Best of the AHA Scientific Sessions 2000

Highlights from the American Heart Association Scientific Sessions 2000
November 12-15, 2000, New Orleans

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The focus was on state-of-the-art information at the American Heart Association Scientific Sessions 2000 in New Orleans. Here, Contributing Editors of *Reviews in Cardiovascular Medicine* describe important presentations they think deserve special attention.

Help for Heart Failure Management

Nesiritide is a recombinant form of B-type natriuretic peptide, a naturally occurring hormone secreted during heart failure. Nesiritide had been evaluated previously in 700 patients with acutely decompensated congestive heart failure (CHF) and had been found effective in decreasing preload and afterload as well as in improving dyspnea and fatigue, in a fixed-dose infusion at rates of 0.015 and 0.03 µg/kg/min.[1]

VMAC. Investigators with the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) study,[2] led by James B. Young, MD, of the Cleveland Clinic Foundation, evaluated this agent in a study of 498 patients hospitalized with decompensated CHF. Patients were randomized to fixed- or adjustable-dose intravenous nesiritide or nitroglycerin, in addition to standard therapy, which may include diuretics, dobutamine, and dopamine. In the study, 216 patients were given a titrated dose of nitroglycerin; 211 received a 2-µg/kg bolus and a 0.01-µg/min infusion of nesiritide; and 62 received a 2-µg/kg bolus and a 0.01-µg/min infusion of nesiritide for the first 3 hours, followed by an adjustable dose that could be increased to 0.03 µg/kg/min.

Nesiritide significantly reduced pulmonary capillary wedge pressure, with an 8-mm Hg decrease in as little as 15 minutes. By 3 hours, nesiritide was more efficacious than placebo or nitroglycerin. This hemodynamic effect was maintained at 24 and 48 hours. In addition, dyspnea improved significantly more in patients receiving nesiritide than in patients receiving nitroglycerin.

Nesiritide did not induce tachyphylaxis. Fewer patients receiving nesiritide had headaches than did patients receiving nitroglycerin (8% and 20%, respectively). Symptomatic hypotension occurred in 4% of patients receiving nesiritide and in 5% of patients receiving nitroglycerin. Dr Young said this study demonstrated that "nesiritide, compared with nitroglycerin, is faster, safe, easy to use, and is thus a vastly better vasodilator in the decompensated heart failure patient."

This trial demonstrates that nesiritide confers significantly greater benefits than does a standard treatment, nitroglycerin, for patients with acute CHF. The study suggests a significant and important role for nesiritide in the management of decompensated CHF.

COPERNICUS. β-Blockers have been shown to benefit patients with class II-III heart failure, but many clinicians believe the risk/benefit ratio would be unfavorable in patients with more severe heart failure. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial[3] evaluated 2289 patients with severe heart failure. The trial results were presented by principal investigator Milton Packer, MD (Columbia University College of Physicians and Surgeons, New York). The study included patients with heart failure who had symptoms at rest or with minimal exertion and who had an ejection fraction (EF) of less than 25% despite optimal medical therapy. Hospitalized patients were eligible for enrollment provided they were not in an ICU. Patients receiving 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 or to carvedilol, beginning with a dose of 3.125 mg bid. The dose was then doubled every 2 weeks, if tolerated, to a target dose of 25 mg bid. Carvedilol was very well tolerated. At 6 months, this drug was discontinued in 6% of patients, compared with 9% of patients receiving placebo. Titration to the target dose was successful in 74% of patients. The mean age of patients in the trial

Key Words
Acute coronary syndrome • Anorexigens • Aortic stenosis • Atherosclerosis • β-Blockers • Cholesterol • Congestive heart failure • Coronary artery disease • Hypertension • In-stent restenosis • Mitral regurgitation • Myocardial infarction • Valvular heart disease

Main Points

- In patients with decompensated heart failure, nesiritide, a natriuretic peptide, is more effective than intravenous nitroglycerin. In patients with class IV congestive heart failure, carvedilol is safe and effective.
- Beta radiation delivered with a source wire end-sensoring catheter was effective treatment for patients with in-stent coronary restenosis.
- Aortic valve replacement at the time of coronary artery bypass graft surgery in patients with mild to moderate stenosis is associated with improved long-term survival.
- There is a strong inverse relationship between dietary intake of folic acid and stroke.
- Failure to diagnose peripheral arterial disease may prevent initiation of effective treatment to prevent cardiovascular events.
- Imaging with resting technetium Tc 99m sestamibi gated single-photon emission CT in patients with possible unstable syndromes significantly reduces the number of unnecessary hospital admissions in patients without coronary ischemia.
- In patients with unstable angina and high-risk characteristics, treatment should include an intravenous glycoprotein inhibitor, such as tirofiban, and aggressive use of coronary angiography.
- Abciximab reduces the end point of death, myocardial infarction, or revascularization at 30 days more than tirofiban in patients undergoing percutaneous coronary intervention. The findings of no significant difference between abciximab and tirofiban in the US population and the trend toward more efficacy with tirofiban in the lower-risk patients without acute coronary syndrome need to be studied further to determine clinical implications.
- Angiotensin-converting enzyme inhibitors may offer greater cardioprotection than other classes in the management of hypertension.
- Primary coronary angioplasty can be performed safely in high-volume centers without on-site cardiovascular surgery.

was 63. The mean left ventricular (LV) EF was only 19.8%.

There was a marked reduction in death and hospitalizations with carvedilol (Figure 1). Mortality was reduced from 18.5% with placebo to 11.4% with carvedilol; odds ratio (OR), 0.65 (95% confidence interval [CI], 0.52 to 0.81), $P = .00013$. There was a significant reduction in the combined end point of death and heart failure hospitalizations, from 31.5% to 23.4%, $P = .000004$. Carvedilol had a favorable effect on symptoms. In addition, the quality-of-life global score was more likely to improve and less likely to worsen in the carvedilol group. The findings were consistent across all subgroups, including groups divided by age, sex, EF, etiology, and blood pressure. In the subgroup of patients who were hospitalized at study entry, who had received intravenous therapy with a positive inotropic or vasodilator drug within 2 weeks, or who had been hospitalized 3 or more times during the previous year, the annual mortality rate for patients receiving placebo was 25.3%; this was reduced by 50% in patients receiving carvedilol.

Carvedilol has a dramatic impact on mortality, hospitalization, and quality of life in patients with heart failure, including those with symptoms at rest or with minimal exertion.

Val-HeFT. Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in patients with heart failure but do not completely suppress angiotensin II formation. The Valsartan Heart Failure Trial (Val-HeFT) evaluated the addition of the angiotensin receptor antagonist valsartan to usual heart failure therapy; results were reported by principal investigator Jay Cohn, MD (University of Minnesota, Minneapolis).[4]

The study included 5010 patients from 300 centers in the United States and Europe. At baseline, most patients were in New York Heart Association (NYHA) class II (61.7%) or III (36.2%). At baseline, 93% of patients were receiving ACE inhibitors and 36% receiving β-blockers. Patients were randomized to receive placebo or valsartan. Valsartan was initiated at a dose of 40 mg bid, then was titrated to a target dose of 160 mg bid. Valsartan was well tolerated, with an average dose of 254 mg/d.

After about 2 years of follow-up, analysis of the data showed no effect of valsartan on the outcome of all-

cause mortality: 19.7% with valsartan versus 19.4% with placebo; OR, 1.02 (95% CI, 0.90 to 1.15), $P = .800$. There was a reduction with valsartan in the combined end point of death, hospitalization, resuscitated sudden death, and need for an intravenous inotropic agent or vasodilator. This was decreased from 32.1% to 28.8%, a 13% reduction, $P = .009$. Modest improvements in patients' NYHA functional class, EF, and signs and symptoms of heart failure were shown. Most of the benefit with valsartan was confined to the 7% of patients who were not receiving ACE inhibitors. Of concern: the patients receiving an ACE inhibitor and β-blocker did not benefit from the addition of valsartan and, in fact, there was a trend toward increased events: OR, 1.10 (95% CI, 0.90 to 1.40).

Standard therapy for heart failure caused by systolic dysfunction remains an ACE inhibitor, a β-blocker, and an aldosterone antagonist. For patients who cannot tolerate an ACE inhibitor, this study demonstrates a beneficial effect to adding valsartan to the medical regimen. For patients who cannot tolerate a β-blocker, adding an angiotensin receptor antagonist to an ACE inhibitor can be considered, but the benefits are modest. [Gregg C. Fonarow, MD]

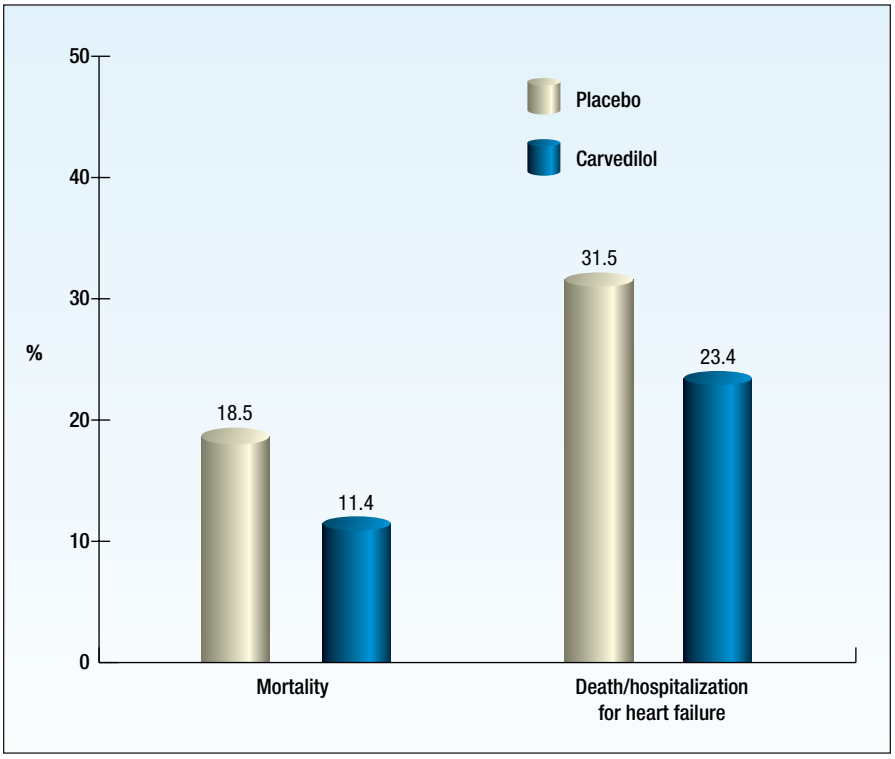

Figure 1. Reduction in death and hospitalization for heart failure in patients receiving the β-blocker carvedilol.

Effects of Lipid Lowering

To date, 3 secondary prevention and 2 primary prevention cholesterol-lowering trials have demonstrated concordant 24% to 40% reductions in mortality, cardiovascular events (including stroke), and need for revascularizations and hospitalizations in stable patients with average to elevated cholesterol levels and low to average high-density lipoprotein (HDL) cholesterol levels. Several important questions regarding ideal management remain, including:

- Does cholesterol lowering work in patients with unstable coronary syndromes?
- Is aggressive cholesterol lowering safe?
- When should cholesterol lowering be started?

MIRACL. Initial answers to these questions were provided by the results of the Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) study.[5] This randomized, controlled trial studied the 4-month effect of atorvastatin, 80 mg/d, on cardiovascular events in patients who had unstable coronary syndrome, with therapy started within 4 days of hospital admission. Entry requirements were the presence of unstable angina (based on more than 15 minutes of chest pain within 24 hours of admission, objective evidence of ischemia by ECG changes, elevated troponin level [1 to 2 times normal], or new wall motion abnormality) or non–Q wave myocardial infarction (MI) (a troponin level higher than 2 times normal or an elevated creatine kinase [CK] or CK-MB enzyme level). Patients were excluded if revascularization was planned or if cholesterol was higher than 270 mg/dL. Importantly, there was no lower limit of cholesterol for inclusion. The primary end-point measure was time to death, nonfatal MI, cardiac arrest with resuscitation, or hospitalization for recurrent ischemia.

A total of 3086 patients with a mean age of 65 (65% male, 15% non-Caucasian) were randomized to treatment (1538 received atorvastatin; 1548, placebo). Previous MI was present in 25% of patients and previous bypass surgery, in 11%. Twenty-five

percent of patients were smokers, 23% were diabetic, and 55% were hypertensive. The mean initial lipid values were as follows: cholesterol, 206 mg/dL; low-density lipoprotein (LDL) cholesterol, 124 mg/dL; HDL cholesterol, 46 mg/dL; and triglycerides, 182 mg/dL. Forty-six percent of patients had unstable angina, and 54% had non-Q MI. Randomization and treatment were started a mean of 63 hours after admission. Concomitant medical therapy included aspirin (91%), nitrates (90%), β-blockers (78%), heparin (75%), ACE inhibitors (50%), and calcium channel blockers (48%).

Preliminary findings at 6 weeks showed that atorvastatin lowered total cholesterol to 147 mg/dL (−27%), LDL cholesterol to 72 mg/dL (−40%), and triglycerides to 139 mg/dL (−16%), and raised HDL cholesterol to 48 mg/dL (+5%). The mean LDL cholesterol level in the treatment group was the lowest for any study to date. Placebo group lipid levels at this time were: total cholesterol, 217 mg/dL; LDL cholesterol, 135 mg/dL; HDL cholesterol, 46 mg/dL; and triglycerides, 187 mg/dL. The lipid changes in the placebo group are compatible with postinfarction effects.

The composite primary end point of events was significantly lower in the atorvastatin group (14.8%) than in the placebo group (17.8%, −16%, P = .048). Nonsignificant reductions were observed, respectively, in death (64 vs 68), nonfatal MI (101 vs 113), and resuscitation (8 vs 10), but a significant reduction was observed in recurrent ischemia requiring hospitalization (95 vs 130, P = .02). A significant reduction in a secondary end point, stroke, was also observed with atorvastatin (12 vs 24, P = .045). This is an important finding because of the theoretic possibility of increasing hemorrhagic stroke with aggressive lipid lowering. High-dose atorvastatin therapy was well tolerated. Serious adverse events caused by therapy occurred in 8% of the placebo group and 9% of the atorvastatin group (P = NS). Elevated liver function levels occurred in 0.6% of the placebo group and 2.5% of the treatment group. No myositis was experienced.

The MIRACL study suggests that aggressive cholesterol lowering should be started as soon as the diagnosis of unstable coronary disease is made, regardless of the initial cholesterol level; that time to subsequent coronary events is reduced with as little as 4 months of therapy; and that aggressive cholesterol lowering is safe.

HATS. The HDL-Atherosclerosis Treatment Study (HATS) evaluated the effect of 2 therapies (2 × 2 factorial design) on quantitative coronary artery disease (CAD) progression over a 3-year period in patients with moderate LDL cholesterol and low HDL cholesterol (lower than 35 mg/dL) levels.[6] One hundred sixty patients were randomized to 4 treatment groups: simvastatin (10 to 20 mg/d) and niacin (2 to 4 g/d) plus placebo; triple antioxidant vitamins (vitamin C, 1000 mg/d; vitamin E, 800 IU/d; beta-carotene, 25 mg/d; and selenium, 100 µg/d) plus placebo; simvastatin, niacin, and vitamins; or only placebo. The simvastatin + niacin groups had almost no progression of coronary disease (+ 0.3% stenosis change), whereas the groups without lipid therapy had a mean of 2.2% stenosis worsening. No benefit to coronary disease progression was observed in the antioxidant vitamins group. A significant (P = .01) reduction (9 vs 29) in coronary events was observed with lipid treatment but not with antioxidant vitamins.

Antioxidant vitamins appeared to reduce the benefit of lipid treatment with regard to atherosclerosis progression and events. This was possibly because of a reduction in HDL cholesterol, especially in the HDL2 subgroup, in patients given vitamins. This effect is reminiscent of the effect of probucol on HDL cholesterol and may represent a class effect of potent antioxidants. The HATS study suggests that combined statin and niacin therapy is safe and effective in patients with mixed dyslipidemia and also supports an absence of benefit for high-dose antioxidant vitamins. [Robert A. Vogel, MD]

Outlook in Valvular Heart Disease

The diet drugs fenfluramine (fen) and dexfenfluramine (dex) have been linked to the development of aortic regurgitation in placebo control and case control studies. Little is known, however, about the natural history of aortic regurgitation following cessation of therapy. Two reports presented data on 1-year follow-up of patients previously treated with phentermine/fenfluramine (phen-fen) or dexfenfluramine.

Anorexigens. Gardin and colleagues[7] compared post-treatment and 1-year follow-up echocardiograms in 1142 treated patients and controls. In the majority of cases (dexfenfluramine, 91.9%; phentermine/fenfluramine, 95.5%; and control, 98.1%), there was no change in the severity of regurgitation on blinded, side-by-side examinations. In the remaining cases in which change occurred, a majority of patients in both treatment groups showed significant decreases in severity of regurgitation. Factors associated with a decrease in severity included a history of hypertension, duration of treatment, and time elapsed since the end of treatment. A similar study, by

Kahn and associates,[8] examined 159 anorexigen-treated patients and controls with initial post-treatment echocardiography and a follow-up study a mean of 11 months later. In 109 patients, there was no change in severity of aortic insufficiency (AI) between the 2 studies. Of the remaining 50 patients, 45 improved and 5 worsened. In the control cohort, there was no significant difference between the 2 studies using the same statistical methods. The investigators concluded that previous users of appetite suppressants were 9 times more likely to experience improvement in AI than worsening. These 2 reports are consistent with other data suggesting that in patients who develop AI following anorexigen treatment, there is no tendency for progression after the medication has been stopped and that, in some cases, regression is noted over a period as short as 1 year.

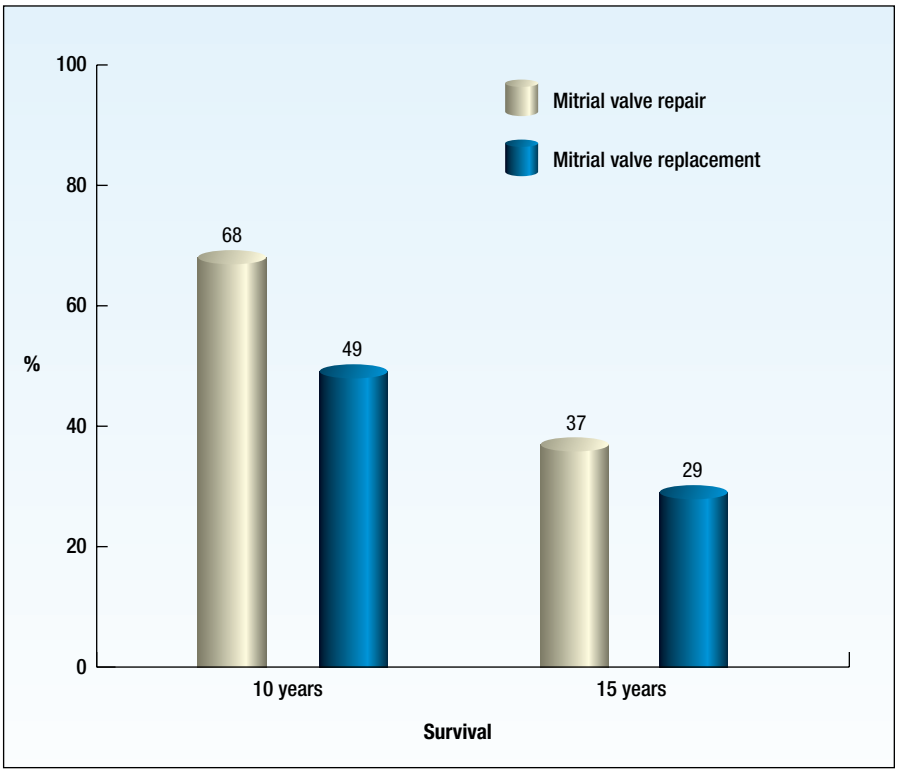

Figure 2. Survival of patients with mitral regurgitation in a study of mitral valve repair versus replacement.

Aortic valve. A problem frequently faced by clinicians is whether to replace a mild or moderately stenotic aortic valve at the time of coronary artery bypass graft (CABG) surgery. A report by Balaban and coworkers from the Cleveland Clinic[9] compared 129 patients who underwent CABG surgery alone with 82 patients who received CABG and aortic valve replacement (CABG-AVR) for mild or moderate stenosis between 1985 and 1995. Patients were followed for a mean of 6.5 years postsurgery. There was similar in-hospital mortality for the 2 groups (3.1% and 3.7% for the CABG and CABG-AVR groups, respectively) but, compared with the CABG group, the CABG-AVR group had significantly improved long-term survival. Multivariate analysis revealed that the predictors of decreased survival were age, failure to replace the stenotic aortic valve, diabetes, peripheral vascular disease, and previous MI. The group concluded that AVR at the time of CABG for mild or moderate aortic stenosis is associated with improved long-term survival without increased operative mortality. Apart from age, AVR is the main predictor of survival.

Mitral regurgitation. Mitral valve repair, rather than replacement, has become a widely accepted procedure for patients with severe mitral regurgitation. Because patients do not require anticoagulation postoperatively, many centers have urged earlier valve repair to protect against the development of LV failure and associated complications. Despite the widespread use of valve repair, neither the very long-term durability of this procedure nor the relationship of type of repair to outcome has been established. Two studies addressed this question. Mohty and colleagues[10] (Mayo Clinic) examined long-term survival and need for reoperation in 917 patients with mitral regurgitation caused by mitral valve prolapse. Surgery was performed between 1980 and 1995—mitral valve repair in 74% and mitral valve replacement (MVR) in 26%. The mean age of patients in both groups was not significantly different. Mitral valve repair demonstrated excellent long-term durability, compared with MVR. Survival was 68% $\pm$ 2% for repair versus 49% $\pm$ 3% for MVR at 10 years and 37% $\pm$ 4% for repair versus 29% $\pm$ 4% for MVR at 15 years (Figure 2). Reoperation rates were not significantly different: 11% $\pm$ 2% for repair versus 15% $\pm$ 3% for MVR at 10 years and 16% $\pm$ 3% for repair versus 23% $\pm$ 4% for MVR at 15 years.

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The patients undergoing mitral valve repair for mitral valve prolapse were subclassified based on the type of repair performed (ie, anterior or bileaflet repair vs posterior leaflet repair). There was no difference in survival at 10 years; however, a higher rate of reoperation was noted in patients with anterior leaflet prolapse, compared with those with posterior leaflet prolapse, at 10 years (18% ± 4% vs 8.2% ± 2%, respectively). Anterior mitral leaflet repair was performed more commonly in the 1990s than in the 1980s, with a trend toward a decreasing rate of reoperation at 7-year follow-up.

The authors concluded that in patients with mitral regurgitation caused by mitral valve prolapse, the durability of mitral valve repair is at least as good as that following MVR, with similar rates of reoperation and improved survival. Mitral valve repair proved to be superior for patients with posterior mitral leaflet prolapse, compared with those with anterior leaflet prolapse, with similar survival but lower reoperation rates. This excellent long-term durability of mitral valve repair was felt to strengthen the argument for early intervention in patients with significant mitral regurgitation.

In a similar study, Braunberger and coworkers[11] (Hospital Broussais, Paris) reported on 162 consecutive patients who underwent mitral valve repair between 1970 and 1984. Annuloplasty was performed in all patients, valve resection in 126 patients, and shortening or transposition of chordae in 49 patients. Median follow-up was 17 years. One-month mortality was 1.9%, with an additional 3 patients with severe mitral regurgitation requiring early valve replacement (2) or revision of the repair (1). The 20-year Kaplan-Meier survival rate was 48%. Seven late reoperations were required after 3, 7 (2), 8 (2), 10, and 12 years. MVR was necessary in 5 patients and repair, in 2. Repair provided excellent long-term results, with mortality similar to that in the general population.

Taken together, these studies from experienced centers provide confirmation of the excellent long-term results of mitral valve repair and support the argument for early intervention in patients with severe nonrheumatic mitral regurgitation.

Aortic regurgitation. Sudden death is rarely reported as a complication of severe aortic regurgitation in patients treated medically. Between 1985 and 1994, Avierinos and associates[12] studied 246 patients with grade III or IV aortic regurgitation (determined by echocardiography). The mean follow-up was 84 ± 21 months; 43 deaths occurred, 12 of which were sudden. The sudden death rates at 5 and 10 years were 7.1% and 10.1%, respectively, and the linearized rate was 1.3% per year. At presentation, the patients experiencing sudden death were older (71 vs 55 years), were more often female, and more frequently had CHF. The percentage of patients with an LV EF of less than 55% or an LV end systolic diameter/BSA of more than 25 mm was higher among the group with sudden death.

By multivariate analysis, only LV dysfunction and CHF at presentation were predictors of sudden death. The sudden death rate among patients who did not present with LV dysfunction or CHF was 3.8% at 5 years, with a linearized rate of 0.5% per year. This report is consistent with previous data from this group in emphasizing the risk of sudden death in patients with CHF caused by valvular regurgitation. The potential salutary effect of surgical intervention remains to be determined. [Arthur E. Weyman, MD]

Aortic Stenosis: An Old Disease Attracts New Attention

For decades, degenerative aortic stenosis has been considered a progressive disorder that requires surgery when it becomes severe and symptomatic. Such conventional wisdom is being questioned now. Increasing attention is paid to factors responsible for the evolution of degenerative aortic stenosis, to approaches designed to halt its progression, and to the management of aortic stenosis. A few studies presented at the American Heart Association Scientific Sessions noted that LDL cholesterol could be a risk factor for progression of aortic stenosis and that statin therapy has the potential to attenuate such progression.[13-15]

Stenosis. A case-controlled study of 101 patients with aortic stenosis showed high leptin levels and suggested the possibility that leptin could be an important link between metabolic dysfunction and the development of calcific aortic valve disease in old age.[16] The role of inflammation in the evolution of aortic sclerosis has also been raised by studies that noted a strong correlation between C-reactive proteins, aortic sclerosis, and adverse cardiac events.[17] Analysis of excised human aortic valve in patients with aortic valve lesions has shown that ACE is present in these structures and suggested that the extracellular presence of these enzymes may be associated with retained lipoproteins.[18] These observations raise the interesting possibility that macrophage-generated and/or lipoprotein-associated ACE may play a role in the pathogenesis of aortic stenosis. This and the role of in-

flammation are areas that are likely to undergo further research.

Valve surgery. An innovative effort to find a new approach to aortic valve surgery is tissue engineering of valvular structures. Taylor and colleagues[19] (Imperial College School of Medicine, United Kingdom) have demonstrated the feasibility that aortic valve interstitial cells seeded in a biodegradable collagen sponge can be nurtured to grow and yield a viable valve structure that exhibits the dynamic morphology and several of the phenotype markers found in a normal valve. This could pave the way for future implantation of such valves, rather than of traditional prosthetic valves, in patients with valvular disease. [Natesa G. Pandian, MD]

Beta Radiation for In-Stent Restenosis

Ron Waksman, MD[20] (Washington, DC, Heart Center), presented the results of the prospective, multicenter, blinded Intimal Hyperplasia Inhibition with Beta In-Stent Trial (INHIBIT) in patients with in-stent restenosis. The purpose of the trial was to assess the safety and effectiveness of intracoronary beta radiation using a radioactive phosphorus (^{32}P) source wire delivered into a centering balloon catheter via an automatic afterloader.

Restenosis. Included in the trial were patients older than 18 years who had angina and more than 50% (by visual estimate) in-stent restenosis. Target lesion reference diameter was between 2.4 and 3.7 mm, with the length of the treated lesion less than 47 mm. Patients were excluded if there was a greater than 30% residual stenosis following treatment, recent MI, unprotected left main CAD, prior chest or vessel radiotherapy, or contraindication to antiplatelet therapy. In the study, 332 patients were randomized to ^{32}P or placebo. The 2 groups had target vessels and lesions of similar character.

At 9-month follow-up, major adverse cardiac events (MACE = death + Q wave MI + target lesion revascularization) were reduced by 56% (P = .0001) in the group receiving brachytherapy. MACE with any target vessel revascularization was reduced by 33% (P = .037). The late thrombosis rate of 1.8% was similar to that seen in the placebo group of 0.6%.

The results of INHIBIT are consistent with the improved restenosis rates seen with other brachytherapy trials, including BERT (Beta Energy Restenosis Trial)[21] and BETA WRIST (Beta-Washington Radiation for In-stent Restenosis Trial).[22] The delivery system used in INHIBIT is notable for its ease of use for more distal disease as well as for its use of a centering balloon to deliver the appropriate radiation dose to opposing vessel walls, particularly in tortuous vessel segments. [Norman E. Lepor, MD]

IIb/IIIa Inhibitors: The TARGET Trial

TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Outcomes)[23] was one of the most anticipated trials presented in New Orleans. This study attempts to determine if the small molecule glycoprotein (GP) IIb/IIIa inhibitor tirofiban is equivalent to the monoclonal antibody abciximab in a head-to-head comparison.

TARGET. A total of 4812 patients undergoing percutaneous coronary intervention (PCI) was randomized to either tirofiban or abciximab in a blinded fashion. A placebo infusion bag was hung with the active drug bag to maintain the blinded intent. The primary composite end point was death, MI, or urgent revascularization at 30 days.

The primary end point occurred in 7.55% of the tirofiban group and in 6.01% of the abciximab group (P < .037; hazard ratio, 1.27). The death rate was no different at 0.5% for tirofiban and 0.4% for abciximab; urgent revascularization also was not statistically different at, respectively, 0.9% and 0.7%. The MI rate was 6.88% for tirofiban and 5.43% for abciximab (P = .040; hazard ratio, 1.27), while the periprocedure MI rate for these medications was 6.05% and 4.97%, respectively (P = .109; hazard ratio, 1.22).

The increased incidence of MI seems to occur across all sizes of infarction (creatine phosphokinase [CPK]-MB > 5%, >10%, Q wave MI). Thus, the major overall difference between the 2 agents is an absolute increase of just 1.45 additional MIs in 100 patients treated with tirofiban, compared with no significant difference in mortality or need for revascularization between tirofiban and abciximab.

Several unsolved issues remain to be determined in the upcoming months, after the data have been analyzed more thoroughly. There seems to be no significant difference in the composite events between the treatment groups among US patients: 7.64% versus 6.72% (hazard ratio, 1.14). Among non-US patients receiving abciximab (n = 999), compared with the US patients receiving it (n = 4600), there is a surprisingly low event rate: 2.88%, compared with 7.37% (hazard ratio, 2.59). It is unclear why this is the case. The recent GUSTO-IV[24] trial (patients with acute coronary syndrome [ACS] receiving abciximab) seems to suggest that abciximab has much less effect in upstream use in patients with ACS.

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Why abciximab is so much more effective in patients undergoing PCI is perplexing. Some possibilities include the use of different heparin and medical stabilization before PCI, potentially leading to the formation of older thrombus. Of interest are other preliminary results of TARGET: in non-ACS patients, the event rates for tirofiban and abciximab are very similar (4.8% vs 5.6%, respectively).

Nevertheless, abciximab seems to be superior to tirofiban by a small but significant margin. What are the possible mechanisms?

- One possibility is that the tirofiban dose used in TARGET was insufficient to achieve the 90% platelet inhibition that may be required in PCI (as suggested by the GOLD study[25]).
- Liu and colleagues[26] suggested that the tirofiban dose used in TARGET may be insufficient to inhibit platelet aggregation above 90% at 10 minutes.
- Another possibility is that the benefit of abciximab is caused by the non-GPIIb/IIIa effect; that is, binding to Mac-1 or the vitronectin receptor.

So how do we integrate these results into our clinical practice? We have several choices:

- Perform all PCIs using abciximab; this will reduce MIs by 1.5 per 100 patients treated and will cost approximately $100,000 per 1.5 MIs saved.
- Switch all treatment to eptifibatide. What do we know about how it compares with abciximab? Not much, because there is no head-to-head comparison. The ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy Trial)[27] data show a composite end point of 6.4% versus placebo in a relatively lower risk group of patients.
- Continue current practice and await further analysis of TARGET data to see if any subgroups treated have more equivalence, so we can better risk-stratify patients.

There is certainly no dull moment in the GPIIb/IIIa world! [Alan C. Yeung, MD]

Lowering the Risks in Vascular Medicine

Epidemiology of PAD and stroke. Epidemiologic features of peripheral arterial disease (PAD) derived from large population-based studies were the focus of several featured research presentations. Dr Alan T. Hirsch (University of Minnesota Medical School), and colleagues[28] reported findings from a national survey of PAD in office-based practices that participated in the PARTNERS (Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival) program.

In this epidemiologic survey, the prevalence of PAD and other cardiovascular diseases was assessed in 6979 persons considered to be at risk for atherosclerosis. These included patients aged 50 to 69 who had a history of either cigarette smoking or diabetes and patients aged 70 or older. The diagnosis of PAD was established by chart review and measurement of the ankle/brachial index (ABI). Other cardiovascular diseases included CAD, cerebrovascular disease, and aortic aneurysms.

Of the population included in this survey, 13% had evidence of PAD only, and 16% had both PAD and other cardiovascular diseases, totaling 29% with PAD. Physicians had made the diagnosis in only 45% of persons who had PAD alone. Fewer than half of all patients with PAD had been aware of the diagnosis. Thus, this study detected a high prevalence of PAD in patients at risk for atherosclerosis. The authors suggested that failure to diagnosis PAD might prevent the initiation of effective treatment to reduce adverse cardiovascular events.

Dr Wouter T. Meijer and coworkers[29] (the Netherlands) presented a study examining the determinants of PAD in the elderly based on the Rotterdam study. This population-based study included 6450 persons aged 55 or older. PAD was established by an ABI measurement of less than 0.90. Several factors were independently associated with PAD, including age of 75 years or older, fibrinogen level, cigarette smoking, diabetes mellitus, and systolic blood pressure. There was an inverse relationship between HDL cholesterol and PAD. The authors emphasized that prevention of PAD should include measures that address each of these risk factors.

In a separate report, Dr Meijer and associates[30] assessed the association between glucose and insulin and the progression of PAD (as defined by an ABI of less than 0.9). The ABI was measured on 2 occasions, 2 years apart. Baseline glucose, but not insulin, was associated with a decline in the ABI. These findings point further to the importance of an elevated serum glucose level as a risk factor for PAD.

Dr Joanne M. Murabito and colleagues[31] (Framingham, Mass) reported on the prevalence and clinical determinants of PAD in the Framingham Offspring Study. They examined the prevalence of PAD and its risk factors in 1554 men and 1759 women whose mean age was 59 years and who attended a Framingham Offspring Study examination. PAD was established by an ABI measurement of less than 0.90. The prevalence of PAD was 3.9% in men and 3.3% in women. In men,

age, smoking, high blood pressure, and the presence of coronary disease were significantly associated with PAD. In women, diabetes, smoking, high blood pressure, and fibrinogen level were independently associated with PAD. The authors emphasized the importance of smoking cessation and treatment of hypertension as a means of reducing both the prevalence of PAD and the associated risk of other cardiovascular diseases.

The relationship between dietary intake of folic acid and the risk of stroke, over an average of 19 years of follow-up, in the 9776 men and women who participated in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study was reported by Dr Lydia A. Bazzano and colleagues[32] (New Orleans and Bethesda, Md). Dietary folic acid intake was divided into quartiles. Median intake was 405 µg/d in the highest quartile and 99 µg/d in the lowest quartile. There were 928 stroke events. The relative risk for a stroke was 0.86 in the highest quartile, compared with those in the lowest quartile. Thus, the authors' observations suggest a strong inverse relationship between dietary intake of folic acid and subsequent risk of stroke.

Reducing risk of vascular surgery. Risk assessment of patients undergoing noncardiac vascular surgery and the effect of treatment in these patients were the subjects of several presentations. Dr Don Poldermans and associates[33] (the Netherlands) examined the long-term prognostic value of dobutamine stress echocardiography (DSE) and other clinical cardiac risk factors in 1326 patients who were screened before vascular surgery. Clinical cardiac risk factors were defined as age older than 70, angina, MI, CHF, diabetes mellitus, cardiac arrhythmias, or reduced exercise capacity. Patients were divided into groups of those with no risk factors, those with 1 or more risk factors but no new wall motion abnormalities on DSE, and those with 1 or more risk factors who had new wall motion abnormalities on DSE. The annual incidence of adverse cardiovascular events in those with no risk factors was 0.8%; in those with risk factors but no wall motion abnormalities, 3.4%; and in those with risk factors and new wall motion abnormalities, 12.7%. The authors concluded that DSE was useful in determining long-term prognosis in terms of adverse cardiovascular events in patients who had undergone vascular surgery.

The need for preoperative screening by DSE in patients already treated with β-blockers was the subject of a presentation by Dr Eric Boersma and colleagues[34] (the Netherlands). Data from patients scheduled for vascular surgery were used to develop a risk score for adverse cardiovascular events, including cardiac death or MI within 30 days of surgery. Clinical predictors of adverse outcomes included age older than 70, angina, previous MI, CHF, and previous stroke. Each of these clinical predictors was given a risk score. DSE did not provide additional prognostic information in patients already treated with β-blockers who had a low summed risk score, whereas the test did add additional prognostic information in patients with high summed risk scores. Thus, the use of DSE can be targeted to specific patients with multiple clinical predictors of adverse outcomes to identify those in whom additional cardiac evaluation might be indicated before vascular surgery.

The benefit of β-blocker therapy in reducing long-term adverse cardiovascular events in high-risk patients after major vascular surgery was reported also by Dr Poldermans and colleagues.[35] High-risk patients were defined by the presence of 1 or more cardiac risk factors, including age older than 70, angina, MI, heart failure, diabetes mellitus, cardiac arrhythmias, or reduced exercise capacity, and by a positive dobutamine stress echocardiogram (demonstrating new wall motion abnormalities). Of 1351 patients screened before major vascular surgery, 112 patients with 1 or more risk factors and abnormal dobutamine stress echocardiograms were randomized to bisoprolol therapy or standard care. Of these, 11 died in the perioperative period.

Long-term follow-up was conducted in the remaining patients. Cardiac events, defined as cardiac death or nonfatal MI, occurred in 8.8% of patients randomized to bisoprolol and in 27% of patients randomized to standard care, accounting for a hazard ratio for cardiac death or MI after surgery of 0.24. The authors concluded that bisoprolol reduced long-term adverse cardiovascular events in high-risk patients after they had undergone successful major vascular surgery.

Management of abdominal aortic aneurysm. The results of the Department of Veterans' Affairs Aneurysm Detection and Management (ADAM) study were reported by Drs F. A. Lederle, S. E. Wilson, and G. R. Johnson.[36] This was a multicenter randomized trial conducted at 16 Veterans' Affairs medical centers and involved 1136 veterans with abdominal aortic aneurysms (AAAs) ranging from 4.0 to 5.4 cm in diameter. Patients were randomized to immediate open surgical repair of the AAA or to image surveillance with elective repair of AAAs larger than 5.5 cm. Operative mortality at 30 days,

including those who had immediate surgery as well as those who had surgery during the surveillance period, was 1.8%. Over a mean of 4.8 years of follow-up, death occurred in 141 of the 569 patients treated with immediate surgery and in 121 of the 567 patients randomized to surveillance (relative risk, 1.20; $P = .14$). AAA rupture occurred in 9 patients in the surveillance group, accounting for a risk of 0.5% per year. The authors concluded that long-term survival is not improved by repair of an AAA smaller than 5.5 cm even when the operative mortality is low; they recommended deferring repair until the AAA increases to 5.5 cm. [Mark A. Creager, MD]

The Stories Imaging Is Telling

Although issues of women's health in cardiovascular disease have been the focus of investigations for a number of years, some questions have not been addressed adequately. We know that women have a survival benefit relative to men, probably related to hormonal status, but that this advantage disappears with advancing age. Further, it has been shown that women fare worse than men when diabetes is present.

Coronary flow. DiCarli and colleagues[37] (Wayne State University and the University of California, Los Angeles) examined coronary flow in premenopausal diabetic women, using nondiabetic premenopausal and postmenopausal women as controls. At baseline, positron emission tomography (PET) imaging with ammonia as the flow agent measured coronary flow during peak hyperemia (using intravenous adenosine, a measure of vasodilator function) and in response to a cold pressor test (a measure of endothelial function).

Baseline flow in the premenopausal diabetic women was similar to that in the premenopausal and postmenopausal controls, after adjusting for rate pressure product. The increase in coronary flow during hyperemia relative to baseline in the premenopausal diabetic women (163% mean increase) was significantly less than that in the premenopausal control patients (249% mean increase; $P < .01$) and was similar to that in the postmenopausal control patients (203% mean increase; P = NS). Similarly, the increase in coronary flow in response to cold pressor testing in the premenopausal diabetic women (24% mean increase) was less than that in the premenopausal control patients (60% mean increase) and was comparable to that in the postmenopausal control patients (27% mean increase).

These results indicate that diabetes (both type I and type II) may negate the beneficial effects of estrogen on microvascular function in premenopausal women, creating a "premature menopause" at the microvasculature level. This report supports the need for a more aggressive approach to the management of diabetes, a conclusion also supported by data from other recent clinical trials.

Myocardial imaging. The identification of viable but dysfunctional myocardium is a vital step in the identification of patients who will benefit from revascularization. Both metabolic imaging (using thallium Tl-201 single-photon emission CT [SPECT]) and low-dose catecholamine stimulation (eg, low-dose dobutamine echocardiography [LDDE]) are methods commonly used to identify viable myocardium. Perrone-Filardi and colleagues[38] (Naples) identified 69 patients with ischemic cardiomyopathy (mean EF, 40%) who underwent rest Tl-201 imaging and LDDE on the same day before revascularization and resting echocardiography at a mean of 40 days postrevascularization. These 69 patients had 183 myocardial segments found by resting echocardiography to be akinetic or dyskinetic. These segments were categorized as having high, intermediate, or low levels of Tl-201 uptake (demonstrated on rest SPECT).

The ability of positive and negative predictive values of LDDE to identify segments in which function improved on the postrevascularization echocardiogram varied as a function of the amount of resting Tl-201 uptake. The positive predictive value of the dobutamine echocardiogram was 95% and 81% in the setting of high and intermediate Tl-201 uptake, respectively, but decreased to 46% in the setting of low Tl-201 uptake. Conversely, the negative predictive value of the dobutamine echocardiogram was 81% and 56% in the setting of low and intermediate Tl-201 uptake, respectively, but decreased to 29% in the setting of high Tl-201 uptake.

Thus, echocardiographic determination of viability produces frequent false positives when there is little or no viability demonstrated by Tl-201 uptake and produces more false negatives than true negatives when there is viability demonstrated by Tl-201 uptake. If confirmed by other investigators, this study suggests that a metabolic examination of viability may be required as an adjunct to LDDE to enhance accurate detection of optimal revascularization candidates.

ERASE. The ERASE (Emergency Room Assessment of Sestamibi for Evaluating Chest Pain) trial (see review in *Rev Cardiovasc Med.* 2000;1[1]:14-15) was a prospective, multicenter,

randomized clinical trial investigating the impact of rest myocardial perfusion imaging with technetium Tc 99m sestamibi (^{99m}Tc sestamibi) SPECT in emergency room (ER) patients presenting with chest pain suggestive of unstable syndromes (during or within 3 hours of symptoms) in 7 hospitals in the United States. From these sites, 2456 patients (85% of all enrolled) were randomized to 2 arms: usual ER assessment and subsequent care (usual care) versus usual care plus resting, gated sestamibi SPECT imaging. The initial results, presented at the 2000 American College of Cardiology Scientific Session, revealed that the use of acute imaging with resting ^{99m}Tc sestamibi gated SPECT in patients presenting to the ER with possible unstable syndromes significantly reduces the number of unnecessary admissions in patients without coronary ischemia and is cost-effective.[39]

A major concern regarding the use of sestamibi studies in the ER is that of symptoms at the time of sestamibi injection. If the patient is no longer having chest discomfort when sestamibi is injected, is the meaning of a normal scan the same as if the patient is having chest pain when injected? At the current meeting, the ERASE investigators presented the results of the trial with respect to the relationship between outcomes and the presence or absence of chest discomfort at the time of sestamibi injection in the ER.[40] Of the 1215 patients randomized to the sestamibi arm, 1050 were found to have had noncardiac chest discomfort and 815 to have had normal SPECT studies.

The presence of normal studies was similar in patients with and without chest pain at the time of sestamibi injection, although patients injected before resolution of chest pain more frequently received a diagnosis of acute coronary ischemia, compared with patients without pain at the time of injection (11% vs 6%, respectively; $P < .01$). (Of note: patients with a positive follow-up stress test were also considered to have had a diagnosis of acute coronary ischemia.)

Patients without versus with chest pain at the time of sestamibi injection had similar frequencies of, respectively, cardiac death (0% vs 0.2%), MI (0.5% vs 0.9%), catheterization (5% vs 4%), and revascularization (2% vs 1%) (all, $P > .1$). Thus, these results suggest that as long as sestamibi is injected within 3 hours of resolution of pain, the presence of symptoms at the time of injection does not impact the frequency of scan abnormalities or subsequent patient outcomes. [Rory Hachamovitch, MD]

Primary Angioplasty in the Community: New Answers, More Questions

As enthusiasm for primary angioplasty continues to escalate, more and more hospitals are beginning to offer this procedure to patients with acute MI. To date, however, the results of the randomized trials reporting improved outcomes with primary angioplasty in comparison with thrombolytic therapy[41-43] have not been reproduced by the large-scale registries wherein mortality is similar between groups.[44,45]

C-PORT. To determine whether primary angioplasty is superior to thrombolysis when practiced in community hospitals without on-site cardiac surgery, the Cardiovascular Patient Outcomes Research Team (C-PORT)[46] randomized 453 thrombolysis-eligible patients in 11 community hospitals to coronary angiography and angioplasty or to thrombolytic therapy within 12 hours of symptom onset of acute MI with ST-segment elevation (or with left bundle branch block). The trial design included a door-to-needle time of 30 minutes and 48 hours of heparin administration in patients randomly assigned to thrombolytic therapy, an ER-to-balloon time of 90 minutes, and a liberal use of stents and GPIIb/IIIa receptor antagonists (and no angioplasty if Thrombolysis in Myocardial Ischemia [TIMI] grade 3 flow and resolution of ischemia were present) in patients randomly assigned to coronary angioplasty. Baseline demographic and clinical characteristics were similar between groups.

Of the patients assigned to thrombolytic therapy, 90% received such treatment with a door-to-needle time of 53 ± 35 minutes, a clinical success rate of 81%, and a nonprotocol angiography/angioplasty rate at 6 months of 75%. Of the patients assigned to the primary angioplasty strategy, 93% underwent angiography, of whom 75% underwent angioplasty with an ER-to-balloon time of 105 ± 34 minutes and an initial success rate of 91%. No patient was referred for emergency CABG surgery.

The primary end point of the study (a composite of death, nonfatal MI, and stroke at 6 months), occurred in 15.4% of patients in the thrombolytic therapy group and in 10.6% of patients in the primary angioplasty group (31% reduction, $P = .13$). More favorable outcomes occurred in the angioplasty group in patients treated at hospitals performing more than 1 primary angioplasty procedure per month; no difference in outcomes occurred between groups in patients treated at hospitals performing less than 1 primary angioplasty procedure

per month. It was concluded that in thrombolysis-eligible patients with ST-segment elevation MI, coronary angioplasty may be superior to thrombolytic therapy when performed at relatively high-volume primary angioplasty centers in community hospitals without on-site surgery.

These data, while promising, need to be interpreted with caution. It should be noted that the overall sample size was small and that, because of lack of funding, the trial was stopped prematurely after entry of only 18% of the target enrollment. In addition, all institutions participating in the C-PORT Trial underwent a 3- to 6-month period of implementation, during which time the development of a formalized primary angioplasty program was instituted that included the setting of standards, training of (ER, coronary care unit, and cardiac catheterization laboratory) staff, detailed logistic development, and creation of a quality- and error-management system. Each hospital had a written agreement with a tertiary facility to provide additional cardiac invasive services, including cardiac surgery, and an agreement with an advanced cardiac life support and intra-aortic balloon pump–capable transport service to arrive at the C-PORT institution within 30 minutes of a call. Furthermore, participating interventionists performed a minimum of 75 coronary intervention procedures per year.

These pilot data should support our enthusiasm for continued evaluation of patients undergoing primary angioplasty in diagnostic cardiac catheterization laboratories in the hope of corroborating these findings in larger patient populations. Current trends and clinical intuition make it likely that a community hospital (without on-site surgery but with an institution-wide commitment to a program of primary angioplasty that assures adequate institution and operator procedural volume) will be able to offer the procedure to patients with ST-segment elevation MI, in anticipation of outcomes superior to those associated with thrombolytic therapy. [Alice K. Jacobs, MD]

Effective Management of Obtuse Coronary Syndrome

The TACTICS (Treat Angina with Aggrastat and determine Costs of Therapy with an Invasive or Conservative Strategy, TIMI-18) trial, reported by Christopher Cannon, MD,[47] provides important new information regarding the preferred, contemporary treatment strategy for patients with unstable angina and non–Q wave myocardial infarction.

TACTICS. This multicenter, randomized clinical trial enrolled 2220 patients from 169 sites in 9 countries. The United States was the principal enrolling country. Patients were enrolled if, within 24 hours of admission, they experienced accelerated angina, prolonged angina, or recurrent angina pain at rest or with minimal effort and had at least 1 of the following: ischemic ECG changes, elevated cardiac markers, or a history of CAD. All patients received current medical therapy, including aspirin, heparin, β-blockers and, in some patients, lipid-lowering agents. In addition, all received the GPIIb/IIIa inhibitor tirofiban on admission to the hospital and for 48 to 108 hours thereafter. Patients were then randomized to an early invasive strategy or to conservative therapy.

Patients in the invasive strategy group underwent coronary angiography within 4 to 48 hours (average, 24 hours) and, if indicated, revascularization with CABG or PCI. Those in the conservative therapy group underwent cardiac catheterization only if they had refractory angina, hemodynamic changes, positive exercise test, new MI, or rehospitalization for unstable angina, or for having cardiovascular class 3 to 4 angina with a positive stress test.

The primary end point of the study was a composite of death, MI (defined as a CPK elevation of greater than 3 times normal Q waves), or rehospitalization for acute coronary syndromes within 6 months. The study was powered to detect a 5% difference in outcomes. The study also examined whether patients with an elevated troponin level benefit from an invasive strategy, the so-called "troponin hypothesis." The incidence of revascularization over a 6-month period in these patients averaged 44% in the conservative group and 61% in the invasive group.

The trial demonstrated a clear and statistically significant superiority for the invasive strategy. At 6 months, the primary end point occurred in 19.4% of patients in the conservative group and in 15.9% of patients in the invasive group (OR, 0.78, $P = .025$). Although there was no difference in mortality, the combined end point of death or MI was noted in 9.5% treated conservatively and in 7.3% treated invasively (OR, 0.74, $P < .05$). Differences were evident within 30 days of follow-up, with a primary end point reached at 10.5% of the conservative group and at 7.4% of the invasive group.

A benefit occurred in all subgroups except in those who did not demonstrate ST-segment changes on admission. The troponin hypothesis was also validated with patients who had positive troponin values (54% of pa-

tients). In this group, the primary end point was reduced from 24.2% in the conservative group to 14.3% in the invasive group (OR, 0.5, $P < .001$). Differences between treatment strategies in patients without elevated troponin levels were not significant, but the event rate was actually higher in the invasive arm (16.9% vs 14.5%) (C. Cannon: personal comment).

Major bleeding occurred more frequently in the invasive group (5.5% vs 3.3% in the conservative group), but this was easily managed. When stratified by the severity of TIMI unstable angina risk grade, patients in moderate- to high-risk subgroups (75% of patients) experienced significant benefit from an invasive strategy. Importantly, the groups that failed to show significant benefit from an invasive strategy were those who were troponin-negative (conservative, 14.4%, vs invasive, 16.9%) and those who were low-risk unstable angina patients (conservative, 11.8%, vs invasive, 12.8%).

There have been several previous trials of aggressive versus conservative strategies in patients with unstable angina/non–Q wave MI. The TIMI IIIb[48] and Medicine versus Angiography in Thrombolytic Exclusion (MATE)[49] trials demonstrated no differences between the 2 strategies. In the Veterans Affairs Non–Q Wave Infarction Strategies in Hospital (VANQWISH)[50] trial of non–Q wave MI, patients in the conservative arm fared significantly better at 1 year. Patients in that trial were somewhat less unstable and did not have pretreatment with a GPIIb/IIIa agent; current interventional techniques were not used. In addition, a majority of the patients underwent surgery in the VANQWISH trial; these patients had a high mortality, which resulted in increased risk for the invasive group. The more recent FRagmin and Fast Revascularisation during InStability in Coronary Artery Disease (FRISC) II[51] trial demonstrated the benefit of an invasive strategy following a period of stabilization. TACTICS is the most relevant of these studies in regard to clinical practice in the United States, which is based on the use of stents; a GPIIb/IIIa inhibitor, Tirofiban; and a relatively short delay between admission and angiography in the invasive arm.

All of the previous trials have their strengths and weaknesses but have been helpful in developing therapeutic strategies for patients with non-ST-segment elevation acute coronary syndromes.

- The initial pharmacologic step of stabilization need *not* be followed by an aggressive policy of "routine" angiography in *all* patients. Within these trials and the nonrandomized studies, it is possible to define subgroups at high and low risk within the overall umbrella of unstable angina/non–Q wave MI. Risk stratification is the *key* to management and is based on the use of clinical, demographic, and electrocardiographic variables in addition to serum markers, which (in turn) identify patients with and without severe CAD, LV dysfunction, extensive myocardial jeopardy and, perhaps, an unstable lesion.
- Patients with unstable angina who have no recurrence of pain, no enzyme elevation, and no significant ST-segment depression demonstrated on the ECG are managed, ideally, in a chest pain unit. Such patients can undergo stress testing and be discharged within 24 hours without formal admission to a hospital cardiology service, depending on the results of the stress test.
- Patients with recurrent pain; ST-segment depression; or other features of increased risk, such as previous MI, chronic angina, transient LV failure, and (perhaps) diabetes; and, by definition, patients with non–Q wave MI (based on a troponin level rise or an increase in CPK-MB isoenzymes) should be treated with a GPIIb/IIIa inhibitor and transferred expeditiously for catheterization.

The results of the TACTICS trial do not mandate early angiography in all patients with non–ST-segment elevation ACS but strongly support an aggressive approach in patients considered at higher risk. Moreover, by definition, patients with non–Q wave MI comprise a substantial proportion of all patients with ACS in the absence of ST-segment elevation. TACTICS provides additional strong support for a policy of stabilization followed by risk stratification and early angiography in patients considered at high risk. [David P. Faxon, MD; Bernard J. Gersh, MB, ChB, DPhil]

Is One Antihypertensive Drug Better Than Another?

At a joint American Heart Association/European Society of Cardiology Symposium entitled Implications for Hypertension of Recent Clinical Trials, 5 international authorities summarized their views on how information from recent trials will affect clinical practice decisions. Much attention was directed to the issue of whether any class of antihypertensive drugs is better than another at protecting the cardiovascular system.

HOPE. Peter Sleight, MD[52] (Oxford, England), reported on implications of the Heart Outcomes Prevention Evaluation (HOPE) study,[53] noting the improved cardiovascular morbidity and

mortality with ramipril therapy and the corresponding lack of effect with vitamin E supplementation. The question remains as to whether the benefits in HOPE were the results of independent effects of ramipril or were dependent on blood pressure reduction. Because the blood pressure data in HOPE were not gathered in a truly systematic way, the question cannot be answered definitively. Although both normotensive and hypertensive patients benefited from ACE inhibitor therapy, there was a tendency for greater benefit in those with the highest blood pressures.

Heart failure. Philip Poole-Wilson, MD[54] (London, England), described the relationship between heart failure and hypertension. His most important conclusion was that the treatment of hypertension was significant both in preventing heart failure and in optimizing outcomes among those with established heart failure. In analyzing the respective roles of ischemic heart disease and hypertension in the etiology of heart failure, he found little evidence that the incidence of heart failure was directly dependent on blood pressure. His conclusion that ischemic heart disease is more important than hypertension in the etiology of heart failure differs from that of the Framingham heart study, which said that hypertension is more important than coronary heart disease as an etiologic factor in heart failure.

CAPPP/STOP-2. Lennart Hansson, MD[55] (Uppsala, Sweden), reported the results of the Captopril Prevention Project (CAPPP)[56] and the Swedish Trial in Old Patients with Hypertension-2 (STOP-2).[56] In CAPPP, ACE inhibition conferred benefit equal to that of diuretic-based therapy, but Dr Hansson did not discuss whether CAPPP had the necessary statistical power to draw any conclusions regarding equivalence of drug effect.

In STOP-2, Dr Hansson again concluded that it was the lowering of blood pressure rather than a specific class effect that conferred benefit. His analysis of the STOP-2 data is extremely problematic. STOP-2 had 3 treatment arms: diuretic (with or without β-blocker), ACE inhibitor, and calcium antagonist. The statistical analysis, however, lumped together "newer therapy" (the ACE inhibitor and calcium blocker treatment arms) before comparing "newer therapy" with "older therapy" (the diuretic arm). This analysis defies logic because of the heterogeneous results obtained in the ACE inhibitor and calcium antagonist treatment arms.

In a secondary analysis, calcium antagonists were slightly superior to ACE inhibitors in stroke protection, but ACE inhibitors were clearly superior to calcium antagonists in preventing cardiac events (ischemia- and heart failure–related). These divergent results for "newer therapy" underscore the problem of lumping the 2 classes together before comparing them with the thiazide diuretic. Although not discussed directly, the more appropriate statistical analysis, a 3-way ANOVA comparison, was probably not done, because the study was substantially underpowered to answer the question of equivalency.

Diabetes. Norman Kaplan, MD[57] (Dallas), described the recent trials for diabetic hypertensive patients, including Systolic Hypertension in Europe (Syst-EUR),[58] Hypertension Optimal Treatment (HOT),[56] Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET),[59] Appropriate Blood Pressure Control in Diabetes (ABCD),[60] and UK Prospective Diabetes Study (UKPDS).[61] He concluded that it was rigorous blood pressure lowering, to a systolic target of 130 mm Hg or less, that was the principal reason for reduced morbidity and mortality in patients in these trials. Dr Kaplan identified greater absolute benefit of therapy for patients with diabetes—a high-risk population—compared with patients in a lower-risk population, commenting that the statistical benefits achieved in the HOT trial were related to the benefits in the diabetic subgroup rather than to those in the population as a whole. He suggested that calcium blockers were more effective than ACE inhibitors at reducing stroke but conceded that there was a trend toward more favorable effects of ACE inhibitors in preventing cardiac effects in patients with diabetes. Despite this trend, Dr Kaplan concluded that there is no definitive evidence of superiority of 1 class of antihypertensive drugs for overall cardiovascular protection.

ALLHAT. Curt Furberg, MD[62] (Winston-Salem, North Carolina), reviewed the existing knowledge in the area of hypertension outcomes and identified criteria for future hypertension trials to answer the question of whether 1 class of agents is superior to the others. He cited the recent discontinuation of the α-blocker arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[63] as evidence that all antihypertensive drugs do not have equal power to protect the cardiovascular system despite similar effects on blood pressure. In discussing the number of events needed to demonstrate statistical superiority of 1 class of drugs over another, he indicated that, to date, no single trial has included the minimum number of

events needed to achieve sufficient statistical power to claim superiority. His own meta-analyses have sufficient statistical power to demonstrate superiority of ACE inhibitors over calcium antagonists in reducing cardiac events. New clinical trials with sufficient sample size to answer the question prospectively are needed.

At the end of the symposium, the listener was left with the feeling that while progress has been made, more questions remain unanswered than have been answered. There was a general consensus that blood pressure control to a target of 140/90 mm Hg in uncomplicated patients, or to 130/85 mm Hg or lower in diabetics and other high-risk patients, was important in reducing morbidity and mortality. In some trials, particularly in those involving diabetics, ACE inhibitors have shown a trend toward enhanced cardiovascular protection (HOPE, ABCD, FACET, STOP-2). The Furberg meta-analysis confirms this trend. Those studies in which ACE inhibitors were not found to be superior to other classes (UKPDS, CAPPP) did not have sufficient statistical power to answer the question of possible ACE inhibitor superiority. Thus, it seems likely that ACE inhibitors may offer greater cardioprotection than do other classes, but definitive proof is lacking. It is also important to understand that there are no data suggesting that the use of calcium antagonists should be minimized or discontinued. Quite the contrary; to optimize blood pressure reduction, calcium antagonists are often required. To be prudent, it may be wise to combine calcium antagonist therapy with ACE inhibitors or β-blockers, but there is an absence of definitive outcomes data using these combinations. More competent clinical trial data will be required to definitively test the assertions of drug class superiority. [Joseph L. Izzo, Jr, MD] ■

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