

## Meeting Highlights

# American Heart Association Scientific Sessions 2004

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More than 26,000 cardiologists, cardiothoracic surgeons, research scientists, and other health care professionals gathered from around the world to hear the latest developments in the diagnosis, prevention, treatment, and control of cardiovascular diseases at the American Heart Association (AHA) Scientific Sessions 2004, held in New Orleans, Louisiana, from November 7 to 10, 2004. Studies of particular interest included a lipid-lowering combination to slow atherosclerotic progression, an angiotensin II type-1 receptor blocker for hypertensive patients with the metabolic syndrome, a low-cost

generic infusion useful in acute myocardial infarction (AMI), a novel nitric oxide synthase inhibitor for patients with AMI complicated by cardiogenic shock, a fixed-dose combination of a nitrate and a diuretic for African-Americans with heart failure (HF), a comparison of the value of isotopes versus vasodilators in hospitalized patients with HF, a unique drug for long-term weight loss, a statin that slows the development of Alzheimer's disease, and a major new marker that can independently predict coronary artery disease.

### Extended-Release Niacin/Statin Combination for Atherosclerotic Patients with Coronary Heart Disease

**Speaker:** Allen J. Taylor, MD, Director of Cardiovascular Research, Cardiology Service, Walter Reed Medical Center, Washington, DC

Results from the ARBITER-2 (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol) trial indicate that the combination of prescription extended-release (ER) niacin (Niaspan®, Kos) and statin therapy slows the progression of atherosclerosis in individuals with coronary heart disease (CHD) and moderately low high-density lipoprotein-cholesterol (HDL-C) by 68%, compared with statin monotherapy, as measured by plaque buildup in the carotid artery.

The ARBITER-2 trial enrolled 167 patients with known CHD and low HDL-C levels (below 45 mg/dl). All patients were already receiving treatment with statin monotherapy at the start of the trial, when they were randomly assigned to add either ER niacin tablets at a daily oral dose of 500 mg for 30 days (which was then increased to 1,000 mg/day for the rest of the 12-month study period) or a matched control.

There were no differences in cardiac risk factors or in the use of other cardiovascular medications between groups. Disease progression was measured by the change in carotid intima-media thickness (CIMT), a sanctioned marker in which a submillimeter increase in arterial wall thickness (i.e., plaque buildup) predicts an increased risk of heart disease.

A total of 149 patients completed the 12-month study period and were included in the primary endpoint analysis.

At 12 months of treatment, CIMT increased significantly, by 0.44 mm in the placebo group of patients, and remained

unchanged in the patients taking ER niacin. Although the difference in CIMT between these two groups was not significant, a subgroup analysis showed that CIMT progression in patients without insulin resistance was significantly reduced in the ER niacin group compared with the placebo patients. In fact, placebo-treated patients experienced the greatest CIMT progression, regardless of insulin resistance status.

HDL-C levels rose significantly, by 21% in the ER niacin patients (from 39 to 47 mg/dl) but remained unchanged in the placebo group. Triglyceride levels decreased significantly in the ER niacin patients in contrast to the patients receiving statin monotherapy only, from  $154 \pm 82$  mg/dl at the baseline evaluation to  $134 \pm 87$  mg/dl at 12 months for ER niacin versus  $172 \pm 104$  mg/dl at baseline to  $164 \pm 83$  mg/dl at 12 months for placebo.

Furthermore, in a population in which all patients had CHD, clinical cardiovascular events declined by 60% among patients taking ER niacin compared with those on statin monotherapy, although this was not a specified endpoint. Clinical cardiovascular events occurred in three patients (3.8%) taking ER niacin versus seven patients (9.6%) taking placebo.

### Telmisartan in Hypertensive Patients with the Metabolic Syndrome

**Speaker:** Giuseppe M. Rosano, MD, Cardiologist, San Raffaele Hospital, Rome, Italy

In a study of two well-known angiotensin II type-1 receptor blockers (ARBs), telmisartan (Micardis®, Boehringer Ingelheim) improved glucose metabolism in patients with the metabolic syndrome and hypertension, and it significantly reduced 24-hour mean ambulatory blood pressure (BP) compared with losartan potassium (Cozaar®, Merck).

The glycemic effects of these two ARBs were compared in patients with the metabolic syndrome in a double-blind, parallel-group study. Forty patients with newly diagnosed arterial hypertension, metabolic syndrome, impaired glucose

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tolerance, insulin resistance, or type-2 diabetes were randomly assigned to receive telmisartan 80 mg daily or losartan 50 mg daily for three months. Patients were assessed at baseline and after three months of treatment for levels of glycosylated hemoglobin (HbA<sub>1c</sub>), ambulatory BP, and free plasma glucose and free plasma insulin levels. A homeostasis model (HOMA-1R) was used to measure insulin resistance. Patients also underwent an oral glucose tolerance test (OGTT) and were evaluated for the incidence and severity of adverse drug effects (ADEs).

Telmisartan significantly decreased free plasma glucose by 18%, free plasma insulin by 10%, insulin resistance by 26%, and HbA<sub>1c</sub> by 9%. Losartan did not have a meaningful effect on any of these parameters. Levels of glucose and insulin following the OGTT were also significantly reduced with telmisartan in comparison with losartan.

After three months, although both ARBs reduced BP, telmisartan showed a significantly greater reduction in 24-hour mean systolic BP and diastolic BP. No significant correlation between a decrease in BP and a change in glucose or insulin levels was observed.

### Glucose–Insulin Infusion in Patients with Acute Myocardial Infarction

**Speaker:** Shamir R. Mehta, MD, MSc, Associate Professor of Medicine, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada

High-dose glucose insulin-potassium (GIK) infusion, a promising low-cost intervention developed in Mexico in the 1950s, maintains its reputed beneficial effects in patients with ST-segment elevation myocardial infarction (STEMI). It was found to improve myocardial energetics, decrease free fatty acids, and reduce the incidence of serious ventricular arrhythmias, with no impact on mortality, cardiac arrest, or cardiogenic shock.

In an exploratory subgroup of patients receiving primary percutaneous cardiovascular intervention (PCI) or thrombolytic therapy with recombinant tissue-plasminogen activator (rt-PA) (Activase®, Genentech), mortality was significantly reduced, but this was not part of the specified analyses.

A total of 20,201 patients with STEMI, presenting within 12 hours, were enrolled into the CREATE–ECLA (Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiológicos Latinoamérica) study from 518 centers in 21 regions, including North America, South America, Europe, the Middle East, India, China, and Pakistan. Patients were randomly selected to receive a GIK infusion plus the usual care or the usual care alone for 24 hours.

A subset of 15,500 patients in China and India (the CREATE trial) were also randomly assigned to receive a simple regimen of the low-molecular-weight heparin reviparin as an anti-coagulant. The primary endpoints in the CREATE–ECLA trial were 30-day all-cause mortality. Secondary endpoints included nonfatal MI, cardiogenic shock, and a second MI at either the seventh day or up to the 30th day. The primary endpoints in the CREATE trial were death, a second heart attack or stroke at seven days, and refractory ischemia at seven days.

Mortality from any cause occurred in 10% of GIK patients and in 9.7% of controls. The rates of cardiac arrest were 1.4%

in the GIK group and 1.5% in the controls; for cardiogenic shock, the rates were 6.6% and 6.3%, respectively; and for re-infarction, the rates were 2.3% and 2.4%, respectively. There was, however, a significant reduction in the rate of recurrent ischemia at seven days: 4.6% for the GIK patients and 6.5% for the controls.

The subgroup analyses were consistent with the overall result on mortality, including diabetic patients, patients with congestive heart failure, and patients receiving primary PCI or rt-PA.

### Tilarginine for Acute Myocardial Infarction Complicated by Cardiogenic Shock

**Speaker:** Vladimir Dzavik, MD, Director of Interventional Cardiology, University Health Network–Toronto Hospital, Toronto, Ontario

Tilarginine (*L*-*N*-monomethyl arginine) (ArgiNOx Pharmaceuticals, Inc.), a novel nonselective nitric oxide synthase (NOS) inhibitor capable of blocking the substantial increase in overall nitric oxide (NO) production during inflammatory events, was found to be safe and well tolerated in patients with acute myocardial infarction (AMI) complicated by cardiogenic shock. Although there was no significant difference in mortality between actively treated patients overall and those taking placebo, there was a reduction in the mortality rate of approximately 25% in the highest-dose treatment groups of patients compared with those taking placebo.

The SHOCK-2 (SHould we inhibit nitric Oxide synthase in Cardiogenic Shock) study, a phase 2, dose-ranging clinical trial, was designed to assess the efficacy and safety of four different doses of tilarginine to determine the optimal dosage for use in a pivotal phase 3 trial. A total of 79 patients (mean age, 68 ± 10 years) with persistent cardiogenic shock caused by left ventricular failure complicating AMI, were enrolled in the study.

The patients were randomly selected to receive a bolus of tilarginine, followed by a five-hour infusion of the NOS inhibitor in four dosage groups, with 13 to 15 patients assigned to each dose: at doses of 0.15 mg/kg bolus and 0.15 mg/kg per hour; 0.5 mg/kg bolus and 0.5 mg/kg per hour; 1.0 mg/kg bolus and 1.0 mg/kg per hour; and 1.5 mg/kg bolus and 1.5 mg/kg per hour; or placebo. The primary endpoint was a change in mean arterial pressure at two hours. Secondary endpoints included mortality at 30 days and six months and a change in urine output and creatinine.

Tilarginine proved to be safe and well tolerated in these patients. All of the patients were very sick, many were very old, and a high proportion of them had diabetes. The drug's safety profile was similar to that seen in the placebo group.

Although there was no significant difference in mortality between the overall active-treatment groups and the placebo subjects, this was not surprising. In a small study of this type, with only 79 patients in five study arms, the randomization was unbalanced. There were fewer very sick patients in the placebo arm, compared with those receiving active treatment; cardiogenic shock resolved in 90% of the patients taking placebo. Because of the imbalance, the mortality rate in the placebo group was lower than expected, resulting in no significant

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difference between the overall active-treatment patients and the placebo patients. However, mortality was significantly reduced in the highest-dose treatment groups of patients compared with the placebo group.

There is a need for an adequately powered randomized study, and the findings of the SHOCK-2 study support the expanded clinical testing of tilarginine as a drug with the potential to treat the often fatal condition of AMI complicated by cardiogenic shock. A phase 3 clinical trial, therefore, is being planned.

### Isosorbide Dinitrate/Hydralazine Combination for African-American Patients with Heart Failure

**Speaker:** Ann L. Taylor, MD, Professor of Medicine and Associate Dean for Faculty Affairs, University of Minnesota Medical School, Minneapolis, Minnesota

The addition of a nitric oxide-enhancing, fixed-dose combination of isosorbide dinitrate plus hydralazine (ISDN/HYD) (BiDil®, NitroMed) to standard therapy for heart failure increases survival significantly compared with standard therapy alone.

A total of 1,050 African-American patients with New York Heart Association (NYHA) class III or IV heart failure with dilated ventricles were enrolled into the African-American Heart Failure Trial (A-HeFT). They were randomly assigned to receive a fixed dose of ISDN/HYD or placebo. The initial dose of ISDN/HYD was 37.5 mg/20 mg three times daily. The dose was then increased to two tablets three times a day, for a total dose of 225 mg/120 mg, depending on the absence of drug-induced side effects.

The primary endpoint was a composite score made up of weighted values for death from any cause, a first hospitalization for heart failure during the 18-month follow-up period, and a change in quality of life at six months.

On the unanimous recommendation of the independent data and safety monitoring board, the study was terminated early on July 19, 2004, after 1,050 of the planned 1,100 patients had undergone randomization as a result of the significantly higher mortality rate in the placebo group compared with the ISDN/HYD group. When the trial was halted, the mortality rate was 10.2% in the placebo group (54 patients had died), compared with 6.2% in the ISDN/HYD group (32 patients had died), for a significant 43% improvement in survival ( $P = .01$ ). The mean duration of follow-up was 10 months.

The rate for a first hospitalization was reduced by 33% in the active-treatment group; the actual rates for a first hospitalization were 16.4% for the treated patients and 22.4% for those taking placebo. Median quality-of-life scores also improved more in the ISDN/HYD patients than in the placebo group, with questionnaire scores of  $-5.6 \pm 20.6$  versus  $-2.7 \pm 21.2$ , respectively. (Lower scores indicated a better quality of life.)

### Isotope versus Vasodilator Therapy During Hospitalization for Heart Failure

**Speaker:** Uri Elkayam, MD, Professor of Medicine, Division of Cardiovascular Medicine, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California

In an assessment of the use of isotopes and vasodilator therapy in hospitalized patients with recurrent heart failure (HF), inotropes were associated with an increased risk of death. Patients who received vasodilator medications such as nesiritide (Natreacor®, Scios) had no increased risk.

Initially, 433 patients hospitalized for recurrent HF were enrolled in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial to determine whether pulmonary artery catheterization (PAC) would improve clinical outcomes in these patients. Patients were randomly assigned to guided therapy using PAC plus clinical assessment or clinical assessment alone.

The use of PAC to lower pulmonary capillary wedge pressure (PCWP) without a specified treatment regimen had no impact on mortality and hospitalization. Whereas the routine use of PAC in hospitalized patients with recurrent HF is not generally indicated, it may result in greater functional improvement. It appears reasonable, therefore, to use PAC to tailor therapy in patients with persistent symptoms of HF.

Because intravenous (IV) inotropes and vasodilators are frequently used during hospitalization for HF and may affect outcomes, predictors of inotrope and vasodilator use and subsequent events for the patients in the ESCAPE trial were identified. Isotropes were used in 43% of patients; low sodium, low blood pressure, and high cardiac filling pressures, when known, were predictors of inotrope use, and the study site was the only independent predictor. Vasodilators were used in 29% of patients, and their administration was predicted by PCWP.

After an adjustment for renal function and blood pressure was made, inotrope usage was associated with an increased risk of death, with a hazard ratio (HR) of 1.75 ( $P = .032$ ) and an increased risk of death plus hospitalization, with an HR of 2.12 ( $P < .001$ ). The increased six-month mortality associated with inotrope use may be a reflection of unmeasured assessment factors triggering inotrope use or a late deleterious impact of inotrope use during hospitalization.

Vasodilator use was not associated with any increase in risk, whether or not baseline variables were adjusted.

### Rimonabant for Long-Term Weight Loss Management

**Speaker:** F. Xavier Pi-Sunyer, MD, MPH, Professor of Medicine, Columbia University College of Physicians and Surgeons, and Chief, Division of Endocrinology, Diabetes and Nutrition, Obesity Research Center, St. Luke's–Roosevelt Hospital, New York, New York

Data from the second year of a two-year phase 3 study have confirmed the long-term benefits of rimonabant (Acomplia™, Sanofi–Aventis), the first of a new class of therapeutic agents called selective CB1 blockers, with respect to weight loss and reduction of associated cardiovascular risk factors.

The Rimonabant In Obesity–North America (RIO–NA) trial was a multinational, multicenter randomized, double-blind, placebo-controlled study designed to assess the effect of this agent on weight reduction, weight maintenance, and prevention of regained weight in overweight to obese patients with or without comorbidities. The study included 3,040 patients at 72 centers in the U.S. and Canada.

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After a screening period of one week, patients were prescribed a mild hypocaloric diet designed to reduce daily caloric intake by 600 kilocalories (kcal). The patients were enrolled into a four-week, single-blind run-in period. Afterward, they were randomly assigned to receive placebo, rimonabant 5 mg, or rimonabant 20 mg for 52 weeks. A randomization ratio of 1:2:2 was used.

After one year of treatment, patients taking rimonabant were given either the same dose of rimonabant or placebo for a second year. A randomization ratio of 1:1 was used.

At one year, the reduction in waist circumference was 8.2 cm with rimonabant 20 mg, 4.7 cm with 5 mg, and 3.9 cm with placebo.

At two years, waist circumference was reduced by 8 cm for the rimonabant 20-mg group of patients, by 5 cm for the 5-mg group, and by 3.8 cm for the placebo group.

A total of 62.5% of patients who took rimonabant 20 mg for two years lost more than 5% of their initial body weight; 36.7% of those taking rimonabant 5 mg lost this amount; and 33.2% of the placebo group lost this amount.

During the same period, 32.8% of patients treated with rimonabant 20 mg lost more than 10% of their initial body weight; these numbers compared with 20% of subjects taking 5 mg and 16.4% taking placebo.

Throughout two years, metabolic parameters were also significantly improved in patients receiving rimonabant 20 mg. Levels of HDL-C increased by 24.5% in the high-dose rimonabant group, by 15.6% in the rimonabant 5-mg group, and by 13.8% in the placebo group. Triglyceride levels declined by 9.9% with rimonabant 20 mg, by 5.9% with rimonabant 5 mg, and by 1.6% with placebo.

Although diabetic patients were not included in the study, patients taking rimonabant 20 mg experienced significantly improved insulin sensitivity compared with those taking either the 5-mg dose or placebo.

Of particular note was the positive effect of rimonabant in patients with the metabolic syndrome. At baseline, 34.8% of patients who took rimonabant 20 mg met the criteria for metabolic syndrome. At the end of two years of treatment, this figure was reduced to 22.5%.

### Atorvastatin Delays Progression of Alzheimer's Disease

**Speaker:** D. Larry Sparks, PhD, Senior Scientist and Head, Roberts Laboratory for Neurodegenerative Disease Research, Sun Health Research Institute, Sun City, Arizona

The cholesterol-lowering drug atorvastatin (Lipitor®, Pfizer) slowed cognitive decline and improved depressive symptoms in patients with mild-to-moderate Alzheimer's disease (AD) and was safe and well tolerated over a one-year period.

Because both animal and human studies have shown that elevated cholesterol is an important risk factor for AD, a double-blind, placebo-controlled pilot study was designed to assess whether lowering cholesterol with atorvastatin could stabilize or improve cognition in people with mild-to-moderate AD. This proof-of-concept trial, entitled The Alzheimer's Disease Cholesterol-Lowering Treatment Trial (ADCLT), enrolled 87

patients with a diagnosis of probable or possible AD of mild-to-moderate severity.

The patients were randomly assigned to receive either atorvastatin 80 mg/day or placebo for one year. Sixty-three patients were considered evaluable at three months, and 46 individuals completed the 12-month study.

Patients taking cholinesterase inhibitors for AD were required to be on a stable dose for at least three months at study entry. The patients were evaluated at baseline, no more than 14 days after screening, and at three-, six-, nine-, and 12-month visits for assessment of cognition, overall mental function, and depression.

The Mini-Mental State Examination (MMSE), the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS-Cog), and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) were administered at baseline and quarterly. Semiannually, the Neuropsychiatric Inventory and the ADCS-ADL were administered to assess behavior and activities of daily living. The Geriatric Depression Scale was administered at baseline and at the first visit.

Blood chemistries were evaluated quarterly for levels of cholesterol, the protein ceruloplasmin, the gene apolipoprotein E, and the antioxidant superoxide dismutase (DMSO).

At the start of the study, average ADAS-Cog scores for both groups was 20. Performance on the ADAS-Cog in the atorvastatin group was approximately three to five points higher than in the placebo group at six months and 12 months. The differences were significant at six months and approached significance at 12 months.

A trend toward a difference in ADCS-CGIC scores was achieved at nine months and 12 months in favor of atorvastatin versus placebo. Improvement on the Geriatric Depression Scale in the atorvastatin group and deterioration in the placebo group represented a significant benefit for atorvastatin.

Overall, 53% of the atorvastatin patients showed improvement or stabilization of AD in contrast to only 28% of those in the placebo group. After one year, patients taking atorvastatin exhibited significant improvement in their symptoms of depression.

Atorvastatin also decreased low-density lipoprotein-cholesterol (LDL-C) levels by more than 50% (from 124 to 57 mg/dl). Total cholesterol fell by more than 40% (from 210 to 130 mg/dl).

Levels of DMSO were unaffected in both groups. Ceruloplasmin concentrations were reduced in the statin group by about 10% to 15% compared with placebo.

### A Key Marker, Lp-PLA<sub>2</sub>, for Predicting Coronary Artery Disease

**Speaker:** Wolfgang Koenig, MD, Professor, Department of Internal Medicine II-Cardiology, University of Ulm Medical Center, Ulm, Germany

Elevated levels of the enzyme lipoprotein-associated phospholipase A<sub>2</sub> (Lp-PLA<sub>2</sub>) (PLAC™ test, diaDexus) independently predict stable coronary artery disease (CAD), potentially offering an important therapeutic target to treat this disease.

To examine the association between Lp-PLA<sub>2</sub> concentra-

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tions in plasma and risk of CAD, investigators measured Lp-PLA<sub>2</sub> levels using the enzyme-linked immunosorbent assay (ELISA) in 312 patients with CAD and in 479 age-matched and sex-matched blood donor controls. Various lipid and lipoprotein parameters, as well as inflammatory and hemostatic parameters, were obtained to assess the relationship between Lp-PLA<sub>2</sub> and sensitive inflammatory and hemostatic markers and a complete lipoprotein profile.

The results from this study support a growing body of evidence that Lp-PLA<sub>2</sub> is a novel, independent risk marker for CAD. Lp-PLA<sub>2</sub> concentrations were significantly higher in patients with CAD (296.1 ng/ml) than in controls (266 ng/ml) ( $P < .0001$ ), and they were positively correlated with total cholesterol, LDL-C, and apoprotein B.

In a multivariate analysis, the age-adjusted and sex-adjusted hazard ratio (HR) for the presence of CAD in the patient group with the highest levels of Lp-PLA<sub>2</sub> was a statistically significant near-doubling of 1.61, the amount for patients in the bottom level.

Adjusting for traditional cardiovascular risk factors and statin use resulted in a hazard ratio (HR) of 2.04. After the researchers further controlled for other inflammatory and hemostatic parameters, such as C-reactive protein, among others, the HR was slightly attenuated to 1.84 but was still statistically significant.

On the basis of these results, as well as several other large case-control studies, the Food and Drug Administration cleared the test for Lp-PLA<sub>2</sub> for use in the U.S. The test is indicated for the quantitative determination of Lp-PLA<sub>2</sub> to aid in predicting an individual's risk for a coronary event, in conjunction with clinical evaluation and patient risk assessment.