Best of the AHA Scientific Sessions 2003

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In conjunction with the 2003 Scientific Sessions of the American Heart Association (AHA), abstracts were published reporting significant recent findings in every major area of cardiovascular medicine. Here, our editorial board members report on selected findings of particular importance.

SPORTIF V

Patients with atrial fibrillation at high risk for stroke require long-term anticoagulation. For decades, the drug of choice to achieve this treatment goal has been warfarin. More recently, a direct thrombin inhibitor, ximelagatran (Exanta,® AstraZeneca LP, Wilmington, DE) has been studied in patients with atrial fibrillation to evaluate its efficacy and safety profile in the prevention of stroke. The previously presented Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III trial, comparing ximelagatran with warfarin, demonstrated non-inferiority of ximelagatran in the prevention of stroke, without any significantly increased risk of bleeding. At this year's AHA meeting, the results from SPORTIF V were presented by Dr. Jonathan L. Halperin[1] of the Mount Sinai Medical Center in New York, NY.

In SPORTIF V, 409 sites in the United States and Canada enrolled 3,922 patients. Eligibility required presentation with nonvalvular atrial fibrillation and at least one stroke risk factor. Patients were randomized to dose-adjusted warfarin or to ximelagatran, 36 mg twice daily, with an attempt to target international normalized ratio (INR) for prothrombin activity between 2.0 and 3.0. Statistical analysis evaluated ximelagatran for noninferiority to warfarin in the prevention of strokes and systemic embolic events. This was the primary objective of the study.

The results of SPORTIF V showed the primary endpoint reached in 51 and 37 patients with ximelagatran and warfarin, respectively. The absolute difference was 0.45% using an intention-to-treat analysis, which was not significant. Of note, the on-treatment analysis demonstrated a + 0.55% per year absolute difference for ximelagatran compared with warfarin.

The safety results were divided into intracerebral hemorrhage and major bleeding, defined as bleeding

leading to death, affecting a critical anatomical site, requiring transfusion, or decreasing hemoglobin by 2 g/dL. For both treatment groups, these two major endpoints for safety occurred relatively infrequently, with intracerebral hemorrhage rates of 0.06% per year for ximelagatran and 0.06% per year for warfarin, (P = ns). Major bleeding occurred in 2.4% and 3.1% per year for ximelagatran and warfarin, respectively, (P = ns). Of note, combining major and minor bleeding yielded a slight advantage to ximelagatran at 37% per year compared with warfarin at 47% per year (P = ns).

The results of SPORTIF V support and extend those previously documented in SPORTIF III.

Consistent with previous SPORTIF trials, ximelagatran therapy was associated with a significant increase in elevated serum transaminase enzymes. Elevations more than three times the upper limit of normal occurred significantly more often in patients receiving ximelagatran (6%) compared with the warfarin group (0.8%). According to Dr. Halperin, liver enzyme elevations typically occurred within the first two to six months of starting treatment but often normalized, whether or not treatment was continued.

Discussion

The results of SPORTIF V support and extend those previously documented in SPORTIF III. As a clinician who commonly treats patients with atrial fibrillation and prescribes warfarin on a weekly, or even daily, basis, I am very excited by the potential impact of ximelagatran on patient care. Few issues are more troublesome to physicians and patients than the long-term management of INR levels. Even in the best circumstances, as with patients closely watched in randomized clinical trials, nearly 33% of the time, patients are outside the boundaries of ideal INR values. Clinicians know that it only takes a few extra salads in a particular patient to upset previously controlled values.

Studies have documented that nearly 50% of patients with atrial fibrillation who require anticoagulation are not receiving it. Oft-quoted reasons include physician fear of bleeding complications in patients and the unwillingness of patients to undergo frequent blood draws for regulation of INR. Assuming ximelagatran continues with its current efficacy and safety profile, I anticipate that the majority of patients now receiving warfarin will be switched. In addition, many more patients who require anticoagulation will hopefully receive it. This should result in a marked decrease in stroke, without an increase in complications. On the other hand, a risk-management program will need to be developed regarding liver enzyme abnormalities prior to widespread use of ximelagatran and cost issues may be a factor as warfarin is obviously inexpensive and the cost of ximelagatran is not known.

DEFINITE TRIAL

Dr. Alan Kadish[2] of Northwestern University in Chicago, IL, reported on the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial. This was a multicenter randomized investigation that enrolled 458 patients with nonischemic dilated cardiomyopathy and a left ventricular ejection fraction lower than 35%. Also required for enrollment was a history of spontaneous nonsustained ventricular tachycardia or premature ventricular complexes. Patients were randomized to receive standard medical therapy or standard medical therapy plus an implantable cardioverter defibrillator (ICD). The primary endpoint was all-cause mortality.

At two years, the primary endpoint rates in patients receiving standard medical therapy (n = 229) compared with standard medical therapy plus ICD (n = 229) was 13.8% versus 8.1% (P = 0.06). There were 33 deaths in the standard treatment group compared with 23 deaths in the ICD group. This 34% reduction in all-cause mortality approached but did not clearly reach statistical significance. Of note, 11 of the 14 arrhythmic deaths occurred in the standard medical therapy group, resulting in a 74% relative reduction in risk for patients receiving an ICD ($P < 0.05$).

Discussion

Primary prevention of sudden death with ICDs has been the focus of much research during the past 10 to 15 years. Three studies in patients with coronary artery disease and left ventricular dysfunction (MUSTT, MADIT, and MADIT II) have shown conclusively that, in selected patients, ICD therapy can reduce risk of total mortality. However, similar data are not available for patients with nonischemic dilated cardiomyopathy. The DEFINITE study is a well-executed investigation that has addressed this important question. Survival data correlates with similar findings noted in other trials utilizing ICDs in patients with coronary artery disease, although they did not reach statistical significance. On the other hand, total patient enrollment was

not high and the overall mortality rate was lower than anticipated. It seems logical that larger patient numbers might have yielded a significant result. Regardless, at the present time one cannot use these data solely to justify implantation of an ICD in a patient with characteristics similar to those identified in DEFINITE. Hopefully this issue will be clarified with the results from SCD HeFT, which should be presented within the next six months.
[Eric N. Prystowsky, MD]

Heart Failure

Dr. Claude Yancy of the University of Texas Southwestern Medical Center in Dallas, TX, reported on the FUSION Trial,[3] a randomized, open-label, pilot trial that evaluated the efficacy, safety, and tolerability of serial outpatient therapy with nesiritide (NES) in patients with chronic decompensated heart failure, a population at high risk for re-hospitalization for heart failure and death. The trial included 210 patients with New York Heart Association (NYHA) Class III/IV heart failure on optimal oral medical therapy, randomized to low-dose NES (0.005 μg/kg/min), standard-dose NES (0.01 μg/kg/min) or standard care + placebo (SC) for 12 weeks, with a one month follow-up. NES was administered 1-2 times weekly for 4-6 hours. Randomization was stratified to high (> 4 risk factors) or low risk (< 4 risk factors). Risk factors included serum creatinine > 2.0 mg/dL, NYHA Class IV, age > 65 years, sustained ventricular tachycardia, ischemic etiology of heart failure, diabetes, and outpatient use of NES or inotropes within the last six months.

After 12 weeks, 52% of the NES patients were alive and free of hospitalization versus 42% of SC patients ($P = 0.185$). For the high risk cohort, NES resulted in a median of 83 days alive and out of hospital and a mortality rate of 4.6% ($P = 0.027$). For SC patients at high risk, the median result was 77 days alive and out of hospital and mortality of 17.4% ($P = 0.079$). The authors concluded that weekly infusions of NES administered to patients with chronic decompensated heart failure are well-tolerated, safe, and promote improved clinical outcomes compared to SC, particularly in patients at high risk.

At the present time, few outpatient treatment options are available for the most severely ill heart failure patients, who seem to spend more time in the hospital than out. The use of outpatient inotropic-based therapies has been shown to increase the mortality of patients with chronic decompensated heart failure. The results of the FUSION trial provide hope that, with the use of NES, we will have an outpatient treatment option that not only enhances the clinical status of these patients, but also reduces mortality and hospitalization rates. We look forward to a definitive clinical trial.

NES has also been shown to be an effective vasodilator for the treatment of acute decompensated heart failure. It is currently administered as an intravenous infusion. However, clinical data suggesting a benefit when administered long term on an outpatient basis makes the potential for subcutaneous delivery a major improvement in convenience. Dr. Horng H. Chen of the Mayo Clinic in Rochester, MN, presented a study[4] conducted as a pilot trial in five subjects with NYHA Class II or III heart failure, where 10 μg/kg of NES were administered twice daily, subcutaneously, for eight weeks. Chronic subcutaneous administration of NES resulted in a reduction of angiotensin II levels from 101 pg/mL to 12 pg/mL ($P < 0.05$) and trends toward a reduction of left atrial and left ventricular volumes, with no evidence for tachyphylaxis. The authors conclude that the results of this pilot trial support further evaluations for the use of subcutaneous NES in heart failure patients.

CT Assessment of Coronary Atherosclerosis

A series of abstracts were presented on the ability of noninvasive computed tomography (CT) coronary imaging to detect the presence of atherosclerosis. New 16-slice technology has created the impetus for this exciting, fast-progressing area of investigation.

Dr. Alex Leber[5] of the Klinikum Grosshadern, Munich, Germany, reported on noninvasive detection and differentiation of coronary plaques using 16-slice CT versus intracoronary ultrasound. Of the original 46 consecutive patients who were selected for participation, 7 were excluded due to insufficient heart-rate control and 2 for renal insufficiency. In the remaining 37 patients, 68 coronary vessels were evaluated by 3-dimensional intracoronary ultrasound as the gold standard. Of the 68 coronary vessels, 58 (85%) could be imaged with the 16-slice CT (Sensation 16, Siemens Medical Solutions USA, Inc., Malvern, PA) with sufficient image quality, based on analysis performed by blinded observers. The 16-slice CT method correctly classified 62 out of 80 (78%) of the sections containing soft plaque with a derived density measurement of 49 HU ± 22, 87/112 (78%) sections containing fibrous plaque with a density measurement of 91 HU ± 22, and 150/158 (95%) of sections containing calcified plaques with a density measurement of 391 HU ± 156. In 484/525 (92%) of sections atherosclerosis was correctly excluded.

Dr. Thomas Athanasiou[6] of Tuebingen University in Tuebingen,

Germany reported a study of 9 human popliteal arteries derived from amputations and investigated to determine the ability to identify plaque morphology, utilizing 16-slice CT imaging. Plaques were evaluated according to the Stary classification. Density values of lipid-rich plaques (Stary III, V), fibrotic plaques (Stary VIII), and calcified plaques (Stary VII) were significantly different ($P < 0.001$).

The authors concluded that multislice CT scanning has the capability to differentiate plaque morphology in an isolated arterial specimen. The ability to distinguish plaque morphology in a noninvasive fashion may allow us to follow the effects of various plaque stabilizing therapies, including lipid-lowering therapies, and help identify those plaques that may be at the highest risk of rupture.

Oral Direct Thrombin Inhibition

The oral direct thrombin inhibitor ximelagatran has been shown to be very effective compared to warfarin for the prevention of thromboembolic complications in patients with atrial fibrillation and the prevention and treatment of venous thromboembolism. The ability of ximelagatran with aspirin to prevent complications of acute myocardial infarction (MI), including death, nonfatal MI, and recurrent severe ischemia (RSI) was evaluated in a phase II, placebo-controlled, double-blinded, multicenter dose guiding trial as reported by Dr. Lars Wallentin[7] of the Uppsala Clinical Research Center in Uppsala, Sweden. 1883 patients who had suffered an ST-elevation or non-ST-elevation MI within 14 days of inclusion were randomized in a 2:1:1:1:1 fashion to aspirin (180 mg) + placebo or aspirin with oral ximelagatran 24 mg, 36 mg, 48 mg or 60 mg twice daily for 6 months. The risk of the composite endpoint (death, MI, and RSI) in the combined ximelagatran groups versus the aspirin alone group was reduced from 16.3% to 12.7% ($P = 0.036$). There were no significant differences among the varying dosing regimens of ximelagatran. The incidence of major bleeding was similar, occurring in 1.8% of patients in the combined ximelagatran group and 0.9% of patients in the aspirin-alone group. Elevations in serum alanine aminotransferase (ALT) > 3 × the upper limit occurred more often in the ximelagatran group versus the aspirin cohort but were mostly asymptomatic and returned to normal.

The ability to distinguish plaque morphology in a noninvasive fashion may allow us to follow the effects of various plaque stabilizing therapies, including lipid-lowering therapies, and help identify those plaques that may be at the highest risk of rupture.

Dr. Anders Bylock[8] of AstraZeneca Research and Development in Molndal, Sweden, evaluated antithrombotic effects and bleeding tendencies in two different doses of ximelagatran versus clopidogrel (Plavix,® Sanofi Synthelabo/Bristol-Myers Squibb Corp., New York, NY), all in combination with aspirin therapy, in a human-arterial-thrombosis model, open-label, randomized trial. Aspirin was administered to 62 healthy men (160 mg per day) plus either clopidogrel (300 mg bolus followed by 75 mg a day) for six days or a single dose of ximelagatran (36 or 42 mg) on day 6. The combination of ASA + ximelagatran had a greater antithrombotic effect than aspirin + clopidogrel with less effect on capillary bleeding time.

The results of these two studies suggest that a combined oral antiplatelet-thrombin inhibitor may provide benefits in the prevention and treatment of arterial thrombotic disorders not accorded by a combination of two antiplatelet agents. These exciting results with ximelagatran compliment earlier investigations showing its safety and efficacy in preventing thromboembolic complications associated with atrial fibrillation and venous thrombosis.

Diabetes, the Metabolic Syndrome, and Lipid Disorders

Dr. William Sauer[9] of the University of Pennsylvania School of Medicine, Philadelphia, PA, presented a case control study of patients between the ages of 40-75 years of age with a first myocardial infarction, conducted among 36 hospitals in a 5-county area, during a 36-month period. Information on medicine use and other demographic data was obtained by telephone interview. Compared with sulfonylurea monotherapy, monotherapy with metformin was associated with a 52% reduction in myocardial infarction. Thiazolidinedione (TZD) monotherapy was associated with a 70% reduction. The addition of a TZD but not metformin to sulfonylurea treatment was associated with a reduced risk of MI. Compared to metformin treatment, TZD therapy was associated with a 42% reduction of MI risk.

The results of this trial do not come as a surprise. Knowing the vascular protective effects of insulin-sensitizing agents, enhanced cardiovascular outcomes should be expected in patients with known coronary artery disease who are treated with these agents compared to sulfonylurea monotherapy.

Dr. Jerome Cohen of St. Louis

University in Saint Louis, MO, reported follow-up experience from the MRFIT Trial,[10] which provided an excellent opportunity to follow patients with the metabolic syndrome over a long period of time. Recently, the impact of the metabolic syndrome on cardiovascular risk has become clearer as well as the need to focus cardiovascular risk reduction strategies in these patients. The metabolic syndrome (MS) is defined by the Adult Treatment Panel (ATP)-III guidelines as including at least three of the following components: hypertension (≥ 130/85 mm Hg); low high-density lipoprotein cholosterol (HDL-C) (< 40 mg/dL); high triglycerides (≥ 150 mg/dL); high fasting glucose (≥ 110 mg/dL); and waist girth (> 40 inches in men). In the MRFIT trial, a body mass index (BMI) ≥ 30 kg/m^2 was used as a substitute for waist girth measurement. Of 11,188 men, 4,699 (42%) met the definition for MS. The prevalence of each component of the MS was measured and compared to the prevalence in non-MS subjects: hypertension (91% vs 62%); low HDL-C (82% vs 27%); high fasting glucose (45% vs 8%); elevated triglycerides (89% vs 31%) and obesity (46% vs 9%). After adjustment for age, race, smoking and other clinical factors, the hazard ratio for total mortality cardiovascular disease, (CVD), and congestive heart disease (CHD) mortality for MS vs non-MS subjects was 1.24, 1.45, and 1.49 respectively. Compared to those subjects with no features of MS, those with 1, 2, 3, 4 and 5 components of the MS had an adjusted CVD hazard ratio of 1.09, 1.27, 1.48, 1.84, and 2.78 respectively.

The authors conclude that these findings show the "importance of a strategy to target individuals with MS"[10] and target those at particularly high risk (> 3 components) for aggressive CVD prevention strategies.

Dr. Shaista Malik[11] of the University of California at Irvine, Irvine, CA, presented a database complementing MRFIT. The Second National Health and Nutrition Examination Survey (NHANES II) evaluated data on 9,250 subjects with a mean follow-up of 13 years on the importance of the different components of the MS on overall and cardiovascular mortality. A summary of this data is shown in Table 1.

Table 1
Metabolic-Syndrome Risk-Factor Analysis from the NHANES II Data

	13-Year Cumulative Incidence	
Number of MS risk factors	**Cardiovascular-related death, %**	**Overall mortality, %**
0 (reference group)	2.7	10.4
1	7.0	16.8
2	6.3	17.6
3	9.7	20.7
4-5	7.4	17.4
Diabetes	16.0	36.0
Pre-existing CVD	23.2	40.1
Diabetes and pre-existing CVD	38.4	58.4

CVD, cardiovascular disease, MS, metabolic syndrome, NHANES II, Second National Health and Nutrition Examination Survey. Data from Malik et al.[11]

These results clearly show an increased risk of CVD mortality in persons with 1 or more components of the MS. Overall mortality did not increase in risk until 3 or more components of the MS were present. Diabetes was associated with a mortality risk factor even greater than that of persons with 4-5 components of the MS.

Patients with chronic kidney disease (CKD) represent a very high cardiovascular-event-risk group. Though one would think that elevated risk would invite aggressive risk-factor modification efforts, patients with CKD seem to be undertreated. This may be related to the perception that CKD increases the risk associated with preventive strategies, including cholesterol modification. Statins are first-line agents for cholesterol modification. However, titration of these agents from their recommended starting doses to higher doses results in limited additional low-density lipoprotein cholesterol (LDL-C) reduction with an increase risk of adverse events. Approaches to lipid modification may need to more closely approximate those of hypertension and heart failure treatments, where combining drugs with different mechanisms of action provides greater efficacy and safety.

Dr. Martin Landray[12] of Oxford University, Oxford, UK, presented results of the second UK-Heart and Renal Protection Study. In this trial, 203 patients were randomized to

Knowing the vascular protective effects of insulin-sensitizing agents, enhanced cardiovascular outcomes should be expected in patients with known coronary artery disease who are treated with these agents compared to sulfonylurea monotherapy.

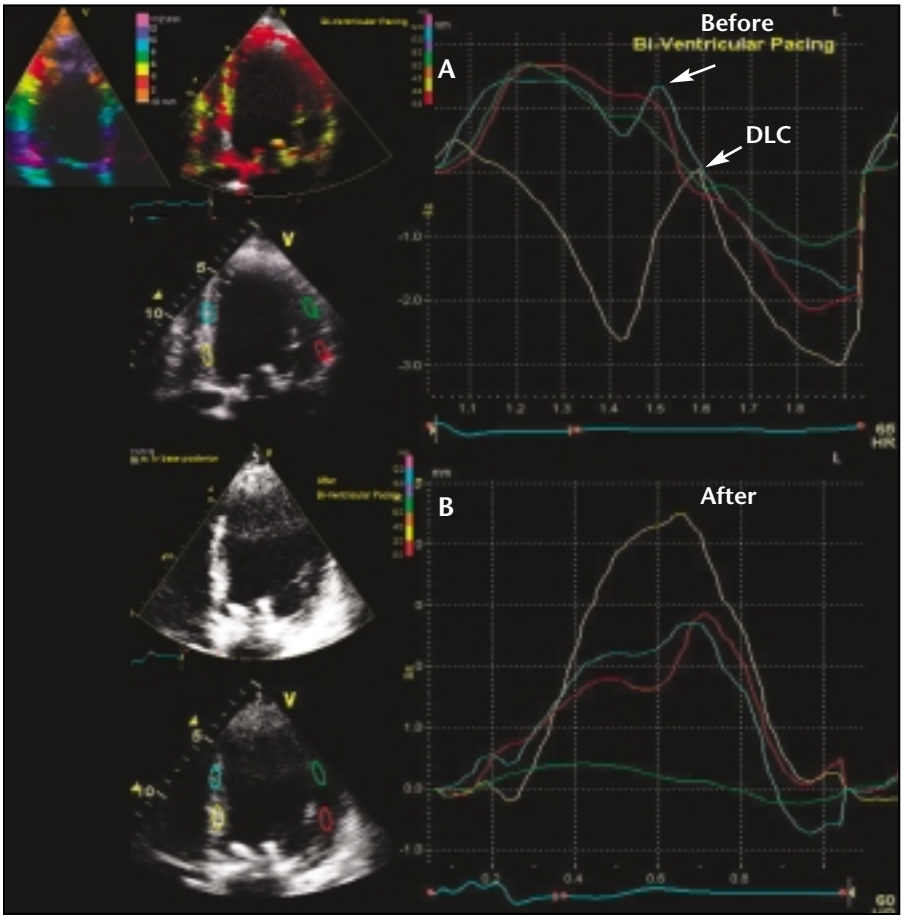

Figure 1. *Q-tissue tracking analysis before* **(A)** *and after* **(B)** *bi-ventricular pacing. Tissue tracking images in apical 4-chamber views and placement of sample volumes in the left ventricular lateral wall and interventricular septum are shown at the left. Tissue velocity curves with colors representing motion of segments selected are on the right. Note presence of delayed longitudinal contraction (DLC) in the basal and mid-interventricular septum, which disappears after cardiac resynchronization therapy (CRT). Color encoding on the left represents tissue displacement. Red and yellow colors represent longitudinal displacement of 4-6 mm and purple represents tissue displacement of >12 mm. Three chamber view showing normal tissue tracking velocities are shown on the left for comparison. Note diffuse decreased longitudinal displacement velocities before CRT.*

receive the specific cholesterol absorption inhibitor, ezetimibe (Zetia,™ Merck/Schering-Plough Pharmaceuticals, Whitehouse Station, NJ), 10 mg daily, plus simvastatin (Zocor,® Merck and Co., Inc., Whitehouse Station, NJ), 20 mg daily, or simvastatin alone. After six months of treatment, combination therapy resulted in an additional 14% reduction of LDL-C and 14% reduction of triglyceride levels versus simvastatin monotherapy. There were no serious adverse events noted due to study treatment.

Outcomes Following PCI

Dr. J. Kevin Harrison[13] of Duke University, Durham, NC, presented results from the VICC Trial, a multicenter, randomized, double-blind trial comparing the use of iodixanol to iopamidol in 1,276 patients who underwent percutaneous coronary intervention (PCI). The primary endpoint of the trial was in-hospital major adverse cardiac events (MACE) within 48 hours of the index procedure, which included cardiac death, emergency ischemia-driven recatheterization, repeat PCI, coronary artery bypass graft (CABG) surgery, subacute thrombosis, stroke/transient ischemic attack (TIA)/embolus, and Q-wave and non-Q-wave MI. The secondary endpoint was 30-day MACE, which included cardiac death, repeat catheterization for ischemia, repeat PCI, CABG, stroke/TIA/embolus, and MI.

There was a significant reduction in in-hospital MACE with iodixanol versus iopamidol, from 9.0% to 4.8% (P = 0.003), and a trend towards reduction of 30-day MACE from 14.1% to 12.2% (P = 0.32). The reduction of the in-hospital MACE rate was driven mainly by a reduction of non-Q-wave MI events, from 7.5% to 3.4% (P = 0.002) with the use of iodixanol. A significant reduction in 30-day MI rates was also observed with the use of iodixanol versus iopamidol (5.3% vs 9.4%, P = 0.005).

The results of this large clinical trial showing a reduction in MACE with the use of iodixanol compared to iopamidol complements previous studies showing lowered rates of contrast-induced nephropathy with the use of iodixanol.

The efficacy of the everolimus-eluting stent (EES), with a bioabsorbable polymer coating, versus a metallic stent was studied in a randomized, blinded study of de novo lesions and presented by Dr. Ricardo A. Costa[14] of the Cardiovascular Research Institute at Lenox Hill Hospital in New York, NY. Patients with a mean vessel diameter of 3.09 mm and lesion length of 8.87 mm were studied (n=42). In-stent late loss assessed in a 6-month angiogram was reduced by 88% with the EES from 0.83 mm to 0.10 mm (P < 0.0001). In-stent restenosis was 0.0% with the EES and 9.1% with the metal stent (P = 0.3). Though the sample size of this trial was not powered to detect significant differences in restenosis, the significant reduction of late stent

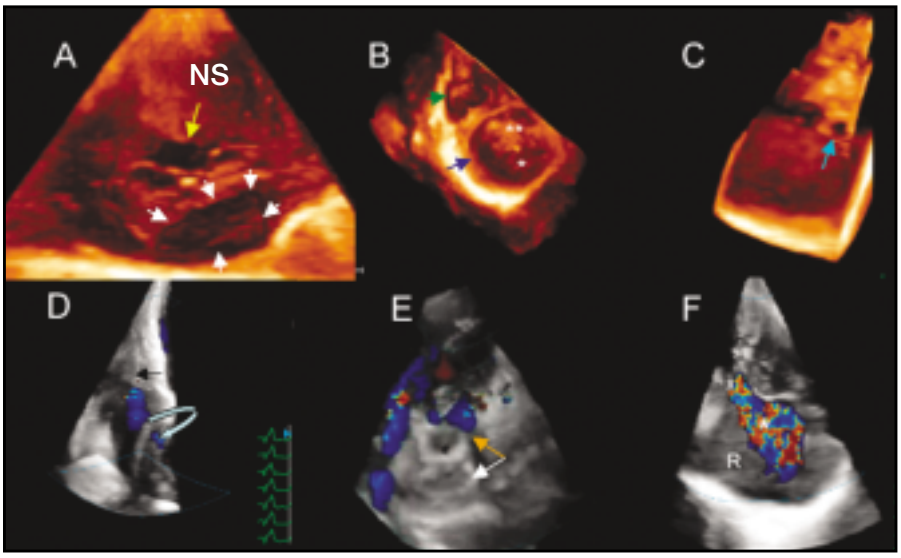

Figure 2. *Three-dimensional echocardiographic images obtained with Philips Sonos 7500 showing ventricular septal defect (yellow arrow) and atrial septal defect (white arrows) seen from left ventricular cavity* **(A)***; short axis view from LA and RA showing mitral (blue arrow) and tricuspid annuli (green arrow) and myxomatous anterior (double white asterisk) and posterior mitral valve leaflets (single white asterisks) and mitral valve prolapse* **(B)***, orifice of patent foramen ovale shown on color Doppler in the next panel (light blue arrow) from right atrium* **(C)***; pacing catheter in RV (black arrow) and color Doppler showing flow across PFO (curved arrows)* **(D)***; right (orange arrow) and left (white arrow) atrial discs of Amplatzer device and small degree of left to right through the central orifice of RA disc in a patient post-percutaneous closure of atrial septal defect* **(E)***; tricuspid regurgitation jet (white asterisk) in RV inflow view and tricuspid regurgitation jet (white arrow) by 3D color Doppler* **(F)***. RA, right atrium; RV, right ventricle.*

loss observed with the EES warrants further study in a larger clinical trial. [Norman E. Lepor, MD, FACC, FAHA]

Tissue Doppler Imaging

Cardiac resynchronization therapy (CRT) has emerged as a significant development in the management of patients with dilated cardiomyopathy, of both ischemic and non-ischemic etiology.[15-20] Despite benefit in approximately 66% of patients, the remaining one third either do not derive any benefit or actually deteriorate after CRT.[21] Although selection criteria in all major studies has included patients with a QRS duration of greater than 120-140 ms, the magnitude of benefit of CRT appears to be only vaguely related to QRS width.[22,23] Mechanical dyssynchrony as defined by echocardiography has emerged as a stronger predictor of response to CRT than electrical dyssynchrony.[24,25] Echocardiography helps to select responders by defining presence and extent of mechanical dyssynchrony prior to CRT (Figure 1), allowing selection of optimal lead placement during CRT, optimizing AV and VV delay after implantation, and evaluating short- and long-term effects of CRT on cardiac remodeling.

Investigators have proposed several methods for echocardiographic assessment of mechanical dyssynchrony. These include assessment of septal to posterior wall motion delay (SPWMD) by M-mode echocardiography,[26] septolateral delay measured at mitral annulus by tissue Doppler imaging,[27] degree of intraventricular dyssynchrony as measured by standard deviation of peak time to peak systolic contraction in the basal and mid-left ventricle (LV),[25] and delayed longitudinal contraction (DLC) measured at the mitral annulus by tissue Doppler imaging (TDI) and strain rate imaging[24] (Figure 2). The ability to alter VV delay in current CRT devices has been shown by echocardiography to result in further optimization of cardiac performance.[28]

At this year's AHA, data were presented by several groups utilizing the above-discussed methods. Dr. Emily Rose of the University of California San Francisco, San Francisco, CA, presented echocardiographic findings in 162 patients who participated in the CONTAK CD trial. She determined that, while SPWMD correlated with a decrease in LV dimensions post-pacing, it did not correlate with improvement in left ventricular ejection fraction (LVEF) or with any of the parameters of functional improvement.[29] At a threshold of SPWMD > 130 ms, the positive predictive value to detect a responder was 50% for LV systolic diameter, diastolic diameter, and LVEF. Negative predictive values were 58%, 73%, and 60%, respectively. The authors concluded that SPWMD cannot be reliably used to predict responders to CRT.

Although selection criteria in all major studies has included patients with a QRS duration of greater than 120-140 ms, the magnitude of benefit of CRT appears to be only vaguely related to QRS width.

Echocardiographic findings in a subset of 95 patients from the MIRACLE study, who underwent baseline and follow-up echocardiograms at 6 and 12 months post-CRT, were reported by Dr. Martin St. John Sutton of the University of Pennsylvania Medical Center in

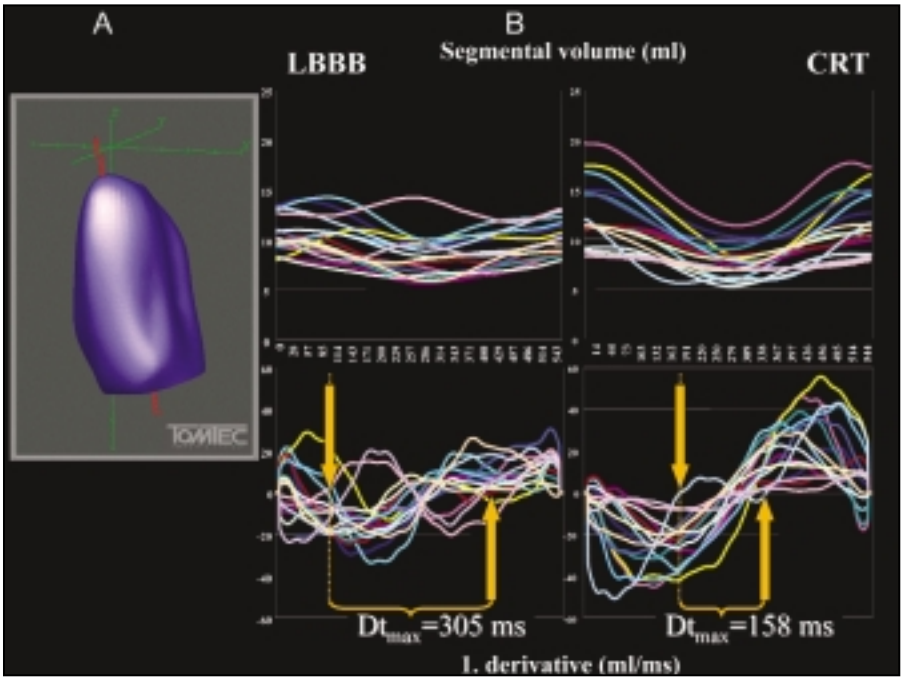

Figure 3. *Quantitative analysis of regional left ventricular volumes in patients treated with cardiac resynchronization therapy (CRT) using real-time 3D echocardiography. 3D data were analyzed off-line using a semi-automated contour tracing algorithm (LV Analysis 1.2RT, TomTec) over a complete heart cycle.* ***A*** *shows reconstructed LV cavity.* ***B*** *shows temporal volume changes of LV segments in systole and diastole with colors representing different LV segments before and after cardiac resynchronization therapy (CRT). Upper panels show the segmental volume-time curves (color coded for all 16 segments) during left bundle branch block (LBBB) and during reprogramming of the pacer with biventricular pacing. The bottom panels show the first mathematical derivative, which aids in the identification of the segmental local systolic minimum of the segmental volume (crossing point between curve and x-axis). The time from beginning of QRS (0 on the x axis) to the segmental minimum of each segment is called T. A mean of all 16 Ts, a standard deviation (SD-Ts) and a maximal intersegmental delay (Dtmax) was calculated. The last two parameters seem to be capable of estimating the degree of asynchrony. Both decrease significantly from LBBB to CRT. The arrows point to the very first and the very last segment reaching a local volume minimum. Time difference between these points is then Dtmax. Image courtesy TomTec Imaging Systems and Andreas Franke, MD.*

Philadelphia, PA.[30] The study found that whereas all patients derived sustained benefit from CRT at 6 and 12 months, with reduced LV volumes and improvement in LVEF, patients with nonischemic cardiomyopathy had a 2- to 3-fold greater response compared to those with ischemic cardiomyopathy. There was a 10% overall improvement in LVEF in the nonischemic group compared to 5% in the ischemic group and a reduction in LVED volume of 61 mL in the nonischemic group, versus 6 mL in the ischemic group, at 1 year.

Dr. Salvatore Rosanio of the San Raffaele University Hospital in Milan, Italy, presented data[31] confirming findings originally reported by Sogaard and associates,[28] showing the benefit of VV delay in optimizing cardiac performance. Biventricular pacing improved LVEF from 22.5% to 28.5%. Echocardiography-guided non-simultaneous pacing of the right and left ventricles, 2 months post-CRT, was associated with additional improvement in EF to 35%. This was accompanied by concurrent improvement in NYHA functional class and 6-minute walk score. These investigators did not find a significant relationship between electrical asynchrony and LVEF improvement. A reduction in QRS width was only observed with simultaneous biventricular pacing, not sequential pacing.

Dr. C. M. Yu of the Chinese University of Hong Kong, Hong Kong, China, found standard deviation of time to peak systolic contraction as the most powerful predictor for reverse remodeling at 3-month follow-up (r = -0.76, P <0.001) compared to TDI parameters and DLC. Time to peak strain failed to predict reverse remodeling.[32]

Another study, presented by Dr. Hideaki Kanzaki of the University of Pittsburgh, Pittsburgh, PA, offered insight into the mechanism for reduction of mitral regurgitation post-CRT.[33] He demonstrated the shortening of time delay between peak systolic strain in the anteromedial and posterolateral papillary muscle sites post-CRT (81 ± 69 to 57 ± 61 ms, P < 0.05 vs. baseline) upon mid-ventricle interrogation, adjacent to the papillary muscle insertion. Studies were performed at baseline and one day following CRT. The improvement in papillary muscle coordination was correlated with reduction of percent MR regurgitant fraction (r = 0.72, P < 0.01).

Three-Dimensional Echocardiography

The advent of live three-dimensional (3-D) echocardiography technology provides the opportunity for assessment of intracardiac anatomy similar to a surgeon's eye view (Figure 3). Precise assessment of involved mitral valve scallops in patients with mitral valve prolapse is possible when compared to multiplane transesophageal echocardiography (TEE) (Figure 3, panel B). In 16 patients with mitral valve prolapse who had TEE identification of prolapsed leaflet, the sensitivities of real time 3-D for detecting lesions at A1, A2, A3, P1, P2, and P3 were, respectively, 67%, 100%, 100%, 75%, 100%, and 100%. The specificities at A1, A2, A3, P1, P2, and P3 were 92%, 100%, 92%, 100%, 100%, and 100%.[34]

Dr. Andreas Franke of the University Hospital in Achen, Germany, examined the effect of CRT on regional and global LV volumes and EF.[35] In 18 patients (72 ± 6 years), 3-D echocardiographic data sets (Live3D, Philips Medical Systems, Cleveland, OH) were acquired, the first during intrinsic rhythm (IR) with left bundle branch block (LBBB), the second during CRT. 3-D data were analyzed off-line using a semi-automated contour tracing algorithm (LVAnalysis 1.2RT, TomTec Imaging Systems GmbH, Unterschleissheim, Germany) over a complete heart cycle. The resulting volume curves were analyzed for the complete LV and 16 LV segments separately with regard to the extent (global and regional volumes; EF) and the temporal pattern of regional wall motion during both intrinsic rhythm and CRT. Global LVEF improved from 28% ± 8% (IR) to 34% ± 10% (CRT, $P < 0.01$). Time difference of maximal inward wall motion between the first and last of the 16 segments decreased from 301 ms (± 82; IR) to 214 ms (± 76) (CRT; $P < 0.001$). Maximum change was observed between septolateral segments (215 ± 110 ms [IR] to 144 ± 64 ms [CRT; $P < 0.05$]), followed by anteroinferior segments (194 ± 86 ms [IR] to 147 ± 102 ms [CRT; $P < 0.05$]) whereas no significant change was seen between posterior base and anterior septum.

Comment

Since its first use, biventricular pacing has proven a significant development in the treatment of patients with congestive heart failure; the clinical indications for CRT in general are likely to expand beyond treatment of electrical delay in heart failure patients. Studies are required to determine benefit of CRT in patients with mechanical asynchrony, in the absence of electrical asynchrony. In addition, the degree and type of mechanical asynchrony that determine benefit needs to be examined carefully, particularly because some degree of mechanical asynchrony is found, and increases in severity with aging, even in normal ventricles[36] as well as in patients with congestive heart failure. Echocardiography helps identify mechanical asynchrony in patients with or without electrical dysynchrony and CHF. The role of mechanical asynchrony in patients with acute myocardial infarction, as well as its relationship to reperfusion, needs to be explored further.

Perfusion Echocardiography

Myocardial contrast echocardiography (MCE) may differentiate myocardial necrosis from stunning in post-acute myocardial infarction (AMI) patients.[37,38] Dr. Duk-Hyun Kang of the Asian Medical Center, Seoul, Republic of Korea, presented a study examining the prognostic value of MCE utilizing a continuous infusion of perfluorocarbon-exposed sonicated dextrose albumin (PESDA) during intermittent power Doppler harmonic imaging to diagnose AMI and predict MACE, mortality, MI, and severe ischemia requiring revascularization. The study was conducted in 114 patients with acute coronary syndrome without ST elevation.[39] In a multiple logistic regression analysis comparing ECG, troponin 1, wall-motion abnormality on routine echo, and perfusion defect on MCE, perfusion defect on MCE (OR = 87, $P < 0.001$) was the only independent predictor for MACE. Perfusion defect (OR = 21, $P = 0.001$) and troponin 1 (OR = 3, $P = 0.009$) were independent predictors for MI during hospitalization.

Dr. Esther Perez-David of the Hospital Universitariuo Gregorio Marañon, Madrid, Spain, reported on quantitative myocardial perfusion assessment in akinetic segments, performed utilizing sulphur hexafluoride (SonoVue, Bracco International, Princeton, NJ) in 27 patients who presented with acute MI and were treated with primary percutaneous transluminal coronary angiography (PTCA). Myocardial blood flow index was compared against TIMI flow on angiography to predict follow-up improvement in wall motion at 3 months.[40] Perfusion MCE parameters correlated well with wall motion score index (WMSI) improvement, ($R = 0.61$, $P = 0.009$), whereas no significant correlation was seen between TIMI myocardial perfusion grade (MPG) and WMSI improvement ($R = 0.1$, $P = 0.8$).

Dr. Kohsuke Hagisawa of the National Defense Medical College in Tokorozawa, Japan, examined the value of targeted microbubbles tagged with antibodies against platelet and white-cell antigens.[41] In a rabbit model of acute iliofemoral thrombosis, *in vivo* ultrasonic thrombus imaging was enhanced by perfluorocarbon containing microbubbles with Arg-Gly-Asp (RGD) sequence peptides on their surface lipid layer, which specifically bind to activated platelet glycoprotein IIb/IIIa complex. The authors concluded that this method to enhance ultrasonic thrombus imaging *in vivo* could be useful in diagnosing acute thrombotic vessel occlusion.

Comment

Technical limitations have discouraged the clinical adoption of myocardial perfusion echocardiography. However, recent understanding and exploitation of microbubble physics in imaging techniques have made perfusion imaging a more viable option. Targeted microbubbles hold significant promise for local drug delivery as well as in detecting plaque components.

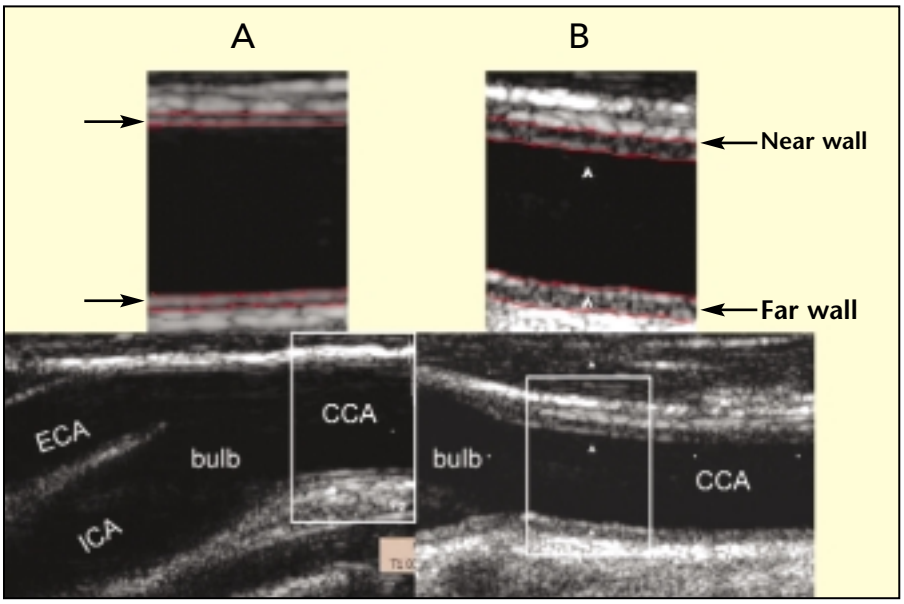

Figure 4. *Common carotid artery, carotid bifurcation (bulb) and external and internal carotid arteries of a healthy 50 year old male showing normal carotid intima-media thickness* **(A)** *and common carotid artery and carotid bifurcation of a 55-year-old African American female showing diffuse thickening of intimal-medial layer along the near (near the skin) and far (furthest from skin) wall of common carotid artery and carotid bifurcation* **(B)**. *CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery.*

Carotid Intima-Media Thickness

Carotid intima-media thickness (cIMT) may serve as an important noninvasive marker of early vascular disease and can be measured using an ultrasound system equipped with a high-frequency transducer (Figure 4). The AHA writing group has recommended that cIMT measurements be requested by physicians for further risk stratification in a patient with intermediate likelihood of atherosclerosis.[42] African Americans have a higher rate of cardiovascular mortality and morbidity compared with Whites. Dr. Wendy Post of The Johns Hopkins University, Baltimore, MD, studied the utility of IMT assessment in this high-risk population.[43] Carotid B-mode ultrasound was performed in 392 siblings of probands with documented coronary disease. Patients were less than 60 years of age (mean age 47 ± 7 years), 63% female, 70% African American. A comprehensive risk factor assessment was performed. The mean far wall IMT of a 1 cm section of the left and right common carotid arteries was measured using an automated edge detection system. Mean cIMT was higher in African Americans (0.709 ± 0.149 mm) compared with whites (0.634 ± 0.109 mm), $P < 0.0001$. Using multivariate linear regression analysis, African American race remained a strong, significant, independent predictor of cIMT ($P < 0.0001$) after adjustment for all conventional risk factors known to affect vascular disease. Low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, smoking, and education were not significant risk factors in the model. African American race accounted for a significant amount of the total explained variance in cIMT, and remained a potent predictor even after adjustment for known powerful risk factors such as male gender, body mass index, blood pressure, glucose intolerance, and age.

Comment

Carotid intima-media thickness assessment by ultrasound has been shown by several studies to provide a reasonably accurate profile of atherosclerotic burden and correlation with the presence and severity of coronary artery disease. However, the technique requires training and expertise. In expert hands it can now be used for clinical risk assessment of cardiovascular disease.

[Tasneem Z. Naqvi, MD]

The AHA writing group has recommended that carotid intima-media thickness measurements be requested by physicians for further risk stratification in a patient with intermediate likelihood of atherosclerosis.

ApoA-I Milano

At an adjunct symposium to the AHA meeting, just-published results were presented on the effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes (ACS).[44] In this small, randomized Phase II clinical trial, 47 patients, aged 30-75 years and recovering from ACS, were allocated to receive intravenous placebo (n=11) or intravenous recombinant ApoA-I Milano-phospholipid complex (ETC-216) in two different doses (15mg/kg [n= 21] or 45mg/kg [n=15]), once a week for 5 weeks. Intravascular ultrasound was utilized to assess coronary plaque size in an unintervened coronary artery with no more than a 50% stenotic plaque, involving a 30 mm segment, both before initiation of treatment and at the conclusion of treatment, to determine the effect of

this therapy on atherosclerotic plaque size. The primary endpoint was change in percent atheroma volume from baseline to follow up in the ETC-216 treated group. Secondary endpoints included change in total atheroma volume and the average maximal atheroma thickness (Table 2).

The absolute reduction in atheroma volume was 14.1 mm^3 (4.2% reduction from baseline) in the ETC-216 group. Treatment with ETC-216 was generally well-tolerated. The authors concluded that treatment with ETC-216 resulted in a rapid regression of atherosclerosis within 5 weeks.

Table 2
Percent Change in Atheroma Volume in the ApoA-I Milano Trial

	ETC-216 group (n = 36)	Placebo group (n = 11)
Mean change, %	–1.06	0.14
Median change, %	–0.81	0.03
95% Confidence interval	–1.53 to -0.34	–1.11 to 1.43
P value	0.02	0.97

ETC-216, ApoA-I Milano phospholipid complex.

Commentary

From 1980 to 1985, Drs. Cesare Sirtori and Guido Franceschini of the University of Milan reported that about 40 out of a population of approximately 1100 individuals living in the town of Limone sul Garda in northern Italy had very low high-density lipoprotein (HDL) levels with elevated triglycerides. Despite this seemingly pro-atherogenic lipid phenotype, these individuals had no evidence of atherosclerotic vascular disease and their ancestors had enjoyed general longevity.[45] These 40 individuals were shown to have a mutant form of ApoA-I, the major protein component of HDL particles. This mutant, which had an arginine to cysteine substitution at position 173, was named ApoA-I Milano. It was speculated that this mutant form of ApoA-I may confer unique properties to HDL, making it more effective as an antiatherogenic agent.

In a series of experimental studies conducted from 1992 to 2003 in cholesterol-fed rabbits, ApoE knockout mice, and pig models , Dr. P. K. Shah and his investigative team at the Atherosclerosis Research Center at Cedars-Sinai Medical Center in Los Angeles, CA, showed that intravenous injections of a recombinant form of ApoA-I Milano coupled with a phospholipid carrier to simulate a synthetic form of HDL dramatically reduced the extent and prevented progression of atherosclerosis. At high doses it induced regression of atherosclerosis (within 5 weeks), rapidly removed plaque lipid and inflammation (within 48 hours of a single large dose), and prevented in-stent restenosis when given locally at the stented segment in porcine coronary arteries.[46-49] Two additional studies in rabbits done by Sirtori, Franceschini and colleagues in Milan further confirmed these observations.[50,51]

Collectively, these experimental findings stimulated Esperion Therapeutics, Inc., (Ann Arbor, MI) to launch a human clinical trial of recombinant ApoA-I Milano (ETC-216). This important Phase 2 study provides proof for the concept that synthetic-HDL therapy can rapidly change human coronary plaques, confirming the pre-clinical observations reported from Cedars-Sinai, and later from the University of Milan. While this study had a small number of patients, the rapidity of regression, although modest in amount, was impressive and is likely to stimulate further development of this product through additional, larger Phase IIB and Phase III trials to demonstrate efficacy in terms of reduction in clinically relevant cardiovascular events.[44] In addition, durability of effect will need to be demonstrated. This form of intravenous therapy, if proven effective and safe in additional larger trials, has the potential to establish an important role in the management of atherosclerotic vascular disease. It is conceivable that rapid change in atherosclerotic plaque size and/or composition (towards a more stable plaque phenotype with less lipid and less inflammation) can be achieved using intravenous HDL therapy over a short period of time with maintenance of benefits through orally effective agents that either increase HDL, improve efficiency of HDL, and/or simulate the functions of HDL. Thus, these promising results are likely to further focus attention on HDL-based therapeutics for vascular disease as recently described.[52-55]

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

Dr. Shah serves as a consultant and scientific advisory board member for Esperion Therapeutics, Inc.

Renal Dysfunction and Contrast-Induced Nephropathy

This year's AHA meeting indexed 41 original papers to renal dysfunction as a cardiovascular risk condition. Contrast-induced nephropathy (CIN) was a focus of interest, with three meta-analyses and three new randomized trials of N-acetylcysteine (NAC) as a preventive strategy in the

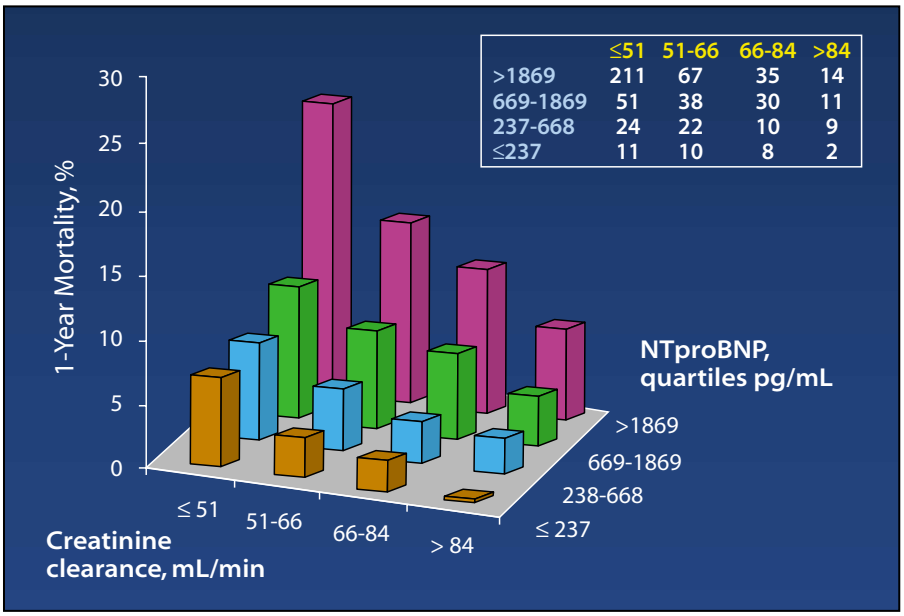

Figure 5. *Relationship between renal function in creatinine clearance, baseline N-terminal proBNP (NTproBNP), and one-year mortality in acute coronary syndromes.*

catheterization laboratory presented. Several papers reported supportive information for renal dysfunction as a cardiovascular risk condition in atherosclerosis, during revascularization, and, importantly, as a powerful predictor of mortality in heart failure.

Fifty abstracts were indexed to natriuretic peptides. Clearly, study and use of B-type natriuretic peptide (BNP) has advanced our understanding of cardiovascular disease and proven it to be an innovative therapeutic agent for heart failure. Several of these papers highlighted the interaction between the natriuretic peptides, renal dysfunction, and inflammation as a threat to patients with acute myocardial infarction. It also appears that BNP offers important complementary information to patient history, examination, echocardiography, and other blood biomarkers.

Contrast Nephropathy

Lindsay and coworkers[56] of the Washington Hospital Center, Washington, DC, demonstrated, in a consecutive series of 5397 patients undergoing PCI, that CIN was a more powerful predictor of one-year mortality than a rise in creatine kinase myocardial band (CK-MB). It follows that attempts to reduce CIN rates would reduce mortality after PCI. Because over 40 trials have been neutral or negative in the prevention of CIN, there are few potential contenders for treatment. One commonly practiced prevention strategy is the administration of NAC, given either orally or intravenously, before and after the procedure. Three meta-analyses of 5-8 previously published randomized trials demonstrated a ~50% risk reduction for CIN with NAC therapy.[57-59] However, three new randomized trials of NAC were presented this year. Two were negative and one was positive. The largest trial (n = 476) compared 500 mg of NAC versus placebo, before PCI, and found CIN rates of 24% versus 21% (P = 0.31). There are now approximately 16 trials of NAC published and reported to date, and likely a meta-analysis of these trials would demonstrate that it does not reduce the rate of CIN. Clearly, a large, randomized trial would need to be conducted to definitively answer this question.

Three new randomized trials of NAC were presented this year. Two were negative and one was positive.

Natriuretic Peptides: Cardiorenal Neurohormones

Abstracts concerning atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), its cleavage fragment N-terminal proBNP (NTproBNP), and C-type natriuretic peptide provided more information about this important cardiac, vascular, and renal communication system. James and coworkers[60] from Uppsala University in Uppsala, Sweden, presented data from the Global Utilization of Strategies to Open Occluded Arteries (GUSTO) IV trial in acute coronary syndromes (ACS), indicating that measurement of NTproBNP is dependent on baseline renal function. Importantly, those with a creatinine clearance < 41 mL/min and a markedly elevated NTproBNP > 1869 pg/mL, had an ~25% rate of one-year mortality (Figure 5). This relationship was independent of the size of the infarct as estimated by the rise in troponin.

Havranek and coworkers[61] from the Denver Health Medical Center, Denver, CO, demonstrated that BNP measured in chronic heart failure patients, over time and in an outpatient setting, was almost completely unrelated to self-reported quality of life. In addition, the change in BNP

over six weeks did not predict future risk of death or hospitalization.

What can we learn from these data? It appears that baseline levels of BNP are very important in both acute coronary syndromes and heart failure, but how frequently the test should be done in the clinic, and what serial changes in BNP mean, remain unknown.

Lastly, there was a provocative paper from Hiramatsu and associates[62] of Shinshu University, Matsumoto, Japan, linking BNP and adipose tissue and suggesting that BNP may be lipolytic. This may explain why advanced heart failure patients with very high BNP tend to have reduced body mass index, and, conversely, why heart failure patients with lower BNP values tend to have higher amounts of adipose tissue.

Baseline levels of BNP are very important in both acute coronary syndromes and heart failure, but how frequently the test should be done in the clinic, and what serial changes in BNP are mean, remain unknown.

Commentary

The 2003 Scientific Sessions demonstrated continued growth in cardiorenal research, with, unfortunately, some negative news on the prevention of CIN with NAC. However, it appears that the natriuretic peptides will be of value in patients with combined heart and kidney disease and measurement of baseline BNP in ACS and heart failure appears to be strongly supported.

[Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA]

Facilitated Angioplasty

Results of randomized, clinical trials have shown a significantly higher proportion of positive short- and long-term outcomes following primary angioplasty, when compared to thrombolytic therapy, in patients with ST-segment elevation MI (STEMI). Keeley and associates[63] recently reviewed 23 randomized trials, showing an absolute reduction of 2% in short term mortality with percutaneous coronary intervention (PCI) that was preserved after 1 year. However, the benefit of primary angioplasty is significantly related to door-to-balloon time. A recent review by Nallomathu showed that treatment delays of greater than one hour for primary angioplasty versus thrombolysis results in equal or less benefit for primary angioplasty.[64]

It has been well-accepted that primary angioplasty should be done within 90 minutes of symptom onset in order to achieve optimal benefit over thrombolysis. A concept of combining these two reperfusion strategies might overcome the limitations of each. Thrombolysis can be administered early, even prior to hospitalization, and would start the reperfusion process early. Angioplasty is well-recognized as resulting in complete reperfusion and can rescue those patients who do not achieve any reperfusion through thrombolysis. However, it requires mobilization of a cardiac catheterization team, as well as transfer to a referral hospital if primary angioplasty is not available. This strategy is not new, and three prior studies executed early in the investigation of thrombolytic agents failed to show benefit from a combined approach. However, primary angioplasty is today a much safer and more effective procedure than in the past and new thrombolytic agents have also resulted in improved outcomes. The value of combining therapies is that it may buy time, allowing performance of primary angioplasty beyond the 90-minute window, with equal benefit. If so, this would have a profound effect on how patients with STEMI would be managed.

The value of combining therapies is that it may buy time, allowing performance of primary angioplasty beyond the 90-minute window, with equal benefit.

At this year's AHA, Dr. Francisco Fernandez-Aviles of the Hospital Clinico Valladolid, Valladolid, Spain, presented results of the GRACIA-1 Trial,[65] studying 500 patients with STEMI who received thrombolysis. Patients were randomized into an invasively-treated group, who underwent angiography on an average of 16.7 hours after admission (80% underwent immediate angioplasty), and a conservative, medically-managed group, guided by the presence of ischemia. Of the latter group, 19% underwent angiography prior to hospital discharge due to recurrent ischemia. The duration of hospitalization was shorter in the invasive group (7 vs 11 days). The combined endpoint of death or MI was similar (4.8% vs 6.0%), but recurrent ischemia was significantly more common in the conservative group (4% vs 18.4%, $P = 0.001$). At one year, there was a trend toward a lower death and MI rate in the invasive group that did not meet statistical significance (7% vs 12%). However, rehospitalization and revascularization were signifi-

cantly less common. This study importantly showed no increased risk of bleeding between the two groups. The authors concluded that an early invasive strategy offers benefits, and should be routine practice.

Where events rates were lower in the invasive group, they were largely related to recurrent ischemia, revascularization, and rehospitalization. At one year, 88% of the invasive group underwent revascularization, 80% acutely and the remainder during follow-up, compared with 34% of the conservative group. However, shorter hospitalization and less morbidity were clearly seen in the invasive approach. In addition, the study used a rather delayed invasive approach, with angiography and PCI performed 17 hours after admission, raising the question of whether greater benefit would have occurred had it been performed earlier.

Dr. Fernandez-Avila also presented the GRACIA-II trial,[66] which evaluated the benefit of immediate thrombolysis and early angiography (3-12 hours) versus primary angioplasty (within 3 hours) in 212 patients with STEMI. The primary endpoint was infarct size, ST-segment resolution and left ventricular (LV) function at six weeks. No differences were seen in infarct size or LV function, but a significantly higher proportion of patients showed complete ST-segment resolution at six hours in the facilitated cohort (61% vs 43.2%, $P > 0.03$). Importantly, the time from door to balloon was one hour in the primary PCI group, and almost six hours in the facilitated group. This study demonstrated an equal outcome between the two approaches, with some potential benefit for the facilitated approach, as demonstrated by more rapid ST-segment resolution. These findings support the concept of facilitated PCI, but the study was too small to adequately show benefit on firmer and more convincing endpoints.

In a plenary session on late-breaking trials, Dr. Adnan Kastrati of the Technische Universitat Munchen, Munich, Germany presented data from the BRAVE trial.[67] This study was designed to evaluate whether reteplase plus abciximab was superior to abciximab alone in patients undergoing primary angioplasty. The study was small, evaluating only 253 patients. The primary endpoint was infarct size determined by nuclear imaging, 5-10 days following treatment. The average door-to-balloon time was two hours in each group. Initial TIMI flow was normal (TIMI III) in 40% of the combined reteplase and abciximab group, but only 18% in the abciximab alone group. However, at 30 days, infarct size as well as clinical events (death, MI and stroke) were not different between the groups. The study failed to show superiority of the combination of thrombolysis and abciximab before primary angioplasty when primary angioplasty is performed immediately.

While transfer from one hospital to another has been shown to be safe and effective in Europe, it is rare that patients can be transferred in the United States in less than one hour and have primary angioplasty performed within 90 minutes of hospital presentation.

Comment

These 3 small trials raise a number of significant issues concerning facilitated angioplasty. GRACIA-1 and the previously reported SIAM Trial[68] demonstrated benefit of facilitated angioplasty over thrombolysis. The benefit, however, is largely confined to recurrent ischemia. GRACIA-2 and the BRAVE Trial showed equivalency between facilitated angioplasty and primary angioplasty, but the results of GRACIA-2 are the most intriguing because equivalency was demonstrated despite a very significant time difference between the two strategies. This latter trial suggests that facilitating angioplasty may in fact buy time for treatment without significant penalty, such as increased infarct size or morbidity. If this finding is documented in subsequent larger trials, it will greatly aid in the decision whether or not to transfer patients from non-PCI centers to primary angioplasty facilities. While transfer from one hospital to another has been shown to be safe and effective in Europe, it is rare that patients can be transferred in the United States in less than one hour and have primary angioplasty performed within 90 minutes of hospital presentation. The ongoing FINESSE, CARESSE, and ASSENT-IV trials should help define the role of facilitated angioplasty in the future.

[David P. Faxon, MD, FACC, FAHA]

REVERSAL Trial

The HMG CoA reductase inhibitors, often referred to as statins, have shown benefit in patients at high risk for cardiovascular mortality and morbidity, with positive effects observed in both primary and secondary prevention. Recent studies have emphasized that even in patients with dyslipidemias and only moderate cardiovascular risk, or patients with only moderate cardiovascular risk and essentially healthy lipid profiles, statins also significantly reduce clinical events. All of these studies,

however, have compared statins to placebo. No head-to-head comparisons within this class of drugs have been made. Dr. Steven Nissen of the Cleveland Clinic, Cleveland, OH, presented results of A Prospective, Randomized, Double Blind, Multi-Center Study Comparing the Effects of Atorvastatin vs. Pravastatin on the Progression of Coronary Atherosclerotic Lesions as Measured by Intravascular Ultrasound (REVERSAL),[69] which was designed to address this issue, comparing the effects of two statins on the important intermediate outcome of coronary atherosclerotic disease progression.

Background

Although it is recognized that major coronary events can occur even in the absence of large luminal atherosclerotic lesions, it is generally thought that preventing progression of atherosclerosis is an important step in preventing adverse clinical outcomes. Early studies of the effects of statin therapy on atherosclerosis depended on angiography to identify disease and measure any treatment-induced changes. This type of imaging is relatively insensitive because it only identifies those lesions that are clearly impinging on the vascular lumen. Nonetheless, some findings from these trials suggested that statins could slow the progression of atherosclerosis. The newer technique of intravascular ultrasound (IVUS) provides a far more quantitative method for measuring the disease process, as it is able to measure the full volume of atheromas within the walls of coronary arteries. The objective of REVERSAL was to use this technique to compare the effects of two types of statin therapy on atheromatous disease progression in high-risk patients.

Hypothesis

The hypothesis of REVERSAL was that intensive reduction of low-density lipoprotein (LDL) cholesterol with a high dose of atorvastatin (Lipitor,® Pfizer, Inc., New York, NY) would be superior to "more moderate" reduction of LDL cholesterol with pravastatin (Pravachol,® Bristol-Myers Squibb Corp., New York, NY) in preventing atheromatous disease progression. One rationale for selecting pravastatin as a comparator was that this agent had previously received a formal indication for slowing progression of this condition. To some observers this hypothesis was slightly confusing since it seemed to be asking two distinct questions: 1) Are there real differences between these drugs? 2) Does all atherosclerotic disease progression stem from raised LDL levels? Many felt the trial was not designed to deal with this dual issue.

The primary endpoint of the REVERSAL study was percent change in atheroma volume: it increased by 2.7 % in the pravastatin group, but did not change (decrease of 0.4%) in the atorvastatin group, a significant difference.

Methods

The study was performed with 654 patients, all with symptomatic coronary heart disease or angiographic evidence for coronary obstruction, and with LDL cholesterol values between 125 and 210 mg/dL. An 8-week washout period from any previous therapy was observed. IVUS was performed in each patient at baseline using a selected single-target coronary artery, with at least a 30 mm accessible length, for study. The patients were randomized to receive atorvastatin, 80 mg daily, or pravastatin, 40 mg daily, for an 18-month treatment period. By the end of the study, 249 patients on pravastatin and 253 patients on atorvastatin were available for follow-up IVUS of the target artery. The principal measurements were of changes in atheroma volume and obstructive volume.

Results

Patients averaged 56 years of age; 72% were men, 88% were white, and 27% were active smokers. In addition, 70% of patients had a history of hypertension and 20% had a history of diabetes mellitus. The average baseline LDL cholesterol measurement was 150 mg/dL, and average HDL cholesterol measured at 43 mg/dL. The mean C-reactive protein level was 3 mg/L.

Principal findings are shown in Table 3. LDL cholesterol was reduced to 110 mg/dL in the pravastatin group and 79 mg/dL in the atorvastatin group, a highly significant difference. Changes were also greater for triglycerides in the atorvastatin group, though there was no difference between the two drugs and their effects on HDL cholesterol. The primary endpoint of the study was percent change in atheroma volume: it increased by 2.7% in the pravastatin group, but did not change (decrease of 0.4%) in the atorvastatin group, a significant difference (P = 0.02). This result was consistent across virtually all prespecified subgroups: it was similar in men and women, in younger and older patients, patients with or without a history of statin therapy, and diabetic and nondiabetic patients. The one exception was in patients who did not have a history of hypertension and in whom, unlike hypertensives, there was no difference between the drugs' effects.

For the secondary endpoints of absolute atheroma volume and

Table 3
Key Changes from the REVERSAL Trial

	Atorvastatin, 80 mg (n = 253)	Pravastatin, 40 mg (n = 249)	*P* value*
LDL cholesterol	- 71 mg/dL	- 40 mg/dL	< 0.0001
C-reactive protein	- 36.4 %	-5.2 %	< 0.0001
Percent atheroma volume	- 0.4	+ 2.7	0.02
Absolute atheroma volume	- 0.9 mm^3	+ 4.4 mm^3	0.02
Percent obstructive volume	+ 0.2	+ 1.6	0.0002

*For differences between treatments.

change in percent obstructive volume, there was also a significant advantage to atorvastatin, which, unlike pravastatin, prevented any progression of disease. Finally, there was a 36% reduction in C-reactive protein with atorvastatin, which was significantly greater than the reduction of 5% with pravastatin. This latter finding may be of some interest. In the subgroup of patients whose C-reactive protein was greater than the mean, atorvastatin actually produced a regression of percent atheroma volume.

Comment

REVERSAL demonstrated that intensive LDL cholesterol-lowering therapy with atorvastatin completely halted progression of atheroma, whereas more moderate treatment with pravastatin did not. Because there was no placebo in the study, it is not possible to fully interpret these findings, but it seems likely that the more complete prevention of progression observed with atorvastatin may well provide a further advantage beyond that observed with pravastatin in the doses used.

The investigators actually did a further analysis in which they considered only those patients treated with pravastatin who achieved LDL cholesterol values below 100 (mean: 88) mg/dL. In these individuals, there was still evidence for some atheroma progression, allowing speculation that there might be some property of atorvastatin, beyond its powerful LDL cholesterol-lowering action, that could mediate its atheromatous benefit. One speculation is that this advantage could be due to the marked reduction in C-reactive protein produced by atorvastatin. But, until further evidence is provided, most observers will probably conclude that the ability to prevent progression of atheroma by atorvastatin in this study reflected its 46% reduction in LDL cholesterol.

Almost certainly, these findings will create growing pressure on guidelines committees and practitioners to be even more aggressive in their management of lipids.

Almost certainly, these findings will create growing pressure on guidelines committees and practitioners to be even more aggressive in their management of lipids. As the investigators themselves point out, studying progression of atheroma gives insight into an interesting and potentially important surrogate endpoint, but does not have the same impact as a trial in which clinical endpoints are measured. Regardless, the message of REVERSAL is likely to resonate.

[Michael A. Weber, MD]

High-Density Lipoprotein Function

Epidemiological data have demonstrated that plasma high density lipoprotein (HDL) is inversely related to CHD incidence.[70-72] These same studies have also suggested that the risk for CHD decreases by 2%-3% for each 1 mg/dL increase in HDL. Thus, increasing HDL can potentially have an even greater impact on reducing CHD morbidity and mortality than low-density lipoprotein (LDL) cholesterol reduction. Until recently, however, most research, drug development, and clinical interest have centered around lowering LDL, rather than raising HDL. The reasons for this are complex, but probably relate to the complexity of HDL, as well as the lack of a potent HDL-altering drug.

HDL is felt to be protective because of its ability to remove LDL from artery walls (reverse cholesterol transport).[73] Newer data, however, suggest that HDL also inhibits inflammation, improves endothelial function, and prevents oxidation of LDL.[74-76] These mechanisms may also account for the protective properties of HDL. This complexity emphasizes that HDL function, rather than merely plasma HDL levels, may be important in determining the antiatherogenicity of HDL. Two presentations at this year's AHA meeting evaluated HDL function as a prognostic factor and as a therapeutic target to prevent atherosclerosis.

Navab and associates[77] from the David Geffen School of Medicine at UCLA, Los Angeles, CA, reported on patients with elevated HDL-cholesterol levels and documented CHD,

characterizing their HDL as pro-inflammatory. In this study, 20 patients with documented CHD and elevated HDL-cholesterol levels (95 ± 14 mg/dL, range: 84 to 145 mg/dL) were compared to 20 age- and gender-matched controls. The inflammatory/anti-inflammatory properties of HDL were determined using 2 novel asssays developed by the investigators. The first assay was based on the ability of a subject's HDL to alter LDL-induced monocyte chemotactic activity. The second assay was a cell-free method which evaluated the ability of a patient's HDL to prevent lipid oxidation. Induction of monocyte chemotaxis or lipid oxidation by a standard control LDL was determined in the absence or presence of HDL, and values in the absence of HDL were normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated pro-inflammatory or pro-oxidant HDL; values less than 1.0 indicated anti-inflammatory or anti-oxidant HDL.

In the monocyte chemotaxis assay, the patient values were 1.28 ± 0.29 compared to 0.35 ± 0.11 in the controls, ($P = 1.7 \times 10[-14]$). None of the patients had monocyte chemotaxis values less than 0.6, whereas all of the controls had values less than 0.6. The patient values calculated through the cell-free assay were 1.37 ± 0.19 compared to values of 0.66 ± 0.21 for the controls ($P = 4.4 \times 10[-12]$). Only 1 of the 20 patients had values of less than 1.0 in the cell-free assay, while 18 of the 20 controls had values of less than 1.0. The authors concluded that most of the patients with documented CHD and elevated HDL-cholesterol levels had pro-inflammatory and pro-oxidant HDL, while most of the control patients had anti-inflammatory and anti-oxidant HDL.

Another study, carried out by researchers from the same group, evaluated the effect of statin therapy on HDL function. Ansel and associates[78] reported on the inflammatory/anti-inflammatory properties of HDL from patients with CHD or CHD risk equivalents as distinguished from healthy controls, along with investigation of their treatment with simvastatin.

The hypothesis for this study was that HDL function is impaired more often in high-risk individuals (defined as those with CHD or CHD risk equivalents) compared with controls, and that this impairment improves with statin treatment. Thirty-two patients with stable CHD or CHD risk equivalents were entered into the study; 6 of the 32 were subsequently excluded because they were found to have elevated high-sensitivity C-reactive protein levels. Twenty-six age- and gender-matched controls were also studied. Patients were tested before and after 6 weeks of treatment with simvastatin, 40 mg daily. The inflammatory/anti-inflammatory properties of HDL were determined using the same two assays as presented in the Navab and coworkers study above.

The authors concluded that patients with CHD or CHD risk equivalents have pro-inflammatory HDL cholesterol, and that the inflammatory/anti-inflammatory properties of HDL distinguished patients from controls better than HDL cholesterol concentration alone.

Prior to simvastatin therapy, the mean value for the patients' HDL in the monocyte chemotaxis assay was 1.38, compared with 0.38 for controls. After simvastatin treatment, the patients' mean monocyte chemotaxis value decreased to 1.08, which was improved, but still pro-inflammatory. In the cell-free assay, the mean value for patients' HDL was 1.19, compared with 0.53 in the healthy controls. Post-therapy, the mean value for patient HDL decreased to 0.91.

The authors concluded that patients with CHD or CHD risk equivalents have pro-inflammatory HDL cholesterol, and that the inflammatory/anti-inflammatory properties of HDL distinguished patients from controls better than HDL cholesterol concentration alone. They further conclude that the anti-inflammatory properties of HDL are favorably impacted by simvastatin.

These two presentations represent a new wave of thought about HDL. While HDL has been related epidemiologically to cardioprotection, we know that not all HDL particles are protective. In fact, Fogelman and colleagues have described HDL as a "chameleon-like" lipoprotein,[79] anti-inflammatory in the basal state and proinflammatory during an acute-phase response such as occurs during infection or trauma. Furthermore, proinflammatory HDL particles have been associated with atherosclerosis in mouse models.[80-82] The two assays used in these presentations allow researchers to specifically test the function of HDL, not just the numerical value, and may one day allow us to more accurately target HDL, promoting therapies by using HDL function as a therapeutic target. [Karol E. Watson, MD, PhD]

CREST Trial

Despite the promise of drug-eluting stents to reduce the incidence of restenosis following PCI, additional pharmacologic strategies continue to be evaluated. Based on the demonstrated efficacy of cilostazol

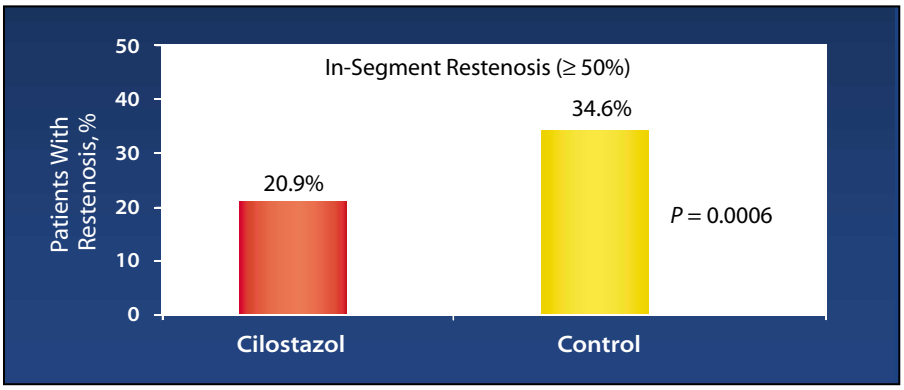

Figure 6. *Restenosis rates as measured at 6 months, cilostazol treatment versus placebo, in the Cilostazol for Restenosis (CREST) trial.*

(Pletal,® Otsuka Pharmaceutical, Inc., Rockville, MD), a phosphodiesterase III inhibitor, which reduced restenosis rates following PCI in several small trials, a multi-center, randomized, double-blind, placebo-controlled trial was conducted. Dr. John S. Douglas of the Emory University School of Medicine in Atlanta, GA, presented findings from the Cilostazol for Restenosis (CREST) Trial.[83] Following successful coronary stent implantation, 705 patients were randomly assigned to receive cilostazol, 100 mg, twice daily, or placebo for 6 months. All patients received standard therapy with clopidogrel and aspirin and patients with acute myocardial infarction, intracoronary thrombus, bifurcation stenoses, and hepatic or renal insufficiency were excluded. The primary endpoint of the study was minimal lumen diameter (MLD) at six months, assessed using quantitative coronary angiography. Secondary endpoints included percent stenosis, binary restenosis (> 50% diameter stenosis), target vessel revascularization (TVR), major adverse cardiac events (MACE), stroke, bleeding, and re-hospitalization.

Angiographic follow-up was obtained in 507 patients. The MLD of the cilostazol-treated patients was 1.81mm for the analysis segment (stent + 5 mm borders) in comparison to 1.67 mm ($P = 0.019$) in the placebo group. Late loss (0.52 mm vs 0.70mm, $P = 0.0035$) and in-stent restenosis (20.1% vs 31.4%, $P = 0.0038$) were also significantly reduced in the cilostazol and placebo groups, respectively. Furthermore, binary restenosis occurred in the analysis segment in 20.9% of treated patients in comparison to 34.6% of patients receiving placebo ($P = 0.0006$), a 39.5% relative risk reduction (see Figure 6). Of note, subgroup analysis revealed that cilostazol significantly reduced restenosis in diabetic patients and in vessels less than 3.0 mm in diameter. Importantly, there was no significant difference in bleeding, re-hospitalization, TVR, and MACE between groups.

Surprisingly, cilostazol administered within six hours following successful stent implantation significantly reduced angiographic restenosis in comparison to placebo.

Comments

Surprisingly, cilostazol administered within 6 hours following successful stent implantation significantly reduced angiographic restenosis in comparison to placebo. The mechanism of its effect is unclear but favorable modulation of platelet aggregation, inflammation and mitogenesis have been implicated. The less than ideal angiographic follow-up rate of 72% and the absence of a difference in TVR notwithstanding, the results of this study will likely be considered in future trials of patients undergoing PCI, particularly those using drug-eluting stents.

WITTI Women Study

Despite widespread dissemination of clinical practice guidelines, multiple barriers continue to exist that prevent the transfer of new knowledge to the patient and public. Interventions and systems approaches that increase adherence to guideline recommendations are under active evaluation. The Secondary Prevention Beyond Walls Intervention Trial In (WITTI) Women was designed to determine whether a systematic intervention course would improve adherence to AHA secondary prevention goals in women with coronary heart disease when compared to standard care. Results of the study were presented by Dr. Lori Mosca of New York-Presbyterian Hospital, New York, NY.[84]

After discharge from 3 academic medical centers following treatment for coronary artery disease, 304 women (mean age 62.3 years, 48% white, 37% black, 15% Hispanic) were randomly assigned to systematic intervention or usual care. The primary endpoint of the study was achievement of 8 secondary prevention goals including: complete smoking cessation, blood pressure less than 140/90 mmHg, LDL cholesterol measurements less than 100 mg/dL,

exercise three times per week or enrollment in a cardiac rehabilitation program, body mass index in the range of 18.5 to 24.9 and waist measurement less than 35inches, use of aspirin or an anticoagulant, use of an ACE inhibitor (unless creatinine > 2.0mg/dL), and use of a ß-blocker.

The intervention included a structured 1-hour educational session prior to discharge, conducted by a health educator, regarding the 8 prevention goals as well as strategies to attain them. Structured follow-up occurred at 2 and 4 weeks and at 3 months by phone with office visits scheduled at 6 weeks and 6 months. In addition, enrollment in a cardiac rehabilitation program was facilitated and a standardized prevention checklist was sent to each patient's primary care physician.

As expected, baseline characteristics were similar between the 2 groups and there was no difference in the mean summary score for individual goals that had already been met. Interestingly, lifestyle-adherence goals had a low compliance rate, with only 13% of participants at their weight-management goal and only 20% at their exercise goal. At 6 months, the intention-to-treat analysis revealed no difference in the mean number of goals met or in individual goals between the 2 groups. Of note, members of minority populations, who received the intervention, were 2.3 times more likely to achieve blood pressure goals than were minorities receiving usual care. Conversely, if left to usual care, whites were significantly more likely to be at target blood pressure than minorities.

Comments

It is well-known that prescribed behavioral and lifestyle changes are particularly difficult to make and follow consistently. This study addressed behavioral change in both patients and providers. Although promising, systematic education to improve adherence to prevention goals in women with established coronary artery disease was no more effective than usual care. These disappointing results highlight the need to establish new methods to improve adherence to secondary prevention goals in women. This systematic intervention may have potential in minority populations and additional studies should include diverse and high-risk subpopulations.

[Alice K. Jacobs, MD, FACC, FAHA]

Members of minority populations, who received the systematic intervention in the WITTI Women Study, were 2.3 times more likely to achieve blood pressure goals than were minorities receiving usual care.

B-Type Natriuretic Peptide and Valvular Heart Disease

Elevated neurohormones are proven, reliable outcomes predictors in patients with heart failure and primary pulmonary hypertension. However, little is known about their role in patients with severe asymptomatic valvular heart disease. Three reports at this year's AHA addressed the prognostic value of BNP levels in asymptomatic patients with severe mitral regurgitation (MR) and aortic stenosis (AS). Because the optimal timing of surgery in asymptomatic patients with severe valvular lesions represents one of the most clinically vexing problems faced by cardiologists, these findings may have important clinical implications.

Dr. Ursula Klaar of the University of Vienna in Vienna, Austria,[85] examined 85 consecutive patients (57 ± 15 years, 33 female) with severe mitral regurgitation due to organic mitral valve disease (mitral valve prolapse, n = 79; rheumatic heart disease, n = 4; endocarditis, n = 1; cleft mitral valve, n = 1). Patients were followed for a mean of 260 (± 49) days. Nineteen patients presented with heart failure symptoms and 66 were asymptomatic. Fractional shortening (38 ± 9 % in symptomatic versus 42 ± 6 % in asymptomatic patients, $P < 0.04$) and left ventricular end systolic diameter (37 ± 8 mm vs 32 ± 5 mm, $P < 0.01$) but not LVEF (61 ± 9 vs 63 ± 6, P = ns) differed between the 2 groups but did not exceed the cut off values where surgery is recommended in asymptomatic patients. BNP levels were significantly higher in symptomatic versus non-symptomatic patients (337 ± 331 pg/mL vs 65 ± 92 pg/mL, $P < 0.0001$) but did not correlate with LV dimensions or fractional shortening. However, all patients had normal or only slightly reduced LV function and only 4 had a left ventricular end diastolic diameter > 65 mm, indicating a rather early stage of disease in the majority of patients. BNP levels were significantly higher in asymptomatic patients who developed symptoms during the follow-up period compared to those who remained asymptomatic (147 ± 161 pg/mL vs 33 ± 27 pg/mL). Thus plasma BNP levels were higher in symptomatic compared to asymptomatic patients with severe MR and normal or mildly reduced LV function. More importantly, BNP levels were significantly higher in asymptomatic patients who subsequently became symptomatic, thus identifying patients at risk. BNP may detect early changes in myocardial function even before they are echocardiographically detectable and may prove useful in determining the opti-

mal timing for surgery in severe MR.

Amino-terminal brain natriuretic peptide (N-BNP) is elevated in symptomatic patients with AS. However, its role in asymptomatic patients remains to be determined. Dr. Ivor Gerber of the Green Lane Hospital, Auckland, New Zealand,[86] studied 29 asymptomatic patients (NYHA Class I) with AS, mean age 65 (± 15) years. Patients underwent clinical evaluations along with BNP determination at 6-month intervals as well as annual echocardiography, including measurement of peak velocity (V_{max}) and aortic valve area (AVA). After a mean follow-up of 17.4 (± 7) months, 8 patients (28%) developed cardiac symptoms (NYHA Class > II, n = 7; angina, n = 1).

The authors conclude that in patients with severe aortic stenosis, BNP levels increase with functional class and impairment of LV function.

At baseline, V_{max} and AVA were similar whereas N-BNP levels were higher in patients who developed symptoms compared to those who remained asymptomatic at follow-up. At follow-up there was a similar change in AVA and V_{max} in those who developed symptoms and those who did not. In contrast, there was a greater increase in N-BNP in patients who developed symptoms compared to those who did not, which remained significant after adjustment for age, baseline AVA, and baseline N-BNP. The authors concluded that, in patients with initially asymptomatic AS, the baseline and change over time in N-BNP levels predicts symptom onset independent of echocardiographic measures of AS severity.

In another study of patients with AS, Dr. Jutta Bergler-Klein of the University of Vienna in Vienna, Austria,[87] determined BNP, N-terminal BNP, and N-terminal ANP levels in 130 patients with severe AS and characterized by mean age of 71 (± 11) years; 43 (33%) presenting as asymptomatic; mean gradient of 64 (± 21) mmHg; and valvular area of 0.64 (± 0.15) cm.^{2} Patients were followed for 377 (± 150) days. At entry, symptomatic patients had significantly higher neurohormone levels than asymptomatic patients. Natriuretic peptides increased with increasing NYHA Class (BNP 120 [± 84] in Class II patients, 484 [± 330] in Class III patients, and 1756 [± 1137] in Class IV patients) and decreasing EF (r = -0.51, $P < 0.0001$). Asymptomatic patients who developed symptoms during follow-up had higher BNP levels at entry compared to patients remaining asymptomatic (256 [± 218] vs 89 [± 256]). A significant increase in BNP was noted in patients becoming symptomatic, whereas BNP levels did not change in those who remained asymptomatic. A BNP level > 130 pg/mL was a significant predictor of symptom development during follow-up. BNP levels were also predictive of postoperative functional class and survival likelihood. The authors conclude that in patients with severe AS, BNP levels increase with functional class and impairment of LV function. Importantly, BNP or N-BNP predict symptom-free survival in asymptomatic patients.

These 3 studies confirm the correlation of neurohormones with functional class in patients with severe AS and MR. They all suggest that BNP levels are also predictive of the development of symptoms in patients who are asymptomatic at entry as well as symptom-free short-term survival in patients with low BNP levels. Since the prediction of natural history and determination of the optimal timing for surgery in asymptomatic patients with severe valvular lesions can be difficult, these studies suggest an alternative or adjunct to simple echocardiographic measurements of valve area, gradients, and LV function. The observation that increased BNP levels may precede echocardiographic changes may be particularly useful in identifying patients for whom intervention is appropriate before overt LV dysfunction become manifest.

[Arthur E.Weyman, MD]

VALIANT Trial

Dr. Marc Pfeffer of the Brigham and Women's Hospital in Boston, MA, presented the Valsartan in Acute Myocardial Infarction (VALIANT) Trial, a large, multinational study, which provides clear-cut answers regarding the use and efficacy of an angiotensin-receptor blocker (ARB), in this case valsartan (Diovan,® Novartis Pharmaceuticals Corp., East Hanover, NJ), versus an angiotensin-converting-enzyme inhibitor (ACEI), captopril, in high-risk post-myocardial infarction survivors.[88]

Inclusion criteria consisted of myocardial infarction 12 hours to 10 days prior to randomization, complicated by clinical or radiological signs of congestive heart failure, depressed left ventricular systolic function, or both. Patients were randomized into 3 groups: valsartan (titrated to 160 mg, bid), captopril (titrated to 50 mg, tid), and the combination of valsartan (titrated to 80 mg, bid) and captopril (titrated to 50 mg, tid). The primary endpoint was death from any cause. A prespecified analysis was designed to demonstrate the noninferiority or equivalence of valsartan to captopril. Median follow-up was 24.7 months and the results were

quite negatively conclusive. Mortality was 19.9% in the valsartan group, 19.5% in the captopril group, and 19.3% in the combination group. Hazard ratios demonstrated that there was no difference whatsoever between the 3 groups regarding mortality and the composite endpoint of fatal and nonfatal cardiovascular events. In regard to side effects, hypotension and renal dysfunction were more frequent with valsartan. Cough, rash, and taste disturbance were more common in captopril-treated patients. Moreover, adverse effects were less with monotherapy compared to the combination, and the latter showed no benefits regarding survival.

In summary, this study conclusively demonstrated that 160 mg of valsartan twice daily is as effective as 50 mg of captopril 3 times daily. In a previous trial, Survival and Ventricular Enlargement (SAVE), in a similar group of postinfarction survivors, captopril in these doses significantly reduced left ventricular mortality and morbidity in comparison with placebo. From a clinical standpoint, an accompanying editorial[89] pointed out that ACEIs are still the drugs of initial choice in high-risk postinfarction survivors. The amount of trial data on ACEIs is extensive, whereas the total experience with ARBs is limited. Moreover, the cost of 160 mg of valsartan twice daily compared to generic captopril is 4- to 6-fold higher. Nonetheless, this trial tells us that we have an excellent alternative for patients who do not tolerate ACEIs. Moreover, we now know that the combination offers no additional advantages—an important consideration among elderly patients, who often do not tolerate multiple medications.

Comment

This large, well-conducted trial completes another chapter in the tale of renin-angiotensin system blockade in patients with acute myocardial infarction, an on-going story that has continued to unfold for the past 20 years.[90]

The earliest trials of ACEIs in patients with cardiovascular disease were confined to subjects with severe, chronic congestive heart failure. One study, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) II of intravenous enalapril in patients with acute myocardial infarction, demonstrated a trend in an adverse direction, suggesting that if ACEIs are to be administered, patients should be hemodynamically stable. The rest of the story, however, is one of good news.[91]

In summary, the VALIANT study conclusively demonstrated that 160 mg of valsartan twice daily is as effective as 50 mg of captopril three times daily.

The pioneering animal data from Drs. Marc and Janice Pfeffer paved the way for an entirely new approach in regard to the use of ACEIs to prevent ventricular remodeling, dilatation, and subsequent congestive heart failure.[92] This led to the SAVE Trial followed by three other trials (Acute Infarction Ramipril [AIRE], Trandolapril Cardiac Evaluation [TRACE], and Survival of Myocardial Infarction Long-Term Evaluation [SMILE]), which consistently demonstrated the benefits of ACEIs in high-risk myocardial infarction survivors with either left ventricular systolic dysfunction, transient congestive heart failure, or anterior myocardial infarction, the so-called selective approach to the use of these agents.[91,93]

The next series of trials (Fourth International Study of Infarct Survival [ISIS-4], Gruppo Italiano per lo Studio Della Sopravvivenza nell'Infarto miocardico [GISSI-3], and the Chinese Captopril Trial) included all patients with acute myocardial infarction, an "inclusive" approach.[91] These trials were also positive, and clinicians were left with 2 options: the selective use of ACEIs for high-risk patients with indefinite duration of therapy or an inclusive approach requiring the use of ACEIs for approximately six weeks, followed by reassessment.[90]

At this point, a series of observations from the SAVE and the Studies of Left Ventricular Dysfunction (SOLVD) Trials (the latter comprising patients with symptomatic and asymptomatic left ventricular dysfunction with an ejection fraction of 35% or less) took a different path.[94] Both trials showed a consistent, highly significant reduction in recurrent ischemic events, a somewhat surprising outcome, given that the major indication for use of ACEIs was to prevent ventricular remodeling and its hemodynamic consequences. Perhaps we should not have been surprised. Basic scientific investigators had previously and consistently demonstrated that angiotensin II is a pro-inflammatory, pro-thrombotic, and proliferative agent, which, in addition, mediates sympathetic nervous system activity.[94]

The next phase of trials logically focused upon the use of ACEIs in the primary and secondary prevention of cardiovascular events in patients without left ventricular dysfunction but with known coronary artery disease.

The Heart Outcomes and Prevention (HOPE) Trial of ramipril and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) Trial, were both strongly

positive.[95,96] HOPE included patients at extremely high risk due to diabetes, peripheral vascular disease, and hypertension, whereas the EUROPA population, all of whom had evidence of coronary artery disease, were at somewhat lower risk. The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial using trandolapril in a patient population among whom the majority had undergone successful coronary revascularization and were treated with ß-blockers and statins, will be presented in November 2004.[97]

Hopefully, all 3 trials will complement one another and provide a body of objective evidence covering a wide spectrum of patients. Whether the benefits of ACEIs are due to the lowering of blood pressure, hemodynamic effects, other pleomorphic actions, or all of these in combination, remains a subject of some controversy and vigorous (to say the least) discussion. Nonetheless, it is interesting to see how the use of ACEIs has been expanded to progressively include populations at lower risk, with consistently positive trial results.

This leads back to the VALIANT Trial, a worthwhile addition to an already large body of evidence. Prior trials of ARBs and ACEIs tended to favor ACEIs despite the fact that ACEIs only block 13% of the total production of angiotensin II.[98,99] The editorial accompanying the published study points out that this may have been "a matter of dose."[89] The higher doses used in VALIANT are likely the explanation for the demonstration of equivalence in this trial as opposed to other trials, but one cannot discount the possibility of the lack of a class effect.

In conclusion, renin-angiotensin blockade in patients with diverse manifestations of cardiovascular disease has, in general, provided a diet of continued success. Ongoing trials will clarify the issue of "class effects" versus individual drugs. Further clarification of the mechanisms of benefit may, in turn, lead down another road, toward an understanding of the treatment and prevention of cardiovascular disease.

[Bernard J. Gersh, MB, ChB, DPhil, FRCP]

The higher doses used in VALIANT are likely the explanation for the demonstration of equivalence in this trial as opposed to other trials, but one cannot discount the possibility of the lack of a class effect.

Peripheral Arterial Disease

The AHA has developed several initiatives in the area of atherosclerotic vascular disease, including the formation of an Interdisciplinary Working Group on Peripheral Atherosclerotic Vascular Disease. At the 2003 Annual Scientific Sessions, there were a number of programs devoted to atherosclerotic vascular disease. One of these was a special session on peripheral arterial disease (PAD). In this session, the epidemiology, clinical presentation, diagnostic evaluation, medical management, and endovascular therapies for PAD were discussed.

Dr. Michael Criqui, Professor of Epidemiology at the University of California San Diego, San Diego, CA, began the session by reviewing the epidemiology and prognosis of patients with PAD. He noted that several questionnaires have been developed to evaluate the presence of intermittent claudication in population-based studies. These include the Rose questionnaire, Edinburgh questionnaire, and San Diego questionnaire, each of which has unique characteristics for defining intermitting claudication. Based on studies using these questionnaires, approximately one-third of PAD patients have classic symptoms of claudication, whereas many others have atypical symptoms or no symptoms whatsoever. Indeed, many patients with relatively severe PAD do not complain of intermittent claudication. Thus, the clinician must be particularly vigilant in looking for evidence of PAD to identify patients at increased risk for vascular events.

Dr. Criqui cited the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) study, which surveyed office-based physician practices to determine the prevalence of PAD in high-risk patients.[100] Specifically, this study sought to identify PAD among all patients over 70 years of age and in patients between the ages of 50 to 69 years who either had diabetes or smoked cigarettes. Based on an abnormal ankle/brachial index (ABI) of less than 0.9, 29% of these targeted individuals were found to have PAD. The importance of identifying PAD is underscored by studies indicating that such patients have a 5- to 6-fold increased risk of adverse cardiovascular events compared to age-matched subjects who do not have PAD. Therefore, identification of PAD will improve the likelihood that physicians will institute appropriate risk-factor modifications and antiplatelet therapies to reduce the probability of myocardial infarction, stroke, or vascular death in these individuals.

Dr. Mary McDermott, Associate Professor of Medicine at Northwestern Medical Center, Chicago, IL, elaborated on the symptoms and impaired walking function experienced by patients with PAD. She noted that previous studies have found atypical

symptoms in 20%-60% of patients, with prevalence varying among different studies.[100-102] Symptoms included reduced walking speed and maximum distance, along with other gait difficulties. There is a direct relationship between low ABI scores and the need to stop during a 6-minute walk. Indeed, some patients who appear asymptomatic may be relatively inactive, not ever walking 6 minutes at a time. Thus, physicians must be aware of the fact that impaired walking ability, particularly in healthy patients, may reflect the presence of severe PAD, and not simply a function of the aging process.

Duplex ultrasonography, a technique readily available in most noninvasive vascular laboratories, can be used to identify peripheral arterial stenoses with approximately 90% sensitivity and 95% specificity.

The use of imaging techniques to evaluate PAD has evolved considerably in recent years and, in many instances, supplanted the need for conventional contrast angiography prior to revascularization procedures. Dr. John Kaufman, Professor of Radiology at the Oregon Health and Sciences University, Portland, OR, reviewed contemporary diagnostic imaging methods for the evaluation of patients with PAD.

Dr. Kaufman noted that duplex ultrasonography, a technique readily available in most noninvasive vascular laboratories, can be used to identify peripheral arterial stenoses with approximately 90% sensitivity and 95% specificity. Magnetic resonance angiography (MRA) is an imaging modality that is increasingly utilized, in lieu of conventional angiography, to define vascular anatomy, identify lesions, and plan appropriate revascularization procedures. Using current technology, MRA has a sensitivity of approximately 98% and specificity of approximately 96% to identify significant stenoses.[103] Computed tomographic angiography (CTA) with acquisition of 1-3 ml axial slices and the use of post-processing imaging technique also provides excellent resolution, approaching that achieved by conventional angiography. Reformatting and volume rendering of CTA produces 3-dimensional images that are particularly useful in assessing anatomy prior to revascularization. Digital subtraction angiography remains the gold standard with the highest resolution. Although its utility as a diagnostic tool has been replaced in many situations by the aforementioned noninvasive studies, it is still used to plan procedures and in the performance of endovascular interventions.

The pharmacotherapy of PAD was reviewed by Dr. Mark A. Creager, Professor of Medicine at Harvard Medical School, Boston, MA. He emphasized that medical treatment should be informed by 2 major considerations: treatment that reduces cardiovascular morbidity and mortality in patients with PAD and the improvement of functional capacity and quality of life in patients with PAD. Risk factor modification, including cholesterol reduction, intensive glucose control in diabetic patients, antihypertensive therapies, and antiplatelet drugs are important considerations in the management of PAD in order to reduce adverse cardiovascular events.

The Heart Protection Study, which included 3748 patients with PAD and no prior evidence of coronary heart disease, found that simvastatin, compared to placebo, reduced the risk of adverse cardiovascular events in PAD patients by approximately 20%.[104] The United Kingdom Prospective Diabetes Study found that intensive blood glucose control versus conventional treatment of patients with type 2 diabetes reduced microvascular disease (retinopathy, nephropathy) by 25% and myocardial infarction by 16%. There was a non-significant (35%) reduction in amputation or death from PAD.[105] The Heart Outcomes Prevention Evaluation (HOPE) included 4046 patients with PAD in whom ramipril, compared to placebo, reduced the risk of adverse cardiovascular events by over 20%. The Antithrombotic Trialists Collaboration evaluated 42 trials of over 9000 patients with PAD and found that antiplatelet therapy, compared to control, reduced cardiovascular events by 22%. The CAPRIE study, comparing clopidogrel to aspirin, found that clopidogrel reduced the risk of adverse cardiovascular events in PAD patients by 24%. Thus, risk factor modification, particularly control of dyslipidemia, diabetes, and high blood pressure (as well as smoking cessation and the institution of antiplatelet therapy) can have a significantly positive impact on improving cardiovascular outcome in patients with PAD.

Iliac percutaneous transluminal angioplasty (PTA) should be considered not only for patients with critical limb ischemia, but also those with claudication if there is significant impairment to quality of life.

Drug therapies used for treatment

Main Points

- Assuming ximelagatran continues with its current efficacy and safety profile, as shown in SPORTIF V, many more patients who require anticoagulation will hopefully receive it and this should result in a marked decrease in stroke without an increase in complications.
- The DEFINITE Trial investigated the use of implantable cardiac defibrillators to treat patients with nonischemic dilated cardiomyopathy. Although results were positive, the study population was too small to significantly demonstrate an effect on mortality.
- The results of the FUSION trial provide hope that, with the use of nesiritide, there will be an outpatient-treatment option that not only enhances the clinical status of acutely decompensated heart failure patients, but also reduces mortality and hospitalization rates.
- Several small trials have yielded promising results in the use of new 16-slice computed tomography scanning as a non-invasive diagnostic tool for coronary atherosclerosis.
- New advances in echocardiographic imaging, particularly 3-dimensional echo and perfusion echo, are allowing well-trained clinicians to make more accurate diagnoses and apply therapies such as biventricular pacing more effectively.
- A Phase 2 study of ApoA-I Milano provided proof for the concept that synthetic-HDL therapy can rapidly change human coronary plaques. While this study had a small number of patients, the rapidity of regression, although modest in amount, was impressive and is likely to stimulate further development of this product through additional larger Phase IIB and Phase III trials to demonstrate efficacy in terms reduction in clinically relevant cardiovascular events.
- There are now approximately 16 trials of n-acetylcysteine published and reported to date, and likely a meta-analysis of these trials would demonstrate that it does not reduce the rate of contrast-induced nephropathy. A large, randomized trial would need to be conducted to definitively answer this question.
- Three small trials, GRACIA-1, GRACIA-2, and BRAVE, have shown a possible benefit to facilitated angioplasty, suggesting that immediate thrombolytic therapy in ST-segment elevated MI can lengthen acceptable door-to-balloon time for angioplasty, with no adverse effect on short- or long-term outcomes.
- The REVERSAL trial demonstrated that intensive low-density lipoprotein cholesterol-lowering therapy with atorvastatin completely halted progression of atheroma, whereas more moderate treatment with pravastatin did not. Lack of placebo comparison and clinical endpoint data leave the question of mechanism for this outcome undetermined.
- Recent research in high-density lipoprotein (HDL) shows that HDL function (pro-inflammatory vs anti-inflammatory) is as important, if not more important, an indicator in coronary heart disease than simple measurements of plasma HDL levels.
- In the CREST trial, cilostazol administered within 6 hours following successful stent implantation significantly reduced angiographic restenosis in comparison to placebo. The mechanism of its effect is unclear but favorable modulation of platelet aggregation, inflammation, and mitogenesis have been implicated.
- Recent data suggest that natriuretic peptide levels are a valuable predictor in the prognosis of both symptomatic and asymptomatic patients with mitral regurgitation and aortic stenosis, and can help to determine the proper course of treatment, including surgery.
- The VALIANT trial of patients with recent myocardial infarction and related complications, demonstrated a similar rate of efficacy amongst monotherapy with angiotensin-receptor blockers (ARBs), angiotensin-converting-enzyme inhibitors (ACEIs), and combination therapy utilizing both drug classes. It conclusively shows ARBs to be a viable alternative for patients intolerant of ACEIs and discourages the use of combination therapy as it bestows no benefit.
- Recent peripheral arterial disease research from the PARTNERS Trial has shown a higher prevalence of concomitant claudication, both symptomatic and asymptomatic, than formerly suspected. Treatment with cilostazol has proven the best pharmacologic option for this problem, significantly improving walking distances and showing greater efficacy than pentoxifylline in a direct-comparison trial.

of claudication include pentoxifylline, a methylxanthine derivative, and cilostazol, a phosphodiesterase III inhibitor. Cilostazol has been shown in multiple studies to improve walking distance in patients with claudication, and was significantly more efficacious than pentoxifylline in a comparative trial.[106,107] Atorvastatin has recently been shown to improve pain-free walking time in patients with intermittent claudication.[108] Propionyl-L-carnitine, a substance that improves mitochondrial metabolism of fatty acids, also has been shown to improve peak walking time in patients with claudication.[109] Angiogenic growth factors are undergoing investigation for similar treatment. Therapy with recombinant FGF-2 via the femoral artery caused a modest increase in claudication in 1 study, whereas gene transfer therapy with VEGF-121 did not confer improvement in claudication compared to placebo.

Catheter-based endovascular interventions for PAD were reviewed by Dr. Christopher White of the Cardiology Department at the Ochsner Clinic Foundation, New Orleans, LA. He noted that indications for endovascular treatment of PAD have recently evolved, due to increased experience and improved outcomes. For example, iliac percutaneous transluminal angioplasty (PTA) should be considered not only for patients with critical limb ischemia, but also for those with claudication if there is significant impairment to quality of life. Four-year patency of iliac artery stenting exceeds 90%, an outcome comparable to that of open surgical procedures, yet with the advantage of shorter hospital stays and less morbidity. Similarly, for many patients with popliteal stenoses and short segment occlusion, PTA is achieving 50%-60% long-term patency rates, approaching those of reconstructive surgery. PTA is also utilized increasingly in crural vessels of patients with critical limb ischemia, particularly those with focal stenoses less than 6 cm in length. Tibioperoneal angioplasty may be used in lieu of surgery, in selected patients with critical leg ischemia, for the relief of pain, to heal ulcers, or to avoid amputation. Some studies indicate an approximate 80% 2-year limb-salvage rate following infrapopliteal angioplasty. Several studies have suggested that restenosis following PTA of the superficial femoral artery is reduced by adjunctive brachytherapy.[110] Small studies using drug-eluting stents in the periphery have been encouraging,[111] but additional clinical trials are necessary to determine the utility of stents to reduce restenosis in the peripheral circulation. ■

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