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Myocardial Ischemia and Infarction

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This has been an exciting meeting with much new information presented about myocardial ischemia and infarction. We covered several areas, including: new treatment modalities and care strategies for patients presenting with ST-segment elevation myocardial infarction (MI); new treatments for non–ST-segment elevation acute coronary syndromes (ACS); and acute ischemic heart disease in women, a key theme this week for the overall meeting. We discussed the growing importance of understanding risk, including diabetes and inflammation, among ACS patients and also addressed some interesting new and relevant information in coronary artery bypass graft surgery. Finally, we closed with an important message from this meeting—the application of evidence-based medicine in our practices.

ST-segment elevation acute MI. Dr. Stone presented the Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) study, a randomized trial that compared a distal embolization protection device versus control in patients undergoing primary angioplasty (1). Overall, this trial showed no benefit of the guide wire technology in these patients, despite having met its mechanistic goal of capturing embolic material in upwards of 75% of patients. There are two important lessons here for physicians involved in the care of ST-segment elevation MI patients. First, remember that intuition is not data. Although it is important to understand the mechanism behind why things work, we need to study them in randomized clinical trials to know if the new therapy or technology actually provides clinical benefit. Second, we need to think about moving beyond the epicardial coronary vessel to understand ways to better protect the myocardium.

A major topic at these meetings has been the notion of centralization of care and transfer of the acute MI patient. There has been a great deal of uncertainty about the optimal strategy for ST-segment elevation MI. Is it fibrinolysis? Is it primary angioplasty? Is it some combination of these? What about transfer to regional care centers? Important work was presented from the American College of Cardiology (ACC)-National Cardiovascular Data Registry (NCDR) database regarding patients who were transferred for ST-segment elevation primary angioplasty (2). Approximately one-half of those patients received fibrinolysis before transfer, and after adjusting for other variables there was a better mortality rate among these patients. This opens up the question of what is actually optimal care. It is probably not one therapy or the other, but likely involves combinations of care. And a key question that the ACC and investigators need to address is: what are the most appropriate systems for acute MI care regarding transfer and the centralization or regionalization of heart attack centers?

Holmes et al. (3) from the Mayo Clinic presented some important information on shock in the ST-segment elevation population. He provided an 11-year follow-up on the original Global Utilization of Streptokinase and TPA for Occluded arteries (GUSTO I) shock cohort. Such patients account for approximately two-thirds of the early deaths associated with acute MI. However, for patients who are able to survive that early shock period, the rate of death over the next decade is very similar to that of the non-shock population. This has important ramifications as we think about emerging therapies for the care of shock.

Non–ST-segment elevation ACS. Much information has been presented at these meetings regarding antithrombotic therapy, which remains the cornerstone of therapy for this group of patients. Currently, there are oral antiplatelet, intravenous antiplatelet, and antithrombin therapies, as well as emerging therapies that inhibit coagulation more proximally rather than downstream in the coagulation cascade, trying to get at what might be optimal therapies for better patient outcomes while balancing the risk of bleeding. Two small pilot trials were presented that provided preliminary information on coagulation inhibition of tissue factor and activated factor X (4,5). Both investigations, while preliminary, suggested that more potent and more proximal inhibition of coagulation is a promising strategy for ACS care and deserves more research.

Mahaffey and Ferguson (6) presented preliminary data from the recently completed 10,000-patient Superior Yield of the New strategy of Enoxaparin, Revascularization, and GlYcoprotein IIb/IIIa inhibitors (SYNERGY) trial, as part of the Late-Breaking Clinical Trials section. This trial enrolled high-risk ACS patients and tested enoxaparin, a low-molecular-weight heparin, against unfractionated heparin. This was done on the backdrop of an early invasive management strategy and other therapies, including other antithrombotics, as recommended by the ACC/American Heart Association (AHA) guidelines. The primary end point of the trial was the 30-day occurrence of death or MI. The overall trial results showed no benefit of enoxaparin over unfractionated heparin; however, the investigators reported that the trial did meet a prespecified secondary objective demonstrating non-inferiority.

Several important messages emerged from the SYNERGY trial. The first is that despite very aggressive therapy, including a high use of cardiac catheterization and revascularization, these patients had 30-day event rates (composite of death or MI) approaching 14%. These are very sick

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patients for whom important new advances are needed. Second, we need to understand these therapies in the context of broader real-life clinical trials, where we can assess whether or not a therapy offers advantages, particularly to older patients and patients with multiple comorbidities, as we begin to combine multiple medicines.

Cannon et al. (7), from the Brigham and Women's Hospital and the Thrombolysis In Myocardial Infarction (TIMI) study group, presented a very important trial that was published simultaneously on-line in the *New England Journal of Medicine*—the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial. This trial compared intensive and moderate lipid-lowering using proven doses of pravastatin and untested, very high doses of atorvastatin among patients who had a recent ACS. This was a randomized trial of over 4,000 patients, with approximately 2,000 in each treatment group. The trial, interestingly, was designed to demonstrate the non-inferiority of pravastatin compared with the higher dose of atorvastatin. The trial showed exactly the opposite: more intensive lipid-lowering was associated with improved clinical outcomes for this group of patients. This was a very important observation and a very practical one for clinicians taking care of such patients.

Ischemic heart disease in women. One of the key themes of this ACC meeting has been to better understand the gender issues related to treatment modalities, as well as to strategies of care. Information was presented by Blomkalns et al. (8) from the University of Cincinnati using data from the large Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) registry, which involves over 400 U.S. hospitals dedicated to the evaluation of guideline-based care among patients with non–ST-segment elevation ACS. She observed and reported that there was more use in men versus women of a number of guideline-recommended acute therapies, including aspirin, antithrombin therapy, intravenous antiplatelet therapy, beta-blockade, and clopidogrel. With the exception of beta-blockade, there was more use of each therapy in men, even after adjusting for other severity markers of illness, suggesting that we are offering differential treatment to female compared with male patients.

This is important information, and it is not just with regard to evidence-based medications, but other evidence-based strategies as well. Women were less likely than men to get an electrocardiogram within 10 min of arrival. They were less likely to undergo early diagnostic catheterization and revascularization procedures. This work reported data from an observational registry, with all its inherent limitations, but it warrants further research to understand these possible gender disparities in care.

Diabetes. Diabetes has emerged as a national epidemic and has particular relevance for those taking care of patients with coronary atherosclerosis. Potentially important information was presented by Miller et al. (9) from the Mayo Clinic on behalf of the Collaborative Organization of Rheo-thRx Evaluation (CORE) trial investigators. This trial evaluated infarct size, as measured by technetium sestamibi, and examined the outcomes stratified by the presence or absence of diabetes. The group with diabetes had larger infarcts, as measured by left ventricular ejection fraction and when measured as a percentage of left ventricular involvement. Both diabetes and infarct size also emerged as important predictors of six-month mortality.

McGuire et al. (10), from Dallas, used the National Registry of Myocardial Infarction database, totaling almost 1.5 million patients, to examine the evolution of care of the diabetic population from the early 1990s to 2002. They observed that the outcome of patients with diabetes mimics the overall improvement in acute MI outcome; that is, although overall acute MI care is improving, we can also see an improvement in mortality in diabetic patients, particularly among women with diabetes. So, there is some potentially promising work being done here regarding both gender and high-risk features of MI.

Inflammation. Inflammation has received much attention as a marker or predictor of risk among patients with ACS, including acute MI. We are now beginning to think about targeting inflammation as a treatment strategy. Work presented by Theroux et al. (11), from the Montreal Heart Institute, on behalf of the COMplement Inhibition in Myocardial infarction treated with Angioplasty (COMMA) investigators, concerned the complement inhibitor, pexelizumab; they noted that whether looking at C-reactive protein or interleukin-6, pexelizumab had the effect of reducing measures of inflammation. Pexelizumab is now being studied in a large-scale primary angioplasty trial, one of the first major tests of the inflammation hypothesis in acute MI care.

Bypass surgery. Few issues in contemporary surgical revascularization have gotten more attention and generated more controversy than off-pump surgery. An important paper presented at these meetings was a systematic overview of 41 studies evaluating off-pump surgery (12). Although early studies demonstrated almost a 30% increased risk of early death with off-pump surgery compared with conventional surgery, later studies indicated a survival advantage to off-pump surgery. The current analysis attributed the better outcomes in the later studies to the greater use of cardiac stabilization devices. This is a topic that continues to evolve, and more information is needed as clinicians consider which type of surgical revascularization to recommend for patients.

Cellular therapy. Cell-based treatment strategies are on the cusp of moving into the clinical research realm. Right now, much data are emerging from very early phase studies about the variety of ways to deliver cell-based therapies to patients with ischemic heart disease. One of the areas currently undergoing most investigation is how to deliver cell-based therapy to areas of infarction during bypass surgery. In a preliminary project, 22 patients undergoing elective bypass surgery had skeletal muscle—expanded

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myoblast populations—injected into an infarct zone at the time of surgery (13). The positron emission tomographic scans and technetium scans showed that there was recovery of myocardial viability in the infarct zone after cell implantation.

Evidence-based medicine. Eagle et al. (14), from the University of Michigan, provided updated information from the Guidelines Applied in Practice (GAP) program as part of a Late-Breaking Clinical Trials session. This program evaluates adherence to evidence-based therapies in acute MI in Michigan. It involves a large cohort of Medicare patients and is measuring both short- and long-term mortality. The current project was able to demonstrate that adherence to the GAP program provided a better mortality gain than not adhering to the GAP program. This is an important message that continues to emerge: hospitals and practitioners who prescribe according to evidence-based techniques have better outcomes for their patients.

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