Clinical Studies Reported in the 75th Annual Scientific Sessions of the American Heart Association (Chicago, November 17-20, 2002)

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In the 75th Congress of the American Heart Association, the results of some clinical trials selected for their special importance were presented in special sessions (late breaking clinical trials). The majority[1,2] of these studies have not yet been published, so the results reported here should be considered preliminary. Below we summarize the background, objectives, methods, and results of these studies.

REVASC

(Efficacy and Safety of Gene Therapy in Patients with Advanced Coronary Heart Disease and No Options for Revascularization)

Presented by Duncan J. Stewart, MD. Toronto, Canada.

Background: Although initial studies of the use of gene therapy to stimulate angiogenesis in patients with ischemic heart disease seemed promising, later, more extensive, studies have not demonstrated a clinical benefit. The REVASC Study is the first large randomized study designed to analyze this hypothesis in patients with coronary artery disease using an intramyocardial injection of angiogenic growth factors to stimulate the formation of collateral vessels.

Methods: The REVASC Study is a phase 2, multicenter, randomized study to assess the safety and effectiveness of AdvVEGF121 (a non-replicating adenovirus that carries the 121-residue isoform of the endothelial growth factor [VEG-121]) in patients with severely symptomatic coronary disease who are not candidates for conventional revascularization. Treatment was administered by minimally invasive surgery. The patients in the control group received maximum medical treatment. Patients from 20 North American hospitals were included and all of them continued with angina despite maximum medical treatment. None of them were candidates for coronary bypass or angioplasty. Patients were stratified in accordance with the number of previous coronary interventions. In the treatment group (32 patients), AdvVEGF121 (4×10^{10} particles in 30×10 µL) was administered in direct intramyocardial injections (30 injections) through the free wall of the left ventricle after a minithoracotomy. In the control arm (35 patients) patients received optimized medical treatment (nitroglycerin, other antianginal platelet inhibiting medication).

The main endpoint of the analysis was the duration of exercise in conventional exercise stress testing (ACIP protocol) until predefined electrocardiographic criteria were reached (1-mm ST depression). Analysis was centralized at an independent center. A modified intention-to-treat analysis that was designed beforehand made it possible to exclude serious violations to the protocol (finally, 27 patients were analyzed in the treated arm and 29 in the control group).

Results: The main endpout (duration of exercise until a 1-mm ST depression occurred) significantly improved in the patients randomized to treatment with AdvVEGF121 at 26 weeks of treatment ($P=.024$), although the results were not evident at 12 weeks ($P=.35$). All the other parameters evaluated, which represented secondary endpoints, also improved: time to appearance of angina in week 12 ($P=.006$) and in week 26 ($P=.002$), and total duration of exercise in week 12 ($P=.011$) and week 26 ($P=.014$). The number of patients who improved their functional class (at least one grade in the classification of the Canadian Society) was greater after AdvVEGF121 in week 6 (48% vs 10%), week 12 (82% vs 14%), and week 26 (85% vs 24%). In addition, this functional improvement of the group treated with AdvVEGF121 was also observed in the 5 functional dominions of the Seattle angina questionnaire. There were no differences in the number of serious adverse drug reactions in both groups (10 in group AdvVEGF121 and 11 in the control group). In 4

patients, these complications were attributed to the minithoracotomy-injection of AdvVEGF121. In addition, major adverse drug reactions were documented in 3 treated patients and 9 control patients. Three patients died, 2 in the AdvVEGF121 group due to postoperative complications, and one in the control group after a myocardial infarction. A patient in the AdvVEGF121 group presented recurrence of a preexisting bladder cancer. In the control group, 3 patients were finally treated by heart transplantation, coronary surgery, or coronary angioplasty. Cultures for adenovirus were negative in every case and no changes were detected in the plasma concentrations of AdvVEGF121.

Conclusions: The REVASC Study has been the first to validate the indication for VEGF therapy as a method for stimulating angiogenesis. This treatment significantly improved the functional capacity and symptoms of patients with coronary disease not susceptible to revascularization. Treatment with AdvVEGF121 was safe and its effects were lasting, although the surgery required for application involves a certain risk. For this reason, the next step will be to design a larger randomized study in which treatment is administered percutaneously by catheter.

ASSENT III PLUS

(Assessment of the Safety and Efficacy of New Thrombolytic Regimens III Plus)

Presented by Lars Wallentin, MD. Uppsala, Sweden.

Background: Study to evaluate treatment with enoxaparin versus conventional heparin associated with thrombolytics administered «pre-hospital» in special ambulances. The time gain and results compared with hospital regimens were also studied. In the original ASSENT III study (4038 patients with myocardial infarction and ST-segment elevation of less than 6 h duration), treatment with tenecteplase plus enoxaparin or abciximab reduced the number of ischemic complications with respect to a regimen of tenecteplase and unfractionated heparin. As the combination of tenecteplase with abciximab increased the risk of severe hemorrhage, it was suggested that the combination of tenecteplase with enoxaparin could be more favorable.

Methods: From July 2000 to July 2002, 1639 patients with myocardial infarction and ST segment elevation of less than 6 hours duration were included in 88 European (11 countries) and North American centers in the ASSENT III Plus study. The design was open, with parallel groups, and random assignment to two regimens: *1)* complete dose of tenecteplase plus enoxaparin (one 30-mg bolus followed by 1 mg/kg

s.c./12 h until discharge or up to 7 days), and *2)* complete dose of tenecteplase with adjusted unfractionated heparin (i.v. bolus of 60 U/kg followed by an infusion of 12 UI/kg/h [aPTT 50 to 70 s]). Unlike the original ASSENT III study, in ASSENT III Plus the Killip grade could not be assessed in the ambulance.

Results: A delay of an hour was observed from onset of symptoms until the ambulance was called, 15 min until the ambulance arrived, and 30-40 min until tenecteplase treatment was begun. In comparison with the original ASSENT III study, 45 min was saved in ASSENT III Plus (from onset of pain to thrombolytic treatment) due to the prehospital strategy. In the ASSENT III Plus study, more than 50% of the patients received treatment in less than 2 h versus only 30% of the patients included in the original ASSENT III study

A non-significant reduction in the absolute risk of 3% in the main effectiveness endpoint (death, reinfarction, or refractory ischemia in the first 28 days) was found in favor of enoxaparin compared to unfractionated heparin (14.2%, [95% CI, 11.8-16.6] vs 17.4% [95% CI, 14.8-20.0; *P*=.08], respectively), as well as in the main combined endpoint of effectiveness and safety, which also included the incidence of intracranial hemorrhage or severe hemorrhage (18.3% [95% CI, 15.6-20.9] vs 20.3% [95% CI, 17.5-23.1; *P*=.29], respectively) in favor of enoxaparin. There was a tendency to a higher mortality at 30 days in the enoxaparin group (7.2% [95% CI, 5.4-8.9] vs 5.4% [95% CI, 3.9-7.0]; *P*=.15). Although the group treated with enoxaparin had less risk of reinfarction (3.5% [95% CI, 2.2-4.8] vs 5.8% [95% CI, 4.2-7.4]; *P*=.028) and refractory ischemia (4.4% [95% CI, 3.0-5.8] vs 6.4% [95% CI, 4,7-8,1]; *P*=.06), it had a greater risk of cerebrovascular accident (2.9% [95% CI, 1,7-4,0] vs 1.34% [95% CI, 0,5-2,1]; *P*=.026) and intracranial hemorrhage (2.2% [95% CI, 1,2-3,2] vs 0.97% [95% CI, 0,3-1,6]; *P*=.047). The analysis of subgroups revealed that the excess of intracranial hemorrhage in the enoxaparin group was observed only in patients over 75 years old (which explains the tendency to a greater mortality), and demonstrated a significant interaction between enoxaparin and the risk of hemorrhage in older persons (*P*=.04). Other subgroups with a greater risk of hemorrhage included women, hypertensives, and patients who weighed less.

Conclusions: Prehospital thrombolysis made it possible to reduce the time to the onset of treatment by 45 min. The prehospital use of TNK-tPA and unfractionated heparin had a safety and effectiveness comparable to hospital use. Since the positive effects of enoxaparin associated with thrombolytics in ischemic problems still involve a major risk of hemorrhage, additional studies are needed to evaluate

the correct dose of enoxaparin in this context (fundamentally in patients >75 years). For this reason, the ExTRACT-TIMI 25 study was undertaken to determine the most adequate dose of enoxaparin used in combination with fibrinolytic treatment.

CARDINAL

(Complement And ReDuction of INfarct size after Angioplasty or Lytics)

Presented by Christopher B. Granger, MD. Durhan, North Carolina (U.S.)

Background: Despite achieving optimal coronary reperfusion by means of thrombolysis or a percutaneous coronary intervention (PCI), serious complications continue to occur in the acute phase of myocardial infarction. Activation of complement by different inflammatory processes could condition cellular damage secondary to ischemia or reperfusion. Nevertheless, no studies have demonstrated beneficial effects after the use of strategies designed to achieve protect the myocardium at the cellular level. Pexelizumab is a fragment of monoclonal antibody against C5 complement that prevents activation of the complement cascade.

Methods: The CARDINAL study analyzed the effectiveness of pexelizumab to reduce the size of infarction in patients treated with *a)* thrombolytics (COMPLY: Complement inhibition in myocardial infarction treated with thrombolytics; n=920) or *b)* primary PCI (COMMA: Complement inhibition in myocardial infarction treated with PTCA; n=814). Both substudies randomized patients with acute myocardial infarction and elevation of the ST segment of less than 6 h of evolution to three different strategies: *1)* a bolus of pexelizumab 2.0 mg/kg; *2)* a similar bolus followed by an infusion of pexelizumab 0.05 mg/kg/h during 20 h, and *3)* placebo. The main endpoint of both substudies was the size of the infarction determined by the area under the curve of CPK-MB release after 72 h. The secondary endpoints included a compound endpoint (death, congestive heart failure, cardiogenic shock, and invalidating cerebrovascular accident) and each event separately, at 90 days.

Results: The baseline characteristics of the patients were well balanced in all the branches of the study. The main endpoint of the COMPLY study (infarction size) was negative (*P*=.85) and there were no differences in the combined clinical endpoint (18.6%, 18.4%, and 19.7% for the patients in the placebo, bolus, and bolus+infusion arms, respectively). There was a non-significant tendency toward fewer combined events or heart failure in the group treated with a bolus of pexelizumab. Nevertheless, this group showed a non-significant tendency to more frequent cardiogenic shock and greater mortality. The main endpoint of the COMMA study was almost identical in the 3 groups and the combined endpoint was also similar (11.1%, 10.7%, and 8.5%; *P*=.39, for the placebo, bolus, and bolus+infusion groups, respectively). However, the mortality at 90 days (5.9%, 4.2%, and 1.8%; *P*=.014, for the bolus+infusion group) and at 6 months of follow-up (7.4%, 4.2%, and 3.2%; *P*=.018, for the bolus and bolus+infusion groups) was significantly lower in the patients treated with pexelizumab. No significant adverse effects were recorded. In the combined analysis of the COMPLY and COMMA studies, the mortality at 90 days did not decrease substantially (*P*=.24), although in the pre-specified subgroup of North American patients (1248 patients), mortality decreased significantly in the bolus+infusion group.

Conclusions: Pexelizumab is safe and well tolerated and reduces complement activity in patients with acute myocardial infarction treated with coronary reperfusion strategies. Nevertheless, treatment with pexelizumab did not reduce the size of infarction or the combination of adverse drug reactions studied. The COMMA Study with primary PCI demonstrated that pexelizumab in a bolus+infusion significantly reduced mortality, although this was a secondary endpoint that occurred in a relatively small number of patients. Therefore, new studies are needed to clarify the value of pexelizumab in acute myocardial infarction.

TETAMI

(Treatment with Enoxaparin and Tirofiban in Acute Myocardial Infarction)

Presented by Marc Cohen, MD. Philadelphia, Pennsylvania (U.S.).

Background: Patients with acute myocardial infarction and ST-segment elevation (AMISTE) currently receive reperfusion treatment in the form of thrombolytics or coronary angioplasty. Nevertheless, up to 30% of patients with AMISTE do not receive any reperfusion treatment, fundamentally because they arrive too late at the hospital (more than 12 h), or due to age, comorbidity, or the lack of hospital resources. The treatment of patients with AMISTE who are not candidates for reperfusion — a subgroup with an especially unfavorable prognosis — is not well established.

Methods: The TETAMI Study assessed the effect of a low-molecular-weight heparin (enoxaparin) compared with unfractionated heparin in patients with AMISTE of less than 24 h evolution who were not candidates for reperfusion treatment, some of which were treated with tirofiban. Patients in shock or with

revascularization scheduled in the next 48 h were excluded. The aim of the study was to know if enoxaparin, associated or not with tirofiban, reduced events (death, recurrent myocardial infarction, or angina) at one month compared with unfractionated heparin. The treatment included unfractionated enoxaparin (30-mg bolus i.v. followed by 1 mg/kg s.c. every 12 h) or heparin (bolus i.v. of 70 UI/kg follwed by infusion i.v. of 15 U/kg/h). In addition, each group received tirofiban (bolus i.v. of 10 μg/kg followed by infusion i.v. 0.1 mg/kg/min) or placebo.

Results: Altogether, 1224 patiens were randomized: 299 patients to treatment with enoxaparin, 305 enoxaparin+tirofiban, 306 unfractionated heparin, and 314 unfractionated heparin+tirofiban. The baseline demographic and clinical characteristics were similar in all 4 groups. The mean time to the onset of treatment was 16-18 h from the beginning of symptoms and 77% of the patients arrived more than 12 h after onset. The main reasons why these patients did not receive reperfusion treatment were time since infarction over 12 h and the non-availability of a hemodynamics laboratory. There were no differences between the 4 groups in the main study endpoint (death, reinfarction, or recurrent angina at 30 days: 15.4% enoxaparin; 16.1% enoxaparin+tirofiban; 17.3% unfractionated heparin, and 17.2% unfractionated heparin+tirofiban; P=.84). Likewise, the primary endpoint was similar in the patients treated with enoxaparin vs unfractionated heparin (OR, 0.89; 95% CI, 0.66-1.21) and in patients treated with tirofiban versus placebo (OR, 1.02; 95% CI, 0.75-1,38). There were no differences in the incidence of serious hemorrhagic complications or cerebral hemorrhage (1/0% enoxaparin; 2/0.3% enoxaparin+tirofiban; 1/0% unfractionated heparin, and 1.6/0.3% unfractionated heparin+tirofiban).

Conclusions: The results of this study demonstrated that patients with AMISTE who are not candidates for reperfusion do not benefit from treatment with enoxaparin or tirofiban. Enoxaparin has an effectiveness and safety similar to those of unfractionated heparin and could therefore be a valid alternative for this type of patients. The addition of tirofiban to enoxaparin or unfractionated heparin does not seem to produce clinical benefits.

CREDO1

(Clopidogrel for the Reduction of Events During Observation)

Presented by Steven R. Steinhubl, MD. Chapter Hill, North Carolina (U.S.)

Background: After a percutaneous coronary intervention (PCI), short-term treatment with clopidogrel, in addition to treatment with aspirin,

provides better protection against thrombotic complications than aspirin alone. Nevertheless, the optimal duration of this combination of oral antiplatelet aggregants is not known. In addition, although the present clinical findings suggest a benefit when beginning with a loading dose of clopidogrel before PCI, the practical application of this strategy has not been studied prospectively.

Objectives: To evaluate the benefit of long-term treatment (one year) with clopidogrel after PCI, and to determine the possible benefit of initiating clopidogrel with a loading dose before the procedure, always in addition to aspirin.

Methods: A randomized, double-blind, placebo-controlled study was made in patients who were going to undergo scheduled PCI or had a high probability of requiring PCI. From June 1999 to April 2001, 2116 patients were included in 99 North American centers. The patients were randomized to receive a loading dose of 300 mg of clopidogrel (n=1053) or placebo (n=1063) from 3 to 24 h before PCI. Later, all the patients received clopidogrel (75 mg/day) for 28 days. Finally, the patients in the group treated with a loading dose received 75 mg/day of clopidogrel for a year while the patients in the control group received placebo. Aspirin was administered to both groups throughout the study.

The study endpoints were: *1)* incidence of combined events (death, myocardial infarction, or cerebrovascular accident) at one year analyzed by «intention to treat», and *2)* incidence at 28 days of the combined event of death, myocardial infarction, or emergency revascularization of the target vessel by analysis «by protocol.»

Results: At one year of follow-up, clopidogrel treatment was associated with a relative reduction of the risk of death, infarction, or cerebrovascular accident of 27% (95% CI, 3.9-44.4; P=.02), and an absolute reduction of 3%. Pretreatment with clopidogrel did not significantly reduce the risk of death, infarction, or revascularization at 28 days (reduction of 18.5%; 95% CI, –14.2 to 41.8; P=.23). Nevertheless, in a prespecified analysis of subgroups, the patients who received clopidogrel at least 6 h before PCI experienced a relative reduction in risk of 39% (95% CI, –1.6 to 62.9; P=0.051) compared with the patients treated less than 6 h before PCI. The risk of severe hemorrhage at one year of follow-up increased, but not substantially (8.8% for clopidogrel treatment vs 6.7% for the placebo group; P=0.07).

Conclusions: After PCI, long-term treatment (one year) with clopidogrel significantly reduced the risk of adverse ischemic events. Treatment with clopidogrel must begin more than 6 hours before PCI.

ISAR-COOL

(Intracoronary Stenting with Antithrombotic Regimen)

Presented by Franz-Josef Neumann, MD. Munich, Germany

Background: In patients with acute coronary syndromes, it has been suggested that «passivation» of the atheroma plaque in the affected artery could help to improve the results of percutaneous coronary interventions (PCI) and reduce complications. Nevertheless, controlled studies have not validated the effectiveness of this «cooling» strategy.

Methods: Four hundred ten patients with unstable angina and elevation of troponins or depression of the ST segment were randomized to immediate PCI or to a «cooling» strategy in which patients were given aspirin, clopidogrel, tirofiban, and heparin for 72-120 hours before the intervention. The medical treatment of the patients in which immediate PCI was indicated was similar to that of the group in which «cooling» and deferred PCI were programmed. Tirofiban was continued for 24 h after PCI, clopidogrel for 4 weeks, and aspirin indefinitely. Immediate PCI (more than 6 h) was performed 2.4 h after the onset of pain, whereas in the other group PCI was delayed for a mean 86 h (72-120 h: 3-4 days).

Results: Sixty-seven percent of the patients had positive troponins and 65% had depression of the ST segment. The definitive treatment was similar in both groups (67% PCI and 8% coronary surgery). The main study endpoint (death or infarction at 30 days) was reduced significantly in the group assigned to early PCI (5.9% vs 11.6%; RR, 2. 95% CI, 1.01-3.94; P=.04), fundamentally due to a reduction in the incidence of acute myocardial infarction (5.9% vs 10.1%). Before catheterization, 13 events occurred in the «cooling» group, one in the early PCI group. After the intervention, a total of 10 events occurred in each group. In addition, hemorrhagic complications that required transfusion were more frequent in the «cooling» group (3.4% vs 1.0%). These findings demonstrated the benefit of shortening the time to PCI and the lack of additional protection from prolonging preintervention antithrombotic treatment. Likewise, benefits were obtained in the subgroup with troponin elevation as well as in the subgroup with electrocardiographic abnormalities.

Conclusions: In patients with unstable angina who present elevation of cardiac markers and/or ST-segment depression, once treatment with antiplatelet aggregants and GP IIb-IIIa inhibitors began, the strategy of early PCI is better than delaying the indication to avoid the acute period and achieve a supposed «cooling» of the disease.

REPLACE-2

(Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events)

Presented by A. Michael Lincoff, MD. Cleveland, Ohio (U.S.).

Background: Although the use of bivalirudin is associated with a greater effectiveness and lower incidence of hemorrhage than heparin during balloon angioplasty, its usefulness in current percutaneous coronary interventions (PCI) (stents and intense antiaggregant treatment) has not been adequately evaluated. Bivalirudin, a small molecule that directly inhibits thrombin, was approved in December 2000 as a substitute for unfractionated heparin in patients undergoing PCI. Approval was based on the BAT, CACHET, and REPLACE I studies, which demonstrated that the use of bivalirudin reduced serious cardiac adverse events and also partially reduced hemorrhagic complications in comparison with heparin.

Methods: REPLACE-2 is a randomized, double-blind study that included 6010 patients who underwent scheduled or emergency PCI (patients treated with bivalirudin [bolus of 0.75 mg/kg+infusion 1.75 mg/kg/h during PCI] [+possible GP IIb-IIIa inhibitors], the rest of the patients were randomized to heparin [65 UI/kg] and programmed treatment with GP IIb-IIIa inhibitors). In every case an attempt was made to obtain an ACT of more than 225 s and pretreatment with clopidogrel was suggested. The main endpoint of the study was the appearance of combined events (death, myocardial infarction, emergency revascularization, or serious hemorrhage) at 30 days. The secondary endpoints included death, myocardial infarction, or emergency revascularization at one month; death, infarction, or the need for revascularization of the target vessel at 6 months, and mortality at one year of follow-up. A study was designed to demonstrate the superiority of bivalirudin versus heparin alone and the equivalence or inferiority of bivalirudin vs heparin associated to the systematic use of GP IIb-IIIa inhibitors.

Results: Between October 2001 and August 2002, a total of 6010 patients were included in the study (233 hospitals in 9 countries). The baseline characteristics of the patients, including previous treatment with thienopyridines, were similar in both groups. No significant differences were found between the two groups in any of the combined endpoints studied. The main endpoint (death, infarction, emergency revascularization, and hemorrhage) was 9.2% in the bivalirudin group and 10% in the control group (P=.32), and the secondary endpoint of death, infarction, or revascularization was 7.6% vs 7.1% (P=.4), respectively. GP IIb-IIIa inhibitor drugs were

used in only 7.2% of the patients assigned to treatment with bivalirudin. This group had a lower incidence of severe hemorrhage (2.4% vs 4.1%; $P<.001$) than the group of heparin with GP IIb-IIIa inhibitors (prevention of 1.7 episodes of severe hemorrhage per 100 treated patients).

Conclusions: During PCI, bivalirudin — with the selective addition of GP IIb-IIIa inhibiting drugs — is better than isolated heparin in terms of ischemic events and bleeding episodes. This association is no worse than the combined use of heparin and GP IIb-IIIa inhibitors and has a lower risk of hemorrhagic complications. The use of bivalirudin and, eventually, GP IIb-IIIa inhibitors when necessary is currently a valid strategy during PCI.

X-TRACT

(Prospective Randomized Comparison of Stent Implantation in Thrombotic Native Coronary Arteries and Saphenous Vein Grafts With versus Without Thromboatherectomy)

Presented by Gregg W. Stone, MD. New York City, New Jork (U.S.).

Background: Percutaneous coronary interventions (PCI) in saphenous vein bypasses (SAPH) and native coronary arteries on lesions with thrombi are associated with a high incidence of complications. Although their use is attractive, it is not known if these results could improve with the use of thrombectomy systems before the intervention.

Methods: A total of 797 patients (75 centers in the U.S.) who underwent PCI with stent implantation (72% SAPH and 28% native coronary arteries with evidence of an associated thrombus) were randomized to conventional PCI or PCI preceded by thromboatherectomy with the X-SIZER device.

Results: The baseline characteristics were similar in both groups, with the exception that the X-SIZER group had a greater frequency of thrombi (70% vs 58%; $P<.001$) and slightly more severe stenosis (70% vs 67%; $P<.005$). The use of GP IIb-IIIa platelet inhibitors (78%) was similar in both groups. The incidence of TIMI 3 flow (95.4% vs 95%) and non-reflow (2.2% vs 3.2%) at the end of the procedure was similar in both groups. In addition, the incidence of combined adverse events at 30 days (including death, infarction, or revascularization of the responsible vessel, 17% vs 17.4%) was similar in both groups. The appearance of any infarction (15.8% vs 16.9%) or of a Q wave infarction (1% vs 1.3%) was also similar in both groups. Only the appearance of large infarctions (defined as Q-wave infarctions or large non-transmural infarctions [CPK-MB increases more than

8-fold]) was less frequent in the group assigned to X-SIZER (5.5% vs 9.6%; $P=.03$). In addition, in patients not treated with GP IIb-IIIa inhibitors, its unscheduled use was required more frequently in the patients in the control group (10.3% vs 2.1%; $P=.02$). After adjusting for imbalance in the baseline characteristics, use of the X-SIZER was an independent protective factor of the appearance of a large infarction and of death or large infarction.

Conclusions: The use of the X-SIZER system before stent implantation in patients with SAPH or native artery lesions with a thrombus reduces the incidence of complications related to the procedure (need to use IIb-IIIa inhibitors) and improves the survival free of large infarctions; however, its use does not reduce the appearance of combined clinical events at one month of the intervention.

SAPPHIRE

(Stenting and Angioplasty With Protection in Patients at High-Risk for Endarterectomy)

Presented by Jay Yadav, MD. Cleveland, Ohio (U.S.).

Background: The NASCET and ACAS studies demonstrated the benefits of carotid endarterectomy (CE) in symptomatic and asymptomatic patients with this pathology (carotid stenosis of more than 70% and 60%, respectively). The implantation of carotid stents began in 1994 at the University of Alabama as an alternative to surgical CE. Later, systems of distal protection became a popular way to prevent cerebrovascular complications associated with percutaneous treatment.

Methods: The SAPPHIRE Study was a randomized, multicenter study (28 hospitals) that compared the technique of carotid stent implantation using systems of protection against distal embolization with CE in patients at high surgical risk. The patients assigned to the percutaneous intervention were treated with nitinol-impregnated self-expanding stents and the AngioGuardTM protection device. In order to participate in the study, it was required that the surgical team have extensive experience with the technique (30 CE per year) and a rate of serious complications lower than 1%. Likewise, the interventional teams had to perform a large number of interventions (mean annual of 64) with a rate of cerebrovascular complication lower than 2%. Patients were required to have carotid stenosis of more than 50% in the internal or common carotid if they were symptomatic, or a stenosis of more than 80% if they were asymptomatic. In addition, they were required to have one or more diseases catalogued as comorbidity (heart failure, chronic bronchitis, severe coronary

artery disease, previous CE, radical surgery of the neck, and radiotherapy). Before the patient was randomized, the consensus of a multidisciplinary team consisting of a neurologist, surgeon, and an interventional specialist was required. Of a total of 723 patients included in the study, consensus for randomization was reached in 307 (156 in the stent group and 151 in the CE group), whereas the rest were included in a prospective registry. The stent registry included 307 patients rejected by vascular surgeons, whereas the surgical registry only included the 7 rejected by the interventional teams. In June 2002, the study was interrupted prematurely due to the low inclusion rate, which was considered secondary to the reluctance of patients and physicians to refer patients for CE. The primary endpoints of the study included the combined analysis of death, cerebrovascular accident, or myocardial infarction at 30 days and another endpoint that included ipsilateral cerebrovascular accident or death during one year of follow-up.

Of the patients included in the randomized study, the patients in the stent group had a greater prevalence of coronary surgery or cardiovascular history than the patients in the CE group. The baseline characteristics of the patients included in the stent registry were similar to those of the randomized group. The presence of a previous CE or post-radiotherapy treatment were common causes for rejecting the indication of CE in patients who were finally included in the registry. Although the incidences of death (0.6% vs 2%), cerebrovascular accident (3.8% vs 5.3%), and myocardial infarction (2.6% vs 7.3%) were lower than in the stent group, the differences did not reach statistical significance. Nevertheless, and in spite of the premature interruption of the study, the main endpoint at 30 days (combined analysis of death, myocardial infarction, or cerebrovascular accident) was significantly better in the stent group (5.8% vs 12,6%; P=.047). The analysis of symptomatic and asymptomatic patients showed no differences with respect to the general findings. Two of the secondary endpoints, transitory ischemic accident and serious hemorrhage, were similar in both treatment groups, but the frequency with which cranial nerves were damaged (0% vs 5.3%; P<.01) was greater in the group treated with CE. Of the patients rejected for surgery but included in the stent registry, 7.8% (32/409) presented adverse events. Of the 7 patients included in the surgical registry, one (14.3%) presented adverse events.

Conclusions: The SAPPHIRE study is the first randomized study to compare carotid stents associated with distal protection to CE in patients at high surgical risk. The study emphasized the importance of interdisciplinary collaboration, although CE was always rejected at the surgeon´s discretion. The patients assigned to the stent group had a lower rate of serious complications (death, infarction, or cerebrovascular accident) than the patients assigned to CE.

CQI-CABG

(National Randomized Trial of Continuous Quality Improvement in Coronary Artery Bypass Grafting)

Presented by T. Bruce Ferguson, MD. Chicago, Illinois (U.S.)

Background: Until now, no rigorous evaluation has been made in large-scale studies of the impact of continuous quality improvement (CQI). Using the national cardiology database of the Society of Thoracic Surgeons (STS), an evaluation was made of whether a CQI initiative for coronary surgery (CABG) could be implemented effectively on a national scale.

Methods: The objective of the study was to assess if a low intensity CQI action could increase the speed of adoption of two measures for the improvement of care in coronary surgery. The STS, the largest association for cardiothoracic surgery in the U.S., in collaboration with the Institute of Clinical Investigation of Duke University, made a study in which 359 hospitals were randomized to: *1)* intervention 1: increased use of preoperative beta-blockers; *2)* intervention 2: increased use of the internal mammary artery in patients over the age of 75 years, and *3)* non-intervention. Both intervention arms received educational products, visits, and continuous follow-up of the program. Two analysis systems were used: *a)* local analysis of the differences before and after intervention, and *b)* hierarchical analysis, adjusting for the patient's risk and the effect of the center per se.

Results: From January 2000 to July 2002, the use of both intervention measures increased at the study centers (beta-blockers from 59% to 67%, and the mammary artery from 74% to 85%). The baseline clinical characteristics of the patients were similar in all three study groups. The use of beta-blockers was adopted more rapidly in the intervention group than in the control group (increment of 7% vs 4%), a difference that was significant in both types of analysis used. The use of internal mammary artery in patients over 75 years old increased more substantially in the centers assigned to this intervention, although the differences did not reach statistical significance (increment of 9% vs 5%). Nevertheless, an interaction (P=.02) was found between use of the mammary artery and the number of interventions. In centers with a low volume of interventions, the increase observed in the group assigned to intervention (14%) was greater than in the control group (8%).

Conclusions: This study demonstrated that with a

multidisciplinary approach and direction by healthcare professionals, a low-intensity CQI effort can have an appreciable impact on the implantation of care processes on a national scale. The favorable results of this CQI study in CABG suggest that this model could be extrapolated to other medical disciplines.

DIAL

(Randomized Trial of Telephonic Intervention in Chronic Heart Failure)

Presented by Daniel R. Nul, MD. Buenos Aires, Argentina.

Background: Almost 1% of the population of Argentina (300 000 patients) present heart failure. The annual mortality of this population can be as high as 10%-20%. Compliance with treatment and the medical supervision of these chronic patients can be difficult and it has been suggested that closer monitoring to ensure compliance with the prescribed treatment could improve the prognosis.

Methods: The DIAL study compared the morbidity and mortality of patients with heart failure who were treated and followed up conventionally using a centralized program of telephone intervention carried out by specialized nurses. This study is part of the GESSICA study (Grupo de Estudio de la Sobrevida de la Insuficiencia Cardíaca en Argentina [Study Group of Survival in Heart Failure in Argentina]). Nurses were trained to carry out educational tasks, counseling, and monitoring during follow-up (asking about functional state, weight, edema, diet, and maintenance treatment), and were authorized to change the guidelines for diuretic treatment. The frequency of calls was protocolized in accordance with the severity of symptoms. A group of 1518 patients from 51 centers in Argentina were randomized (760 to the telephone program and 758 to the control group) and had a follow-up of 457 days. It was required that the patient with heart failure be clinically stable for at least 2 months after optimal medical treatment. Patients without access to a telephone and those with serious associated diseases (restrictive or hypertrophic myocardiopathy, cardiac valve disease, pulmonary hypertension, or congenital heart disease) were excluded.

The main compound endpoint was overall mortality and admissions for heart failure. The secondary endpoints included total and cardiovascular mortality, hospitalization for any reason, quality of life, and a cost-effectiveness analysis.

Results: The baseline clinical characteristics and type of treatment were similar in both groups. In the patients assigned to the telephone intervention, there was a reduction of 20% in the main combined endpoint (death or admission for heart failure, 26.5% vs 31%; *P*=.026) and a reduction of 29% in admissions for heart failure (16.8% vs 22.3%; RRR, 28%; *P*=.005). It was calculated that one admission for heart failure was avoided for every 18 patients included in the telephone supervision program. In addition, the overall hospitalization rate (34.3% vs 39.1%; RRR, 15%; *P*=.05) or hospitalization for cardiovascular causes also decreased in the intervention group. Nevertheless, overall mortality (15.3% vs 16,1%; *P*=.69) was similar in both groups.

Conclusions: A centralized telephone intervention program managed to reduce the morbidity of patients with chronic heart failure, fundamentally by reducing the number of hospital admissions for heart failure. These results indicate that regular communication with these patients makes it possible to identify symptoms or processes that must be assessed during an outpatient visit, thus preventing the need for hospitalization.

PROSPER[2]

(The PROspective Study of Pravastatin in the Elderly AT Risk)

Presented by James Shepherd, MD. Princeton, New Jersey (U.S.).

Background: Cardiovascular diseases are the main cause of mortality in patients over the age of 70 years and are associated with LDL concentrations. Although various earlier studies have demonstrated the benefit of statins in middle-aged patients with normal or high total cholesterol concentrations, there are no similar data for populations of older patients.

Objectives: To evaluate if pravastatin at a dose of 40 mg/day can reduce the appearance of cardiac and cerebral adverse events in older patients with known cardiovascular disease or at high risk of presenting cardiovascular disease or cerebrovascular accident.

Methods: Controlled, randomized, double blind study that, after an initial assessment of 23 770 patients, finally included 5804 (2913 assigned to placebo and 2891 to treatment with pravastatin). The patients had to have pre-existent vascular disease (coronary, vascular, or cerebral) or an increased risk due to smoking, hypertension, or diabetes. In addition, total cholesterol had to be 155 to 350 mg/dL and triglyceride concentration <200 mg/dL. A mean follow-up of 3.2 years was carried out.

The main study endpoint was the appearance of a combination of adverse events (cardiovascular death, myocardial infarction, and cerebrovascular accident) at 3 years of follow-up.

Results: The baseline clinical characteristics and lipid profiles were similar in both groups. Overall,

pravastatin treatment reduced LDL concentration by 34%, total cholesterol by 23%, and triglycerides by 13%. It increased HDL concentration by 5%. The main endpoint of the study (cardiovascular death, myocardial infarction, or cerebrovascular accident) was reduced by 15% in the pravastatin group (14.1% vs 16.2%; P=.014) (HR, 0.85; 95% CI, 0.74-0.97). In this group, the incidence of cardiovascular death or myocardial infarction also decreased by 19% (10.1% vs 12.2%; P=.006; HR, 0.81; 95% CI, 0.69-0.94) and cardiovascular mortality decreased by 24% (3.3% vs 4.2%; P=.043). However, the incidence of cerebrovascular accident was similar in both groups (4.7% vs 4.5%; P=.8). Pravastatin treatment did not reduce the need for admissions for heart failure or revascularization procedures, nor did it produce significant changes in cognitive functions. The incidence of myalgia or rhabdomyolysis was similar in both groups. An unexpected finding of the study was a 25% increase in new cases of cancer in the pravastatin group (8.5% vs 6.8%; P<.05) (HR, 1.25; 95% CI, 1.04-1.51), although the incidence of this problem in any case was low compared to the expected incidence in this age group. In addition, the follow-up time, which was relatively short although relevant in this population, could explain the absence of any difference in the incidence of cerebrovascular events and cognitive deterioration.

Conclusions: The results of this study demonstrate that the same benefits observed with statin treatment in middle-aged patients are also seen in patients over 70 years old. Pravastatin at a dose of 40 mg/day has good tolerability and produces a 15% reduction in unfavorable events and of 24% in cardiovascular mortality after a follow-up of 3.2 years.

WAVE

(Women´s Angiographic Vitamin and Estrogen)

Presented by David D. Waters, MD San Francisco, California (U.S.).

Background: Despite the lack of evidence of a possible benefit obtained from controlled studies, hormone replacement therapy (HRT) and antioxidant vitamins are widely used for secondary prevention in postmenopausal women with coronary artery disease. The aim of this study was to determine if HRT or supplements of antioxidant vitamins, separately or in combination, influence the progression of coronary artery disease (analyzed by quantitative angiography) in postmenopausal women.

Methods: In a randomized, double blind study carried out from July 1997 to January 2002 at 7 North American centers, 423 postmenopausal women with coronary artery disease (at least one coronary lesion of 15% to 75%) were included. The study was conceived with a 2×2 factorial design and randomization to treatment with conjugated equine estrogen (0.625 mg/day) (medroxyprogesterone acetate, 2.5 mg/day, in women with an intact uterus) or placebo, and to treatment with vitamin E (400 UI/12 h) plus vitamin C (500 μg/12 h) or placebo.

The main endpoint was the annual mean change in minimum luminal diameter (from the first to the last angiography) of all the lesions included for each patient. In case of death or myocardial infarction, the angiographic study showing the most unfavorable findings was used.

Results: The time interval between angiographic studies was 2.8±0.9 years. With regard to the main endpoint, there was a greater risk in women assigned to HRT (P=.045) and a greater risk was suggested in the group assigned to vitamin treatment (P=.093). The angiographic changes in terms of mean annual progression of the minimal luminal diameter (mm) were –0.047±0.15 and –0.024±0.15 for HRT and placebo, respectively (P=.17), and –0.044±0.15 vs –0.028±0.15 for antioxidant vitamins and placebo, respectively (P=.32). The mortality was 14 and 8 for the HRT and placebo groups (HR, 1.8; 95% CI, 0.75-4.3), and 16 and 6 for the vitamin and placebo groups (HR, 2.8; 95% CI, 1.1-7.2). When the combined events of death, infarction, or cerebrovascular accident were analyzed, the tendencies were similar.

Conclusions: In postmenopausal women with coronary artery disease, treatment with HRT and antioxidant vitamin supplements did not produce a cardiovascular benefit; in fact, both treatments may have deleterious effects.

TEMPEST

(Trial to Evaluate the Management of PSVT during Electrophysiologic Study with Tecadenoson)

Presented by Kenneth Ellenbogen, MD. Richmond, Virginia (U.S.).

Background: Tecadenoson is a new drug derived from adenosine that prolongs AV conduction. However, since it is selective for A1 receptors, it could prevent adverse effects of adenosine like hypotension (which is mediated by A2 receptors of adenosine) and bronchospasm (mediated by A2b and A3 receptors of adenosine). In addition, the half-life of adenosine is very short (seconds), whereas tecadenoson has a half-life of 30 min. Finally, up to 15% of the patients in which adenosine was given for the treatment of supraventricular paroxysmal tachycardia (SVPT) developed atrial fibrillation.

Methods: The usefulness of this antiarrhythmic drug in converting SVPT to sinus rhythm was evaluated. Patients with one or more episodes of symptomatic tachycardia that required an electrophysiological study «to evaluate or treat» this arrhythmia were included. SVPT was induced and maintained for 2 min, then an i.v. bolus of tecadenoson or placebo was administered. If the arrhythmia persisted 1 min after the drug, a second bolus was administered. Five different tecadenoson regimens were tested randomly (1st/2nd dose): 75/150, 150/300, 300/600, 450/900, and 900/990 µg). The main objective of the study was the conversion to sinus rhythm within 1 min without the appearance of second or third-degree AV block.

Results: The conversion to sinus rhythm in the placebo group was 7%, whereas it was much greater (50, 59, 90, 83, and 87%) with the different active drug regimens (all $P<.001$ vs placebo). The median time to conversion with the three highest doses was less than 1 min In addition, at these doses most patients achieved conversion to sinus rhythm after the first bolus versus only 50% of patients given the lowest doses. The most frequent adverse effect was paresthesia (6% vs 3% in the placebo group). With the 3 highest doses, some patients developed transitory AV block. Nevertheless, with the highest dose (900/900), 2 patients entered atrial fibrillation and required electrical cardioversion and another patient developed atrial flutter and required pacing. None of the 10 patients with chronic obstructive pulmonary disease or asthma developed bronchospasm.

Conclusions: Tecadenoson is a safe and effective treatment in patients with SVPT that eliminates the side effects of adenosine. Studies are needed to compare this drug with conventional adenosine treatment in patients with SVPT.

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