Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (New Orleans, USA, November 7-10, 2004)

Clinical studies of particular interest were chosen for presentation during the 2004 Scientific Sessions of the American Heart Association. These studies were selected for their importance and their findings were presented orally. The abstracts of the communications have been published in electronic format. The objectives, methods and findings of these studies, as presented in these special sessions, are briefly described. Given that most of these studies have not yet been published as an original article, the information presented here should be considered preliminary.

HEART FAILURE

Clinical Evaluation of the Corcap Cardiac Support Device in Patients With Dilated Cardiomyopathy

Presented by Douglas L. Mann, DeBakey Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas, USA

Progressive left-ventricular remodeling is one of the main adverse effects in the natural course of patients with heart failure. The "Corcap" cardiac support device, which is still under investigation, consists of a mesh that is surgically implanted around the heart to lower wall stress. It is the first device designed specifically to treat ventricular remodeling. Preliminary studies have shown that the device is safe and that its use is associated with structural improvement of the left ventricle (LV) and decreased symptoms.

The present multicenter prospective study included 300 patients with New York Heart Association (NYHA) class III-IV congestive heart failure (CHF), secondary to dilated cardiomyopathy. Of these, 193 patients were randomized to either mitral valve replacement (MVR) alone or MVR and device implantation. Another group of 107 patients were randomized to continue medical treatment alone or undergo, in addition, device implantation. Follow up lasted 12 months after the inclusion of the last patient. Median follow up time was 22 months.

The primary endpoint was a composite of death, major cardiac procedures indicative of progression of CHF (transplant, implantation of mechanical assist device or need for further mitral valve surgery), or a change in NYHA functional class. In the group of patients randomized to receive the device, 38% improved their functional class compared to 27% in the control group. Moreover, in the group who received the device, the functional class deteriorated in fewer patients than in the control group (37% vs 45%; odds ratio [OR]=1.73 in favor of the group treated with the device).

A significant reduction was also seen in the number of surgical procedures indicative of progression of CHF in patients who received the device in comparison with control subjects (19% vs 33%; *P*=.01). In addition, a larger decrease in LV end-diastolic and end-systolic volume was found (*P*=.009 and *P*=.017, respectively) in the groups who received the device, as well as a larger reduction in the LV sphericity index. The quality of life scores for patients assigned to the device also showed greater improvement.

Despite the benefit observed for the composite primary endpoint in the group treated with the device, no differences were seen between the 2 groups in mortality or functional class after therapy. Likewise, no differences were found in the number of admissions to hospital or the length of stay in hospital for CHF. Adverse effects were re-

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ported in 118 control patients and 120 patients who received the device. No adverse events related to device implantation or indicative of restrictive pericardial disease were reported.

In conclusion, patients with advanced heart failure who are symptomatic despite receiving optimal medical treatment may benefit from a cardiac support device of this type because it seems to improve natural course of the disease. This finding is supported by the improvement in the size and shape of the LV, functional capacity and quality of life, and a need for fewer surgical procedures.

Long-Term Impact of a Strategy of Specific Disease Management in a Broad and Diverse Population of Patients With Heart Failure

Presented by Gregory Freeman, University of Texas Health Science Center, San Antonio, Texas, USA

"Specific disease management" has been proposed as a useful strategy for reducing the number of admissions to hospital for patients with congestive heart failure (CHF). The aim of specific disease management programs is to improve prognosis at the same time as lowering health costs. Researchers do not know the long-term impact of this type of intervention on a large scale in populations of patients with CHF, thus a randomized controlled study of specific disease management by telephone was done in a group of 1069 patients with systolic and diastolic CHF (mean age, 70.9 years), confirmed by echocardiography. Follow up lasted 18 months.

Patients were randomized in a ratio of 2:1 to disease management and control groups, respectively. The disease management group was attended by a specialist disease manager, who was responsible for educating the patient and adjusting pharmacological treatment in conjunction with the primary care physician. All patients assigned to the disease management group were given bathroom scales to monitor their weight. Furthermore, patients in the disease management group were randomized a second time and half the patients received devices, including electronic sphygmomanometers and pulse oximeters, for use at home. Patients who underwent disease management were analyzed according to these 2 subgroups. An echocardiogram was done on inclusion and after 18 months, and a follow up visit was scheduled every 6 months. These visits included a medical history, a physical examination, a 6-minute walk test and biochemical laboratory tests.

A significant reduction in mortality was found in the disease management group (*P*=.037), who survived a mean of 76 days longer than the control group. The subgroup analysis showed the benefit of disease management in patients with systolic CHF in worse functional classes (risk ratio, 0.62; *P*=.04). No differences in survival or event-free survival were observed between the 2 groups of patient with diastolic CHF. Improvement in functional class was more frequent in the disease management group, but no differences were observed in the 6-minute tests, though data were only available for 217 patients.

In 92% of the patients, complete data were obtained for use of health resources. The findings showed no overall differences between groups, whether specifically with regard to drug use, the number of scheduled visits, emergency room visits, admissions to hospital, or with regard to the number of procedures. Similarly, no differences were seen between groups with respect to the overall health cost.

In conclusion, although specific disease management leads to a reduction in mortality of patients with CHF, particularly among those with functional class III-IV heart failure, the extension to broad unselected populations with CHF does not necessarily reduce health costs.

Evaluation of the Effectiveness of Pulmonary Artery Catheterization in Patients With Congestive Heart Failure (ESCAPE: Evaluation Study of Congestive heArt failure and Pulmonary artery cathEterization)

Presented by Monica R. Shah and Lynne W. Stevenson, of the Columbia University Medical Center, New York City, New York, and the Cardiomyopathy/Heart Failure Program, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Recent studies have suggested that the systematic use of pulmonary artery catheterization (PAC) may increase hospital mortality. In contrast, nonrandomized studies in patients with congestive heart failure (CHF) suggest that PAC may improve symptoms and quality of life and reduce the number of admissions to hospital.

The ESCAPE study was a multicenter, randomized, controlled study financed by the National Heart, Lung and Blood Institute of the United States. A total of 433 patients with recurrent episodes of severe CHF were enrolled from 26 hospitals throughout the United States of America. The

patients included were adjudged by the investigators to have sufficiently severe disease to justify the procedure, but were considered sufficiently stable so as not to require emergency PAC. Therefore, patients who were admitted to hospital with signs and symptoms of congestion, those who had received intensive diuretic treatment as outpatients, those who had been admitted to hospital, or those who had attended an emergency room in the previous 6 months were included. Patients were randomly assigned to receive treatment guided by PAC monitoring and clinical assessment or by clinical assessment alone. Other key inclusion criteria were ejection fraction below 30%, systolic blood pressure below 125 mm Hg and CHF symptoms during the last 3 months despite treatment with angiotensin converting enzyme inhibitors and diuretics.

Treatment in both study groups aimed to reduce clinical congestion, with the goal of reaching pulmonary capillary wedge pressure (PCWP) in the right ventricle of 15 mm Hg and right atrial pressure of 8 mm Hg. The protocol did not specify treatments, but the use of inotropic agents was avoided if possible. The primary endpoint was the number of days of life without need for hospitalization over a 6-month period. Secondary endpoints included time to death or readmission to hospital, exercise tolerance and quality of life. The quality of life was determined by specific questionnaires and, moreover, included the self-assessment question "If you had 24 months to live in your current state of health, how many months would you trade in order to live the remaining time in good health?"

In patients assigned to PAC, the treatment goals were reached. Pulmonary capillary wedge pressure decreased from 25 mm Hg to 17 mm Hg and right atrial pressure from 14 mm Hg to 10 mm Hg. The use of PAC did not affect the primary treatment outcome (hazard ratio [HR]=1.0) or the endpoints of time to death or hospitalization or days in hospital. The use of inotropic agents (44% in the PAC group vs 39% in the control group) did not have any effect on the primary outcome. Complications associated with PAC were observed in 4.2% of the patients assigned to the procedure versus 0.5% of the patients randomized to receive clinical treatment alone (P=.01), without any deaths related to PAC being reported. The quality of life and exercise outcomes improved in both groups, with a tendency towards greater improvement in patients assigned to PAC. Significant differences were found for the response to the specific question about "months to trade." At the time of inclusion in the study, patients were prepared to trade 9 months on average to live the rest of their lives in their current state of health. At all times after randomization when the question was repeated, the patients in the PAC group had twice the improvement in this outcome compared to those who did not undergo the procedure.

In conclusion, the use of PAC to reduce PCWP without any established therapy did not have any impact on mortality or hospitalization. Therefore, the systematic use of this technique in patients admitted with recurrent CHF was not indicated, but it might result in an improvement in functional capacity as perceived by the patients themselves. Given that the safety of the procedure was demonstrated because the number of days of life without further admission to hospital was the same for the PAC group and the control group, it seems reasonable to use PAC to guide treatment in patients with persistent symptoms of CHF. Finally, patients with CHF are prepared to trade life expectancy for better health.

Study of Heart Failure in African Americans (A-HeFT: African-American Heart Failure Trial)

Presented by Anne L. Taylor, MD, Minnesota Medical School, Minneapolis, MN, USA

This study has now been published in full.[1]

ISCHEMIC HEART DISEASE

Impact of a Simplified Regimen of Low-Molecular Weight Heparin (Reviparin) in the Prevention of Mortality and Reinfarction or Stroke in More Than 15 500 Patients With ST Segment Elevation Acute Myocardial Infarction (CREATE: Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation)

Presented by Salim Yusuf, Population Health Research Institute, McMaster University, Hamilton, Canada

The CREATE study forms part of a large-scale study, CREATE-ECLA, designed to assess whether rivaparin is beneficial in patients with acute myocardial infarction (AMI). The studies that showed the benefit of administration of heparin after AMI in terms of reduced mortality were done before thrombolytic treatment and aspirin were used systematically. Since then, no large-scale clinical trial has been done to evaluate the efficacy of treatment with low-molecular weight heparin.

In the CREATE study, 7780 patients were randomized during the first 12 hours after the onset of pain to receive rivaparin 2 times a day for 7 days, and 7790 patients were randomized to receive placebo. The mean age was 59 years, 76.5% were men and 99% had elevated ST segment. The primary endpoint was a composite of all-cause mortality, reinfarction and ischemia refractory to treatment 7 days after inclusion. The secondary endpoints were death, reinfarction, stroke or bleeding complications within 30 days.

The primary endpoint was found to be significantly reduced in patients who received the drug—9.6% for the treatment group compared to 10.9% for the placebo group (HR=0.87; *P*=.006). After 30 days, the benefits of rivaparin persisted, with 11.8% of treated patients reaching the secondary endpoint versus 13.6% of the patient in the control group (*P*=.001). When the endpoints were analyzed individually, all-cause mortality after 30 days was 11.3% in the placebo group compared to 9.8% in the treatment group (HR=0.87; *P*=.005), and the rate of reinfarction was 2.6% in the placebo group and 2.0% in the treatment group (HR=0.77%; *P*=.014). No differences were observed in the incidence of stroke between the 2 groups.

An increase in the incidence of serious bleeding that was not included in the primary study endpoint was reported in 0.2% of the treated patients versus 0.1% in the placebo group (*P*=.07). This increase in risk was small (2 cases for every 1000 patients) and, in any case, was lower than the benefit observed for the primary endpoints (17/1000 patients) and for mortality (15/1000 patients).

The benefit of the drug was greater the sooner after the onset of symptoms that treatment started. The HR was 0.70 for patients treated in the first 2 hours; 0.81 for those treated between 2 and 4 hours after onset; 0.85 for those treated between 4 and 8 hours after onset, and 1.06 for those treated after more than 8 hours.

Impact of Infusion of Glucose-Insulin-Potassium on Mortality and Morbidity in More than 20 000 Patients With Acute Myocardial Infarction (CREATE-ECLA International Study)

Presented by Shamir R. Mehta, McMaster University, Hamilton Health Sciences, Hamilton, Canada

The objective of this study was to investigate whether an intravenous infusion of glucose, insulin and potassium (GIK) administered during the acute phase reduced the mortality from acute myocardial infarction (AMI) when compared to normal treatment. The investigators also assessed whether GIK could provide a low cost treatment that would be of use in developing countries with limited health budgets, given that more than 80% of the cases of AMI in the world occur in such countries. In previous small studies, GIK has been shown to improve ventricular function and reduce free fatty acids and ventricular arrhythmias after AMI, and to reduce mortality by 18%.

In the present study, 20 201 patients with ST segment elevation AMI admitted to hospital within 12 hours of the onset of pain were included. A total of 518 centers in 21 countries participated in the study. All patients received the usual treatment of reperfusion, thrombolytics and aspirin. Half the patients were randomized to receive a solution of 25% glucose, 50 U/L of insulin and 80 mEq/L of potassium at a dose of 1.5 mL/kg/h for 24 hours. The other half acted as the control group. The mean age of patients was 58.6 years and 77.8% were men. Both groups had similar baseline characteristics. Beta-blockers were taken by 70% of the patients, lipid-lowering agents by 67%, angiotensin converting enzyme inhibitors by 72%, and reperfusion therapy by 82.8%.

The primary study endpoint was all-cause mortality after 30 days and the secondary endpoints were cardiac arrest, cardiogenic shock and reinfarction after 7 and 30 days. The study was designed to detect a decrease of 15% in the relative risk with a power of 95%, assuming 10% mortality after 30 days.

However, the investigators did not find any difference in mortality after 30 days between the treatment group and the control group. Overall all-cause mortality was 10% in the GIK group and 9.7% in the control group, cardiac arrest was reported in 1.4% versus 1.5%, cardiogenic shock in 6.6% versus 6.3%, and reinfarction in 2.3% versus 2.4%, respectively. Differences were found in the rates of recurrent ischemia—5.6% in the treatment group versus 6.5% in the control group (*P*=.004), but this was not the primary endpoint of the study. Likewise, no differences were found for diabetic patients, patients with heart failure or those who received fibrinolytic treatment or underwent percutaneous revascularization in the subgroup analyses. A significant reduction in mortality was observed in patients who received revascularization therapy of any type, but this finding should be interpreted with caution because this analysis was not prospectively defined.

Effects of Angiotensin Converting Enzyme Inhibitors in Patients With Stable Coronary Heart Disease (PEACE Study: Prevention of Events With Angiotensin-Converting Enzyme Inhibition study)

Presented by Marc A. Pfeffer, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA

This study has now been published in full.[2]

PRIMARY AND SECONDARY PREVENTION

Study of the Effects of Beta-Blockers on Glycemic Control in Diabetic Patients (GEMINI Study: Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives)

Presented by George Bakris, Hypertension/Clinical Research Center, Rush University Medical Center, Chicago, Illinois, USA

Although conventional beta-blockers are known to lower blood pressure (BP) and reduce cardiovascular risk in patients with hypertension and type-2 diabetes, these drugs are often not used because glycemic and metabolic control has been shown to deteriorate. In previous studies, metoprolol was associated with deterioration of insulin resistance, whereas carvedilol, which has associated antioxidant and alpha-1 blocking activity, has been shown to improve insulin sensitivity. The objective of the GEMINI study is to compare the effect on glycemic and metabolic control of these 2 agents with different pharmacological profiles in hypertensive patients with type-2 diabetes mellitus. Furthermore, the effect of 2 drugs on cardiovascular risk factors was compared.

The GEMINI study was conducted in 205 centers and included 1235 patients with controlled type-2 diabetes (baseline HbA_{1c}: 6.5%-8.5%) and stage 1 or 2 hypertension, who were already receiving treatment with a renin-angiotensin system blocker. The patients were randomized to receive carvedilol 6.25-25 mg or metoprolol 50-200 mg, taken twice a day, and followed for 35 weeks. If necessary, 12.5 mg of hydrochlorothiazide and a dihydropyridine calcium antagonist could be added in either group to reach the BP treatment goal of less than 130/80 mm Hg. The primary endpoint was the difference between the 2 groups with respect to change in HbA_{1c} from baseline after 5 months of sustained treatment. Moreover, the effect of treatment on BP, insulin sensitivity estimated by the homeostatic model (HOMA-IR) and microalbuminuria was also assessed.

Levels of HbA_{1c} increased significantly (0.15%; $P<.001$) in patients in the metoprolol group but remained unchanged in the carvedilol group (0.02%; $P=.65$). An increase in HbA_{1c} of more than 1% was observed in 14.2% of the patients in the metoprolol group (which was associated with an increase in risk of cardiovascular events) compared to 7% of the patients who received carvedilol ($P<.001$). Insulin sensitivity, estimated by HOMA-IR, improved with carvedilol (–9.1%; $P=.004$), but remained unchanged with metoprolol (–2.0%; $P=.48$). In the metoprolol group, 2.2% of the patients abandoned the study because of deterioration in glycemic control compared to 0.6% of the patients who received carvedilol ($P=.04$). The BP levels attained were similar in both groups, and approximately two-thirds of the patients in each group reached the target BP of less than 130/80 mm Hg. The mean doses required to reach this goal were 17.5 mg/twice a day of carvedilol and 128 mg/twice a day of metoprolol. In the metoprolol group, it was often necessary to limit the dose because of the appearance of bradycardia. The mean treatment duration was also shorter in the group treated with metoprolol because of a greater rate of treatment interruption due to adverse effects.

In the group that received carvedilol, the decrease in the ratio of albumin to creatinine was 16% larger than in the one that received metoprolol ($P=.003$). At the time of inclusion in the study, 80% of the patients did not have microalbuminuria. In these patients, the risk of presenting albuminuria decreased by 47% with carvedilol (6.6%) compared to metoprolol (11.1%) ($P=.03$). Weight gain was reported in the metoprolol group but not in the carvedilol group.

In conclusion, unlike metoprolol, carvedilol has a neutral effect on glycemic control and improves several components of the metabolic syndrome in hypertensive patients with type-2 diabetes mellitus as concomitant treatment with renin-angiotensin system blockers.

Effect of Rimonabant on Weight Loss and Maintaining Weight Loss: (RIO-NA study: RIO North American Study)

Presented by F. Xavier Pi-Sunyer, Department of Endocrinology, Diabetes and Nutrition, St. Luke's Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, USA

Rimonabant is the first selective type-1 cannabinoid receptor antagonist to be developed for control

of cardiovascular risk factors such as obesity and smoking. Patients showed a significant weight loss in 2 recently completed studies carried out in obese patients or overweight patients with untreated dyslipidemia (RIO-Lipids), with or without associated comorbidity (RIO-EU). Beneficial effects on the lipid profile and glycemic control were also seen. Moreover, the safety profile of the drug was confirmed to be favorable.

Seventy-two centers in North America participated in the randomized, double-blind, placebo-controlled, 2-parallel group RIO-NA study, in which 2 rimonabant treatment regimens (5 and 20 mg once a day) were compared with placebo in 3040 patients who had been prescribed a mild hypocaloric diet (to decrease calorie intake by 600 kcal). To participate in the study, patients had to have a body mass index (BMI) greater than 30 kg/m^2, or 27 kg/m^2 if associated with comorbidity. The primary endpoints were the following: *a)* change in weight during the first year, and *b)* prevention of weight gain after randomization (second year). The study endpoints also included the expected changes in cardiovascular risk factors associated with abdominal fat (measured by waist circumference), dyslipidemia, glucose metabolism, and metabolic syndrome.

The patients were randomized to receive placebo, rimonabant 5 mg or rimonabant 20 mg for 52 weeks in double-blind conditions. After the first year, the patients who received the drug were once again randomized to receive the same doses of the drug or placebo for the next 52 weeks. Of the patients who completed the study, the decrease in waist circumference after the first year was 3.9 cm in the placebo group, 4.7 cm in the group treated with 5 mg of the drug and 8.2 cm in the group treated with 20 mg ($P<.001$ vs placebo). After 2 years, the waist circumference of the patients treated with the drug decreased by 8 cm in the 20 mg group versus 4.9 cm in the 5 mg group and 3.8 cm in the placebo group ($P<.0001$).

In the group who received 20 mg a day of rimonabant for 2 years, 62.5% of the patients lost more than 5% of their initial weight compared to 36.7% of those who received the low dose and 33.2% of those who received placebo ($P<.001$). During the same period, 32.8% patients reduced their initial weight by more than 10% in the 20 mg dose group, compared to 20% for the 5 mg dose group and 16.4% for the placebo group.

Over the 2-year period, the levels of cholesterol bound to high-density lipoproteins (HDL-C) increased 24.5% in the group who received 20 mg of rimonabant, 15.6% in the low dose group and 13.8% in the placebo group ($P<.0001$). Triglycerides were reduced in the same groups by 9.9%, 5.9%, and 1.6%, respectively ($P<.05$). At the time of inclusion in the study, 34.8% of the patients who received the 20 mg dose met the criteria defining metabolic syndrome. At the end of the study, this percentage had decreased to 22.5% ($P<.0001$). No significant differences were seen among the 3 groups in the proportion of patients with serious adverse reactions or interruptions in treatment. Likewise, no differences were seen on depression scales.

In conclusion, the results of the RIO-NA study agree with previous studies done with the drug, that is, treatment with rimonabant leads to a significant decrease in waist circumference, significant weight loss and an improved metabolic profile. The efficacy observed in the first year was retained in the second year, and the drug has a good safety profile.

Comparison of the Effects on Lipids and Glucose Metabolism of Pioglitazone and Rosiglitazone in Patients With Type-2 Diabetes and Dyslipidemia

Presented by Ronald B. Goldberg, Professor of Medicine, University of Miami School of Medicine, Miami, Florida, USA

Pioglitazone (PIO) and rosiglitazone (ROSI), both members of the thiazolidinedione group of drugs, have been shown to be effective for controlling blood glucose in type-2 diabetic patients through an improvement in insulin sensitivity. Furthermore, both drugs have effects on the lipid profile although some uncontrolled studies have shown that these effects are different for PIO and ROSI.

The objective was to compare the effect on lipids of PIO and ROSI in a big, multicenter, randomized, placebo-controlled study of patients with type-2 diabetes (defined according to the criteria of the World Health Organization) and associated dyslipidemia, defined as fasting triglyceride levels of 150-600 mg/dL and fasting levels of cholesterol bound to low density lipoproteins (LDL-C) less than or equal to 130 mg/dL.

A total of 735 patients were randomized, 25% of whom had been previously treated with diet alone and 25% with a drug for glycemic control. After a washout period of 4 weeks, 363 patients were randomized to receive PIO 30 mg once a day and 356 patients to receive ROSI 4 mg once a day. After 12 weeks, the medication was titrated to a maximum of 45 mg/day for PIO and 4 mg/day for ROSI, and treatment continued for a further 12 weeks. Patients were

forbidden from taking any other lipid-lowering medication.

Both drugs showed a similar effect on HbA_{1c}—the fasting levels of which had changed by –0.7% for PIO and by –0.6% for ROSI at week 24. However, PIO induced a mean decrease of 12% in triglycerides, compared to a mean increase of 14.9% in the group treated with ROSI. The investigators also reported a mean increase of 14.9% in HDL-C in the PIO group compared to an increase of 7.8% in the ROSI group, whereas mean LDL-C increased by 15.7% and 23.3%, respectively.

The size and concentration of LDL particles was also analyzed. Pioglitazone decreased the concentration of LDL particles by a mean of 7.8%, whereas ROSI increased the concentration by a mean of 12%. Both agents increased the size of the LDL particles.

In conclusion, these drugs have different effects on the lipid profile. Treatment with PIO leads to a significant improvement in triglycerides, high-density lipoproteins (HDL) and the concentration and size of LDL particles, compared to ROSI. More studies are needed to determine whether these beneficial effects on the lipid profile can reduce the risk of cardiovascular disease in type-2 diabetic patients.

Effect of Extended-Release Niacin on the Progression of Atherosclerosis in Secondary Prevention of Patients Treated With Statins (ARBITER-2 study)

Presented by Allen Taylor, Director of Cardiovascular Research, Walter Reed Army Medical Center, Washington, DC, USA

Statins have been shown to improve cardiovascular prognosis regardless of the baseline values of LDL-C and niacin can reduce cardiovascular morbidity and mortality when taken in association with statins or alone. However, no previous study has investigated the effect of increasing HDL-C by adding niacin to a statin treatment. The aim of this study was to analyze whether extended-release niacin could reduce atherosclerosis.

A total of 167 patients with known coronary heart disease, who had been receiving treatment with statins for a mean time of 4.8 years (mean age of the patients, 67 years), were enrolled. The subjects were randomized to receive, in addition to statin treatment, 1000 mg a day of extended-release niacin or placebo for 12 months. No differences were found between groups with respect to cardiovascular risk factors or the use of other cardiovascular drugs. All patients had HDL-C less than 45 mg/dL at the time of inclusion. The objective was to analyze the decrease in the carotid intima media thickness (CIMT) after 1 year.

The study was completed by 149 patients. Treatment compliance in the group on active treatment was 90%. Baseline CIMT was 0.884 mm and LDL levels were 89 mg/dL. These values were similar for the 2 groups. At the end of follow up, HDL-C increased 21% in the treatment group, but remained unchanged in the placebo group (P=.003).

Carotid intima media thickness increased significantly in the placebo group by 0.044 mm (P<.001), but remained unchanged in the group who received niacin. Although differences in final CIMT between the 2 groups were not significant, a subgroup analysis showed that progression in patients without insulin resistance was lower with the drug (P=.026). Moreover, a decrease of 60% in the number of cardiovascular events was observed in the treatment group, but this difference was not significant.

Therefore, adding a dose of 1000 mg of extended-release niacin to statin treatment halts the progression of atherosclerosis in patients with known coronary heart disease. It was highlighted that all patients met the criteria of the Adult Treatment Panel (ATP) III, regarding both LDL and HDL-C levels. A decrease of 67% in the rate of progression of CIMT for patients who took the drug suggests that it should be more widely used in clinical practice.

Randomized, Blinded Study of the Perioperative Use of Metoprolol Versus Placebo in Diabetic Patients Who Undergo Major Noncardiac Surgery (DPMMT Study: Diabetic Postoperative Mortality and Morbidity Trial)

Presented by Anne Benedicte Juul, Copenhagen University Hospital, Copenhage, Denmark

Perioperative myocardial ischemia is the most serious cardiac complication arising after major surgery in patients at risk of or suffering from coronary heart disease. In a previous study, perioperative administration of atenolol induced an improvement in event-free survival in patients who underwent noncardiac surgical intervention, and was associated with better survival at 2 years in diabetic patients. This observation prompted organizations such as the American Heart Association and the American College of Cardiology to recommend the use of beta-blockers during the perioperative phase in diabetic patients who were scheduled to undergo major noncardiac surgery.

The investigators themselves were responsible for managing this randomized and placebo-controlled study, in which the effect of metoprolol on cardiovascular mortality and morbidity was compared with that of placebo in diabetic patients who were not taking these drugs and who were scheduled for noncardiac surgery. The administration regimen of metoprolol was 50 mg administered the night before surgery, 100 mg administered 1 to 2 hours before surgery, followed by 100 mg a day (or 5 mg i.v. every 6 hours if the patient was unable to take oral medication). Treatment continued for up to 8 days.

A total of 921 patients were randomized to receive either metoprolol or placebo. More than half the patients included in the study underwent orthopedic or abdominal surgery. The mean duration of treatment was 4.6 days in the metoprolol group and 4.9 days in the placebo group. Mean heart rate was lower in the group assigned to receive metoprolol (72 beats/min vs 78 beats/min).

The primary endpoint (a composite of all-cause mortality, acute myocardial infarction, unstable angina and congestive heart failure) was reached in 21% of treated patients and in 20% of those in the placebo group. The Cox survival analysis, adjusted for age, sex, history of coronary heart disease, and malignant disease, showed a risk ratio of 1.10 in the treatment group (P=.53). The mortality rate was 16% in both groups.

In conclusion, brief perioperative treatment with metoprolol did not have any effect on mortality and morbidity or on adverse effects in diabetic patients who underwent major surgery, but the confidence intervals for the effects were wide. There was no evidence to recommend perioperative treatment with beta-blockers just because the patients scheduled for major noncardiac heart surgery have diabetes mellitus. The dose, duration, type of drug, and type of surgery should be investigated in subsequent studies.

ARRHYTHMIAS

Evaluation of Syncope in Emergency Rooms (SEEDS: Syncope Evaluation in the Emergency Department Study)

Presented by Win K. Shen, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Patients who visit the emergency room due to syncope often require admission to hospital to study the cause. The difficulty in establishing the cause of the episode in the emergency room and the concern about arrhythmias has led to a liberal policy towards the admission of these patients to hospital for study of their syncope. However, it is not known whether this policy is accompanied by improved prognosis for these patients. The main hypothesis of the SEEDS was that a specific unit within the emergency room could improve the diagnostic yield and lower the rate of hospital admissions among patients who had an intermediate prognosis of cardiovascular events. The primary objective was therefore to test this hypothesis.

This was a prospective, randomized, single-center study, in which standard care and that offered by a specialized unit within the emergency room in the study of syncope was compared. This unit provided continuous electrocardiographic monitoring for 6 hours and orthostatic examination of blood pressure every hour. Similarly, the unit provided the possibility of carrying out a tilt test, massage of the carotid sinus and an electrophysiological examination. All patients included met the criteria of the American College of Emergency Physicians for admission to hospital. The primary outcome was the diagnostic yield and the rate of hospital admission on discharge from the emergency room.

Although the study was designed to include 200 patients of intermediate risk, a preliminary analysis of the first 103 showed large differences between the 2 strategies in the diagnostic yield, and so it was decided to interrupt the study. Preliminary diagnosis was established in 67% of the patients studied in the syncope unit compared to just 10% of the patients who were followed with the standard care (P<.001). The total time in hospital decreased from 140 patient-days in the standard care group to 64 patient-days in the group studied in the syncope unit. The survival free from death and survival free of recurrent syncope after 2 years were 97% and 88% for the group attended by the syncope unit, respectively, compared to 90% and 89% in the control group, respectively (P=NS).

In conclusion, the specifically designed unit significantly improved diagnostic yield and decreased the rate of admissions to hospital and the time spent in hospital, without increasing either the incidence of recurrent syncope or the mortality in patients with intermediate risk.

Analysis of the Cost-Effectiveness of Use of Implantable Cardioverter Defibrillators as Primary Prevention of Sudden Death in Patients With Heart Failure (SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial)

Presented by Daniel Mark, Director of Outcomes Research, Duke Clinical Research Institute, Durham, North Carolina, USA

The SCD-HeFT study included 2521 patients with stable functional class II and III congestive heart failure and a left-ventricular ejection fraction less than or equal to 35%. Patients were randomized

to receive an average dose of amiodarone of 300 mg, standard medical treatment or a single-chamber, shock only, implantable cardioverter defibrillator (ICD). The main findings (reported briefly in another congress) showed a benefit for ICD therapy in that all-cause mortality, the primary endpoint, decreased by 23% compared to the control group. No benefit was found for use of amiodarone. The objective of the present study was to analyze the cost-effectiveness in this population.

The cost of amiodarone was calculated with a 10% discount on the listed price and a cost of an ICD was estimated to be $17 500. This included the price of the electrode but not the cost of implantation. The health costs during a 5-year period were calculated from the clinical histories and the medical billing information, in order to include the costs of admission to hospital and those of outpatient consultations and physicians' fees according to Medicare rates. The data for the costs were modeled using empirical data, to which the costs of the subsequent device implantation were added, as well as costs associated with late complications related to the devices and the need to replace the ICD. The database of the clinical study was used to calculate the life expectancy of each patient. The cost-effectiveness of treatment with ICD was calculated as the increase in life expectancy divided by the increase in costs related to this longer survival.

The cumulative costs after 5 years were $49 443 for amiodarone, $43 078 for placebo, and $61 968 for ICD. Costs related to survival were $90 759 for placebo and $159 147 for ICD. Life expectancy in the placebo group was 8.41 years compared to 10.67 years in patients with an implanted device. Therefore, the cost of therapy with ICD was $33 192 per year of extra life and the results were reasonably robust during the entire study.

These data indicate that treatment with ICD is more effective and more expensive than amiodarone treatment, but this cost is lower than the standard cost calculated by Medicare for hemodialysis—estimated at $50 000 per year of survival. Therefore, the device can be considered to provide added economic value in the treatment of patients with class II and III heart failure.

Randomized, Placebo-Controlled Study of the Efficacy of Azimilide in Reducing Shocks From Implantable Cardioverter Defibrillators (SHIELD Study: SHock Inhibition Evaluation with azimiLiDe study)

Presented by Paul Dorian, Director, Arrythmia Service, St. Micheal's Hospital, Toronto, Canada

The objective of the study was to assess the efficacy of azimilide, a class III antiarrhythmic agent, for decreasing the number of shocks and antitachycardia pacing in patients with an implantable cardioverter defibrillator (ICD).

In the SHIELD study, 633 patients from 121 centers in 9 countries with a recently implanted ICD who had experienced severe arrhythmia in the 42 days prior to implantation or who had an ICD implanted for longer than 30 days but who had received a shock in the 180 days prior to randomization were included. The patients were randomized to receive treatment with 75 mg (n=220) or 125 mg (n=199) of azimilide, or placebo (n=214) for 1 year.

The primary endpoint of the study included the total number of shocks for any reason and the number of ventricular tachycardias (VT) terminated by antitachycardia pacing. An independent committee, blinded to the treatment received, evaluated all arrhythmic episodes and classified them as appropriate if they were secondary to VT or ventricular fibrillation, or inappropriate if they were secondary to supraventricular arrhythmias or other causes.

Over the year of the study, antitachycardia pacing or appropriate shocks were recorded in 63% of the patients treated with placebo, corresponding to 3963 events, in 61% of the patients in the group receiving 75 mg of drug (2849 events), and in 55% of the group on 125 mg of azimilide (1436 events).

A decrease of 57% (HR=0.43) was observed for the composite endpoint in the 75 mg group and of 47% (HR=0.53) in the placebo group. However, the difference in the number of all-cause shocks did not reach statistical significance in any of the intervention groups when compared to the placebo group.

The rates of interruption of treatment were similar in both groups. One patient from the placebo group, 2 from the 75 mg group and 3 from the 125 mg group had episodes of *torsade de pointes,* all of which were satisfactorily terminated by the ICD. One patient developed severe but reversible neutropenia while receiving the 125 mg dose of azimilide. The incidence of appearance or deterioration of heart failure was significantly lower in the treated patients (9% in the low dose group, 11% in the high dose group, and 16% in placebo).

These results indicate that azimilide reduces the symptoms of VT and might represent an alternative in patients with an ICD requiring additional antiarrhythmic therapy, who represent more than half of all patients with ICD.

INTERVENTIONAL CARDIOLOGY/SURGERY

Coronary Revascularization Prior to Elective Vascular Surgery Does Not Improve Prognosis (CARP Study: Coronary Artery Revascularization Prophylaxis study)

Presented by Edward McFalls, Division of Cardiology, University of Minnesota, USA

Coronary revascularization is often done before peripheral vascular surgery in order to improve the prognosis of the patients. However, no study has previously assessed the effect on long-term prognosis of this strategy, and the current guidelines of the AHA/ACC state that elective coronary angiography should not be used as a screening tool to select candidates for elective coronary revascularization.

The aim of the CARP study was to investigate whether elective coronary revascularization—either a coronary artery bypass graft or a percutaneous coronary intervention—scheduled before peripheral revascularization surgery could improve prognosis in such patients.

Of a total of 5850 patients from 18 Veterans Affairs Medical Centers in the United States, 510 were finally included in the study and randomized to receive coronary revascularization or no coronary revascularization before surgery. The indications for surgery were revascularization of the legs in 67% of the patients and abdominal aortic aneurysm in 33%. The Eagle criteria, the revised heart risk index and imaging techniques identified 74% of the patients in the study with a high risk of heart complications during surgery. All patients underwent angiography, although those who were clinically unstable were excluded. The primary endpoint was long-term survival, and the median follow up time was 2.7 years after randomization.

Percutaneous coronary interventions were performed in 59% of the patients in the treatment group and bypass surgery in the remaining 41%. The median time from randomization to surgery was 54 days in the treatment group compared to 18 days in the group with no intervention ($P<.001$). Mortality associated with coronary revascularization was 1.7%. No complications such as stroke, amputation or dialysis were reported in either of the 2 groups.

Mortality after 30 days of vascular surgery was 3.1% in the treatment group compared to 3.4% in the group with no intervention ($P=.87$). At the end of the follow up period, mortality was 22% in the coronary revascularization group compared to 23% in the group with no treatment ($P=.92$). The incidence of AMI (using elevated troponin after vascular surgery as a marker) was 11.6% and 14.3% in the groups with and without prior revascularization, respectively ($P=.37$).

These results do not support the hypothesis that elective coronary revascularization prior to peripheral vascular surgery can improve prognosis.

Rescue Angioplasty in Patients With Acute Myocardial Infarction and Failed Thrombolysis (REACT: REscue Angioplasty versus Conservative Therapy of repeat thrombolysis study)

Presented by Anthony Gershlick, University of Leicester, Leicester, United Kingdom

The main aim of the 2 therapeutic strategies currently used in acute myocardial infarction (AMI) is to restore arterial patency and normal coronary blood flow to the infarct-related artery as soon and as effectively as possible. However, 30% to 50% of patients with AMI do not obtain adequate myocardial reperfusion after thrombolysis and this is associated with poor prognosis. The studies that have previously analyzed the potential benefits of new thrombolytic treatment in this setting showed a decrease in infarct size compared to patients treated with placebo. However, it is important to remember that these studies were done with a small number of patients. Percutaneous coronary intervention (PCI) could help to improve prognosis and lower the number of complications in such patients.

The REACT study randomized patients with AMI who failed to show signs of reperfusion 90 minutes after starting thrombolytic treatment to a conservative treatment, repeat thrombolysis or rescue PCI. Although it was initially planned to include a total of 450 patients, the study was discontinued prematurely in March 2004 because of recruitment problems and budget constraints. The primary study endpoint was a composite of death, episodes of reinfarction, cerebrovascular events or severe heart failure after 6 and 12 months of follow-up. The baseline demographic characteristics were similar in the 3 treatment groups. The door-to-first thrombolytic treatment time was 27 minutes; the pain-to-first thrombolytic treatment time was 140 minutes; and the pain-to-second thrombolytic treatment time was 330 minutes. The time elapsed between the 2 thrombolytic treatments was 190 minutes, the time between onset of pain and rescue PCI was 414 minutes and the time between the first thrombolytic treatment and rescue PCI was 274 minutes, with a difference of 84 minutes between the second thrombolytic treatment and rescue PCI.

After 6 months, the primary composite endpoint was significantly lower in the group assigned to res-

cue PCI (15.3%) compared to patients assigned to conservative treatment (29.8%) and those assigned to repeat thrombolysis (31.0%) (*P*=.002). Among the components of the primary outcome, a clear tendency was noted towards lower mortality in patients assigned to treatment with rescue PCI—9% in the rescue PCI group compared to 18% in the other 2 groups. All severe bleeding was related to the site of vascular access, and the incidence of such complications was significantly greater among patients assigned to rescue PCI (18.7% vs 4.9% in the conservative treatment group and 2.1% in the repeat thrombolysis group).

In conclusion, the REACT study is the first trial to demonstrate the benefit of rescue PCI after failed thrombolysis. The results after 6 months show the superiority of rescue PCI versus conservative treatment or repeat thrombolysis. Therefore, rescue PCI should be considered the treatment of choice in patients who fail to show signs of reperfusion after thrombolysis.

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