Summary of the Clinical Studies Reported in the 51st Annual Scientific Sessions of American College of Cardiology (Atlanta, 17-20 March 2002)

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Several clinical studies were presented at the 51st Annual Scientific Session of the American College of Cardiology. These studies were chosen because they were considered particularly relevant and because the findings were presented orally. What follows is a summary of the objectives, methods, and results of these studies. Since the results have not yet been published, the information offered in this article should be considered preliminary.

ARTERIAL HYPERTENSION

Security and Efficacy of Treatment with Eplerenone, Enalapril, and a Combination of Both in Patients with Left Ventricular Hypertrophy: Study 4E

Presented by Bertram Pitt, Ann Arbor, Michigan, USA.

The study was performed on patients with light to moderate arterial hypertension and left ventricular hypertrophy randomly assigned to treatment with enalapril or eplerenone, a new aldosterone antagonist. The aim of the study was to evaluate whether eplerenone is as effective as spironolactone, without the side effects of this drug, in these patients.

Two hundred and two hypertensive patients were randomly assigned to receive 1 of the 3 treatments: eplerenone (200 mg), enalapril (40 mg), or a combination of both (200 mg/10 mg). Clinical follow-up was performed at 9 months. Rescue treatment was provided with either a concurrent diuretic (hydrochlorothiazide, 12.5 mg to 25 mg) or amlodipine (10 mg) in those cases in which arterial pressure was not reduced to adequate levels (diastolic arterial pressure >90 mm Hg or systolic pressure >180 mm Hg) by the end of the 8th week of therapy. The principal objective was to measure left ventricular mass by magnetic resonance imaging. A total of 153 patients underwent magnetic resonance imaging upon entry in the study and at the end of 9 months.

The 3 treatments induced a significant decrease of the ventricular mass. Eplerenone proved to be as effective as enalapril in reducing ventricular mass (a reduction of 14.5 for eplerenone and 19.7 g for enalapril from baseline; *P*=NS), and the combination of both drugs (27.2 g) was more effective than eplerenone alone (*P*<.05 for combined treatment as compared to eplerenone alone; *P*=NS compared with enalapril alone) to decrease hypertrophy (*P*=.007 reduction with combined treatment compared with single-drug treatment).

The 3 treatment strategies reduced diastolic arterial pressure and the albumin to creatinine ratio in urine. Combined treatment was more effective than the 2 single treatments (reduction of 74% for combined treatment, 62% for eplerenone alone, and 45% for enalapril alone). The need for complementary rescue treatment occurred in 20% of the combined treatment group, 30% of the eplerenone group, and 59% of the enalapril group.

The Effect of Losartan on Hypertrophy, Morbidity, and Mortality in Hypertensive Patients: The LIFE Study (Losartan Intervention for Endpoint Reduction in Hypertension)

Presented by Bjorn Dahlof, Goteborg, Sweden.

The study was designed around the hypothesis that losartan, a selective angiotensive (AT-1) receptor, is potentially more effective than beta-blocker treatment to reverse left ventricular hypertrophy and reduce the mortality and morbidity of hypertensive patients. In this model, losartan would reduce the incidence of combined cardiovascular mortality, cerebrovascular accident, or death in comparison with atenolol.

The study included 9222 patients, aged 55 to 80 years of age, with essential arterial hypertension (previously treated and untreated) and left ventricular hypertrophy on electrocardiogram (ECG), 9193 of who were available for follow-up based on «intention to

treat». After an average of 54 months, arterial pressure was similar in both groups. At the time of the episode or at the end of the follow-up period, the median losartan dose was 82 mg, and 50% of the patients were taking 100 mg of losartan without needing additional treatment. The average atenolol dose was 79 mg; 43% of the patients took 100 mg.

After adjusting the findings to the patients´ level of arterial pressure achieved and the Framingham score for risk of cardiovascular episode, losartan therapy was associated with a 13% reduction of arterial pressure compared with atenolol (*P*=.021). The adjusted risk of cardiovascular mortality with losartan was reduced by 11.4% (*P*=.21). The adjusted risk of fatal or non-fatal ictus was reduced by 24.9% in the group taking losartan (*P*=.001). There was also a small insignificant decrease in the risk of fatal or non-fatal myocardial infarction in the etenolol group (*P*=.49). The occurrence of diabetes mellitus at follow-up was reduced by 25% in the group treated with losartan (*P*<.001) compared with the atenolol group. In addition, the patients who had diabetes mellitus upon inclusion in the study (13%) benefited the most from losartan treatment: in these patients—they had a 24% reduction in the rate of combined episodes (*P*=.031) and a 39% reduction in overall mortality rate (*P*=.002) vs treatment with atenolol.

ARRITHMIAS

Survival in Patients with Atrial Fibrillation: The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) Study

Presented by D. George Wyse, Calgary, Alberta, Canada.

The objective of the AFFIRM study was to compare the initial treatments aimed at controlling rhythm with initial treatment aimed at controlling ventricular frequency in older patients with atrial fibrillation, in a random, controlled study at 213 institutions. The study included 4060 adults with a mean age of 69.7 years with atrial fibrillation on ECG. To be included in the study, patients had to have a documented event of atrial fibrillation for at least 6 hours during the previous 6 months, as well as an episode 12 weeks before inclusion in the study. The drugs used for the control of cardiac frequency were generally digoxin, beta blockers, and calcium antagonists. Amiodarone, sotalol, or propafenone were used for rhythm in the control arm. The use of dicoumarins was 85% to 95% in the group subjected to control of cardiac frequency and 70% in the rhythm control arm.

The prevalence of a sinus rhythm progressively decreased, and at the end of 5 years follow-up was 60% in the group assigned to rhythm control and nearly 40% in the group with control of cardiac frequency. At the end of the 5th follow-up year, effective control of cardiac frequency was achieved in more than 80% of the patients assigned to this treatment group. The principal outcome measure of the AFFIRM study was mortality due to any cause. After an average of 3.5 years of follow-up, there were 306 deaths in the cardiac frequency control group and 356 deaths in the rhythm control group (*P*=.058). The incidence of ischemic cardiovascular accidents was 5.7 in the cardiac frequency group and 7.3% in the rhythm control group (*P*=NS). Most events occurred in patients in whom anticoagulant treatment was suspended. The study established that control of cardiac frequency is an acceptable primary strategy in patients with atrial fibrillation. It appears that oral anticoagulants should be continued in all patients with risk factors for cerebrovascular accidents.

Control of Cardiac Frequency or Electrical Cardioversion in Patients with Persistent Atrial Fibrillation. Comparison of Mortality and Morbidity with 2 Random Treatment Strategies: The RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) Study

Presented by Harry Crijns, Maastrich, Holland.

This study was designed to compare the treatments for controlling cardiac frequency with those for controlling rhythm (in this case, by electrical cardioversion) in patients with persistent atrial fibrillation in a multicenter design of 35 institutions in Holland. The null hypothesis was that control of ventricular response in persistent atrial fibrillation is not less efficacious in terms of mortality and morbidity than treatment to control rhythm. The study included 522 patients with persistent atrial fibrillation or flutter were included in the study; all patients had undergone 1 or 2 electrical cardioversions in the 2 years prior to inclusion in the study. The patients were randomized to treatment that controlled cardiac frequency using beta-blockers, digoxin, or calcium antagonists with a goal of cardiac frequency less than 100 beats per minute or randomized to control of cardiac rhythm via electrical cardioversion and prophylaxis with sotalol to prevent relapse. Oral anticoagulants were used in the group treated for control of cardiac frequency that had an International Normalized Ratio (INR) of 2.0 to 3.5. In the rhythm control group, oral anticoagulants were administered during the preceding month with the intent of cardioversion and were suspended if regular sinus rhythm was obtained.

The defined outcomes of the study were a combination of cardiovascular death, hospital admissions due to

cardiac insufficiency, thromboembolic complications, serious hemorrhage, pacemaker implantation, and serious side effects related to treatment. The incidence of these combined episodes was 17.2% in the control of cardiac frequency group and 22.6% in the rhythm control group (*P*=NS). In hypertensive patients, the episode rate was 17.3% in the patients in the cardiac frequency control group and 30.8% in the rhythm control group.

Treatment that controlled ventricular function did not result in greater morbidity or mortality than treatment that aimed for cardiac rhythm control in patients with a high rate of recurrence of atrial fibrillation. A treatment strategy that controls rhythm is especially attractive for patients at high risk for suffering side-effects from anti-arrhythmia drugs and for hypertensive patients.

Improvement in Survival With the Use of Automatic Implantable Defibrillators Prophylaxis in Patients With Acute Myocardial Infarction and Left Ventricular Systolic Dysfunction: The MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) Study

Presented by Arthur J Moss, Rochester, New York, USA.

The aim of the MADIT-II study was to evaluate if implantation of an automatic defibrillator provides a survival benefit for patients with a previous myocardial infarction and advanced left ventricular dysfunction without ventricular arrhythmias or need for an electrophysiological study. The study was based on the concept that in these patients the scar on the myocardium constituted a substrate for ventricular arrhythmias and, therefore, a risk of suffering sudden death.

The study began in July 1997 and included 1232 patients from 71 centers. All patients were 21 years of age or older and had suffered a myocardial infarction at least 1 month prior to inclusion in the study corroborated by an abnormal Q-wave on ECG, elevation of myocardial necrosis enzymes, fixed defect on thallium perfusion studies, or a localized ventricular akinesia associated with angiographic evidence of occlusion of a coronary artery. All patients had a documented FEV less than 30% during the 3 months prior to inclusion in the study, documented by angiography, nuclear medicine, or echocardiography. Patients with functional class IV cardiac insufficiency, myocardial infarct (during the previous month), and revascularization procedures (during the previous 3 months) were excluded.

The patients were assigned in a 3:2 ratio to receive a defibrillator implant (n=742) or conventional treatment (n=490). After a 20-month follow-up period, the safety evaluation committee recommended premature interruption of the study because of evidence of improved survival in the group with the defibrillator. The mortality rates were 19.8% in the group with defibrillators and 14.2% in the group who underwent conservative treatment, with a risk ratio for mortality from any cause in the defibrillator group of 0.69 (95% CI, 0.51-0.93; *P*=.016), representing a relative 31% reduction in mortality for patients with defibrillator.

An analysis of subgroups demonstrated that the defibrillator had a beneficial effect on survival independent of age, sex, ejection fraction, functional class, or QRS width. The benefit occurred independently of the presence or absence of left branch block, atrial fibrillation, or time elapsed since the infarct. Nevertheless, the incidence or worsening of cardiac insufficiency was greater in patients who received the defibrillator, probably due their increased overall survival rate.

ISCHEMIC CARDIOPATHY

Study of Adenosine in Acute Myocardial Infarction: The AMISTAD II (Acute Myocardial Infarction Study with Adenosine II) Study

Presented by Allan M. Ross, Washington DC, USA.

The search for complementary treatments for reperfusion strategies to reduce size of the infarct has, to date, produced discouraging results. In the AMISTAD I study, adenosine combined with thrombolitic treatment reduced the size of the infarct by 33% compared with patients treated with placebo plus thrombolitic therapy. The AMISTAD II study included 2118 patients with acute myocardial infarction in 13 countries, randomized to 2 different adenosine doses (50 or 70 µg/kg/min for 3 hours) or placebo, followed by fibrinolitic treatment or primary percutaneous angioplasty. In a subgroup of 243 patients, the infarct size was measured gammography with sestamibi at least 5 days after the administration of treatment. The incidence of clinical episodes in the 3 groups was compared after 6 months of clinical follow-up.

For the analysis of the clinical groups, the 2 groups of patients who underwent adenosine treatment were grouped together and compared with the patients who received placebo. In an analysis based on «intent to treat», the combined mortality or cardiac insufficiency rate was 16% in the group of patients who were treated, compared with 18% in the placebo group (relative reduction of 11%; *P*=NS). It was observed that the benefit of adenosine was greater in the patients in whom reperfusion strategy was effective, and when the treatment was instituted before the development of the infarct. The gammography study revealed a 27% reduction in the size of the infarct in those patients who

received a higher dose of adenosine compared with the placebo group.

Effects of Short-Term Azithromycin Treatment on Recurrence of Ischemic Episodes in Patients with Acute Coronary Syndromes: The ARIEPACS (Azithromycin on Recurrent Ischemic Events in Patients with Acute Coronary Syndrome) Study

Presented by Bojan Cercek, Los Angeles, USA.

A random, double-blind, controlled study with placebo, designed to evaluate the effect of a short-term course of the antibiotic azithromycin on the incidence of clinical episodes in patients with acute coronary syndromes. The hypothesis of the study was that the vascular inflammation that leads to rupture of atherosclerotic plaque may be partially mediated by an infection. Therefore 1439 patients with acute coronary syndrome were randomized to receive azithromycin (500 mg the first day, followed by 250 mg/day for 4 days) or placebo. The principal outcome measure was the combination of episodes of death, non-fatal acute myocardial infarct, and recurrent ischemia that required revascularization at 6 months follow-up. The incidence of these episodes was not different between the 2 groups: 14.3% of the placebo group and 14.9% of the treated group. The incidence of clinical episodes after hospital discharge was also similar between the 2 groups (12.6% in patients who received placebo vs 12.3% in the patients who were treated). Also there was no difference observed in the rate of episodes in patients with elevated *Chlamydia* serology values (12.5% for the placebo group vs 13.1% for the azithromycin treatment). In conclusion, short-term treatment with azithromycin does not reduce the incidence of ischemic events or death during 6-month follow-up period.

Weekly Intervention With Azithromycin for Atherosclerosis and Associated Complications: The WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) Study

Presented by Michael Dunne, London, UK, and Christopher O´Connor, Durham, North Carolina, USA.

The WIZARD study was designed to study the effect of 12 weeks of treatment on clinical events in patients who had acute myocardial infarct. The study population included 7747 patients at least 6 weeks after infarct and who had high serological values of *Chlamydia pneumoniae*. The patients were randomized to receive treatment with azithromycin (600 mg/day for 3 days, followed by 600 mg/week for 11 weeks) or placebo. Study outcomes measured combined death by any cause, recurrence of acute myocardial infarction, vascularization procedure, and hospitalization secondary to infarction an average of 2.1 years after inclusion in the study. A non-significant decrease of 7% (relative) was noted in the incidence of primary events in the group treated with azithromycin. A non-significant tendency toward a benefit from treatment was also noted in men, diabetic patients, and smokers. There was no association found between initial serological values and the prognosis. The incidence of side-effects was 13.6% in patients who received the antibiotic and 5.2% in those who received placebo.

Random Evaluation of Combined Treatment with Integrelin and Enoxaparine for Treatment of Acute Coronary Syndrome: The INTERACT (Integrelin and Enoxaparine Randomized Assessment of Acute Coronary Syndrome) Study

Presented by Shaun Goodman, Toronto, Canada.

Initial treatment of high-risk patients with acute coronary syndrome involves the use of a glycoprotein IIb/IIIa inhibitor. The safety and efficacy of combination treatment with a glycoprotein IIb/IIIa inhibitor and a low molecular weight heparin are unknown. The INTERACT study was designed to determine the effect of a glycoprotein IIb/IIIa inhibitor, eptifibatide, and enozaparin in high-risk patients with acute coronary syndrome without ST segment elevation.

The study consisted of 746 patients with thoracic pain and without ST segment elevation, all of who received 160 mg aspirin, followed by 80 mg to 325 mg per day. An intravenous bolus of etifibatide 180 µg/kg was administered, followed by an infusion of 2.0 µg/kg/min for 48 hours. Afterwards, the patients were randomized to also receive non-fractionated heparin or enoxaparine. Other medication, cardiac catheterization, and the use of percutaneous revascularization techniques were left to the investigator´s discretion.

The primary outcome (serious hemorrhage at 96 hours) was more common in the group that received enoxaparine than in the group that received non-fractionated heparin (1.8% vs 4.6%; P=.03). The incidence of hemorrhage at 30 days following inclusion in the study was 5.3 in the group that received enoxaparine and 8.5% in the group that received non-fractionated heparin (P=.083).

The mortality or non-fatal myocardial infarction rate at 30 days was 9% in the group that received heparin

and 5% in the group that received enoxaparine (*P*=.31). The incidence of combined episodes of death, re-infarction, and recurrent ischemia with changes on ECG was observed in 12.6% of patients who received non-fractionated heparin vs 8.4% of the patients in the enoxaparine group (*P*=.064).

INVERVENTIONIST CARDIOLOGY

Multicenter Danish Study of Primary Angioplasty vs Fibrinolysis for the Treatment of Acute Myocardial Infarction: The DANAMI-2 (Danish Multicenter Randomized Trial on Thrombolytic Therapy versus Primary Coronary Angioplasty in Acute Myocardial Infarction-2)

Presented by Henning R. Anderson, Aarhus, Denmark.

The study included 1572 patients with acute myocardial infarction from 24 hospitals and 5 centers specialized in performing percutaneous intervention. The patients were randomized to receive either 100 mg of tPA (n=782) or immediate angioplasty with the implantation of a stent (n=790). The baseline characteristics were similar in the 2 groups in terms of arterial pressure, cardiac frequency, diabetes, and previous infarct. The average amount of time elapsed between the appearance of symptoms and treatment was 160 minutes (slighter longer in the patients who had to be transferred to a center different than that to which they were originally admitted for the performance of a revascularization procedure).

The initial results at 30 days follow-up showed a relative reduction of 40% in the rate of combined episodes (death, re-infarct, or ictus) in the patients who received intravenous treatment compared with patients with angioplasty. The greatest benefit was observed in the reduction of the rate of re-infarction (1.6% for the angioplasty group vs 6.3% in the fibrinolysis group), with slight improvement in the overall survival rate (6.6% vs 7.6%) and in the incidence of ictus (1.1% vs 2%). The studied was interrupted prematurely because of clear evidence of benefit of treatment with angioplasty.

Consequently, each of the 18 patients with acute myocardial infarction treated with primary angioplasty was able to avoid an ictus, re-infarct, and cardiovascular death. In addition, 16.6% of the patients originally treated with fibrinolysis underwent percutaneous revascularization or surgery during follow-up. The study confirmed the results of previous studies that demonstrated that early invasive treatment offers a 40% reduction in the risk of major events compared with fibrinolitic treatment with tPA.

Effects of the Thickness and Stent Design on the Long-Term Prognosis After Implantation of Intracoronary stent: The ISAR-STEREO-2 (Intracoronary Stenting and Angiographic Results-Strut Thickness Effect on Re-stenosis Outcome) Study

Presented by Helmut Schülen, Munich, Germany.

The purpose of the ISAR-STEREO-2 study was to evaluate the impact strut thickness of the stent on the rate of angiographic re-stenosis in patients with symptomatic heart disease who had percutaneous revascularization with stents. The study included 611 patients with symptomatic heart disease and stenosis in 1 native coronary artery measuring more than 2.8 mm. The patients were randomized to implantation of a stent with small struts (50 μm) or thick struts (140 μm). The diameter of the vessel, the length of the lesion, and the lumen diameter were compared in the 2 groups, as was the use of glycoprotein IIb/IIIa inhibitors. The procedure had a more than 99% success rate in both groups.

Quantitative angiography at 6 months revealed greater minimum lumen diameter and less late loss of lumen in patients who received stents with small struts. The angiographic rate of re-stenosis at 6 months was 17.9% in the patients with stents with small struts and 31.4% in the patients who received stents with thick struts (*P*<.001). The rate of clinical re-stenoisis (revascularization of vessel treated) was also significantly less in the patients who received stents with small struts (12.3% vs 20.9%; *P*=.002).

In conclusion, the thickness of the strut had a significant impact on the course of patients who had revascularization with stents. Angiographic re-stenosis was reduced to 43% and revascularization of the treated vessel wase reduced to 44% with the use of stents with small struts.

Implantation of Intracoronary Stents: A Random Study of 1000 Patients Comparing the Pre-dilation Treatment With the Direct Stent Method: The TRENDS (Tetra Randomized European Direct Stenting) Study

Presented by Keith D. Dawkins, Southampton, United Kingdom.

In comparison to the pre-dilation treatment, the implantation of a direct stent in the coronary arteries reduced procedure time, use of resources, risk of non-protected barotraumas on the artery, and embolization. Nevertheless, direct stent implantation can have a greater rate of failure by crossing the lesion or by incomplete stent expansion. Treatment with direct stent im-

plantation is widely used in Europe, but there is little evidence to support its generalized use. The TRENDS study included 1000 patients with symptomatic angina and single re-stenosis or *de novo* lesions in the native coronary arteries. Patients with acute myocardial infarction 24 hours prior to the study were excluded, and more than 90% of the patients in each treatment group had single vessel disease. The patients were randomly assigned to either pre-dilation or direct stent strategies, and the results were compared at 30-day follow-up. No increased incidence of serious side effects (death, myocardial infarct, coronary revascularization surgery, or a need to repeat the revascularization procedure) were observed in the patients who underwent the direct stent procedure at 30-day follow-up (3.4% for the direct stent group vs 4.2% in the pre-dilatation group; *P*=NS). Failure was observed in the stent implantation if only 5.8% of the patients who underwent direct stent strategy.

Heparin-Covered Stents in Small Coronary Arteries: The COAST (Heparin-Coated Stents in Small Coronary Arteries) Study

Presented by Michael Haude, Essen, Germany.

The COAST study randomized 600 patients from 21 European centers with vessel lesions between 2 mm and 2.6 mm in size into 3 treatment groups: conventional angioplasty, non-covered stent, and heparin-covered stent. Eight percent of the patients presented with multi-vessel disease, and patients with a developing acute myocardial infarction were excluded. All patients were pre-treated with aspirin and 10 000 units of heparin. The patients in the 2 groups with stents also received conventional doses of ticlopidine for 4 weeks following the procedure. The 3 groups had similar baseline clinical and angiographic characteristics at the time of inclusion in the study. At the end of the 6-month follow-up period, the number of patients available for clinical and angiographic evaluation was, respectively, 195 and 155 in the conventional angioplasty group, 196 and 156 in the non-covered stent group, and 197 and 155 in the covered stent group. There were no differences observed in restenosis between the 3 groups at the end of the 6-month follow-up period (32% in the group with balloon angioplasty, 25% in the group with uncovered stent, and 30% in the group of patients with heparin-covered stents; *P*=NS); this difference may have been due to a weakness in the study design. Also, an identical rate of late loss among the 3 groups was observed, and no difference in the rate of side-effects, death, or survival free of events was observed in the treatment groups.

Random Study of the MULT-LINK Stent, with or Without Supplement Directional Arterectomy for Revascularization of Coronary Artery Lesions: The AMIGO (Atherectomy and Multilink Stenting Improves Gain and Outcome) Study

Presented by Antonio Colombo, Milan, Italy.

Seven hundred fifty-three patients from 6 European centers were randomized, 381 of who received directional arterectomy followed by stent and 372 who received stent alone. Both groups were similar with regard to size of the lesion (14.6 in the stent only group vs 14.3 in the arterectomy-stent group). At the end of 8 months no significant differences were observed in the rates of re-stenosis by angiography (24.1 arterectomy-stent group vs 19.7 in the stent group). In the centers with a higher success rate with the arterectomy procedure, it was observed that the technique may improve the efficacy of the stent. The re-stenosis rate in these centers was 21.8% for the group with stent only, 31.8% for those with a suboptimal arterectomy, and 16.2% for those with optimal arterectomy. Nevertheless, only 21.5% of the lesions treated achieved optimal arterectomy. The re-stenosis rate for bifurcated lesions was 9.8% in the patients in the DCA/stent group and 20.9% for the stent only group.

Safety and Efficacy of the Tacrolimus-Covered Stent: Short- and Medium-Term Results of the PRESTENT (Preliminary Safety Evaluation of Nonporous Tacrolimus Eluting Stents) and EVIDENT (Endo-Vascular Investigation Determining Safety of a New Tacrolimus Eluting Stent Graft) Studies

Presented by Eberhard Grube, Siegburg, Germany.

The results of phase I of the study on tacrolimus-covered stents (PRESTENT) and EVIDENT did not report any cases of death, acute myocardial infarction, or the necessity for revascularization of the artery in question. The PRESENT study included 30 patients who received a stent covered with ceramic material, and another 30 patients who received an identical stent that also included 60 µg of tacrolimus. Follow-up was scheduled at14 days, and at 6 and 12 months. Two patients who received the coated stent developed coronary side-effects (unstable angina), 1 at 67 days post-implant and the other at 59 days post-implant. In the EVIDENT study, 15 patients received the stent covered with µg of tacrolimus and did not experience any clinical episodes. The presenter concluded that, given the

preliminary data, the ceramic covering is effective, although 2 patients, both of whom received low doses of the drug, did experience negative side-effects.

Random, Double-Blind, Controlled Study with Placebo on the Usefulness of Fluvastatin Following Percutaneous Coronary Revascularization in Patients with Heart Disease: The LIPS (Lescol Intervention Study)

Presented by Patrik W. Serruys, Rotterdam, Holland.

The LIPS study is the first prospective study to evaluate the benefit of using statins in patients after implantation of an intracoronary stent. A total of 1677 patients from 57 centers in 10 countries were randomized to receive 40 mg of fluvastatin (n=844) or placebo (n=833) twice a day following coronary revascularization. Unlike other studies that have evaluated the efficacy of statins, a great number of patients in both groups had a previous history of acute myocardial infarction (44%) or angina (89%). The principal aim of the study was to evaluate the time elapsed until the occurrence of an episode (cardiac death, non-fatal infarct, percutaneous revascularization, or surgery) during a 4-year period following the intervention.

A 22% reduction in the combined episode rate was noted with fluvastatin vs (*P*=.013). The benefits were greatest in diabetic patients (12% of the study population), in whom there was a 47% reduction in the episode rate vs placebo (*P*=.041). In the patients with multiple-vessel disease, the reduction in the number of episodes was 34% (*P*=.001).

The cholesterol values decreased significantly in the group treated with 131.7 mg/dL to 99.1 mg/dL at the end of the 4-year follow-up period, without there being any change in the placebo group. There was no increase in creatin kinase in the patients who received fluvastatin. In conclusion, treatment of 19 patients with fluvastatin for 4 years prevented a serious event during that period.

CARDIAC INSUFFICIENCY AND TRANSPLANT

Prospective Blind Study on the Utility of Type B Natriuretic Peptide as a Diagnostic Test for the Diagnosis of Cardiac Insufficiency in the Emergency Department: NBP (Not Breathing Properly) Study

Presented by Alan S. Maisel, San Diego, California, and Marc A. Pfefer, Boston, Massachusetts, USA.

The aim of the study was to evaluate the safety of the immediate bedside use of type B natriuretic peptide to diagnose cardiac insufficiency compared with a clinical diagnosis based on the criteria of the Framingham and NHANES studies. The study included 1586 patients from 7 centers seen between April 1999 and December 2000. All the patients were of legal age, provided informed consent, and had dyspnea as the reason for presenting in the emergency department. Patients on dialysis, with acute myocardial infarction, or with an obvious cause of the dyspnea, such as cardiac trauma, were excluded from the study.

The final diagnoses were cardiac insufficiency in 744 patients, absence of cardiac insufficiency in 770 patients, and signs of ventricular dysfunction without cardiac insufficiency in 72 patients. Mean BNP for each of these groups was 600 pg/mL for the patients with cardiac insufficiency, 150 pg/mL for the patients with ventricular dysfunction, and 50 pg/mL for the patients without cardiac insufficiency. The BNP value for determining patients with and without cardiac insufficiency was 0.91. The BNP values as a function of NYHA functional class were 150 pg/mL for class I patients, 250 pg/mL for class II patients, 550 pg/mL for class III patients, and 900 pg/mL for class IV patients. Using a cut-off point of 100 pg/mL, the BNP provided an exact diagnosis in 81.1% of patients vs 74% diagnosed clinically (73% by Framingham classification and 67% by NHANES classification). In addition, 43% of the patients were unclassifiable by clinical criteria, and this number could have been reduced to 11% using the BNP criteria. This study suggests that BNP is superior to clinical criteria for the diagnosis of cardiac insufficiency and should be included in the clinical diagnostic guidelines for this disease.

Effects of an Endothelin Receptor Antagonist (Bosentan) on the Mortality-Morbidity of Patients with Chronic Cardiac Insufficiency: Results of the ENABLE 1 and 2 (Effects of Endothelin Receptor Antagonist Bosentan on the Morbidity and Mortality in Patients with Chronic Heart Failure) Studies

Presented by Milton Packer, New York, USA.

Bosetan is a new endothelin receptor antagonist that has been approved for use in the USA for treatment of arteriopulmonary hypertension. The aim of the ENABLE studies was to evaluate whether a low dose of this drug could produce a beneficial effect on patients with chronic cardiac insufficiency.

One thousand six hundred thirteen patients with cardiac insufficiency were randomized to receive placebo (n=808) or 62.5 mg of bosentan twice a day for 4 weeks followed by 125 mg twice a day (n=805). These doses of bosetan were between 10% and 25% lower than those previously studied. The patients were followed for 600 episodes or 1.5 years.

The results showed there was no benefit of treatment with the drug in terms of mortality or hospitalization due to cardiac insufficiency. The rate of episodes was 40% in the patients in the placebo group vs 39% in the treated group (risk factor, 1.01; 95% CI, 0.86 to 1.18; *P*=.9). There was no difference in terms of death due to any cause in the 2 groups (risk factor, 94; 95% CI, 0.75 to 1.16; *P*=.54).

Treatment with bosetan was associated with unexpected retention of liquid in the patients treated, resulting in changes in body weight and the hemoglobin rate from the first 2 weeks of treatment, using a low dose of the drug. Although this side-effect did not worsen with increases in the bosetan dose, they did persist during follow-up, in spite of that fact that the investigators increased the use of diuretics. The patients with a greater degree of hydrosaline retention had the greatest risk of mortality and cardiovascular episodes. Use of this type of drug for cardiac insufficiency will require much more aggressive use of diuretics and even lower doses of bosetan.

Results of the InSync-ICD Study

Presented by James B. Young, Cleveland, Ohio, USA.

The InSync-ICD study was performed to verify the usefulness of the combination of a device with 2-chamber resynchronization, the detection of tachycardia and ventricular fibrillation, cardioversion therapy, defibrillation therapy, biventricular stimulation, and exclusive sensation of the right ventricle. Patient with cardiac insufficiency in NYHA functional class II to IV, with QRS longer than 130 ms, a VI ejection fraction less than 35%, and a telediastolic VI diameter larger than 55 mm were included in the study once medical treatment had been established. The device was implanted in all patients who were then randomized to activation or non-activation of the resynchronization function. The defibrillation function remained active in all patients.

Six hundred and thirty-six patients were included, although only 371 patients ultimately received the implant, with a safety and efficacy rate of 88% and 90% of the implants being successful.

A clinical improvement in the patients treated with resynchronization vs the control group was noted: 63% of the treated group improved in functional class compared with 47% of the control group; 34% of the treated group and 48% of the control group had no change in functional class; 3% of the treated group worsened in comparison with 5% of the control group. A 55% improvement in combined clinical episodes was observed in the group of patients treated vs 40% in the control group.

The Maximum Benefit of Ventricular Assistance Devices is Observed in Patients Who Receive IV Inotropic treatment: A Sub Analysis of the REMATCH (Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart failure) Study

Presented by Lynne Warner Stevenson, Boston, Massachusetts, USA.

A sub analysis of the results of the REMATCH study demonstrated that patients who received IV inotropic treatment were those who most benefited from implantation of ventricular assistance devices. Previously published results of the REMATCH study showed a 46% mortality rate with implantation of ventricular assistance devices compared with those who received medical treatment alone. At the end of 1 year, the survival rate was 51% in patients who received mechanical assistance vs 28% in patients who only received medical treatment. At the end of 2 years, the mortality rate in both groups was 28% in the group who received mechanical assistance vs 10% in the medical treatment only group.

This sub-study analyzed the results in a subgroup of 129 patients with an FEVI of less than 25%, functional class IV cardiac insufficiency, non-candidates for cardiac transplant, and under medical treatment during the previous 3 months. These patients had a more serious clinical picture than participants in other studies of cardiac insufficiency did. A total of 91 of the 129 patients were receiving intravenous inotropic drugs at the time of inclusion in the study. A tendency toward a worse survival rate was observed in these patients than those in the rest of the REMATCH study. Nevertheless, the sub-analysis showed that use of IV inotropic drugs was not associated with worse survival rates in the patients assigned to the group with implantation of mechanical assistance devices. At the end of 1 year, 49% of the patients with ventricular assistance who received IV drug treatment were alive, compared with 22% of the patients treated only medically. Therefore, the investigators concluded that the maximum benefit of implantation of a mechanical device occurs in patients who also receive IV inotropic medication. The use of these devices in less seriously ill populations is not expected to provide the same benefit.

Treatment with a Vasopeptidase Inhibitor, Omapatrilat, vs Enalapril in Patients with Cardiac Insufficiency: The OVERTURE (Omapatrilat versus Enalapril Randomized Trial of Utility in Reducing Events) Study

Presented by Milton Packer, New York, USA.

This is the largest study to date to evaluate the usefulness of treatment with a new type of vasopeptidase

inhibitors for cardiac insufficiency. The study included 5770 patients, with the following inclusion criteria: NYHA functional class II and IV cardiac insufficiency, symptoms for more than 2 months, hospitalization for cardiac insufficiency during the previous year, and an EF of less than 30%. The patients were randomized to receive a target dose of 10 mg of enalapril twice a day or 40 mg of omapatrilat once a day. The principal outcome studied was the combination of death or hospitalization due to cardiac insufficiency. More than half the patients also received beta-blocker treatment and more than 40% were undergoing treatment with spironolactone upon inclusion in the study. A follow-up period was established of 8 months from the inclusion of the last patient or until 80 deaths had occurred. The study was designed around the hypothesis that the efficacy of omapatrilat was the same as enalapril.

The results showed an incidence of events in 34% of the enalapril group vs 32% in the group treated with omapatrilat (non-significant reduction of 6%, with 0.94 risk factor). In conclusion, the OVERTURE study demonstrated equivalent, but not superior, effects of omapatrilat in comparison with enalapril.

Rejection of Heart Graft Through Detection with Low Level Alkanes on Respiratory Testing: The HARDBALL (Heart Allograft Rejection: Detection with Breath Alkanes in Low Levels) Study

Presented by Michael Phillips, New York, USA.

The study included 539 patients scheduled for endomyocardial biopsy to detect rejection of a cardiac graft, with the aim of analyzing the use of a new method of analyzing the breath. This test was also used in a control group consisting of the same number of healthy volunteers. The technique analyzes the air samples to identify the presence or absence of methylated previously identified as rejection markers (c4 to C20) by mass spectography. Nine of these composites have shown an association with grade 3 rejection.

The result of this study was that the analysis of exhaled air was as effective as an endomyocardial biopsy in determining the absence of rejection (negative predictive value of both techniques was 97.3% and 97.5%, respectively). Therefore, although measurement of alkanes showed a specificity and positive predictive value inferior to that of a biopsy, the high predictive negative value indicates that patients with transplant with a negative respiratory test would have nothing to gain by undergoing an endomyocardial biopsy. With use of the respiratory test, the number of endomyocardial biopsies in transplant patients could be reduced by 41%.