Drug-Eluting Stents for Coronary Artery Lesions

**Speaker:** Antonio Colombo, MD, Professor of Medicine, EMO Centre Cuone Columbus Hospital, Milan, Italy.

A 12-month follow-up of the paclitaxel stent (Taxus™, Boston Scientific) study (TAXUS II) demonstrated that paclitaxel-eluting coronary stents were highly effective at one year after implantation with sustained benefits, as measured by decreased rates of major adverse coronary events (MACEs), restenosis, and revascularization. These stents performed better than the metal stents in patients who had undergone percutaneous coronary intervention (PCI) with stenting for *de novo* coronary artery lesions.

TAXUS II is a 15-country, randomized, double-blind, controlled study of the safety and efficacy of paclitaxel-eluting coronary stents. In the study, 536 patients with standard-risk, *de novo* coronary artery lesions underwent stent placement. Overall, 270 patients received bare metal stents as controls, 131 patients received slow-release paclitaxel-eluting stents, and 135 patients received moderate-release paclitaxel-eluting stents. Clinical endpoints included 12-month major adverse coronary events, target lesion restenosis, and the need for a repeated revascularization procedure.

At 12 months, findings were as follows:

- A 21.7% rate of major adverse coronary events and a 14.4% rate of target lesion restenosis were reported for the control group.
- A 10.9% rate of major adverse coronary events and a 4.7% rate of target lesion restenosis were reported in the group receiving the slow-release formulations.
- A 9.9% rate of major adverse coronary events and a 3.8% rate of target lesion restenosis were reported in patients randomly assigned to receive the moderate-release paclitaxel stents.

The MACE-free survival rate difference between the control group and the TAXUS group increased over time, favoring the paclitaxel-eluting stents. The findings suggest that these stents prevent, rather than delay, restenosis.

Calcium-Channel Blocker for Stable Angina Pectoris

**Speaker:** Stephen P. Glasser, MD, Professor of Epidemiology, University of Minnesota School of Public Health, Minneapolis, Minnesota.

Nighttime dosing of a newly approved chemotherapeutic graded-release, long-acting diltiazem (Cardizem® LA, Biovail) formulation may give patients with chronic stable angina pectoris added protection in the morning hours, when potentially life-threatening heart attacks are more likely to occur, improving key angina efficacy variables more than 200% over those associated with morning doses.

In a double-blind, multicenter, randomized, three-week study, 311 patients with exercise-induced ischemia and angina symptoms were randomly assigned to receive graded-release diltiazem, administered once daily at 10 PM, in doses of 180, 360, and 420 mg. Placebo or graded-release diltiazem was given once daily at 8 AM in a dose of 360 mg.

Stress tests using the standard Bruce protocol treadmill were performed at baseline and study endpoints to evaluate changes in exercise tolerance. Patients were tested at two different time periods: between 6 PM and 8 PM and between 7 AM and 11 AM. The time windows were designed to measure effects of the two dosing schedules at peak and trough levels. Efficacy variables included changes from baseline in total duration of exercise, time to onset of angina, and time to greater than 1 mm ST-segment depression.

At peak levels, the morning and nighttime doses of graded-release diltiazem demonstrated comparable efficacy with that of placebo. At trough, however, the true advantages of nighttime dosing emerged.

The median duration of exercise at trough was 30.8 seconds for the 180-mg PM dose, 39 seconds for the 360-mg PM dose, and 36 seconds for the 420-mg PM dose. The duration was...
only 19.5 seconds for the 360-mg AM dose.

Between the critical hours of 7 AM and 11 AM, nighttime dosing, compared with morning dosing, doubled the duration of exercise tolerance. Specifically, the duration of morning exercise ranged from 41 to 49.5 seconds for the various PM doses but only 19.5 seconds for the 360-mg AM dose. Similar results favoring PM dosing were demonstrated for the other efficacy variables, including time to onset of angina and time to ischemia, as measured by time to greater than 1 mm ST-segment depression.

**Direct Thrombin Inhibitor for Percutaneous Peripheral Intervention**

**Speaker:** David E. Allie, MD, Director of Cardiothoracic and Vascular Surgery, Cardiovascular Institute of the South, Lafayette, Louisiana.

Bivalirudin (Angiomax®, The Medicines Company), a novel direct thrombin inhibitor, has been shown to be safe and feasible as the sole anticoagulant in patients undergoing renal and iliac percutaneous peripheral interventions (PPIs) for peripheral vascular disease.

In an effort to overcome the many limitations of heparin by the use of a direct thrombin inhibitor, a study was designed whereby bivalirudin, given as a 0.75-mg/kg bolus with an infusion of 1.75 mg/kg per hour for the duration of the procedure, was administered to 255 patients with peripheral vascular disease, 180 patients with renal disease, and 75 patients with iliac disease; all of the patients were undergoing PPI. These findings were compared with those of a historical heparin control. Variables assessed included (1) sheath removal time, (2) access complications, (3) time to ambulation, and (4) in-hospital length of stay.

Overall, there were no reports of thrombotic events, intracranial bleeding, or major surgical complications in the patients receiving bivalirudin. Compared with the historical heparin controls, sheath removal time, time to ambulation, and length of hospital stay were all significantly reduced in the bivalirudin group. Repeated PPIs were required in 7 of the 180 patients who underwent renal PPI and in 3 of the 75 patients who underwent iliac PPI. At six months’ follow-up, the success rate of PPI was 100% in this group of individuals, comparable with a rate of 98.8% observed in the historical heparin controls by renal and iliac duplex ultrasound.

**New Statin for Hypercholesterolemia**

**Speaker:** Peter H. Jones, MD, Associate Professor of Medicine, Baylor College of Medicine, Houston, Texas.

New data from the STELLAR (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) clinical trial demonstrates that the investigational lipid-lowering agent rosvastatin (Crestor®, AstraZeneca) is more effective in improving the lipid profiles of patients with hypercholesterolemia compared with other available statins, and offers significantly greater reductions in low-density lipoprotein-cholesterol (LDL-C) and consistently higher increases in high-density lipoprotein-cholesterol (HDL-C).

Investigators enrolled 2,431 adults with hypercholesterolemia in a six-week, randomized, open-label, phase III study that compared the efficacy of specific doses and the overall dose range of rosvastatin, as an adjunct to diet, with specific doses and the dose ranges of atorvastatin (Lipitor®, Parke-Davis/Pfizer), pravastatin (Pravachol®, Bristol-Myers Squibb), and simvastatin (Zocor®, Merck) in patients with primary hypercholesterolemia. After discontinuing previous lipid-lowering treatments and after a six-week dietary lead-in period, patients were randomly assigned to 15 parallel, open-label treatments for six weeks. Treatments included (1) rosvastatin 10, 20, 40, or 80 mg; (2) atorvastatin 10, 20, 40, or 80 mg; (3) simvastatin 10, 20, 40, or 80 mg; and (4) pravastatin 10, 20, or 40 mg. Log-dose/response curves and selected pairwise comparisons were used to carry out the analyses.

**LDL-Cholesterol**

Overall, across doses, the results were as follows:

- Rosuvastatin reduced LDL-C from 46% at 10 mg to 55% at 80 mg.
- Atorvastatin reduced LDL-C from 37% at 10 mg to 51% at 80 mg.
- Simvastatin reduced LDL-C from 28% at 10 mg to 46% at 80 mg.
- Pravastatin reduced LDL-C from 20% at 10 mg to 30% at 40 mg.

As observed in the log-dose/response-curve analyses, rosvastatin was statistically more effective in lowering LDL-C than all three comparators across dose levels as follows:

- an 8.2% difference in reduction of LDL-C favoring rosvastatin over atorvastatin
- a 26% difference in reduction of LDL-C favoring rosvastatin over simvastatin
- a comparable difference in reduction of LDL-C favoring rosvastatin over pravastatin

**HDL-Cholesterol**

Across all dose levels, rosvastatin was superior in elevating HDL-C levels; it raised HDL-C by 7.6% to 9.8%, compared with 2.0% to 5.7% for atorvastatin, 5.3% to 6.8% for simvastatin, and 3.2% to 5.5% for pravastatin. In some comparisons, differences in elevations in HDL-C reached almost 50% between rosvastatin and its comparators.

**Improved Lipid-Lowering Formulation for Diabetic Patients with Dyslipidemia**

**Speaker:** Rosario A. Mercado-Young, MD, Fellow in Cardiology, University of Texas Health Science Center, San Antonio, Texas.

An extended-release niacin formulation (Niaspan®, Kos) has been found to be safe, well tolerated, and effective in a wide range of patients with dyslipidemia, including those with diabetes.

Data were collected from a consecutive sample of 95 patients with dyslipidemia, 39 of whom were diabetic. The patients were given extended-release niacin from June 1999 to June
2002. Primary outcomes were glucose and lipoprotein responses, alteration in hepatic enzymes, and any other drug-related adverse effects, as documented from the patients’ medical records. Treatment was begun at a dose of 500 mg daily, and the dose was titrated to a maximum of 2,000 mg/day.

Baseline characteristics between diabetic and nondiabetic patients were comparable except for the use of angiotensin-converting enzyme (ACE)–inhibitors, which are generally given to most diabetic patients with cardiovascular disease.

Overall, extended-release niacin was well tolerated in diabetic patients, with only a small percentage change in fasting plasma glucose from a baseline value of 149 mg/dl at the 1,000-mg dose; however, this situation did not worsen when the niacin was given continuously. The mean percentage change in glycosylated hemoglobin (hemoglobinA1C) from the baseline evaluation did not change at any dose level for niacin. There were no significant changes in hepatic enzyme levels. Adverse effects that were considered to be drug-related (e.g., flushing, skin rash, and pruritus) were reported in only one patient each.

With regard to the effect of extended-release niacin on dyslipidemia, the mean percentage decrease in LDL-C levels proved to be dependent on the dose, ranging from 6.8% at 500 mg to 14.2% at 2,000 mg. Total cholesterol and triglyceride levels also declined significantly. The mean percentage changes in HDL-C increased significantly from a baseline value of 35 mg/dl at a dose level of extended-release niacin of 1,000 mg and above.

Oral Antidiabetic Agent for a Lowered Risk of Cardiovascular Disease

Speaker: Ernest J. Schaefer, MD, Director, Lipid and Heart Disease Prevention Clinic, Division of Endocrinology, Diabetes, Metabolism, and Molecular Medicine, and Professor of Medicine, Tufts University School of Medicine, Boston, Massachusetts.

The type-2 diabetes agent rosiglitazone (Avandia®, GlaxoSmithKline) has been shown to provide an extra benefit in reducing the risk of cardiovascular disease, not only in controlling blood glucose levels by reducing insulin resistance but also by increasing HDL-C and improving the ratio of total cholesterol to HDL-C.

Investigators analyzed data from open-label extensions of two placebo-controlled, double-blind studies retrospectively to examine the long-term effect of rosiglitazone on HDL-C. The study encompassed 269 patients with type-2 diabetes who took rosiglitazone 8 mg/day for 24 months. Data were assessed according to baseline HDL-C values (below 40 or 40 mg/dl or greater) and the ratio of total cholesterol to HDL-C (below 5 or 5 mg/dl or greater).

Over the 24 months, in all patients, HDL-C levels increased from baseline levels by 25% in patients with HDL-C below 40 mg/dl and by 10% in patients with HDL-C of 40 mg/dl or more. The ratio of total cholesterol to HDL-C improved for all patients in the study, with an overall decrease from 5.06 to 4.7 over the treatment period.

The ratio of total cholesterol to HDL-C is a commonly used tool for the assessment of cardiovascular risk; a lower ratio is associated with a lower risk. In patients with a ratio greater than 5, the mean ratio decreased from 6.25 to 5.6.

Beta Blockade for Complicated Myocardial Infarction

Speaker: Robert M. Califf, MD, Professor of Medicine, Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina.

Baseline data from the VALsartan in Acute Myocardial Infarction Trial (VALIANT) demonstrated that the early use of beta blockade in patients with an acute myocardial infarction (AMI), complicated by heart failure and/or left ventricular systolic dysfunction (LVSD), was associated with lower mortality.

VALIANT is an ongoing prospective trial in which 14,808 patients with AMI and heart failure and/or LVSD were randomly assigned to receive valsartan (Diovan®, Novartis), captopril (Captopril®, Mylan), or both to assess the safety and efficacy of the angiotensin II receptor blocker valsartan in the long-term treatment and management of patients with heart failure and/or LVSD after an AMI. The use of beta blockers was not mandated in this study, but 10,390 patients (70% of the total study population) received beta-blockade therapy.

The patients who received beta blockers were younger than those who did not (64 years of age vs. 69 years, respectively) and tended to be assigned to a lower Killip classification (Killip class above level I, 68% vs. 82%, respectively). Mortality at 30 days after enrollment in the study was significantly lower in patients receiving beta blockers than in those not receiving them, even after an adjustment for a risk model in the population, with mortality rates of 3.0% and 6.5%, respectively. This occurred even with high-intensity beta blockade of the renin-angiotensin system.

Antiplatelet Inhibition plus a Statin for Acute Coronary Syndrome

Speaker: Michael J. Lim, MD, Interventional Cardiology Fellow, University of Michigan Health System, Ann Arbor, Michigan.

Although recent in vitro data have suggested that the antiplatelet aggregation effects of clopidogrel (Plavix®, Bristol-Myers Squibb/Sanofi-Synthelabo) might be mitigated by the concomitant use of a statin, the Global Registry of Acute Coronary Events (GRACE) has demonstrated no clinical evidence of pharmacological interaction between statin medications and clopidogrel. In actuality, there is a trend toward reduced mortality in patients who take aspirin plus clopidogrel plus a statin, compared with mortality rates in other treatment groups, suggesting a synergistic effect.

Using the database from GRACE, which covered all patients with acute coronary syndrome from hospitals around the world, investigators evaluated six-month mortality and stroke rates in four groups on the basis of treatments upon discharge. The regimens were as follows, for a total of 8,493 patients:

- aspirin alone (3,342 patients)
- aspirin plus clopidogrel (866 patients)
For patients taking aspirin plus clopidogrel plus a statin, mortality rates were significantly lower than the rates for the other three groups. The hazard ratio for mortality was lowest for the patients receiving triple therapy.

Overall, for patients taking aspirin therapy, the mortality rate was 7.2%; for patients taking aspirin plus clopidogrel plus a statin, it was 3.0%. On the basis of the reporting in GRACE, it was not possible to identify the usage of individual statins.

**Recombinant Human B-Type Natriuretic Peptide for Acute Heart Failure**

**Speaker:** J. Thomas Heywood, MD, Director of the Cardiomyopathy Program, Loma Linda University Medical Center, Loma Linda, California.

The initial use of the intravenous drug nesiritide (Natrecor®, Scios), a recombinant form of human B-type natriuretic peptide that acts as a vasodilator, appears to result in a significantly reduced length of hospital stay for patients with acutely decompensated heart failure, even though patients who received this drug had been much sicker than other patients upon admission.

To determine the effect of nesiritide on length of hospital stay and on renal function, investigators assessed the demographic characteristics, concurrent medications, and laboratory values retrospectively in 130 patients with acutely decompensated heart failure who were discharged from the coronary-care unit at Loma Linda University Medical Center. Analyses were conducted to compare 58 patients who received nesiritide with 72 patients who did not. Patients in the nesiritide group initially received the drug for a mean duration of 2.2 days.

At baseline evaluation, although patients in the nesiritide group had lower left ventricular ejection fractions (LVEFs) and lower systolic pressures, higher serum creatinine levels, and longer QRS durations on electrocardiograms than patients not receiving nesiritide, their hospital stays were significantly shorter: 2.87 days versus 3.79 days for the non-nesiritide group. Furthermore, nesiritide treatment resulted in no significant changes in renal failure and in the same decrease in weight in a shorter period of time as in the patients not receiving nesiritide. These findings suggest that nesiritide-treated patients might be able to leave the hospital more rapidly without deleterious effects on renal function.