Best of the AHA Scientific Sessions 2001

Highlights from the American Heart Association Scientific Sessions 2001
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Key words: ALIVE Trial • Angiography, noninvasive • Antioxidants • Arrhythmia disorders, heritable • Cardiac resynchronization therapy • Cardiovascular disease • Carvedilol • Cholesterol ester transfer protein • Chronic kidney disease • Computed tomography • Diabetes • E2F decoy • Echocardiography • Ezetimibe • Gene therapy • Heart failure • Hypertension • Intermittent claudication • Left ventricular assist device • Magnetic resonance imaging • Myocardial infarction • Peripheral arterial disease • Positron emission tomography • Renal disease, end-stage • Restenosis • Statin therapy • Tezosentan • Vascular endothelial growth factor

Nearly 4000 abstracts were published in conjunction with the 2001 Scientific Sessions of the American Heart Association. Here, our editorial board members have selected, in their respective areas of expertise, the presentations they find most worthy of review.

Drugs and Lipid Metabolism

Ezetimibe

Ezetimibe is a novel, first-in-its-class, potent selective cholesterol absorption inhibitor. By a mechanism that has yet to be described, ezetimibe reduces the absorption of cholesterol across the intestinal villus. This results in reduced levels of serum low-density lipoprotein cholesterol (LDL-C). Dujovne and colleagues[1] presented an evaluation of ezetimibe in a randomized, double-blind, placebo-controlled trial of patients with primary hyperlipidemia. Patients were randomized to receive either ezetimibe, 10 mg once a day or placebo for 12 weeks. Compared to placebo, ezetimibe resulted in a 17% reduction of LDL-C, a 13% reduction of total cholesterol, a 17% reduction of ApoB, a 3% increase in high-density lipoprotein cholesterol (HDL-C), and an 11% reduction of serum triglycerides. This agent was exceptionally well tolerated, showing a safety profile comparable to placebo. There were no significant differences in laboratory or clinical safety parameters or gastrointestinal, liver or muscle side effects.

Table 1
Survival Rates by Treatment Group in the REMATCH Trial

Time Point	LVAD (n = 68)	Medical Therapy (n = 61)	*P* value
1 year	52%	25%	.002
2 years	23%	8%	.09

LVAD, left ventricular assist device.

This agent seems to represent an important addition to our armamentarium of lipid therapies. Because of its safety profile, ease of administration and effect on LDL-C, ezetimibe may supplant much of the current use of binding resins, which although safe have significant gastrointestinal side effects and require more complex dosing. Patients who would potentially benefit from this therapy include those who do not tolerate statin therapy, children and adolescents, and women of childbearing potential. Ezetimibe could also be co-administered with statins to reach lipid treatment goals.

CETP

Cholesterol ester transfer protein (CETP) is a plasma glycoprotein responsible for the transfer of cholesterol ester from HDL-C to apolipoprotein B–containing lipoproteins (VLDL) in exchange for triglycerides. This results in reduced levels of HDL-C, the impact of which in patients with coronary artery disease is not known. A study by DeGrooth and colleagues[2] was a double-blind, randomized trial of this agent in doses of 300, 600, and 900 mg/day for 12 weeks in comparison to placebo in patients with mild elevations of LDL-C. This agent led to an increase in HDL-C levels of 34% and a 7% reduction of LDL-C.

This drug is in early phase of clinical investigation, in terms of safety and efficacy. If reproducible, the clinical significance of these effects in terms of a reduction of clinical events will be eagerly awaited.

[Norman E. Lepor, MD, FACC, FAHA]

Heart Failure

Use of a Left Ventricular Assist Device for End-Stage Heart Failure

Patients with severe heart failure refractory to medical therapy have a very poor prognosis, with heart transplantation being the only viable treatment option in most cases. For patients who are not heart transplant candidates, there have been no viable treatment options. Implantable left ventricular assist devices have benefited patients with end-stage heart failure as a bridge to heart transplantation, but their long-term use for the purpose of enhancing survival and quality of life in patients who are not candidates for heart transplantation has not previously been evaluated.

Ezetimibe represents an important addition to our armamentarium of lipid therapies.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial recruited 129 patients from 20 participating U.S. centers who were in New York Heart Association (NYHA) class IV heart failure and ineligible for heart transplantation.[3] Patients were randomized to receive either the left ventricular assist device (HeartMate vented electric device, Thoratec, Pleasanton, CA) or optimal medical therapy. The primary endpoint of the trial was death from any cause. The results were presented by Dr. Eric Rose (Columbia University, New York) on behalf of the REMATCH Study Group.

The patients enrolled in the trial had an average age of 68 and a mean left ventricular ejection fraction (LVEF) of 0.17. Hemodynamics at baseline revealed a severe compromise in this group of heart failure patients, with mean pulmonary capillary wedge pressure of 25 mm Hg and mean resting cardiac index of 2.0 L/min/m^2. Serum sodium was 135 mmol/L, and serum creatinine was 1.8 mg/dL. In the trial, 68 patients were randomized to receive left ventricular assist devices (device group) and 61 to receive optimal medical therapy. The study showed a reduction of 48% in the risk of death from any cause in the group receiving the assist device; the relative risk was 0.52 (95% confidence interval [CI] 0.34-0.78), a significant difference with a *P* value of .001 (see Table 1).

The most common cause of death in the medical therapy group was terminal heart failure, accounting for 50 of the 54 deaths in this group. In the device group, the most common cause of death was sepsis (17 patients), followed by failure of the device (7 patients) and miscellaneous noncardiovascular causes (5 patients). The frequency of serious adverse events in the device group was 2.35 (95% CI, 1.86-2.95) times that in the medical therapy group, with a pre-

dominance of infection, bleeding, and malfunction of the ventricular assist device. Quality of life was significantly improved at 1 year in the device group. This study demonstrated that left ventricular assist device placement improved survival in patients with Class IV heart failure not eligible for transplantation. Although survival was improved with this device, there was a substantial risk of complications, costs were substantial, and over 75% of the device patients did not survive 2 years. Destination left ventricular device therapy appears to be an important new treatment option for patients with end-stage heart failure not eligible for transplant; however, advances in device technology are needed to further improve on these results.

Left ventricular assist device therapy may be an important new treatment option for patients with refractory heart failure not eligible for transplantion.

Carvedilol Reduces the Frequency and Severity of Hospitalizations in Severe Heart Failure

Beta-blockers have been shown to benefit patients with Class II–III heart failure, but many clinicians believed the risk-benefit ratio would be unfavorable in patients with more severe heart failure. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial evaluated 2289 patients with severe heart failure. The study included heart failure patients who had symptoms at rest or with minimal exertion and who had an LVEF less than 25% despite optimal medical therapy. Hospitalized patients were still eligible for enrollment, but not if they were in an intensive care unit. Patients on intravenous diuretics were allowed into the trial, but not if they had received an intravenous vasodilator or positive inotropic agent within 4 days of entry. Those with marked fluid retention were also excluded. Patients were randomized to placebo (n = 1133) or to carvedilol (n = 1156), beginning with a dose of 3.125 mg b.i.d. The dose was then doubled every 2 weeks, if tolerated, up to a target dose of 25 mg b.i.d. The mean age of patients in the trial was 63, and the mean LVEF was only 19.8%.

The main results of the study have recently been published.[4] Dr. Michael Fowler (Stanford University) presented a detailed analysis of the effect of carvedilol on the frequency and severity of hospitalizations.[5] There was a marked reduction in death and hospitalizations with carvedilol. Mortality was reduced from 18.5% with placebo to 11.4% with carvedilol (odds ratio 0.65 [95% CI 0.52-0.81], P = .00013). There was a significant reduction in the combined endpoint of death and heart failure hospitalizations, from 31.5% to 23.4% (P = .000004). When hospitalizations were analyzed alone, patients in the carvedilol group were less likely than those in the placebo group to be hospitalized at least once (32.2% vs 38.1%, P = .0029) or be hospitalized multiple times (13.1% vs 16.6%, P = .021). Carvedilol also reduced the total number of hospitalizations for any reason (674 vs 827, P = .0017), for any cardiovascular reason (386 vs 528, P = .0002), and for heart failure (302 vs 441, P = .0001). Carvedilol not only reduced the number of hospitalizations but also lessened the severity, as evidenced in the carvedilol group by a shorter duration of each hospital stay (11.4 vs 12.5 days, P = .015), lower utilization of intravenous diuretics (17.1% vs 22.9%, P = .0006) and less use of intravenous positive inotropic agents (9.1% vs 13.5%, P = .0008) to treat worsening heart failure. The findings were consistent across all subgroups including age, sex, ejection fraction, etiology, and blood pressure. Carvedilol was very well tolerated, having been discontinued in 6% of patients receiving it versus 9% of those receiving placebo at 6 months. Carvedilol has a dramatic impact on mortality, hospitalization frequency, and severity of illness during hospitalization in patients with heart failure, including those with symptoms at rest or on minimal exertion. Every effort should be made to ensure the initiation and maintenance of β-blocker therapy in patients with heart failure.

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Cardiac Resynchronization Therapy Improves Clinical Status in Heart Failure

Heart failure frequently results in the loss of synchronization between right and left ventricular contraction (desynchronization), and patients with intraventricular conduction delays are at increased risk for progression of heart failure. Biventricular pacing (resynchronization) therapy involves placement of an additional coronary sinus pacing lead for left ventricular pacing, along with standard atrial and right ventricular lead

placement. This form of therapy has recently been approved by the FDA as a heart failure therapy based on the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, which was the first large prospective, randomized, double-blind, controlled trial of cardiac resynchronization therapy (CRT) in patients with heart failure.

This trial utilized CRT via atrial synchronous biventricular pacing with the InSync® pacing device (Medtronic, Minneapolis, MN). The initial results involving functional status and quality-of-life endpoints were previously presented. An expanded analysis of 266 patients in the study was presented by Dr. Milton Packer (Columbia University, New York).[6] Discoordinate contraction of the right and left ventricles was evidenced from the surface electrocardiogram (ECG). Patients with NYHA Class III or IV heart failure, QRS complex duration ≥ 130 milliseconds, and LVEF < 35% had a Medtronic InSync device placed. The patients were also treated with standard heart failure medications. After successful implantation (93%), the patients were then randomized to "device on" or "device off" for the next 6 months. The physicians performing the heart failure assessments were blinded to the device on/off status.

The mean age of the patients was 64 years. Of these, 90% were Class III, the mean LVEF was 22% ± 6%, and left ventricular end-diastolic dimension (LVEDD) was 69.5 ± 9 mm. At baseline, mean HR was 76, with BP 115/69 mm Hg and QRS complex duration of 165 ± 19 msec. Nearly all of the patients (95%) were taking a diuretic, 90%–95% an ACE inhibitor, and approximately 60% a β-blocker. All background pharmacologic therapy for heart failure was continued for the duration of the trial. The study's primary endpoints were improvement in quality of life, as assessed by the Minnesota Living with Heart Failure Questionnaire; improvement in NYHA functional class; and improvement in exercise capacity, as evidenced by an increase in 6-minute walk distance of 50 meters or more. The primary measure of efficacy in this analysis was the clinical composite score. Patients' status is judged to be improved, unchanged, or worse.

After 6 months of treatment, the number of patients in the resynchronization group whose status improved was 60%, compared with only 34% in the control group.

After 6 months of treatment, the number of patients in the resynchronization group whose status improved was 60%, compared with only 34% in the control group. Only 5% of the patients in the resynchronization group were deemed worse, compared with 17% in the control group ($P < .001$). This adds to the previously presented results, which showed an average improvement in quality-of-life score in the CRT group of 19 points. Improvement in NYHA functional status by at least one class occurred in 69% of CRT patients, versus 34% of no-CRT patients. The 6-minute walk distance was unchanged in control patients but increased by 39 meters on average in CRT patients ($P < .01$). In addition, LVEF improved by 6 units and LVEDD decreased by 0.5 millimeters in CRT patients, whereas it did not change in no-CRT patients. This study demonstrates that CRT improves clinical status, functional status, and quality of life in patients with heart failure over a 6-month period. There also appears to be evidence for improved ventricular structure and function. This promising device therapy opens a new era for heart failure management and should be further evaluated to determine the impact on mortality. Cardiac resynchronization appears to be a useful adjunct to pharmacologic treatment of heart failure.

Endothelin Receptor Antagonists in Patients with Heart Failure and Acute Coronary Syndromes

Plasma endothelin-1 levels are elevated in patients with decompensated heart failure; this elevation may contribute to the high ventricular filling pressures and systemic vasoconstriction that characterize the decompensated state. Endothelin receptor antagonists have been developed to block this neurohumoral system and are being evaluated as a treatment for acutely decompensated heart failure (ADHF).

Tezosentan (Veletri™, Actelion, Allschwil, Switzerland) is an intravenous dual endothelin receptor antagonist being investigated in ADHF patients. The Randomized Intravenous Tezosentan (RITZ-4) trial was a multicenter, randomized, double-blind, placebo-controlled trial assessing the safety and efficacy of tezosentan in patients with ADHF associated with an acute coronary syndrome (ACS), defined by the presence of ischemic symptoms and ECG or elevated cardiac marker evidence of myocardial ischemia and/or acute myocardial infarction.[7] The study was presented by Dr. Wendy A. Gattis (Duke Medical Center, Durham, NC). The trial enrolled 293 patients who were randomized to placebo infusions or tezosentan at 25 mg/hr for 1 hour, then 50 mg/hr

for 23–47 hours. The primary endpoint set by trial investigators was a composite of death, worsening heart failure, recurrent ischemia, and recurrent or new myocardial infarction within 72 hours. The secondary endpoints included heart failure score after 24, 48, and 72 hours; recurrent ischemia; and recurrent myocardial infarction within 72 hours.

No significant differences were found between the placebo and tezosentan 50 mg/hr patients in the composite primary endpoint (24% and 29%, P = .5152). There was, however, no evidence that tezosentan increased ischemia in the patients studied. Patients taking tezosentan did experience a statistically significant increase in worsening heart failure, renal impairment, and nausea, factors that were likely linked to the increased systemic hypotension seen in the treated group. Disappointing results were also presented for the RITZ-1 study, a phase III trial looking at improvement in dyspnea in heart failure patients. This study, presented by John Teerlink (San Francisco VA Medical Center), also failed to meet study endpoints.[8] This study randomized 669 heart failure patients with dyspnea at rest or on minimal exertion hospitalized with heart failure to tezosentan 50 mg/hr or placebo. There was no difference between tezosentan and placebo for the primary endpoint of dyspnea score or for any of the secondary endpoints. The fact that less than one quarter of the 669 patients in RITZ-1 had dyspnea at rest at baseline makes it difficult to assess improvement in symptoms and, more importantly, to determine whether drug benefits would have been more evident in people with more serious heart failure. Previously, the phase II trial, RITZ-2, had shown tezosentan to significantly increase cardiac index and lower pulmonary wedge pressure. Hypotension, a result of possible excess dosing, was also assumed to be the underlying cause of the adverse effects seen in RITZ-1. In patients with ACSs and ADHF patients, the tezosentan dose of 50 mg/hour did not appear to improve clinical status and was associated with an increased incidence of adverse effects within 72 hours after randomization. The status of this class of agents for ADHF is in question, but further studies using lower doses are planned.

[Gregg C. Fonarow, MD]

Cardiorenal Update

Chronic Kidney Disease and Acute Coronary Syndromes

This year's meeting provided more analyses implicating chronic kidney disease (CKD) as a risk factor for major adverse cardiac events, hemorrhage, and cardiac death in patients with acute coronary syndromes (ACS). Analyses from this meeting support the use of aspirin, β-blockers, enoxaparin, and bivalirudin. New information presented about outcomes after valvular surgery in patients with end-stage renal disease (ESRD) suggest that tissue valves may be favored over mechanical prostheses given the shortened lifespan and excessive bleeding risks of those on hemodialysis.

In a session titled "Acute Myocardial Infarction: Diabetes, Renal Insufficiency, and Other Risk Stratifiers," Askari and coworkers presented an analysis from the Global Utilization of Strategies To Open Occluded Coronary Arteries IV (GUSTO-IV) study, in which 7800 patients presenting with ACS were randomized to placebo, abciximab bolus plus 24-hour infusion, or abciximab bolus plus 48-hour infusion.[9] Thirty-day outcome data were available for 7718 patients who had their baseline serum creatinine (Cr) levels recorded. Baseline renal insufficiency, defined as Cr > 1.5 mg/dL, was present in 489 (6.3%), diabetes in 1656 (21.5%), and the combination of diabetes and renal insufficiency in 170 (2.2%).

The primary outcome, death or myocardial infarction (MI), occurred in 8.1% of those without diabetes or renal insufficiency, 10.7% of those with diabetes alone, 20.4% of those with renal insufficiency alone, and 23.5% of those with combined diabetes and renal insufficiency (Figure 1). Multivariate analysis for the outcome of nonfatal MI or death revealed that the combination of

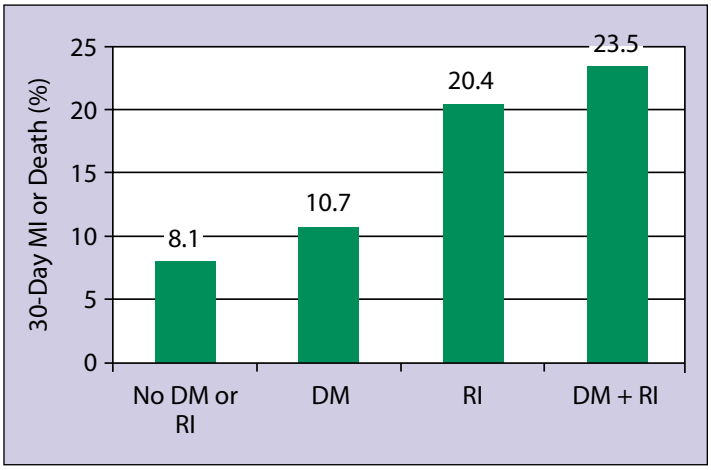


Figure 1. *Thirty-day data for primary outcome of nonfatal myocardial infarction (MI) or death from GUSTO IV in 7718 patients with acute coronary syndromes stratified by diabetes mellitus (DM) and renal insufficiency (RI), defined as baseline serum creatinine > 1.5 mg/dL. Data from Askari et al.*[9]

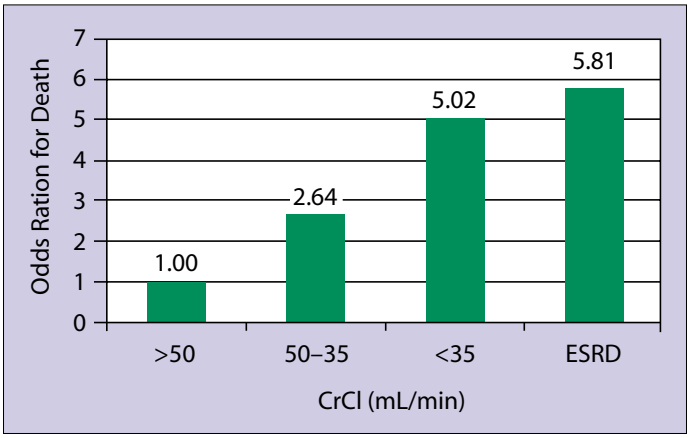


Figure 2. *The graded independent increased risk, expressed as adjusted odds ratios, of death following acute myocardial infarction in 2971 patients, stratified by calculated creatinine clearance (CrCl) and end-stage renal disease (ESRD). Data from Wright et al.*[10]

diabetes and renal insufficiency had a stronger, independent relationship with the primary outcome (odds ratio [OR] = 1.38, P = .02), than the covariates in the model, including a history of prior stroke, MI, coronary artery disease, heart failure, positive troponin test, ST-segment deviation, elevated c-reactive protein, or treatment with abciximab, angiotensin-converting-enzyme inhibitors, or aspirin.

This paper highlights the fact that even a low-risk ACS population selected for a clinical trial that excludes patients with severe CKD can demonstrate the powerful, independent relationships among diabetes, renal insufficiency, and the short-term outcomes of nonfatal MI and death. It could have been strengthened by use of estimated glomerular filtration rate or creatinine clearance (CrCl) as the measure of CKD. Approximately 30% of individuals with Cr < 1.5 mg/dL will have a CrCl < 60 mL/min, indicating at least mild CKD. This form of misclassification bias attenuated the independent association reported in this paper.

In another analysis, from Wright and coworkers, a single-center database was used to determine the risk for all-cause mortality in the first 5 years after acute MI.[10] A total of 2971 consecutive patients, including 664 with severe renal impairment (CrCl < 35 mL/min and 41 mL/min with ESRD on dialysis. Those patients with CrCl < 35 mL/min and ESRD had similar, poor survival, with 3-year survival rates of approximately 30%. There were graded increases in the adjusted risk of death following acute MI across descending levels of renal function (Figure 2). This finding is consistent with a recently published paper by Beattie and coworkers from another single-center registry.[11] These data help to confirm the graded effect of renal dysfunction on the risk of death. The implications of these findings include a call for additional research into the mechanisms by which renal disease confers risk.

Three papers addressed special treatment issues in patients with ACS and CKD. Collet and coworkers presented a renal-adjusted dose strategy for use of the low-molecular-weight heparin, enoxaparin.[12] They evaluated anti–factor Xa activity and bleeding events in 111 ACS patients stratified by renal function. Based on the optimal anticoagulation to bleeding ratio, they propose the following enoxaparin dose schedules: for CrCl > 60 mL/min, 1 mg/kg every 12 hours; for CrCl 30–60 mL/min, 0.84 mg/kg/every 12 hours; and for CrCl < 30 mL/min, 0.64 mg every 12 hours. Gershutz and colleagues presented an analysis from the Bivalirudin Angioplasty Trial, in which 3791 patients undergoing elective percutaneous coronary intervention (PCI) were randomized to the direct thrombin inhibitor bivalirudin or to unfractionated heparin.[13] The study group was stratified by baseline renal function. Interestingly, there was a graded increase in the absolute risk reduction for the composite outcome of death, nonfatal MI, target vessel revascularization, and major hemorrhage, as shown in Figure 3. A previously published analysis from this trial would suggest that the majority of the benefit from bivalirudin in patients with CKD comes from its reduced rates of bleeding compared to those of unfractionated heparin.[14] Lastly, McCullough and coworkers presented an analysis of 1724 patients with acute ST-segment-elevation MI. Although confounded by higher risk features in those patients who did not receive aspirin (ASA) or β-blockers (BBs), there was a consistent relative risk reduction in favor of ASA and BBs across all renal insufficiency groups (Figure 4).[15] In the absence of targeted randomized trials of ACS in CKD, these papers taken together support the use of ASA, BBs, renal-dose-adjusted enoxaparin, and possibly bivalirudin for CKD patients undergoing coronary angioplasty.

Selection of Cardiac Valve Prosthesis

The current guidelines for management of cardiac valvular disease state that use of tissue valves in patients with ESRD is a class III recommendation, essentially stating that mechanical prostheses are preferred. This is based primarily on two small case series showing higher rates of valve failure in ESRD patients who received tissue valves. Using the U.S. Renal Data System, Herzog and colleagues reported on the outcome of all-cause mortality in 6788 ESRD patients. Of

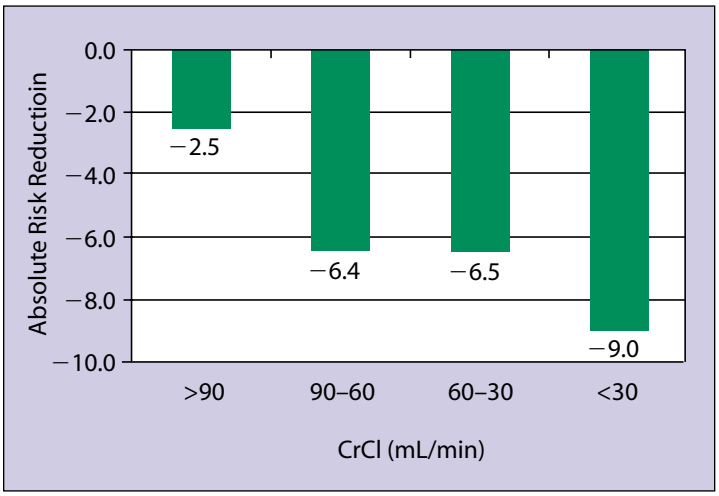


Figure 3. *Absolute risk reduction for major adverse cardiac events and hemorrhage by level of renal dysfunction, estimated by creatinine clearance (CrCl), favoring the use of bivalirudin over unfractionated heparin in elective angioplasty. Data from Gershutz.*[13]

those, 1074 (15.8%) received tissue valves.[16] Survival analysis adjusting for multiple comorbidities revealed identical survival rates for those who received tissue and mechanical prostheses. Because the indication for valve replacement was not analyzed, it is possible that this study contained selection bias for sicker patients or those with endocarditis to receive tissue valves. This bias would have if anything, biased the results to favor prosthetic valve surgical outcomes. In fact, the outcomes were the same for both prosthetic and tissue valves. Given the complications of chronic warfarin use in patients with ESRD undergoing hemodialysis, this paper raises the issue in its title of changing the guidelines concerning the selection of prosthetic valves in ESRD. The authors appeared to be justified in this claim that tissue valves are not contraindicated, but indeed may be a reasonable choice in patients with ESRD.

Commentary

There are four basic explanations for the cardiorenal risk relationship: 1) excess comorbidities in CKD patients; 2) less use of beneficial therapies in CKD patients, or therapeutic nihilism; 3) excess toxicities from conventional therapies used; and 4) special biology of the chronic renal failure state that leads to accelerated and more severe cardiovascular disease. The 2001 Scientific Sessions witnessed continued growth in cardiorenal research, with some of the first data on which treatment recommendations can be based. In addition, this growing body of literature is setting the stage for future randomized trials in patients with CKD presenting with cardiac events. [Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA]

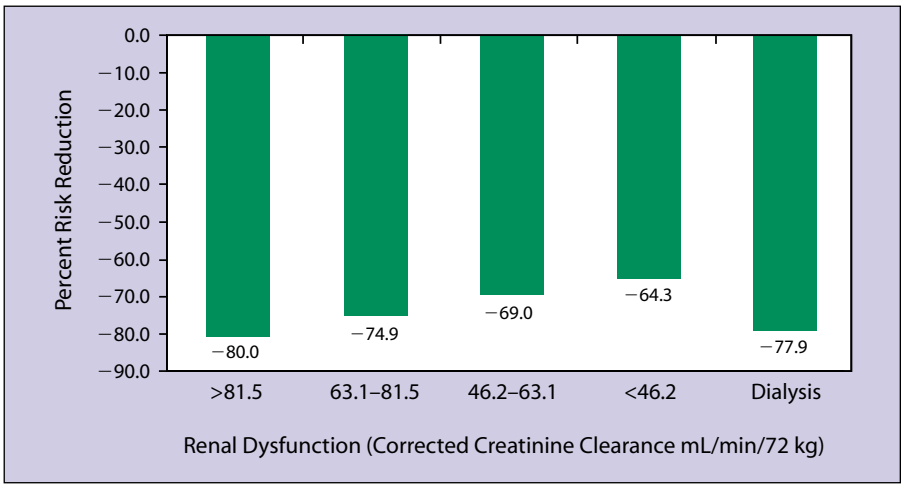
Symposium: Peripheral Arterial Disease: New Therapeutic Strategies

The objectives of the symposium on peripheral arterial disease (PAD) were to review recent epidemiologic data regarding the prevalence of PAD, discuss contemporary concepts regarding the pathogenesis of intermittent claudication, and provide a critical review of approved and innovative experimental therapeutic strategies for treating patients with PAD. These therapies include antiplatelet drugs, prostacyclins, and angiogenic growth factors.

Demographics of PAD in Community-Based Practices

A contemporary epidemiologic survey regarding the prevalence of PAD and its recognition by physicians and patients was provided by Dr. Alan T. Hirsch from the University of Minnesota Medical School. He reviewed the results of the Peripheral Arterial Disease Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study published recently in the *Journal of the American Medical Association*.[17] This study screened 6979

Figure 4. *Age-adjusted relative risk reduction for the combination of aspirin (ASA) and β-blockers (BB) in in-hospital mortality, according to level of renal dysfunction in patients not in shock or heart block;* P < *.0001 for all. The referent group is those who received neither ASA nor BB. Adapted from McCullough.*[15]



at-risk individuals from 350 primary care practices in the United States. The specific aims of the study were to: 1) assess the prevalence of PAD in the community; 2) evaluate the current rates of physician and patient awareness of PAD; 3) determine the prevalence of risk factors for atherosclerosis in a PAD population; and 4) measure the frequency of therapies administered to patients with PAD.

There is low awareness of PAD on the part of both patients and physicians.

At-risk individuals were defined as patients between the ages of 50 and 69 who had a diagnosis of diabetes or who smoked cigarettes and all persons over the age of 70, irrespective of the presence of these risk factors. PAD was diagnosed if the ankle/brachial index was ≤0.9. Additional criteria for PAD were derived from a chart review; these included a previous diagnosis of PAD or a prior peripheral arterial revascularization procedure. The prevalence of cardiovascular diseases was also assessed. Cardiovascular diseases were defined as coronary artery disease manifested by angina, myocardial infarction, prior coronary revascularization procedure; cerebrovascular disease, including history of stroke, transient ischemia attack, or carotid endarterectomy; and aortic aneurysm.

Among the patients screened in this study, 47% had no evidence of cardiovascular disease or PAD; these were designated as the reference group. Cardiovascular disease only was found in 24% of patients, both cardiovascular disease and PAD were found in 16%, and PAD only was found in 13%. Taking the latter two categories together, 29% of patients in this at-risk population were determined to have PAD. The study demonstrated further that PAD was underrecognized by both physicians and patients. Approximately one half of the patients with PAD were not previously known to have PAD, the diagnosis having been made at the time of screening by measurement of the ankle/brachial index. This underrecognition of PAD was associated with relatively low utilization of appropriate therapies to reduce the risk of adverse cardiovascular events in patients with PAD, including lipid-lowering drugs and antiplatelet agents. Only 66% of patients with newly diagnosed PAD were being treated with a lipid-lowering agent, compared to 76% with prior diagnosis of PAD and cardiovascular disease. Similarly, approximately 40% of patients with PAD only were being treated with an antiplatelet drug, compared to over 70% of patients with cardiovascular disease.

The conclusions from this study, therefore, are that PAD is prevalent in an at-risk population that makes up a substantial portion of practices of primary care physicians and that there is low awareness of PAD on the part of both patients and physicians. As a result, appropriate therapies that reduce the risk of adverse cardiovascular events such as myocardial infarction and death are underutilized in this population. Dr. Hirsch suggests that educational programs should be developed for physicians and at the grassroots level for patients to increase knowledge about PAD so that these therapies can be implemented in a timely and effective manner.

Pathophysiology of Intermittent Claudication

A lecture on the pathophysiology of intermittent claudication was presented by Dr. William Hiatt, Director of the Colorado Prevention Center at the University of Colorado in Denver. Claudication is a clinical manifestation of PAD that adversely affects a person's walking speed and distance. Pathophysiologic factors that may account for this include hemodynamic perturbations imposed by stenotic or occlusive lesions in peripheral arteries, microcirculatory dysfunction, and alterations in muscle metabolism. It is generally appreciated that stenosis causing obstruction of more than 50% of the diameter of a peripheral artery causes loss of kinetic energy and a reduction in distal perfusion proportionate to the severity of the stenosis. This concept is represented in Poiseuille's law, which states that,

$$F = \frac{\pi \Delta \mathrm{Pr}^4}{8 \cdot \eta \cdot l}$$

where F is flow, P is pressure, r is radius, η is viscosity, and l is length of the stenosis.

The pressure drop across a hemodynamically significant stenosis is reflected by calculation of the ankle/brachial index. Although this index is inversely proportional to the severity of stenosis, it does not predict exercise performance. Dr. Hiatt notes that improvement in ankle/brachial index resulting from percutaneous transluminal angioplasty or reconstructive surgery does not correlate with improvement with functional capacity. Yet supervised exercise training may improve exercise performance without imparting any change to the ankle/brachial index. The pathophysiology of claudication, therefore, must take into account disturbances in other areas, such as the microcirculation and skeletal muscle.

The microcirculatory environment may be adversely affected by increased blood viscosity and altered function of the blood's cellular components.

There is evidence of endothelial injury, including expression of von Willebrand factor, P-selectin, and thromboxane B_2, as well as increased white blood cell activation, platelet aggregation, and red blood cell aggregation in the microcirculatory environment. This may lead to formation of microthrombi that further impair blood flow and the exchange of oxygen and nutrients from capillaries to the subjacent skeletal muscle. In addition, there is evidence of increased oxidative stress, due in part to free-radical generation in the ischemic skeletal muscle. This may cause mitochondrial DNA injury as well as induce abnormalities in the electron transport chain, resulting in further alterations in oxidative metabolism. Evidence of altered muscle metabolism in individuals with PAD includes findings of increased muscle concentrations of metabolic intermediates. Taken together, therefore, it is the hemodynamic abnormalities imparted by flow-limiting lesions, alterations in microcirculatory function, and abnormal skeletal muscle metabolic activity that contribute to the pathophysiology of intermittent claudication in patients with PAD.

Therapies are most effective if they correct pathophysiologic abnormalities. Thus, reperfusion of skeletal muscle blood flow via catheter-based or surgical procedures will improve blood flow but not necessarily correct metabolic abnormalities. Antioxidants can potentially be beneficial by limiting free-radical injury. Exercise training improves skeletal muscle metabolism as well as exercise performance. Potential pharmacologic therapies that target the metabolic environment are under development; these include propionyl-L-carnitine as well as ranolazine.

Antiplatelet Therapy and PAD

Dr. Mark Creager, from Brigham and Women's Hospital and Harvard Medical School in Boston, spoke about the role of antiplatelet therapy in the management of patients with PAD. The rationale for administering antiplatelet agents to these patients stems from the observations that patients with PAD frequently have coexisting coronary artery disease as well as cerebrovascular disease. As a result, their long-term survival is significantly decreased compared to age-matched populations that do not have PAD. The risk of cardiovascular death is increased approximately sixfold in patients with PAD. It is recognized that myocardial infarction and subsequent death result from rupture of an unstable plaque in the coronary arteries. Plaque rupture frequently leads to superimposed thrombus formation with occlusion of the coronary lumen and consequent myocardial infarction.

Patients with PAD frequently have coexisting coronary artery disease as well as cerebrovascular disease.

Platelets play an important role in the development of thrombus following plaque rupture. Platelets adhere to atherosclerotic plaque, particularly when they come in contact with von Willebrand factor. GPIb receptors on the platelet surface bond to von Willebrand factor, which also binds to collagen, making the platelet adhere to the vascular wall. Collagen is a strong agonist for subsequent platelet activation. Downstream events following activation of the platelet by collagen includes the release of adenosine diphosphate (ADP) and serotonin from dense granules, as well as activation of phospholipase A and subsequent synthesis of thromboxane A_2 via the cyclooxygenase pathway. ADP, serotonin, and thromboxane A_2, as well as thrombin, activate receptors on other platelets, initiating a cascade of platelet activation and further release of these substances. In addition, these platelet-derived substances, particularly ADP, contribute to the surface expression and activation of platelet glycoprotein IIb/IIIa receptors. These receptors bind fibrinogen, which serves as a bridge between platelets, culminating in platelet aggregation and the formation of a platelet plug. The platelet also has surface receptors for soluble coagulation factors, including factor Xa, which contribute to the conversion of prothrombin to thrombin. Fibrinogen is integrated into the platelet thrombus, which is converted by thrombin to fibrin. This series of events enables the rapid formation of thrombus superimposed on a ruptured plaque.

The benefits of antiplatelet therapy in reducing adverse cardiovascular events in patients with atherosclerosis is now well established. The Antiplatelet Trialists' Collaboration reported that patients with clinical manifestations of atherosclerosis, either myocardial infarction, stroke, or transient ischemic attack, and patients in other high-risk groups, including those with PAD, had a 27% odds ratio reduction in the risk of adverse cardiovascular events when treated with an antiplatelet regimen compared to controls.[18] In trials of patients with PAD, including those with intermittent claudication, peripheral bypass grafts, or percutaneous transluminal angioplasty, point estimates of the odds ratio for myocardial infarction, stroke, or vas-

cular death consistently favored antiplatelet therapy compared to controls. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study found that clopidogrel, compared to aspirin, reduced the risk of adverse cardiovascular events by 8.7% among the 19,185 patients who were enrolled in this trial because of acute myocardial infarction, recent ischemic stroke, or PAD.[19] In the patients with PAD, there was a 24% risk reduction for adverse cardiovascular events in patients receiving clopidogrel compared to those who received aspirin. The major adverse effect of antiplatelet drugs is bleeding. Based on 35 randomized controlled studies, it is estimated that the risk of major nonfatal bleeding in patients with PAD is increased relative to that in controls by approximately 30%. The Antiplatelet Trialists' Collaboration also suggests that antiplatelet therapy reduces the risk of a peripheral arterial occlusion, particularly in patients who have received an infrainguinal bypass graft. The thienopyridine derivative ticlopidine improved the 2-year patency rate of saphenous vein bypass grafts compared to placebo in one study.[20] A recent study found that aspirin and oral anticoagulants were equally effective in maintaining graft patency following infrainguinal bypass grafting, though the risk of bleeding was higher in patients who received oral anticoagulants.[21] Current guidelines for antithrombotic therapy in patients with PAD recommended by the American College of Chest Physicians include a grade IA recommendation for aspirin, particularly in patients with clinical evidence of coexisting coronary artery or cerebrovascular disease. The guidelines provide a grade IIA recommendation for clopidogrel, indicating that it may be superior to aspirin in reducing ischemic complications.[22]

Current guidelines for antithrombotic therapy in patients with PAD include a grade IA recommendation for aspirin, particularly in patients with clinical evidence of coexisting coronary artery or cerebrovascular disease.

Prostaglandin Therapy in PAD

Clinical evidence supporting and refuting the potential benefit of vasodilator prostaglandins in patients with PAD was reviewed by Dr. Emile Mohler of the University of Pennsylvania in Philadelphia. He noted that vasodilator prostaglandins, such as prostacyclin, may be of benefit in patients with PAD, in part because of their inhibitory effects on platelet function and their potential vasodilator properties. In some previous studies, prostacyclin analogs have been shown to confer benefit in patients with PAD. For example, in one study, intravenous administration of epoprostenol reduced pain in patients with critical limb ischemia.[23] Iloprost has been reported to decrease ischemic pain and improved healing in patients with thromboangiitis obliterans and ischemic digits secondary to Raynaud's phenomenon. Dr. Mohler found that a prostacyclin analog increased femoral blood flow in patients with PAD, though it had no effect on pulse volume recording. The BERCI II trial, conducted in Europe, had reported that beraprost, a prostacyclin analog, improved walking distance as assessed by treadmill testing in patients with PAD.[24] However, a recent study in the United States failed to confirm this finding. Thus, although preliminary studies have suggested that prostacyclin analogs may be effective in patients with PAD, efficacy has not been demonstrated uniformly, particularly in trials involving patients with intermittent claudication.

Therapeutic Angiogenesis for PAD

The topic of therapeutic angiogenesis for patients with PAD was reviewed by Dr. Brian Annex, of Duke University in Durham, North Carolina. Pathologic angiogenesis occurs in diabetic retinopathy, age-related macular degeneration, tumors, and even components of atherosclerosis. In contrast, therapeutic angiogenesis is the development of new vessels induced by administration of an angiogenic agent to treat disease. Vascular endothelial growth factor (VEGF) is the prototype of a substance that promotes blood vessel growth. It has five to six isoforms that act on specific receptors. The VEGF R-1 and VEGF R-2 receptors mediate angiogenesis, whereas the VEGF R-3 receptor mediates lymphangiogenesis.

Phase 1 trials suggested that VEGF administration reversed segmental ischemia and improved stress-induced wall motion abnormalities.

There have been several clinical trials in which VEGF was administered to patients with coronary artery disease.[25,26] These phase 1 trials suggested that VEGF administration reversed segmental ischemia and improved stress-induced wall motion abnormalities. There have been several uncontrolled clinical trials of

angiogenic factors in patients with PAD. These have utilized intramuscular administration of plasmid VEGF, as well as intraarterial and intravenous administration of recombinant basic fibroblast growth factor (bFGF). These safety trials have shown equivocal findings regarding the benefit of angiogenic growth factors in terms of limb blood flow or ulcer healing. Several trials are in progress in which hypoxia-inducible factor-1α, αFGF, or $VEGF_{121}$ is being administered with either plasmid or adenovirus vectors.

Dr. Annex also reviewed the results of the recently completed Therapeutic Angiogenesis with Recombinant Fibroblast Growth Factor-2 for Intermittent Claudication (TRAFFIC) trial, in which recombinant FGF-2 or placebo was administered via the femoral artery on one or two occasions 30 days apart in patients with stable intermittent claudication and infrainguinal atherosclerotic disease.[27] The primary endpoint was the change in peak walking time on a treadmill at 90 days. In the placebo group, the change in peak walking time was 14%; in the single-dose group it was 34%; and in the double-dose group it was 20%. There was a significant difference between the results in the group receiving a single dose and those in the placebo group. Thus, angiogenic therapies have the potential for improving symptoms in patients with PAD. The vascular community eagerly awaits the results of trials that are currently in progress.
[Mark A. Creager, MD]

Gene Therapy Shows Efficacy and Continued Safety

Gene therapy for vascular disease is finally showing promise. Numerous basic science studies have demonstrated the important role of vascular endothelial growth factor in angiogenesis. In addition, other growth factors, including fibroblast growth factor (FGF), have also been shown to be critically important in the creation of new blood vessels. A number of laboratories have demonstrated that either injection of the growth factor itself or induction of growth factor production by gene therapy has resulted in improvement in ischemia and coronary collateral flow. Clinical studies, however, have not yet demonstrated clear-cut efficacy. At this year's AHA Scientific Sessions, a number of investigators reported on both efficacy and safety in the use of genes to deliver vascular endothelial growth factor to ischemic tissue. The studies were largely performed through the pioneering work of Dr. Jeffrey Isner and his group at St. Elizabeth's Hospital in Boston. Tragically, Dr. Isner died suddenly one week prior to the American Heart Association meetings. At the meetings, his colleagues articulated the tremendous loss his untimely death is to the scientific community and the major contributions he made to this particular field.

These studies are important, as they demonstrate the long-term safety of gene therapy and the potential value of gene transfer growth factors for the generation of new blood vessels.

VEGF-2 Gene Transfer to Improve Myocardial Function

Dr. Isner's most important contribution was the report of a phase 1, placebo-controlled, double-blind trial of vascular endothelial growth factor (VEGF-2) gene transfer in patients with chronic myocardial ischemia.[28] In this study, 19 patients were randomized. All patients had class III/IV angina, despite maximum medical therapy. Patients received gene transfer of the plasmid VEGF-2 DNA or placebo. The patients were randomized on a ratio of 2 to 1 and received six left ventricular injections using an 8F catheter (Biosense, Diamond Bar, CA) guided by NOGA™ electromechanical mapping (Biosense). No adverse effects were reported, and during a follow-up 3 months later there was a significant improvement in anginal class by at least two Canadian Cardiovascular Society classes in 4 of the 12 patients. One patient became asymptomatic. There was a reduction in the number of anginal episodes in the treated group and no change in the placebo group. Exercise duration increased by 91.8 seconds in the VEGF-2 group and only 3.9 seconds in the placebo group. These differences attain statistical significance despite the small number of patients studied. In addition, patients also underwent single photon emission computed tomography (SPECT) imaging, which showed a significant increase in average stress perfusion scoring in the abnormal segments following VEGF-2 treatment, whereas there was no change in those receiving placebo. The NOGA electromechanical mapping system demonstrated improved myocardial function.

This is an important study, because it is a randomized, double-blind, placebo-controlled trial and, despite the small number of patients, it shows a very dramatic difference between those receiving VEGF-2 gene transfer and those receiving placebo. Also, the same group reported long-term follow-up of a 30-patient, open-label study demonstrating the persistence of clinical improvement up to 1-year following the procedure.[29] In a separate, 2-year, follow-up study,

improvement was also shown.[30] Importantly, no adverse effects were noted. In particular, there was no development of vascular tumors or occurrence of cancer during the follow-up period.

These studies are important, as they demonstrate the long-term safety of gene therapy and the potential value of gene transfer of growth factors for the generation of new blood vessels to improve blood flow to ischemic territories. Prior large randomized trials using the protein itself, either VEGF-2 or FGF-2, have been negative and suggest that the manner in which the protein is delivered to the ischemic myocardium may be critically important to overall success. Clearly, larger randomized trials are necessary to demonstrate the efficacy of VEGF-2 gene transfer, but these small studies provide strong evidence that larger studies need to be conducted to validate the clinical usefulness of this new and promising therapy.

The studies reviewed here confirm that gene therapy does have a role in the treatment of cardiovascular disease.

Gene Therapy to Prevent Intimal Hyperplasia

Coronary artery bypass graft (CABG) remains the therapy of choice for patients with multi-vessel disease, compromised left ventricular function, and diabetes. However, the longevity of the venous bypass conduits is limited, with 50% of the vein grafts failing in 5–10 years. One-year vein graft graft failure rates are about 10%–15 %. Early vein-graft failure is usually due to technical problems in handling of veins during harvesting, anastomosis, and early thrombosis, whereas later on intimal hyperplasia, accelerated atherosclerosis with plaque rupture, and thrombosis account for the majority of graft failures. Intimal hyperplasia due to smooth muscle cell proliferative activity is believed to be the underlying substrate for development of vein graft atherosclerosis. Arterial conduit has substantially better durability, but its supply is limited. Thus, a novel technique to "convert" venous conduits into "arterial" conduits is attractive.

Another gene therapy trial evaluated the effect of an E2F decoy in the prevention of neointimal hyperplasia of saphenous vein grafts.[31] E2F is a pivotal cell-cycle transcription factor, and its inhibition prevents neointimal hyperplasia after vascular injury. A decoy oligodeoxynucleotide (a short strand of DNA) that binds E2F has been shown to inhibit intimal hyperplasia and stimulate medial hyperplasia when the decoy is inserted into the vessel wall. In this study, 101 patients were randomized to E2F, and 99 patients were untreated. They were high-risk patients, undergoing nonelective CABG, who required at least two vein grafts each. At the time of cardiac surgery, harvested saphenous vein grafts were incubated in E2F decoy prior to vein graft insertion. One of the difficulties in bringing gene therapy to clinical use has been the toxicity of the delivery agents, such as adenovirus or retrovirus. The method of delivery in this study is novel in that instead of using virus or vector to insert the DNA into the cells, hydraulic pressure was used. The process takes approximately 10 minutes after the vein is harvested, and because the therapy is performed "ex-vivo," the systemic exposure is limited.

The primary endpoint at 1 year was angiographic stenoses, as well as the degree of intimal hyperplasia as determined by intravascular ultrasound. By angiography, there was a 30% reduction in severe stenoses (defined as greater than 75%) in the treated group when compared to the untreated group (27.3% vs 38.7%, $P = .03$). When patients with initially normal blood flow were compared, this difference was even more striking (18.3% vs 30.3%). Intravascular ultrasound in a subset of patients demonstrated a highly significant decrease in the degree of intimal hyperplasia in the treated group ($P = .024$). Major adverse cardiac events, including death, repeat revascularization, and myocardial infarction were similar between the groups: 12% in the E2F group and 16% in the untreated group.

This is one of the first studies to demonstrate the effectiveness of gene therapy in preventing intimal hyperplasia following bypass surgery. In addition, the study demonstrated no evidence of adverse events from administration of this gene therapy and suggests that gene therapy may provide significant promise in the future in the prevention of graft failure, as well as restenosis.

Taken together, the studies reviewed here confirm that gene therapy does have a role in the treatment of cardiovascular disease, and most of the concerns about safety appear to be unfounded. Further studies are clearly needed to elucidate the benefit of other potential gene targets.

[David P. Faxon, MD, FACC, Alan C. Yeung, MD, Prediman K. Shah, MD, FACC, FACP, FCCP]

Electrophysiology

Azimilide

Azimilide is a new antiarrhythmic agent with Class III activity that is not yet approved by the U.S. Food and Drug Administration for use in the United States. A major randomized

prospective placebo-controlled trial, AzimiLide post Infarct surVival Evalution (ALIVE) was reported at this year's AHA meeting. This trial evaluated the effect of 75 mg and 100 mg of azimilide on all-cause mortality in 3717 recent myocardial infarction (MI) patients (5–21 days post-MI) at risk for sudden death. The major focus of the trial was on the 100-mg azimilide dose. The primary objectives of ALIVE were to determine the effect of 100 mg azimilide on all-cause mortality in recent MI patients with a left ventricular ejection fraction (LVEF) of 15%–35%, and to evaluate a subgroup at presumed higher risk with low heart rate variability.

Using the intent to treat analysis, there were 1690 patients who received placebo and 1691 who received 100 mg azimilide. All-cause mortality was 11.6% for both groups. The patient dosing was initiated once daily in 73% of patients in-hospital and 27% out of hospital. Fewer patients in sinus rhythm at baseline developed atrial fibrillation/flutter taking 100 mg azimilide (0.5%) compared with placebo (1.2%) ($P = .04$).

The 100-mg and 75-mg azimilide doses gave a similar safety profile. For those patients who received 100 mg azimilide, serious adverse events and serious cardiovascular events occurred in 38.2% and 28.4%, respectively, and were similar with placebo (37.8% and 30.8%, respectively). The Event Committee classified five cases of torsade de pointes in the azimilide group (0.3%) compared with one patient receiving placebo (0.1%). The cases of torsade de pointes were associated with one or more risk factors, including age > 65 years, female gender, diuretic use, hypokalemia, and/or hypomagnesemia or bradycardia.

Patients who received the 100-mg azimilide dose had severe neutropenia more frequently compared with those given placebo (0.9% vs 0.2%). All cases of neutropenia occurred between 25 and 48 days in the azimilide group. No patients experienced life-threatening infections, and all patients recovered in 1–18 days, except 1 patient in whom a new myocardial infarction was associated with death.

In summary, azimilide given to high-risk, post-MI patients who had substantial left ventricular dysfunction demonstrated no difference in all-cause mortality compared with placebo, and there appeared to be some positive effect on prevention of atrial fibrillation/flutter. There is a small increased risk in severe neutropenia, which occurs relatively early and is reversible. Azimilide is a promising new antiarrhythmic drug that is undergoing prospective trials in patients with atrial fibrillation.

Azimilide is a promising new antiarrhythmic drug that is undergoing prospective trials in patients with atrial fibrillation.

Genomic Advances in Heritable Arrhythmia Disorders

Doctor Michael Ackerman delivered a state-of-the-art lecture on heritable arrhythmia disorders. The following is a synopsis of his lecture.

Long QT syndromes. Much work has been done to identify the genetics of the long QT syndrome. This syndrome can manifest as syncope, seizures, or even sudden cardiac death, and there are many patients who remain asymptomatic. Although more than five varieties have been identified, most data have been published on LQT1, LQT2, and LQT3. LQT1 (KVLQT1) involves the IKs ionic current, and accounts for nearly 25% of all known cases of the long QT syndrome. Exertional triggers for arrhythmias are relatively common with this defect. LQT2 (Herg) involves the IKr ionic current. Triggers for arrhythmias include arousal and emotional upset. LQT3 involves the *SCN5A* gene and is a defect of the sodium current; arrhythmias during sleep are relatively common with this defect. It should be noted that triggers for arrhythmias are not uniform, and there is crossover between genetic defects.

Brugada syndrome. Approximately 80% of cases of Brugada syndrome have an unknown genetic defect. In a substantial number of patients, the defect appears on chromosome 3 and involves *SCN5A* (sodium ion channel defect). The electrocardiogram has a characteristic appearance of a right bundle branch block with ST segment elevation usually in the early precordial leads. Lethal ventricular arrhythmias occur in this disorder.

Catecholaminergic polymorphic ventricular tachycardia. This syndrome is characterized by syncope, seizures, or sudden death related to physiologic or emotional stress, and frequently occurs in children. The disease gene appears to be located on chromosome 1, and at least one variety involves a mutation of the ryanodine receptor. The hypothesis is that there may be an increased sensitivity of calcium-induced activation of the calcium-release channel complex intracellularly as a potential cause of the malignant arrhythmias in this syndrome.

Sudden infant death syndrome (SIDS). There are many theories to describe this problem. However, in some cases this may be related to the long QT syndrome. In a postmortem molecular analysis of *SCN5A* defects in SIDS, 2 of 93 cases had a *SCN5A* mutation. This substantiates that an

ion channelopathy can be responsible for some cases of SIDS.

Brief mention was made of a syndrome of sinus node dysfunction that involves chromosome 15 and pacemaker currents. Andersen's syndrome, a defect that includes prolongation of the QT interval and tachyarrhythmias, appears to involve the inward rectifier potassium current.

It was clear from this well-organized and excellent lecture that much has been learned about genetic defects that can lead to cardiac arrhythmias, but it is obvious that many fascinating discoveries await further investigations into this field.

[Eric N. Prystowsky, MD]

[Note: Dr. Prystowsky acts as a consultant and has received a research grant from Procter & Gamble Pharmaceuticals.]

Canadian Antioxidant Restenosis Trial (CART-1)

Previous studies have provided evidence that oxidants that promote atherogenesis are released in response to arterial injury.[32] In addition, percutaneous coronary intervention is known to cause the release of oxygen free radicals that stimulate growth factors that, in turn, stimulate smooth muscle cell proliferation.[33] Data from animal studies have shown a beneficial effect of antioxidants on both cellular proliferation and arterial remodeling after balloon angioplasty.[34,35] Furthermore, the antioxidant probucol has been shown to decrease restenosis following coronary balloon angioplasty in a randomized, placebo-controlled clinical trial.[36] In a similarly designed study, the same authors have evaluated AGI-1067 (AtheroGenics, Alpharetta, GA), a new vascular protectant that possesses strong antioxidant properties equipotent to those of probucol.

On behalf of his colleagues, Dr. Jean-Claude Tardif reported the results of CART-1,[37] a randomized, placebo controlled trial of the efficacy of probucol and multiple doses of AGI-1067 in the prevention of restenosis following percutaneous coronary intervention (PCI) (with stents used in 81% of patients). Two weeks prior to the procedure, 305 patients were randomly assigned to one of five treatment groups: placebo, probucol 500 mg b.i.d., AGI-1067 70 mg, 140 mg, or 280 mg once daily and continued for 4 weeks. The primary endpoint of the trial was the size of the luminal area as measured by intracoronary ultrasound at 6 months. Luminal area at the site of the target lesion at follow-up was 2.66 ± 1.58 mm^2 for placebo, 3.69 ± 2.69 mm^2 for probucol, and 2.75 ± 1.76 mm^2, 3.17 ± 2.26 mm^2, and 3.36 ± 2.12 mm^2 for AGI-1067 70, 140, and 280 mg groups, respectively ($P = .02$ for the dose-response relationship; $P \leq .05$ for both AGI-1067 280 mg and probucol vs placebo). Measurement of angiographic restenosis revealed similar findings, with a reduction in restenosis rate of 32% and 31% by probucol and AGI-1067, respectively. Interestingly, there was also an increase from baseline to follow-up in lumen dimensions of the reference segments among the AGI-1067 140 and 280 mg groups ($P = .05$ for the 140 mg group vs placebo; $P = .077$ for the AGI-1067 dose-response relationship). It was concluded that the vascular protectant AGI-1067 and the antioxidant probucol reduce restenosis following coronary intervention. However, in contrast to probucol, AGI-1067 also results in a dose-dependent improvement in luminal dimensions of the reference segments. This latter finding may represent clinical evidence of vascular protection against the atherosclerotic process.

This well-designed and well-conducted trial reports on a promising new vascular protectant that not only reduces restenosis following contemporary coronary intervention, but unlike probucol also appeared to induce regression or favorable remodeling of native atherosclerosis with no significant adverse effect on QTc interval compared to placebo.

The CART-1 trial reports on a promising new vascular protectant that not only reduces restenosis following contemporary coronary intervention but may have a direct effect on the progression of atherosclerosis as well.

Certainly, additional studies (some of which are currently underway) will be necessary to validate this provocative preliminary finding. From a practical standpoint, AGI-1067 for the prevention of restenosis will be limited to stable patients undergoing elective revascularization who are willing to wait 2 weeks for their procedure, a strategy that is much less frequently practiced in the United States. Perhaps future studies will evaluate whether starting AGI-1067 at the time of or shortly following the procedure will result in similar beneficial effects on restenosis and atherosclerosis.

[Alice K. Jacobs, MD, FACC, Prediman K. Shah, MD, FACC, FACP, FCCP]

CT Imaging of Coronary Arteries and the Late-Breaking Trials

The AHA Scientific Sessions provided a wealth and breadth of important presentations. Of particular interest were the sessions dealing with computed tomographic (CT) imaging of coronary arteries and the late-breaking trials.

The evolution of CT imaging tech-

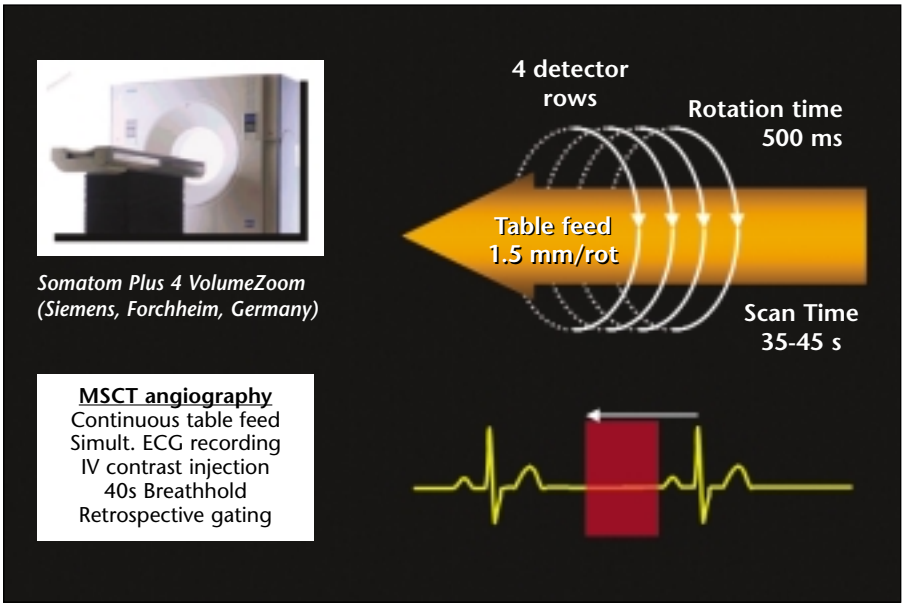


Figure 5. *Multislice computed tomography data acquisition.*

nology has allowed its use to progress from use of electronic beam computed tomography (EBCT) to screen for atherosclerosis to techniques that define stenosis severity. Dr. Koen Nieman from the Department of Cardiology, Thoraxcenter, in the Netherlands presented a paper titled "Noninvasive Coronary Angiography with Multislice Spiral CT—A Comparison with Conventional Angiography in 62 Patients." Forty-seven patients with suspected de novo coronary artery disease and 15 patients with suspected recurrent coronary artery disease underwent assessment of proximal and distal segments; 77% of all segments were found to be assessable (95% left main, 92% left anterior descending [LAD], 74% right coronary artery [RCA], and 57% circumflex [CX]). Overall, 87% of proximal segments and 64% of midsegments were assessable. Factors related to limitations of assessability included motion artifact and the presence of heavy calcification. (Figures 5 and 6 depict specifications of multislice CT data acquisition and a sample CT angiographic image, respectively.)

The overall sensitivity and specificity for detecting >50% stenosis in assessable segments were 88% and 95%, respectively, with a range of 100% and 100% for left main, 96% and 94% for RCA, 83% and 92% for LAD, and 71% and 97% for CX disease. The overall positive predictive value was 73% and the negative predictive value 98%.

The conclusions were that multislice CT has good sensitivity and excellent specificity for significant coronary artery disease in assessable proximal and middle coronary arteries. Limitations were the substantial number of segments that were not assessable due to motion artifacts and calcifications. New prototype 15-slice scanners will allow enhanced imaging by providing the ability to reduce slice thickness, increase the number of slices, and decrease the rotation time. There is definite hope that this technology will evolve to the point that it will replace conventional coronary angiography for identifying the presence of significant obstructive disease.

Heart Protection Study

The largest statin trial to date, the Heart Protection Study, (principal investigator: Dr. Rory Collins, Oxford University) recruited 20,536 subjects from 69 centers in the United Kingdom during 1994-1997

Figure 6. *An example of computed tomography angiography: lesion of the left anterior descending artery.*

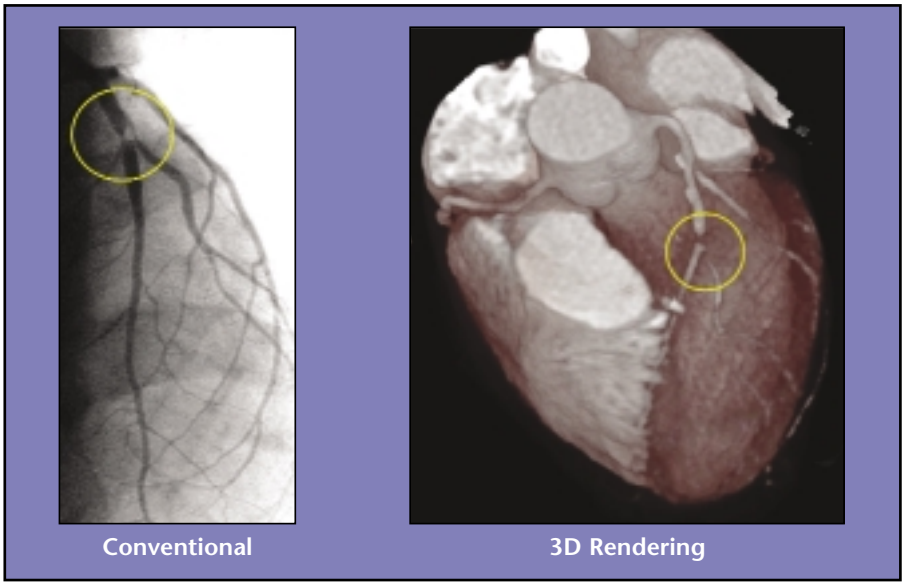


Table 2
Primary Endpoints Among Patients on Simvastatin Versus Placebo

	Simvastatin	Placebo	*P*
All-Cause Mortality	1328 (12.9%)	1503 (14.6%)	<.001
Cardiovascular Mortality	791 (7.7%)	943 (9.2%)	<.002

Table 3
Vascular Events in Patients on Simvastatin Versus Placebo

	Simvastatin (n = 10,269)	Placebo (n = 10,267)
Women	366 (3.6%)	458 (4.5%)
Age > 75 y	138 (1.3%)	208 (2.0%)
Diabetes	279 (2.7%)	369 (3.6%)
Baseline LDL Cholesterol		
<100 mg/dL	285 (2.8%)	360 (3.5%)
<130 mg/dL	670 (6.5%)	881 (8.6%)
>130 mg/dL	1087 (10.6%)	1365 (13.4%)
Major CV Events	2042 (19.9%)	2606 (25.4%)

LDL, low-density lipoprotein; CV, cardiovascular.

to evaluate both statin and antioxidant therapy in patients with prior cardiovascular disease or increased cardiovascular risk (cerebrovascular or peripheral vascular disease, diabetes mellitus, or hypertension). The study recruited women (n = 5082), diabetics (n = 5963), and elderly patients older than 65 years (n = 9515). The primary endpoint was cardiovascular mortality; the mean follow-up was 5.5 years. Using a 2 × 2 factorial design, patients ages 40–80 years with baseline cholesterol > 135 mg/dL were randomized to (a) simvastatin 40 mg daily versus placebo and (b) antioxidant vitamins (vitamin E: 600 mg; vitamin C 250 mg; β-carotene 20 mg) versus placebo. Statistical analysis was performed based on a 70% adherence to assignment. At the study's close, 791 (7.7%) and 943 (9.2%) cardiovascular deaths occurred in the simvastatin group and placebo group, respectively, conferring a 17% reduction in the primary endpoint ($P < .0002$). Noncardiovascular death rates were similar in the two groups (5.2% and 5.5%, respectively). All-cause mortality was reduced by 12% ($P < .001$), and cardiovascular events were reduced by 24% ($P < .00001$) (Table 2).

All subgroups benefited significantly from simvastatin therapy. Table 3 shows rates of CV events in various subgroups. The Heart Protection Study confirmed the efficacy of statin therapy among women and diabetic subjects found in prior studies. It also highlighted the benefit in older subjects and in those with low or normal low-density lipoprotein (LDL) cholesterol. In a retrospective analysis, the Cholesterol and Recurrent Events (CARE) study found no benefit in postmyocardial infarction subjects using pravastatin with baseline cholesterol < 125 mg/dL. This finding raised the question about the threshold to which statins may not confer benefit. In the much larger Heart Protection Study, however, benefit was observed in patients with LDL cholesterol below both 100 and 116 mg/dL. Simvastatin was well tolerated and was not associated with adverse hepatic effects (Table 4).

In contrast to the broad efficacy demonstrated with cholesterol lowering, antioxidant vitamin therapy was associated with no reduction in mortality or events for vitamins or placebo. These antioxidant data from the Heart Protection Study confirm the consensus of prior trials, demonstrating no benefit of antioxidant therapy on cardiovascular risk.

Very Elderly Individuals with Severe Coronary Artery Disease also Benefit from Statin Therapy

The benefits of statin therapy in older individuals was also confirmed in an observational study presented by Chloe Allen Maycock, LDS Hospital, University of Utah, which followed 7220 post–myocardial infarction (31%) or coronary artery

These antioxidant data from the Heart Protection Study confirm the consensus of prior trials, demonstrating no benefit of antioxidant therapy on cardiovascular risk.

disease (≥70% diameter stenosis) patients for a mean of 3.3 years after index hospitalization according to discharge statin use. The subjects were divided into 5 age groups, including 23% of the subjects > 75 years of age. All-cause mortality in the statin and non-statin treatments groups according to age is presented in Table 5.

As with the Heart Protection Study, this study suggests that cholesterol lowering significantly reduces cardiovascular risk, irrespective of baseline cholesterol, age, gender, and other treatments, with a low level of side effects.

AASK – African American Study of Kidney Disease and Hypertension

The African American Study of Kidney Disease and Hypertension (AASK) was designed to 1) examine the impact of two different blood pressure goals; and 2) compare the effects of treatment with angiotensin-converting enzyme inhibitor (ACE-I), β-blocker, or calcium channel antagonist on the progression of hypertensive kidney disease in African Americans. AASK is the largest drug intervention trial aimed at renal outcomes in any population, and the first clinical endpoint trial sufficiently powered to evaluate the effects of renin–angiotensin–aldosterone system inhibition in African Americans. Trial results were presented by Dr. Janice G. Douglas (Case Western Reserve University Medical School University Hospitals, Cleveland, OH).

African Americans ages 18–70 years with hypertensive renal disease, defined by glomerular filtration rate (GFR) of 20–65 mL/min per 1.73 m^2 were randomized to three treatment groups (ramipril, metoprolol, or amlodipine). Patients with diabetes mellitus, diastolic blood pressure < 95 mm Hg, or serum creatinine levels higher than 2.5 mg/dL were excluded.

Table 4
Hepatic Dysfunction and Myositis on Simvastatin Versus Placebo

	Simvastatin	Placebo	*P*
Hepatic Dysfunction (>3× ULN)	0.8%	0.6%	ns
Myositis (CK > 10× ULN)	0.09%	0.05%	ns

CK, creatine kinase; ULN, upper limit of normal.

Within each treatment arm were two target blood pressure groups: 1) normal mean arterial pressure (MAP) goal = 102–107 mm Hg; and 2) low MAP goal ≤ 92 mm Hg). Other antihypertensive agents were permitted in order to reach blood pressure goal.

The primary endpoint was rate of change in GFR. Secondary endpoints were composite reduction in GFR of >50%, end-stage renal disease, or death. Mean follow-up was 3 years in the amlodipine arm and 4 years in the other groups.

A total of 1094 patients were randomized. The mean age was 54 years. Mean systolic and diastolic BP was 150/96, with a mean GFR of 45.7. Patients had a history hypertension on average of 14 years. The presence of baseline proteinuria of a urinary protein-to-creatinine ratio (UP/C) of >0.22 or 300 mg protein per day was associated with a more rapid progression of kidney disease

Blood pressures did not differ significantly among the three randomized drug groups during follow-up. A 10 mm Hg separation of MAP was observed between the usual and low target blood pressure groups.

The ramipril group experienced a 25% reduction in GFR decline and a 22% clinical event reduction compared to metoprolol over the 4 years. In patients with baseline UP/C of >0.22, both ramipril and metoprolol reduced the risk of clinical events by 46% and 37%, respectively, compared to amlodipine. In patients with baseline UP/C < 0.22, there was no evidence of a benefit with metoprolol compared to amlodipine.

AASK demonstrated the efficacy

Table 5
All-Cause Mortality in Statin and Non-Statin Treatment Groups in the LDS Hospital Study

Age (y)	Statin	No Statin	*P*
<50	2%	7%	.35
50–59	2%	8%	.04
60–69	5%	13%	.04
70–79	7%	21%	.003
>80	9%	30%	.04

of both the ACE-I ramipril and the β-blocker metoprolol compared to amlodipine in slowing the progression of hypertensive kidney disease. This study also revealed the predictive value of baseline proteinuria in identifying patients who are at risk for more rapid deterioration of renal function. Achieving a more aggressive target for blood pressure lowering did not prevent the progression of renal dysfunction.

[Stacey B. Gross, MS, RN, CS, Norman E. Lepor, MD, FACC, FAHA, Robert A. Vogel, MD, FACC]

Echocardiography

Amongst the recent advances in echocardiography, tissue Doppler-based imaging and myocardial perfusion imaging have been of great interest. Important advances are the development of portable ultrasound devices and intracardiac ultrasound catheters that perform two-dimensional (2-D), color Doppler, and spectral Doppler imaging. Three-dimensional (3-D) imaging remains largely a research tool, until live, real-time 3-D imaging becomes available.

Hand-Held Ultrasound Devices

Several abstracts validated hand-held devices as excellent screening tools for assessment of left ventricular (LV) size, LV systolic function, and valvular regurgitation using two currently available systems: OptiGo™, (Agilent Technologies, Andover, MA)[38,39] and SonoSite (SonoSite, Inc., Bothell, WA).[40] These studies suggest that an excellent correlation was present between interpretations made by residents with minimum echocardiography training using these devices and those from a standard echo machine performed and read by an expert sonographer.

Commentary. These devices may be valuable for emergencies such as pericardial temponade, during cardiopulmonary resuscitation, and for bedside rounds by expert echocardiographers. The current limitations of these devises are lack of spectral Doppler, electrocardiogram (EKG) gating, and digital capture; they also produce somewhat inferior images. It should be understood that interpretation of these images requires at least as much training as the current standard for advanced echo training. Though better than a "stethoscope" for a physician, one needs to exercise caution in making treatment decisions based on interpretation of images from these devices by personnel with inadequate training in echocardiography.

Tissue Doppler-Based Imaging

Excellent data is obtainable from basal myocardial segments and mitral annulus with current tissue Doppler imaging (TDI). Cardiac translation motion and suboptimal angle of incidence of Doppler beam pose a problem, as does obtaining data from distal myocardial segments. Strain rate imaging overcomes these limitations, however at present it is only available in one system (GE Vingmed, Horten, Norway). New software (PowerView, Toshiba, Tokushima, Japan) now allows angle correction on TDI data.

TDI can aid in identification and quantification of LV asynchrony in patients with dilated cardiomyopathy (DCM) and congestive heart failure (CHF) by measuring the interval between Q-wave to the beginning of the systolic signal in basal myocardial segments. In 33 CHF patients biventricular pacing eliminated the difference between septal and lateral electromechanical delay as measured by DTI, thus synchronizing LV contraction, and lengthening LV filling time. In addition, mitral regurgitant jets were significantly reduced at 4 months follow-up.[41] Color kinesis (CK), a digital technology allowing real-time quantification of systo-diastolic endocardial motion, was shown to detect immediate improvement in LV filling and contraction by biventricular pacing.[42] Doppler tissue systolic velocities were more sensitive to changes in LV systolic function with biventricular pacing than conventional 2-D/Doppler-based assessment.[43] This simple assessment may also prove valuable in helping determine the optimal atrio-ventricular (A-V) delay and heart rate.

Preclinical disease detection. TDI detected early myocardial dysfunction in Golden Retriever Muscular Dystrophy, a model of dilated cardiomyopathy caused by spontaneous mutation of the dystrophin gene.[44] There was a marked decrease in endocardial velocities in mutant dogs when all other echo parameters, including LV size, fractional shortening, and LV ejection fraction were normal.

In 30 patients with familial hypertrophic cardiomyopathy and an otherwise normal echo, 13 positive for mutation but without LV hypertrophy, and in 38 gender-matched controls, Nagueh and colleagues found no significant differences in 2-D echocardiographic or mitral and pulmonary vein flow Doppler indices between the mutation-positive patients without LV hypertrophy and the controls.[45] However, both systolic and early diastolic tissue Doppler velocities were significantly lower in both groups as compared to controls ($P < .001$). Reduced tissue Doppler velocities had a sensitivity of 100% and a specificity of 93% for identifying the mutation-positive patients without LV hypertrophy.

Commentary. These studies suggest that myocardial motion detected by TDI reflects myocardial architectural

abnormality before it becomes clinically evident, potentially bringing tissue Doppler to the area of pre-clinical disease detection. TDI might provide a more practical, less expensive, and less ethically threatening tool for family members of patients with clinical diagnosis of familial hypertrophic cardiomyopathy and other genetic diseases with cardiac involvement.

Angle-corrected tissue Doppler velocities (PowerView, Toshiba) allow differentiation of cardiac hypertrophy due to hypertension from that due to cardiac amyloid. The systolic myocardial velocity profile showed characteristic serrated pattern and the peak myocardial velocity gradient was markedly decreased in cardiac amyloidosis, making TDI a clinically feasible method to characterize myocardial tissue in cardiac amyloid and differentiate it from hypertension.[46]

Newer TDI parameters of DTI velocities during isovolumic contraction and isovolumic relaxation are emerging as better measures of regional function than peak velocity during ejection during ischemia.[47] Myocardial velocity profiles and velocity gradients using angle-corrected TDI can differentiate nontransmural from transmural myocardial infarctions.

Kalra and coworkers[48] examined the relationship between tissue Doppler velocities and myocardial tumor necrosis factor α (TNFα) and inducible nitric oxide syntheses (NOS2) levels. In five patients undergoing coronary artery bypass surgery, the investigators compared TDI to intramyocardial biopsy findings. They found preserved tissue Doppler velocities in normal and mildly hypokinetic segments compared to severely dysfunctional segments. Corresponding to preserved tissue Doppler velocities, these normal and mildly hypokinetic segments also had a lower number of negative inotropic cytokines messenger RNA copies of TNFα and NOS2, with a significant inverse correlation between systolic velocities and TNFα and NOS2 (ranging from 0.63 to 0.79, $P < .05$) and between diastolic velocities and TNFα and NOS2 (ranging from 0.63 to 0.65, $P < .05$).

These findings suggest that tissue Doppler has a sound functional basis.

Commentary. These findings suggest that tissue Doppler is the functional manifestation of underlying biochemical abnormalities.

Diagnosis of restrictive cardiomyopathy. A group from the Mayo clinic extended their earlier observations of the value of tissue Doppler velocities in differentiating restrictive cardiomyopathy from constrictive pericarditis.[49] In a larger cohort of patients (n = 72) with restrictive cardiomyopathy of varying etiology, and 19 patients with surgically confirmed constrictive pericarditis, the group found that tissue Doppler velocities are preserved in patients with constrictive pericarditis and are significantly abnormal in patients with restrictive cardiomyopathy. A cut-off value of 8 cm/sec for early diastolic tissue Doppler velocity allowed separation of the two groups In a separate study, the same authors[50] reported that the discriminatory value of TDI in constrictive pericarditis is particularly evident in those patients who do not show any respiratory variation in their Doppler mitral inflow. Respiratory variation used as an echocardiographic hallmark of constrictive pericarditis was only seen in 53% of patients in this study.

This landmark study brings [tissue Doppler-based imaging] as a noninvasive tool for surveillance of post-cardiac transplant patients.

TDI in cardiac transplant surveillance. A study by Dandel and colleagues[51] was the most important clinical study validating the use of DTI in the assessment of abnormal myocardial architecture before morphologic abnormalities of myocardial rejection are evident following heart transplantation. The authors examined two groups of heart transplant recipients, one group (76 patients) underwent a noninvasive strategy to detect transplant rejection in the first post-transplant year, with endomyocardial biopsy performed only in patients suspected for rejection based on noninvasive data; the other group (22 patients) underwent noninvasive surveillance as well as routine endomyocardial biopsy screening at predefined intervals. Noninvasive surveillance included telemetric monitoring of the intramyocardial electrocardiogram (IEMG) from a dual-chamber pacemaker and echocardiograpic pulsed wave TDI recording during each clinical exam. The mean number of endomyocardial biopsies per patients was 10 times lower in the noninvasive arm than in the invasive arm. In the noninvasive arm, 21% of patients did not require any endomyocardial biopsy during the first post-transplant year, whereas 94% of endomyocardial biopsy had no therapeutic consequences in the invasive arm. The average number of rejection therapies per patient as well as the number

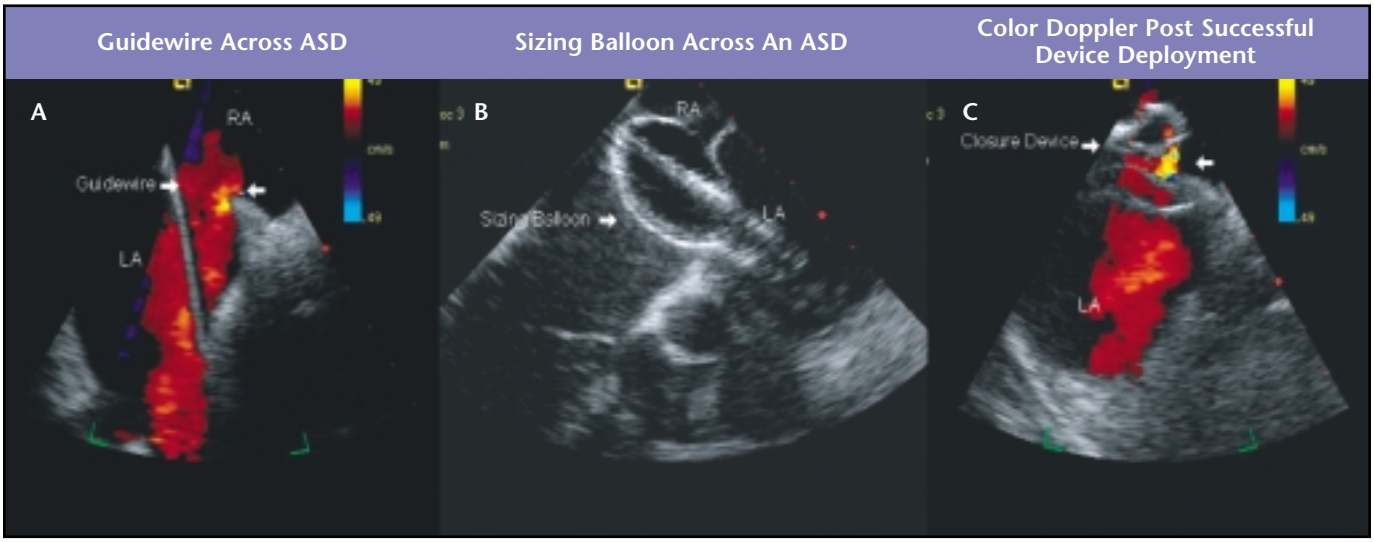


Figure 7. *Photographs of intracardiac echocardiographic images showing device closure of a large atrial septal defect (ASD), obtained by Acunav catheter (Acuson, Mountain View, CA) seated in the right atrium.* **(A)** *Left-to-right color flow across a larges secundum ASD (white arrowhead); a guide wire placed across the septal defect (white arrow).* **(B)** *A sizing balloon inflated across the ASD to measure the stretched diameter of the defect.* **(C)** *Closure device successfully deployed across the ASD, with a small residual shunt. LA, left atrium; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RA, right atrium. Image courtesy Acuson, a Siemens Company.*

of morphologically significant (International Society of Health and Lung Transplant > grade 2) rejection episodes per patient was similar in the two groups. As many as 51% of acute rejection episodes suspected on the basis of noninvasive strategy and confirmed by endomyocardial biopsy were clinically relevant and made augmented immunosuppression necessary. Rejection episodes were treated successfully, and no patient died during the study.

Commentary. Although it is difficult to separate out the value of TDI in comparison with IEMG recordings from these data, pulsed-wave TDI could reduce the frequency of routine biopsy performed in cardiac transplant patients. This landmark study suggests an important role for TDI in surveillance of patients following cardiac transplant.

Intracardiac Echocardiography

Monitoring during pulmonary vein ablation. The recently released "AcuNav" 10-French catheter from Acuson (Mountain View, CA) provides detailed anatomic images, including 2-D, color, and spectral Doppler, particularly of the pulmonary veins and atrial septum. The device is advanced through inferior vena cava (IVC) and seated in the right atrium. The device is being used during pulmonary vein ablation as well as for guiding device closures for atrial septal defect and patent foramen ovale (see Figure 7).

In a study from the Mayo clinic, Monahan and coworkers performed intracardiac echo during pulmonary vein ablation in 41 patients.[52] Overall, 78 veins were ablated (right superior, left superior, and left inferior). In 12 veins, 2-D imaging detected thickening of the orifice musculature and a significant diameter decrease (3mm to >6mm). There was a concomitant abnormality in color Doppler studies showing aliasing and pulsed-wave Doppler studies showing increase in systolic velocity of >.5 m/sec from baseline. These intracardiac echo features provided a useful feedback for eliminating further ablation.

Commentary. With wider use of pulmonary vein ablation as treatment for atrial fibrillation, intracardiac monitoring by ultrasound can help detect complications, prevent pulmonary vein stenosis, and substantially decrease fluoroscopic time. The limitation of the intracardiac echcocardiography (ICE) technique is a restricted field of vision. On the other hand, patient comfort, lack of requirement of anesthesia for TEE, and ability to perform prolonged intracardiac monitoring are advantages to the ICE technique.

The AcuNav device has the potential to assist electrophysiologists in performing electrophysiologic mapping and at the same time provide 3-D assessment of cardiac anatomy.

Derumeaux and colleagues com-

pared TDI from ICE to that obtained from epicardial echo in dogs that underwent left anterior descending artery (LAD) occlusion followed by reperfusion.[53] Both modalities showed a significant decrease in myocardial velocity gradient from epi- to endocardium with ischemia and a reversal to normal upon reperfusion. Intracardiac echocardiography might therefore be useful to monitor myocardial function during of interventional procedures or in the intensive care unit.

Rao and colleagues[54] used a new catheter system based on a 10-French sheath that carried a 64-electrode lumen probe on the outside and central ICE catheter (9 French, 9 MHz) on the inside to examine cardiac anatomy and perform electrophysiological mapping in five dogs. 3-D electrical–anatomical images were reconstructed with a spatial error of 2 mm and an activation error of 6.5 msec. The technique correctly associated right atrial anatomy with activation sequences originating from the sinus node region above the crista terminalis during sinus rhythm, from the coronary sinus ostium during coronary sinus pacing, and above the fossa ovalis during superior left atrial pacing.

Commentary. This catheter system has the potential to assist electrophysiologists in performing electrophysiologic mapping by providing 3-D assessment of cardiac anatomy. A catheter able to perform ICE as well as ablation may the next technological advancement in this area.

Myocardial Contrast Echocardiography

Post–acute myocardial infarction. Several recent abstracts suggest that myocardial contrast echocardiography (MCE) may differentiate myocardial necrosis from stunning in post–acute myocardial infarction (AMI) patients.

Senior and colleagues[55] assessed 98 patients post-AMI with dobutamine stress echo and MCE using Optison (Molecular Biosystems, San Diego, CA). Dobutamine viability was absent in 45 of the 111 segments that recovered at 6 months follow-up. Myocardial contrast was, however, present in 21 (47%) of these dobutamine nonresponsive segments, suggesting that myocardial contrast enhancement in the area of infarct may be a better predictor of functional recovery.

In another study, Main and coworkers,[56] assessed 20 acute anterior MI patients with patent LADs dobutamine stress echo as compared to MCE using Optison to differentiate stunning from necrosis. Dobutamine at low dose predicted functional recovery at 1 month with a sensitivity of 30%, whereas MCE increased sensitivity to 73%. In segments where both dobutamine and contrast were concordant, even though sensitivity was still low (56%), there was high specificity (97%), positive predictive value (77%), negative predictive value (92%), and overall accuracy (91%).

Assessment of cardiac ischemia. Rinkevich et al[57] assessed the diagnostic and prognostic value of MCE using Optison in 120 patients presenting to the emergency room with chest pain. Perfusion defects were present in 45%. All patients who were eventually confirmed to have AMI showed perfusion defects (n = 10). Perfusion defects on myocardial echo predicted cardiac death, AMI, and congestive heart failure at 5 months (46% vs 8%, $P < .001$).

Concordance of perfusion echocardiography with Gated SPECT. The current U.S. Food and Drug Adminstration (FDA)-approved contrast agents are approved only

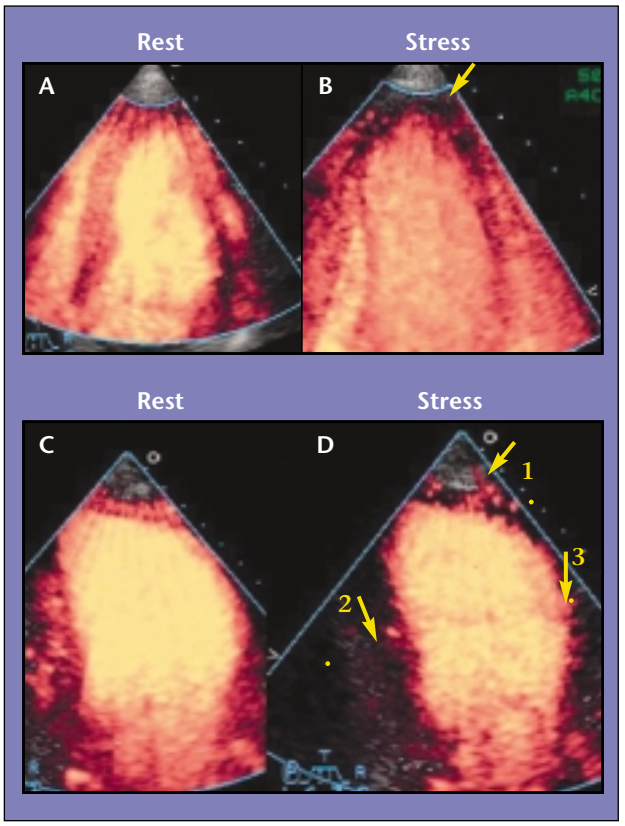


Figure 8. *Photographs of myocardial perfusion stress echocardiograms obtained during infusion of a myocardial contrast agent under investigation, PB 127 (POINT Biomedical, San Fransisco, CA) Top panel shows myocardial perfusion in the apical four chamber view before* **(A)** *and after* **(B)** *dipyridamole stress. A large reversible apical defect is evident with dipyridamole stress (yellow arrow). Bottom panel shows apical two-chamber views from another patient during PB 127 infusion, before* **(C)** *and after* **(D)** *dipyridamole stress. There is a large filling defect in apical territory (1), posterior territory (2), and anterior territory (3).*

for endocardial border detection, and no contrast bubble is yet approved for myocardial contrast assessment. Specific bubbles under development are being tested for myocardial enhancement.

Phase 2 multicenter trial results of a new myocardial contrast agent, PB 127 (nitrogen bubble with a protein outer and a polymer inner shell; POINT Biomedical, San Fransisco, CA) specifically being developed for myocardial contrast enhancement were presented.[58] In 54 patients referred for single photon emission computed tomography (SPECT) for clinical reasons, MCE was able to classify the study as normal, or abnormal in 91% of patients. When corrected for angiographic findings (performed in a subset of 15 patients), MCE showed 78% concordance with SPECT. Sensitivity of PB 127 MCE for detection of reversible defects was 94%. (Figure 8).

Commentary. These clinical studies of MCE from different centers, using different contrast agents and different ultrasound systems, suggest that perfusion echocardiography is moving closer to being used in the clinical echo labs. Capability of background subtraction within the ultrasound systems will improve qualitative assessment of myocardial perfusion. Contrast hormonics, power Doppler, dual pulse inversion, triggering during high mechanical index imaging and more recently low mechanical index real time imaging with high mechanical index flash techniques have improved assessment of myocardial perfusion. However, attenuation, scan line, lateral field, anisotropy and motion artifacts still preclude assessment in a significant minority of patients. Multicenter studies particularly in the United States in echocardiography are a welcome addition, not only in the area of contrast echocardiography but to echocardiography in general.

Assessment of graft patency intraoperatively. Myocardial contrast may be used interoperatively to assess graft failure and to predict perioperative myocardial infarction. Chen and colleagues[59] found that Optison injection into the bypass grafts in 15 patients with suspected graft occlusion after administration of protamine help detect graft occlusion. In their study, 11 of the 15 patients who had no or delayed perfusion underwent graft revision. One of 8 patients who underwent graft revision had preoperative MI versus all 3 for whom no graft revision was performed for technical reasons.

Myocardial contrast may be used interoperatively to assess graft failure and to predict perioperative myocardial infarction.

Thus, the above technique may be of value in assessing myocardial viability in specific myocardial segments intraoperatively.

Assessment of ablated regions. Khoury and colleagues examined the role of MCE in localizing and quantifying lesions created by ablation.[60] In seven dogs, MCE was performed at baseline and following radio frequency energy delivery to create 16 LV lesions, both linear and focal. Intracardiac echo was performed using a 9-French, 9-MHz, 2-D catheter (Boston Scientific Cooperation, Natick, MA). Optison contrast was infused to the left coronary artery. After ablation, MCE identified the lesions as low contrast areas within the normally opacified myocardium. The anatomical extent of ablation as detected by MCE correlated well with pathologic diameters (r = .95, $P < .001$). Thus, echocardiography delineates the extent of ablation.

Targeted microbubbles. Two abstracts from Virginia assessed the diagnostic and therapeutic potential of targeted mitral bubbles.

In the first study, Christiansen and colleagues examined the value of micro-bubbles targeted to platelet IIb-IIIa integrilin in detecting thrombi that were created in the arterioles and venules of the cremasteric muscles of mice.[61] The fluorescently labeled micro-bubbles bearing the peptide sequence recognized by IIb-IIIa platelet receptor were injected intravenously. Micro-bubbles adherence to microvascular thrombi was significantly greater for the bubbles bearing the active peptide sequence compared to control (3 ± 4 vs $.3 \pm 1$, $P < .05$). There was a close relationship between thrombus size and number of adhered micro-bubbles (r = .85).

Another abstract from the same group used a micro-bubble preparation targeted to the phosphatidylserine shell of activated leukocytes in an open chest ischemia reperfusion dog model.[62] The extent and severity of inflammation as detected by targeted microbubbles was compared to radionuclide imaging with leukocyte-targeted technetium, and to myeloperoxidase activity in post-mortem tissue. Infarct size was delineated by triphenyl tetrazolium chloride staining. The location of the region of inflammation was very similar with MCE and radionuclide imaging, although the extent of inflammation was consistently larger with MCE. The regional measurements of radio intensity in the infarct zone, the risk area, and the remote area correlated with myelo-peroxide activity (r = .64, $P < .05$).

Commentary. Detection of thrombi using ultrasound and targeted

micro-bubbles has significant clinical implications. These include detection of microvascular thrombi in acute coronary syndromes as well as implication for ultrasound-mediated thrombolysis. Detection of activated leukocytes by targeted microbubbles may not only allow detection of the extent and severity of myocardial inflammation but also extend its role to detection of inflammation at non-myocardial sites.

3-D Echocardiography

A study by Macnab et al suggested that 3-D was superior not only for complete visualization of the mitral valve but also for the accurate localization and identification of pathology, particularly of the anterior leaflet and commissures.[63] Adequate visualization was more frequently obtained with 3-D imaging (97% of segments visualized by 3-D vs 85% by TEE; $P < .001$). In this study, 3-D reconstruction was performed during routine multiplane TEE assessment prior to surgery. Even though 3-D matched more closely to the surgical findings, achieving accuracy in 89% of visualized segments, TEE proved accuracy in as many as 81% of visualized segments.

Commentary. 3-D echocardiography has thus far remained an investigational tool. The biggest limitation is the inability to obtain online 3-D data. There has been a significant shortening in the reconstruction time. Advances in technology may make live 3-D imaging feasible (work in progress, Agilent, Philips). If so, this would be an excellent modality to use intraoperatively, particularly in evaluating mitral valve anatomy both pre- and post-repair.

Echocardiography Summary

True to its promise of portability, ultrasound is now a hand-held device. This will promote its use in the intensive care setting and extend its use for early diagnosis and management, provided it is used under continued supervision. Tissue Doppler-based techniques have the potential for being used as screening tools for myocardial pre-clinical disease detection. Future refinement in bubble characteristics and imaging technology will soon bring contrast echo into clinical labs. Intracardiac echo is already being used to assist interventionists, and it has the potential to further enhance vascular imaging and decrease fluoroscopic guidance. Plaque characterization and drug delivery are other ramifications of contrast bubbles targeted to plaque components.

[Tasneem Z. Naqvi, MD, MRCP, FACC]

Dr. Naqvi would like to thank Dr. James Forrester for his comments on this review.

Nuclear Cardiology

Cardiovascular magnetic resonance imaging (MRI) is considered by many to be the ultimate frontier in noninvasive testing and cardiac imaging. Although with respect to most applications this modality is "not ready for prime time" quite yet, development of this modality continues at an accelerating pace. Investigators at the AHA 2001 Scientific Sessions presented new applications and potential applications for MRI.

Wireless Stents for MRI

Although noninvasive coronary angiography is touted as one of the major applications of MRI, a limitation of the modality was thought to be the widespread use of intracoronary stents. Because many patients with stents would be potential candidates for visualization of stent restenosis, a means to image these patients would be helpful. Busch and colleagues from Berlin, Germany[64] presented data on a wireless stent that would permit MRI assessment of inner stent volume. The investigators designed a pulse sequence that would enhance signal from inside the stent. This was achieved by designing the stent to be "tuned" to the resonance frequency of the MRI. These properties would permit assessment of stent volumes and flows, as well as construction of flow-time curves and assessment of the lumen volume proximal and distal to the stent. Importantly, the authors demonstrated no change in intra-stent temperature when imaging was being performed.

This study is a first step toward incorporating imaging potential into stent technology. If stent manufacturers can maintain stent efficacy while enabling their stents to be imaged with MRI, evaluations of stent restenosis, flow through the stent, etc, can be performed safely and noninvasively in the future.

Assessing Preservation of Wall Thickening in Non-Q wave MI: Role of MRI

Because of the remarkable resolution of cardiovascular MRI as compared to other noninvasive modalities, an immediate research application of MRI is physiological investigations of various clinical phenomenon that will "fine tune" our knowledge of cardiovascular pathophysiology. An example of this application was shown by the highly successful team of Drs. Kim and Judd, recently relocated to Duke University Medical Center.[65]

Previous work[66] performed in dogs revealed that in regions where >20% of the thickness of the myocardium was infarcted (non-Q wave MI), no systolic thickening occurs. In the current study, cine and contrast MRI was performed on 31 human subjects who had recent acute myocardial infarction in the

setting of single-vessel disease with catheterization-documented reperfusion. Cardiovascular MRI was performed 28 days post-infarct. Using a highly detailed 72-segment model (6 slices/12 segments per slice) of the left ventricle, the investigators quantitated wall thickness and transmural extent of hyperenhancement (brightening of myocardium after infusion of gadolinium, a finding validated to be a marker of infarcted myocardium).

The ability [of MRI] to accurately visualize and quantitate these small infarctions may play an important role in patient care in light of recent AHA guidelines defining acute myocardial infarction as any rise in enzymes.

The authors found that in segments in which <25% of the thickness was infarcted (192 segments), wall thickening was not different when compared to 1800 segments without any infarction. Segments with >25% of total thickness having infarction had statistically significant reductions in percent thickening. Interestingly, in patients with small transmural infarction (<3% of the total left ventricular mass), wall motion was preserved by a tethering effect (normal contracting myocardium pulling the small infarcted region inward). Thus, the ability of myocardial regions with significant infarction to maintain wall thickening post-infarction was clearly shown by these investigators—up to 25% of the thickness of the myocardial wall can be infarcted without discernable compromise of wall thickening.

In the larger scheme, the ability to accurately visualize and quantitate these small infarctions may play an important role in patient care in light of recent AHA guidelines defining acute myocardial infarction as any rise in enzymes. It appears that this modality alone can keep up with this definition of myocardial infarction by visualizing even the smallest infarctions. This study also demonstrates that MRI has the potential to fill in details of many aspects of cardiovascular pathophysiology previously described with broad brushstrokes, in this case the relationship between myocardial infarction and post-infarction wall motion.

PET and MRI for Detection of Scar

The use of gadolinium hyperenhancement as a putative marker of necrotic myocardium has gained great popularity and was the focal point of comparison in a number of other abstracts presented at this meeting. In one of these comparisons, Markus Schwaiger and colleagues from Munich[67] evaluated gadolinium hyperenhancement to fluorodeoxyglucose (FDG) uptake measured by positron emission computed tomography (PET), an accepted gold standard for viability. In this study, 31 patients with left ventricular dysfunction (mean ejection fraction 28% ± 9%) were imaged with both MRI and PET. Scar was defined as concurrently reduced perfusion and glucose metabolism by PET and gadolinium hyperenhancement 20 minutes after injection on MRI. The sensitivity and specificity of gadolinium hyperenhancement for identifying regions of scar defined by PET was 96% and 100%, respectively. When assessed on a segmental basis (1023 total segments), the sensitivity and specificity of MRI was 86% and 94%, respectively. Visually assessed defect score and estimated infarct mass for the two modalities closely agreed (r = .91, r = .81, respectively, both $P < .0001$). Importantly, wall thickening measured by MRI, an extremely accurate measure given the resolution of MRI relative to conventional modalities such as echocardiography, was found to insufficiently classify viable versus nonviable myocardium. This would suggest that for identifying scar (myocardial infarction), modalities that assess myocardial flow and viability are superior to those utilizing measures of wall thinning. More importantly, this demonstration of similar results with PET and MRI for detection of scar bodes well for future clinical applications of MRI.

[Rory Hachamovitch, MD, MSc, FACC]

Diabetes

The power of diabetes as a risk factor for cardiovascular disease is now fully appreciated.[68] The driving forces behind this new appreciation include 1) the increasing prevalence of diabetes and its earlier onset; 2) the realization that optimization of glycemic control alone may not significantly reduce cardiovascular mortality, despite dramatically reducing microvascular disease; 3) recent observational data indicating that diabetes should be considered a coronary heart disease equivalent in The National Cholesterol Education Program Adult Treatment Panel III guidelines; and 4) numerous clinical

The failure of a diabetic person to experience angina during an ischemic episode is directly related to the severity of autonomic nervous system dysfunction.

trials showing that diabetes still confers a doubling of risk for mortality after myocardial infarction and stroke. As coronary disease is often present at the time of diagnosis of diabetes, and as diabetic patients have a defective anginal warning system, a strategy of screening for coronary artery disease (CAD) in asymptomatic diabetic people has been proposed.[69]

A session at the AHA examined the issue of screening for CAD in various patients at high risk for coronary events.[70] Dr. Nesto examined this issue in diabetic patients, and Dr. Daniel Berman highlighted the added prognostic information derived from nuclear perfusion imaging over electrocardiogram (ECG) assessment alone.[71] Dr. Nesto indicated that the failure of a diabetic person to experience angina during an ischemic episode is directly related to the severity of autonomic nervous system (ANS) dysfunction. A screening algorithm has been recommended

Main Points

- Ezetimibe, a selective cholesterol absorption inhibitor, is a safe and effective new therapeutic option for cholesterol reduction.
- The REMATCH Trial showed an improved survival of left ventricular assist device (HeartMate) among patients with refractory heart failure compared to medical therapy, at the cost of substantial device-related complications.
- The β-blocker carvedilol markedly reduced mortality as well as frequency and severity of hospitalizations in patients with severe heart failure.
- After 6 months of treatment, cardiac resynchronization therapy resulted in improved clinical status, 6-minute walking distance, and left ventricular ejection fraction in patients with severe congestive heart failure.
- Use of tezosentan was not effective in acute decompensated heart failure patients with acute coronary syndromes and was associated with worsening heart failure, renal impairment, and nausea, probably linked to increased systemic hypotension.
- The risk of death and myocardial infarction in patients with renal insufficiency presenting with acute coronary syndromes is increased by nearly three-fold compared to patients with normal renal function.
- Peripheral arterial disease (PAD) is under-recognized in at-risk patients in clinical practice, owing to lack of screening intensity. Compared to patients with coronary artery disease, there seems to be less utilization of antiplatelet and lipid-lowering therapies in patients with PAD.
- Antiplatelet therapy with clopidogrel prevents adverse cardiovascular events in patients with PAD; mixed results have been reported with prostaglandins and therapeutic angiogenesis.
- Therapeutic angiogenisis with intra-arterial administration of fibroblast growth factor-2 was shown to improve symptoms in patients with severe claudication.
- Gene thereapy studies–of vascular endothelial growth factor-2 (VEGF-2) gene transfer to improve myocardial function and of E2F decoy to prevent intimal hyperplasia of saphenous vein coronary artery bypass grafts–confirm that gene therapy does have a role in the treatment of cardiovascular disease and that most of the concerns about safety appear to be unfounded.
- The Canadian Antioxidant Restenosis Trial concluded that the vascular protectant AGI-1067 and the antioxidant probucol reduce restenosis following coronary intervention.
- The Heart Protection Study confirmed the benefit of statin therapy in reducing cardiovascular mortality and event rate in patients with documented atherosclerotic disease and those at high risk for coronary heart disease who have low or normal cholesterol levels. No benefit was seen with the use of antioxidants.
- The African American Study of Kidney Disease and Hypertension demonstrated the superiority of both the ACE inhibitor ramipril and the β-blocker metoprolol compared to the calcium channel antagonist, amlodipine, in slowing the progression of hypertensive kidney disease.
- Myocardial motion detected by tissue Doppler-based imaging (TDI) reflects myocardial architectural abnormality before it becomes clinically evident and suggest the potential utility of TDI in the area of pre-clinical disease detection, such as heart transplant rejection surveillance.
- Myocardial contrast echocardiography may be useful to differentiate myocardial necrosis from stunning in post–acute myocardial infarction patients.
- Data was presented on a wireless stent that would permit MRI assessment of stent restenosis; MRI discerned that in regions with non-Q wave MI up to 25% of wall thickness, wall thickening is preserved; and MRI and PET were found to have similarly high sensitivity and specificity in differentiating scarred or nonviable myocardium.

for these patients by the American College of Cardiology/American Diabetes Association,[69] but the results of such screening on a widespread basis are not known. In "low-risk" patients (no proteinuria, no history of vascular disease, no ANS dysfunction), the detection rate for asymptomatic ischemia is approximately 10%, and in "high-risk" diabetics, the yield may rise to 25% or greater. Dr. Berman indicated that the use of summed segment scoring of either reversible and/or fixed defects can separate patients into defined risk categories. Rather than deeming a test positive or negative, this method of risk quantification is particularly useful when making decisions in asymptomatic subjects. It was debated whether a stress perfusion study negative for CAD carried the same prognostic information in a diabetic compared to a nondiabetic individual. Dr. Nesto suggested that the biology of CAD was sufficiently different in these patients and that "surveillance" testing for CAD should be performed every 2 years. Further invasive studies, such as coronary angiography with its own inherent risks, can then be used more appropriately in the high-risk group.

Studies are needed to accurately depict the yield of screening for CAD in the presence of diabetes across the spectrum of background coronary risk factors and diabetes-related complications. Is it valuable to screen *all* diabetic individuals for CAD, or should screening with its inherent sensitivity and specificity concerns regardless of the technique used be reserved for the higher-risk groups? Such questions will be answered as studies now underway examine this issue. ■

[Richard W. Nesto, MD, FACC]

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