Low HDL-Cholesterol and the LDL-Cholesterol/HDL-Cholesterol Ratio as Predictors of Cardiovascular Events

Speaker: Philip Barter, MD, PhD, Director, Heart Institute, Camperton, Australia, and Professor of Medicine, University of Sydney, Sydney, Australia

Although the control of low-density lipoprotein-cholesterol (LDL-C) remains a pivotal focus of preventing cardiovascular disease (CVD), the Treating to New Targets (TNT) study suggests that high-density lipoprotein-cholesterol (HDL-C) and the ratio of LDL-C to HDL-C provide additional information in predicting cardiovascular events and should be considered potential targets for future drug therapy.

In the randomized, double-blind, parallel-group, multicenter TNT study, 10,001 patients with clinically evident stable coronary heart disease received atorvastatin (Lipitor, Pfizer) at a dose of 10 mg/day during an eight-week, open-label, run-in phase. After the run-in phase, patients with an LDL-C concentration above 130 mg/dl were selected to receive atorvastatin 10 or 80 mg/dl. These patients were observed for a median of 4.9 years. The initial results showed that intensive lipid-lowering therapy provided clinical benefits far beyond that afforded by treatment with atorvastatin 10 mg.

An analysis was then designed to investigate the relationship between the frequency of major cardiovascular events and HDL-C levels in treated patients during the TNT study and to determine whether this relationship was modified by “on-treatment” LDL-C levels. The frequency of major events was calculated by quintiles of on-treatment HDL-C levels below 38 mg/dl, between 38 and 43 mg/dl, between 43 and 48 mg/dl, between 48 and 55 mg/dl, and at 55 mg/dl or higher. These patients were observed for a median of 4.9 years. The initial results showed that intensive lipid-lowering therapy provided clinical benefits far beyond that afforded by treatment with atorvastatin 10 mg.

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The data strongly suggest that HDL-C levels and the ratio of LDL-C to HDL-C are predictive of CVD risk. Although lower on-treatment HDL-C levels were correlated with an increased incidence of major cardiovascular events, an increment of 1 mg/dl in on-treatment HDL-C was associated with a decrease of approximately 2% in the risk of experiencing a major event. This compared with a reduction of 0.7% in the risk of a major event for every 1-mg/dl reduction in on-treatment LDL-C levels in this study.

HDL-C levels remained predictive of the frequency of major cardiovascular events at both high and low LDL-C concentrations. This suggests that HDL-C levels are a major consideration even when LDL-C levels are being managed intensively. There was also a comparable direct relationship between the frequency of major cardiovascular events and the on-treatment LDL-C/HDL-C ratio; every reduction of 1.0 in the ratio resulted in a 31% reduction in risk.

Long-Term, Extended-Release Niacin Raises HDL-Cholesterol Levels

Speaker: Leonard M. Keilson, MD, Director, Maine Center for Lipids and Cardiovascular Health, Scarborough, Maine

Ten years of continuous treatment with extended-release (ER) niacin (Niaspan, Kos Pharmaceuticals), combined with two to 10 years of statin therapy, resulted in long-term positive benefits, with 5% of patients proving to be niacin hyperresponders (i.e., achieving HDL-C levels 50% above their baseline values).

Overall, 11,000 patient records covering 15 years were screened at The Maine Center for Lipids. The investigators collected data on body mass index (BMI), blood glucose levels, and medications used, and they performed a manual chart review. The medical database identified 270 patients who had received ER niacin therapy for as long as 10 years continuously.

The purpose of the study was to describe ER niacin-treated patients with a greater than 50% increase in HDL-C over baseline measurements. The medical database uncovered 13 ER niacin-treated patients who had made more than three office visits and included baseline values, values during treatment, and an HDL-C level greater than 50% of the baseline value. In this group, 69% of patients received a statin for the entire treatment period and 100% received a statin for at least two years.

These 13 niacin hyperresponders made 22 office visits per...
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Darusentan Beneficial in Resistant Hypertension

**Speaker:** Henry Black, MD, Charles J. and Margaret Roberts Professor of Preventative Medicine, Rush University Medical Center, Chicago, Illinois; Adjunct Professor of Preventative Medicine, Northwestern University School of Medicine; and Adjunct Professor of Health Resources Management, School of Public Health, The University of Illinois at Chicago

Darusentan (Mycogen, Inc.), a novel, once-daily, oral endothelin-A receptor antagonist in clinical development, offers additional BP-lowering benefits as an add-on antihypertensive therapy.

A randomized study was performed to compare the efficacy of once-daily darusentan 104 to 300 mg with that of placebo in patients with “resistant” hypertension, as defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC 7) criteria. Overall, 115 patients who did not achieve treatment BP goals after taking three or more antihypertensive agents, including a diuretic at full doses, were assigned, in a 2:1 ratio, to receive oral darusentan or placebo once daily.

After a two-week, run-in phase with placebo, the darusentan dose was escalated every two weeks, starting with a dose of 10 mg daily until a maximum of 300 mg daily was attained. Over a two-week period, darusentan therapy and placebo therapies were withdrawn.

Sitting and standing BP and heart rates were measured at every study visit via standard sphygmomanometry and physical examination. Hematological laboratory tests and electrocardiography were performed at screening and periodically throughout the study.

The co-primary efficacy endpoints were changes from baseline through weeks 8 and 10 (at doses of 150 and 300 mg) at the lowest (in trough) sitting systolic BP. Secondary variables included:

- changes from baseline in 24-hour systolic BP, as measured by ambulatory BP monitoring.
- the percentage of patients who achieved systolic BP goals.
- changes from baseline in trough sitting diastolic BP

Eighty-seven percent of patients completed the study. The mean duration of treatment was 78.6 ± 18 days (range, 60.6–96.6 days).

At the baseline evaluation, mean systolic BP was 149.4 ± 13.1 mm Hg and mean diastolic BP was 81.5 ± 13 mm Hg. Beginning at the fourth week of therapy, significant improvements in mean trough sitting diastolic BP, compared with placebo, were evident (–6.2 mm Hg; P < .001) and were maintained throughout the study.

At the 10th week of darusentan therapy, the placebo-corrected mean trough sitting systolic BP at a dose of 300 mg was 11.5 ± 3.1 mm Hg (P = .015); the diastolic BP at the same dose, was reduced by 6.3 ± 2 mm Hg (P = .004). Also at week 10, 51% of the darusentan-treated patients achieved JNC 7
systolic BP goals, compared with only 33% of those in the placebo group ($P = .069$).

### Perindopril Beneficial for Stable Coronary Artery Disease

**Speaker:** Maarten L. Simoons, MD, Professor of Medicine, Thoraxcenter, Erasmus Medical Center, University Hospital, Rotterdam, The Netherlands

According to a subgroup analysis of patients in the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA), perindopril (Aceon, Solvay) 8 mg daily, when added to standard therapy, helped to prevent cardiac events. The benefits pertaining to all stable patients with coronary artery disease, including those who had had revascularization surgery and no previous myocardial infarction (MI).

Initially, the EUROPA trial had indicated that perindopril, an angiotensin-converting enzyme (ACE)–inhibitor with a high affinity for tissue, significantly decreased the composite risk of major cardiac events by 20% in patients with stable CAD without apparent heart failure. Examples of major cardiac events included cardiovascular death, MI, and resuscitated cardiac arrest.

Approximately 55% of the 12,218 patients (6,709 patients) in the EUROPA trial had undergone revascularization. Approximately equal numbers of patients had had a percutaneous coronary intervention (PCI) (3,122 patients) or coronary artery bypass graft (CABG) surgery (3,136 patients). It was noted that 3,047 patients had not experienced a previous MI.

Of the total group of patients who had undergone revascularization, 3,340 had received perindopril and 3,369 had received placebo. Baseline characteristics and demographics were comparable in the two groups. Overall, the incidence of the composite endpoint of major cardiac events was 6.6% with perindopril and 8% with placebo, for a significant risk reduction of 17.3% favoring perindopril ($P = .036$).

The incidence of MI alone was 4.6% for the perindopril patients and 5.9% with placebo, for a significant risk reduction of 23% favoring perindopril ($P = .015$).

In the 3,047 patients who had undergone revascularization who had no history of MI, the incidence of MI was 3.8% with perindopril and 5.5% with placebo, for a significant risk reduction of 31.7% favoring perindopril ($P = .026$).

### Bivalirudin Monotherapy Improves Outcomes in Acute Coronary Syndrome Patients Undergoing Early Cardiac Catheterization

**Speaker:** Gregg W. Stone, MD, Professor of Medicine and Director of Cardiovascular Research and Education, Cardiovascular Research Foundation, Columbia University Medical Center, and Lenox Hill Hospital, New York, New York

A randomized study was conducted to compare the effectiveness of bivalirudin (Angiomax, The Medicines Company), a direct thrombin inhibitor, with heparin, an indirect thrombin inhibitor, plus a glycoprotein IIb/IIIa inhibitor, or bivalirudin alone in patients with acute coronary syndrome (ACS). Bivalirudin alone was found to be as effective as more complicated dual regimens and resulted in the most positive net clinical outcomes with less bleeding and ischemia.

The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial was designed to test several combinations of drug therapies in patients at moderate-to-high risk for ACS. Typical drug therapy consists of aspirin, clopidogrel bisulfate (Plavix, Bristol-Myers Squibb/sanofi aventis), heparin, and a glycoprotein IIb/IIIa inhibitor. All of these drugs interfere in the blood-clotting process in the coronary artery. Even though together they achieve better efficacy, the combination may compromise safety in the process.

The ACUITY study enrolled more than 13,800 patients who underwent cardiac catheterization within 72 hours, followed by percutaneous coronary intervention (PCI) or surgical revascularization when necessary. The patients received one of three treatments:

- heparin, either unfractionated conventional, or a low-molecular-weight heparin, enoxaparin (Lovenox, sanofi aventis) plus a glycoprotein IIb/IIIa inhibitor
- bivalirudin plus a glycoprotein IIb/IIIa inhibitor
- bivalirudin alone

One month after treatment, the investigators measured the net clinical benefit, which balanced the risks of ACS itself against the major bleeding risks of anticoagulation therapy. At this point, the comparison of ischemic events met the predefined criteria for non-inferiority between bivalirudin plus a glycoprotein IIb/IIIa inhibitor or bivalirudin alone and heparin plus a glycoprotein IIb/IIIa inhibitor.

Patients in the bivalirudin monotherapy arm had the most positive outcomes, with rates of major bleeding significantly lower than those in the control arm who received a glycoprotein IIb/IIIa inhibitor.

With bivalirudin plus a glycoprotein IIb/IIIa inhibitor, the endpoints also demonstrated non-inferiority, with no significant increase in either ischemic or bleeding complications, compared with heparin plus a glycoprotein IIb/IIIa inhibitor. Although bivalirudin plus a glycoprotein IIb/IIIa inhibitor is an acceptable substitute for heparins plus a glycoprotein IIb/IIIa inhibitor, no ischemic benefit resulted from this combination.

### Statin Pre-treatment Reduces the Risk of Postoperative Atrial Fibrillation

**Speaker:** Germano Di Sciascio, MD, Professor and Chairman of Cardiology, and Director, Department of Cardiovascular Sciences, Campus Biomedico, University of Rome, Rome, Italy

Pre-treatment with the statin atorvastatin (Lipitor, Pfizer) for one week before elective cardiac surgery reduced the risk of postoperative atrial fibrillation, according to findings from the ATorvastatin for Reduction of Myocardial Dysrythmias After Cardiac Surgery (ARMYDA-3) study.

The randomized study enrolled 200 patients scheduled for elective cardiac surgery for coronary artery bypass graft surgery or heart valve repair or placement. These patients had not received previous statin treatment and had no history of atrial fibrillation.
The patients received atorvastatin 40 mg daily (n = 101) or placebo (n = 99) starting seven days before the operation. The primary endpoint was the incidence of postoperative atrial fibrillation. Levels of C-reactive protein (CRP), a marker of inflammation, were routinely measured before surgery and every 24 hours postoperatively until discharge.

An analysis of the data indicated that atorvastatin significantly reduced the rate of atrial fibrillation from 57% with placebo to 35% with atorvastatin. CRP levels were higher in patients who developed atrial fibrillation. Although the researchers observed no differences in the duration or time of the beginning of the arrhythmic episodes after surgery between the two study groups, the atorvastatin patients had significantly shorter hospital stays (6.3 days) than the placebo patients (6.9 days) (P = .001).

**Darbepoetin alfa Beneficial for Patients with Anemic Heart Failure**

**Speaker:** Dirk J. Von Veldhuisen, MD, PhD, Professor and Chairman, Division of Cardiology, University Medical Center, Groningen, The Netherlands

Treating anemia with darbepoetin alfa (Aranesp, Amgen), a recombinant erythropoietin protein, in patients with symptomatic heart failure (HF) has been found to be safe and well tolerated, effectively raising hemoglobin levels and alleviating symptoms.

Because anemia is common in patients with HF and is associated with severe symptoms and outcomes, a phase 2 multicenter study was performed to assess the value of two dosing regimens of darbepoetin alfa on the rate of hemoglobin elevation, exercise performance, symptoms, and clinical status. Darbepoetin stimulates the production of red blood cells and has been approved by the Food and Drug Administration to treat chemotherapy-induced anemia in patients with non-myeloid malignancies.

A randomized, 26-week study enrolled 165 patients with symptomatic HF (New York Heart Association Class II to III) of three months’ duration or more, a left ventricular ejection fraction (LVEF) below 40%, and hemoglobin levels ranging from 9 to 12.5 g/dl. The patients received darbepoetin alfa subcutaneously every two weeks at starting doses of 75 mcg/kg (n = 56), a fixed dose of 50 mcg/kg (n = 54), or placebo (n = 55) to achieve and maintain target hemoglobin concentrations of 14 ± 1 g/dl (range, 13–15 g/dl).

The primary endpoint was the rate of hemoglobin increase per week during the titration period. Other endpoints included changes from the baseline examination to the sixth month in the six-minute walking distance and scores from various tests: the Patient’s Global Assessment (PGA), the Minnesota Living with Heart Failure Questionnaire (MLHFQ), the Kansas City Cardiomyopathy Questionnaire (KCCQ), and a safety profile.

In the patients with symptomatic HF and anemia, darbepoetin alfa effectively raised hemoglobin levels and was associated with improved total scores of symptoms in the Kansas City Questionnaire: from 1.5 with placebo to 8.2 with darbepoetin alfa (with higher scores indicating better health).

Fixed doses were as effective as doses based on weight in raising hemoglobin levels, with a difference of only 0.05 g/dl per week. Statistically nonsignificant improvements were recorded as follows:

- Patient’s Global Assessment: darbepoetin alfa, 65% improvement; placebo, 49%
- Minnesota Questionnaire: darbepoetin alfa, a score of 10.1; placebo, a score of 7.4
- Six-minute walking distance: darbepoetin alfa, 34.2 meters; placebo, 11.4 meters.

Adverse events were comparable in all treatment groups.

**Carvedilol Improves Survival in Patients with Heart Failure after Hospital Discharge**

**Speaker:** Gregg C. Fonarow, MD, The Eliot Corday Chair in Cardiovascular Medicine and Science; Professor of Clinical Medicine, Division of Cardiology; Director, Ahmanson University of California, Los Angeles (UCLA) Cardiomyopathy Center; and Co-Director, UCLA Preventative Cardiology Program, David Geffen School of Medicine, UCLA, Los Angeles, California

Carvedilol (Coreg, GlaxoSmithKline), a well-known beta-blocking agent, when prescribed upon hospital discharge to patients with heart failure (HF), has been associated with improved treatment and survival rates at 60 to 90 days and is exceptionally well tolerated.

These findings were derived from a new analysis from the HF registry and performance improvement program for patients with HF (Organized Program To Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure [OPTIMIZE-HF]). This program collects data from participating hospitals in the U.S.

Data were collected from 2,720 patients with HF who were discharged to home from the hospital with left ventricular systolic dysfunction and who were eligible for beta-blocker therapy. The patients were observed for the first 60 to 90 days after discharge. Carvedilol was prescribed at the time of discharge to 1,146 patients, and 94% of the patients continued with their therapy for the rest of the follow-up period. For the 361 eligible patients who were not discharged home with any beta-blocker regimen, only 30.4% of them later received prescriptions for a beta blocker.

Patients taking carvedilol after hospital discharge experienced a significantly decreased risk of death, and death or rehospitalization, without an early risk of recurrent worsening HF. Their risk of death was less than half that in the untreated patients (odds ratio, 0.46 [0.30–0.72]; P = .006), and they were one third less likely to need rehospitalization than untreated patients (odds ratio, 0.71 [0.53–0.91]; P = .02).

As a result of this analysis and earlier studies, the use of carvedilol or one of the other recommended beta blockers upon discharge from the hospital should be adopted as the standard of care among all hospitalized patients with HF and left ventricular systolic dysfunction unless such a regimen is absolutely contraindicated.