Best of the ACC Scientific Session 2001

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Results from the CAPRICORN, MIRACLE, CURE, MASS II, and BETA-CATH trials were presented at the American College of Cardiology's 50th Annual Scientific Session in Orlando, Florida. Here, the Contributing Editors of *Reviews in Cardiovascular Medicine* discuss these and other trials, as well as other important presentations from this year's meeting.

Heart Failure

Carvedilol reduces mortality after acute myocardial infarction accompanied by left ventricular dysfunction. β-Blockers have been shown to reduce mortality in patients with acute myocardial infarction. The previous trials showing benefit from β-blockers in the post-myocardial infarction (MI) setting were done prior to routine use of reperfusion therapy and angiotensin-converting enzyme (ACE) inhibitors. These trials also generally excluded patients with heart failure. Although the ACC/American Heart Association (AHA) guidelines advise physicians to start β-blockers in high-risk post-MI patients, including those with left ventricular dysfunction, many of these patients do not receive β-blocker treatment due to physician reluctance.

The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial set out to examine the effects of carvedilol in patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] < 40%) after acute MI, with or without clinical heart failure.

Carvedilol is a β-blocker with α-blocking properties that has previously been shown to reduce mortality in patients with mild, moderate, and severe heart failure. CAPRICORN randomized 1959 patients from 163 centers in 17 countries to treatment with carvedilol or placebo. Three to 21 days after MI, patients, who were treated with an ACE inhibitor for >48 hours, were randomized to carvedilol (6.25 mg b.i.d. starting dose titrated to a target dose of 25 mg b.i.d.) versus placebo. The mean patient age was 63 years, and the mean LVEF was 32.7%. The original primary endpoint of the CAPRICORN trial was all-cause mortality. Secondary endpoints included all-cause mortality or cardiovascular hospitalization, sudden death, and hospitalization for heart failure.

The trial results were presented by Dr. Henry J. Dargie (University of Glasgow). All-cause mortality was reduced from 15% with placebo to

12% with carvedilol (odds ratio [OR] 0.77; 95% confidence interval [CI] 0.60–0.98; $P = .03$). The composite endpoint of all-cause mortality or cardiovascular hospitalization did not reach statistical significance (37% vs 35%; OR 0.92; 95% CI 0.80–1.07; $P = .30$). Nonfatal MI was reduced by 41% ($P = .014$). Carvedilol was well tolerated, with serious adverse effects more frequent with placebo. The addition of the β-blocker carvedilol to post-MI patients with left ventricular dysfunction (with or without symptomatic heart failure) already treated with an ACE inhibitor reduces mortality, as well as the risk of nonfatal MI. The number needed to treat (NNT) is 43 patients treated for 1 year to prevent 1 death, which is similar to the NNT for ACE inhibitors for post-MI patients with left ventricular dysfunction.

These data strongly suggest that the benefit of carvedilol should be extended to high-risk patients with MI who have left ventricular dysfunction. The combination of ACE inhibitors and β-blockers should be the standard of care for all acute MI patients without contraindications or documented intolerance.

Cardiac resynchronization therapy improves clinical status in heart failure. Patients with heart failure and intraventricular conduction delays are at increased risk for heart failure progression. It has been hypothesized that the loss of synchronization between right and left ventricular contraction (desynchronization) contributes to the pathophysiology of heart failure progression. Biventricular pacing (resynchronization) therapy is being evaluated as a potential heart failure treatment. This involves placement of an additional coronary sinus pacing lead for left ventricular pacing along with standard atrial and right ventricular lead placement.

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial is 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 Medtronic (Minneapolis, MN) InSync® pacing device. In this study 266 patients with class III and IV heart failure, QRS duration ≥ 130 ms, and LVEF < 35% had a Medtronic InSync device placed. Patients were treated with standard heart failure medications. After successful implant (93%), the patients were then randomized to device on (n = 125) or device off (n = 119) for the next 6 months. The physicians performing the heart failure assessments were blinded to the device on/off status.

It has been hypothesized that the loss of synchronization between right and left ventricular contraction (desynchronization) contributes to the pathophysiology of heart failure progression.

The study results were presented by Dr. William T. Abraham (University of Kentucky). The mean age of the patients was 65 years, 90% were class III, the mean LVEF was 22 ± 6%, and left ventricular end-diastolic dimension (LVEDD) was 69.5 ± 9 mm. At baseline, the mean heart rate was 76, with blood pressure 115/69, and QRS duration of 165 ± 19 ms. The study's primary endpoints were improvement in quality of life, as assessed by the Minnesota Living with Heart Failure Questionnaire, improvement in New York Heart Association (NYHA) functional class, and improvement in exercise capacity as evidenced by an increase in a 6-minute walk distance of 50 m or more.

The study results showed that a statistically significant proportion of patients in the treatment group responded positively to CRT compared with the control group, with improvements noted in all of the study's primary efficacy endpoints. Although there was a significant placebo effect on the quality of life score, the treatment effect far exceeded it and reached statistical significance from baseline in the CRT group. The average improvement in quality of life score in the CRT group was 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 test was unchanged in control patients but increased by 39 m on average in CRT patients ($P < .01$). In addition, LVEF improved by 6 units, and LVEDD decreased by 0.5 mm in CRT patients compared with no change in no-CRT patients. Although the trial was not powered for clinical events, mortality was similar, with 10 deaths in the controls and 8 deaths in the CRT patients over 6 months. This study demonstrates that cardiac resynchronization therapy improves functional status and quality of life in patients with heart failure. There also appears to be evidence for improved ventricular structure and function. This promising device therapy that may open up a new era for heart failure management should be further evaluated.

Oral endothelin antagonist worsens clinical status in chronic heart failure. Plasma endothelin-1

(ET-1) levels are elevated in heart failure patients, correlating with disease severity and associated with poor prognosis. Endothelin receptor antagonists have been developed to block this neurohumoral system. Enrasentan is an orally active mixed ET-A and ET-B receptor antagonist. The Enrasentan Cooperative Randomized Evaluation (ENCOR) was designed as a randomized, double-blind, dose-ranging study to assess the efficacy, tolerability, and safety of enrasentan in patients with chronic NYHA class II and III heart failure. The trial randomized 419 patients on standard background therapy to receive one of six treatment regimens: four different doses of enrasentan, high-dose ACE inhibition, or placebo. Daily oral doses of enrasentan ranged from 30 to 90 mg. There was a 12-week titration phase followed by a 6-month treatment period. The primary endpoint was a clinical heart failure composite of improved NYHA class or global assessment.

The results were also reported by Dr. William T. Abraham (University of Kentucky). The mean age of patients in the trial was 65 years, 60% had an ischemic etiology to their heart failure, and 78% were male. The mean LVEF was 0.25. In an analysis pooling the enrasentan dosing groups together, clinical status tended to worsen with erasentan. Withdrawals due to adverse effects increased from 8.3% with placebo to 21.2% with enrasentan. Mortality also tended to be higher in the enrasentan-treated patients. The survival free from death, heart failure hospitalization, or withdrawal due to worsened heart failure was decreased from 92.5% with placebo or high-dose ACE inhibitor to 75% with enrasentan by 250 days of follow-up (P = .007). In patients with class II or III heart failure, the addition of the oral mixed endothelin receptor antagonist to standard therapy did not improve clinical status, was not well tolerated, and appeared to worsen clinical outcomes. Although other trials are ongoing, the lack of benefit of enrasentan in this patient population raises concerns regarding the utility of endothelin antagonists in the management of chronic heart failure. [Gregg C. Fonarow, MD]

There was general agreement on the value of sophisticated mapping systems to locate the circuit or focus for atrial tachycardias.

Electrophysiology

Sophisticated mapping systems for the electrophysiology laboratory: When are they needed? In the "old" days, catheter mapping in the electrophysiology laboratory to identify the origin or a critical component of a tachycardia circuit (eg, an accessory pathway) involved using multiple catheters positioned at various portions of the heart. During tachycardia these catheters were sequentially repositioned, if necessary, to accomplish the mapping goal. Increased knowledge of arrhythmia mechanisms and technological improvements in radiofrequency catheter ablation systems have enabled the clinical electrophysiologist to ablate successfully multiple varieties of both supraventricular and ventricular tachycardia. In some instances (eg, atrioventricular [AV] node reentry), sophisticated mapping systems appear to add little to the current mapping approach. On the other hand, arrhythmias such as atrial tachycardia and atrial fibrillation are prime candidates for the use of sophisticated mapping systems to reduce procedure time and to enhance success rates.

A symposium was held at the ACC meeting to discuss issues related to complex mapping systems. Participants included Eric N. Prystowsky, MD, John Miller, MD, Bruce Lindsay, MD, Greg Feld, MD, and Wyn Davies, MD. The speakers demonstrated examples of a variety of arrhythmias in which sophisticated mapping systems have been used, and a discussion took place regarding the need for these systems. In general, advanced mapping systems are of two types: One employs an electroanatomical approach, in which the mapping catheter is sequentially moved to different parts of the heart to generate a computerized map; alternatively, systems are available that use non-contact mapping with a multipolar electrode array in the heart that can locate a sequence of activation even from a single heart beat. These systems have advantages and disadvantages, depending on the arrhythmia under study.

There was general agreement on the value of sophisticated mapping systems to locate the circuit or focus for atrial tachycardias. These systems are particularly useful in patients with corrected congenital heart disease who have atrial arrhythmias. Although many electrophysiologists use an electroanatomical mapping system in the ablation of atrial flutter, the consensus was that in most cases a sophisticated mapping system is not necessary for successful ablation of this arrhythmia. On the other hand, in complicated cases or in previously failed attempts to ablate atrial flutter, several speakers thought that these mapping sys-

tems were helpful. Sophisticated mapping systems are not needed as a general rule to map AV node reentry. There was lively discussion on the usefulness of mapping systems in patients undergoing ablation for ventricular tachycardia. Some felt these systems were particularly useful for ablation of right ventricular outflow tract tachycardia but marginally helpful to ablate ischemic ventricular tachycardia. Regarding ablation of atrial fibrillation, one or more of these mapping systems may prove very useful in the future, but few data are available at present.

To summarize, sophisticated mapping systems will likely be standard equipment in most electrophysiology laboratories in the future, but their greatest present application appears to be mapping of atrial tachyarrhythmias.

Biventricular pacing for congestive heart failure. There have been increasing data and growing excitement in the application of biventricular pacing to treat congestive heart failure. Previous studies have demonstrated the feasibility of pacing the left ventricle using an epicardial electrode introduced through the coronary sinus system. A second ventricular pacemaker is introduced into the right ventricular apex, and the ventricles are paced simultaneously in an effort to produce cardiac resynchronization therapy. This form of pacing has been applied to patients with wide QRS complexes in sinus rhythm, and preliminary data have demonstrated improvement in congestive heart failure symptoms.

At the ACC meeting, the results from the MIRACLE trial were reported. This was a large, prospective, randomized, double-blind, clinical trial of resynchronization therapy in patients with congestive heart failure. The sponsor of the trial was Medtronic, Inc. Inclusion criteria were NYHA Class III or IV for heart failure, QRS duration ≥ 130 msec, LVEF ≤ 35%, left ventricular end diastolic dimension ≥ 55 mm, and optimal stable drug regimen for 1 to 3 months prior to entry into the study. Following implantation of the leads and device, randomization to resynchronization therapy (n = 125) or no resynchronization therapy (n = 119) was accomplished for a period of 6 months. The mean age was 64 years, and mean LVEF was 22%.

Sixty-nine percent of patients with resynchronization therapy had an improvement in at least one New York Heart Association Class, compared with 34% without resynchronization therapy.

The outcomes of the study were very impressive: 69% of patients with resynchronization therapy had an improvement in at least one NYHA Class, compared with 34% without resynchronization therapy. There was also significant improvement with resynchronization therapy in the 6-minute hall walk distance of 55 meters or more. Finally, the quality of life indices were improved with resynchronization therapy.

This study from Medtronic supports and extends the pioneering results from Guidant and further studies from ELA Medical on the use of cardiac resynchronization therapy to improve congestive heart failure symptoms. This form of therapy will likely be added to the multiple-drug armamentarium that already exists to reduce symptoms in patients with congestive heart failure. The larger question regarding improved survival remains to be determined, and prospective randomized trials evaluating this issue are in progress.

Atrial pacing in the treatment of patients with atrial fibrillation. Cardiac pacing has played an integral role in the therapy of patients with atrial fibrillation for several decades. In its simplest form, it is used to support heart rate in patients with tachycardia–bradycardia syndrome. Some patients receive atrial-based pacemakers to prevent bradycardia-initiation of atrial fibrillation, but the value of this form of therapy in a particular patient is often unclear. When pacing is necessary in a patient who has atrial fibrillation, recent data suggest atrial or dual-chamber pacing to be the mode of choice. For several years there has been increasing interest in a variety of pacing techniques to prevent atrial fibrillation. These techniques have included bi-atrial pacing, multisite atrial pacing, right atrial pacing near Bachmann's bundle, and incorporation of unique pacing algorithms in otherwise standard pacemakers.

The results of the Dual-Site Atrial Pacing for Prevention of Atrial Fibrillation (DAPPAF) trial were presented by Dr. Sanjeev Saksena. In this trial, two leads were positioned in the right atrium, one in the high right atrium and the other in the ostium of the coronary sinus. A variety of pacing methods were compared, including overdrive high right atrial pacing, support pacing for patients with atrial fibrillation and bradyarrhythmias, and overdrive dual-site right atrial pacing. Of 120 patients enrolled, 118 received a pacemaker and lead implantation. The follow-up was for an average of 1 year. There appeared to be some advantage to dual-site pacing. The investigators suggested that a

prominent role for dual-site right atrial pacing may be in synergy with drug therapy. In other words, patients receiving minimal benefit from certain antiarrhythmic drugs might do much better with drugs plus dual-site pacing.

This study is one of many evaluating the role of pacing to prevent atrial fibrillation. Overall, the results from a variety of studies have been quite mixed, and it appears too early to suggest that any particular form of pacing therapy is warranted for general use to prevent atrial fibrillation. Although the results from DAPPAF are promising for a subgroup of patients, the broad application of this concept still remains to be tested.

[Eric N. Prystowsky, MD]

[Note: Dr. Prystowsky serves as a consultant for Guidant Corporation.]

Dyslipidemia

The ACC sessions were rich in oral and poster presentations in the field of heart disease prevention. A very concise review of these abstracts, mostly dealing with important issues in dyslipidemia, will be presented here.

1. Stein et al[1]: Rosuvastatin (ZD4522) was evaluated in a series of abstracts. In patients with heterozygous familial hypercholesterolemia, rosuvastatin was found to be superior to "usual care," consisting of high-dose statin and combination therapy, in some patients by decreasing TC and LDL-C and triglycerides by an additional 23%, 18%, and 9%, respectively, and was well tolerated.
2. Paoletti et al[2]: Rosuvastatin, 5 and 10 mg/day, was found to reduce LDL-C by 42% and 49%, respectively, with a 6% and 7% increase in HDL-C in patients with LDL-C levels > 160 mg/dL. This compared to a 28% reduction of LDL-C with pravastatin 20 mg/day and 37% reduction with simvastatin 20 mg/day.
3. Stein et al[3]: Rosuvastatin in a forced titration model of 20/40/80 mg/day was superior to a similar forced titration with atorvastatin in patients with heterozygous familial hyperlipidemia. A greater reduction of LDL-C was attained with rosuvastatin (58% vs 50%) and greater elevation of HDL-C (12% vs 3%).
4. Kosoglou et al[4]: Ezetimibe (SCH 58235) is a new selective cholesterol absorption inhibitor that was found to be safely administrated with 10 mg atorvastatin and when coadministered produced a greater reduction of LDL-C in healthy hypercholesterolemics. Ezetimibe reduced LDL-C by 23%, atorvastatin by 40%, and coadministration by 56%.
5. Matalka et al[5]: Alternative-day dosing of atorvastatin (Lipitor) was found to be effective in reducing LDL-C in patients who met NCEP guidelines for therapy in the ADDAS trial, which compared alternate-day dosing to daily dosing. A similar reduction in LDL-C was attained using this dosing schedule, which suggests that alternate-day dosing may be as effective a treatment and may provide cost savings relative to the daily dosing regimen.
6. Grundy et al[6]: Long-acting niacin (Niaspan) was evaluated in patients with type 2 diabetes to determine whether it exacerbates glycemic control. Of these patients, 50% were already on statin therapy. There was no significant change in HbA1c levels from baseline at the 1.0 g dose of the long-acting niacin with a 20% increase of HDL-C and no difference in LDL-C. At 1.5 g/day niacin, there was a small increase of HbA1c (7.21 to 7.48) with a 24% increase in HDL-C, 8% decrease in LDL-C, and 29% reduction in triglyceride levels. Low doses of extended-release niacin appear to have positively modified lipid profiles without adversely affecting glycemic control.
7. Morse et al[7]: The HDL Atherosclerosis Treatment Study (HATS) studied the ability of combination niacin, 2 to 4 g/day and simvastatin (Zocor), 10 to 20 mg/day, to protect against atherosclerosis progression, compared to placebo. The study included 160 patients with low HDL-C and either impaired glucose tolerance or diabetes mellitus. There was a decrease in the angiographic progression of atherosclerosis by quantitative coronary angiography and coronary events in the group receiving combination therapy, without a significant worsening of glycemic control.
8. Backes et al[8]: A comparison of lipid profiles of hypertriglyceridemic patients receiving gemfibrozil or fenofibrate (Tricor) in a crossover design revealed greater reduction of total cholesterol (TC), triglycerides, and TC/HDL with fenofibrate. There was no differential LDL-C effect between these two fibric acid derivatives.[1]
9. Isaacsohn et al[9]: Simvastatin was found to lower the levels of C-reactive protein in hyperlipidemic patients. This effect was seen at the 40 mg and 80 mg/day doses but not at the 20 mg/day dose.
10. Koh et al[10]: Simvastatin, when administered in doses of 20 to 40 mg/day in 16 patients with established coronary disease,

resulted in lowered levels of metalloproteinase-9 (MMP-9) and increase in nitric oxide bioactivity. MMP-9 plays an important role in plaque destabilization.

11. Matar et al[11]: DRACULA Trial evaluated the effect of 1 year of pravastatin (Pravachol) therapy on coronary plaque regression by intravascular ultrasound. With LDL-cholesterol (LDL-C) levels dropping from 148 mg/dL to 86 mg/dL, there was a very small increase in plaque mass, with most of the increase due to conversion of the soft fatty plaque mass to the more stable fibrocalcific plaque mass.
12. Ford et al[12]: The West of Scotland Coronary Prevention Study (WOSCOPS) three-year poststudy follow-up followed patients past the randomized period and found a persistent reduction of cardiac events. A 27% reduction in cardiovascular death was seen in these patients with elevated cholesterol and no previous history of coronary artery disease treated with pravastatin.
13. Colquhoun et al[13]: Pravastatin reduced major coronary events in patients with low levels of LDL-C and HDL-C. This subset of the LIPID study (patients with coronary artery disease and hyperlipidemia) included patients who would have met the inclusion criteria for the VA-HIT study, which evaluated the efficacy of gemfibrozil in a similar setting. These inclusion criteria were a HDL-C < 40 mg/dL, LDL < 140 mg/dL, and triglycerides < 300 mg/dL. At the 5-year end point, pravastatin reduced coronary events by 24%, compared to the similar 22% reduction with gemfibrozil seen in VA-HIT.
14. Hague et al[14]: The LIPID study found a reduction in coronary heart disease–related deaths of 31% versus 23% in women treated with 6 years of pravastatin treatment compared to placebo. Similar results were seen in men with a CHD death rate reduced to 9.2% from 11.6% in men. This study provides the largest experience on the effects of lipid reduction in women with coronary artery disease.
15. Burke et al[15]: The coronary artery plaques of 66 nondiabetic men and women dying of severe coronary artery disease were compared with 66 age- and sex-matched diabetic patients. Plaque burden was greater in the diabetic patients than in nondiabetics, as were the greater lipid core areas. Plaque burden was greater in insulin-dependent diabetics than in their non-insulin-dependent counterparts.
16. Osende et al[16]: The hypercoagulable state of type 2 diabetes mellitus was found to be strongly influenced by the level of glycemic control. Using an ex vivo Badimon perfusion chamber, the amount of thrombus formed was reduced when triglitazone was added to chronic regimens in poorly controlled diabetic patients to achieve glycemic control.

[Norman E. Lepor, MD]

The CURE Trial

The management (in particular, the optimal antithrombotic strategies) of the non-ST-segment elevation acute coronary syndromes has been a focus of continued investigation and some controversy for almost two decades. From the earlier studies of aspirin in unstable angina, followed by aspirin and heparin, clinical trials have evaluated a variety of compounds, including thrombolytic agents, thienopyridines, the IIb/IIIa platelet glycoprotein inhibitors, low-molecular-weight heparins, and the direct antithrombins. To some extent, initial reaction to the results of these trials reflects a spectrum of emotions ranging from elation to disillusionment, followed by a more realistic appreciation of the risks and benefits of these agents. This is a dynamic area of investigation that remains in a state of flux, but the (Clopidogrel in Unstable Angina to Prevent Recurrent Events) CURE trial, discussed by Dr. S. Yusuf at the Annual Scientific Sessions of the American College of Cardiology, is a major development in the field. Moreover, this trial is a classic example of a hypothesis-driven trial providing answers that in turn generate new questions. I am not sure who is responsible for the saying, "just when I found out the answers to life's questions they changed the questions," but perhaps this is an apt reflection of the impact the CURE trial will have on the field.

The CURE trial randomized 12,562 patients from 28 countries with non-ST-segment elevation acute coronary syndromes to clopidogrel 300 mg on day 1 followed by 75 mg per day with 75 to 325 mg aspirin per day, or placebo in addition to aspirin for 3 to 12 months (a mean of 9 months. Patients were eligible if they had been hospitalized within 24 hours of the onset of symptoms, indicative of an acute coronary syndrome, and did not have significant ST-segment elevation. The primary composite outcome was cardiovascular death, MI, and stroke, and the coprimary outcome was defined by the addition of refractory in-hospital ischemia.

The results are quite positive. The composite endpoint occurred in 11.4% of the placebo cohort and in 9.28% of the clopidogrel-treated patients (relative risk 0.79, 95% confidence intervals, 0.71–0.88, $P = .00004$). Evaluating the endpoints singularly, there was a significant 23% reduction of MI with trends towards reductions of cardiovascular death and stroke. The coprimary endpoint (with refractory ischemia added to cardiovascular death, MI, recurrent infarction, and stroke) occurred in 1201 (19.1%) of placebo patients and 1041 (16.6%) of clopidogrel patients (relative risk 0.86, 95% CI, 0.79–0.93, $P = < .00003$). This was accompanied by an excess of major bleeds (relative risk 1.36, $P = < .002$) but no significant excess in life-threatening or intracranial bleeds. The benefits of clopidogrel accrued within the first day of therapy, with a 20% relative reduction of the composite endpoint of death, MI, and stroke.

A strength of this trial was that the benefits were observed essentially across all subgroups, including smokers, diabetics, and patients with prior MI, prior percutaneous transluminal coronary angioplasty (PTCA), or prior coronary bypass surgery; the effect appeared to be similar in men and women and in patients above and below the age of 65. A further strength of this trial is that the benefits were obtained despite the fact that approximately 25% of patients subsequently underwent angiography, many of whom received interventions and in whom the code was broken and clopidogrel was started. This would have had a diluting effect on the major outcomes of the trial, but despite this, the trial is positive.

The implications of the CURE trial for the management of non-ST-segment elevation acute coronary syndromes are quite profound. It is possible that clopidogrel will become part of a new standard of care together with aspirin and unfractionated or low-molecular-weight heparin and β-blockers, and in many patients this will be followed by early coronary angiography. This is also the first trial that confirms the longer-term efficacy of this agent in patients presenting with acute coronary syndromes, which would extend its use past the usual 2 to 4 weeks following coronary stent implantation.

It is possible that clopidogrel will become part of a new standard of care together with aspirin and unfractionated or low-molecular-weight heparin and beta blockers.

This is also the first trial that confirms the longer-term efficacy of the combination of clopidogrel and aspirin in patients presenting with *acute* coronary syndromes. This complements the findings of the (The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) CAPRIE trial, which showed the superiority of long-term use of clopidogrel over aspirin in reducing the endpoints of MI, stroke, or vascular death in patients with preexisting vascular disease. The financial implications will need to be addressed, but at a cost of approximately $3 a day and over $1,000 a year, the economic implications of clopidogrel as standard therapy are substantial.

In regard to the use of IIb/IIIa inhibitors, the impact of this trial may be quite significant. The use of intravenous platelet IIb/IIIa inhibitors will continue in patients undergoing percutaneous coronary intervention (PCI), for which the data are rich and consistent. In patients who do not undergo angiography, the use of IIb/IIIa inhibitors is not supported by the results of recent trials. In the event that a decision has been made to perform coronary angiography, it is clearly reasonable to start the IIb/IIIa inhibitor based upon the likelihood that PCI will be performed at the time of angiography. Of interest would be the subset analyses from CURE of patients receiving intravenous IIb/IIIa inhibitors versus those who did not and of the approximately 25% of patients who underwent angiography and coronary revascularization.

The CURE results have changed the landscape upon which new trials of adjunctive, antithrombotic treatments in the acute coronary syndromes will take place. This may apply particularly to proposed trials of the direct antithrombins, IIb/IIIa platelet inhibitors, and perhaps the low-molecular-weight heparins and pentasaccharides. The results of CURE nonetheless apply to those high-risk patients with non-ST-segment elevation acute coronary syndromes, but not to patients who receive aspirin for the primary prevention of coronary disease. Clopidogrel and aspirin use produced significant increased major bleeding risks over aspirin alone. In lower-risk patients who may need aspirin for primary prevention, the addition of clopidogrel cannot be justified. The results of ongoing trials of clopidogrel in patients with cerebrovascular disease, ST-segment elevation MI, and

congestive heart failure, and in patients receiving stents will now be awaited with increased anticipation. [Bernard J. Gersh, MB]

[Note: Dr. Gersh is a member of the Steering Committee of the CURE Trial.]

Coronary Angioplasty Versus Surgery in Multivessel Disease: Long-Term Follow-Up

The three classic angioplasty versus surgery trials performed in the late 1980s and early 1990s have now entered the 10-year follow-up period. These trials in general excluded patients with recent MI, left main disease, and previous PTCA or coronary artery bypass graft surgery (CABG). Thus, the patients studied represent a selected lower risk population.

The Emory Angioplasty Versus Surgery Trial (EAST), the Bypass Angioplasty Revascularization Investigation (BARI), and the Coronary Angioplasty Versus Bypass Revascularization Investigation (CABRI) trials were designed to address the issue of whether patients with multivessel disease were better served by balloon angioplasty compared with bypass surgery. Patients were randomized into either treatment, with the goal being complete revascularization. These three trials were completed before the widespread use of coronary stents and intravenous platelet inhibitors. No significant differences were seen in the rates of death, nonfatal MI, or other variables such as quality of life indices between the patients randomized to PTCA versus CABG.

Long-term follow-up in the BARI trial shows no significant survival difference (PTCA vs CABG: 70% vs 74%) The only significant difference was a predictably higher rate of revascularization in the PTCA group, most of which occurred in the first 2 years; half of these were repeat PTCA and half were CABG. In the CABRI trial, repeat revascularization occurred in 30% of patients treated with PTCA and in 2% of patients treated with CABG at 1 year. In the EAST trial, the repeat revascularization rate was 60% in the PTCA group versus 20% in the CABG group at 8 to 10 years.

In the BARI study, diabetic patients did worse overall, with a survival rate of 57% versus 44% compared with nondiabetics. Of the patients in the PTCA group, 70% required repeat revascularization during the long-term follow-up period. The 5-year mortality was 34.5% in patients randomized to PTCA versus 19.4% in patients randomized to CABG.

Of interest is the lack of a mortality difference in the BARI trial registry between the PTCA and CABG groups. The mortality rates were not significantly different in nondiabetics randomized to the two different groups. Similar trends were also noted in the CABRI and EAST trials. The higher incidence of events in the PTCA cohort relates to the higher incidence of clinically symptomatic new lesions in vessels that were not treated with PTCA initially. The superior revascularization outcomes of CABG over PTCA may be related to the lesion-specific treatment nature of PTCA and the vessel-specific nature of CABG.

With the advent of stents, the above trials are clearly outdated and do not provide the clinician with current data for clinical decisions. The National Heart, Lung, and Blood Institute (NHLBI) Dynamic PTCA Registry has shown that the repeat revascularization rate is about 19% using the current generation of coronary stents. Clearly, stent implantation reduces repeat revascularization in patients undergoing multivessel intervention compared with PTCA.

The Coronary-Artery Bypass Surgery And Stenting For The Treatment Of Multivessel Disease (ARTS) and the Stent or Surgery (SOS) trials, performed in Europe and South America, respectively, have shed some modern light onto the stent versus surgery debate. The ARTS trial randomized 1200 patients into CABG or multivessel stent implantation. The death and cumulative death/cerebrovascular accident (CVA)/MI rates were not different between the two groups. However, the repeat revascularization rate was 14% higher in the stent group (26.5% vs 12.2%). In diabetic patients, the absolute death rate was 2% to 3% higher in the stent group, but a difference of only 1.5% is seen if MIs and CVAs are included. The rate of repeat revascularizations was increased by 26% in the group undergoing stent implantation. No glycoprotein IIb/IIIa inhibitors were used in the stent group.

Clearly, stent implantation reduces repeat revascularization in patients undergoing multivessel intervention compared with PTCA.

The SOS trial randomized 1000 patients into the two arms, stent or surgery. The two arms had equivalent death/nonfatal MI rates over a 2-year follow-up period. The death rates for stent versus surgery were 4.1% versus 1.2%, with a surprisingly low surgical in-hospital complication rate of 0.8%. The repeat revascularization rate for stent versus surgery was 20% versus 6%. Again, IIb/IIIa platelet inhibitors were not commonly used.

No diabetes subgroup analysis was available for this study.

What do these trials tell us? We learn that:

1. Diabetic patients with multivessel disease are at a higher risk for complications whether they are treated with CABG or stent implantation;
2. Nondiabetic patients can be treated using either strategy, with the penalty of an increased rate of revascularization in the stent group (Δ = 15% to 20%);
3. Aggressive medical therapy and risk factor modification to prevent new lesion formation as well as progression of disease in the stent group will be especially important since stenting does not provide an alternate route for blood flow. Any progression of lesion or plaque rupture will lead to clinical events in the stent group.

What do we still have to learn? We do know that intravenous glycoprotein IIb/IIIa platelet inhibitors can lower the event rate in patients undergoing stent implantation, especially in the diabetic subset. The 3-year follow-up of the Evaluation Of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT) trial shows that mortality is reduced by 33%, suggesting that the stent group mortality can be reduced further. With better treatment and prevention of in-stent restenosis (brachytherapy and drug-eluting stents), the future of stenting as the preferred treatment of multivessel angioplasty indeed remains bright. [Alan C. Yeung, MD]

Better Outcomes with Surgery in MASS II

Several randomized trials of coronary artery bypass surgery versus coronary angioplasty in patients with multivessel disease have reported that patients treated with surgery have a higher event-free survival than patients treated with angioplasty, owing primarily to a lower incidence of repeat revascularization following the procedure. To determine the influence of contemporary coronary revascularization strategies on outcomes in patients with symptomatic multivessel disease, several trials have been undertaken. The 1-year event rates of one such trial, MASS II (Medicine, Angioplasty or Surgery Study), were reported for 611 patients eligible for medical therapy (n = 203), coronary bypass surgery (n = 203), or angioplasty (n = 205). In patients undergoing surgery, an average of 3.1 vessels were grafted, and an average of 1.9 vessels were dilated in patients undergoing percutaneous coronary intervention, with 70% of patients receiving intracoronary stents.

The primary endpoint of the study, the combined occurrence of unstable angina, myocardial infarction, and cardiac death was present less often in patients treated with surgery or medical therapy than with angioplasty (P = .00002), although survival at 12 months was similar among groups. Q-wave myocardial infarction in relation to the procedure occurred more frequently in the angioplasty group (8.7%) than in the surgery group (1.9%; P = .0015), and patients in the angioplasty group required additional revascularization (8.2%) more often than patients in the surgical group (0.5%). As expected, at 1 year, angina occurred least often among surgery patients (6%) in comparison to medical (13%) and angioplasty (25%) patients.

Interestingly, medical treatment alone was associated with a low incidence of endpoints and was superior to percutaneous coronary intervention for both the primary and anginal endpoints. Revascularization was superior to medical therapy only in relation to anginal status.

Therefore, despite the inability to demonstrate a survival advantage in patients treated with surgery in comparison to angioplasty or medical therapy for multivessel disease, freedom from angina is higher and repeat revascularization lower in patients treated with coronary bypass surgery, despite the use of stents in the majority of patients. However, at 1 year, it should be noted that coronary bypass surgery was avoided in over 90% of patients treated with percutaneous coronary intervention. [Alice K. Jacobs, MD]

Radiation to Prevent Restenosis

Two major clinical trials were reported on at the ACC Scientific Session concerning coronary radiation to prevent restenosis after angioplasty: the BETA-CATH Trial and the saphenous vein graft Washington Hospital Radiation for InStent Restenosis Trial (SVG WRIST).

The BETA-CATH study, a randomized, multicenter, placebo-controlled trial, enrolled 1455 patients and compared the use of an active 30-mm strontium 90 β-radiation source with an inactive source. All patients were initially treated with angioplasty and underwent stent implantation only for suboptimal results. Approximately 50% of the patients underwent stenting. The average lesion length was 12.5 mm, and the luminal diameter was 3.0 mm. There was a nonsignificant 12% improvement in target lesion revascularization (TLR), a 10% improvement in target vessel revascularization (TVR), and a 9% reduction in major cardiac events (MACEs) in the radiation-treated cohort versus placebo.

Table 1
Low-Density Lipoprotein (LDL) Values Before and After Treatment with Pravastatin

	LDL (mg/dL)	Stress Score	Rest Score	Ischemia Score
Baseline	134 ± 33	12.6 ± 5.7	4.8 ± 4.3	7.9 ± 4.1
6 Weeks	90 ± 18	12.0 ± 7.5	5.9 ± 4.7	6.1 ± 6.9
6 Months	95 ± 21	9.4 ± 6.2	5.6 ± 5.0	3.8 ± 6.5

When the angioplasty cohort was evaluated separately from the stent cohort, a significant reduction of events was seen in the angioplasty group, with TLR, TVR, and MACE reduced by 35%, 28%, and 30%, respectively. In the stent plus radiation cohort, TLR, TVR, and MACE were surprisingly increased, by 14%, 9%, and 13%, respectively. Late stent thrombosis was not seen more frequently in the radiated group. Following initiation of prolonged clopidogrel use in the stent-treated group, an inspection of the stent cohort results showed that radiation reduced restenosis within the lesion treated. However, in the analysis segment that spanned the treated target segment and areas proximal and distal to the treated segment, there was an increase in restenosis. This finding was felt to be due to geographical miss: segments adjacent to the lesion were treated with reduced doses of radiation, which could have paradoxically induced a proliferative response in those areas.

The SVG WRIST Trial, a multicenter, randomized clinical study, compared γ-radiation using the Checkmate™ γ-radiation system with placebo in 120 patients with in-stent restenosis in saphenous vein grafts. These patients were older and had more risk factors than those included in previous studies of in-stent restenosis. Radiation reduced the restenosis rate by 53% to 65%, with reductions from 45% to 21% in the entire dilated area analysis segment and from 43% to 15% within the stent itself. In addition, TLR and TVR were reduced from 48.3% to 10% and from 53.3% to 18.3%. At 6-month follow-up angiography, there was no increased risk of late stent thrombosis with the use of prolonged clopidogrel administration.

It is well known that stents prevent unfavorable remodeling, and some animal studies have suggested that certain doses of radiation may induce unfavorable remodeling.

Given the disparate results between these two clinical trials, the differences between them need to be emphasized. First, different sources were used in each trial (β- and γ-radiation), although this may not be as critical as the use of radiation in de novo lesions compared with in-stent restenosis. It is well known that stents prevent unfavorable remodeling, and some animal studies have suggested that certain doses of radiation may induce unfavorable remodeling. In addition, geographical miss was not well recognized as a problem during the BETA-CATH study but was well recognized during the SVG WRIST trial and could explain the differences in results. The observations, however, confirm the usefulness of radiation for the treatment of in-stent restenosis and continue to raise concerns about the use of radiation in de novo lesions. Until further studies have been performed to illuminate the dose–response relationship and the mechanism for restenosis in de novo lesions, application to this group of patients should be avoided. The ongoing SUPPRESS Trial sponsored by Guidant Corp. will help address this issue.

[David P. Faxon, MD, and Norman E. Lepor, MD]

Nuclear Cardiology

Far more interesting and important abstracts were presented at the American College of Cardiology Scientific Sessions this year compared with recent years. Abstracts in several diverse areas of nuclear cardiology were among the more interesting and original of these contributions.

Myocardial perfusion imaging for following the efficacy of medical therapy. The remarkable ability of 3-hydroxy-3-methylglutaryl (HMG)-reductase inhibitors to reduce risk of cardiac death, myocardial infarction, need for revascularization, cost of care, and stroke are widely known. The biologic effects of these drugs begin shortly after treatment initiation, and a change in outcomes can be observed in as little as 6 months. Whether these changes are sufficient to be detected and followed by routine single-photon emission computed tomography (SPECT) examination is not known. Ronald Schwartz, MD and colleagues from

the University of Rochester hypothesized that serial monitoring of these patients should reveal improvements in stress perfusion defects during the course of therapy with this class of agents. To this end, the authors identified 20 dyslipidemic patients (35% women) with stress-induced perfusion abnormalities on baseline SPECT and performed serial stress SPECT studies at 6 weeks and 6 months after initiation of pravastatin (40 mg qhs).

Scores for the extent and severity of stress defects, rest defects, and inducible ischemia were determined using widely available quantitative software. Patient compliance with these medications, assessed by pill count, revealed that compliance was ≥95% in all patients. Compared with baseline values (Table 1), low-density lipoprotein (LDL) values were reduced by 33% in 6 weeks of treatment ($P < .001$), and no further reduction occurred at 6 months. Stress defect and ischemia scores, on the other hand, decreased modestly by 6 weeks, but greater reductions occurred by 6 months that reached statistical significance ($P < .01$). No changes in the extent and severity of rest defects occurred, nor did left ventricular ejection fraction or volumes change with treatment.

This abstract is the first demonstration of reductions in SPECT perfusion abnormalities with cholesterol reduction therapy. The authors concluded that in dyslipidemic patients with inducible ischemia, perfusion defects will improve over a similar time course as clinical risk, and the efficacy of therapy can be followed with stress SPECT. Future studies may further define which patient subsets benefit from adjunct revascularization and which patients are not responding to aggressive medical therapy.

Performing stress myocardial perfusion imaging. As the number of patients with severe atherosclerotic disease or advanced age continues to grow, pharmacologic stress is increasingly used for stress imaging studies. For pharmacologic stress myocardial perfusion SPECT, adenosine has gained increasing popularity, but dobutamine is still used in many patients. Both of these agents have been thought to have specific physiologic advantages, the former inducing hyperemia via adenosine receptors, resulting in near maximal coronary vasodilation, and the latter increasing coronary flow secondarily to increased cardiac workload, thus being more similar to exercise. Investigators from the MRC Clinical Sciences Centre and St. Mary's Hospital, London (Jagathesan et al) utilized positron emission tomography (PET) imaging, a noninvasive means of quantitating absolute blood flow accurately, to compare the effects of adenosine and dobutamine on this parameter in normal subjects.

Rest and peak myocardial blood was measured using PET imaging in 20 normal males (age 46 ± 7 years) randomized to two study arms, each with 10 age-matched subjects (adenosine versus dobutamine stress). The investigators found that rest flow (mL/min/g) was similar in the two arms (adenosine:1.23 ± 0.23 versus dobutamine: 1.22 ± 0.28 mL/min/g; P = ns), but both peak myocardial flow and coronary flow reserve was significantly greater with adenosine versus dobutamine (4.04 ± 0.51 versus 3.18 ± 0.96; $P < .03$, and 3.36 ± 0.48 versus 2.62 ± 0.58; $P < .01$, respectively). Thus, adenosine results in 25% greater maximal flow and coronary reserve compared with dobutamine. The authors concluded that these findings were consistent with the higher sensitivity of adenosine for detecting coronary artery disease (CAD). It must be pointed out, however, that this study examined normal subjects, younger than those ordinarily undergoing pharmacologic stress testing, and that both the presence of atherosclerosis and advanced age alter coronary artery physiology. Furthermore, SPECT imaging discerns relative rather than absolute flow differences; thus the 25% estimated difference found in this study may underestimate the actual difference in flow between these agents that occurs in patients undergoing pharmacologic stress testing.

The true measure of test utility is whether the use of this test results in a reduction in the catheterization of patients with no discernable benefit from this invasive procedure.

How is myocardial perfusion SPECT used in clinical practice? Now more than ever before, the use of various tests and procedures and their resultant costs are important indices that are carefully followed. The validation of any new technology now includes careful analyses of added value and cost effectiveness. These measures are particularly helpful when the proposed test is assessed as part of an overall testing strategy. With respect to tests that are used in a gatekeeper role to determine which patients should go on to catheterization, the true measure of test utility is whether the use of this test results in a reduction in the catheterization of patients with no discernable benefit from this invasive procedure.

Howard Lewin, MD and colleagues (Cedars-Sinai Medical Center, Los

Angeles) investigated whether noninvasive nuclear testing reduced the rate of normal coronary angiograms (NCA; defined as <50% luminal diameter in any epicardial artery) in their institution. Patients with prior MI, PTCA, or CABG were excluded from this analysis, and the remaining patients were categorized as having either no prior stress myocardial perfusion SPECT or MPS within 60 days prior to catheterization. Of 9975 patients who underwent diagnostic coronary angiography between 1992 and 1998, a significantly lower NCA rate was found in patients undergoing MPS prior to angiography compared with those who did not (11.4% versus 17.6%, $P < .001$), but NCA decreased significantly during the years 1992 to 1998 in both sexes with and without the use of SPECT. A risk-adjusted analysis revealed that the NCA rates: 1) were lowered in both men and women when SPECT was used prior to catheterization; 2) were greater in women compared with men even with SPECT use; and 3) have declined for both women and men for a number of years, but have occurred concomitantly with increasing use of precatheterization SPECT imaging. This study demonstrates that enhancement in an important measure of health care quality (NCA rate) can be further augmented by the use of noninvasive testing. Thus, the potential cost savings, reduced NCA, and enhanced patient care that can result from appropriate use of noninvasive testing may be more than just a theoretical observation. Further insights can be gained from these data by use of multivariable modeling to take into account differences in cardiac risk factors, likelihood of CAD, and other factors that would have influenced resource use.

When do we use electron beam computed tomography? The development of newer medical therapeutics that can reduce the incidence of conventional events (cardiac death, myocardial infarction), revascularizations, and progression of CAD has extended our medical therapy candidate pool to include asymptomatic patients without epicardial disease but with early stages of CAD. Properly applied, current therapy can delay or prevent the development of CAD in these patients. However, identifying which patients have early or subclinical CAD is challenging in that none of our currently used noninvasive tests are capable of this type of diagnosis or imaging, and we await the further development of magnetic resonance imaging (MRI) and electron beam computed tomography (EBCT) to fill this void. EBCT is a potentially powerful clinical tool for the practicing cardiologist in identifying asymptomatic younger patients at risk for developing CAD, but its utilization remains limited by a lack of evidence regarding its incremental value and role in current practice strategies. Data presented by investigators from the Cedars-Sinai Medical Center (Miranda et al) at this ACC meeting take a long step in defining how to use this test.

As many as 40% to 45% of patients in published follow-up studies of SPECT are actually inappropriate candidates for SPECT on the basis of their symptoms and risk factors.

The authors studied 355 consecutive asymptomatic patients (80% male; age 59 ± 0.5 years) who underwent both EBCT and myocardial perfusion SPECT within 180 days, with the goal of determining the incremental value of EBCT calcium score over standard clinical assessment to predict the likelihood of the patient having an abnormal nuclear scan. Of these patients, 329 had normal and 26 had abnormal stress SPECT. Logistic regression revealed that after adjusting for the calculated likelihood of CAD, calcium score yielded significant information for predicting the occurrence of abnormal SPECT (receiver operator characteristic curve area increase from 0.65 to 0.77, $\chi^2 = 12$). The value of this study is that EBCT may be an appropriate test for patients with very low risk who otherwise are referred for SPECT. As many as 40% to 45% of patients in published follow-up studies of SPECT are actually inappropriate candidates for SPECT on the basis of their symptoms and risk factors. If, in addition to their low likelihood of CAD and low risk of adverse outcomes, these patients also have a very low calcium score, the need for additional testing is highly questionable. Larger studies are needed, preferably with outcomes data. Nonetheless, this study is an important first step toward incorporating EBCT into regular clinical practice.

Important clinical insights gained by use of nuclear imaging. The importance of diabetes mellitus as a cardiac risk factor has gained considerable recognition of late due to the finding of different success rates for revascularization procedures in these patients. It has been assumed that the cardiovascular risk associated with diabetes mellitus is greater in type 1 (insulin-deficient) than in type 2 (insulin-resistant) diabetics, although the evidence

supporting this has been unclear. Although coronary vascular tone has been shown to be impaired in diabetic patients, the contributing factors—hyperglycemia and insulin resistance—remain controversial. Marello Di Carli, MD and colleagues (Wayne State University) examined endothelium-dependent and -independent coronary vasodilator function in patients with type 1 and type 2 diabetes.

The authors used PET imaging to quantitate myocardial blood flow at rest, during adenosine-induced hyperemia (a measure of endothelium-independent vasodilation) and in response to cold pressor testing (a measure of endothelium-dependent vasodilation) in 34 diabetic patients (age 42 ± 7 years, half with type I, half with type II) who were free of overt cardiovascular complications. In addition, this was performed in 10 age-matched healthy controls. The authors found that although the two diabetic groups were similar with respect to age and glycemic control, type 1 compared with type 2 diabetics had longer duration of diabetes (21 ± 12 versus 6 ± 4 years; $P < .05$) and higher high-density lipoprotein-C levels (52 ± 14 versus 39 ± 9 mg/dl; $P < .05$). Although basal myocardial flow was similar in the three groups examined, type 1 and type 2 diabetics did not differ with respect to the increase in flow with either adenosine (161% ± 18% versus 185% ± 19%, respectively; P = ns) or cold pressor testing (23 ± 4% versus 19% ± 3%, respectively; P = ns), and control values for both interventions were significantly different (351% ± 43% and 66% ± 12%, respectively; both $P < .001$ versus either diabetic group). Importantly, even after adjusting for diabetes-associated metabolic abnormalities and the presence of autonomic neuropathies, these findings remained significant. The authors concluded that both type 1 and type 2 diabetics had similarly compromised endothelium-dependent and -independent coronary vasodilator function. These results support a key role for hyperglycemia in the pathogenesis of diabetic vascular dysfunction and, for clinicians, point to the need to consider that both types of diabetics have similar high risks for cardiovascular disease and adverse outcomes. [Rory Hachamovitch, MD]

In general it seems that mitral valve repair leads to better survival than mitral valve replacement in centers having this expertise.

Surgery in Asymptomatic Mitral Insufficiency: Point-Counterpoint

Protagonist: A Jamil Tajik, MD: Asymptomatic patients with severe mitral insufficiency should have surgery. The etiology of mitral regurgitation (MR) has evolved significantly over the last 35 years, when postinflammatory conditions were most common, to the present when 78% of cases are related to myxomatous degeneration. Flail mitral leaflets are the most common cause of surgical MR. The conventional wisdom is that patients with asymptomatic severe MR do well for many years. Preoperative symptoms affect the long-term survival following mitral valve replacement, with 76% 10-year survival in patients with NYHA class I or II, and 48% with class III or IV. The survival in class III and IV patients undergoing mitral valve replacement was worse than the natural progression of untreated mitral insufficiency. An early surgical approach to flail mitral leaflet led to a 10-year survival of 80% versus 65% in the nonsurgically treated cohort.

Patients with MR have an incidence of sudden death of 1.8% per year. In patients with flail mitral valve leaflets the rate of sudden death is 7.8% in class III/IV, 3.1% in class II, and 1.0% in class I. However, because the prevalence of class I and II patients is greater, sudden death is observed more often in these patients. Patients with ejection fractions less than 50% have an annual rate of sudden death of 13% versus about 1% in patients with ejection fractions greater than 50%.

With earlier surgical intervention in chronic MR, long-term mortality is significantly enhanced. With an ejection fraction <0.5, the 10-year postoperative survival was 32%. In patients undergoing mitral valve repair, the operative survival was about 99%, with higher mortality rates seen in patients older than 75 years (3.7%) than in younger patients (0.7%), and no deaths in patients who were class I or II. In general it seems that mitral valve repair leads to better survival than mitral valve replacement in centers having this expertise. In patients undergoing surgical treatment of mitral valve prolapse, the 15-year survival was 42% (anterior or posterior leaflet repair), and for those treated with valve replacement it was 31%. The reoperation rate within 10 years of repair of mitral valve is 10% for anterior leaflet and 5% for posterior leaflet repair.

The protagonist conclusion is that in view of the improved surgical outcomes in patients undergoing mitral valve repair, those with severe mitral insufficiency, class I or II and ejection fractions > 60% should be treated surgically.

Antagonist: Shahbudin Rahimatoola, MD. The protagonist's argument for early surgical treatment in patients with class I/II symptoms may not have relevance to patients who are truly asymptomatic (class 0). In the patients discussed above who presented with class I/II symptoms, only 48% were truly asymptomatic, and 28% initially presented with class III or IV symptoms. In addition, some of the bad outcomes in the class I/II patients could have been related to coronary artery disease, because 60% of these patients did not undergo coronary angiography rather than progression of mitral regurgitation.

In the protagonist's discussion of sudden death and mild MR, co-morbidities not related to the MR, including hypertension, smoking history, and coronary disease were common, suggesting that the sudden death may not necessarily be primarily related to the valvular pathology. Of patients suffering sudden death, 80% had preceding symptoms of heart failure, suggesting that there could have been a relationship with worsening MR, and 30% died after mitral valve replacement.

The antagonist conclusion was that at present there is no data to support the surgical treatment of truly asymptomatic patients with normal left ventricular function. If the decision is made to proceed with early surgical treatment of mitral regurgitation, repair rather than replacement of the mitral valve should be performed in centers with excellent track records for both 30-day mortality and durability of repair. Early mitral valve replacement is not recommended, because of the poorer outcomes relative to mitral valve repair. A prospective trial comparing surgical and medical intervention in asymptomatic patients would be critical to answer this question regarding the most effective approach for these patients.

The [ACC/AHA] consensus document recommended against using EBCT as a general population screening tool performed without a physician prescription.

General agreement. Surgical repair of the mitral valve is indicated in the presence of the following:

- Associated obstructive coronary artery disease
- Left ventricular ejection fraction < 0.6
- Elevated pulmonary artery pressures
- Atrial fibrillation or supraventricular tachycardia
- Progressive decrease left ventricular function or increase left ventricular volumes

[Norman E. Lepor, MD]

EBCT is Useful in Asymptomatic Patients: Point-Counterpoint

Protagonist: John Rumberger, MD. The presence of coronary calcium establishes the diagnosis of coronary atherosclerosis with the square root sum of calcium closely related to coronary plaque area. Higher calcium scores also correlated with multi-vessel coronary artery stenosis. The presence of calcium does not distinguish those stable plaques from those that rupture or develop erosions. The presence of significantly elevated coronary calcium scores was associated with an increased risk of myocardial infarction, sudden cardiac death, or ischemia in initially asymptomatic patients. When coronary artery calcium is found and scored in a sex- and age-specific manner, EBCT adds incremental prognostic information to conventional risk factor assessment.

Antagonist: Robert Detrano, MD. Trials evaluating EBCT have a wide variance in terms of the determination of relative risk associated with abnormal calcium scores. The relative risk seems to be similar to that seen with the Framingham scoring, which takes into account traditional coronary artery disease risk factors. The incidence of coronary calcium increases with age and is more common in men at earlier ages. In the age group 30–40 years of age, it is seen in 18% of men and 10% of women. In the age group 60–70 years of age, coronary calcium was seen in 60% of women and 80% of men.

The ACC/AHA consensus document on EBCT recommends its possible use when ordered by a physician when faced with a patient with an intermediate likelihood for the presence of coronary artery disease. The consensus document recommended against using EBCT as a general population screening tool performed without a physician prescription. The cost associated with the use of EBCT as a screening tool is prohibitive. Its use in low-likelihood populations would yield a high false-positive rate. This would result in additional unnecessary diagnostic testing such as stress imaging and coronary angiography performed in those false-positive patients.

[Norman E. Lepor, MD]

Preventive Cardiology

It is estimated that more than 40% of the U.S. population uses some form of complementary and alternative medicine, ranging from vitamins

and food additives to long-term chelation therapy,[17] and amounting to an annual expenditure of $30 billion. In part, this growing trend reflects the increasing appreciation of the "whole person" approach of complementary and alternative medicine combined with a skepticism regarding traditional medicine fostered by recent commercial trends. It is also estimated that one half of these patients do not tell their physicians that they are employing these therapies. Although some of these therapies have proven value, several are of uncertain efficacy, and a few are either harmful or have adverse interactions with traditional therapies. Complementary and alternative cardiac therapies were discussed at several sessions of the March 2001 American College of Cardiology Annual Scientific Sessions in Orlando. This review highlights some of the popular alternative and herbal therapies considered by cardiac patients as well as the first selective estrogen receptor modulator trial in postmenopausal women.

Chelation therapy. Chelation therapy using serial infusions of ethylene diamine tetra-acetic acid (EDTA) is a widely used and expensive therapy designed to eliminate heavy metals from the body, which theoretically could participate in the oxidative process that underlies atherosclerosis. In clinical practice, EDTA infusions are usually coupled with vitamin administration. Although the current literature includes two randomized trials of chelation therapy in patients with peripheral artery disease[18,19] and several case reports in coronary artery disease, no adequately sized randomized cardiac trials have been performed. To evaluate objectively the effect of chelation therapy, 84 coronary heart disease subjects (angiographic disease or past myocardial infarction) were screened from 3140 patents and were randomized to biweekly chelation plus vitamin therapy or placebo infusions for 15 weeks, followed by monthly infusions for an additional 3 months.[20] The infusions followed the recommendations of the American College for Advancement in Medicine chelation therapy guidelines. Patients with recent myocardial infarctions or past chelation therapy were excluded. The subjects' mean age was 65 years, and 85% were male. The primary end point was the change in time to 1 mm ST segment depression on treadmill testing at 6 months. The secondary end points were the functional reserve (gas exchange anaerobic threshold and VO2 max) and sense of well-being (Duke Activity Status Index [DASI], SF-36 Health Survey, Seattle Angina Questionnaire).

Statistically significant improvements in time to ST depression were observed in both groups (placebo 57.2 seconds vs chelation therapy 65.5 seconds; both $P < .001$), but there was no significant difference between the two therapies. The time to anaerobic threshold and VO2 max improved slightly in both groups, but again, there was no significant difference between the groups. The DASI scores did not change in either group. The physical capacity scores improved to a similar extent in both groups, but the mental component scores of the SF-36 did not change in either group. Six subjects in the chelation therapy group and three subjects in the placebo group required hospitalization for unstable angina, but no deaths or myocardial infarctions occurred. One chelation therapy subject was withdrawn from treatment due to a rise in creatinine, a recognized complication of chelation therapy.

This study documents the finding that chelation therapy is equivalent to placebo in managing myocardial ischemia and explains why many patients report an improvement in exercise capacity with chelation treatment. Numerous studies such as this have reported improvement in angina and exercise capacity with placebo treatment over 6 to 12 months time. Therefore it is not surprising that placebo-equivalent treatments report the same favorable changes. This study documents the lack of value of this frequently used and expensive therapy and supports the position of the American College of Cardiology that chelation therapy has no proven value in coronary heart disease.

This … supports the position of the American College of Cardiology that chelation therapy has no proven value in coronary heart disease.

Herbal cardiac medicine. Drs. John Cooke, Noel Bairey-Merz, and Salim Yusuf reviewed frequently used herbal treatments with cardiac value and/or potential adverse interactions with traditional therapies. A major problem in this area is the variability of active ingredients in these preparations, which are not regulated with regard to content or efficacy. The more commonly used herbs and foods with cardiac implications include the following.

Ephedra (Ma Huang), commonly used as an energy booster, decongestant, and anorexic, contains the alkaloids ephedrine and pseudoephedrine. Hypertension, cardiac

arrhythmias, and strokes have been reported.[21]

Garlic, composed of sulfur-containing compounds, reduces cholesterol and platelet aggregation and may lower blood pressure. The active ingredient, allicin, is variably present in different preparations and is destroyed by cooking. Meta-analyses of the effects of garlic on cholesterol report 3% to 10% decreases.[22,23] Small decreases in blood pressure and a retardation of atherosclerosis progression have been reported but, as with the effect on cholesterol, any possible effects are small. The antiplatelet effect of garlic can be problematic in patients on anticoagulants, and bleeding has been reported.

Licorice possesses mineralocorticoid activity, thereby producing a potassium-wasting syndrome and inhibition of the effects of aldactone. Hypertension, arrhythmias, and cardiomyopathies have been reported.

St. John's Wort (hypericum) has been shown to be an effective antidepressant and is widely used, especially in Germany.[24] Its actions may be due to inhibition of the reuptake of serotonin. It increases the P450 3A4 cytochrome oxidase and decreases levels of cyclosporine. Two deaths due to cardiac graft rejection have been reported in patients taking St. John's Wort.

Tea consumption, especially green tea, is epidemiologically associated with reduced cardiovascular disease prevalence. Recently, black tea was shown to improve brachial artery flow–mediated vasodilation, an index of endothelial function,[25] probably related to its antioxidant content. Tea contains theophylline and caffeine, and therefore has the potential to produce arrhythmias.

Selective estrogen receptor modulators. Although numerous observational trials have demonstrated decreases in cardiovascular events in postmenopausal women taking hormone replacement therapy (HRT), the Heart Estrogen/Progestin Replacement Study (HERS)[26] and the Estrogen Replacement Atherosclerosis (ERA) study[27] recently demonstrated no benefit to either the progression of coronary atherosclerosis or cardiovascular events in postmenopausal women given HRT. The selective estrogen receptor modulators (SERMs) have also been associated with observational decreases in cardiovascular events found during studies evaluating their use in decreasing breast cancer rates. In general, they have beneficial lipid effects similar to estrogen.

To test the effect of the SERM raloxifene on cardiovascular events, the Multiple Outcomes of Raloxifene Evaluation (MORE) study randomized 7705 osteoporotic postmenopausal

Main Points

- The CAPRICORN trial has shown reduced mortality in post–myocardial infarction patients with left ventricular dysfunction treated with the β-blocker carvedilol.
- In the results of the MIRACLE trial, 69% of patients with resynchronization therapy had an improvement in at least one New York Heart Association Class, compared with 34% without resynchronization therapy.
- In patients with heterozygous familial hypercholesterolemia, rosuvastatin was found to achieve superior lipoprotein effects than currently available high-dose statin and combination therapy in some patients.
- The CURE trial confirms the longer-term efficacy of the combination of clopidogrel and aspirin in patients presenting with acute coronary syndromes.
- Data from MASS II showed that combined occurrence of unstable angina, myocardial infarction, and cardiac death was present less often in patients treated with surgery or medical therapy than with angioplasty; at 1 year, angina occurred least often among surgery patients (6%) compared to medical (13%) and angioplasty (25%) patients.
- Radiation is effective in treating saphenous vein graft in-stent restenosis and preventing restenosis in native vessels treated with PTCA without stent implantation.
- Brachytherapy at the time of stent implantation in native vessels can be associated with poorer outcomes due to the "geographic miss" phenomenon.
- Cholesterol reduction therapy with pravastatin reduces myocardial perfusion abnormalities, as shown by single-photon emission computed tomography (SPECT).
- Hyperglycemia seems to play a key role in the pathogenesis of vascular dysfunction in both type 1 and type 2 diabetics.
- A recent study of raloxifene supports the growing concept of a null effect for all hormone replacement therapies on cardiovascular events.

women to placebo and raloxifene (60 and 120 mg/day) for 3 years.[28] Raloxifene therapy resulted in decreases in total (6%) and LDL (10%) cholesterol and fibrinogen (10%). Despite these effects, no differences in coronary events (myocardial infarction, unstable angina, coronary ischemia) or cerebrovascular events (stroke, TIA) were observed between the groups. The risk ratios for any cardiovascular event at 3 years were 0.89 and 1.00 for the 60 mg and 120 mg doses, respectively. This lack of efficacy was observed in women with and without evidence of preexistent cardiovascular disease. Importantly, no early increase in thromboembolic events was observed (risk ratios 1.1 and 1.01 at 1 year for the 60 mg and 120 mg doses, respectively), as was seen in the HERS trial. These findings support the growing concept of a null effect for all hormone replacement therapies on cardiovascular events.

[Robert A. Vogel, MD]

[Note: Dr. Vogel will be acting as Co-Chairman of the First American College of Cardiology Conference on the Integration of Complementary Medicine in a Traditional Cardiology Practice, to be held October 18–20, 2001 in Santa Barbara, CA.] ■

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