Evolving Standards in Cardiovascular Care

Acute Coronary Syndromes
What Have We Learned about What We Still Need to Know?

It’s both an exciting time and a challenging time in the field of acute coronary syndromes. It’s exciting because of the amazing work done over the last 5 to 10 years, as our understanding of the pathophysiology and management of this disease state advances. It’s challenging, because keeping up with all of this information is really hard to do. This talk provides a conceptual framework for thinking about new clinical data—things that you’ll hear about today, tomorrow, and all the rest of the week at these AHA Scientific Sessions.

A big-picture view of how we progress clinically involves integrating basic-science research with clinical investigation and refining this information in order to identify beneficial therapies and develop “optimal” therapy for our patients. We’re relatively good at identifying new targets for therapy, designing new therapeutic interventions directed at these targets, and then taking the data from the clinical trials and incorporating them into guidelines. The next step involves moving beyond setting up the guidelines—it involves applying those guidelines to our own practice, critically assessing the quality of the care we deliver, and then trying to improve that care. Over the last year or so, this has become extremely important, because all indicators point to a forthcoming link between reimbursement and the “quality” of care we provide.

I’d also like to focus on 4 specific things that are of interest in clinical investigation and clinical practice: 1) modern-day clinical trial challenges, 2) concerns about bleeding in the acute coronary syndrome population, 3) difficulties with funding to support the research infrastructure, and 4) implementing guideline-directed therapies into clinical practice using local quality-improvement initiatives.

In regard to clinical research, there are some key principles to consider. Human disease is complex and multifactorial. We need to find safe and effective therapies, but we also need to test them in the clinical environment. In order to advance our understanding, we require comparisons not only of new therapy versus placebo, but of new therapy versus old therapy. Our evidence base for practice cannot and should not be extrapolated from our “theoretical” pathophysiologic understanding or from underpowered clinical trials.

Our ability to evaluate the benefit of new drugs compared with standard therapeutic strategies can be made more difficult by the design of the trials themselves. For example, in SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) investigators were loath to relinquish their old practice pattern of using unfractionated heparin in the cath lab. Off-protocol switching of antithrombin agents occurred and was associated with increased bleeding, to the detriment of outcomes in the low-molecular-weight group. In OASIS 5 (Organization for the Assessment of Strategies in Ischemic Syndromes 5), switching from low-molecular-weight heparin to unfractionated heparin in the cath lab was actually part of the protocol, but there too it appeared to be associated with more bleeding.

As you look at the results of new trials as presented at these meetings, or even subgroup analyses of old trials and databases, I would encourage you to be careful, be critical, and be thoughtful. Ask questions and think about what the data mean, because any good data set can generate a myriad of hypotheses. However, we do need to think carefully about when it is appropriate to extrapolate results of clinical trial populations and apply them to broader groups of patients, outside the rigid framework.
confines and restrictions of a clinical trial. The mortality from acute coronary syndromes is going down as our treatment strategies continue to evolve. However, the incremental benefit of new therapies is more limited and more difficult to detect, unless trials are large and well designed (Fig. 1).

What about bleeding? For many years, as new antithrombotic agents were being developed and studied, we accepted a risk of increased bleeding as we reduced the risk of thrombotic complications in patients who had acute coronary syndromes or were undergoing percutaneous coronary interventions. But now, the development of even newer pharmacologic agents—and, more importantly, the ability to adjust and combine multiple older conventional agents—may give us a chance to reach the Holy Grail of reduced thrombotic risk in the presence of decreased potential for hemorrhagic complications (Fig. 2).

Bleeding is common. In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) Quality Improvement Initiative (500 hospitals in the United States, with over 100,000 patients enrolled to date), the incidence of major bleeding that requires transfusions varies from as low as 5% to as high as 20%, depending on the age of the patient and the drugs that are being used. We’re not talking about oozing from the groin or minor skin ecchymoses, but major bleeding. When the patient has taken multiple anticoagulants, the risk of bleeding is even higher, particularly in the elderly. Other high-risk cohorts for bleeding include patients with renal insufficiency, lower-weight individuals, and women. Transfusion rates in the 10% to 20% range are telling us something else, too. Yes, patients who bleed need blood products. But a number of different data sets have also shown that patients who get blood products are at a substantially higher risk for death: both short-term (30-day) and long-term (6-month). There is a 3- to 4-fold excess in death even after adjusting for baseline demographics and reasons for transfusion, including coronary artery bypass grafting.

One important way to limit excessive bleeding is to use appropriate dosing of antithrombotic and antiplatelet agents. In CRUSADE, when there was excessive dosing of antithrombin and antiplatelet agents either alone or in combination, the risk of transfusion rose dramatically. Conversely, when appropriate dosing was used, bleeding rates were substantially lower.

Over the last 3 or 4 years, there has been exponential growth in the funding for medical research. Zerhouni’s recent article1 in JAMA nicely lays out the National Institutes of Health (NIH) perspective on the spending for modern-day biomedical research. Probably for the first time in a long while, the limitations on advancing our therapy arise not from the basic sciences’ inability to identify new targets and new therapies, but from our inability to perform good clinical trials effectively and efficiently.

The number of physicians participating in clinical trials has actually decreased in recent years. Obviously, there are serious financial and time constraints on all of us in clinical practice. There’s a growing shortage of cardiovascular specialists. Also, getting through the United States regulatory process and setting up the necessary institutional contracts for clinical research studies has gotten more complex. We also need to look closely at the ivory towers of academic medicine—whether or not we are actually training people to go into clinical research. Do we encourage our students and trainees? Do we mentor them? I spend a great deal of time in academic medicine, and if I’m not having fun, I have to sit back and ask myself, Why am I doing it? I think that we all need to get more enthusiastic and figure out ways to make clinical research enjoyable.

One of the initiatives that we are participating in at Duke Clinical Research Institute is the Clinical Trials Network as part of the NIH Roadmap. This is an op-
portunity to re-engineer the clinical research enterprise, to develop creative and visionary strategies and support tools—mechanisms—by which investigators and interested clinicians can do research.

How do we go about implementing guideline-directed therapies into clinical practice and refining our approaches to risk stratification? We’ve done a tremendous job over the years in identifying the key clinical characteristics, and laboratory markers such as MB and troponin. But clearly the best and most effective way of doing this is through a multi-marker strategy that includes all available patient characteristics and multiple markers to predict risk for long-term consequences.

We’ve actually gone one step further. We’ve gone from just identifying patients who are at high risk for long-term adverse outcomes to identifying patients who have the most to gain from proven therapies. Patients who have had troponin-positive test results have clearly benefited from glycoprotein IIb/IIIa inhibitors in 3 of the large-scale trials. Conversely, in the troponin-negative population, there was essentially no benefit from glycoprotein IIb/IIIa inhibitors. There are specific adrenergic receptor genotypes that predict response to β-blockers. Biomarkers are useful, not only in predicting disease, but in predicting the risk of subsequent events after an acute event; and they identify therapies that will provide the most benefit for a given patient.

There is room for improvement; in CRUSADE, 10% of patients without contraindications who have had a myocardial infarction are not being treated with a β-blocker. Seventeen percent are not getting an antithrombin as part of their initial medical therapy for an acute infarction. There is also a dramatic increase in mortality when you do not use 1, 2, or more of the proven therapies in the guidelines: aspirin, β-blockers, heparin, and glycoprotein IIb/IIIa inhibitors. Do you remember the Institute of Medicine document “To Err is Human”? The good news is that we can get better. Just the exercise of looking at the data at our own institutions (as in CRUSADE) can help us to identify problem areas and then improve them.

The best way to improve the care of our patients with acute coronary syndromes is to improve the system. By that I mean that we need to improve the data we collect; to improve the means by which we judge quality; to improve the quality of the clinical trial data (and the clinical trials); and to improve the process whereby these data are incorporated into guidelines as our standards continue to evolve. It takes commitment, it takes time, and it takes perseverance. We’ll never know what we don’t know until we understand what we really do.

References