SPECIAL ARTICLE

Summary of the Clinical Studies Reported in the 52nd Annual Scientific Session of the American College of Cardiology (Chicago, USA, March 30-April 2, 2003)

Javier Bermejo,[a] Fernando Alfonso[a] and Xavier Bosch[b]

[a]Editores Asociados. [b]Editor Jefe de REVISTA ESPAÑOLA DE CARDIOLOGÍA.

A number of clinical trials were selected for presentation at special sessions during the 52nd Annual Scientific Session of the American College of Cardiology. These were chosen because of their parti-cular importance; the results were communicated orally. The following summarizes their aims, methods and results as presented at the meeting. Since the majority of these results have not yet been published, the information provided here should be understood as preliminary.

PRIMARY PREVENTION

Reduction in the incidence of acute myocardial infarction following the introduction of a smoke-free by-law

This study evaluated the effect of a local ordinance prohibiting smoking in any public place on the incidence of acute myocardial infarction in a large communality. Performed in Helena, Montana (USA) (population over 46 000), this is the first study of this kind ever undertaken. In June 2002, the citizens of this town approved a local ruling that prohibited the use of tobacco in bars, restaurants, casinos, bowling alleys and other public places It was rescinded, however, after a legal battle.

The study was performed by researchers from the St Peter's Community Hospital, the main hospital for practically everyone in the area. The rate of acute myocardial infarction during the period in which the by-law was in force was compared with earlier statistics at the hospital, and with the trend observed during the same period amongst patients who received treatment at the hospital but who were from outside the area affected. Using multivariate techniques, it was shown that the prohibition of smoking in public places was associated with a 60% decrease in the number of patients presenting with acute myocardial infarction (P=.02). There was no decrease, however, in the numbers of patients admitted for the same reason but who were resident outside the prohibition zone. These results are biologically plausible given the well-known immediate effect of passive smoking on platelet aggregation, the endothelium and cardiac variability. The authors of the report suggest a similar study be performed in larger US cities to reinforce legislation restricting passive smoking.

ISCHEMIC HEART DISEASE

Safety and efficacy of eplerenone treatment in patients with post acute myocardial infarction heart failure (the EPHESUS study)

This study shows that eplerenone (a selective antagonist of aldosterone receptors) treatment is associated with an overall reduction in mortality of 15% in patients with left ventricular systolic dys-

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function and with symptoms of post-myocardial infarction heart failure. Eplerenone was also shown to reduce the relative risk of mortality or cardiovascular complications by 13% compared to conventional medical treatment. The final results were published[1] at the same time they were presented at the meeting.

HYPERTENSION

The Anglo-Scandinavian cardiac outcomes trial (the ASCOT trial): results from the lipid-lowering arm

The ASCOT (Anglo-Scandinavian Cardiac Outcomes trial) trial is the largest, randomized, controlled, prospective trial on hypertension ever undertaken in Europe. The lipid lowering arm of this study showed that atorvastatin used indiscriminately with hypertensive patients, and independently of their cholesterol levels, was associated with a 36% reduction in the rate of fatal coronary episodes and non-fatal infarctions compared to patients receiving placebo. These results were published[2] at the same time they were presented at the meeting.

Verapamil and trandolapril versus conventional medication for the treatment of hypertension in patients with ischemic heart disease (the INVEST study)

The aim of the INVEST (International Verapamil ST/Trandolapril study) trial was to compare the effect of a strategy of tratment with verapamil, a non-dihydropyridine calcium antagonist, with a strategy with atenolol in hypertensive patients with documented ischemic heart disease. The trial included 22 576 patients from 15 countries, all aged over 50 (mean age 66 years) and all of whom suffered hypertension and coronary disease. As well as these latter problems, the majority also presented some other risk factor including smoking (46%), diabetes mellitus (27%) and dyslipidemia (53%). The target arterial blood pressure values for treatment were set according to current re-commendations: 140/90 mm Hg for patients with hypertension alone, and 130/85 for diabetic patients who also suffered diabetes or associated kidney failure. An increasing treatment criterion was used with respect to blood pressure achieved with trandolapril followed by hydrochlorothiazide in the verapamil group, and hydrochlorothiazide followed by trandolapril in the atenolol group. The primary outcome was composite all-cause mortality, non-fatal ictus and non-fatal myo-cardial infarction.

At the end of the 2.7 (2-5) year study period, more than 80% of the patients were receiving two drugs. No differences were seen in arterial blood pressure between the two groups; a large proportion of patients in both reached the treatment targets. Primary endpoint analysis showed no difference between the two treatment strategies: no significant differences were seen in global mortality, ictus or non-fatal heart attacks. Neither were any differences seen between the pre-esta-blished subgroups. However, an absolute reduction of 1.5%-2% was observed in the incidence of new-onset diabetes mellitus in the verapamil group. This was related to the reduced use of hydrochlorothiazide in the group treated with calcium antagonists: it has been shown that the use of this diuretic is a great predictor of the appearance of diabetes.

CORONARY INTERVENTIONISM

12-month follow-up of patients implanted with a paclitaxel-eluting stent (the Taxus II trial)

The Taxus program is based on a series of clinical trials designed to evaluate the use of paclitaxel-eluting stents for reducing restenosis after percutaneous coronary angioplasty. The Taxus II study specifically evaluates the efficacy of two types of biphasic-release stent: *1)* slow but sustained release, and *2)* rapid release (8-10 times faster) in the first 48 h, followed by slow elution. After 48 h, paclitaxel elution was identical in both devices. The cohorts treated with Taxus stents were not compared with one another, rather, patients were randomized to receive either a drug-coated stent or a conventional metallic stent. The one year follow-up results were presented of 131 patients who received the slow elution stent (compared to 136 controls), as well as those of 135 patients who received the rapid elution stent (compared to 134 controls). The baseline demographic and angiographic characteristics of the treated groups and their respective controls were comparable.

The primary endpoint of the study was the in-stent net volume proliferation as evaluated by intravascular ultrasound (IVUS) at 6 months. Secondary endpoints were the success of the procedure and the incidence of major cardiac events (cardiac death, acute myocardial infarction, or revascularization of the treated artery) at 6 and 18 months of follow-up. Angiographic and IVUS secondary endpoints were also established.

At 6 months, in-stent net volume obstructions of 21.9% and 7.9% were seen in the control group and

both Taxus stent groups respectively (*P*<.0001). Angiographic studies showed a restenosis rate of 19% in the control group compared to 2.3% and 4.7% in the slow and fast elution Taxus stent groups respectively. At 12 months (96% of the patients) there was a lower incidence of major cardiac events among patients receiving a Taxus stent. This was mainly due to the lower number of revascularizations of the vessel and the treated lesion among these patients than among those in the control group. Only one acute occlusion of a stent was seen among patients receiving a drug-eluting stent; no deaths were recorded among them. The benefits in the need to revascularize during follow-up were maintained at 12 months and were also seen in diabe-tic patients.

Cost-efficiency of sirolimus-eluting stents for the treatment of complex coronary lesions (the SIRIUS trial)

This cost-efficiency study investigated whether the greater cost of drug-coated stents is compensated by their demonstrated reduction of the need to re-hospitalize and repeat revascularization.

The data of the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) trial were examined and the total medical costs calculated at one year. The SIRIUS study compared the clinical and angiographic results of 533 patients who randomly assigned to receive a sirolimus-coated stent with those of 525 patients who were implanted with a conventional stent. For the present study, drug-eluting stents were priced at $3000 and conventional stents at $1000. Since the number of devices, balloons and guides were identical in both groups, the relative cost of the drug-eluting stent procedure was some $3000 higher. The results of the SIRIUS trial showed a reduction in the need for revascularization from 28.4% in the conventionally-treated group to 13.3% in the drug-eluting stent group. This led to a drastic reduction in costs at 12 months with a difference of $2571 in the latter's favor. Combined with the difference in the cost of initial implantation, the final net difference was $309 less for conventional treatment. Maximum economic benefit was seen in patients with reference vessels under 2.5 mm and with lesions longer than 20 mm.

A randomized study to compare paclitaxel-eluting stents and metallic stents for the treatment of coronary lesions (the DELIVER trial)

The DELIVER trial was designed to investigate the safety and efficacy of a new, sustained-elution, paclitaxel-coated stent compared to a conventional metallic stent in the treatment of de novo coronary lesions.

The study involved 1041 patients with the following inclusion criteria: reference vessel 2.5-4.0 mm in diameter, lesion to treat equal to or less than 25 mm in length, lesion equal to or greater than 50% stenosis, but with no complete occlusions, and a blood flow in the vessel to treat equal to or greater than 1. The exclusion criteria included aorto-ostial lesions, unprotected left main coronary artery angiographic evidence of clotting, serious calcification, extreme tortuosity, and LVEF of under 30%. The primary endpoint of the study was the composite of death, acute myocardial infarction, or revascularization of the lesion or the treated vessel. Restenosis was evaluated angiographically in all patients 240 days after entry to the study.

No significant differences were found in the baseline characteristics of the two groups. The angiographic study revealed a greater minimum lumen diameter and less late loss during follow-up. No significant differences were observed with respect to the primary endpoint of the study, although a strong (but non-significant) trend was seen towards lower rates of revascularization for the treated vessel in the paclitaxel group (*P*=.1). The restenosis rates were 16.7% and 22.4% in the paclitaxel and control groups respectively (*P*=.14). Multivariate analysis showed that the factors associated with restenosis during follow-up were diabetes, a smaller vessel diameter, and the use of glycoprotein IIb/IIIa inhibitors. In conclusion, the use of this device was safe and it appeared to be very effective in preventing neointimal hyperplasia. However, at the dose studied, the specified endpoints were not reached. In addition, a harmful effect was detected when the experimental stent was used with glycoprotein IIb/IIIa inhibitors.

Effect of abciximab in patients undergoing coronary stenting after pre-treatment with a high loading dose of clopidogrel

The aim of this study was to determine whether the use of the powerful anti-aggregation agent abciximab, a glycoprotein IIb/IIIa inhibitor, provided protection beyond that obtained with an orally active tienopyridine, clopidogrel, in patients subjected to percutaneous coronary stent implantation.

All patients were treated with 600 mg of clopidogrel at least 2 h before implantation, as well as with aspirin and a heparin bolus (70 U/kg). Later, they were randomized to receive either an infusion of abciximab or a placebo for 12 h. After the procedure, all patients were

treated with clopidogrel 75 mg twice a day until release from hospital, and then once a day for four weeks. Aspirin was administered at a dose of 100 mg/day. All patients included suffered stable ischemic heart disease and had been subjected to percutaneous revascularization.

The main efficiency endpoint was the composite of death, myocardial infarction or urgent revascularization of the treated vessel within 30 days of treatment. Safety was analyzed by examining major and minor hemorrhagic complications, serious thrombocytopenia, and the need for transfusion within 30 days of the procedure.

One thousand and seventy nine patients were assigned to the abciximab group and 1080 to the placebo group. The demographic and baseline clinical and angiographic characteristics of the two groups were identical. Analysis of the primary endpoint results for efficiency showed there to be little difference between the groups (4.2% for the abciximab group compared to 4.1% for the control group; *P*=.82). Further, separate analyses of each group with respect to primary endpoint events were also very similar. No differences were seen in either major or minor bleeding complications, although the abciximab-treated patients showed higher rates of thrombocytopenia and a greater need for transfusion of blood-derived products.

Effect of folate administration after percutaneous intervention (the FACIT trial)

The FACIT (Folate After Coronary Intervention Trial) study was a randomized, placebo-controlled, multi-center clinical trial, performed in Germany and Holland, designed to analyze the efficacy of a combination of vitamins (folic acid, B_6 and B_{12}) in reducing homocysteine levels and preventing restenosis following the implantation of an intracoronary stent.

Three hundred and sixteen patients received the vitamin treatment as an intravenous bolus followed by daily oral intake for six months; 310 patients received a placebo. Patients with intra-stent restenosis, recent myocardial infarction and chronic kidney failure were excluded, as were those who regularly took vitamin supplements.

The demographic and clinical characteristics of the patients were similar, as were their baseline homocysteine levels. However, after four weeks follow-up, the homocysteine levels of the vitamin-treated group were reduced, and remained reduced at six months.

Angiographic studies at six months favored the control group: those treated with vitamins showed smaller minimum lumen diameters, and greater late loss and late loss indices. Further, the restenosis rate and the need for revascularization were greater in the treated patients than in the controls. At 250 days into the follow-up period, the rate of clinical events was similar in the two groups, with the exception of major cardiac events, which were more frequent in the treated group (17% compared to 11% in the control group). In conclusion, this well designed and well performed study showed that a combination of folic acid and vitamin B does not prevent restenosis in intracoronary stent patients, and may even be harmful.

HEART FAILURE

A comparison of medical therapy, pacing, and defibrillation in chronic heart failure (the COMPANION trial)

Several studies have demonstrated the positive effect of cardiac resynchronization on quality of life, functional capacity and tolerance of effort in patients with chronic heart failure.

The MADIT II study showed the benefit of implanting an automatic implantable defibrillator (AID) into patients with ventricular dysfunction. The COMPANION trial is the most ambitious cardiac resynchronization study undertake to date. The primary endpoint was the composite of cardiovascular mortality and hospitalization in a population of patients with chronic heart failure undergoing optimum medical treatment. A parallel, randomized, open-label study with three treatment arms was designed, which involved 128 centers across the USA. The inclusion criteria were functional class III or IV heart failure, sinus rhythm, a QRS wave equal to or longer than 120 ms plus a PR of over 150 ms, an LVEF below 35%, and a left ventricular end-diastolic dimension equal to or greater than 60 mm. All patients received optimum medical treatment including beta blockers, diuretics, angiotensin converting enzyme inhibitors, or inhibitors of angiotensin and spironolactone. The patients were randomized following a 1:2:2 sequence to receive either *a)* optimum medical treatment; *b)* optimum medical treatment plus the implantation of a rescynchronizing pace-maker, or *c)* optimum medical treatment plus the implantation of an AID with rescynchronizing capacity. An initial sample size of 2200 patients was established, but the study was prematurely interrupted after 1634 patients had been enrolled since the pre-established target of 1000 endpoint events had been reached.

The preliminary follow-up results at one year showed a fall in the number of endpoint events of 18.6% with pace-maker resynchronization treatment, and 19.3% with AID resynchronization, compared to patients receiving only optimum medical treatment (*P*<.01 for both). The reduction in mortality by any cause was 23.9% with pace-maker resynchronization and 43.4% with AID resynchronization compared to patients who received only optimum medical treatment (*P*<.002). These differences were confirmed in the different subgroups analyzed.

ARRHYTHMIAS

Prevention of embolic complications with a new oral thrombin inhibitor in patients with atrial fibrillation (the SPORTIF III trial)

The SPORTIF III trial is the third study to evaluate the safety and efficacy of ximelagatran (an orally administered, direct inhibitor of thrombin) compared to warfarin for the prevention of embolic complications in high risk atrial fibrillation patients. The study involved 3407 patients from 23 countries in Europe, Asia and Oceania. These were randomized to non-blindly receive either conventional treatment with warfarin (adjusted for an INR target of 2-3) or ximelagatran (36 mg twice per day). Ximelagatran treatment offers the advantages of efficacy without the need for periodic clotting tests and dose adjustments, plus an almost complete lack of pharmacological interactions. The inclusion criterion for patients was atrial fibrillation with indication for treatment with anticoagulants. Patients with non-valvular atrial fibrillation had also to show at least one risk factor for stroke (previous cerebrovascular accident or peripheral embolism, hypertension, systolic dysfunction of the LV, age above 75 years or above 65 years with diabetes mellitus).

The demographic characteristics of the patients were similar in both groups. Good INR control was achieved in the group treated with dicoumarinics (mean INR 2.5). After a follow-up of 4941 patient-years of exposure, and a mean follow-up of 17 months per patient, 56 primary events were observed (ischemic or hemorrhagic cerebrovascular accident and systemic thromboembolisms) in the warfarin group —2.3%/year— compared to 1.6%/year in the ximelagatran group. This translated into a relative reduction of 29% and an absolute reduction of 0.7% in the composite endpoint. No significant differences were seen in the rate of fatal hemorrhages, although the rate of minor hemorrhages was lower in the ximelagatran group. Overall mortality was similar in both groups. Of those treated with ximelagatran, 6.5% showed transaminase levels over three times normal, typically between 2-6 months into treatment. Approximately half of these patients continued to receive the drug, and transaminase levels returned to normal in all of them. The net benefit of ximelagatran was a 6.1% reduction in combined overall mortality, primary event and serious hemorrhage rates (*P*=.02).

HEART SURGERY

A randomized comparison of stent implantation and off-pump bypass surgery in patients referred for coronary angioplasty (the Octostent Trial)

The aim of this study was to compare the percutaneous implantation of a stent with off-pump bypass surgery in patients referred for elective coronary angioplasty. Of 581 patients considered eligible for the study, 280 actually took part: 138 in the coronary angioplasty group and 142 in the no-pump surgery group. The composite endpoint of the study included the absence of all cause mortality, cerebrovascular accident, acute myocardial infarction, and further bypass surgery 12 months after inclusion. The secondary endpoints included symptomatic state, use of anti-angina drugs, quality of life and cost-efficiency.

The majority of subjects included were low risk patients. A large proportion had one vessel disease. The mean age was 60 years. The majority of the conduits used in surgery were arterial. In the interventionism group, a mean of 1.4 stents per patient were used. Only 12% received concomitant treatment with a glycoprotein IIb/IIIa inhibitor. At the end of follow-up, total mortality, cardiac mortality and the number of myocardial infarctions were all very low (<5% of the total) and very similar in both groups. No significant differences were found between the groups with respect to the main endpoint (91.5% compared to 85.5%; *P*=.01), nor were differences seen in quality of life. A trend towards a greater number of patients without angina was noticed in the surgery group. Cost analysis showed the economic advantage of the percutaneous treatment over surgery ($7304 compared to $9518).

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