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In the 74th annual scientific sessions of the American Heart Association, some clinical studies were selected for presentation in special sessions. These studies were chosen due to their special impact and their results were communicated orally. The objectives, methods, and results of these studies were then summarized as presented at the meeting. Since results have not yet been published, the information offered in this article must be interpreted as preliminary.

INTERVENTIONIST CARDIOLOGY

ELUTES Study *(European Evaluation of Paclitaxel Eluting Stent)*

Effectiveness and safety of the paclitaxel-pretreated stent in the prevention of the restenosis after intracoronary stent implantation.

Presented by Anthony H. Gershlick, Great Britain, for the investigators of the ELUTES study.

Background/objectives

The taxans are a new class of antitumoral chemotherapy agents whose mechanism of action resides in favoring the formation of a type of microtubules that are devoid of functional activity, but extraordinarily stable. This entails the reduction of numerous cell functions like proliferation, migration, and signal transduction. Paclitaxel is the first drug of this group tested in the treatment of cancer of ovary and breast, among others, and it has already shown promising results.

Unlike other antiproliferative drugs, paclitaxel has numerous advantages for local administration aimed at inhibiting the proliferation of smooth muscle cells and restenosis after percutaneous revascularization procedures. Its high lipophilia favors fast cellular assimilation and it has a prolonged effect, even after the administration of single brief doses at very low concentration. Recent studies have shown the antiproliferative effect of this drug in smooth muscle cells of rats *in vitro* and *in vivo,* as well as in cell cultures of human myocytes.

The ELUTES study was designed to analyze the effectiveness and safety of stents coated with various doses of this drug. The primary effectiveness endpoints were evaluated at 6 months by angiography (reference laboratory), percentage stenosis by diameter and late loss, as well as clinical parameters, need for a new revascularization procedure of the treated lesion.

Methods

Double blind, placebo-controlled study randomized to 5 treatment groups: control (n=34), and paclitaxel in doses of 0.2 μg/mm (n=35), 0.7 μg/mm (n=34), 1.4 μmm (n=37), and 2.7 μmm (n=32). A grooved, stainless-steel tube stent was used, 3.5 or 3.0-mm in diameter and 16-mm long, on lesions *de novo*. The drug coated the arterial surface of the stent, to which it was reversibly adhered by nonpolymeric compounds. The safety and incidence of major cardiac events was analyzed after a follow-up of 6 and 12 months.

Results

The mean age of the patients treated was 60 years, 82% were men, 16% diabetics, and 43% had multivessel disease. No differences were observed in the clinical and angiographic variables of the patients. The success rate of the implantation procedure was 99%. The reference size of the vessel was approximately 3 mm before and after stent implantation. The minimum percentage of residual stenosis and luminal diameter after the procedure were

8% and 10%, and 2.68 mm and 2.78 mm, respectively; no differences between groups were observed. The mean length of the lesion was about 10 mm.

At the end of the follow-up period, the control group had 34% luminal stenosis versus 14% for the group treated with the maximum dose of paclitaxel (*P*<.01). The late loss was 0.73 mm for the control group, but only 0.1 mm in the group with the maximum dose in the coating (*P*<.005). The rate of restenosis was 21% in the control group versus 3% in the group treated with the highest dose. The group that received the lowest dose of paclitaxel had a percentage of luminal stenosis, late loss, and a rate of restenosis very similar to the placebo group. The intermediate-dose groups achieved intermediate angiographic results. No significant differences between groups were observed with regard to the need to repeat the revascularization procedure on the target lesion: 3 patients in the control group, 2 in the low-dose group, and 1 in the other treated groups. One death occurred in the control group. Two subacute stent occlusions occurred, one in the control group after the first month of follow-up and the other one in the group treated with the maximum dose in the first month after implantation.

Conclusions

Paclitaxel reduces restenosis from 21% to 3%. The primary effectiveness endpoints were satisfied in the follow-up and the reduction in the diameter of stenosis and late luminal loss was significant. Likewise, the primary safety endpoints were satisfied. A linear dose-response relation was demonstrated in the decrease of restenosis, percentage stenosis, and late luminal loss. Finally, the results of this study and the ASPECT study show that the minimum effective dose of paclitaxel is approximately 3 μg/mm.

Cart-1 study *(Canadian Antioxidant Reestenosis Trial)*

Effects of treatment with AGI 1067 to prevent restenosis after percutaneous coronary intervention.

Presented by Jean Claude Tardif, Montreal, Canada, for the investigators of CART1.

Background/objectives

Agent AGI-1067 is a drug with an intense vascular and lipophilic affinity and potent antioxidant properties similar to those of probucol. Previous studies in animals have demonstrated that probucol has an anti-atherosclerotic effect that is disproportionately greater that its lipid-lowering action. This effect has been related to its capacity to interfere with the oxidation of LDL-C. Likewise, two clinical trials have demonstrated that probucol protects against restenosis after stent implantation in percutaneous transluminal coronary angioplasty procedures (PTCA). It is believed that this is due to its capacity to inhibit the production and release of platelet-derived growth factor (PDGF) and cytokines like interleukin 1 (IL-1). Nevertheless, its pharmacokinetics and toxicity have kept its use from becoming generalized. The CART-1 study was designed as a preliminary study of the equivalence of AGI-1067 versus probucol for the prevention of restenosis; the clinical advantage of this drug is that it has fewer side effects and is safer. The main objective was to determine if AGI-1067 reduces restenosis evaluated by means of intravascular ultrasound (IVUS).

Methods

Multicenter, double-blind, placebo-controlled study of 5 randomized treatment groups: placebo (n=42); probucol, 500 mg/day (n=48); AGI-1067, 70 mg/day (n=41); AGI-1067, 140 mg/day (n=38); and AGI-1067, 280 mg/day (n=42). Treatment began 2 weeks before and continued 4 weeks after the PTCA procedure.

Results

There were no differences between the 5 study groups in demographic, clinical or angiographic parameters, or baseline IVUS measurements. A stent was implanted in 81% of the patients. The minimum luminal area at follow-up was 3.69 mm in the group treated with probucol, 3.36 mm in the group treated with 280 mg/day of AGI 1067, and 2.66 mm in the group given placebo. This response was dose-dependent in the AGI 1067 group. The rate of restenosis was 25.5% in the group treated with probucol, 37.5% in the placebo group, and 26% for the 3 groups treated with AGI 1067 (*P*=.03).

Conclusions

AGI-1067 and the probucol reduce the incidence and severity of restenosis after PTCA procedures.

Unlike probucol, the group treated with AGI-1067 showed an increase in the size of the reference segment. AGI-1067 did not prolong the QTc interval of the electrocardiogram. Prolonged treatment with AGI-1067 could be effective in the prevention of restenosis and in delaying the progression of coronary atherosclerosis. Studies of a larger number of patients will make it possible to determine the true usefulness of the drug, as well as to clarify important aspects of its clinical application, such as the need for 2 weeks of pretreatment (thus limiting its application in patients with acute coronary syndromes) and its definitive role in the era of stents with local drug release.

PRESTO study *(Prevention of Restenosis with Tranilast and its Outcomes)*

Study of the effectiveness of tranilast administered orally to prevent restenosis after percutaneous revascularization procedures.

Presented by David R. Holmes, Rochester, Minnesota, for the investigators of the PRESTO study.

Background/objectives

Tranilast is an antiallergy drug administered *per os* that is used extensively in Japan to prevent the formation of cheloids and hyperplastic scars. It acts by inhibiting spontaneous and TGF-beta 1 induced collagen synthesis, glycosaminoglycan synthesis, and the PDGF-induced migration and proliferation of vascular smooth muscle cells. In addition, tranilast suppresses the expression of the proto-oncogen *c-myc*. The PRESTO study is a large double-blind, placebo-controlled multicenter study that included more than 11 500 patients after a successful percutaneous revascularization procedure. It is the largest study of anti-restenosis measures made to date, and the largest substudy of intravascular ultrasound ever made.

Methods

A total of 11 500 patients were included within 48 h of the revascularization procedure, and randomized to one of 5 treatment groups: placebo for 3 months (n=2300), tranilast 300 mg for 3 months (n=2300), tranilast 450 mg for 3 months (n=2300), tranilast 300 mg for 1 month (n=2300), and tranilast 450 mg for 1 month (n=2300). At the end of the treatment period, patients began a blind follow-up for another 6 months, then underwent angiographic study 9 months

after inclusion. The predefined endpoint for analysis was the combination of death, acute myocardial infarction, or need for revascularization due to myocardial ischemia.

Results

No differences were observed in the clinical and angiographic characteristics of the patients in the 5 groups. There were 358 episodes in the placebo group, 363 in the group of 300 mg/3 months, 364 in the group of 450 mg/3 months, 353 in the group of 300 mg/1 month, and 351 in the group of 450 mg/1 month (*P*=ns), with a cumulative rate of events of approximately 15.5% in the 5 groups. The incidence of restenosis was 33% in the control group, and 35%, 32%, 35%, and 33% for each of the groups described above, respectively (*P*=ns). A posterior subanalysis of age, sex, weight, or clinical characteristics failed to identify a subgroup of patients more likely to benefit from treatment with tranilast.

Conclusions

Although this is a drug that in theory is attractive for the prevention of restenosis, this large-scale, rigorous study unequivocally demonstrated the absence of any beneficial effect of tranilast on restenosis or clinical events after a percutaneous coronary revascularization procedure.

SURGERY

REMATCH Study *(LV Assist Device for Cardiac Heart Failure)*

Clinical effectiveness of an artificial circulatory assistance device in patients with terminal refractory heart failure.

Presented by Eric A. Rose, New York, for the investigators of the REMATCH study.

Background/objectives

The mean survival of patients undergoing heart transplantation is currently almost 10 years. Unfortunately, in recent years a gradual increase in the number of patients who are candidates for heart transplant has been observed, together with a decrease in the number of organs available. The ultimate consequence has been a significant decrease in the

ratio of transplants performed to the number of candidates. This has been an important stimulus for the development of alternatives to transplantation like artificial hearts and circulatory assist devices. Initially designed as a bridge to definitive transplantation, several important lessons have been learned from experience with circulatory assist: *1)* it is possible to achieve acceptably short periods of extrahospital stay; *2)* the morbidity related with the devices is not prohibitive; *3)* failure of the device does not necessarily involve reoperation, and *4)* an acceptable quality of life can be expected. The working hypothesis for the REMATCH study was that circulatory assist devices can reduce mortality by 33% (compared with a control group receiving optimal medical treatment) in patients with terminal heart failure, not candidates for heart transplantation, during a 2-year follow-up period; in addition, the quality of life of the group with ventricular assist would be better than that of the control group.

Methods

Independent, prospective, open, multicenter study, with 1:1 randomization and the participation of a total of 140 patients. The inclusion criteria were: *1)* non-candidate for heart transplantation; *2)* heart failure of functional class IV of the New York Heart Association, for more than 90 days, on treatment with angiotensin-converting enzyme inhibitors, digoxin, and diuretics; *3)* left ventricular ejection fraction 25%; *4)* cardiac index 2.2 l/min; *5)* pulmonary capillary pressure 18 mm Hg, and *6)* peak oxygen consumption (VO_2) 14 ml/kg/min, or dependence on an inotropic drug. The main endpoint of the study was the 2-year survival after implantation of the ventricular assist device, compared with the control group. The secondary endpoints were adverse events, hospitalization, cost, and the cost-benefit relation.

The two groups were similar in age (67±8 years), ejection fraction (17±5%), cardiac index (approximately 2 l/min/m), serum creatinine level (1.75±0.7 mg/dl), and proportion of patients receiving inotropic agents. Treatment in the control group entailed the use of angiotensin-converting enzyme inhibitors, digoxin, and diuretics, unless contraindicated. The beta-blocker drugs and spironolactone were used at the discretion of the investigator. The *Toratec Heartmate VE* model device was used, which is implanted in a subdiaphragmatic site and pumps blood from the apex of the left ventricle to the ascending aorta.

Results

The mortality of the control group was 75% at one year and 92% at the end of the second year. In contrast, the mortality of the ventricular assist group was 48% and 77% in the same periods, respectively. This is a decrease in the relative risk of death of 48%. The main cause of death in the control group was left ventricular dysfunction (93%), whereas most of the patients in the ventricular assist group died of sepsis (25%). Seven patients in the treated group died of failure of the assist device and four of cerebrovascular cause. Quality of life was evaluated objectively using specific tests during 1 year. A significant improvement was found in the group of patients with the assist device. This improvement in quality of life was obtained in spite of numerous serious adverse effects, as well as periods of prolonged hospitalization, habitually due to device malfunction.

Conclusions

Artificial circulatory support devices can substantially improve the survival and quality of life of patients with terminal heart failure who are not candidates for heart transplantation. Efforts to improve the technical qualities of these devices and the management of these patients are justified to improve the prognosis of terminal patients, as well as to extend this therapeutic alternative to patients with less severe forms of heart failure.

E2f Decoy study: gene therapy in aortocoronary grafts

Phase II study to evaluate the results of genetic manipulation of aortocoronary saphenous vein grafts for the purpose of imitating the characteristics of arterial grafts.

Presented by Eberhard Grube of Sieburg, Germany, for the investigators of the E2F Decoy study.

Background/objectives

One of the endemic problems of coronary revascularization surgery is graft dysfunction, with only 50%-60% of grafts remaining permeable 10 years after surgery. The mechanism of graft dysfunction is intimal hyperplasia, which develops in response to

vessel damage induced by the intervention. In the first week after surgery, the smooth muscle cells activate, migrate, and proliferate, originating profuse hyperplasia of the intima. This, together with the formation of atherosclerotic plaques, eventually leads to progressive stenosis of the graft and occlusion. It is known that this effect is significantly smaller in arterial grafts than in venous grafts. Therefore, it could be useful to submit venous grafts to a genetic treatment to convert it histologically into an artery.

To do this, the tissue of the saphenous vein is bathed for 10 min in a solution at 0.6 atmospheres. The solution contains the decoy of E2F transcription factor, It is constituted by a short double-helix of DNA that contains a specific consensus sequence for transcription and acts like a «trap» to block and prevent gene transactivation. It induces increased hypertrophy of the middle layer of the saphenous graft, thus imitating a natural artery. The working hypothesis was that the intraoperative and *ex vivo* treatment of saphenous vein graft with E2F decoy would inhibit graft degeneration. The main endpoint was the determination of the safety, effectiveness, and incidence of graft stenosis (luminal reduction >75%), estimated by means of quantitative angiography and intravascular ultrasound.

Methods

Double-blind, randomized study of 200 patients who underwent revascularization surgery with two or more coronary grafts. A total of 101 patients underwent pretreatment with E2F decoy, whereas the remaining 99 constituted the control group of untreated grafts. No differences were observed in the clinical characteristics of the two groups: mean age approximately 67 years, 84% men. A total of 172 venous grafts were made in the treated group and 137 in the control group. The number of patients in which angiography was performed during follow-up was 69/101 in the treated group and 54/99 in the placebo group. IVUS analysis was made in 108 cases, 65 of which were finally considered apt for interpretation.

Results

In a 1-year follow-up period, 12 major clinical events occurred in the group undergoing gene therapy compared to 16 in the control group, with 6 and 10 deaths in each group, respectively. Three patients in the placebo group required a new surgical revascularization compared with none in the treated group. The rate of angiographically significant stenosis was 27% in the group treated with E2F decoy versus 39% in the placebo group. Analysis of the IVUS studies showed that the intimal volume was smaller in the treated group than in the control group (79 to 114 mm, respectively; *P*<.02).

Conclusions

This is the first randomized and controlled study of a drug for genetic suppression used on grafts in patients undergoing surgical revascularization. Pretreatment with E2F decoy is safe, well tolerated, and does not require any change in the usual surgical technique. A decrease in graft stenosis and intimal volume of the wall by intravascular ultrasound was found after a 12-month follow-up period. Phase III studies of this product are already under way.

COPPA-II Study (*Clinical Outcomes from the Prevention of Post-Operative Arrhythmia*)

Effectiveness of propafenone in preventing atrial arrhythmias after coronary surgery in a large-scale multicenter study.

Presented by Peter R. Kowey of Wynnewood, Pennsylvania, for the investigators of the COPPA-II study.

Background/objectives

Atrial fibrillation and flutter (AF/F) take place in approximately 30%–50% of patients after coronary revascularization surgery and their incidence has not decreased with the introduction of new surgical techniques. These arrhythmias are associated with important morbidity and incur economic costs by prolonging the hospital stay and requiring more intensive monitoring. The use of beta-blockers in patients undergoing revascularization surgery has reduced the incidence of AF/F in the postoperative period by 50% (from 40% to about 20%), as was demonstrated the COPPA I study. Nevertheless, there is contradictory evidence regarding the potential benefit of class I/III antiarrhythmic drugs for the prevention of AF/F after revascularization surgery. The COPPA II study was designed to establish the effectiveness of propafenone in a randomized study after surgical coronary revascularization, and to

determine if a brief intrahospital cycle of this drug is safe and effective in preventing these arrhythmias. An episode of FA/F>5 min was considered an event.

Methods

Patients who underwent surgery without complications and could receive oral medication in the first 24 h after the procedure were included. Major exclusion criteria were drug intolerance, performance of a concomitant procedure, presence of left ventricular dysfunction, severe cardiac insufficiency (class IV of the New York Heart Association), tachycardia or clinically relevant bradycardia, and incomplete revascularization. Propafenone was administered in the first 24 h after surgery and during hospitalization or for a maximum of 15 days.

Results

The study included 293 patients, 97 of which received placebo, 99 propafenone at a dose of 150 mg/8 h, and 97 at a dose of 225 mg/8 h. The mean age of the study population was 63 years and 83% of the patients were men. Most of these patients received concomitant treatment with beta-blockers (>80%), digoxin (90%), and/or calcium antagonists.

The proportion of patients who completed treatment was 58%, 63%, and 70% for the placebo, low-dose propafenone, and high-dose propafenone groups, respectively. The number of patients that discontinued treatment and presented adverse effects was similar in the 3 groups. The incidence of AF/F events was 23% in the placebo group and 22% and 12% in the low-dose and high-dose propafenone groups, respectively. However, this did not translate into a decrease in the hospital stay (7.3±3; 6.9±2.5, and 7.5±4.5 days, for the placebo and low-dose and high-dose propafenone groups, respectively). A detailed study was made of the adverse effects of treatment. Only one death occurred in the group treated with high-dose propafenone. One patient in each group suffered a cerebral ischemic episode. Five patients in the low-dose propafenone group presented ventricular tachycardia, compared with only two in the placebo group. The incidence of extracardiac complications was similar in the 3 groups.

Conclusions

Propafenone in moderate doses exerted a superior and complementary benefit to that provided by beta-blockers in the prevention of AF/F after coronary revascularization surgery. However, this did not result in a decrease in the duration of the hospital stay. Although the overall rate of complications was similar in the 3 groups, a slightly greater incidence of adverse cardiovascular events was observed in patients treated with propafenone. Further studies are needed to clarify if propafenone is safe at doses higher than those analyzed in this study.

ARRHYTHMIAS

ALIVE Study (*Azimilide Post Infarct Survival Evaluation*)

Effectiveness of a new class III antiarrhythmic drug in preventing sudden death in high-risk patients after acute myocardial infarction.

Presented by A. John Camm, London, Great Britain, for the investigators of the ALIVE study.

Background/objectives

Atrial fibrillation is the most frequent rhythm disorder of the heart. This arrhythmia affects 1.5% of the population under 60 years and its incidence is even higher in older patients. Atrial fibrillation does not represent a special danger *per se* to the patient, but it can be associated with dizziness, dyspnea, and a five-fold greater risk of embolic phenomena than the general population. Azimilide is a new class III antiarrhythmic drug that has been developed especially for the treatment of atrial fibrillation. The ALIVE study was designed to evaluate the effect of 100 mg of this drug in patients with high risk of sudden death after acute myocardial infarction (AMI).

Methods

The study included 3381 patients with left ventricular dysfunction (EF 15% to 35%) and a low index of variability of heart rate 5-21 days after AMI The patients were randomized to receive 100 mg of azimilide or placebo, although 336 patients received only one dose of 75 mg of the drug and were not considered in the analysis. The number of patients finally analyzed was 1690 in the placebo group and 1691 in the azimilide group. The study population was subdivided, in turn, into high-risk and low-risk subcohorts according to the criterion of variability of

heart rate of more or less than 20 (n=642 high-risk patients in the placebo group and 622 in the treated group). Safety and effectiveness were analyzed after one year of follow-up. The main endpoint was the effect of azimilide on mortality of any cause.

Results

No differences were observed in the baseline characteristics of the two groups with respect to age, prevalence of mellitus diabetes, sex, functional class, left ventricular ejection fraction. The mortality of the high-risk subcohort was significantly greater to that of the group with conservation of the variability of the heart rate (15% versus 9.5%, respectively; *P*=.0005). In the subcohort of high-risk patients, no differences in mortality between the placebo group and azimilide-treated group were observed (15.0% versus 14.1%, respectively). In the overall cohort the mortality was identical in both groups (11.6%). The mortality due to cardiac causes was slightly lower in the placebo group than in the group treated with azimilide in both the general cohort (10.3% versus 9.3%, respectively) and high-risk subcohort (11.1% versus 11.9%, respectively). The incidence of side effects was similar in both groups. Of the patients treated with azimilide, 0.9% versus 0.2% of the patients of the placebo group presented neutropenia. The incidence of ventricular arrhythmias was no greater in the treated group. A smaller number of patients treated with azimilide developed atrial fibrillation or flutter than in the placebo group.

Conclusions

Azimilide had no beneficial or adverse effect on mortality due to any cause 1 year after AMI in high-risk patients. The decrease in the variability of the heart rate allowed the identification of the population with a greater risk of mortality after AMI The incidence of ventricular arrhythmias and neutropenia in patients treated with azimilide is low. These results support the development of this drug for the treatment of atrial fibrillation and flutter.

ISCHEMIC HEART DISEASE

CARISA study (*Combination Assessment of Ranolazine in Stable Angina*)

Multicenter phase III study to evaluate the safety and effectiveness of ranolazine for the treatment of

stable chronic angina.

Presented by Bernard R. Chaitman, of St. Louis, Missouri, for the investigators of the CARISA study.

Background/objectives

Ranolazine belongs to a new type of antianginal drugs known as fatty acid oxidation inhibitors (pFOX). Studies in animals have demonstrated that the normal myocardium generates ATP from fatty acids by means of a metabolic process requiring intense oxygen consumption. During myocardial ischemia, as the oxygen supply decreases, the fatty acid level increases quickly. The drugs of this therapeutic group increase the effectiveness of oxygen use during ischemic stress by shifting metabolism toward a more effective source of energy, glucose, instead of fatty acids. The CARISA study was designed as a phase III, multicenter, multinational, double-blind, placebo-controlled, and randomized study to evaluate the safety and effectiveness of ranolazine for the treatment of chronic stable angina. The main objective was the duration of exercise in ergometry performed 12 h post-dose (trough period of plasma concentration) after 12 weeks of treatment. The secondary endpoints of effectiveness included the duration of exercise 4 hours postdose (peak plasma concentration), time to the appearance of angina, ST-segment depression during peak and trough treatment, as well as the frequency of angina recurrence.

Methods

Eight hundred twenty-three patients with stable angina were randomized to 12 weeks of treatment with ranolazine (2 doses of treatment, 750 or 1000 mg, twice a day) or placebo. All patients remained under conventional antianginal treatment (atenolol 50 mg, diltiazem 180 mg, amlodipine 5 mg). Stress tests were made 2, 6, and 12 weeks after inclusion in the study.

Results

In both treatment groups, the duration of exercise limited by symptoms 12 h after administration of the drug was significantly greater than in the placebo group (116 versus 92 s; *P*=.01). With respect to secondary endpoints, ranolazine reduced the frequency of episodes of angina to 1.3 and 1.7 episodes per week (for doses of 750 and 1000 mg, respectively), in comparison with a decrease of 0.6 attacks in the

placebo group (*P*<.01). Likewise, ranolazine reduced the mean time to the electrocardiographic appearance of ischemia and the duration of exercise (115 s, 116 s, and 92 s in the groups of 750 mg, 1000 mg, and placebo, respectively; *P*<.03).

Mild side effects (dizziness, nausea, constipation, or anemia) were observed in<8% of the patients. Serious side effects were observed in 6 and 7 patients of the treatment groups, and in 7 patients of the placebo group (*P*=ns).

Conclusions

Ranolazine is a potent and effective antianginal drug that can be useful in patients with chronic angina who remain symptomatic in spite of conventional medical treatment with calcium antagonists and beta-blockers.

IONA study *(Impact of Nicorandil in Angina)*

Effects of nicorandil in the treatment of patients with stable angina.

Presented by Henry J. Dargie, Glasgow, Great Britain, for the investigators of the IONA study.

Background/objectives

Nicorandil acts by opening potassium channels and as a mixed arterial and venous vasodilator. It has been used widely in Europe for the treatment of angina since 1994, and has demonstrated its effectiveness in monotherapy and associated with other antianginal drugs. It is thought that nicorandil can exert a cardioprotective action favoring ischemic reconditioning, by which brief periods of ischemia increase collateral circulation and myocardial resistance to subsequent episodes of ischemia. The IONA study was designed by investigators of the University of Glasgow with the aim of evaluating if nicorandil has cardioprotective properties that could be beneficial to patients with angina. A primary endpoint established was the combination of mortality due to coronary causes, acute nonfatal myocardial infarction, and unscheduled hospitalization due to angina. The study was designed as a double-blind, randomized, placebo-controlled study carried out exclusively in the United Kingdom. Patients were randomized to receive either 10 mg/12 h of nicorandil, increasing the dose to 20 mg after 2 weeks, or placebo. The analysis was made on the basis of «intention to treat». Patients with stable angina and high-risk criteria were included, such as previous infarction, left

ventricular dysfunction (EF<45%), age over 65 years, diabetes mellitus, and hypertension. Uncontrollable heart failure, unstable angina, uncontrolled hypertension, concomitant treatment with sulfonylureas (drugs that block the effect of nicorandil on potassium channels), and a percutaneous revascularization procedure in the 6 months before inclusion were established as exclusion criteria.

Methods

The study included 5126 patients, 2561 in the placebo group and 2565 in the nicorandil group. The mean follow-up was 1.6 years and the clinical characteristics at the time of inclusion were similar in the 2 groups (mean age 67 years, 76% men, 66% of patients with previous infarction and 89% in functional classes I and II).

Results

Treatment with nicorandil resulted in a significant decrease in the main combined endpoint of death due to coronary cause, acute myocardial infarction, and admission for precordial pain (13.1% in the treated group versus 15.5% in the placebo group; *P*=.01). No significant differences were observed in the combination of death due to ischemic cause and myocardial infarction (4.2% versus 5.2%, in the groups treated with nicorandil and placebo, respectively), and mortality due to any cause (4.3% versus 5%), but differences were observed in all cardiovascular events (14.7% versus 17%, respectively).

Conclusions

In patients with chronic stable angina, nicorandil significantly reduces the incidence of major cardiovascular events and all cardiovascular events. The IONA study is the first large-scale study to describe the effects of a specific antianginal medication on the clinical prognosis.

PENTUA study *(Pentasaccharide in Unstable Angina)*

Dose-finding study of fondaparinux used in patients with acute coronary syndromes.

Presented by Maarten L. Simoons, Rotterdam, Holland, for the investigators of the PENTUA study.

Background/objectives

Antithrombin III is a weak natural coagulation inhibitor that impedes the production of thrombin and fibrin in the coagulation cascade by blockade of the action of activated Xa factor, among other factors. Heparin binds to antithrombin III, causing conformational changes in the molecule and increasing its affinity to bind to and deactivate IIa (thrombin), Xa, XIa, and IXa factors, and other components of the coagulation cascade. The binding nexus of heparin to antithrombin resides in 5 molecules of glycoside that constitute the basis for the creation of orally active synthetic pentasaccharides, of which fondaparinux has been the first to be studied widely. Fondaparinux binds specifically to antithrombin, which is why it inhibits Xa factor very selectively, without interfering with other factors.

The PENTUA study is a double-blind, randomized, placebo-controlled study of the dose of fondaparinux in patients with acute coronary syndrome, defined as chest pain of <24 h in duration, dynamic changes in the ST segment, or a level of troponin T or –I<0.1 ng/ml. The patients were randomized to one of 4 doses of fondaparinux (2.5; 4; 8 or 12 mg *per os*) versus enoxaparin (1 mg/kg/12 h). The mean duration of treatment was 5 days (range of 3 to 8 days).

Results

Although 1147 patients were included, of which 1134 were randomized, 126 did not receive the medication and 71 were controlled for less than 12 h. Therefore, only 929 patients were finally randomized. The mean age was 62 years and 77% were men. Forty-one percent presented troponin elevation, 56% ST depression, and 26% previous infarction. The primary endpoint at 9 days (combination of death, myocardial infarction, or recurrence of the ischemic episode) occurred in similar proportions in the enoxaparin group (40.2%) and fondaparinux groups, although the incidence was slightly lower in the group with smaller drug doses (30%; 43.5%; 41%, and 34.8%, for the groups of 2.5 mg; 4 mg; 8 mg, and 12 mg). The same endpoints evaluated 30 days after inclusion were smaller in the group with the lower dose, although no dose-response curve was observed. The angioplastic revascularization by the ninth day was similar in the different groups, although slightly lower in the group than received the lower dose. The incidence of major hemorrhagic complications was 0%; 0.9%; 0.9%; 0.4% and 0% for the 4 groups of fondaparinux and enoxaparin, respectively. No differences were observed in the incidence of mild hemorrhage in the groups.

Conclusions

Fondaparinux (a specific inhibitor of Xa factor), active orally, is at least as effective as enoxaparin in reducing the incidence of thrombotic events. No differences were observed in the frequency of major and minor hemorrhagic events. Fondaparinux at a dose of 2.5 mg seems to be as effective as enoxaparin in preventing the primary and secondary endpoints. Phase III studies must be made to study the potential benefit of fondaparinux at the lower dose.

PREVENTIVE CARDIOLOGY

HPS Study (*Heart Protection Study*)

The effect of treatment with simvastatin and antioxidant vitamins on a large population at risk of suffering coronary artery disease.

Presented by Roy Collins, Oxford, Great Britain, for the investigators of the Heart Protection Study.

Background/objectives

Patients were considered candidates for inclusion in the study if they presented some of the following inclusion criteria: acute myocardial infarction or some other manifestations of coronary artery disease, occlusive vasculopathy in other territories aside from the coronary tree, diabetes mellitus, or arterial hypertension under pharmacological treatment. The rate of plasma cholesterol had to be higher than 135 mg/dl and therapy with antioxidant statins and/or vitamins should not be indicated or contraindicated by the patient´s physician.

Methods

A total cohort of 20 536 patients was included, randomized to simvastatin (40 mg/day), antioxidant therapy with a combination of vitamin E (600 mg), C (250 mg), and beta-carotene (20 mg), or placebo. A study duration of 5 years was planned.

Results

No beneficial effect was observed in the group that received vitamin treatment compared to placebo with

respect to vascular mortality (8.7% versus 8.2%), nonvascular mortality (5.3% versus 5.3%, respectively), or mortality due to any cause (14.1% versus 13.5%, respectively). Likewise, no beneficial effect of multiple vitamin treatment on the reduction of major vascular events was demonstrated (22.7% versus 22.6%, respectively). Nevertheless, the treatment group that received simvastatin presented a significant reduction in mortality due to any cause of 27% with respect to the placebo group (12.9% versus 14.6%, respectively), especially in the reduction of mortality due to vascular phenomena (7.7% versus 9.2%, respectively), although also due to nonvascular phenomena (5.2% versus 5.5%, respectively). The main cause of the decrease in mortality was bound to the decrease in cerebrovascular accidents (4.4% in the group with simvastatin versus 6% in the placebo group), principally in episodes of ischemic origin, without an increase in hemorrhagic accidents. The reduction in the number of vascular events was 25.4% in the placebo group versus 19.9% in the treated group. These benefits on mortality were independent of age, sex, total cholesterol and LDL-C levels, and the benefits increased progressively with every year of treatment. The sustained benefit was observed even in patients with a LDL-C at the time of inclusion below 100 mg/dl. No more adverse effects were observed in the group treated with simvastatin, not even elevation of the muscle or liver enzymes, than in the placebo group.

Conclusions

A dose of 40 mg/day of simvastatin reduces the risk of cardiac mortality, cerebrovascular accident, and need for coronary revascularization by at least one-third. This benefit is independent of total cholesterol and LDL-C levels, and is obtained safely and without adverse effects. Five years of treatment enable the prevention of major vascular events in the following proportions: 100 events per 1000 patients with previous acute myocardial infarction, 70 events per 1000 diabetic patients, 80 events per 1000 patients with another risk factor, 70 events per 1000 patients with peripheral vascular disease, and 70 events per 1000 patients with cerebrovascular accident. Treatment with antioxidant vitamin compounds did not have any effect on cardiovascular disease. The use of simvastatin at a fixed, moderately high dose is capable of preventing one-third of the events in patients who follow the treatment, independently of

the initial lipid values, even in patients with levels lower than those recommended in secondary prevention. Patients over 75 years also benefited substantially from treatment. Finally, a benefit was demonstrated in diabetic patients without previous vascular disease.

AASK study *(African-American Study of Kidney Disease and Hypertension)*

Effect of pharmacological treatment in African-American patients with hypertensive nephropathy.

Presented by Janice G. Douglas of Cleveland, Ohio, for the investigators of the AASK study.

Background/objectives

Whereas diabetes mellitus is the most frequent cause of terminal kidney failure in the general population, in the African-American population this cause is surpassed by hypertensive nephropathy. For that reason, the AASK study was designed to clarify aspects of hypertensive treatment in this population. For that reason, diabetic patients were excluded and African-American patients with mild-to-moderate kidney failure were selected. The study was designed to determine the best antihipertensive agent and target blood pressure in this population. The main endpoint established was the combination of: *1)* reduction of the glomerular filtration rate >50% or >25 ml/min/1.73 m; *2)* evolution to terminal kidney failure, or *3)* death.

Methods

African-American patients of 18 to 70 years age with hypertensive nephropathy (glomerular filtration rate between 20 and 65 l/min/1.73 m) were included. The exclusion criteria established were: diastolic blood pressure<95 mm Hg, history of diabetes mellitus, and protein/creatinine clearance>2.5 ml/min The study had a 3#x2 factorial design pairing 3 pharmacological treatments (metoprolol, amlodipine, or ramipril) with 2 target blood pressure levels (the «recommended target figure» in therapeutic guides of 140/90 mm Hg versus an «intensive target figure» of 120/80 mm Hg). A total of 1094 patients from 21 centers were randomized in the following way: 441 patients received metoprolol, 436 ramipril, and 217 amlodipine. Half of the patients in each group were randomized to a blood pressure control endpoint. The

mean age of the population was 55 years and 39% were women. The mean systolic blood pressure was 150±24 mm Hg and the diastolic blood pressure was 96±14mmHg. The duration of hypertension up to inclusion was 14±10 years (*P*=ns for the differences of these variables between groups).

Results and conclusions

A good control of blood pressure was obtained with the 3 treatment drugs, with mean blood pressure values achieved with metoprolol of 134/81 mm Hg, with amlodipine 131/81 mm Hg, and with ramipril 134/81 mm Hg. The mean blood pressure achieved with the «recommended target level» endpoint was 140/85 mm Hg and with the «intensive target level» endpoint, 127/77 mm Hg. No differences were observed in the progression to terminal kidney failure between groups with different target levels. Regardless of the degree of proteinuria at the time of inclusion, ramipril slowed the progression to kidney failure more than the other two drugs. In patients with proteinuria>0.002 g/day (proteinuria detectable with a reactive strip), ramipril and metoprolol slowed the progression to terminal kidney failure in comparison with amlodipine.

Study of educational reinforcement: intervention in education about coronary artery disease

Effects of education on cholesterolemia in secondary prevention.

Presented by Harlan M. Krumholz, New Haven, Connecticut, for the investigators of the educational reinforcement study.

Background/objectives

The guidelines for action published together by the National Institutes of Health (NIH*), National Heart, Lung and Blood Institute* (NHBLI), and National Cholesterol Education Panel (NCEP) under the acronym of guidelines for the treatment of hypercholesterolemia ATP III (Third Adult Treatment Panel) establish a target goal of LDL-C=100 mg/dl for patients with demonstrated coronary artery disease. Nevertheless, the epidemiological studies made to date have demonstrated that 61% to 90% of patients fail to reach this goal. In order to correct this discrepancy between evidence-based objectives and

those achieved in clinical practice, the NCEP recommends that physicians involve patients in making periodic controls of their cholesterol levels. Unfortunately, evidence continues to show that the degree of commitment of patients to therapeutic objectives and their knowledge of target figures are very low. Consequently, the study was designed to determine if an interventional study designed to educate patients with coronary artery disease about the cholesterol levels they should reach and to motivate them to interact with their physicians can increase the number of patients who reach the objective of LDL-C=100 mg/dl one year after hospital release.

Methods

This was a single-center, randomized and controlled study of a nursing intervention versus conventional management. Patients discharged after hospitalization for coronary disease (acute myocardial infarction, percutaneous coronary angioplasty, coronary revascularization surgery, or coronary stenosis=70%) were included between December 1998 and January 2000. The patients were divided into 2 groups and followed-up for 1 year. The group that followed conventional management guidelines were reminded every 3 months by postcard of their target blood pressure; the intervention group received detailed training, as well as a telephone call every two weeks and monthly letters. Educational measures emphasized the LDL-C endpoint, reviewing the strategies for the control of cholesterol levels and underlining the importance of reciprocal collaboration between physician and patient. The main endpoint established was the number of patients that reached a LDL-C level=100 mg/dl one year after hospital discharge. The secondary endpoint established was the number of patients who knew their target LDL-C level one year after discharge. Of 1188 candidate patients, finally 756 patients were included and randomized(375 to the intervention group and 381 to the routine management group; of them, 336 and 333 finished the study period in each of these groups, respectively).

Results

The mean age of the patients included was 63 years, 30% were women, and about 42% had a LDL-C=100 mg/dl at the time of inclusion. Only 5% knew the therapeutic goal at the time of inclusion. No

differences between the 2 groups were observed in any of these variables.

The number of patients with LDL-C=100 mg/dl at the end of the study was 70.2% in the intervention group and 67.4% in the routine management group (*P*=ns), although the knowledge of target levels was greater in the intervention group (19.6% versus 6.7% in the control group; *P*<.001). In addition, the number of patients who reached the primary endpoint did not correlate with knowledge or not of the target level.

Conclusions

The educational intervention did not improve the attainment of treatment goals with respect to the blood cholesterol level. Intervention was modestly useful in improving knowledge of the target levels. Approximately 30% of patients had not reached the recommended LDL-C level one year after hospital discharge.

ENRICHD study *(Enhancing Recovery in Coronary Heart Disease)*

Effects of the treatment of depression and social isolation after acute myocardial infarction.

Presented by Lisa F. Berkman and Allan S. Jaffé of Rochester, Minnesota, for the investigators of the ENRICHD study.

Background/objectives

Previous studies have demonstrated that the absence of a minimum social support is associated with an increased risk of cardiovascular morbidity and mortality. The prevalence of social isolation and the absence of social support ranges from 15% to 25% in patients with cardiovascular disease, with an adjusted relative risk ranging from 2 to 4. Likewise, the prevalence of major depression in patients with coronary artery disease is approximately 20%, and it is known that it also is associated with an increase in the risk of morbidity and mortality of cardiovascular origin after acute myocardial infarction. Previous studies of psycho-social intervention have yielded contradictory results with respect to cardiac morbidity and mortality. The main objective of the study was to test the hypothesis that the treatment of depression and improvement of social support soon after acute myocardial infarction reduces mortality and the

recurrence of nonfatal myocardial infarctions. Thus, the main endpoint of the study was the combination of mortality of any cause and myocardial infarction.

Methods

The study group included 2481 patients with depression and low psycho-social level in a randomized design of parallel groups to compare the effectiveness of psycho-social intervention with routine treatment. The mean follow-up period was 3.4 years and the results were analyzed on the basis of «intention to treat». The patients were recruited in the 28 days after myocardial infarction and presented major or minor depression and/or a low level of social support. The distribution of patients was 1243 in the routine treatment group and 1238 in the intervention group. The mean age of patients was 61 years and 44% were women. Approximately 40% suffered depression, 26% had low social support, and 35%, both. There were no differences between groups in these variables. The areas addressed in the intervention group were: *1)* cognitive behavioral therapy; *2)* content aimed at activating conduct, cognitive restructuring, social skills training, mobilization, and social resources; *3)* sessions during a 6-month period carried out by trained personal; *4)* pharmacological treatment of patients with severe depression who do not respond to psychological treatment, and *5)* monitoring and quality assessment.

Results and conclusions

A significant, but modest benefit of treatment versus conventional treatment was observed with regard to the level of social support and depression at 6 months, as found with specific tests (ESSI Score of 24.4 versus 22.6 for the intervention and control groups, respectively; Hamilton depression score of 7.6 versus 9.4 for both groups, respectively; *P*<.01 for both tests). Nevertheless, no differences were observed in the primary endpoint of improving mortality or the recurrence of nonfatal myocardial infarction. This is the first large-scale study of conductual medicine that has been made with randomization and controls. Its results should make it possible to better understand the mechanisms involved in the particularly high cardiovascular risk of these populations, and to better know how to intervene in these patients who have an especially difficult management.