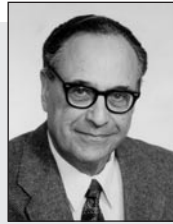


## Meeting Highlights

# 54th Scientific Session, American College of Cardiology

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More than 27,000 cardiologists, cardiovascular surgeons, interventional cardiologists, epidemiologists, research scientists, nurses, and other associated health care professionals from around the world gathered at the 54th Annual Scientific Session of The American College of Cardiology,



held in Orlando, Florida, March 6–9, 2005. Various speakers emphasized new and improved therapies for atherosclerosis, coronary artery disease, hypertension, myocardial infarction, acute coronary syndrome, stroke, and heart failure.

### High-Dose Atorvastatin and Coronary Heart Disease

**Speaker:** John C. LaRosa, MD, President and Professor of Medicine, State University of New York (SUNY) Downstate Medical Center, Brooklyn, New York

Treating patients with established coronary heart disease (CHD) to reduce their levels of low-density lipoprotein-cholesterol (LDL-C) to 77 mg/dl with a high dose of atorvastatin (Lipitor®, Pfizer) 80 mg daily from their starting LDL-C level of 100 mg/dl resulted in a significant reduction in the risk of major coronary events, compared with low-dose atorvastatin 10 mg daily to achieve an LDL-C of 100 mg/dl.

Investigators evaluated 15,464 patients with established CHD whose LDL-C levels were between 130 and 250 mg/dl. Triglyceride values were under 600 mg/dl. The patients were entered into the open-label run-in period of the Treating to New Targets (TNT) study. In the second part of the trial, 10,000 patients were randomly assigned to double-blind therapy with 10 or 80 mg daily.

Patients were observed for a median of 4.9 years from the time of randomization. The primary composite endpoint was the occurrence of a “major cardiovascular event” (death from CHD; nonfatal, nonprocedural-related myocardial infarction [MI]; resuscitated cardiac arrest; or fatal or nonfatal stroke).

At five years’ follow-up, there was a highly significant reduction of 22% in major cardiovascular events with atorvastatin 80 mg compared with 10 mg, over and above the remarkably low event rate of 10.9% reported for the 10-mg group.

The risk of stroke, generally related to severe, long-term physical, mental, and financial burdens, was reduced by 25% with atorvastatin 80 mg, compared with 10 mg. Separate components of the major cardiovascular events composite endpoint were also consistent with those observed for the primary composite endpoint, except for resuscitated cardiac arrest, which showed no difference between the two patient groups.

There were also significant reductions in favor of atorvastatin

80 mg among the secondary endpoints, including major coronary events, cerebrovascular events, and hospitalization for congestive heart failure.

Because the study was not powered to detect a treatment impact on all-cause mortality, there was no difference between the two treatment groups; however, the rate of death from any cause in both groups was lower than that seen in any previous secondary prevention study.

Although there had been concerns about the safety of high-dose statins, essentially no toxicity or negative events (such as death, an excess incidence of cancer, liver dysfunction, myalgia, or rhabdomyolysis) were attributed to the 80-mg dose.

### Sustained-Release Verapamil in Coronary Artery Disease Patients with Hypertension

**Speaker:** Efrain Goxola, MD, Cardiology and Internal Medicine, Instituto Cardiovascular Guadalajara, Guadalajara, Mexico

A further analysis of the data from the INVEST (The International Verapamil SR-Trandopril Study) trial suggested that a regimen of sustained-release verapamil (Isoptin®, Abbott Laboratories) provided an alternative to atenolol (Tenormin®, AstraZeneca) for preventing adverse cardiovascular outcomes, including coronary revascularization in hypertensive patients with coronary artery disease (CAD).

The INVEST trial included 22,576 patients who were randomly assigned to receive either a verapamil SR-based or an atenolol-based regimen. Flexible dose titration and the addition of trandolapril (Mavik®, Abbott) for the verapamil SR patients and/or hydrochlorothiazide (Diovan®, Novartis) for the atenolol patients were used to achieve target treatment goals in accordance with JNC VI (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) of below 140/90 mm Hg or below 130/85 mm Hg for patients with diabetes or renal impairment. The average follow-up period was 2.7 years. The risk for “primary outcome” (first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke) was equivalent for the two regimens.

The objective of the INVEST substudy was to analyze the impact of treatment strategies, baseline risk factors, blood pressure (BP) control and average on-treatment BP on coronary revascularizations during the trial, because patients with hypertension and CAD often require coronary artery bypass

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grafting or percutaneous coronary intervention. The incidence of follow-up coronary revascularization was similar between the two groups (with verapamil, 2.5%; with atenolol, 2.4%), and it remained similar whether or not the patients had undergone a prior revascularization.

The increased risk of revascularization during follow-up was associated with U.S. residency, previous revascularization, hypercholesterolemia, male sex, unstable angina, and diabetes. In addition, patients with a low mean follow-up diastolic BP (below 70 mm Hg) or a high diastolic BP (above 90 mm Hg) were at an increased risk of needing revascularization at follow-up.

### **Pioglitazone Reduces In-Stent Restenosis in Diabetes**

**Speaker:** Jin Yokayama, MD, Instructor in Interventional Cardiology, Cardiology Division, Department of Medicine, Hirosaki University School of Medicine, Hirosaki, Japan

Although drug-eluting stents have dramatically decreased the incidence of in-stent restenosis (ISR) in patients with diabetes mellitus, ISR remains a clinically important problem. Insulin sensitizers have an anti-atherosclerotic effect and seem to reduce neointimal tissue proliferation after coronary stenting in these patients.

A study was conducted to determine whether low-dose pioglitazone (Actos®, Takeda) would reduce the incidence of ISR after coronary angioplasty in 40 patients with type-2 diabetes mellitus who had bare metal stents. Pioglitazone 15 mg/day was orally administered for six months to 16 patients with 24 lesions that had been stented; previous antidiabetic therapy was maintained. The incidence of ISR in these patients was compared with the other 24 patients (with 26 lesions stented) who had received conventional antidiabetic therapy that did not include pioglitazone.

The success rate associated with bare metal stent placement was 100% in both pioglitazone patients and controls. At six months after the procedures, however, the angiographic rate of ISR, defined as stenosis of greater than 50% in diameter, was significantly lower in the pioglitazone patients (8.3%) than in the control patients (42.3%). ISR was documented after angiography in only two of the 24 lesions stented in the treated group.

In patients with controlled glycemic levels (glycosylated hemoglobin below 6.5% at follow-up), ISR and target lesion revascularization rates, as noted with angiography, were significantly lower with pioglitazone.

### **Clopidogrel in Addition to Aspirin for Acute MI**

**Speaker:** Zhengming Chen, MD, Reader in Epidemiology, Oxford University, and Member of the Clinical Trial Service Unit, Radcliffe Infirmary, Oxford, United Kingdom

Adding clopidogrel (Plavix®, Sanofi-Aventis/Bristol-Myers Squibb) to aspirin as well as standard medical therapy was beneficial, compared with aspirin and standard medical therapy alone, in reducing the risk of death and nonfatal vascular events in patients with acute ST-elevation myocardial infarction (MI).

The COMMIT-CC2 (ClOpidogrel and Metoprolol in Myocardial Infarction Trial—Second Chinese Cardiac) Study is one of the largest randomized, double-blind, placebo-controlled

trials of drug therapy ever performed for heart disease. The study, conducted at 1,250 centers across China, enrolled 45,852 patients with ST-elevation myocardial infarction (MI) who were seen by a physician within 24 hours of symptom onset.

The patients were randomly assigned to receive clopidogrel 75 mg/day or placebo for up to four weeks, along with aspirin 162 mg/day, plus fibrinolytic therapy. This regimen was given to 50% of the patients, and anticoagulants were given to 74%. The patients also received standard medical therapy, such as angiotensin-converting enzyme (ACE)-inhibitors, nitrates, antiarrhythmic agents, diuretics, calcium-channel blockers.

The primary endpoints were all-cause mortality and the composite endpoint of death, stroke, or current MI at the end of four weeks in the hospital or before discharge. The mean duration of treatment and follow-up lasted just over two weeks. The primary endpoint of all-cause mortality at hospital discharge was significantly lower with clopidogrel; 1,728 (7.7%) of the treated patients died, and 1,846 (8.1%) of the placebo patients died. A risk reduction of 7% favored clopidogrel.

In the co-primary composite endpoint of death, re-infarction, or stroke, adding clopidogrel to aspirin and standard therapy produced a significant 9% reduction in risk, compared with placebo. There were 2,125 events (9.3%) with clopidogrel and 2,311 events (10.1%) with placebo. The risk of re-infarction also was lower with clopidogrel than with placebo, but the incidence of stroke did not differ between the two patient groups.

There was no significant risk of hemorrhage or other major bleeding episodes in either patient group.

It is estimated that the addition of clopidogrel could potentially save 5,000 lives and prevent another 5,000 nonfatal major vascular events.

### **Enoxaparin for Acute Coronary Syndrome**

**Speaker:** Marc Cohen, MD, Professor of Medicine, Mount Sinai School of Medicine, and Director, Division of Cardiology, Newark Beth Israel Medical Center, Newark, New Jersey

In the recent Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, 76% of patients with non-ST-segment elevation acute coronary syndrome were given antithrombin therapy before being randomly assigned to take enoxaparin (Lovenox®, Sanofi-Aventis) or unfractionated heparin (UFH). Of the 9,978 patients, 2,440 did not receive pre-randomization therapy and 6,138 received consistent therapy. The primary efficacy outcomes were (1) the composite of mortality or nonfatal MI during the first 30 days after randomization and (2) the incidence of severe bleeding.

In the subgroup receiving no prior treatment, the primary outcome occurred in 12.6% of the enoxaparin patients and in 14.8% of the UFH patients. In the subgroup of patients receiving no prior antithrombin therapy or those assigned to take the same antithrombin agent as before enrollment, the primary endpoint occurred in 13.3% of the enoxaparin patients and in 15.9% of the UFH patients. The rates of major or severe bleeding were slightly higher in the former group than in the latter.

After the investigators adjusted for differences in baseline characteristics between pretreatment subgroups, the patients who had not received any previous antithrombin therapy had

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significantly better efficacy outcomes when the initial therapy was enoxaparin but not UFH.

### Aspirin for Stroke Prevention in Women

**Speaker:** Julie E. Buring, ScD, Professor of Medicine, Harvard Medical School, and Deputy Director of the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts

The Women's Health Study, a large randomized, double-blind, placebo-controlled, 10-year trial funded by the National Heart, Lung and Blood Institute and the National Cancer Institute, was conducted to evaluate the benefits of low-dose aspirin 100 mg every other day, as well as vitamin E supplementation 600 IU every other day, for the primary prevention of cardiovascular disease. The trial enrolled 39,876 apparently healthy women 45 years of age and older. The women were monitored for 10 years for first-time myocardial infarction (MI), stroke, and death from cardiovascular causes.

Although it has not been widely recognized, women, when compared with men, tend to have more strokes than MIs. Aspirin was administered because it had been demonstrated to be effective for both men and women in the secondary prevention of cardiovascular disease and acute coronary ischemia.

During the follow-up period, 477 major cardiovascular events were confirmed for the women taking aspirin, compared with 522 with placebo—a 9% overall reduction that was not statistically significant. In a pattern seemingly different to that previously observed in men, the benefit of aspirin in the Women's Health Study was attributed almost entirely to a statistically significant reduction in stroke events but with no reduction in MI rates.

The most consistent benefits were observed among women 65 years of age and older. These patients comprised 10% of the study population, yet they experienced one third of all cardiovascular events. Among such women, low-dose aspirin resulted in a 26% reduction in risk of major cardiovascular events.

Overall, the risk reduction for a first stroke was 17% and that for an ischemic stroke was 24%. Low-dose aspirin (Bayer Aspirin®) reduced the risk of total strokes, ischemic strokes, and transient ischemic attacks but resulted in neither benefit nor harm for endpoints of MI, cardiovascular mortality, or total mortality, which led to the nonsignificant finding with respect to the primary trial endpoint. It showed little benefit for younger women. This finding raises an important issue because low-dose aspirin resulted in a significant risk of gastrointestinal bleeding, with patients needing transfusions, and a nonsignificant increase in hemorrhagic stroke.

### Nesiritide for Refractory Heart Failure After Cardiac Surgery

**Speaker:** Saugato Sanyal, MD, Cardiovascular Surgeon, Division of Cardiothoracic Surgery, Beth Israel Medical Center, New York, New York

When administered to selected patients with refractory fluid overload and congestive heart failure (CHF) after cardiac surgery, nesiritide (Natrecor®, Scios), a recombinant form of human B-type natriuretic peptide (BNP), improved urine out-

put, reduced filling pressures, and enhanced extubation rates.

Because significant fluctuations in endogenous BNP levels occur after cardiac surgery, a study was designed to give nesiritide only to cardiac surgery patients who were unresponsive to conventional therapy (vasopressor agents and diuretics).

The study population consisted of 50 patients with post-operative worsening of CHF and urine output. Nesiritide was added to the conventional therapy for CHF and was titrated to achieve diuresis. Mathematical equations were used to assess hemodynamic parameters, tolerance of medications, and clinical outcomes.

Compared with the pre-nesiritide average trends, pulmonary artery diastolic pressure and central venous pressure were significantly reduced within eight hours of infusion. Urine output increased, from  $46.2 \pm 20$  ml/hour to  $89 \pm 15$  ml/hour; oxygen requirements decreased; and the number of patients needing ventilatory support declined, from 89% to 61%. The cardiac index increased significantly and systemic vascular resistance was markedly reduced. Serum creatinine or blood urea nitrogen at 24 hours did not increase significantly after nesiritide infusion.

### Carvedilol Helps Patients with Heart Failure

**Speaker:** William J. Remme, MD, Professor and Director of Research, STICARES—Cardiovascular Institute, Rhon, The Netherlands

Subgroup analyses of patients in the Carvedilol or Metoprolol European Trial (COMET) suggest that carvedilol (Coreg®, GlaxoSmithKline) is the preferred beta blocker for treating congestive heart failure (CHF), compared with metoprolol tartrate (Lopressor®, Novartis), irrespective of patients' baseline characteristics.

Initial results indicated that at six months' follow-up, carvedilol resulted in a better overall survival than metoprolol in 3,029 patients with New York Heart Association (NYHA) class II–IV CHF and an ejection fraction of less than 35%. Of the 1,112 deaths during the trial, 72 were attributed to cardiovascular causes, 480 to sudden death, 365 to circulatory failures (CHF), and 51 to stroke.

In the subgroup analysis, for each mode of death, the researchers assessed a number of baseline variables: (1) sex, age, NYHA class, ischemic etiology, heart rate, systolic blood pressure, ejection fraction, dilated cardiomyopathy, body mass index, diabetes, atrial fibrillation, previous myocardial infarction, or hypertension; (2) hemoglobin, creatinine, and sodium levels; (3) therapy with ACE-inhibitors, spironolactone, digitalis, aspirin or an anticoagulant, or statins; and (4) allocation of patients into treatment groups.

In the univariate analyses, carvedilol reduced total and cardiovascular mortality, sudden death, and stroke more than metoprolol for all subgroups. For deaths from CHF, this significant difference was found only in patients with low serum sodium levels or in those taking digitalis.

In the multivariate Cox regression analyses, carvedilol remained superior to metoprolol for the total number of deaths ( $P = .0007$ ), cardiovascular mortality ( $P = .0009$ ), sudden death ( $P = .0073$ ) and death from stroke ( $P = .0027$ ). It also showed a nonspecific trend for death from CHF ( $P = .1$ ).