have not been proven to provide substantial benefit relative to the risk of bleeding.

Given the superiority of direct PCI, the question of what to do while transporting the patient to the procedure and while the procedure is being completed remains a “hot topic” and the focus of multiple ongoing clinical trials. The combination of half-dose fibrinolytic therapy and GP IIb/IIIa inhibitors provides an attractive approach because of its proven ability to enhance perfusion4,5 and the high likelihood that the GP IIb/IIIa inhibitor would facilitate the PCI.6 These approaches, along with the question of whether low-molecular-weight heparins (LMWHs) provide an advantage in this regard, remain a focus of trial activity. In the near future, experimental efforts will focus on refinements of direct thrombin inhibition and factor Xa inhibition. Either of these approaches, or some combination of them, may provide a more powerful and controllable approach to reducing the thrombotic and inflammatory components of STEMI.

Just as we are feeling good about progress in STEMI, Cohen et al.7 remind us of the sizable number of patients with STEMI who have a contraindication to reperfusion therapy or arrive at the hospital after >12 h of symptoms. The findings from the Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction (TETAMI) trial and registry are not as encouraging for this group. The morbidity and mortality rates of patients not treated with reperfusion therapy remain high, perhaps because of the lack of a known effective treatment for this population. Because many of these patients are elderly, perhaps regional ACS centers would provide a community-based approach to improving their access to timely therapy. Given that people over 80 years of age have become the fastest-growing segment of the population in developed countries8,9 the issues raised by Cohen et al. will become increasingly important.

An issue not broached by any of the articles herein is the importance of understanding patient preferences. In the young patient, it probably remains quite reasonable to assume that aggressive treatment, involving a tremendous opportunity for benefit as well as significant risk, will be the preferred approach. In the increasingly dominant population of elderly patients, however, only rudimentary work has been conducted...
done on preferences. Early results indicate that these patients are interested in learning about the risks and benefits of proposed treatments, and that in many cases they prefer aggressive treatment when the evidence supports the likelihood of improvement in disability-free survival.8 However, there also is a greater tolerance for conservative therapy. The bottom line is that there is no substitution for talking with the patient to understand how individual preferences play into therapeutic choices.

In patients with NSTE ACS, Braunwald ties recent findings to the revised clinical practice guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA).12 These guidelines now provide clarity about the superiority of the invasive approach to treatment and the critical importance of risk stratification. The prime importance of ubiquitous aspirin and antithrombotic therapy are universally agreed on, but the proper timing of additional antiplatelet therapy and the selection of antiplatelet and antithrombotic drugs remain in dispute.

Perhaps the best way to put these therapies in perspective in high-risk patients is to consider them aids on the “path to cath.” When high-risk patients—identified by positive marker levels, ST-segment abnormality, advanced age, or high composite Thrombolysis In Myocardial Infarction (TIMI) scores or Platelet GP IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT) algorithms—are treated, rapid performance of coronary angiography is now the standard of care. All of these patients should be treated with a GP IIb/IIIa inhibitor and clopidogrel at the time of PCI, if they undergo this procedure; a recent systematic overview showed a significant reduction in mortality when a GP IIb/IIIa inhibitor was used with PCI.13,14 Clopidogrel has shown tremendous benefit in patients undergoing stenting, regardless of the clinical indication. The question is: what should be done between the time that a patient is identified as high risk and the performance of angiography?

Braunwald makes the case that clopidogrel should be held until the anatomy is known, because of the increased risk of bleeding if bypass surgery is done within 5 days of discontinuation of clopidogrel. This approach is rational; however, others feel that it is preferable to begin the clopidogrel immediately in anticipation of angiography and PCI. This decision involves a complex weighing of the risk of bleeding at surgery against the benefit achieved before surgery might be performed.

Kereiakes15 similarly makes the case that GP IIb/IIIa inhibitors should be held until the anatomy is identified and PCI has started because the data for medical treatment with GP IIb/IIIa inhibitors is considered weak. He is also swayed by the massive evidence that abciximab improves survival in patients undergoing PCI, coupled with the findings in Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO)-IV that abciximab has no role in “upstream” treatment.

The alternative perspective, also supported by the ACC/AHA clinical practice guidelines, holds that the best available data indicate a significant benefit of early, upstream use of small-molecule GP IIb/IIIa inhibitors in high-risk patients. In the systematic overview reported by Ronner et al., and in detailed analysis of the PURSUIT database,16–18 the best clinical outcomes occurred in patients treated with early angiography and upstream GP IIb/IIIa inhibition. Importantly, almost half of the events prevented in the patients undergoing early PCI would have occurred before the median time to angiography.17 While the current practice at Duke Medical Center (Figure 1) is to use upstream small-molecule GP IIb/IIIa inhibition, a large outcome trial of upstream use compared with targeted use at the time of PCI will be necessary to eliminate debate about this issue.

Somehow, these complex issues with antiplatelet therapy need to be combined with antithrombotic therapy into a “witch’s brew” of antithrombotic therapy that yields the best result in each patient. Although it is convenient to discuss each individual agent, each pathway of action connects to other important pathways. Thus, thrombin inhibition reduces platelet activation, and platelet GP IIb/IIIa inhibition can...
either reduce or increase the expression of CD-40 ligand, a potent proinflammatory agent, on the surface of the platelet.

Finally, Kereiakes argues for an enhanced focus of attention on inflammation as it relates to outcomes of PCI. Based on a patchwork of interesting pathophysiological studies and clinical outcomes trials, he makes the case that many effective adjuncts to PCI are indeed anti-inflammatory therapies. Importantly, he notes that treatment outcomes cannot be explained by a single pathway, nor can they be solely and directly explained by an effect on inflammation. Indeed, the evidence increasingly points to an intersection of thrombosis and inflammation as a critical issue.

For me personally, the array of articles in this supplement, the topics covered, and the contributing authors represent a rewarding exposure over a career as an academic cardiovascular specialist. Few could argue that any chronic disease, except treatment of HIV infection, has been as well studied and well supported by NHLBI, academia, and the spectrum of products companies. Increasing cost awareness will drive industry to seek earlier evidence about the value of products in the market that would lead to widespread use.

The next several decades will see unprecedented complexity as we strive for improvements. Societal forces are conspiring to place a major responsibility on the clinical research enterprise. We are experiencing a wonderful expansion of the elderly population and a relative decline in the birth rate. At the same time, the benefits of scientific discovery are promising an additional jump in longevity with improved function. Cardiovascular medicine will play a prominent role in this next wave of clinical advancement, particularly with devices such as drug-eluting stents, implantable defibrillators, and total heart-replacement devices. These advances will put unprecedented financial pressure on the health care system.

The only hope for a rational approach to this future, in which cost will be the limiting factor for continued major health benefits, will be to develop a modern clinical research system commensurate with the rapidly evolving science and public health needs. This system will need to have some critical elements:

First, the overall level of knowledge about clinical research will need to be increased; this has been expressed as "raising the national clinical research IQ." The use of quantitative reasoning in decision making has been slow to be adopted by the medical profession compared with other professions. A broader understanding of the principles of therapeutics will also be needed.

Second, clinical research will need to be an expected professional responsibility of health care providers. To prevent the clinical arena from retreating from an increasing reliance on evidence, almost every practice will need to contribute to the clinical-research enterprise. This change will require the recognition that participation in clinical research is a high form of clinical practice, that the best practice with regard to the experimental question is not known, and that participation in a research protocol ensures that background treatment will be consistent with current standards of care.

Third, we will need to develop a markedly different and well-organized approach to the regulation of clinical research,
so that more research can be encouraged. A large portion of the cost of clinical research is driven by interpretation of regulations, ranging from an overly cumbersome system of auditing studies done for regulatory approval to new concerns about privacy, legal liability in clinical research, and defensive contracting. Recent consensus meetings have revealed an unfortunate lack of congruence about regulations governing the interactions among sponsors, investigators, institutional review boards, data monitoring committees, and contracts offices. The lack of standards for contracts between investigative sites and industry sponsors contributes directly to the failure to publish important trial results in a timely fashion.

Fourth, we will need to think differently about public-private partnerships. For the reasons discussed above, the total investment in clinical research must increase. Neither the government nor the private sector will be able to absorb the entire cost. In particular, it is not in society’s interest to do one set of studies to get a product on the market and another set of studies to determine the role of that product in clinical therapeutics. The leading role of the devices branch of the FDA in trying to incorporate the product life cycle into the regulatory process provides a model for other diagnostic and therapeutic technologies.

Finally, the success of the system will depend on development of a common approach to cardiovascular nomenclature and data standards so that medical information is commonly held among practitioners and researchers. Indeed, the artificial distinction between clinical practice and research discussed above can now be bridged by using standard nomenclature and data standards so that medical information is commonly held among practitioners and researchers. Indeed, the artificial distinction between clinical practice and research discussed above can now be bridged by using standard nomenclature across the spectrum of each enterprise. Currently in clinical practice, much of the provider’s time is spent completing forms for billing and clinical records, and research recording is done entirely separately on top of this laborious reporting process. It is also done in such a nonstandard manner that the medical record from across the street is difficult to obtain and interpret when a patient appears for treatment of ACS. Contrast this medical “Tower of Babel” with the banking industry, in which one can obtain money in any part of the world simply with a card. Our greatest hope for conquering this dissonance is to achieve harmony among key United States organizations, including the NIH, FDA, Centers for Medicare and Medicaid Services, and professional and consumer representative groups (e.g., the ACC and AHA), and then develop an international standard of nomenclature through parallel plans. In the United States, all of the practitioners and health care facilities must be compliant with the regulations of at least one of the three key federal organizations, making agreement among these agencies the primary issue to be overcome with regard to medical nomenclature and data standards.

How do we put together the tremendous advances discussed in this ACS supplement with the overwhelming needs of the future? Almost 20 years ago, the coauthors of this supplement became involved in parallel research organizations—the TIMI, Thrombolysis and Angioplasty in Myocardial Infarction (TAMI), and GUSTO groups—that have evolved into complex intersecting partnerships on a global basis. My hope is that these same leaders, in concert with many other talented cardiovascular leaders, will create a system in which all patients with ACS will receive treatment informed by common nomenclature and data standards. This will allow the creation of a cycle of quality in ACS (Figure 1), in which clinical trials are embedded into clinical practice, data can be harvested without the need for separate trial data systems, and effective therapies are rapidly identified for incorporation into clinical practice guidelines and performance indicators. The data systems can also be used to characterize the performance of providers, hospitals, practices, and health care systems, and to identify gaps in performance that can be improved. All of this will depend on the rejuvenation of our medical care system in a manner that emphasizes participation in clinical research both in academia and, through continuing medical education, in clinical practice. Drs. Keriakes, Cohen, Topol, and Braunwald provide excellent examples of the pursuit of knowledge about applying new advances in ACS for others to follow.

References


Supplement on Acute Coronary Syndromes: Introduction
Robert M. Califf

doi: 10.1161/01.CIR.0000086949.66085.f7
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/16_suppl_1/III-1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/