SPECIAL ARTICLE

Summary of the Clinical Studies Reported in the 53rd Scientific Session of the American College of Cardiology (New Orleans, USA, 7-10 March, 2004)

SUMMARY BY TOPICS

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In the 53rd Annual Scientific Session of the American College of Cardiology, some special sessions reported on late breaking clinical trials, that is, studies of particular importance whose results have only become known recently.

The following is a summary of the oral presentations of the main data from these studies. Most of the studies have not been published in written form in full, therefore, the information presented here should be considered as preliminary.

PRIMARY AND SECONDARY PREVENTION

Effects of Atorvastatin at High Doses in Hyperlipidemic Coronary Disease (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events [ALLIANCE] Study)

Presented by Dr Donald Hunninghake, Minneapolis, USA

Decrease in serum lipids in patients with coronary heart disease (CHD) is accompanied by a decrease in cardiovascular events during follow up. The objective of this trial was to determine the optimal decrease in lipid levels.

The study, with a planned follow up of 3 years, enrolled 2442 patients with a history of CHD, defined as the presence of acute myocardial infarction (more than 3 months before inclusion in the study), coronary angioplasty (more than 6 months prior to entry), coronary surgery (more than 3 months prior to entry), or unstable angina (more than 3 months prior to entry). Patients not receiving lipid-lowering agents on enrollment into the study had to have low-density lipoprotein cholesterol (LDL-C) between 130 and 250 mg/dL (3.36 mmol/L to 6.46 mmol/L). In contrast, for those who were receiving prior treatment (two thirds of the patients finally enrolled), values had to lie between 110 and 200 mg/dL (2.84 to 5.17 mmol/L).

Patients were randomized between July 1995 and October 1998 to receive 1 of 2 treatments. One group (n=1217) received atorvastatin, starting at 10 mg/day with dose titration until either LDL-C was below 80 mg/dL (2,07 mmol/L) or a maximum dose of 80 mg/day

was reached. The other group (n=1225) received standard treatment, which was chosen freely by the patient's treating physician and could include diet, weight loss, physical activity, behavior modification and lipid-lowering treatment (including atorvastatin, which was on the market from 1997 onwards). The primary endpoint of the study was a composite of death of cardiac origin, nonfatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization or unstable angina requiring hospitalization. Patients were analyzed according to intention to treat.

Levels of LDL-C were 147 mg/dL at baseline for both groups and decreased during the study to 95 mg/dL in the atorvastatin group (who received a mean of 40.5 mg/day of study drug) and to 111 mg/dL in the standard treatment group ($P<.0001$). The percentage changes in the values of other lipid parameters for the atorvastatin and standard treatment groups were: –56% versus –36% for total cholesterol ($P<.0001$), +2% versus +2% for high density lipoprotein cholesterol (HDL-C) and –27% versus –15% for triglycerides ($P<.05$), respectively.

The primary endpoint of the study was met by 17% fewer patients in the atorvastatin group compared to the group on standard treatment ($P=.026$). The survival curves started to diverge after approximately 1 year of follow up. The incidence of nonfatal myocardial infarction was 47% lower in the atorvastatin group compared to the standard treatment group ($P<.0002$). For the remaining endpoints that formed the primary endpoint, treatment with atorvastatin did not lead to significant reductions. The rate of serious adverse events was similar in both groups (40% in the atorvastatin group and 42% in the standard treatment group). Eight patients (0.7%) in the atorvastatin group and 16 (1.3%) in the standard treatment group had elevations of the hepatic transaminases AST and ALT to more than 3 times the upper limit of normal. No cases of myopathy or rhabdomyolysis were reported during the study.

The ALLIANCE study shows that aggressive lipid-lowering treatment with atorvastatin in the study population increases the beneficial effects provided by standard treatment without increasing undesirable effects.

Effects of High Doses of Atorvastatin After Acute Coronary Syndrome (Pravastatin Or AtorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 [PROVE IT-TIMI 22] study)

Presented by Christopher P. Cannon, Boston, USA

The reduction in serum lipid levels by statins decreases the risk of cardiovascular events, but the optimal value for LDL-C is not known.

In this study, 4162 patients who had been admitted to hospital due to acute coronary syndrome in the 10 days prior to entry were enrolled. The effect of administration of 40 mg/day of pravastatin (standard treatment) was compared with 80 mg/day of atorvastatin (intensive treatment). The primary endpoint of the study was a composite of all-cause mortality, myocardial infarction, documented unstable angina requiring hospitalization, revascularization (performed more than 30 days after enrollment in the study) and stroke. The study was designed to establish noninferiority of pravastatin in comparison with atorvastatin in time-to-event survival. The follow up lasted 18 to 36 months (mean, 24 months).

The median LDL-C attained during treatment was 95 mg/dL (2.46 mmol/L) in the standard pravastatin treatment group, and 62 mg/dL (1.60 mmol/L) in the group treated with high doses of atorvastatin ($P<.001$). The rate of incidence of a primary event at 2 years estimated according to the Kaplan-Meier method was 26.3% in the pravastatin group and 22.4% in the atorvastatin group. Relative risk was therefore 16% lower for atorvastatin ($P=.005$; 95% confidence interval, 5%-26%). The study did not confirm the hypothesis of equivalence, but rather showed the superiority of the more aggressive treatment regimen.

In patients who have recently suffered acute coronary syndrome, a more aggressive lipid-lowering regimen with statins provided greater protection against death or major cardiovascular events in comparison with the standard regimen. The findings indicate that such patients benefit from early and sustained reduction of LDL-C to values substantially lower than currently recommended ones.

Efficacy of Rimonabant, a Type 1 Cannabinoid Receptor Antagonist, on Smoking Cessation (Smoking Cessation in Smokers Motivated to Quit [STRATUS-US] study)

Presented by Robert Anthenelli, Cincinnati, USA

Rimonabant, a selective antagonist of the type 1 cannabinoid receptor, improves the rate of smoking cessation and reduces weight gain associated with quitting when compared with placebo. Although approximately one third of all cases of ischemic heart disease can be attributed to smoking, many patients resist giving up smoking because of possible associated weight gain. The mechanism of this weight gain is the

absence, once the patients stop smoking, of the anorexigenic effect of nicotine mediated by overstimulation of the endocannabinoid system. The aim of the phase 3 STRATUS-US trial was to evaluate the efficacy of rimonabant at restoring the equilibrium of the endocannabinoid system after giving up smoking. Thus, the desire for nicotine or food should be avoided.

In the study, 787 patients who had not been able to give up smoking after a mean of 4 attempts were administered rimonabant at doses of 5 mg/day or 20 mg/day, or placebo. In an initial phase lasting 2 weeks, patients were allowed to continue smoking. In the second phase they were told to quit smoking entirely until completing 10 weeks of treatment, whereupon the study drug was discontinued. Abstinence from smoking was assessed 4 weeks later.

After the study had finished, among patients who had completed all phases of the study, 36.2% of those treated with 20 mg of rimonabant had given up smoking compared to 20.6% of those treated with placebo (*P*=.002). In the intention-to-treat analysis, 27.6% of the patients treated with 20 mg of rimonabant quit smoking compared to 16.1% of those on placebo (*P*=.0004). An important finding is that the patients who took 20 mg rimonabant lost 0.5 pounds (230 g) on average, whereas those who gave up smoking with placebo gained almost 2.5 pounds (1.3 kg). The weight loss with rimonabant occurred in patients who were overweight or obese, but not in those who had normal weight. Adverse effects were reported in 6.1% of the patients in the low dose group and in 6.9% of those who took 20 mg/day, compared to 4.2% in the placebo group. In general, adverse effects were mild and transitory. The most common were nausea and dizziness. Rimonabant did not affect blood pressure, heart rate or QT interval. No differences were found between active treatment groups and placebo in the findings assessing anxiety or depression.

Rimonabant, at a dose of 20 mg/day, increased the probability of smoking cessation in the group of patients studied, and it prevented weight gain associated with giving up smoking observed in the placebo group.

Effects of Rimonabant on Metabolic Syndrome (Rimonabant in Obesity Lipids [RIO-LIPIDS] study)

Presented by Jean-Pierre Després, Québec, Canada

Rimonabant is an antagonist of the type 1 cannabinoid receptor. The drug has aroused great interest because it may facilitate management of some of the most important cardiovascular risk factors such as obesity, smoking, dyslipidemia and metabolic syndrome in patient populations at risk. The aim of the RIO-LIPIDS trial is to assess the role of rimonabant in facilitating weight loss in an obese population with dyslipidemia.

A total of 1036 patients with dyslipidemia and central obesity were enrolled in the study. To be included, patients had to have a body mass index between 27 and 40 kg/m^2. Patients were assigned to 1 of 3 groups: placebo, 5 mg/day rimonabant and 20 mg/day rimonabant. They were advised to follow a moderately low calorie diet and followed up for 1 year.

At the end of follow up, patients treated with high doses of rimonabant had lost 20 pounds on average —15 pounds more than those on placebo (*P*<.001). In the group treated with rimonabant 20 mg/day, 44% of the patients treated had lost more than 10% of their body weight, whereas this endpoint was only reached by 16.3% of the patients in the group treated with the lower dose and in 10.3% of the patients in the placebo group. Moreover, the abdominal perimeter decreased by 9.1 cm, HDL-C increased by 23%, triglycerides decreased by 15%, and there was a significant decrease in small dense LDL-C particles in patients treated with 20 mg rimonabant compared to placebo. The incidence of metabolic syndrome according to the criteria of the Adult Treatment Panel III in the high-dose rimonabant group decreased by 51.9%, compared to a decrease of 25.8% in those treated with placebo. Moreover, there was a decrease of 51.9% in the incidence of type 2 diabetes in the first group, compared to a 41% reduction in the placebo group.

In the study population of obese and dyslipidemic patients, addition of rimonabant at doses of 20 mg/day to a low calorie diet increased weight loss and improved the lipid profile with respect to placebo. This regimen also contributed to a decrease in the prevalence of different components of the metabolic syndrome.

Efficacy of Ezetimibe as an Additional Treatment to Statins (Ezetimibe Add-on to Statin for Effectiveness [EASE] study)

Presented by Thomas A. Pearson, Rochester, USA

Ezetimibe is the first of a new class of drugs that selectively inhibits absorption of cholesterol in the small intestine. It can be added to statin therapy to

enhance efficacy, thus helping patients to reach the cholesterol treatment goals recommended by clinical guidelines.

The EASE study was designed to assess the efficacy and safety of 10 mg of ezetimibe compared to placebo when associated with a statin therapy that had not led to attainment of the cholesterol goals recommended by the NECP (National Education Cholesterol Program) III. The endpoints evaluated in the study were percentage reduction in LDL-C and the percentage of the patients who reached the cholesterol treatment goals recommended by the NECP III.

The study included 3030 patients, who were randomized in a ratio of 2:1 to receive 10 mg/day of ezetimibe or placebo, in addition to the statin they were already receiving. Three quarters had coronary heart disease or its risk equivalent on enrollment in the study. Atorvastatin was the most widely used statin (40% of the patients). A decrease of 25.8% in LDL-C was seen in the ezetimibe group, compared to a decrease of 2.7% in the placebo group ($P<.001$). In all subgroups, the use of ezetimibe was associated with a high proportion of patients who attained the predefined NCEP III LDL-C endpoint ($P<.0019$). Among patients with ischemic heart disease or its risk equivalent, 70% in the ezetimibe group attained the predefined endpoint compared to 17.3% of the patients in the placebo group. Significantly better effects on HDL-C, triglycerides and apolipoprotein B were seen in the ezetimibe subgroup ($P<.001$). The drug was well tolerated, with a safety profile comparable to that of placebo.

The authors conclude that ezetimibe decreased LDL-C in patients treated with statins by an additional 23% compared to placebo, which compares favorably with the 6-8% improvement usually achieved by doubling the statin dose. It seems the drug can be used above all in patients in whom the statin has not caused the desired changes in lipid values.

ISCHEMIC HEART DISEASE

Implantable Defibrillator After Acute Myocardial Infarction in Primary Prevention (Defibrillator IN Acute Myocardial Infarction Trial [DINAMIT])

Presented by Stefan Hohnloser, Frankfurt, Germany

Mortality at 1 year after acute myocardial infarction (AMI) is around 10%, and approximately half of these deaths are due to arrhythmias, but as yet, no randomized controlled study has evaluated the impact of implantable cardioverter defibrillators (ICD) on mortality immediately after AMI.

The DINAMIT is a randomized, parallel group study that compares the usefulness of implantation of ICD with no implantation associated with optimal medical treatment in 674 patients with: *a)* recent AMI (6-40 days prior to entry); *b)* left ventricular ejection fraction (EF) ≤35%, and *c)* impaired cardiac autonomic modulation. Patients who had undergone previous revascularization in the 3 main coronary vessels by surgery or angioplasty were excluded. The mean EF at the time of inclusion in the study was 28%, and half the patients in each group showed signs of heart failure. Most of the patients received optimal medical treatment—80% received beta-blockers, almost 90% received angiotensin converting enzyme inhibitors, 75% received statins, and 80%-90% received antiplatelet agents.

The primary endpoint of the study was all-cause mortality, with death due to arrhythmia and quality of life as secondary endpoints. The study started in 1998 and finished in September 2002. Follow up lasted up to 4 years; mean follow up was 2.5 years.

There was no difference between the 2 groups (one receiving optimal medical therapy plus ICD, the other optimal medical therapy alone) for the primary study endpoint, although the secondary endpoint of mortality due to arrhythmia decreased highly significantly by more than 50% in the group with ICD. Decrease in arrhythmic mortality was associated with a 75% increase in death due to other causes in the treated group. Most of the deaths in the treated group were cardiovascular in origin and included heart failure and reinfarction. The hazard ratio for all-cause mortality was 1.08 for the treated group ($P=.7$), 0.42 for arrhythmic mortality ($P=.0094$), and 1.75 for mortality due to nonarrhythmic causes ($P=.016$).

In conclusion, the study showed that implantation of ICD does not lower mortality in high-risk patients immediately after suffering acute myocardial infarction.

Enoxaparin Versus Unfractionated Heparin in Infarction Without ST Elevation (Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors [SYNERGY] study)

Presented by Kenneth Mahaffrey (Durham, USA) and by James Ferguson (Houston, USA)

The objective of the SYNERGY study was to compare enoxaparin with unfractionated heparin as the

main antithrombotic treatment in patients at high risk of acute myocardial infarction without ST elevation who underwent an invasive treatment strategy. In addition, efficacy of the cardiac catheterization procedure was evaluated in patients who received enoxaparin.

To be included in the study, patients had to meet at least 2 of the following criteria: *a)* age ≥60 years; *b)* transient elevation or depression of the ST-segment, and *c)* elevated creatine kinase-MB isoenzyme or elevated troponin. A total of 10 027 patients were enrolled from 467 centres, and randomized to receive enoxaparin (1 mg/kg subcutaneously every 12 hours) or unfractionated intravenous heparin as a continuous infusion (initial dose 60 U/kg, followed by 12 U/kg/h and then adjusted according to APTT). All patients were submitted to early cardiac catheterization and received medical treatment with beta blockers, aspirin, angiotensin converting enzyme inhibitors, clopidogrel, or glycoprotein IIb/IIIa inhibitors, in accordance with clinical guidelines. The primary endpoint of the study was mortality or acute myocardial infarction at 30 days.

Cardiac catheterization could be performed at any time in patients who were receiving enoxaparin. Additional enoxaparin was not administered for percutaneous coronary intervention within 8 hours of administration of the last dose, but 0.3 mg/kg were administered when revascularization was performed 8-12 hours after the last subcutaneous dose. Enoxaparin was suspended 8 hours before scheduled coronary revascularization surgery, and immediately for emergency surgery. The group treated with unfractionated heparin received infusions with successive boluses to maintain an activated clotting time (ACT) of 250 seconds. The infusion was maintained during diagnostic catheterization and interrupted at least 6 hours before a scheduled revascularization procedure and immediately before emergency surgery.

After 30 days of follow up, no significant differences were found between the enoxaparin group and the unfractionated heparin group for mortality rate (3.2% vs 3.1%, respectively), AMI (11.7% vs 12.7%) or the composite primary endpoint (14.0% and 14.5%, respectively). No significant differences were observed in the incidence of thrombotic events, but the incidence of hemorrhagic complications was higher in the group treated with enoxaparin. The higher incidence of hemorrhages in the enoxaparin group was associated with a higher proportion of patients who suffered a significant decrease in hemoglobin (>5 g/dL) or hematocrit (>15%) and intracranial hemorrhage (15.2% vs 12.5%; *P*=.001).

Interpretation of the findings was confused by the high proportion of patients who changed treatment during the study.

The investigators concluded that enoxaparin is as effective as unfractionated heparin in patients with acute myocardial infarction without ST-segment elevation who are scheduled for invasive treatment.

Perindopril in Diabetics With Ischemic Heart Disease (Perindopril Substudy in Coronary Artery Disease and Diabetes [PERSUADE])

Presented by Kim Fox, London, United Kingdom

The EUROPA (European trial on reduction of cardiac events with perindopril in stable coronary artery disease) study showed that perindopril, an angiotensin converting enzyme (ACE) inhibitor, reduced the primary composite endpoint of cardiovascular death, myocardial infarction and cardiac arrest. Of the 12 218 patients enrolled, 12% were diabetic—a subgroup particularly prone to cardiovascular complications. These patients form the study population of the PERSUADE substudy. In this subpopulation, 85% were men and 65% had a history of myocardial infarction. The primary endpoint of the study was the same as in the EUROPA study. Multiple secondary endpoints were also assessed.

The 1502 diabetic patients included in the study were randomly assigned to receive 8 mg/day of perindopril or placebo. A decrease of 19% was seen in the events that comprised the primary endpoint of the study (*P*=.131). The incidence of any type of myocardial infarction was 23% lower (*P*=.143) and admission due to heart failure decreased by 46% (*P*=.06). These beneficial effects were similar in size to those in the overall population of the EUROPA study, though unlike the EUROPA study (which was more highly powered) differences were not significant, except for decrease in admissions due to heart failure, which was significantly higher in diabetic patients compared to the EUROPA study. These effects were similar in hypertensive and normotensive patients on study entry, and were not correlated with size of decrease in blood pressure. On the other hand, the benefits of treatment with perindopril took up to 3 years to become apparent in diabetic patients compared to the overall group in which effects were noticeable after 1 year.

The authors conclude that the benefits of perindopril in diabetic patients with coronary heart disease (which

are similar to those obtained from ramipril in the HOPE study) justify the addition of this drug to therapies such as beta-blockers, aspirin and statins, which have been shown to have favorable effects in survival of this population.

Effect of Strict Compliance With Clinical Guidelines for Myocardial Infarction (Guidelines Applied to Practice [GAP] Program)

Presented by Kim A. Eagle, Ann Arbor, USA

The treatment applied in practice for acute myocardial infarction (AMI) is often far from optimal according to scientific evidence. Treatment could therefore be markedly improved, particularly for elderly patients.

The GAP program, sponsored by the American College of Cardiology, was applied in 33 hospitals in Michigan. The program is based on the use of a toolkit to ensure close adherence to clinical guidelines for treatment of AMI from admission through to discharge. Tools include standard orders, pocket guidelines, clinical pathways for critical events, patient information sheets and a "discharge contract" for the patient which includes instructions on medication, lifestyle changes, exercise, cholesterol and personal dietary objectives. This study assessed mortality at 30 days and 1 year in a group of 1368 patients admitted before implementation of the GAP program and 1489 patients admitted after its implementation.

Standard orders were used in 19.8% of the patients before the GAP program, compared to 45.5% after implementation. The improvement was most notable for the instructions given on discharge from hospital (usage increased from 1.8% before the program to 30.8% after implementation). The use of beta-blockers increased from 84% to 92%, lipid-lowering treatment from 73% to 78%, use of ACE inhibitors from 77% to 81%, and use of aspirin from 82% to 90%.

In-hospital mortality after implementation of the GAP program decreased from 13.6% to 10.4% (P<.017). Mortality at 30 days decreased from 21.6% to 16.7% (P=.001), and mortality at 1 year decreased from 38.3% to 33.2% (P=.004). A multivariate model showed that the GAP program led to a 26% reduction in mortality at 30 days and a 22% reduction at 1 year. The tool with greatest independent capacity to improve prognosis was the discharge contract.

In conclusion, the GAP program seemed to reduce mortality at 30 days and 1 year by around 25%. This effect is mainly associated with use of a "discharge contract," which clearly establishes the objectives for lifestyle, effective use of medication and assessment of follow up.

Role of Stress Scintigraphy in Postinfarction Stratification (Stress Myocardial Perfusion Scintigraphy for Tracking Prognosis and Monitoring the Success of Antiischemic Therapies in Stable Survivors of AMI [INSPIRE] study)

Presented by John J. Mahmarian, Houston, USA

Increasingly, cardiologists think that coronary angioplasty should be performed in more patients after acute myocardial infarction (AMI). The INSPIRE study was a randomized multicenter study of 728 patients with AMI who underwent single photon emission computed tomography (SPECT) imaging of myocardial perfusion with adenosine and ^{99m}Tc-sestamibi within 10 days of AMI. The examination aimed to quantify severity of left ventricular perfusion defect and left ventricular ejection fraction. Two primary objectives were defined: *a)* to determine whether the examination was able to identify patients at low, high or intermediate risk, and *b)* to compare the efficacy of intensive medical treatment with revascularization at reducing ischemia and perfusion defect in high-risk patients in a second examination.

Patients were classified from the scintigraphy findings as low risk (perfusion defect <20%), medium risk (perfusion defect >20% with reversible ischemic defect <10%) or high risk (perfusion defect >20% with reversible ischemic defect >10%). Patients in the high risk-group with EF less than 35% underwent angiography, and the remaining patients in this group were randomized to receive maximal medical treatment or angiography and coronary revascularization. These patients were submitted to a second SPECT examination at 6-8 months after receiving treatment. All patients were followed up for 1 year.

After this period, the incidence of death and/or acute myocardial infarction was less than 3% in the low risk group, and mortality was less than 1%. In contrast, the rate of AMI and/or death was greater than 10% in the high-risk group. These findings suggest that SPECT imaging can accurately and reliably identify patients at low risk, leading to early discharge from hospital.

Both groups of high-risk patient had a similar decrease in total perfusion defect and reversible

ischemic defect. A reduction of ≥9% in the size of perfusion defect was seen in 75% of the patients randomized to medical treatment and 79% of the patients who received revascularization. Approximately 80% of the patients in each group had at least a 9% decrease in reversible ischemic defect. The prognosis at 1 year for both groups was similar, although this assessment was not one of the objectives of the study.

In conclusion, current radionucleotide techniques for diagnosis of myocardial perfusion can estimate risk and identify patients at low risk who probably would not benefit from coronary angiography and invasive revascularization, and those at high risk who could benefit from intensive medical therapy. Moreover, medical treatment is comparable to revascularization in reducing ischemia quantified by SPECT imaging.

Role of Statins in the Treatment of Myocardial Ischemia (Vascular Basis for the Treatment of Myocardial Ischemia Study)

Presented by Peter H. Stone, Boston, USA

The effectiveness of statins as a treatment for exercise-induced ischemia or ischemia that appears during daily life has not been expressly studied. This study was designed to assess whether the appearance of ischemia with daily activity could improve with high doses compared to moderate doses of lipid-lowering agents, with or without associated antioxidant supplements.

The study included 300 patients with total cholesterol greater than 250 mg/dL and stable ischemic heart disease defined by exercise-induced ischemia with Holter electrocardiogram monitoring. Patients were randomized to 1 of 3 groups: *a)* treatment with atorvastatin until reaching LDL-C values of 80 mg/dL or a maximum dose of 80 mg/day; *b)* treatment with atorvastatin to sustain high values of LDL-C along with vitamin C (1 g/day) and vitamin E (800 mg/day), and *c)* phase II NCEP (National Cholesterol Education Program) diet with low doses of lovastatin to attain cholesterol values below 130 mg/dL. The antianginal medication was discontinued during the baseline evaluation and the evaluations at 6 and 12 months.

After 6 months, LDL-C decreased from 153 to 83 mg/dL in the 2 atorvastatin groups, and from 147 to 121 mg/dL in the control group, whereas HDL-C did not change significantly.

At baseline, patients across all 3 groups had 4.5-5.0 ischemic episodes in 48 hours. These episodes decreased to 2.5-3.0 episodes at 6 and 12 months. Ischemic time at baseline was 90 minutes in all 3 groups, but decreased significantly to 55-60 minutes in all groups, without any changes in the mean heart rate measured by the Holter recorder. At baseline, onset of ischemia occurred after 5-6 minutes of exercise testing. After treatment, onset was delayed by approximately 1 minute, but total exercise time remained unchanged.

The authors suggest in their conclusions that the benefit in terms of reduced ischemia during daily activities associated with lower LDL-C indicates an improvement in endothelial function of coronary arteries, greater vasodilatory capacity and greater coronary flow. The lack of benefit for exercise testing might indicate that the maximum exercise tolerance depends essentially on ischemia caused by fixed obstructions to blood flow. For treatment of patients with stable ischemic heart disease, association of diet and statins to keep LDL-C below 125 mg/dL may be satisfactory. A more aggressive treatment might be needed to prevent progression of atherosclerosis, stabilize platelets and prevent episodes of myocardial infarction and death.

HEART FAILURE

Defibrillator Versus Amiodarone and Placebo in Systolic Heart Failure (Sudden Cardiac Death in Heart Failure Trial [SCD-HeFT])

Presented by Gust H. Bardy, Seattle, USA

Patients with heart failure due to systolic dysfunction are 6-9 times more at risk of sudden death than the general population. Attempts to reduce sudden death with antiarrhythmic drugs have not produced conclusive results, whereas implantable cardioverter defibrillators (ICD) have been shown to be effective at reducing the rate of sudden death in increasingly broader patient groups.

A total of 2521 patients in functional class II or III according to the New York Heart Association (NYHA) definition, with ischemic or nonischemic dilated cardiomyopathy, an ejection fraction below 35%, and no history of sustained ventricular tachycardia or ventricular fibrillation (VF) were included in the study. Patients were randomized to receive an ICD (simple shock-only model for treating VF), amiodarone or placebo. The primary endpoint of the study was all-cause mortality, with analysis by

intention to treat.

Mortality was 17.1% in the ICD group, 24% in the amiodarone group, and 22.3% in the placebo group ($P<.05$ for comparison of the ICD group with the other 2 groups) after 3 years of follow up; and 22% in the ICD group, 28% in the amiodarone group, and 29% in the placebo group at the end of follow up. Overall, use of ICD was associated with a 23% decrease in mortality in comparison with placebo ($P=.007$). Patients with ischemic heart disease (52%) and patients with nonischemic heart disease showed a similar beneficial effect of ICD. In the subgroup analysis, patients with NYHA class II heart failure derived more benefit than class III patients.

In the study population, comprising patients with ischemic heart disease and nonischemic heart disease, implantation of ICD decreased mortality by 23%. Amiodarone, when used as a preventative antiarrhythmic drug, did not improve survival.

Role of Warfarin Versus Aspirin and Clopidogrel in Heart Failure (Warfarin and Antiplatelet Therapy in Chronic Heart Failure [WATCH] study)

Presented by Barry Massie, San Francisco, USA

The WATCH study was designed to determine whether aspirin could have a harmful effect in patients with heart failure (HF). Inhibition of prostaglandins may interfere with the action of angiotensin converting enzyme (ACE) inhibitors—drugs used systematically in such patients. The study was discontinued early because of a low patient recruitment rate.

Initially, the study protocol envisioned 4500 patients in 142 centers randomized to receive 1 of the 3 aforementioned antithrombotic drugs (warfarin, aspirin or clopidogrel) for 2-5 years in order to establish the optimal antithrombotic treatment for this population. Despite premature discontinuation of the study, 1587 patients had been included.

The mean ejection fraction of the study population was 24%, and 56% of the patients were NYHA class III or IV. Three quarters of the patients had ischemic disease, and almost all were taking ACE inhibitors or angiotensin receptor antagonists.

For the primary endpoint, a composite of death, nonfatal myocardial infarction and stroke, the warfarin versus aspirin hazard ratio was 0.99, and the clopidogrel versus aspirin hazard ratio was 1.10. When all primary and secondary endpoints were assessed together (death, myocardial infarction, stroke, hospitalization for HF, pulmonary embolism or need for ventricular assist devices), the hazard ratio of warfarin versus aspirin was 0.94, and that of clopidogrel versus aspirin was 1.03.

Hospitalization due to acute heart failure in patients who took warfarin, however, was 27% lower compared to those who took aspirin ($P=.01$), though this endpoint showed no differences between the aspirin and clopidogrel groups. Hospitalization due to HF was 31% lower for the warfarin group compared to the aspirin group per 100 patient years. There was a higher rate of major bleeding complications in the warfarin group compared to aspirin and clopidogrel (30% vs 19% and 13%, respectively; $P<.01$). There was also a significantly higher number of minor bleeding episodes in the warfarin group.

The findings of this study should be interpreted with care as the planned number of patients was not reached. Even so, fewer hospitalizations due to HF in patients treated with warfarin confirms the findings of a previous pilot study (WASH: Warfarin-Aspirin Study in Heart Failure pilot study) and should be taken into account.

Intramyocardial Infusion of Autologous Myoblasts in Postinfarction Heart Failure (Percutaneous Transvenous Transplantation of Autologous Myoblasts in the Treatment of Postinfarction Heart Failure [POZNAN] study)

Presented by Tomasz Siminiak, Poznan, Poland

The POZNAN study is a phase I study to investigate the safety and feasibility of injecting autologous skeletal myoblasts into patients with postinfarction heart failure. Cells were injected into the myocardium through cardiac veins with a catheter under intravascular ultrasound guidance. The TransAccess catheter (Medtronic) for myoblast "transplantation" combines a needle for intramyocardial injection with an intravascular echographic catheter. Ten patients with postinfarction heart failure were selected. The patients showed no residual myocardial viability in the infarcted area, which had a coronary blood supply because of coronary revascularization or collateral circulation. The procedure was successfully completed in 9 of the 10 patients in whom it was attempted. The anterior interventricular coronary vein was used in 5 patients, and the middle coronary vein in the remaining 4. The system could not be correctly positioned in 1 patient because the guidewire was unable to pass the venous valve. Myoblasts were transplanted through 2-4 intramyocardial channels 1.5-

4.5 cm deep. Ventricular arrhythmias were not detected (patients received amiodarone prophylaxis), except in 1 patient who already had a defibrillator. Symptomatic improvement was seen (assessed by NYHA class) in treated patients in a preliminary follow up (6 patients with 6 months follow up). Moreover, ejection fraction improved (by between 3% and 8%) in 4 of the 6 patients.

In conclusion, myoblast transplantation can restore lost cardiac cells responsible for ventricular remodeling and heart failure after myocardial infarction. The technique of injection of myoblasts into damaged tissue is still in early experimental phases, and phase II and III clinical trials would be needed to determine its true effectiveness.

INTERVENTIONAL CARDIOLOGY

Usefulness of a Device for Prevention of Distal Embolization During Angioplasty (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris [EMERALD] study)

Presented by Gregg Stone, New York, USA

Studies have shown the clinical benefit of using devices that offer distal embolic protection during angioplasty of high risk legions (saphenous vein bypass). Currently, there is strong interest in the development and clinical validation of such devices for protection of microcirculation in acute myocardial infarction.

The EMERALD study is a multicenter, prospective, randomized study in patients with acute myocardial infarction treated conventionally with primary angioplasty or with a device to protect against distal coronary embolization during the procedure. A total of 501 patients with acute myocardial infarction of less than 6 hours with ST-segment elevation of ≥2 mm on contiguous leads were randomized to conventional angioplasty (249 patients) or angioplasty with a device to protect against distal coronary embolization during the procedure (252 patients). The GuardWire Plus system (Medtronic, 0.028”), which allows temporary vessel occlusion and subsequent aspiration of intraluminal material, was used. The primary objective of the study was to compare the incidence of complete resolution of ST-segment elevation in the electrocardiogram within 30 minutes of the procedure. The electrocardiograms were obtained and analyzed using a system of continuous 24-hour electrocardiographic monitoring. An additional primary objective was to measure the infarct size (with SPECT imaging) between 5 and 14 days after coronary angioplasty. Secondary objectives included comparison of patients who had normal or grade 3 myocardial blush (blush or myocardial staining provides an angiographic estimate of the extent of myocardial perfusion), and the adverse cardiac events at 1 month of follow up, including readmission to hospital due to heart failure.

Use of the distal protection system did not manage to improve the percentage of patients with complete resolution of ST-segment elevation in the electrocardiogram (62.2% with protection vs 60.6% without protection; *P*=.77). Similarly, there were no differences between groups regarding the attainment of myocardial blush grade 3 (60% with protection vs 52% without protection; *P*=NS). Likewise, no differences were found in infarct size determined by SPECT imaging with ^{99}Tc (decrease in infarct size of 17.1% in group with protection and 14.3% in the group without protection; *P*=.09), or in reduction in infarct size in patients in whom the infarcted artery was the left anterior descending coronary artery (26.3% vs 22.3%; *P*=.21). In fact, no benefit was obtained in any of the prospectively defined subgroups. However, the protection system used allowed thrombi and atheromatous material to be removed in 76% of the patients, and the technique was not associated with postoperative complications. The patients’ clinical course was similar in both groups. Thus, the incidence of major adverse events at 30 days or modified major adverse events (including death, reappearance of severe heart failure or hypotension, and readmission to hospital due to heart failure) was similar. These negative results might be explained by the fact that the particular system used did not completely prevent risk of distal embolization. Alternatively, given that thrombotic remains were removed by the device, the study may not have been sufficiently powered to detect small variations in infarct size.

Hyperoxemic Therapy in Angioplasty of Infarction (Acute Myocardial Infarction with Hyperoxemic Therapy [AMIHOT] study)

Presented by William O’Neill, Royal Oak, USA

Some initial studies have suggested that hyperoxygenated blood in the artery implicated in acute myocardial infarction may improve regional wall motion of the left ventricle.

AMIHOT is a prospective multicenter randomized study that evaluates the value of intracoronary hyperoxemic therapy in patients with acute myocardial infarction.

The study randomized 252 patients with acute myocardial infarction (primary or rescue angioplasty within 24 hours of onset) to conventional stent implantation or angioplasty plus hyperoxemic therapy. A catheter was used in the second of these groups that allowed the infarct artery to be infused with a 3 ml solution of aqueous oxygen mixed with patient's own blood at 70 mL/min (blood supersaturated with oxygen) after coronary revascularization. The TherOx system combines standard physiologic solution with pure oxygen at 25 000 psi then mixes the resulting hyperoxygenated solution with patient's blood at a ratio of 3/73. We monitored the patients continuously by electrocardiography for 24 hours to assess ST-segment changes. Three primary endpoints were studied: *a)* ST-segment resolution in the electrocardiogram; *b)* infarct size assessed with SPECT imaging, and *c)* regional wall motion evaluated by echocardiography.

For both groups, similar percentages of patients underwent stenting as the primary procedure (88% vs 83%) or as the rescue procedure (12% vs 17%). Use of glycoprotein IIb/IIIa inhibitors (86% vs 83%) and presence of TIMI 0/1 state before the procedure (85% vs 91%) were also similar.

Study of ST-segment resolution in the electrocardiogram at 24 hours and the creatine kinase peak did not show differences between treatment groups. Only the subgroup of patients with anterior myocardial infarction showed a favorable tendency—hyperoxemic therapy increased the number of patients with ST-segment resolution by 25%, but the difference was not statistically significant (*P*=.09). Complications arising from use of the system under study were not observed. Differences between the 2 treatment groups were also not observed for the composite clinical endpoint at 30 days (3.1% in the angioplasty group alone vs 4% in the angioplasty plus hyperoxemic therapy group) or for the components of this endpoint (death [0.8% vs 0.8%], reinfarction [0.8% vs 0.8%], stroke [0 vs 0.8%] or repeat revascularization of the treated lesion [1.6% vs 2.4%]). In the subgroup of 68 patients with anterior infarction who underwent clinical follow up for 3 months, regional wall motion determined by echocardiography increased by 60%. The study has a phase of clinical follow up and another to assess ventricular function which had not been completed in time to be presented at the congress. In any case, the logistic problems associated with implementing a relatively complex system in systematic interventional treatment of patients with acute myocardial infarction have yet to be addressed.

Angioplasty Facilitated With Tirofiban in Acute Myocardial Infarction (Ongoing Tirofiban in Myocardial Infarction Evaluation trial [ON-TIME] study)

Presented by Menko J. de Boer, Zwolle, Holland

Patients suffering from myocardial infarction with ST-segment elevation attended in ambulances or hospitals with no percutaneous coronary intervention (PCI) facilities may experience some delay before reperfusion with primary angioplasty begins. The ON-TIME study assesses the usefulness of facilitated angioplasty (tirofiban administered early) in patients with acute myocardial infarction.

Patients with acute myocardial infarction were randomized to receive tirofiban (10 µg/kg at 0.15 µg/kg/min) or placebo in ambulances (209 patients) or in referral centers (258 patients) before arrival at a tertiary hospital with PCI facilities. After angiography, patients assigned initially to placebo received tirofiban, whereas those initially treated with tirofiban received placebo. After PCI, all patients received an infusion of tirofiban for 24 hours. The mean time between start of treatment and angiography was 59 minutes (range, 11 to 178 min).

The primary endpoint of the study (TIMI 3 flow in initial angiography) was similar in the 2 treatment groups (15% in the group who received in tirofiban initially and 19% in the group who received placebo initially; *P*=NS). Despite this, the rate of appearance of TIMI 3 or 2 coronary flow was higher in patients pretreated with tirofiban. Moreover, the incidence of intracoronary thrombi was lower and myocardial perfusion data were more favorable in the group on active treatment. In contrast, the clinical outcome (mortality and reinfarction) of the 2 groups after 1 year of follow up was similar.

In conclusion, angiographic findings and clinical outcomes of primary angioplasty patients with acute myocardial infarction treated initially in ambulances or hospitals with no PCI facilities do not differ regardless of whether treatment with tirofiban is started early or at the time of angiography.

Caldaret to Limit Reperfusion Damage After Primary Angioplasty for Acute Myocardial Infarction (Caldaret in ST Elevation Myocardial Infarction [CASTEMI] study)

Presented by Dan Tzivoni, Jerusalem, Israel

Primary angioplasty has been shown to be the most

effective reperfusion strategy in patients suffering acute myocardial infarction with persistent ST-segment elevation, but its success is partially clouded by the possible risk of reperfusion damage. Calcium overload is a very important factor in reperfusion damage. Caldaret (MCC-135) is a novel drug that inhibits calcium overload through sodium-calcium exchange, improving calcium uptake by the sarcoplasmic reticulum at times of ischemia/reperfusion.

The CASTEMI study investigated whether intravenous administration of caldaret can decrease infarct size and improve left ventricular function in patients with acute myocardial infarction with persistent ST-segment elevation who undergo percutaneous coronary intervention. A total of 387 patients were randomized in the study to 3 treatment groups: high-dose caldaret (172.5 mg), low-dose caldaret (57.5 mg) or placebo, administered as 48-hour infusions. The investigators found that 247 patients had TIMI 0 or 1 coronary flow at the start of the study. Mortality at 30 days was 2.3%. No differences in infarct size as measured by SPECT imaging was found in any of the 3 groups, but high-dose caldaret did improve end-systolic and end-diastolic left ventricular volume in the subgroup of patients with anterior infarction and TIMI 0 or 1 flow compared with placebo at 7 days, and also after 1 month of follow up. Although differences in overall ejection fraction at 7 days were favorable in the high dose group, a difference was apparent but not significant after 30 days. High-dose caldaret was also associated with a significant decrease in cardiac markers compared to placebo. Use of caldaret was not associated with hemodynamic, biochemical or electrocardiographic abnormalities.

In conclusion, given that anterior infarctions are usually associated with higher morbidity and mortality, patients with this type of infarction are those who stand to benefit most from new therapeutic strategies to save myocardial tissue and limit reperfusion damage. If these favorable findings could be confirmed in larger studies, caldaret would take its place among the therapeutic options for patients who require emergency reperfusion for myocardial infarction.

Angioplasty After Thrombolytic Therapy in Acute Myocardial Infarction (Combined Angioplasty and Pharmacological Intervention versus Thrombolytics Alone in Acute Myocardial Infarction [CAPITAL AMI] study)

Presented by Michel R. LeMay, Ottawa, Canada

Findings from studies in the 1990s in which patients underwent percutaneous coronary intervention immediately after thrombolytic therapy were not encouraging and the risk of bleeding was unacceptable, so facilitated angioplasty was abandoned as a treatment strategy in such patients. Today, intervention techniques and accompanying pharmacological treatment have improved. In the previous PACT study, patients who received half the normal dose of plasminogen tissue activator (t-PA) followed by early intervention achieved faster reperfusion.

This study compared thrombolytic treatment with this same treatment, but followed by percutaneous coronary intervention. A total of 170 patients with high-risk acute myocardial infarction with onset less than 6 hours before enrollment were randomized to thrombolytic treatment alone (84 patients) or thrombolytic treatment followed by percutaneous coronary intervention (86 patients) in 4 Canadian hospitals. Both groups received a full dose of TNK (0.53 mg/kg). If thrombolytic treatment had failed after 90 minutes, patients also underwent angioplasty. The primary endpoint (death, reinfarction, stroke or recurrent ischemia) was assessed after 30 days. The incidence of major bleeding was also studied. The composite primary endpoint was met in 21.4% of the patients treated with thrombolytic agents compared to 9.3% of the patients on combination therapy (P=.034). Mortality was similar for both groups (3.6% in the thrombolysis group vs 2.3% in the combination therapy group). Incidence of stroke was also similar (1.2%) in both groups. However, the incidence of reinfarction was larger in the group treated with thrombolytics alone (11.9% compared to 4.7%; P=NS). The incidence of recurrent ischemia was 17.9% in the group treated with thrombolytics alone compared to 7% in the combination therapy group (P=.037). The incidence of major bleeding was similar in the 2 groups (8.3% in the group treated with thrombolytics alone compared to 9.3% in the combination therapy group). The combination therapy group also showed a tendency towards lower incidence of heart failure and cardiogenic shock.

In conclusion: *a)* a strategy of thrombolytic therapy with TNK plus percutaneous coronary intervention is better than thrombolytic treatment alone; *b)* combination therapy is relatively safe and not associated with increased complications; *c)* all patients

with high-risk myocardial infarction treated with thrombolytics should be considered for early intervention.

Rapamycin-Eluting Stent in Small Vessel Angioplasty (Sirolimus-Eluting and Uncoated Stent in the Prevention of Restenosis in Small Coronary Arteries [SES-SMART] study)

Presented by Diego Ardissino, Parma, Italy

Previous studies have shown the value of drug-eluting stents to prevent restenosis of large- and medium-sized arteries. Investigators are, however, skeptical whether these positive findings can apply to the less favorable or "real world" situation in percutaneous coronary intervention for more complex lesions, including those in small vessels, which have always been a therapeutic challenge.

The SES-SMART study is a prospective, multicenter, randomized study with the objective of assessing whether implantation of rapamycin-eluting stents in small vessels managed to reduce the appearance of angiographic restenosis compared with the conventional metal stent.

Primary endpoint: rate of binary restenosis at 8 months of follow up.

Secondary endpoints: procedural success, minimal luminal diameter, late lumen loss and late loss index after 8 months, and major adverse cardiovascular events.

A total of 257 patients with *de novo* lesions in small vessels (reference diameter ≤2.75 mm) were randomized to receive either a conventional stent *(Bx Sonic,* 128 patients) or a rapamycin-eluting stent *(Bx Velocity,* 129 patients). Patients with total occlusion and lesions whose length could not be fully covered with a 33 mm stent were excluded from the study. Baseline clinical characteristics were similar in both groups. The mean vessel size (2.2±0.3 mm) was also similar in both groups. The primary study endpoint (rate of binary restenosis after 8 months) was significantly lower for the rapamycin-eluting stent (9.8% vs 53.1%; *P*<.001). In fact, use of a rapamycin-eluting stent was associated with a 90% decrease in the risk of restenosis. Moreover, late lumen loss (0.16±0.46 mm vs 0.69±0.61 mm; *P*<.001) and the late loss index (0.11±0.5 vs 0.68±0.68 mm; *P*<.001) were significantly lower in patients who received the rapamycin-eluting stent. Minimal luminal diameter after 8 months was greater (1.7±0.48 mm vs 1.09±0.6 mm; *P*<.001) and the percentage of stenosis was significantly less (29.3% vs 50.8%; *P*<.001) in this group. Finally, the rate of major clinical adverse events during follow up was also significantly lower in the group with the drug-eluting stent (9.3% vs 31.3%; *P*<.001), essentially because further revascularization of the treated vessel was needed less often (7% vs 21%; *P*=.002). Likewise, the rate of acute myocardial infarction was also lower for the rapamycin-eluting stent (1.6% vs 7.8%; *P*=.04).

In conclusion, use of rapamycin-eluting stents in patients with lesions of small coronary vessels significantly decreases the rate of angiographic restenosis and the appearance of adverse cardiac events during follow up.

Direct Implantation Versus Predilation in Rapamycin-Eluting Stents (Direct Stenting Using the Sirolimus-Eluting Bx Velocity Stent [DIRECT] study)

Presented by Jeffrey Moses, New York, USA

Coronary stenting needs to be optimized in light of current technological advances and availability of drug-eluting stents. It has been suggested that direct stenting could reduce trauma to the vessel wall and shorten the procedure as opposed to stenting after predilation of the lesion. Nevertheless, cardiologists are wary of direct implantation of drug-eluting stents because the drug-containing polymer coating may become damaged reducing the effectiveness of the stent.

The objective of the DIRECT study was to compare direct implantation of the *Bx Velocity* rapamycin-eluting stent *(Cypher)* with stenting after systematic predilation of the lesion. The primary endpoint of the study was analysis of late angiographic loss at 8 months. This was a prospective multicenter study, but it was not randomized. The outcome of direct implantation of the rapamycin-eluting stent (225 patients) was compared with that of a historical control group (412 patients), in whom the same stent had been implanted in the conventional manner (that is, after predilation). Patients in the control group were taken from the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) study, which had concluded prior to the present study. Although many of the baseline demographic characteristics were similar in both populations, there were significant differences in number of smokers (59% vs 1%; *P*<.01), proportion of C-type lesions according to the ACC/AHA classification (15% vs 27%; *P*<.01) and length of lesion (12.4 mm vs 14.7 mm; *P*<.01) in groups with direct stenting compared to predilation, respectively. Moreover, stents implanted directly were

longer (22.6 mm vs 21.4 mm; *P*=.04) and greater inflation pressures were used (15.5 atmospheres vs 14 atmospheres; *P*<.001). Thus the ratio of stent length to lesion length was greater in the group with direct stent implantation (*P*<.001). The procedural success rate was similar in both groups and direct stenting was successful in 86% of the patients. The procedure was significantly shorter in for direct stenting (33 min vs 45 min; *P*<.001). Procedural complications (also including transitory minor complications) occurred at similar rates in both groups (1.4% in the direct implantation group compared to 3.7% in the group with implantation after predilation; *P*=.23). At 6 months of follow up, adverse clinical events were similar for the direct stenting group compared to the group with predilation. Rates of major events, including death (0.4% vs 0.5%), myocardial infarction (0.9% vs 2.9%), revascularization of treated lesion (1.3% vs 1.9%) and final failure of the treated vessel (3.1% vs 5.3%), were similar for both groups. A late angiography study was carried out in 76% of the patients of the direct stent implantation group and in 87% of the patients in the SIRIUS study. Late lumen loss at 8 months (0.18 mm) (primary study endpoint) was also similar in both groups. Finally, binary restenosis in the stented segment (3.6% vs 3.2%; *P*=.8) and in the entire lesioned segment (6% vs 9.1%; *P*=.3) was similar in the direct stenting group and the control group. Subgroup analysis showed that restenosis in diabetic patients was also similar for the 2 strategies. A lower rate of late restenosis was found in the subgroup of patients with type-1 diabetes who underwent direct stenting (0 vs 35%; *P*=.03), but the number of patients analyzed was low. A tendency towards a lower rate of restenosis was also observed (8.3% vs 18.3%; *P*=.12) in the subgroup of patients with small infarcted vessels.

The conclusions of the study were: *a)* direct implantation of the rapamycin-eluting stent was not inferior to conventional stenting after predilation for any of the endpoints analyzed, and *b)* direct stenting shortens the procedure by 12 minutes on average.

Percutaneous Treatment of Mitral Regurgitation (Endovascular Valve Edge-to-Edge Repair Study [EVEREST I])

Presented by Ted Feldman, Evanston, USA

Preliminary phase I feasibility and safety results are presented for the EVEREST study. The technique, based on the Alfieri technique, requires percutaneous placement of a metallic clip on the center of the mitral valve leaflets. While the patient is under general anesthetic, the clip is introduced via the femoral artery and guided transseptally with fluoroscopic and echocardiographic imaging to the mitral valve.

The results presented correspond to the first 10 patients of a total of 30 planned for the overall study. All patients had grade III or IV mitral regurgitation, accompanied by symptoms of left ventricular dysfunction. The metallic clip was successfully placed on the mitral valve leaflets in all patients, achieving systolic leaflet coaptation and a double orifice for ventricular inflow during diastole. The extent of mitral regurgitation decreased in 9 of the 10 patients, and in 7 patients, the decrease was 2 or more grades. There were no complications derived from the procedure. At 30 days follow up, benefit was sustained in 6 out of the 7 patients with a decrease of 2 or more grades in mitral regurgitation. An advantage of this technique over catheter treatment is that the clip can be removed and repositioned during the initial placement procedure. If the procedure does not prove satisfactory, the clip can be withdrawn to allow subsequent conventional surgery. New experiments are currently in progress with this device, which could prove a real alternative to valve repair surgery for mitral regurgitation.

Percutaneous Treatment of Carotid Lesions (Acculink for Revascularization of Carotids in High-Risks Patients [ARCHER] study)

Presented by William A. Gray, Seattle, USA

The treatment of choice to manage risk of stroke in patients with severe carotid stenosis is currently carotid endarterectomy, regardless of whether symptoms are present or not. For patients who are not surgical candidates, or when surgery is risky, carotid stents with embolic protection are being used ever more often in carotid arteries within the brain. The ARCHER studies were 3 prospective, nonrandomized studies in which each study evaluated a single group. A total of 581 patients were enrolled at 48 centers in North America, Europe, and Argentina. Patients had to have symptomatic carotid stenosis ≥50% or, if they were asymptomatic, carotid stenosis >80%. Likewise, they were either not candidates for carotid endarterectomy or considered as high-risk surgical candidates. Thus, patients with comorbidities such as diabetes, ejection fraction <30% or an unfavorable

anatomy due to previous radical neck surgery, or surgically inaccessible lesions were included. Patients were treated with the Acculink carotid stent system and Accunet distal protection system. The ARCHER 1 study enrolled 158 patients treated with carotid stent with no embolic protection system, whereas the ARCHER 2 study treated 278 patients with distal embolic protection systems. The primary endpoints of both studies were incidence of death, stroke or myocardial infarction in the first 30 days, plus ipsilateral stroke after the first month but before 1 year. The outcomes for patients in the ARCHER 1 and 2 studies were compared with the results for control patients in the literature who were matched according to baseline characteristics (NASCET and ACAS studies). The expected incidence of the composite primary endpoint according to this control group was 14.5%.

In the ARCHER 3 study, which used a fast exchange system, also with distal protection, the results for the 145 treated patients after 30 days were compared with those obtained in the ARCHER 2 study. The success of the procedure was high, with correct stenting in 99% of the patients. Moreover, the embolic protection filters were also successfully used and withdrawn in 95% of the patients.

The results of the ARCHER 1, 2 and 3 studies were compared. In the ARCHER 1, 2 and 3 studies, the mortality rate (2.5%, 2.2%, and 1.4%, respectively), incidence of stroke (4.4%, 5.8%, and 6.2%, respectively) and the composite primary endpoint of death, stroke or infarction (7.6, 8.6, and 8.3%, respectively) were similar. The incidence of major or fatal stroke was also similar in the 3 groups (1.9% for ARCHER 1, 1.4% for ARCHER 2, and 1.4% for ARCHER 3). The incidence of death, infarction, stroke after 30 days and ipsilateral stroke between 1 month and 1 year of follow up was 8.3% in the ARCHER 1 study and 10.2% in the ARCHER 2 study. These figures compare favorably with the results from the historic control patients adjusted for baseline variables (14.5%). In addition, the need for new revascularization of the treated lesion was low —0.5% after 6 months and 2.5% after 1 year of follow up. Although there were no differences between the ARCHER 1 study (without embolic protection) and the ARCHER 2 and 3 studies, patient selection was less favorable in the latter 2 studies as they included patients with greater vessel angulation.

These data support findings reported previously for the randomized SAPPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Atherectomy) study. The CREST (Carotid Revascularization Endarterectomy vs Stent Trial), in which carotid endarterectomy is compared with stenting with distal protection systems in "low-risk" patients, should indicate the real value of the 2 therapeutic strategies.

In conclusion, this study, which analyses the results from 3 different registers, showed that carotid stenting with a system of embolic protection in high-risk surgical patients obtained results similar to those described in historic controls treated with carotid endarterectomy.

HYPERTENSION

Increased Risk of Myocardial Infarction With Excessive Decrease in Diastolic Blood Pressure: a Post Hoc Analysis of the INVEST (International Verapamil SR-Trandolapril) study

Presented by Franz H. Messerli, New Orleans, USA

The INVEST study enrolled 22 476 hypertensive patients with documented coronary artery disease in order to compare the clinical efficacy of 2 pharmacological regimens (verapamil with or without added trandolapril vs atenolol with added hydrochlorothiazide). The mean systolic blood pressure of the group was 119.2 mm Hg and mean diastolic blood pressure was 84.1 mm Hg. Overall, 75% of the patients attained adequate blood pressure control.

Analysis of the incidence of acute myocardial infarction and stroke as a function of systolic and diastolic blood pressure showed that lowering systolic blood pressure had no effect, but myocardial infarction occurred more often in patients with diastolic blood pressure below 80 mm Hg. The increase in the incidence of infarction in patients with diastolic blood pressure below 80 mm Hg was similar to that observed in patients whose blood pressure remained above 100 mm Hg. Thus, diastolic blood pressure below 60 mm Hg was associated with an incidence of acute myocardial infarction of 14%, whereas diastolic blood pressures in the range of 60 to 70 mm Hg were associated with an incidence of 6% and values between 70 and 90 mg with an incidence close to 3%. This "J-shaped" curve was apparent only in the incidence of nonfatal infarction and not in the incidence of fatal infarction and stroke. The relationship between the diastolic blood pressure J-curve and body mass index or diagnosis of cancer was analyzed, but no interactions were found, so

there was no reverse causation, that is, patients with other morbidities such as cancer were not responsible for the J-shaped curve. Significant interactions were observed with hypercholesterolemia and diabetes, diseases that enhance the "J-curve" effect. Revascularization showed a protective effect in that revascularized patients seem to tolerate lower diastolic blood pressures.

In conclusion, diastolic hypotension is associated with an increase in the incidence of acute myocardial infarction in patients with known coronary heart disease.

Racial Differences in the Benefit of Angiotensin Converting Enzyme Inhibitors in Hypertension: Analysis of the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack) Study

Presented by Curt Furberg, North Carolina, USA

The ALLHAT study explored the role of diuretics, amlodipine and an angiotensin converting enzyme (ACE) inhibitor in the prevention of mortality and other cardiovascular outcomes in the treatment of hypertensive patients. The present substudy investigates the differential effect of these drugs in populations of different races.

In white patients, the ratio of mortality to incidence of other cardiovascular events for patients treated both with diuretics and with lisinopril remained close to one, indicating that the 2 drugs are equivalent in this population. But the ratio of incidence for black patients who were taking lisinopril was 1.10 for the composite of death due to any cause, 1.15 for any type of coronary event and 1.19 for cardiovascular events in general. Other significant differences in the incidence of complications in black patients treated with ACE inhibitors compared to those treated with diuretics is reflected in ratios of incidence of 1.40 for stroke, 1.32 for heart failure and 1.29 for terminal renal failure.

In conclusion, the ALLHAT study showed that ACE inhibitors are less effective than diuretics at reducing blood pressure and the risk of cardiovascular complications in black hypertensive patients, in contrast to white patients. Thus, a combination of an ACE inhibitor and a diuretic is the treatment of choice recommended by the authors of this study for white patients, but an ACE inhibitor and, possibly angiotensin receptor antagonists are not advised as first choice treatment in black patients.

ARRHYTHMIAS

Biventricular Pacemakers After Atrioventricular Nodal Ablation in the Treatment of Atrial Fibrillation (Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation [PAVE] study)

Presented by Rahul N. Doshi, Las Vegas, USA

The PAVE study was a prospective, randomized study designed to compare biventricular pacing with right ventricular pacing in 184 patients with chronic atrial fibrillation (AF), regardless of their left ventricular function or NYHA functional class. To be included, patients had to have had chronic AF for at least 1 month before entry into the study and undergone catheter ablation of the atrioventricular node followed by implantation of a permanent pacemaker. They also had to be NYHA functional class I to III and be unable to cover more than 450 m in the 6-minute walk test.

Patients were randomized 2:1 to undergo biventricular pacing or right ventricular pacing. Follow up lasted 6 months. The mean age of the patients was 69 years. At the end of follow up, patients who underwent biventricular pacing were able to walk 25.55 m further on average than those who underwent right ventricular pacing (primary endpoint; P=.03). The secondary endpoint, peak oxygen uptake (peak VO_2) was 1.02 mL/kg/min larger in the group with biventricular pacing (P <.01). Likewise, exercise duration was 41.6 seconds longer (P<.01).

Left ventricular ejection fraction, which was not a prospectively defined study endpoint, remained unchanged in patients who underwent biventricular pacing but decreased from 44.9% to 40.7% in patients with right ventricular pacing (P=.03 for comparison with baseline). No differences between the 2 groups were found for survival.

In conclusion, in patients with chronic AF treated with atrioventricular nodal ablation, biventricular pacing is associated with better functional capacity as indicated in the 6-minute walk test, peak oxygen uptake and exercise duration. Therefore, biventricular pacing should be the therapy of choice in patients who are to be submitted to nodal ablation to control chronic AF.

HEART SURGERY

Off-Pump Coronary Revascularization Surgery Compared to Surgery With Extracorporeal Circulation (study PRAGUE-4)

Presented by Petr Widimsky, Prague, Czech Republic

This single-center study was carried out by 4 heart surgeons with at least 1 year's experience in off-pump coronary artery bypass surgery. A total of 400 patients were randomized either to on-pump surgery or to off-pump surgery. Initially, 184 patients were assigned to conventional on-pump surgery and 204 to off-pump surgery, but because of crossover, 203 patients were finally underwent an on-pump intervention and 185 underwent an off-pump intervention. The primary endpoint of the PRAGUE 4 study was the incidence of the composite event of death, infarction, stroke, or hemodialysis after 30 minutes.

Results were obtained from the angiographic evaluation after 1 year in 132 patients assigned to conventional surgery and in 123 patients assigned to off-pump surgery. In addition, early angiography was performed before discharge from hospital in 13 patients in the conventional surgery group and 16 patients in the off-pump surgery group. Although patients were selected for the study by cardiologists, the heart surgeons changed the surgical strategy (crossover) in 10%-15% of the patients.

The primary endpoint (for intention-to-treat) was met in 3.8% of the patients who underwent on-pump surgery and in 2.9% of those who underwent off-pump surgery (P=.12). The number of patients who died (4 patients in the on-pump group vs 2 in the off-pump group) was similar in both groups. In the few patients who underwent the angiographic study before discharge, the internal mammary artery bypasses were fully patent, whereas the saphenous vein bypasses were 91% patent. The angiographic patency after 1 year of the left mammary artery bypass was 91% in both groups. However, the saphenous vein was 59% patent after 1 year in the on-pump group and only 49% in the off-pump group (though the trend was not significant). Surgery without extracorporeal circulation was 40% cheaper according to these data for the Czech Republic. The reasons for such unfavorable outcomes in "real-world" surgery is that interventional cardiologists select patients for revascularization and leave the worst cases for heart surgery.

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