Best of the 2000 ACC Annual Scientific Session

Highlights from the American College of Cardiology 49th Annual Scientific Session March 12-15, 2000, Anaheim, Calif.

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The 2000 American College of Cardiology (ACC) Annual Scientific Session in Anaheim, Calif, was packed with practical and state-of-the-art information. Here, Contributing Editors of *Reviews in Cardiovascular Medicine* describe contributions that they feel merit special attention.

Key Words
Angioplasty • Diabetes mellitus • Estrogen replacement therapy • Heart failure • Hypertension • Myocardial infarction • Myocardial perfusion imaging • Percutaneous coronary intervention • Peripheral arterial disease • Platelet antagonists • Stent • Valvular heart disease

Main Points

- Statins can help prevent myocardial infarction (MI) and improve survival in patients receiving statins pre-MI.
- Systolic blood pressure is emerging as the primary end point of diagnostic and therapeutic concern.
- Use of glycoprotein IIb/IIIa receptor inhibitors may reduce complications of percutaneous coronary interventions in patients with diabetes.
- The ankle/brachial index is a simple test to help diagnose peripheral arterial disease.
- Hormone replacement therapy failed to demonstrate benefit for secondary prevention of coronary heart disease.
- Rest myocardial perfusion imaging can identify low-risk patients presenting to an emergency department with chest pain who can be safely discharged.

More Good News for Statins

In the last 6 years, a consistent series of primary and secondary prevention trials have documented 25% to 40% reductions in morbidity and mortality from cardiovascular disease in cohorts with both high and average cholesterol. These studies have ranged from the high-risk cohort with coronary heart disease (CHD) and high cholesterol studied in the Scandinavian Simvastatin Survival Study to the low-risk healthy cohort with low high-density lipoprotein (HDL) cholesterol studied in the Air Force/Texas Coronary Atherosclerosis Prevention Study.

At the ACC meeting, more good news for statins was presented by Kevin A. Bybee, MD, and coworkers[1] from the Mayo Clinic and Foundation (Rochester, Minn). This team evaluated the outcomes of 264 patients with myocardial infarction (MI) admitted between 1993 and 1998. Some patients were already receiving statins (n = 44) or began receiving statins within the first 24 hours of hospitalization (n = 22). These patients were compared with patients who neither had been receiving statins nor began receiving statins within 24 hours of admission (n = 198). The 2 groups were well matched for other risk characteristics. The group receiving statins had a significantly lower inhospital mortality rate (1.5% vs 8.6%, $P < .05$), lower peak creatine kinase levels (416 U/L vs 699 U/L, $P = .02$), and less use of lidocaine for ventricular arrhythmias (6.1% vs 18.2%, $P = .02$). Nonsignificant decreases were also observed in ischemic complications (16.7% vs 26.3%) and electrical and/or mechanical complications (10.6% vs 18.7%). An interesting finding was that angiotensin-converting enzyme (ACE) inhibitor and nitrate use was higher in the statin group, suggesting more consistent aggressive treatment was given to these patients.

The take-away message is that statins not only prevent a first and subsequent MI, but they also improve survival for those patients already receiving statins. [Robert A. Vogel, MD]

continued

Hypertension

One of the most important current themes in the area of hypertension is the paradigm shift toward systolic blood pressure as the principal end point of diagnostic and therapeutic concern. Franklin and coworkers[2] from the University of California, Irvine, reanalyzed the National Health and Nutrition Examination Survey (NHANES) III blood pressure data, which clearly articulate the greater prevalence of systolic versus diastolic hypertension. Using the standard definition of 140/90, these investigators found that 80% of individuals over age 50 had isolated systolic hypertension. This figure stands in direct contrast to those under age 50, in whom diastolic hypertension predominates. Because 75% of all persons with hypertension are over age 50, it can be readily seen that systolic hypertension is the greater public health problem.

Continuing with the theme of systolic hypertension and wide pulse pressure, Pedrinelli and colleagues[3] (University of Pisa, Italy) investigated markers of target organ damage in patients with essential hypertension. They found that urinary microalbumin excretion rates correlate more strongly with pulse pressure than with carotid intima-media thickness or cholesterol. The lack of correlation of microalbumin with atherogenic indices suggests that small vessel disease is more closely related to arterial stiffness than to atherosclerosis.

A related longitudinal observational study of individuals not receiving antihypertensive therapy was reported by Benetos and coworkers[4] from France. In 2 cohorts of French males, the Centre d'Investigations Préventives et Cliniques cohort of more than 15,000 men and the Paris Prospective Study of more than 6000 men, increases in blood pressures within the normotensive range predicted increased cardiovascular mortality. Thus, small, early changes in blood pressure have prognostic significance.

Finally, positive effects of exercise conditioning on exaggerated systolic blood pressure responses to exercise were confirmed by Miyai and associates[5] (Wakayama Medical University, Japan) in sedentary men. Exercise conditioning reduced responses of systolic blood pressure and plasma norepinephrine toward normal and also decreased daytime systolic blood pressure. In this short (12-week) study, no changes were demonstrated in left ventricular mass index, left ventricular fractional shortening, or estimated atrial pressures. [Joseph L. Izzo, Jr, MD]

PTCA vs Medical Therapy in Post-MI Patients

The Percutaneous Transluminal Coronary Angioplasty (PTCA) trial, initiated by the late, outstanding German investigator Karl-Ludwig Neuhaus, MD,[6] studied asymptomatic or mildly symptomatic, recent (1 to 6 weeks) survivors of acute MI who had, primarily, single-vessel disease. Patients with severe symptoms, such as those of Canadian Cardiovascular Society classes III and IV, were excluded. The trial demonstrated a trend toward better outcomes in patients treated with PTCA as opposed to medical therapy. The rates of death and MI were low in both groups, but patients who were initially revascularized had a trend toward lower mortality at 4 to 5 years (5% vs 10%, *P* = NS) as well as a lower use of nitrates. The trial was stopped primarily because of a falloff in enrollment, which emphasizes the difficulties in performing such trials because of investigator and patient bias. Similar results were obtained in the Danish Acute Myocardial Infarction (DANAMI) trial[7] in patients with postinfarct angina or a positive stress test. It should, therefore, come as no surprise that coronary revascularization improves outcomes in patients with postinfarction angina or documented ischemia. The preliminary presentation of this study does not, however, answer questions regarding patients who were truly asymptomatic or patients with a negative stress test. Further analyses will be forthcoming.

A larger issue, which is currently the objective of several large randomized trials (the Open Artery Trial [OAT], The Total Occlusion Study of Canada [TOSCA-II], and the Italian ACTOR Trial[8]), is the role of coronary revascularization in asymptomatic patients with an occluded, infarct-related artery. It is hoped that these trials will bring to resolution the "late open artery hypothesis," which suggests that there may be benefits to late opening of an occluded infarct-related artery *independent* of myocardial salvage.[9-14]

The mechanisms of benefit are perhaps multifactorial and include effects on ventricular remodeling and electrical stability; in the process, a patent conduit may provide a source for future collaterals in the event of progressive disease in other vessels.[12,15-20] Studies of the myocardium using contrast echocardiography suggest that the primary mechanism of benefit is the elimination of "silent ischemic hibernating" myocardium.[21,22] Among patients without any evidence of viability or adequate myocardial perfusion in the area of the infarct, late opening of the infarct-related artery did not improve left ventricular function.[22] In

contrast, in patients with residual perfusion in the area of dysfunctioning myocardium, late reopening had an impressive effect on contraction of the jeopardized segment.

Irrespective of the mechanisms, validation or rejection of the late open artery hypothesis could have a profound and costly effect on clinical practice. In the event that ongoing trials demonstrate a beneficial effect of recanalization of the infarct-related artery in asymptomatic patients, this would make a strong case for routine angiography in all postinfarct patients, regardless of symptoms. A further consequence of a positive trial would be a strong impetus for the development of noninvasive methods that could determine infarct-related patency and coronary flow (eg, intravenous contrast echocardiography, MRI, and ST-segment mapping).[7,23,24]

To maximize event rates, the OAT trial will be confined to patients with ejection fractions of less than 50%; plans are to enroll 3200 patients with occluded vessels and to have a 3- to 4-year follow-up (oral and written communication, J. Hochman). End points will be mortality, reinfarction, and class IV heart failure. The TOSCA-II trial deals with a similar patient population, but the end points are changes in global and regional left ventricular function at 6 months. The ACTOR trial[8] of 500 patients has a 3-year follow-up for the primary end points of mortality, congestive heart failure, and reinfarction and, at 6 months, determination of left ventricular volumes (personal communication, L. G. Bolognese).

These trials are not easy to perform, because the temptation to intervene in the face of an occluded infarct-related artery is strong. Nonetheless, one should remember that the open artery hypothesis is nothing more than a hypothesis that desperately needs to be proved or refuted. The clinical impact of these trials will be substantial indeed. [Bernard J. Gersh, MB, ChB, DPhil, FRCP]

Agents for Heart Failure

PRAISE-2: Calcium channel blockers have been evaluated as a treatment for patients with heart failure in a number of studies, but objective evidence of benefit has been elusive. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE)-1 trial compared amlodipine with placebo in patients with advanced heart failure. The primary end points of death and cardiovascular hospitalization were not significantly different between groups receiving placebo or amlodipine. Post hoc subgroup analysis revealed that there was a nonsignificant trend toward increased hospitalization and death (odds ratio, 1.04; 95% confidence interval, 0.83 to 1.29) in patients with an ischemic cause, and a 46% reduction in all-cause mortality in patients with heart failure from a nonischemic cause (P = .001). The PRAISE-2 trial[25] was conducted to confirm this observation in patients with nonischemic cardiomyopathy.

The trial randomized 1650 patients with New York Heart Association class III and IV heart failure and a nonischemic cause to amlodipine (10 mg/d) or placebo. The trial was designed with a 90% power to detect a 25% difference in mortality. The mean age of patients was 59; the mean left ventricular ejection fraction (EF) in these patients was 0.21. Results showed mortality in 262 (31.7%) of 826 patients receiving placebo and 278 (33.7%) of 826 patients treated with amlodipine (odds ratio, 1.09; P = .28). Amlodipine thus failed to reduce mortality or demonstrate other benefits in this patient population. The principle investigator in both trials, Milton Packer, MD[25] (Columbia Presbyterian Medical Center, New York), concluded that the only plausible explanation for the differences between the 2 trials was that the favorable observation in nonischemic patients in the PRAISE-1 trial was caused by chance.

Calcium channel blockers have failed to reduce morbidity or mortality in patients with heart failure in multiple trials with multiple agents, and their use should generally be avoided. This trial also highlights the hazards of drawing conclusions based on subgroup analysis, even when there are highly significant P values.

OPTIME-CHF: The role of intravenous inotropic agents for the treatment of patients hospitalized with heart failure has not been fully defined. Early use of inotropic agents during hospitalization theoretically could improve cardiac function and facilitate diuresis. On the other hand, longer-term use of inotropic agents has been associated with increased risk of mortality, including sudden death, in patients with heart failure. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)[26] enrolled 951 patients to test the hypothesis that the use of intravenous inotropes would shorten hospital length of stay. Patients hospitalized with heart failure but without cardiogenic shock or hypotension were randomized within 48 hours of hospitalization to a 48-hour infusion of milrinone (0.5 µg/kg/min) or to a control group. Background medical therapy included

diuretics in 90%, ACE inhibitors in 70%, and ß-blockers in 25% of patients.

Results showed the median length of hospitalization to be 6 days for the milrinone group and 7 days for the control group, which was not statistically significant ($P = .71$). During the 60-day follow-up period, mean days of hospital stay were 12.3 ± 14 for patients who had received milrinone and 12.5 ± 14 for patients in the control group. No significant differences in heart failure scores or subjective health status were seen between the 2 groups. Rehospitalization or death occurred in 35% of milrinone and 35.3% of control patients. There was a trend toward increased mortality with milrinone (3.8% vs 2.3%; odds ratio, 1.65; $P = .19$). Mikhai Gheorghiade, MD[26] (Northwestern Medical School, Chicago), who reported this study, concluded that the results do not support the use of intravenous milrinone in patients with heart failure, outside those patients with cardiogenic shock.

An infusion of intravenous milrinone did not reduce the length of hospital stay or mortality in hospitalized patients with heart failure. The results of this trial do not support the routine use of intravenous milrinone or other intravenous inotropic agents in patients hospitalized with heart failure. Treatment of such patients should focus on initial stabilization with loop diuretics and ACE inhibitors and, once compensated, aldosterone antagonists and ß-blockers. [Gregg C. Fonarow, MD]

Diabetes and Outcomes of Percutaneous Coronary Intervention

In a retrospective analysis of 25,545 patients presented by Steven P. Marso, MD,[27] inhospital mortality was significantly higher for patients with diabetes than for nondiabetic patients undergoing elective percutaneous coronary interventions (PCI) (1.4% vs 0.8%) and urgent PCIs (12.7% vs 6.9%) (Figure 1). Serum creatinine levels higher than 1.5 mg/dL and EF less than 40% were most predictive of inhospital mortality in patients undergoing elective PCI, while EF less than 40%, multisegment PCI, and female gender were predictors in the urgent PCI group. The diabetic cohort had a higher-risk profile because more patients were female and had a previous history of congestive heart failure, peripheral vascular disease, and elevated creatinine levels at the time of PCI. In a similar retrospective analysis of diabetic and nondiabetic patients presented by S. Chiu Wong, MD,[28] the 1995 New York State Angioplasty Database revealed a similar increase in inhospital mortality (0.77% vs 1.42%) as well as an increased hospital length of stay (5.5 vs 6.4 days). In this analysis, diabetes was an independent predictor of inhospital mortality.

A 1-year follow-up after PCI for acute MI in diabetic patients from the STENT PAMI (Primary Angioplasty for Acute Myocardial Infarction) trial presented by Luiz Mattos, MD,[29] showed that stenting did not reduce the major complications of acute MI, including death, reinfarction, or stroke. Nor did coronary stenting reduce ischemia-driven, target vessel revascularization in diabetic patients as it did in nondiabetic patients.

Roxana Mehran, MD,[30] studied the effects of diabetes and chronic renal insufficiency on late mortality, nonfatal MI, and target lesion revascularization. Death and MI rates at 30 days and 1 year are increased in patients with diabetes or chronic renal insufficiency. There seems to be an additive effect of these 2 comorbid conditions, with the 1-year end point occurring in 26% of patients with diabetes compared with 4% of patients without diabetes and with normal renal function.

Treating patients with diabetes in the catheterization laboratory has not yielded the same success as treating patients without diabetes. As a group, diabetic persons have characteristics

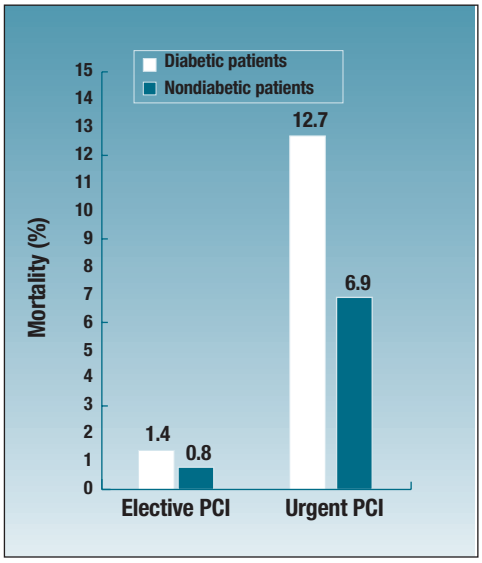

Figure 1. Inhospital mortality for nondiabetic and diabetic patients undergoing percutaneous coronary intervention (PCI).

such as enhanced platelet activity, elevated procoagulant levels, endothelial dysfunction, and impaired fibrinolysis that would seem to predispose them to complications of PCI. The use of intravenous platelet glycoprotein (GP) IIb/IIIa receptor inhibitors may play an important role in reducing events in patients with diabetes, as seen with abciximab and tirofiban. Other treatment strategies, including longer-term combined antiplatelet regimens (such as aspirin and adenosine diphosphate inhibitors), more aggressive management of lipid abnormalities, and the use of intracoronary radiation and growth factor modifiers to reduce restenosis may play roles in reducing short- and long-term major cardiac adverse events. [Norman E. Lepor, MD]

Peripheral Arterial Disease and Intermittent Claudication

Topics at a symposium dedicated to the evaluation and management of peripheral arterial disease (PAD) included epidemiology, diagnosis, pharmacotherapy, endovascular interventions, and vascular reconstructive surgery. The symposium offered a timely and comprehensive review of a field that has generated great interest among cardiologists.

The epidemiology of PAD was discussed by William Hiatt, MD,[31] from the University of Colorado, Denver. The prevalence of PAD increases with age, affecting fewer than 3% of persons under 60 years and approximately 20% of persons 70 years or older. Taking into consideration the demographics of the US population, Dr. Hiatt estimated that 8 to 10 million individuals have PAD. As in other disorders caused by atherosclerosis, the incidence of PAD is influenced by modifiable risk factors. The relative risk of PAD among persons who smoke is 2.5 to 3.0; among those with diabetes, 3.0 to 4.0; and among those with hypertension, 1.5 to 2.5. The risk of PAD increases by 10% for each 10 mg/dL increase in total cholesterol.

Many patients with PAD have coexisting coronary artery disease (CAD) and cerebrovascular disease and, therefore, are at increased risk for cardiovascular morbidity and mortality, including nonfatal MI and stroke. Dr. Hiatt emphasized risk factor modification, including smoking cessation, glucose control, and lipid-lowering therapies to reduce adverse outcomes. In addition, he highlighted the recent Heart Outcomes Prevention and Evaluation (HOPE) study, which found that ramipril, an ACE inhibitor, reduced MI, stroke, and vascular death by 22% in patients with atherosclerosis or with diabetes and at least 1 other risk factor.

The diagnostic evaluation of PAD was reviewed by Jeffrey Olin, MD[32] (Cleveland Clinic Foundation). The importance of the history and physical examination was stressed, particularly querying patients about symptoms of claudication, walking impairment, and foot pain. Salient findings of the examination included the presence of bruits, diminished or absent pulses, subcutaneous atrophy, and skin ulcerations or gangrene of the toes. As an adjunct to the physical examination, use of a hand-held Doppler instrument to measure the ankle/brachial index (ABI) is a simple bedside test to diagnose PAD. PAD is likely to be present if the ratio of the systolic pressure in the ankles to that of the brachial artery (ABI) is less than 0.9. The noninvasive vascular laboratory may play a role in evaluating the presence and distribution of arterial stenoses, with tests such as segmental pressure measurements, pulse volume recordings, and duplex ultrasonography.

The pharmacotherapy of PAD was discussed by Mark Creager, MD,[33] from Brigham and Women's Hospital and Harvard Medical School. Medical therapy has 2 principal objectives: reducing adverse cardiovascular events and improving quality of life. The latter takes into consideration decreased symptoms of claudication and preservation of limb viability. In addition to risk factor modification, as discussed by Dr. Hiatt, treatment of patients with PAD should include an antiplatelet agent, unless contraindicated. The Antiplatelet Trialists Collaborators performed a meta-analysis of approximately 70,000 high-risk patients who either were treated with an antiplatelet drug or were controls. Antiplatelet therapy reduced the risk of MI, stroke, or vascular death by 27%. In a study of approximately 19,000 patients with a history of recent MI or stroke or of PAD, clopidogrel (a thienopyridine derivative), when compared with aspirin, reduced the risk of MI, stroke, or vascular death by 8.1% and by 23.8% in a subgroup of patients with PAD.

Approved agents for management of claudication include pentoxifylline and cilostazol. In pooled studies, pentoxifylline has improved peak walking distance by approximately 20% to 25%. Cilostazol, a phosphodiesterase III inhibitor, improved maximal walking distance by approximately 40% more than placebo and pentoxifylline. Patients with left ventricular dysfunction should not receive cilostazol. Promising investigational therapy for claudication includes L-arginine and propionyl-L-carnitine and, for acute limb ischemia, vasodilator prostanoids and the angiogenic growth factors,

vascular endothelial growth factors, and basic fibroblast growth factors.

The role of endovascular interventions for PAD was discussed by Michael Bacharach, MD,[34] of the North Central Heart Institute in Sioux Falls, SD. Percutaneous transluminal angioplasty (PTA) and stents are indicated primarily for patients with disabling claudication or critical limb ischemia in whom lesions are amenable to angioplasty. Recent analyses of PTA for iliac artery lesions found 4- to 5-year patency rates of approximately 60% to 80%, which increase to 70% to 95% following selective stent placement. For femoropopliteal artery lesions, 5-year patency rates for PTA approximate 45%. For tibioperoneal artery lesions, 2- to 3-year limb salvage rates are 50% to 75%. Catheter-based thrombolysis with streptokinase, urokinase, rt-PA, or reteplase may be indicated for acute limb ischemia secondary to thrombosis or embolism in patients with threatened limbs who present within 1 week of symptoms. Complications from endovascular interventions are infrequent but include thrombosis, dissection, perforation, hematoma, and pseudoaneurysm.

The role of reconstructive vascular surgery was discussed by David Dawson, MD,[35] of the National Aeronautics and Space Administration–Johnson Space Center (Houston). Similar to endovascular interventions, surgery is usually undertaken in patients with disabling claudication or critical limb ischemia manifested by rest pain, ulcers, or gangrene. Aorto-iliac lesions are typically managed by aorto-bifemoral bypass operations using synthetic grafts. Operative mortality is 1% to 3%; the 5-year patency rate is approximately 90%. Alternate extra-anatomic procedures include axillo-femoral-femoral bypass or femoral-femoral bypass. Infrainguinal bypass operations are used to manage disease of the femoropopliteal and tibioperoneal arteries. The bypass graft may be either saphenous vein or polytetrafluoroethylene. Operative mortality is 1% to 3%; 5-year patency rates with saphenous vein grafts are approximately 75% to 80%. Selection of appropriate patients, careful preoperative risk assessment, and attention to technical detail are required to achieve optimal outcomes. [Mark A. Creager, MD]

Anorectic Drugs and Valvular Heart Disease

The extent of the relationship between use of the anorectic drugs fenfluramine/phentermine and dexfenfluramine and valvular heart disease remains controversial. Except for a predominant effect on the mitral and aortic valves in patients receiving anorectic agents, valvular lesions seen in these patients are similar to those seen in patients who have used ergotamines and in those with carcinoid syndrome. Retrospective analyses have shown a consistent increased prevalence of aortic valve regurgitation ranging from 5% to 31% in exposed populations. This represents a significant increase in risk of aortic regurgitation when compared with the non-exposed Framingham Study population and corrected for age and gender. Most patients present with mild aortic insufficiency. A relationship between dose and duration of use and valvulopathy has also been shown. Patients who have been exposed to these drugs for more than 3 months seem to be at an increased risk.

Mast and colleagues[36] reported on the 1-year natural history of fenfluramine-related valvulopathy. They described either worsening or persistence in 62% of patients with aortic insufficiency and in 66% of patients with mitral insufficiency. Some regression was seen in about one third of patients. To evaluate the relationship between anorectic agents and valvulopathy, they recommend that echocardiographic studies use quantitative parameters (such as continuous wave jet density, "e" wave velocity, and left atrial size) instead of the qualitative criteria currently used.

Recommendations for follow-up of patients exposed to anorectic agents include taking a complete history and performing a physical examination. Echocardiography is indicated for patients who have symptoms such as dyspnea, chest pain, and palpitations, or associated physical findings. A caveat: more than 40% of patients with aortic insufficiency do not have a diastolic murmur appreciable on auscultation. Therefore, consideration should be given to performing echocardiography in the higher-risk patient even when there is no audible murmur. Follow-up echocardiography in patients with either mild aortic insufficiency or moderate mitral insufficiency related to the use of dexfenfluramine or fenfluramine/phentermine should be performed within 1 year to evaluate for progression. [Norman E. Lepor, MD]

Platelet Inhibition

Previous studies have shown that there is a significant degree of variability in platelet inhibition during the infusion of a GPIIb/IIIa inhibitor. The clinical significance of incomplete platelet inhibition during infusion of a standard dose of this inhibitor is unknown. In

469 patients, platelet function was determined by a bedside rapid platelet function assay (RPFA, Accumetrics) before and after PCI with GPIIb/IIIa inhibitor infusion.[37] Assays were done at baseline and at 10 minutes and at 1, 8, and 24 hours following PCI. A stent was placed in 82% of these patients. Abciximab was the GPIIb/IIIa inhibitor infused in 84% of patients. The inhospital MACE (major adverse cardiac events, such as death, MI, or urgent tricuspid valve replacement) was 8.7%, with the majority (8.1%) of events being MIs. At 10 minutes postprocedure, 27% of patients had less than 95% platelet inhibition; these patients had a significantly higher MACE rate (14.4% vs 6.4%, $P < .006$). Less than 70% platelet inhibition at 8 hours also predicted adverse outcomes (25% vs 5% to 8%). The degree of platelet inhibition at 1 hour and at 24 hours did not provide clear-cut predictive value.

This important but preliminary study addresses the issue of whether the degree of platelet inhibition, as assessed by a bedside RPFA as agonist, is predictive of clinical outcomes. Clearly, the degree of platelet inhibition at 10 minutes and at 8 hours seems to separate those with higher MACE rates. It is unclear why the 1-hour RPFA is not predictive or why the 8 hour-RPFA becomes important again. It is possible that 2 distinct mechanisms are behind the cause of MI in patients undergoing PCI. The initial mechanism could be embolization of platelet aggregates downstream to arterioles; thus, a high degree of platelet inhibition may be needed to break up this process. If platelet inhibition is suboptimal (less than 80%), particularly as the effectiveness of heparin diminishes, thrombosis of side branches or of the target lesion revascularization site may occur. There are no clinical data, however, that support these observations. It is not known if patients who have less than 95% platelet inhibition are "intrinsically" resistant to the GPIIb/IIIa inhibitors or if their adverse outcomes can be corrected by increasing the dose. Whether these observations are also valid concerning the small molecules is unknown, because the numbers of patients involved are too small. More trials to clarify these issues are on the way. [Alan C. Yeung, MD]

Rest ^{99m}Tc Sestamibi SPECT for Chest Pain Diagnosis

James E. Udelson, MD,[38] from Tufts University–New England Medical Center in Boston, reviewed the results of the ERASE (Emergency Room Assessment of Sestamibi for Evaluating Chest Pain) trial at a nuclear cardiology symposium. The ERASE trial was a prospective, multicenter, randomized clinical trial investigating the impact of rest myocardial perfusion imaging with technetium Tc 99m sestamibi (^{99m}Tc sestamibi) single-photon emission CT (SPECT) in ER patients presenting with chest pain suggestive of unstable syndromes. Patients presenting to the ER with chest, jaw, or arm discomfort during or within 3 hours of symptom onset; age more than 30 years or recent cocaine use; no previous history of MI; and a negative or nondiagnostic ECG were randomized to 1 of 2 arms: usual ER assessment and subsequent care (usual care) or usual care plus resting, ^{99m}Tc sestamibi gated SPECT imaging (ER MIBI).

As soon as possible after initial ER presentation and identification of the patient's clinical status, ^{99m}Tc sestamibi was injected and gated SPECT acquired. The interpretations of these images were made available in "real time" to the treating physicians. All results of electrocardiography, tests of cardiac enzymes, and stress testing, as well as discharge data were reviewed for patients admitted from the ER. Clinical reevaluation at 24 to 48 hours, tests of cardiac enzymes, electrocardiography, and stress testing were mandated in all patients discharged to home from the ER. Follow-up of all patients at 30 days was designed as part of the end point collection and was 99% successful.

The sites for this clinical trial included 7 hospitals in the United States. From these sites, a total of 2889 eligible patients were identified, and 2456 (85%) were randomized to either usual care (n = 1246) or ER MIBI (n = 1210). Of all patients enrolled, 329 had verified acute coronary ischemia —either unstable angina (n = 273) or acute MI (n = 56). There was no difference between the usual care and ER MIBI arms with respect to the number of patients with verified acute coronary ischemia admitted to the hospital, nor were there significant differences with respect to patient age, sex, history of prior coronary artery disease, or chest pain presentation.

Equal proportions of patients were appropriately admitted from the usual care and ER MIBI arms with MI (97%) and unstable angina (87%). Among the 2127 patients who did not have acute coronary ischemia, a 32% reduction in unnecessary admissions was found in the ER MIBI (42%) versus usual care (52%) arms (odds ratio, 0.68, 95% CI [0.57 to 0.82], $P < .001$ versus usual care). While no significant difference was found between the 2 arms of this randomized trial with respect to outcomes (survival, number of

MIs identified), the cost-effectiveness analysis, a designed end point, suggested that 14% of overall hospitalizations might be safely prevented, and that a $60 to $72 net savings per patient could be achieved, by application of the ER MIBI strategy.

The ERASE trial is a rarity in the field of nuclear cardiology—a prospective, multicenter, randomized trial. Thus, it is grade A guidelines data. The results of this study demonstrate that the use of acute rest imaging with ^{99m}Tc sestamibi gated SPECT in patients presenting to the ER with possible unstable syndromes significantly reduces the number of unnecessary admissions in patients without coronary ischemia and is cost-effective.

On the one hand, this strategy failed to improve the identification or triage of patients with confirmed MI or unstable angina, did not alter survival of discharged or admitted patients, and did not reduce the discharge of patients with acute coronary ischemia. On the other hand, as is the case with many other applications of radionuclide myocardial perfusion imaging, this approach resulted in the identification of low-risk patients who could be safely discharged, obviating the use of more expensive resources (such as hospital admission, catheterization). It is this fundamental principle that underlies the use of noninvasive testing to develop cost-effective clinical strategies. By identifying low-risk patients with noninvasive testing—that is, *knowing whom we do not need to treat*—we can limit the use of more costly resources to a smaller number of high-risk patients.

In certain respects, this study may have underestimated the benefit of this clinical strategy. This trial was designed to evaluate effectiveness rather than efficacy. No nuclear cardiology core laboratory overread the local physicians' interpretations of the scans, and it is this interpretation that was used by the patients' physicians. Further, the ER MIBI clinical strategy did not mandate action on the basis of the resting ^{99m}Tc sestamibi results; the physicians who received these results could choose to act on them or ignore the data. The results of ERASE indicate significant variation in the utilization of the resting SPECT results among enrolling centers. Despite the inexperience of the nuclear cardiology readers in certain enrolling centers, and the inexperience of the patients' physicians in incorporating this type of testing into their management plan for patients, a benefit was found.

Because the interpretation of acute SPECT studies has a steep learning curve, as is the case with all imaging studies, the results of ERASE may be exceeded by subsequent experiences. Further gains will also be made when algorithms combine conventional data (symptoms, cardiac risk factors, ECG) and the results of imaging with biochemical markers and other newer means to assess these patients. [Rory Hachamovitch, MD]

The ESPRIT Trial

The use of GPIIb/IIIa platelet antagonists during coronary angioplasty has grown significantly since their introduction and the results of a number of large clinical trials using abciximab. The inclusion of small-molecule GPIIb/IIIa agents, such as eptifibatide or tirofiban, has been limited in this setting, because of inconsistent findings during PCI. These small-molecule agents offer a number of advantages over abciximab, including lower cost and ease of use. The short half-life allows the drug to be stopped if significant bleeding occurs.

Eptifibatide was studied in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) II trial, but the study failed to show short- or long-term benefit. Subsequent studies demonstrated that the dosage used in this trial (135 mg bolus and a 0.75 mg/kg/min drip) was minimally effective, inhibiting the receptor by only 50%.

ESPRIT (European Stroke and Australian Stroke Prevention in Reversible Ischemia Trial) was undertaken to evaluate the effectiveness of high-dose eptifibatide in contemporary practice of PCI, which includes frequent coronary stenting. The dosage chosen was a double bolus of eptifibatide (180 mg) and a 2 mg/kg/min drip. Patients undergoing elective PCI were randomized to placebo plus heparin or eptifibatide plus reduced-dose heparin. Heparin was administered at a dose of 60 U/kg in the eptifibatide group to obtain an activated coagulation time (ACT) of 200 to 300 seconds. The primary end point was adverse events at 48 hours and included death, MI, urgent target vessel revascularization, or bailout use of a GPIIb/IIIa drug.

An interim analysis by the data and safety monitoring committee determined that the study should be stopped before the proposed recruitment of 2400 patients, because of a marked reduction in the primary end point. Thus, the study reported by James E. Tcheng, MD,[39] of Duke University, included 2064 patients who were randomized. Stents were used in more than 96% of patients, and the ACT averaged 260 to 270 seconds in both groups. The results (Figure 2) demonstrated a 37% reduction in the

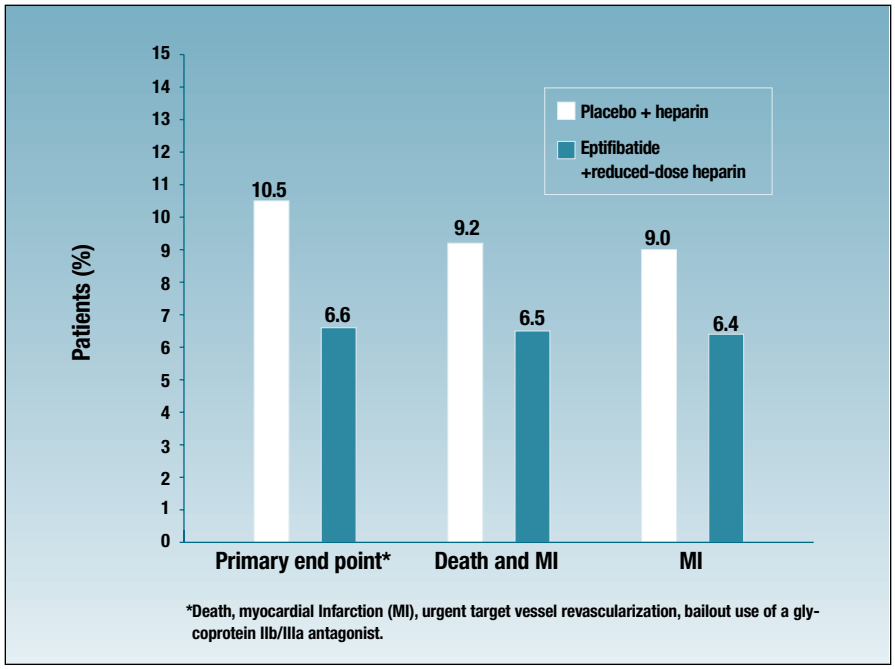

Figure 2. Results at 48-hour follow-up of patients in European Stroke and Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), comparing placebo plus heparin with high-dose eptifibatide plus reduced-dose heparin.

primary end point with eptifibatide (6.6% vs 10.5% for placebo, $P = .0015$). In addition, there was a 29% reduction in the combined end point of death and MI (6.5% vs 9.2%) and reduction in MI (6.4% vs 9.0%). There was no difference in the frequency of major bleeding complications, while minor bleeding complications were slightly more frequent in the eptifibatide group (2.8% vs 1.6%).

The study's importance is that it shows similar benefits to those previously demonstrated by abciximab and further confirms the benefit of GPIIb/IIIa antagonists in reducing complications in patients undergoing elective stenting. The study was limited by having only a 48-hour follow-up; however, 6-month follow-up is ongoing. If the results are upheld during longer follow-up, it will likely make the use of GPIIb/IIIa antagonists standard therapy for patients undergoing routine coronary stenting. In addition, these agents provide a less expensive alternative to abciximab. Further studies are taking place to determine the relative merits of the small-molecule GPIIb/IIIa drugs, such as eptifibatide and tirofiban, versus the monoclonal antibody abciximab, in patients undergoing PCI. [David P. Faxon, MD]

Estrogen Replacement and Atherosclerosis (ERA) Trial

David Herrington, MD,[40] from Wake Forest University (Winston-Salem, NC), revealed more bad news for hormone replacement therapy (HRT). Based on data from observational studies that postmenopausal HRT reduces the incidence of cardiovascular events, many clinicians have recommended HRT to women in their practices for both primary and, especially, secondary prevention. As demonstrated in the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial, HRT reduces low-density lipoprotein cholesterol and increases HDL cholesterol, mimicking a premenopausal state. Two years ago, the Heart and Estrogen-Progestin Replacement Study (HERS) demonstrated no reduction in cardiovascular events during a 4-year period in 2800 postmenopausal women with established CHD. An increase in thromboembolic events was seen soon after initiation of HRT, which negated a later decrease in MI. This finding came as a surprise to many clinicians.

Dr Herrington presented the results of the ERA trial, which reviewed disease progression in women with angiographically established CAD. In this double-blind, placebo-controlled trial, 309 postmenopausal women were randomly assigned to receive 1 of 3 regimens: unopposed estrogen, estrogen plus daily medroxyprogesterone acetate, or placebo. The primary end point of the trial (at a mean of 3.25 years following randomization) was the change in minimal coronary diameter (as measured by quantitative coronary angiography) in patients undergoing follow-up coronary angiography. Women were eligible to participate if they were postmenopausal, not

currently taking estrogen replacement, and had at least 1 epicardial stenosis greater than or equal to 30%. Importantly, at baseline and annually thereafter, all women underwent screening mammography and a gynecologic examination, including an endometrial aspiration or vaginal ultrasound to detect subclinical hyperplasia. As expected, baseline characteristics (including age, risk factors, prior MI, and prior coronary angioplasty) were not different among the 3 randomized groups.

After 3 years of therapy, no differences were found by angiography in the progression of CAD among the 3 groups, despite measurable improvements in lipoproteins consistent with prior studies. No significant treatment effects were detected in the percent stenosis of lesions or the development of new lesions, when stratified by disease severity at baseline. None of the women developed evidence of endometrial cancer during the trial and the rate of breast or other cancers was not different among the 3 groups, with very few events. An interesting observation in this trial was an increase in C-reactive protein levels in women receiving estrogen. This nonspecific marker of inflammation has been shown to decrease in patients receiving statins, suggesting important pathophysiologic differences between these 2 preventive measures.

Because the progression of CAD parallels the incidence of cardiovascular events, the ERA trial strongly supports the HERS study in terms of secondary prevention. The recent news release by the Women's Health Initiative reporting that women receiving HRT had more cardiovascular events than those taking placebo (although statistical criteria for stopping the trial were not met) has major implications for patients weighing the risks and benefits of HRT.

Although HRT has failed to demonstrate benefit for the secondary prevention of CHD, it still has value for managing osteoporosis and vascular symptoms in postmenopausal women. Improving diet and increasing physical activities should remain the first line of treatment in postmenopausal women at risk for cardiovascular events. [Alice K. Jacobs, MD, Robert A. Vogel, MD] ■

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