

Summary of the Clinical Studies Reported in the Scientific Sessions of the American Heart Association (9-12 November, 2003, Orlando, Florida)

A few clinical trials were selected for presentation at special sessions of the American Heart Association Scientific Sessions of 2003. These trials were chosen because of their particular importance and the results were presented orally. Although the structured abstracts of these communications have already been published,¹ we provide herein a summary of their aims, methods and results. It should be borne in mind that the final results of most of these studies have yet to be published as original articles, so the information provided here should be considered preliminary.

PRIMARY AND SECONDARY PREVENTION

Cardiovascular Disease Risk Reduction in Low Income Patients (HDOM Study: Heart Disease on the Mend)

Presented by William L. Haskell, Palo Alto, CA, USA

Numerous studies have demonstrated the effectiveness of multifactorial cardiovascular disease risk prevention programs. The aim of this study was to assess whether this type of program is also effective in very underserved groups who lack medical insurance

and who mostly come from North American ethnic minorities. Patients at very high risk for cardiovascular disease were identified from among those attending centers where low-income groups receive medical care in the county of Santa Clara (California). Forty-nine patients were randomized to receive usual care and 99 were assigned to receive individualized multifactor cardiovascular risk reduction management. Although the patients crossed over to the other treatment arm after the first 12-month intervention period, the results presented here refer exclusively to the first intervention period.

Individualized management, which included life-style recommendations and treatment of major cardiovascular risk factors, in accordance with American recommendations, was undertaken by a nurse practitioner and a dietician who both spoke the patient's language. Life-style interventions focused on smoking cessation, advice on diet and exercise and combating obesity and stress. The patients had a mean of 6 clinical visits during the study year, each lasting about one hour. The mean age of the patients was 59 years. Patients were excluded if they had known heart disease or any other severe disease. English was the mother tongue in just 18% of the patients, and 45% were unable to communicate in English; 57% were Hispanic. Achievement of the primary end point regarding low-density lipoprotein cholesterol was better in the intervention arm (104 mg/dL) compared with those receiving usual care (116 mg/dL; $P=.01$). The other main aim, reduction of systolic blood pressure, was also better in the intervention group compared with the control group (128 vs 137 mm Hg; $P=.001$). The effect of intervention on cardiovascular risk factors was also significant for other secondary objectives, such as

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total cholesterol, triglycerides, glycemia, physical exercise and nutritional status. No significant differences were seen in total body mass or stress reduction. These results show that primary prevention intervention programs can lead to a reduction in cardiovascular risk factors in very low income groups and highlight the need to globalize access to health care resources.

Secondary Prevention in Women (WITTI-Women: Secondary Prevention Beyond Walls Intervention Trial In Women)

Presented by Lori Mosca, New York, NY, USA

The aim of the study was to assess whether educational intervention was related with a risk reduction in women with ischemic heart disease, compared with standard prevention recommendations. The women were randomized to receive standard care (n=153) or structured intervention (n=151), with specific subgroup analysis according to ethnic minority. Management was based on eight specific points: smoking cessation, weight management, physical exercise, blood pressure below 140/90 mm Hg, use of aspirin, beta-blockers and angiotensin-converting-enzyme inhibitors. No differences were noted in any of the 8 goals after 6 months follow-up or in the proportion of goals met between the 2 groups. However, women from ethnic minority groups were 2.4 times more likely to reach the blood pressure goal in the structured intervention group compared with minority women in the control group, a significant difference. In conclusion, the study showed that this particular structured intervention failed to result in increased adherence rates to secondary prevention measures in women. Nevertheless, specific programs may lead to improved blood pressure control in women from ethnic minorities.

Effects of Fosinopril and Pravastatin on Cardiovascular Events in Microalbuminuric Subjects Without Hypertension or Hypercholesterolemia (PREVEND IT Study: Prevention of Renal and Vascular Endstage Disease Intervention Trial)

Presented by Folkert Asselbergs and W.H. van Gilst, Groningen, Holland

Microalbuminuria is associated with an increased risk of cardiovascular and renal disease. This study was designed to assess whether therapy aimed specifically at lowering urinary albumin excretion was

able to reduce adverse cardiovascular and renal events in patients with microalbuminuria but without hypertension or hypercholesterolemia. Of the initial 8592 persons screened, 1439 were eligible for inclusion in the PREVEND trial, and of the 864 patients randomized to receive fosinopril 20 mg or its placebo and pravastatin 40 mg or its placebo, 854 were considered suitable for final analysis. The mean follow-up period was 46 months and the primary end point was cardiovascular mortality, hospitalization for cardiovascular disease and end-stage renal disease. Three point two percent of the patients had a history of cardiovascular events, 4.8% were using cardioactive medication and the median urinary albumin excretion was 22.9 (25.8-41.8) mg/24 hours. The primary end point occurred in 42 (4.9%) patients. Fosinopril reduced urinary albumin excretion by 23% ($P<.001$). The patients treated with fosinopril had a 44% reduction in the incidence of the primary end point (hazard ratio [HR]=0.56; 95% confidence interval [CI], 0.30-1.04; $P=.07$; and after adjusting for covariables, HR=0.53; 95% CI, 0.28-0.995; $P=.048$). Pravastatin had no effect on urinary albumin excretion and was associated with a non-significant reduction in the primary end point of the study compared with patients in the corresponding placebo group (HR=0.75; 95% CI, 0.41-1.38; $P=.35$). Treatment with fosinopril in microalbuminuric patients without hypertension or hypercholesterolemia resulted in a significant effect on urinary albumin excretion. The reduction in urinary albumin excretion was associated with a trend toward a reduction in the incidence of cardiovascular events. Treatment with pravastatin failed to result in a significant reduction in urinary albumin excretion or in adverse cardiovascular events.

ARRHYTHMIAS

Anti-Arrhythmic Effects of Omega-3 Fatty Acids in Survivors of Ventricular Tachyarrhythmias

Presented by Merritt Raitt, Portland, OR, USA

The aim of the trial was to determine whether treatment with omega-3 polyunsaturated fatty acids (fish oil) were related with a reduction in the time to appearance of an episode of ventricular tachycardia (VT) or fibrillation (VF) compared with a placebo in patients with documented ventricular tachyarrhythmias and an implanted automated defibrillator (ADF). In a multicenter study, 200 patients were randomized to receive omega-3 polyunsaturated fatty acids (1.8 g/day) or placebo

(olive oil) and were then followed up for 2 years. No differences were seen in the primary end point between the 2 groups ($P=.19$). Contrary to the initial hypothesis, there was a trend toward an increased incidence of ventricular arrhythmias in the fish oil group. In the subset of patients with an ADF implanted to control VT, the incidence of VT/VF was earlier than in the placebo group ($P=.007$). No differences were detected between the treatments in the group with an ADF implanted to control VF. The incidence of recurrent episodes of VT/VF was also greater in the treated group. There was a trend toward reduced mortality in the fish-oil group ($P=.09$), though the authors recognized that the study lacked the statistical power to detect differences in clinical events. In a subset of patients who also underwent electrophysiological studies, no electrophysiological benefits were noted after treatment (effective ventricular refractory period, inducibility of VT or VF, and defibrillation threshold). In conclusion, unlike observations in patients who have had an acute myocardial infarction, no reduction in the rate of ventricular arrhythmias was seen in this group of patients after treatment with omega-3 polyunsaturated fatty acids.

Ximelagatran for the Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation (SPORTIF V Study: Stroke Prevention Using Oral Thrombin Inhibitor in atrial Fibrillation-V)

Presented by Jonathan Halperin, New York, NY, USA

This program was designed to examine the safety and efficacy of ximelagatran (orally active direct thrombin inhibitor) in patients with non-rheumatic atrial fibrillation and at least one additional risk factor for stroke. The trial was randomized and double-blind, with the hypothesis that ximelagatran is no less effective than warfarin for the prevention of systemic embolic events in these patients. The patients assigned to treatment with ximelagatran underwent sham testing and dose adjustment of dummy warfarin to simulate the experimental conditions of the group of patients treated with warfarin.

The mean international normalized ratio of the patients treated with warfarin was 2.4, and 68% of the measurements in this group were within the range of 2.0-3.0. During a mean follow-up period of 20 months, the annual incidence of stroke or systemic embolism was 1.2% in the patients on ximelagatran and 1.6% in those on warfarin. These rates satisfied the aim of showing that ximelagatran is no less effective than warfarin (absolute increased risk of 0.45%; $P=.13$). No differences were seen in

the combination of the primary end point and all-cause mortality, nor were there any differences between the 2 groups in the incidence of hemorrhagic stroke (0.06% in both groups) or major bleeding ($P=.16$). An elevation of liver enzymes up to three times the normal concentration was seen, more frequently in the ximelagatran group. In conclusion, treatment with ximelagatran is as effective as warfarin for the prevention of stroke and peripheral embolism in patients with nonvalvular atrial fibrillation and an associated risk factor. The advantages of this drug are its fixed dosing and its lack of requirement for coagulation monitoring.

Randomized Controlled Trial to Compare the Safety and Efficacy of Rectilinear Biphasic Defibrillation in Out-of-Hospital Cardiac Arrest (ORBIT Study: Out-of-Hospital Rectilinear Biphasic Investigation Trial)

Presented by Laurie Morrison, Toronto, Canada

This trial was undertaken by professional paramedics involved in the emergency medical care of patients with sudden out-of-hospital death due to ventricular fibrillation or syncopal ventricular tachycardia in the city of Toronto, Canada. The trial was based on prior evidence indicating that a rectilinear biphasic current is superior to a monophasic current for effective defibrillation. The trial included 436 patients (28% were women) with randomization of the defibrillators in the different ambulances. The energy used in the biphasic devices was 120 J, 150 J and 200 J, instead of the 200 J, 300 J and 360 J of the conventional defibrillators. No differences were seen between the 2 groups in the primary end point of conversion after one shock (32% for biphasic vs 26% for monophasic, $P=.2$), or in the recovery of rhythm after 1-3 shocks. The only significant difference favored the biphasic defibrillation group in their response to the first highest-energy shock. There were no differences in survival rates between the 2 groups, and only 6%-7% of patients were alive at discharge. Although biphasic defibrillators are smaller, use less energy and have longer-lasting batteries, they did not prove clinically superior to monophasic defibrillators in restoring normal heart rhythm after sudden out-of-hospital cardiac arrest.

Study on Public Access Automated Defibrillators (PAD Trial: Public Access Defibrillation)

Presented by Joseph P. Ornato, Richmond, VA, USA

The aim of this trial was to determine whether persons trained to undertake cardiopulmonary resuscitation, call the emergency services and use an automated external defibrillator, compared with persons trained to perform just resuscitation maneuvers and phone the emergency services, increases survival of persons who suffer an out-of-hospital cardiac arrest. A total of 993 community units in public or residential sites, but not in homes, were selected because the likelihood of the occurrence of a sudden out-of-hospital cardiac arrest during the previous year was greater than 50%. Approximately 20 000 lay volunteers were trained and 1600 automated external defibrillators installed. The volunteers, randomly assigned to 1 of the 2 strategies, underwent initial training and 1 or 2 retraining sessions during the study period. Public areas with on-site medical personnel, such as industrial zones, or covered by security staff trained to treat sudden out-of-hospital cardiac arrest were excluded from the trial. The primary outcome measure was survival to hospital discharge.

Even though the overall event rate was very low during the 21-month period, the number of patients with sudden out-of-hospital cardiac arrest treated by the group using resuscitation plus defibrillation was higher than the patients treated with resuscitation alone (129 vs 103). The number of survivors was lower in the group receiving just resuscitation compared with the group receiving defibrillation as well (15 vs 29; $P=.042$). The improvement in survival was more notable in public areas than residential units. In conclusion, training of lay volunteers in cardiopulmonary resuscitation and the use of an automated external defibrillator led to increased survival of persons with sudden out-of-hospital cardiac arrest. An ongoing study is in progress to determine the usefulness of resuscitation and defibrillation in the home, where 75% of all out-of-hospital cardiac arrests take place.

Prophylactic Implantation of Implantable Defibrillators in Patients With Non-Ischemic Dilated Cardiomyopathy (DEFINITE Trial: Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation)

Presented by Alan H. Kadish, Chicago, IL, USA

The DEFINITE trial is the first randomized study aimed at evaluating the usefulness of automated implantable cardioverter defibrillators in patients with non-ischemic dilated cardiomyopathy. The trial

included 458 patients with an ejection fraction of less than or equal to 35% and marked nonsustained ventricular extrasystoles or ventricular tachycardia on ambulatory monitoring. The primary end point was all-cause mortality 2 years from inclusion. Each group was composed of 229 patients, more than 85% of whom were being treated with beta blockers. Baseline characteristics were similar between the defibrillator group and the control group, except that patients in this latter group had a longer history of cardiomyopathy. No significant differences were seen in overall mortality at 2 years (13.8% in the control group vs 8.1% in the defibrillator group; $P=.06$). However, fewer sudden deaths occurred in the therapy group (3 vs 11; $P=.01$). Subgroup analysis showed a reduction in overall mortality (33% in the control group vs 13% in the defibrillator group; $P=.009$) in patients with class III heart failure at the time of inclusion (21% of the study population). Thus, this study shows that the prophylactic use of an automated implantable cardioverter defibrillator is related with a non-significant reduction in mortality in patients with non-ischemic dilated cardiomyopathy.

ISCHEMIC HEART DISEASE

Valsartan, Captopril or Both for Acute Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction or Both (VALIANT Trial: VALsartan In Acute myocardial infarction Trial)

Presented by Marc A. Pfeffer, Boston, MA, USA

The VALIANT trial showed no benefit after treatment with valsartan alone or in combination with captopril compared with captopril alone in patients with acute myocardial infarction and ventricular dysfunction or heart failure. The final results of the study have already been published.²

Randomized Controlled Trial of Intracoronary Autologous Bone Marrow Cell Transplantation After Acute Myocardial Infarction

Presented by Kai C. Wollert, Hannover, Germany

The aim of this trial was to determine the safety and efficacy of the intracoronary transfer of bone marrow cells compared with placebo in patients with acute myocardial infarction and ST-segment elevation undergoing primary or rescue angioplasty. This open, randomized study included 30 patients in each group. The intervention group underwent bone

marrow aspiration (approximately 100 mL) by sternal puncture. The nucleated cells were then purified by sedimentation and infused via a catheter into the infarct-related artery. Ventricular function was assessed by cardiac nuclear magnetic resonance imaging at the time of inclusion in the study and after 6 months follow-up. There were no differences between groups in age, time to angioplasty, creatine kinase levels or baseline ejection fraction ($51.3 \pm 9.39\%$ vs $50.0 \pm 10.0\%$ in the control and intervention groups, respectively). At the end of the follow-up period, the left ventricular ejection fraction had improved by $0.7 \pm 8.1\%$ in the control group compared with $6.7 \pm 6.5\%$ ($P < .01$) in the autologous bone marrow transfer group. No evidence of proarrhythmia was detected in the intervention group on repeated Holter monitoring or by electrophysiological study and no differences were found between the 2 groups during the MRI follow-up. This first randomized study of the effect of bone marrow transplantation in patients with an acute myocardial infarction showed a beneficial effect on systolic function after 6 months.

INTERVENTIONAL CARDIOLOGY

Fibrinolysis and Abciximab Versus Abciximab Prior to Primary Angioplasty in Patients With Acute Myocardial Infarction (BRAVE Trial: Bavarian Reperfusion Alternatives Evaluation)

Presented by Adnan Kastrati, Munich, Germany

The aim of this trial was to assess the usefulness of the combined administration of abciximab plus thrombolysis in patients with acute myocardial infarction due to undergo percutaneous coronary revascularization. This open-label, randomized trial undertaken in Germany included 253 patients. The patients were randomized to receive a half dose of reteplase (2 boluses of 5 U) followed by abciximab (a bolus followed by a 12 hour infusion) or abciximab alone prior to percutaneous coronary intervention. Scintigraphic study with technetium sestamibi was undertaken to compare infarct size 5-10 days after randomization (primary end point). The operators were blinded to the study group. The trial included 253 patients, 74% of whom were randomized in community hospitals and transferred to a center with facilities for primary angioplasty (mean distance 39 km). Intracoronary stents were implanted in 92% of the patients. Two patients in each group died during the 30-day follow-up. The infarct size was 13% in the combined treatment group and 11.5% in the control group ($P = .81$). No

differences were seen in the rate of combined events of death, reinfarction and stroke. There was a trend toward major bleeding in the fibrinolysis group. Subset analysis showed no differences related with the type of center at the time of inclusion, a very short time from the onset of pain or a greater delay from inclusion to angioplasty. Thus, the combination of reteplase plus abciximab is no better than abciximab alone in patients with acute myocardial infarction referred for primary angioplasty.

Comparison of Intensive Versus Moderate Lipid-Lowering Therapy in Progression of Coronary Arteriosclerosis Measured by Intravascular Ultrasound (REVERSAL Trial: REVERSing Atherosclerosis with Aggressive Lipid Lowering)

Presented by Steve Nissen, Cleveland, OH, USA

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) lower atherogenic lipoproteins and cardiovascular disease and death. However, the optimal treatment regimen and the initial ideal level of lipid reduction are still not well-defined. The authors therefore compared the effects of moderate and intensive lipid-lowering therapy on the changes in total coronary vessel atheromatous plaque burden, as assessed by intravascular ultrasound. The trial, which was a multicenter, double-blind, randomized study with a control group receiving active treatment, compared the effect of 2 statins, given for 18 months, on the total burden of atheromatous plaque measured by intracoronary ultrasound in 34 community and tertiary care centers in the United States. Of the 2163 patients who initially gave their consent to participate in the study, 605 were eventually randomized, and 502 completed the trial. The patients were randomized to receive moderate lipid-lowering therapy (pravastatin 40 mg) or intensive lipid-lowering therapy (atorvastatin 80 mg) for 18 months. Intravascular ultrasound was undertaken during baseline catheterization and at the end of the follow-up period. The primary end point for efficacy was the percent change in atheroma volume (follow-up minus baseline).

Mean baseline low-density lipoprotein cholesterol levels were reduced from 150.2 to 110 mg/dL in the moderate lipid-lowering therapy group and to 79 mg/dL in the intensive lipid-lowering therapy group ($P < .0001$). C reactive protein levels fell by 5.2% with pravastatin and 36.4% with atorvastatin ($P < .0001$). The primary end point (percent change in atheroma volume) showed progression in the pravastatin arm (+2.7%; $P = .001$, compared with

baseline) but no change in the atorvastatin arm (-0.4% ; $P=.98$, compared with baseline), indicating no progression. The rate of progression was significantly lower in the patients who received atorvastatin ($P=.02$).

Similar data were found when the secondary end points were analyzed by intravascular ultrasound, including the change in total atheroma volume ($P=.02$), the change in percent atheroma volume ($P<.0002$) and the change in atheroma volume in the worst affected subsegment (10 mm long) of the artery ($P=.01$). The atorvastatin group showed no progression of coronary artery disease in the 22 prespecified study subgroups. In patients with low-density lipoprotein cholesterol levels from 125-210 mg/dL, intensive therapy with atorvastatin 80 mg halted progression of coronary atherosclerosis, whereas a more moderate treatment with pravastatin 40 mg was associated with disease progression. These differences could be due to the greater reduction in atherogenic lipoproteins and C reactive protein in the patients treated with atorvastatin. More aggressive lipid-lowering therapy than currently recommended may be necessary in patients with coronary artery disease, especially in those at greater risk for disease and death.

Sirolimus-Coated Stent for the Prevention of Restenosis in Patients With Diabetes (DIABETES Trial: DIABETes and sirolimus Eluting Stent)

Presented by Manuel Sabaté, Madrid, Spain

Patients with diabetes mellitus treated with coronary stents have a higher rate of major adverse events during follow-up than non-diabetic patients. Sirolimus-eluting stents (SES) provide an alternative to standard bare metal stents (BMS) for the prevention of *de novo* lesions with a low to moderate risk for restenosis. DIABETES is a prospective, randomized, multicenter, placebo controlled study to assess the efficacy of SES to prevent neointimal hyperplasia in diabetic patients. To obtain a 56% reduction in late lumen loss, 140 patients were randomized to SES ($n=70$) or BMS ($n=70$) (estimating a late lumen loss of 0.73 mm in the BMS group and 0.32 mm in the SES group, with a standard deviation of 0.7 mm, an alpha error of 0.05 and a beta error of 0.10, assuming a 10% loss to follow-up). The primary end point of the trial is late lumen loss in the whole study segment (stent plus edges), as assessed by quantitative coronary angiography at 9-month follow-up. The secondary end points include the rate of restenosis at 9 months, neointimal hyperplasia assessed by intravascular ultrasound at 9

months, the incidence of subacute and late stent thrombosis, major adverse coronary events and the presence of edge effects, late stent malapposition and coronary aneurysms at 9 months. Diabetic patients who were insulin or non-insulin dependent (in accordance with the World Health Organization 1999 criteria) were considered suitable for inclusion in the study if they had important coronary artery lesions (1, 2, or 3 vessels) and signs or symptoms of myocardial ischemia. The patients were also stratified according to the type of diabetes (insulin dependent or non-insulin dependent). The study protocol recommended the use of abciximab during the procedure and the patients received double anticoagulation therapy (aspirin indefinitely and clopidogrel for one year).

Approximately 62% of the patients were men ($n=87$) and the mean age was 67 ± 9 years. Diabetes was non-insulin dependent in 94 patients (67%) and insulin dependent in 46 (33%). The left anterior descending coronary artery was most frequently treated (44%), followed by the right coronary artery (34%). Multivessel stenting was performed in 35 patients (25%) and multiple stents were implanted in the same vessel in 17 patients (12%). The mean number of stenoses treated per patient was 1.4 ± 0.6 and the mean number of stents implanted was 1.6 ± 0.9 . The mean length of the stents used was 19.2 ± 7 mm and their mean diameter was 2.9 ± 0.9 . There were no clinical or angiographic differences between the 2 groups. At one month follow-up, one patient in the BMS group had died from cardiac rupture and 2 patients developed non-Q-wave myocardial infarction. No patient in the SES group died, nor were there any complications such as acute myocardial infarction, subacute stent thrombosis or need for revascularization in this group during the same period.

Sirolimus-eluting stents may be safely implanted in diabetic patients with no deleterious effects at one-month follow-up. The final results of this trial will demonstrate whether SES is effective for the prevention of restenosis in this group of high-risk patients.

Effect of Cilostazol for the Prevention of Restenosis After Intracoronary Stent Implantation

Presented by John S. Douglas Jr, Atlanta, GA, USA

Cilostazol, a phosphodiesterase type III inhibitor, has been shown to reduce the incidence of restenosis after stent implantation in several small trials. This trial was a randomized, double blind, placebo controlled study of 705 patients (19 sites) after

successful implantation of a coronary stent. The patients received therapy with cilostazol (100 mg/12 hours) or placebo for 6 months. All patients also received aspirin and clopidogrel. Patients with acute myocardial infarction, intracoronary thrombus, bifurcation lesions, and liver or kidney failure were excluded. Patients were followed up clinically at one and 3 months, and underwent a control coronary angiography at 6 months. The primary end point of the trial was to compare the minimum lumen diameter, by quantitative angiography, between the 2 groups at 6 months. The secondary end points included percent stenosis at follow-up, binary restenosis (stenosis >50% lumen diameter), target vessel revascularization, major adverse coronary events, stroke, bleeding and rehospitalization.

Angiography at 6 months was performed in 507 patients. The minimum lumen diameter per segment (stent plus 5 mm edges) in the cilostazol group was 1.81 mm compared with 1.61 mm in the placebo group ($P=.02$). Late lumen loss was 0.52 mm in the cilostazol group versus 0.70 mm in the placebo group ($P=.0035$). Binary restenosis in the segment evaluated was more frequent in the placebo group (34.6 vs 20.8%; $P=.0006$), affording a 39.5% relative risk reduction with cilostazol. Intra-stent restenosis was also more frequent in the placebo group (31.4 vs 20.1%; $P=.0038$). Subset analysis showed that diabetic patients treated with cilostazol had a lower restenosis rate (16.9 vs 37%; $P=.0018$). The restenosis rate was also lower in the subset of cilostazol patients with small vessels (<3 mm) (21.9 vs 34.4%; $P=.0071$). However, no overall differences were seen in bleeding episodes, rehospitalization, myocardial infarction, need for revascularization of the target organ or major adverse coronary events between the 2 groups. This trial showed that patients treated with cilostazol had lower rates of intra-stent restenosis and a greater minimum lumen diameter in the study segment compared with patients receiving just placebo.

HEART FAILURE

Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Patients With Heart Failure (ACTIV in CHF Trial: Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure)

Presented by Mihai Gheorghiade, Chicago, IL, USA

This trial was conducted to assess the acute and chronic effects of tolvaptan, a vasopressin 2

antagonist, compared with placebo in patients with congestive heart failure. The primary acute end point was a weight reduction 24 hours after starting therapy. The primary chronic end point was death, worsening of the heart failure, rehospitalization, emergency room visits or requirement for further treatment of heart failure within 60 days of inclusion in the study. A total of 320 patients were randomly assigned, in equal proportions, to one of 3 dosages of tolvaptan (30, 60, or 90 mg) or placebo. All patients were also given conventional therapy for heart failure, including diuretics, angiotensin-converting enzyme inhibitors, digoxin and beta-blockers (40%). The patients treated with tolvaptan experienced a greater body weight reduction than the patients treated with placebo, although there was no clear dose response with the different dosages in the tolvaptan group. During the acute phase there was an increase in urinary output and improvement in the signs and symptoms of heart failure. Likewise, a greater recovery of sodium levels was also noted in the active treatment group, though the rate of clinical events at 60 days in the treatment group was no lower. The rates of mortality in the subgroups of patients with renal failure, severe congestion or hyponatremia were all reduced. The most important side effect of the drug was thirst; no important episodes of hypotension were seen. In conclusion, tolvaptan, in combination with standard drugs for the treatment of heart failure, produced a rapid and sustained reduction in the body weight of patients with heart failure. The use of this drug was not associated with any important side effects and favored normalization of sodium levels in patients with hyponatremia. There was a trend toward lower mortality with tolvaptan in patients with clinical congestion, hyponatremia or renal failure.

SURGERY

Pexelizumab for the Reduction of Mortality and Infarction in Coronary Artery Bypass Surgery (PRIMOCABG Trial: Pexelizumab for the Reduction of Infarction and Mortality in Coronary Artery Bypass Graft surgery)

Presented by Edward Verrier, Seattle, WA, USA

This study was designed to assess the efficacy of treatment with pexelizumab (anti-C-5 antibody fragment that blocks C-5 complement cleavage, thereby preventing inflammation) in patients undergoing coronary artery bypass graft (CABG). This phase three trial included patients undergoing

CABG alone or in association with valvular surgery. The primary end point was to assess the reduction in the rate of perioperative infarction and death at 30 days after surgery in patients undergoing CABG. Secondary end points were the composite rates of infarction and death at 4 days in the same patients, as well as the composite rates of infarction and death in the overall group at 4 and 30 days. This multicenter American and European study enrolled more than 3000 patients, randomized 1:1 to treatment with pexelizumab or placebo.

Treatment with pexelizumab was associated with a reduction in the perioperative increase of creatine kinase. Nevertheless, 30-day death in the group undergoing CABG alone (primary end point) was not significantly different (9.1 vs 11.9%; $P=.07$). All the secondary end points were met in the treatment group: lower incidence of death and infarction at 4 days for the patients as a whole (11.5 vs 14.0%; $P=.03$), as well as in the group of patients with bypass surgery alone (7.4 vs 10.0%; $P=.014$). Likewise, there was a trend in all patients toward a reduction in death at 90 days ($P=.096$). Thus, pexelizumab significantly reduced the rate of myocardial infarction after CABG.

Effects of Cariporide on Infarction or Death After Coronary Artery Bypass Graft (EXPEDITION Trial: Sodiumhydrogen EXchange inhibition to Prevent coronary Events in acute cardiac CONDITIONS)

Presented by Robert M. Mentzer Jr, Lexington, KY, USA

This trial was designed to assess the safety and efficacy of cariporide compared with placebo in reducing the incidence of death or infarction in patients undergoing coronary artery bypass graft. Cariporide is a sodium-proton exchange inhibitor, which attempts to prevent calcium overload induced by ischemia and the resulting reperfusion injury. Treatment with cariporide or placebo was started 2 hours before surgery and continued for the next 49 hours. This multicenter study was designed to include 3500 patients per group, with a 1:1 randomization. However, after 5770 patients had been enrolled, the safety committee stopped the trial early, due to an increase in the number of adverse events with the drug. Although the primary end point of a reduction in the incidence of infarction or death was achieved in the cariporide group compared with the control group (14.4 vs 18.9% at 5 days and 13.8 vs 18.5% at 60 days; $P<.0001$ for each), this benefit was solely due to a reduction in infarction. Indeed,

overall mortality was greater in the cariporide group than in the control group, at both 5 and 60 days (2.2 vs 1.5% and 6.4 vs 5.4%; $P=.028$ and $P=.11$, respectively). There was an increase in the overall rate of cerebrovascular events in the cariporide group. In conclusion, cariporide showed a potential use for pharmacologic intervention to reduce myocardial injury after coronary artery bypass graft. Although there was an improvement in the cariporide group concerning a reduction in the primary end point, the accumulation of adverse side effects and the worse overall mortality in this group led to the study being interrupted early.

Prophylactic Amiodarone for the Prevention of Arrhythmias After Heart Surgery. Preliminary Results (PAPABEAR Trial: Prophylactic Amiodarone for the Prevention of Arrhythmias that Begin Early After Revascularization, Valvular Repair or Replacement)

Presented by L. Brent Mitchell, Calgary, Canada

Atrial fibrillation (AF) is the most frequent complication in patients undergoing heart surgery and may lead to symptoms of distress, hemodynamic worsening, stroke or other thromboembolic events, harmful effects resulting from antiarrhythmic drugs, a prolonged hospital stay and increased costs. Previous studies of amiodarone prophylaxis for AF, although promising, lacked sufficient statistical power to assess its efficacy in subsets of patients or to evaluate adverse events. The aim of this trial was to evaluate whether amiodarone is an effective, well-tolerated and safe therapy for the prevention of AF after heart surgery. A total of 601 patients due to have heart surgery were randomized to amiodarone (10 mg/kg/day) or placebo for 6 days prior to surgery, the day of surgery and 6 days after surgery. The primary end point of the study was AF longer than 5 minutes requiring therapy within this 6-day period. The secondary end points included AF characteristics, adverse side effects and the duration of hospitalization. The randomization was stratified to enable independent analysis of each subset of interest.

The randomized groups were similar in their baseline demographic, clinical and surgical characteristics. The primary outcome measure of AF occurred less frequently in the amiodarone group than in the placebo group (16.1 vs 29.6%; $P<.001$) (relative risk = 0.48; 95% confidence interval, 0.34-0.69). The same benefit was seen in each of the previously stratified subgroups: age <65 years (11.2 vs 21.2%; $P=.02$), age >65 years (21.7 vs 41.2%; $P=.001$), coronary artery bypass graft only (10.9 vs 23.3%; $P=.002$), both coronary and valvular surgery

(24.5 vs 41.7%; $P=.006$), prior use of beta-blockers (15.3 vs 21.5%; $P=.03$) or no prior use of beta-blockers (16.3 vs 35.8%; $P=.001$) (relative risk =0.40; 95% confidence interval, 0.23-0.67). When AF occurred, the ventricular response was slower in the amiodarone-treated patients (105 ± 24 vs 131 ± 25 bpm; $P<.001$). Adverse events requiring treatment suspension were more frequent in the amiodarone group than in the placebo group (11.4 vs 5.3%; $P=.02$). However, there were no significant differences between the amiodarone and placebo groups in postoperative complication rates. There was a trend toward a shorter postoperative hospital stay in the amiodarone group (8.2 ± 7.4 vs 8.9 ± 8.1 days; $P=.11$). In conclusion, prophylaxis with oral amiodarone for postoperative AF is effective, well tolerated and safe.

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