

# Highlights of the 51st Scientific Session of The American College of Cardiology

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At the 51st Scientific Session of the American College of Cardiology in Atlanta, Georgia, over 25,000 cardiologists, research scientists, nurses, and other health care professionals from around the world gathered to hear the latest advances in the diag-



nosis, treatment, and prevention of cardiovascular diseases. Emphasis was placed on new therapeutic approaches for the treatment of diabetes with hypertension or myocardial infarction, in-stent restenosis, pulmonary hypertension, and heart failure.

## **Aldosterone Blocker in Diabetic Hypertensive Proteinuria**

**Speaker:** Murray Epstein, MD, Professor of Medicine, Nephrology and Hypertension, University of Miami School of Medicine, Miami, Florida.

Eplerenone (Pharmacia), the first selective aldosterone blocker, provided substantial reduction in proteinuria in hypertensive patients with diabetes, compared to the ACE-inhibitor enalapril (Vasotec, Merck), with the two together being even more effective despite similar blood pressure (BP) lowering, thus indicating that renal protection is independent of BP reduction and that selective aldosterone antagonism is renoprotective.

Because preliminary evidence from preclinical and clinical studies suggests that aldosterone contributes to the progression of hypertension and heart failure and might promote renal dysfunction, a study was carried out to investigate whether the selective aldosterone receptor antagonist (SARA) eplerenone would reduce proteinuria in hypertensive patients with type 2 diabetes mellitus and albuminuria. Current antihypertensive agents, such as ACE-inhibitors and angiotensin II receptor blockers (ARBs), do not fully block the effects of aldosterone.

The study compared three antihypertensive strategies: the effects of eplerenone (200 mg), enalapril (40 mg), and eplerenone (100 mg) in combination with enalapril (10 mg), all given once daily, randomly assigned to 257 type 2 diabetic patients with hypertension and albuminuria, over a 24-week period. Eplerenone reduced urinary albumin to creatinine ratio (UACR) by 62% compared to 45% with enalapril, and the combination was even more effective against either eplerenone or enalapril alone (74%). Blood-pressure lowering was equivalent in all three treatment groups (eplerenone: -19.5/-13.2; enalapril: -20.4/-15.0; and combination: -21.8/-16.2).

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## **Statin for Preventing Post-PCI Cardiovascular Events**

**Speaker:** Patrick W. Surruiys, MD, Professor of Medicine, Throaxcenter, Erasmus University Hospital, Rotterdam, The Netherlands.

The use of early statin therapy with fluvastatin (Lescol, Novartis) in patients following their first percutaneous coronary interventions (PCIs) significantly reduces their risk for major adverse coronary events, according to results from the Lescol Intervention Study (LIPS).

The LIPS study was a double-blind, randomized trial designed to compare the effect of fluvastatin (40 mg twice daily) on a major adverse coronary event—cardiac death, non-fatal MI, or repeat coronary artery bypass graft [CABG] or PCI. The event-free survival time was studied in 1,677 patients with coronary heart disease who had recently undergone a first angioplasty or PCI, over a three-year follow-up period.

Patients taking the statin, which was initiated 2.7 days after the procedure, had LDL-cholesterol levels of 137 mg/dL on average, over a three- to four-year period. Those on the statin had a 22% risk reduction for major adverse cardiac events. Looking at secondary endpoints, it was found that fluvastatin also lowered the risk for major adverse coronary events in patients with diabetes or multilevel diseases.

## **Combination Therapy for Diabetic Patients with MIs**

**Speaker:** Hitinder Gurm, Cardiology Fellow, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio.

Although patients with diabetes are at significantly higher risk for ST-segment elevation myocardial infarction (MI) compared to non-diabetics, over the past few years, the increased use of therapy combining beta blockers and ACE-inhibitors has improved survival of these patients, as evidenced by a lower incidence of recurring MI, a less frequent need for urgent revascularization, and fewer incidents of malignant ventricular arrhythmias.

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To reach these conclusions, the data from patients with diabetes who were enrolled in GUSTO (Global Use of Strategies to Open Occluded Arteries in Acute Myocardial Infarction) I, III, and V trials were analyzed to define the trends in the use of adjunctive therapies and in short-term outcomes. The three GUSTO trials enrolled 9,200 patients with diabetes and 52,509 non-diabetics, all with ST-segment elevation MI.

The comparison of treatments in GUSTO I and III versus GUSTO V, which was completed in 2001, pointed out that patients with diabetes were consistently more likely than other patients to die in the hospital or within 30 days thereafter, but the increased use of beta blockers and ACE-inhibitors in the most recent trial (GUSTO V) improved survival (30-day mortality: 10.7%—GUSTO I, 10.9%—GUSTO III, 8.9%—GUSTO V).

In addition, patients with diabetes who did not receive combination therapy were more likely to have a second MI. They were also more likely to need to undergo urgent coronary artery bypass graft (CABG) surgery or stenting within seven days post-MI.

### Antiplatelet Therapy for In-Stent Restenosis Post-Brachytherapy

**Speaker:** Ron Waksman, MD, Clinical Professor of Medicine (Cardiology), Georgetown University School of Medicine, and Associate Director of the Division of Cardiology, Washington Hospital Center, Washington, DC.

Data from a comparison of patient registries of two studies to assess the value of 12 months of therapy with clopidogrel (Plavix, Sanofi Synthelabo/Bristol Myers Squibb) in patients treated with intracoronary radiation therapy for the prevention of recurrent in-stent restenosis post-brachytherapy is safe and is associated with a strong trend in the reduction of late total occlusion (LTO) and a significant decrease in revascularization rates compared to six months of clopidogrel, supporting the use of at least 12 months of clopidogrel after coronary brachytherapy for in-stent restenosis.

The aim of the study was to determine whether 12 months of clopidogrel therapy further reduces the rate of late thrombosis and late total occlusion over that demonstrated earlier with six months of clopidogrel in patients with in-stent restenosis treated with intracoronary radiation therapy. The two patient registries compared were WRIST (Washington Radiation for the Stent Restenosis Trial) PLUS, a prior study of 120 patients with in-stent restenosis treated with gamma radiation and then given six months of clopidogrel and aspirin for the prevention of late thrombosis; and WRIST 12, a registry of 120 patients with entry criteria identical to WRIST PLUS, but with 12 months of aspirin and clopidogrel after intracoronary radiation therapy. The dose of clopidogrel administered in both studies was 75 mg once daily, with an angiographic follow-up at 15 months, in WRIST 12.

A comparison of clinical events of WRIST 12 patients and WRIST PLUS patients pointed out that the rate of reduction in late thrombosis in WRIST PLUS was 4.2%; this was reduced to 2.5% in WRIST 12. Major clinical events at 12 months showed no

differences in the two patient groups in terms of death, Q-wave MI, and only a small difference in non-Q-wave MI, in favor of 12 months of clopidogrel. There were, however, significantly surprising findings with regard to reductions in the need for angioplasty, from 26% in WRIST PLUS to 14% in WRIST 12; in surgery, from 21% to 15%; in target lesion revascularization (TLR), from 33% to 18%; in target vessel revascularization (TVR), from 37% to 19%; and in overall major adverse cardiovascular events (MACE) from 38% to 20%; the reduction in risk of TLR, TVR, and MACE was highly statistically significant in favor of 12 months of clopidogrel treatment.

### Endothelin Receptor Antagonist in Pulmonary Hypertension

**Speaker:** Nazzareno Galie, MD, Professor of Medicine, Institute of Cardiology, University of Bologna, Bologna, Italy.

The administration of bosentan (Tracleer, Actelion), an orally active dual endothelin receptor antagonist, has been shown to improve right ventricular (RV) systolic function and left ventricular (LV) early diastolic filling—improvements that lead to reverse ventricular modeling in patients with pulmonary arterial hypertension and help to explain previously reported improvements in exercise capacity and a delay in time to clinical worsening.

These conclusions were reached from a study of the effects of bosentan on echocardiographic and Doppler variables in a subgroup of 85 patients with World Health Organization (WHO) class III and IV pulmonary arterial hypertension who were enrolled in the prospective, double-blind, placebo-controlled BREATHE-1 (Bosentan: Randomized Trial of Endothelin Receptor Antagonist Therapy) study. In the BREATHE-1 trial, which included 213-patients, bosentan was administered twice daily at 125 or 250 mg, resulting in significant improvements in the primary endpoint of improvement in exercise capacity compared to placebo, as well as significant improvement in functional status in patients with pulmonary arterial hypertension.

In this sub-group analysis, 71 patients (84%) had primary pulmonary hypertension. In a 1:2 randomization procedure, 29 patients received placebo and 56 were given bosentan, with six-minute walk tests and echocardiograms performed at baseline and at 16 weeks. On baseline evaluations, Doppler and echocardiographic variables demonstrated marked abnormalities of RV and LV structure and function. At week 16, the treatment effect (the difference between treatment groups in mean change at 16 weeks) on the six-minute walking distance was 37 meters in favor of bosentan. Time velocity integrals of the LV outflow tract and of mitral inflow were improved in the bosentan group, resulting in an improvement of Doppler-derived cardiac index as well as marked treatment effects of bosentan on other echocardiographic and Doppler parameters, resulting in improved RV systolic function and LV early diastolic filling.

### Beta Blockade in Severe Heart Failure and Extremely Depressed LVEF

**Speaker:** Hugo A. Katus, MD, Professor of Medicine, Universitaets-Klinkenshubeck, Luebeck, Germany.

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A subgroup analysis of data from the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial demonstrated that treatment with the beta blocker carvedilol (Coreg, Glaxo SmithKline) is effective and well-tolerated in patients with severe heart failure (HF) symptoms and an extremely depressed left ventricular ejection fraction (LVEF).

Overall, the study encompassed 2,289 HF patients with symptoms at rest or minimal exertion and an LVEF of less than 25%, who were randomly assigned to placebo or carvedilol and followed for up to 29 months. The primary endpoint was death from any cause; treatment with carvedilol resulted in a highly significant decrease of 35%. Despite the demonstrated survival benefit of beta blockers in HF, many physicians still avoid the use of these drugs in patients with extremely depressed LVEF because of the belief that such patients might be adversely affected by beta-blocker treatment. This analysis, therefore, was carried out to determine the value of carvedilol under such circumstances.

Of the total COPERNICUS population, 371 patients had a baseline LVEF of less than 15%. These patients had a lower mean systolic blood pressure (117 mm Hg) than other persons in the study (125 mm Hg) and were more likely to be given digitalis (75% vs. 65%) than patients with higher LVEF.

Other baseline characteristics were similar in both patient populations. The effects of carvedilol on all-cause mortality in patients with LVEF of less than 15% was comparable to that seen in patients with higher LVEF (reductions in risk of 30% and 35%, respectively). Comparable findings were reported for the composite endpoint of death or hospitalization for any reason for a specific cause. In addition, carvedilol reduced the risk of permanent discontinuation of the study drug in patients with LVEF below 15% and in those with higher LVEF (32% and 19%, respectively).

### ARB Treatment and CHF Quality of Life

**Speaker:** Luigi Tavazzi, MD, Head, Department of Cardiology, IRCCS Policlinico S. Matteo, Pavia, Italy.

A post-hoc analysis of data from the Valsartan Heart Failure Trial (Val-HeFT), revealed that valsartan treatment added to standard congestive heart failure (CHF) therapy provides a significant beneficial effect on quality of life (QOL) compared to placebo.

The Val-HeFT was a double-blind, randomized multi-country trial carried out to compare the effect of the selective angiotensin II-receptor blocker valsartan (Diovan, Novartis) against placebo in 5,010 patients with CHF, when added to standard heart failure therapy, for approximately two years. The primary endpoints were all-cause mortality and combined all-cause mortality and morbidity. Overall, the rate of all-cause mortality was similarly low in both study groups (19.7% on valsartan and 19.4% on placebo). Valsartan, however, reduced morbidity from heart failure by 13.2% and hospitalizations for heart failure by 27.5%, compared to placebo.

Improving the QOL for patients with chronic conditions and poor short-term survival, such as CHF, is a common goal in new

drug development. For this reason, an analysis of Val-HeFT data was assessed to examine the relationship between QOL and morbidity and mortality in this trial. The scores of QOL were measured using the Minnesota Living with Heart Failure (MLWHF) Questionnaire at one, four, and six months, and every three months thereafter. A lower score indicates improved QOL. Scoring is related to the patient's perception of future clinical events. The total sample size for the QOL analysis was 3,010 patients.

The patients in the valsartan group had significantly improved overall MLWHF scores compared to placebo at study endpoint—scores that related to the clinical benefits reported in valsartan-treated individuals. Overall, higher MLWHF scores at baseline, months four and 12, and study endpoint were all associated with a higher risk of morbid events, regardless of study treatment. Similar associations were observed between MLWHF score and mortality. As would be expected, lower MLWHF scores were linked to a reduction in the risk of morbidity and mortality.

### Human BNP for Acute Decompensated CHF

**Speaker:** James B. Young, MD, Medical Director of the Kaufman Center for Heart Failure, and Head, Section of Heart Failure and Cardiac Transplant Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

Nesiritide (Natrecor, Scios, Inc.), a recombinant form of endogenous human B-type natriuretic peptide, but not intravenous (IV) nitroglycerin, has been shown to effectively and rapidly reduce pulmonary pressures in patients with acute congestive heart failure (CHF) and elevated pulmonary pressures.

Initially, a total of 498 hospitalized patients were enrolled in the Vasodilation in the Management of Acute Congestive Failure (VMAC) trial with acutely decompensated CHF and dyspnea at risk to determine the relative hemodynamic and clinical effects and safety of either fixed or adjustable dose nesiritide compared to placebo and IV nitroglycerin, in addition to standard care. A total of 489 patients were stratified by the investigator-determined use of a pulmonary artery catheter for management of their CHF, and then randomized. Enrolled patients who received catheters were randomized to nesiritide (n=124), placebo (n=62), or IV nitroglycerin (n=60). From the VMAC database, the pulmonary artery pressures in catheterized patients during the first three hours of placebo-controlled treatment in patients randomized to nesiritide, IV nitroglycerin, or placebo were compared. After three hours, the placebo patients were randomized to nitroglycerin or nesiritide and monitored for up to 48 hours.

Mean pulmonary artery systolic (PAS) and diastolic (PAD) pressures were elevated at baseline ( $59.2 \pm 12.9$  and  $28.4 \pm 7.09$  mm Hg, respectively), but were comparable in all three treatment arms. During the placebo-controlled period, nesiritide was superior to placebo at all time points, and to IV nitroglycerin at most time points, at reducing PAD and PAS pressures. Nesiritide continued to be more effective than IV nitroglycerin in reducing pulmonary artery pressures for up to 36 hours. ■