SPECIAL ARTICLE

Summary of the Clinical Studies Reported in the Scientific Sessions in the American Heart Association 2005 (Dallas, Texas, USA, 13-16 November 2005)

SUMMARY BY SUBJECT

A group of clinical trials were selected for special sessions presentations in the scientific sessions at the American Heart Association 2005. These studies were chosen due to their critical relevance and the results were communicated orally. Summaries of the reports have been published online. The aims, methods and results of these studies are briefly described below based on what was presented. As the results of most of these studies have not yet been published as original articles, the information presented in the current article should be understood as being preliminary.

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PRIMARY AND SECONDARY PREVENTION

Effects of Protein, Monounsaturated Fat and Carbohydrate Intake on Blood Pressure and Plasma Lipids: the OmniHeart Study

Presented by Lawrence J. Appel, Johns Hopkins Medical Institute University, Baltimore, United States

Reducing saturated fat intake is a well-established recommendation for cardiovascular disease prevention. However, it has still not been clarified which type of macronutrient should be used to replace saturated fat.

The aim of the OmniHeart study was to compare the effect of 3 healthy diets on blood pressure and lipid profile. The 3 diets involved reduced saturated fat intake. The study was designed as a randomized, 3-period, crossover feeding trial, carried out between April 2003 and June 2005 in Boston, Md., and Baltimore, Mass., USA. Subjects included 164 adults with stage 1 hypertension or prehypertension. Each diet period lasted 6 weeks and body weight was kept constant. The diets used were: *1*) a carbohydrate-rich diet; *2*) a protein-rich diet (almost half of which came from plants); and *3*) a diet rich in unsaturated fats, mainly monounsaturated.

Blood pressure, low-density lipoprotein cholesterol (LDL-C) and estimated coronary heart disease risk levels were lower with all 3 diets compared to baseline. Compared to the carbohydrate diet, the protein diet further reduced blood pressure (a difference of 1.4 mm Hg; P=.002, and 3.5 mm Hg; P=.006 in normotensive and hypertensive patients, respectively), LDL-C levels (a difference of 3.3 mg/dL; P=.01), high-density lipoprotein cholesterol (HDL-C) (1.3 mg/dL; P=.02), and triglycerides (15.7 mg/dL; P<.001). Also compared to the carbohydrate diet, the unsaturated fat diet further decreased blood

pressure (1.3 mm Hg; *P*=.005 and 2.9 mm Hg in normotensive and hypertensive patients, respectively), had no effect on LDL-C, increased LDL-C by 1.1 mg/dL (*P*=.03) and lowered triglycerides by 9.6 mg/dL (*P*=.02). Both diets similarly reduced estimated 10-year coronary artery disease risk compared to the carbohydrate diet.

In conclusion, in the context of a healthy diet, substitution of carbohydrates by greater protein or monounsaturated fat intake can be effective in reducing blood pressure, improving lipid profile, and reducing cardiovascular risk.

The final and complete results of this study have already been published.[1]

Effects of Eicosapentaenoic Acid (EPA) on the Incidence of Serious Cardiovascular Events in Hypercholesterolemic Patients: the JELIS Study (Japan EPA Lipid Intervention Study)

Presented by Mitsuhiro Yokoyama, Kobe University Graduate School, Kobe, Japan

Epidemiological studies have demonstrated that an increased intake of n-3 polyunsaturated fatty acids (copious in fish) can have a protective effect regarding mortality and morbidity due to coronary disease. The JELIS study is the first large-scale prospective, randomized, open-label, blinded-endpoint trial including a primary prevention stratum (n=14 981) and a secondary prevention one (n=3 664). The study was designed according to the hypothesis that treatment with highly purified EPA (>98%) at 1800 mg/day combined with statins would be more effective than stain-only treatment in reducing the coronary event rate in hypercholesterolemic patients. The primary endpoint consisted of sudden cardiac death, fatal or non-fatal acute myocardial infarction, and unstable angina requiring hospitalization due to ischemic events or revascularization via any technique. Data relating to the basis for and design of this study, as well as the baseline characteristics of the study population, have been previously published.[2]

After mean follow-up of 4.6±1.1 years, the incidence of primary endpoint events was significantly less in the EPA+statin group than in the statin-only group (2.8% vs 3.5%; hazard ratio [HR]=0.810; 95% confidence interval [CI], 0.689-0.954; *P*=.0113). At 5-year follow-up, there was a 26% reduction in LDL-C in both groups. There was a 5% increase in HDL-C in the EPA+statin group versus 3% in statin-only group. Maximum benefits were obtained with EPA treatment in the secondary prevention stratum (8.7% vs 10.7% events between groups; HR=0.81; 95% CI, 0.657-0.998; *P*=.0476), although an effect in the same direction, albeit nonsignificant, was found in the primary prevention stratum (1.4% vs 1.7%; HR=0.820; 95% CI, 0.632-1.062; *P*=.13).

In conclusion, EPA+statin treatment provides additional benefit in the prevention of major coronary events, mediated by a mechanism independent of plasma lipid levels.

Effects of Fenofibrate on Major Coronary Event Rates in Patients With Type 2 Diabetes Mellitus: the FIELD Study (Fenofibrate Intervention and Event Lowering in Diabetes Study)

Presented by Anthony C. Keech, University of Sydney, Australia

Patients with type 2 diabetes mellitus are at high risk of cardiovascular disease, partly due to associated dyslipidemia, which can be treated with fibrates. Based on this hypothesis, the FIELD study was designed to assess the effect of fenofibrate on the cardiovascular event rate in this population. It was a multicenter, multinational, randomized, placebo-controlled study including 9795 patients, 50 to 70 years old, with type 2 diabetes previously treated with statins.

After a drug and placebo run-in phase, the patients (2131 with previous coronary disease and 7664 without) with a total cholesterol count of 3.0-6.5 mmol/L and total cholesterol/HDL-C ratio of ≥4 or a plasma triglyceride concentration 1.0-5.0 mmol/L, were randomized to receive micronized fenofibrate 200 mg daily (n=4895) or placebo (n=4900). The primary endpoint was non-fatal acute myocardial infarction or death due to coronary artery disease; the endpoint analyzed in the scheduled subgroups was the incidence of cardiovascular events (cardiovascular death, myocardial infarction, stroke and the need for coronary or carotid revascularization). An intention-to-treat analysis was done and the study was prospectively registered.

Data were obtained on vital status during follow-up in all except 22 patients. The dropout rate over 5 years of follow-up was similar in the 2 groups (10% in the placebo group vs 11% in the fenofibrate group) and the use of other hypolipidemic drugs was greater in the placebo group (17%) than in the fenofibrate group (8%; *P*<.0001).

The incidence of coronary events was 5.9% in patients who received placebo versus 5.2% in those receiving fenofibrate (relative reduction of 11%; HR=0.89, 95% CI, 0.75-1.05; *P*=.16). This finding corresponds to a significant reduction in the non-fatal myocardial infarction rate of 24% (HR=0.76; 95% CI, 0.62-0.94: *P*=.01) and to an nonsignificant increase in mortality due to coronary artery disease (HR=1.19; 95% CI, 0.90-1.57; *P*=.22). The total rate of cardiovascular disease events was significantly reduced from 13.9% to 12.5% (HR=0.89; 95% CI, 0.80-0.99; *P*=.035). This included a 21% reduction in the need for coronary revascularization (HR=0.79; 95% CI, 0.68-0.93; *P*=.003). Total mortality was 6.6% in the placebo group versus 7.3% in fenofibrate group (*P*=.18). Furthermore, fenofibrate reduced the rate of progression to albuminuria (*P*=.0002) and the need for retinal laser therapy (5.2% vs 3.6%; *P*=.0003). A slightly higher incidence of pancreatitis (0.5% vs 0.8%; *P* = .03) and pulmonary embolism (0.7% vs 1.1%, *P*=.022) was found in the fenofibrate group, but with no difference regarding other side effects.

In conclusion, fenofibrate did not significantly reduce the risk of primary events. It did reduce the total rate of cardiovascular events, mainly due to a lower incidence of non-fatal myocardial infarctions and revascularization procedures. The greater use of statins in the placebo group may have masked a greater potential benefit due to fenofibrate.

The definitive results of this study have already been published.[3]

Safety and Efficacy of an α4β2 Nicotinic Receptor Partial Agonist for Tobacco Cessation. Results of Varenicline Administration

Presented by Serene Tonstad, Ullevaal University Hospital, Oslo, Norway

Smoking is the leading preventable cause of disease and premature death in the United States and kills over 140 000 people per year due to cardiovascular disease. Varenicline is an α4β2 nicotinic receptor partial agonist and can potentially reduce dependency on nicotine and minimize cessation symptoms. Thus, this drug could diminish the positive reinforcement effects of nicotine. Two identical randomized, double-blind studies (study 1 and 2) compared treatment with varenicline 1 mg b.i.d., bupropion 150 mg b.i.d. and placebo over 12 weeks, followed by a 40-week observation period without treatment. The primary endpoint was remaining smoke-free for 4 weeks confirmed by measuring carbon monoxide concentrations between weeks 9 and 12. Furthermore, the quit rate was measured during weeks 9 and 52. The benefit of 12 additional weeks of treatment was analyzed in a second maintenance study.

The patients who had succeeded in staying smoke-free at the end of 12-weeks open treatment with varenicline were randomized to receive an additional 12-week blinded treatment with varenicline or placebo, followed by a period of 28 weeks without treatment (study 3). The primary endpoint was remaining smoke-free between weeks 13 and 24 and the secondary endpoint was remaining smoke-free between weeks 13 and 52.

Varenicline did not present side effects, was well tolerated and had medication withdrawal rates similar to those of placebo. The incidence of treatment withdrawal due to nausea was 2.3%-2.6% in the short-term studies, 1.4% in unblinded studies, and 0.2% in the double-blind phase of the maintenance study.

In studies 1 and 2, the quit rates in weeks 9-12 (primary endpoint) were 44.4% and 44.0% in the varenicline group, respectively, versus 29.5% and 30.0% in bupropion group, and 17.7% and 17.7% in the placebo group (*P*<.0001 for all groups). The quit rates in weeks 9-52 for studies 1 and 2 in the varenicline group were 22.1% and 23% versus 16.4% and 15.0% in the bupropion group and 17.7% and 10.3% in the placebo group, respectively (*P*<.0001 for all groups). In study 3, the quit rate was 70.6% during weeks 13-24 in the varenicline group, and 44.0% during weeks 13-52. These figures were significantly higher than those found with placebo (49.8% and 37.1%, respectively).

In conclusion, the results of this study demonstrate the efficacy of the drug as an aid to stopping smoking and indicates a great advance in such therapy.

ARTERIAL HYPERTENSION

The Effect of Antihypertensive Drugs on Central Blood Pressure Influences Clinical Events. The CAFE Study (Conduit Artery Function Evaluation), a Substudy of the ASCOT Study

Presented by Bryan Williams, University of Leicester, Leicester, United Kingdom

Normally, the effect of hypotensive drugs is assessed by measuring brachial blood pressure (BBP). However, different hypotensive drugs could have

different effects on the central aortic pressure (CAP) despite their similar effects on BBP and thus hare different prognostic implications. In the ASCOT study (AngloScandinavian Cardiac Outcomes Trial) the impact of 2 hypotensive treatment strategies was analyzed: standard treatment (atenolol + thiazide) versus "current" treatment (amlodipine + peridopril) in 19 257 hypertensive patients. The CAFE substudy analyzed for the first time the impact of these 2 hypotensive treatments on central aortic pressure and systemic hemodynamics.

The working hypothesis was that different hypotensive regimens would produce different effects on CAP and systemic hemodynamics, despite having similar effects on BBP. Furthermore, the effect on CAP would cause prognostic differences between the different regimens.

The CAFE study included 2199 patients from 5 centers participating in the ASCOT study. The characteristics of these patients were representative of the other participants in the ASCOT study. The CAP and hemodynamic indexes were estimated non-invasively using radial artery applanation tonometry and pulse wave analysis (SphygmoCor®). More than 17 000 central blood pressure measurements were done in repeat visits over more than 5 years.

Brachial blood pressure was very similar in both treatment groups (0.7 mm Hg below the mean in the amlodipine group). However, there were substantial reductions in CAP values and hemodynamic indexes in the amlodipine group, such as reductions in central systolic blood pressure of –4.3±0.5 mm Hg, central pulse pressure –3.0±0.5 mm Hg and an augmentation index of –5.8±0.4% (P<.0001 in all groups). In the global ASCOT study, treatment based on amlodipine was associated with a significant reduction in mortality and major cardiovascular and renal events. In the CAFE substudy cohort, central pulse pressure was a significant predictor of total cardiovascular events and of renal events/procedures (P<.001 and P<.05 for a proportional risks model adjusted and unadjusted for baseline characteristics, respectively).

In conclusion, the CAFE study demonstrates for the first time in a large prospective clinical trial that antihypertensive treatments have a markedly different effect on CAP and systemic hemodynamics, despite having similar effects on BBP. Thus, BPP is a suboptimal measure of the effects of these drugs on central hemodynamics. Furthermore, central pulse pressure seems to have a determining effect on clinical events. These findings: *1*) reveal new mechanisms to explain the different prognoses associated with different treatment groups in the ASCOT study and, potentially, of other clinical trials evaluating antihypertensive treatments; and *2*) can help improve treatment guidelines.

HEART FAILURE

The REVIVE II Study: Placebo-Controlled Multicenter Study of Levosimendan in Patients With Decompensated Heart Failure

Presented by Milton Packer, University of Texas Southwestern Medical Center, Dallas, Texas, United States

Most of the treatments used in acute decompensated heart failure episodes have not been assessed in randomized clinical trials. Although there are multiple drugs that can lead to hemodynamic improvement, it is not clear if this translates into clear clinical benefits nor whether such benefits are preserved after the treatment period. The REVIVE II study is the first randomized controlled trial which investigated the effects of a pharmacological treatment on the clinical status and prognosis of patients with decompensated heart failure episodes.

The clinical selection criteria were: *1*) admission due to sudden worsening of heart failure; *2*) left ventricle ejection fraction ≤35% and dyspnea at rest despite intravenous diuretic treatment. In a double-blind study, patients were randomized to receive placebo or levosimendan (12 μg/kg bolus followed by 0.2 μg/kg/min over 24 h). This medication was added to all the other drugs normally used to treat acute heart failure. Levosimendan is a new agent with vasodilator and inotropic properties which can sensitize cardiac myofilaments and facilitate potassium channel opening.

A total of 600 patients from the United States, Australia, and Israel were included. The primary endpoint was a change in symptoms, together with occurrence of death or worsening of heart failure over 5 days after inclusion. The treatments were administered for 24 h. The secondary endpoints included the time to occurrence of death, worsening of heart failure according to criteria defined in the protocol, the subjective assessment of the symptomatic picture at 6 h, extending hospital stay, changes in atrial natriuretic peptide, and all-cause mortality at 90 days. The study was designed to find significant differences between the 2 treatments for the composite endpoint.

After 5 days, the probability of clinical improvement and deterioration was 33% higher and

26% lower, respectively, in the levosimendan group than in the placebo group (*P*=.015). All the sensitivity analyses were favorable to the group treated with the drug.

In conclusion, levosimendan improves the clinical status of patients with decompensated heart failure and these benefits persist after the treatment period.

The SURVIVE-W Study: Comparison of the Effects of Dobutamine Versus Levosimendan on Survival of Patients With Acute Decompensated Heart Failure

Presented by Alexandre Mebazaa, Hospital of Paris, Paris, France, on Behalf of the SURVIVE Study Researchers

Every year approximately 3 million hospitalizations occur in the United States due to a sudden worsening of heart failure. The efficacy of most treatments used in this context has not been proven in randomized clinical trials. Furthermore, many of the drugs used to treat these patients have been associated with increased mortality (e.g., dobutamine, milrinone and nesitride), although, to date, no study has been designed with the purpose of assessing the influence of treatment on mortality.

The SURVIVE study is the first randomized controlled study where mortality related to intravenous treatment is analyzed in patients with sudden worsening of heart failure. It was designed as an actively controlled double-blind study in parallel groups with hospitalized patients. The patients underwent clinical follow-up to detect the incidence of death or major clinical events. Study selection criteria were: *1*) hospitalization due to an acute decompensated heart failure episode; *2*) ejection fraction <30%; and *3*) need for intravenous inotropic support demonstrated by a poor response to treatment with intravenous diuretics and/or vasodilators, in addition to oliguresis (diuresis <30 ml/h for at least 6 h in the absence of hypovolemia), persistence of dyspnea at rest, mechanical ventilation for heart failure, or invasive demonstration of pulmonary capillary pressure ≥18 mm Hg and/or a cardiac index ≤2.2 L/min/m^2.

The patients were randomized to receive levosimendan (as in the previous study) or dobutamine (minimum dose 5 mg/kg/min). This latter medication was added to the full standard treatment (vasodilators, diuretics, etc) for this type of patient. The primary endpoint was all-cause mortality at 180-day follow-up. The study was designed with 90% power to detect a 25% difference in risk between the 2 groups. A total of 1318 patients from nine European countries were included.

No differences were found between the treatment groups in the primary endpoint (26% vs 28% for treatment with levosimendan vs dobutamine, HR=0.91; 95% CI, 0.74-1.13) or in the secondary endpoints of mortality at 31 days (12% vs 14%; HR=0.85; 95% CI, 0.63-1.15) and at 5 days (4% vs 16%; HR=0.72; 95% CI, 0.44-1.16).

In the analyses by subgroup it was found that the patients with recently diagnosed heart failure obtained less benefit than those with chronic decompensated heart failure (HR=0.58; 95% CI, 0.33-1.01). Brain natriuretic peptide (BNP) concentrations dropped by around 50% soon after beginning levosimendan infusion and remained low at the fifth day, while the drop in BNP was lower with dobutamine (*P*<.0001 for the between-groups comparison). The incidence of hypotension and ventricular tachycardia was similar in both groups, whereas there was a greater incidence of atrial fibrillation in the levosimendan group. There were no between-group differences in the incidence of adverse renal effects and creatinine levels.

ISCHEMIC HEART DISEASE

Intracoronary Infusion of Bone Marrow Progenitor Cells in Acute Myocardial Infarction. Randomized, Double-Blind, Placebo-Controlled Study (REPAIR-AMI)

Presented by Volker Schächinger, Frankfurt, Germany

Experimental studies have shown that mononuclear bone marrow progenitor cells can contribute to the functional regeneration of recently infarcted myocardium. Furthermore, several preliminary clinical trials have demonstrated that intracoronary bone marrow progenitor-cell delivery is a feasible and apparently safe strategy in patients with acute myocardial infarction.

The REPAIR-AMI study (Reinfusion of Enriched Progenitor Cells And Infarct Remodeling in Acute Myocardial Infarction) was designed on this basis. This was the first clinical, randomized, double-blind, placebo-controlled, multicenter trial which analyzed the effects of intracoronary delivery of bone marrow progenitor cells immediately after a heart attack. The study was carried out in 17 centers in Germany and Switzerland

and included a total of 200 patients. Three to 6 days after the infarction, they received an intracoronary infusion in the infarct-related artery of a suspension of progenitor cells (isolated from 50 mL bone marrow aspirate via density gradient centrifugation) or a placebo. An average of 236 million cells were infused per patient. The bone marrow aspirates were sent to a central processing center which returned the cell preparation or placebo for intracoronary infusion within 24 h.

The primary endpoint was absolute improvement in left ventricle ejection fraction (LVEF) measured by radionuclide ventriculography at 4 months. A greater LVEF was observed in the patients treated with progenitor cells; at 4 months LVEF improved by 5.5 versus 3%. Analysis by subgroups showed that this improvement was greater in patients with LVEF<49% after AMI (an increase of 7.5% vs 2.5% in the treatment group vs placebo, respectively) and was especially marked in patients who began therapy later (5 days after AMI), with an increase in LVEF of 7.0% versus 1.9% in the treatment group versus the placebo, respectively. This finding must be viewed in relation to immediate post-AMI major tissue damage, inflammation and oxidative stress which might be more harmful to the infused cells.

In the treatment group, improvement was due in particular to a reduction in end-systolic volume, with no change in end-diastolic volume.

Furthermore, a trend was found toward a lower incidence of clinical events (recurrence of AMI, hospitalizations due to heart failure and, in particular, need for revascularization) in the treatment group.

Effects on Left Ventricular Function of Intracoronary Injection of Autologous Mononuclear Bone Marrow Progenitor Cells in Patients With Anterior Acute Myocardial Infarction: the ASTAMI Study

Presented by Ketil Lunde, of the Rijkshospitalet University Hospital, Oslo, Norway

In small randomized studies a small improvement in left ventricular function has been shown through intracoronary delivery of autologous bone marrow cells in the acute phase of an AMI. Patients undergoing heart attack in any location were included in these studies. The aim of the ASTAMI study was to find out if clinical benefit in left ventricular function can be detected with this treatment in patients with anterior myocardial infarction who are at greater risk of presenting extensive myocardial necrosis and remodelling and, thus, of developing heart failure. Furthermore, conventional imaging techniques offer greater precision to detect changes in the anterior face of the left ventricle.

A total of 101 patients were included in the study with anterior ST-segment elevation AMI, defined by typical electrocardiographic changes, creatine kinase (CK) mass higher than 3 times the upper reference limit, and segmentary contraction abnormalities in the anterior wall detected by echocardiography (at least 2 segments). Primary angioplasty was done in all the patients via stent implantation in the culprit artery in the proximal or medial segment of the anterior descending artery 2-12 h from symptom onset. No patient had had a previous infarction. Patients were randomized to receive an intracoronary injection of autologous mononuclear bone marrow cells at 5-8 days (n=52) or placebo. Left ventricle systolic function was analyzed at 6 months after the infarction via 99m Tc-MIBI single photon emission computed tomography (SPECT), echocardiography, and magnetic resonance imaging.

No differences were observed between the 2 groups by age, peak CK mass, the proportion of smokers, sex, and the proportion of hypertensive and diabetic patients.

The results showed no differences in changes in volume and LVEF between the 2 treatment groups. Thus, LVEF measured via SPECT showed an increase of 8.1% in the treatment group versus 7.0% in the control group (*P*=.63). These changes were 3.1% versus 2.1% (*P*=.54) measured via echocardiography, and 1.2% versus 4.3% (*P*=.05) measured via magnetic resonance imaging. There were no between-groups differences in end-diastolic volume variables or infarction size when measured by any of the techniques.

Effects of Acyl-Coenzyme A:Cholesterol O-Acyltransferase (ACAT) Inhibition on Coronary Atherosclerosis. The ACTIVATE Study (ACAT Intravascular Atherosclerosis Treatment Evaluation)

Presented by Steven E. Nissen, MD, The Cleveland Clinic, Ohio, United States

The enzyme acyl-coenzymeA:cholesterol O-acyltransferase (ACAT) is the cause of cholesterol esterification in several tissues. In some animal models (but not in all), ACAT inhibitors have shown marked antiatherosclerotic effects.

An intracoronary ultrasound study was done in 408 patients with angiographically demonstrated coronary artery disease (534 patients were included, although approximately 60 patients in every treatment group were lost to follow-up). All the patients received standard secondary prevention therapy, which included statins when indicated. Furthermore, they were randomized to receive the ACAT inhibitor pactimibe (100 mg/day) or the equivalent placebo. The ultrasound study was repeated at 18 months of treatment to measure the coronary heart disease progression rate. At the time of inclusion in the study the LDL-C level was 95 mg/dL in the 2 groups and baseline characteristics were similar.

The primary endpoint (change in percent atheroma volume) showed a similar progression rate in the pactimibe group as in the placebo group (0.69% vs 0.59%; *P*=.77). However, the 2 scheduled primary efficacy endpoints showed proatherogenic outcomes in the pactimibe group: the normalized total atheroma volume regressed in the placebo group (–5.6 μL; *P*=.001 vs baseline), whereas it did not regress in the treated group (–1.3 μL; *P*=.39 vs baseline). This difference between the treatment groups was significant (*P*=.035). Furthermore, the change in atheroma volume in the most diseased 10-mm segment showed greater regression in the group receiving standard treatment+placebo (–3.2 μL) than in the group that received standard treatment+pactimibe (–1.3 μL; *P*=.01). The incidence of combined clinical events was similar in both groups (*P*=.53).

In conclusion, treatment with an ACAT inhibitor in patients with coronary heart disease did not achieve the primary endpoint (change in percent atheroma volume) and in fact had unfavorable effects on the 2 secondary efficacy measures. Inhibition of ACAT is not an effective strategy to stop atherosclerosis and can be associated with proatherogenic effects.

High-Dose Atorvastatin Versus Standard-Dose Simvastatin for Secondary Prevention After Myocardial Infarction. The IDEAL Study (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering)

Presented by Terje R. Pedersen, Ulleval University Hospital, Oslo, Norway

Evidence suggests that a more intensive lowering of LDL-C concentrations than normally obtained clinically could offer greater protection in patients with stable ischemic heart disease. The aim of the IDEAL study was to compare the efficacy of 2 cholesterolemia reduction strategies on cardiovascular disease risk in patients with previous myocardial infarction. It was a prospective, randomized, open-label, blinded endpoint evaluation trial, carried out in 190 cardiology practices in northern Europe between March 1999 and March 2005. The mean follow-up was 4.8 years and included 8888 patients less than 80 years old with a previous history of infarction. Patients were randomized to receive high-dose atorvastatin (80 mg/day; n=4439) or standard dose simvastatin (20 mg/day; n=4449). The primary endpoint of the study was the incidence of major coronary events, defined as coronary death, non-fatal acute myocardial infarction, or cardiac arrest with resuscitation.

During treatment, the mean LDL-C values were 104±0.3 mg/dL in the simvastatin group and 81±0.3 mg/dL in the atorvastatin group. Major cardiovascular events were recorded in 463 patients in the simvastatin group (10.4%) versus 411 in the atorvastatin group (9.3%; HR=0.89; 95% CI, 0.78-1.01; *P*=.07). Non-fatal myocardial reinfarction was 321 (7.2%) and 267 (6.0%) in the 2 groups (HR=0.83; 95% CI, 0.71-0.98; *P*=.02), with no differences in any of the other components of the primary endpoint. Major cardiovascular events occurred in 608 and 503 in the simvastatin and atorvastatin group, respectively (HR=0.87; 95% CI, 0.77-0.98; *P*=.02). The incidence of any coronary event was 1059 in the simvastatin group and 898 in the atorvastatin group (HR=0.84; 95% CI, 0.76-0.91; *P*<.001). No differences were found between groups regarding non-cardiovascular death or death from any cause. Patients who received atorvastatin had a greater dropout rate due to mild side effects; elevated transaminase levels were the cause of 1% of the dropouts in the atorvastatin group versus 0.1% in the simvastatin group. The incidence of rhabdomyolysis was very low in the 2 groups.

In conclusion, in patients with previous myocardial infarction, intensive treatment to reduce LDL-C did not result in a significant reduction in the primary endpoint of the study, the major coronary events rate. However, it was effective in reducing the risk of other secondary endpoints and the incidence of non-fatal myocardial reinfarction. No differences were found in cardiovascular or all-cause mortality. Patients with myocardial infarction can benefit from more intensive lowering of LDL-C levels, without increasing non-cardiovascular mortality or other serious side effects.

The definitive results of this study have already been published.[4]

Secondary Prevention of Macrovascular Events in Patients With Diabetes Mellitus Type 2: the PROactive Study (Prospective Pioglitazone Clinical Trial in Macrovascular Events)

Presented by Erland Erdmann, University of Cologne, Germany

Patients with type 2 diabetes mellitus present a high risk of fatal and non-fatal myocardial infarction, and stroke. There is indirect evidence indicating that PPAR-gamma agonists (peroxisome proliferator-activated receptor gamma) could reduce macrovascular complications. The aim of the PROactive study was to study if pioglitazone reduces cardiovascular morbidity and mortality in high-risk type 2 diabetes mellitus patients.

It was designed as a prospective, randomized, placebo-controlled study of 5238 patients with type 2 diabetes who presented signs of macrovascular disease. Patients were selected from primary care centers and hospitals. They received oral pioglitazone, titrated from 15 to 45 mg (n=2605), or placebo (n=2633), together with their normal hypoglycemia medication. The primary endpoint was all-cause mortality, acute non-fatal myocardial infarction (including its silent form), stroke, acute coronary syndrome, revascularization procedures in the coronary or leg arteries, or amputation above the ankle. The analysis was carried out by intention to treat.

Two patients were lost to follow-up but were included in the analysis. The mean observation time was 34.5 months. A total of 514 patients in the pioglitazone group and 572 in the placebo group had at least one event from the composite endpoint (HR=0.90; 95% CI, 0.80-1.02; *P*=.095). The main secondary endpoint was all-cause mortality, non-fatal myocardial infarction and stroke. This was observed in 301 patients in the pioglitazone group and 358 in the placebo group (HR=0.84; 95% CI, 0.72-0.98; *P*=.027). Pioglitazone was safe and well-tolerated, with no identifiable change in its safety profile. No between-group differences were found in the hospital admission rate or in mortality due to heart failure.

In conclusion, pioglitazone reduces the composite rate of all-cause mortality, non-fatal myocardial infarction or stroke in type 2 diabetes mellitus patients who have a high risk of macrovascular events.

The definitive results of this study have been already published.[5]

Treatment of Hypercholesterolemia in a Primary Prevention Group of Adult Japanese (MEGA Study)

Presented by Haruo Nakamura, Mitsukoshi Health and Welfare Foundation, Tokyo, Japan

The aim of the MEGA study was to assess the effect of low-dose pravastatin on primary prevention of ischemic heart disease in hypercholesterolemic Japanese patients, in the first large-scale study done in this population.

The study included male patients and post-menopausal women between 40 and 70 years old with hypercholesterolemia (total cholesterol, 220-270 mg/dL), without a previous history of ischemic heart disease. The patients were randomized to receive diet or diet plus pravastatin (10 mg/day) in a prospective, randomized, open-label, blinded-endpoint trial. It had a planned follow-up time of 5 years. The patients who agreed to extend the study were followed up until the end of March 2004. Results were analyzed at the end of 5 years and at the conclusion of the study. The primary endpoint was the diagnosis of ischemic heart disease. The secondary endpoints were incidence of ischemic heart disease plus stroke and all-cause mortality.

The results of a total of 7832 patients were analyzed on an intention-to-treat basis (diet group: 3966 patients, mean age 58.4 years, 68.5% women; diet plus pravastatin group: 3866 patients, mean age 58.3 years, 68.2% women). Mean follow-up time was 5.3 years. Total cholesterol levels decreased by 2.1% and 11.5% in the 2 groups, respectively, and LDL-C levels decreased by 3.2% and 18.0%, respectively. The incidence of ischemic heart disease was significantly smaller in the pravastatin group (3.3/1000 vs 5.0/1000 person years; HR=0,67; 95% CI, 0.49-0.91; *P*=.01). No differences in benefit were found by gender. Regarding side effects, the incidence of ischemic heart disease or stroke was significantly smaller in the pravastatin group (HR=0,70; 95% CI, 0.54-0.90; *P*=.005). The incidence of stroke and mortality was reduced by pravastatin by 17.0% and 28.5%, respectively, but these differences did not reach statistical significance. Even though the results of the analysis at 5 years and at the end of the extended study were similar, treatment with pravastatin was beneficial at 5 years in reducing the stroke and total mortality rate (HR=0.66 and 0,68; *P*=.034 and *P*=.048, respectively). No clinically significant differences were found between groups in the incidence of adverse drug effects or cancer.

In conclusion, low doses of pravastatin significantly reduce the risk of ischemic heart disease and ischemic heart disease plus stroke in hypercholesterolemic Japanese patients, without no observed differences in benefit between sexes.

The design and baseline characteristics of the population included in this study have been previously published.[6]

ARRHYTHMIA

The ACTIVE-W Study (Atrial Fibrillation Clopidrogrel Trial With Irbesartan for Prevention of Vascular Events)

Presented by Stuart J. Connolly, McMaster University, Hamilton, Canada

Atrial fibrillation is the most common arrhythmia and is frequently associated with serious complications. Furthermore, hypertension is the cardiovascular comorbidity that is more frequently associated with the development of atrial fibrillation. Antithrombotic treatment with dicoumarin has been proven to reduce the risk of complications due to cardiac embolism by 66%. However, patients frequently have some contraindication for oral anticoagulation therapy and is used less often in clinical practice. Combined clopidogrel and aspirin has proven to be effective in reducing the rate of vascular events in a large number of high-risk patients. Furthermore, irbesartan is an angiotensin receptor antagonist that has proven effective in lowering blood pressure and that offers other protective effects.

The ACTIVE program evaluated the efficacy of combined clopidogrel and aspirin for the prevention of vascular events in patients with atrial fibrillation. It consisted of interrelated clinical trials, ACTIVE-W, ACTIVE-A, and ACTIVE-I. The ACTIVE-W study was a clinical noninferiority trial of clopidogrel plus aspirin versus warfarin in patients with atrial fibrillation and, at least, 1 risk factor for stroke. The ACTIVE-A study is a double-blind, placebo-controlled study investigating the usefulness of clopidogrel in patients with atrial fibrillation and at least 1 risk factor for stroke, who received aspirin due to contraindications or intolerance to oral anticoagulants. The ACTIVE-I study is a 2×2 factorial design, double-blind, placebo-controlled trial investigating the usefulness of irbesartan in patients participating in some of the previous studies, who do not require angiotensin II receptor inhibitors and who have a systolic blood pressure of at least 110 mm Hg. The primary endpoint of these studies is to evaluate the incidence of vascular events, defined as the incidence of stroke, embolism, myocardial infarction, or cardiovascular death. More than 14 000 patients were included, 6500 of them in the ACTIVE-W study.

The study ACTIVE-W was terminated early after approximately 2-years follow-up when the superiority of warfarin treatment was demonstrated vs combined clopidogrel-aspirin. Thus, the incidence of events was 5.64% per year in the combined-drug group versus 3.63% in the warfarin group (*P*=.0002; relative risk [RR] =1.45). The incidence of bleeding was similar in the 2 groups (2.4% vs 2.2%, clopidogrel-aspirin group and warfarin group, respectively; *P*=.67).

Later subanalyses demonstrated that these difference were due to greater differences in the incidence of cardiovascular events in the patients who had been receiving warfarin treatment previously before its inclusion in the study (approximately 75% of the sample; RR=1.5; *P*=.0006). In contrast, the patients who had not been receiving anticoagulants previously presented a smaller difference in the rate of events depending on the type of antithrombotic treatment administered (RR=1.32; *P*=.17).

INTERVENTIONAL/SURGICAL CARDIOLOGY

Early Hospital Discharge After PTCA Via Transradial Coronary Stenting With Single-Bolus Abciximab: the EASY Study Results at 6 Months

Presented by Olivier F. Bertrand, of the Laval Hospital/Québec Heart-Lung Institute, Québec City, Canada

The clinical usefulness of continuous-perfusion abciximab treatment over 12 h has still not been fully demonstrated. Administration of a single dose of the drug would permit the early discharge of the patient on the same day as the procedure.

The EASY study was a randomized, open-label, single-center, parallel registry trial in which all patients referred for diagnostic catheterization followed by elective percutaneous transluminal coronary angioplasty (PTCA) were eligible. After transradial coronary stenting, patients were randomized to receive a bolus of the drug (not followed by perfusion of the drug in patients who could be discharged 4-6 h after the procedure) or to receive a bolus followed by perfusion for 12 h and discharge the next day. Creatine kinase

(CK), CK-MB isoenzyme (CK-MB), and troponin T levels were measured in all the patients, with clinical and electrocardiographic follow-up at 30 days and 6 months. The primary clinical endpoint was the composite of death, myocardial infarction, need for urgent revascularization, repeat hospitalization, major bleeding, access site complications or thrombocytopenia 30 days after the procedure. The secondary clinical endpoint was death, myocardial infarction or repeat revascularization at the 30 days and 6 months.

Some 1005 patients were randomized and 343 patients were included in the registry. At 30 days, the primary endpoint was reached in 13.9% of patients in the bolus group and in 11.8% of the patients receiving bolus and perfusion (*P*=.35). The secondary endpoint was reached in 1.4% of the bolus group and in 1.6% of the bolus plus perfusion group (*P*=.8). No deaths were recorded. Of the 504 patients assigned to the bolus group, 88% were discharged on the same day. At 6 months, the incidence of death, myocardial infarction and/or target vessel revascularization was 5.7% in the bolus group and 5.4% in the bolus plus perfusion group. Both randomized groups had a lower 30-day and 6-month event rate than the patients included in the registry (12.2% at 30 days and 21.3% at 6 months; *P*<.0001 for both groups).

In conclusion, at 30 days, the clinical results of abciximab infusion in bolus complement the results of drug perfusion for 12 h, after transradial coronary stenting. This enables early discharge in a broad group of patients with favorable results persisting at 6 months.

Safety and Efficacy of Edifoligide for Prevention of Vein Graft Failure in 3014 Patients Following Coronary Artery Bypass Graft Surgery. Preliminary Results of the PREVENT IV Randomized Clinical Trial

Presented by John H. Alexander, Duke University Medical Center, Durham, NC, United States

Vein graft failure following coronary artery bypass graft (CABG) surgery may be due to neointimal hyperplasia and is the main long-term limitation of surgical revascularization. Edifoligide (Corgentech, Inc.) is a double-stranded oligonucleotide decoy that inhibits transcription E2F factors. The PREVENT IV study investigated the effect of edifoligide versus placebo on vein graft patency in patients undergoing surgical revascularization.

It was a phase 3, randomized, double-blind, placebo-controlled study of 3014 patients undergoing primary CABG in whom at least 2 saphenous vein grafts were planned. The first 2400 patients were scheduled as a cohort referred for angiography. Vein grafts were bathed with edifoligide ex vivo for 10 min under 6 psi pressure. The primary endpoint was per patient death or stenosis ≥75% in at least 1 graft measured via quantitative angiography at 12-18 months after revascularization. The long-term follow-up phase (5 years) of major clinical events (death, acute myocardial infarction, or need for revascularization due to vein graft failure) is still in progress.

Of the 2400 patients in the angiography cohort, data were available for the primary endpoint in 80% (91 deaths and 1829 patients with quantitative angiography). Baseline characteristics were representative of the population currently undergoing surgical revascularization and is similar to those of the Society of Thoracic Surgeons National Cardiovascular Database registry: 64±57 years old, 79% males, 38% diabetic, left ventricle ejection fraction 50%, 21% off-pump, 92% internal mammary artery grafts, and 2.4 vein grafts per patient. The primary end point was reached in 436/965 (45.2%) in the treatment group and in 442/955 (46.3%) in the placebo group (*P*=.66). No differences were found in any secondary event or in the rate of secondary events between the 2 groups.

In conclusion, failure in at least one vein graft is very frequent within 12 to 18 months after surgery. Edifoligide is safe and well-tolerated, but no more effective than placebo in the prevention of vein graft stenosis. Long-term follow-up is required, as well as more research, to shed light on mechanisms of the vein graft failure and to improve the durability of this type of surgical revascularization.

The definitive and complete results of this study have been already published.[7]

Javier Bermejo,[a] Javier Segovia,[a] and Fernando Alfonso[b]

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