SPECIAL ARTICLE

Summary of the Clinical Studies Reported in the Scientific Session of the American College of Cardiology 2006 (Atlanta, Georgia, USA, 11-14 March 2006)

In the annual scientific sessions of the 55th Congress of the American College of Cardiology, corresponding to 2006, preliminary results of late breaking clinical trials were presented. Thus, the findings of studies of particular importance could be quickly made available.

What follows is a brief summary of the objectives, methods, and results of these studies as presented orally. Given that many of them have yet to be published in their full version, the information given here should be considered as preliminary. If the results of a study have been published in full when these summaries reach the reader, we recommend that the reader consults the publication, which will normally have been written directly in English.

SUMMARY BY TOPICS

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EPIDEMIOLOGY

REACH (Reduction of Atherothrombosis for Continued Health) Registry

Presented by Deepak L. Bhatt, Ohio, United States of America

See full publication in JAMA. 2006;295:180-9.

Background. Atherothrombosis is the leading cause of cardiovascular disease and mortality throughout the world. No international database has yet characterized the profile of risk factors for arteriosclerosis or the aggressiveness of treatment in patients with atherothrombosis. The aim of this study was to determine whether the prevalence of risk factors and treatment of this disease show comparable patterns in different countries.

Methods. The REACH registry collected data on risk factors for arteriosclerosis and its treatment. Between 2003 and 2004, the study included 67 888 patients aged 45 years or more from 5473 clinics in 44 countries. All patients presented with vascular disease (coronary artery disease, n=40 258; cerebrovascular disease, n=18 843; peripheral vascular disease, n=8273) or 3 or more risk factors for atherothrombosis (n=12 389). The prevalence of risk factors, treatments used, and degree of control of risk factors were recorded.

Results. Patients with atherosclerosis throughout the world have a similar profile of risk factors: a high proportion had hypertension (81.8%), hypercholesterolemia (72.4%), and diabetes (44.3%).

The prevalence of overweight subjects (39.8%), obese subjects (26.6%), and morbidly obese subjects (3.6%) was similar in most geographic regions, but was highest in the United States of America (overweight subjects, 37.1%; obese subjects, 36.5%; and morbidly obese subjects 5.8%; *P*<.001 vs other regions). In general, patients were undertreated with statins (69.4% for the whole population; range, 56.4% for cerebrovascular disease to 76.2% for coronary artery disease), antiplatelet agents (78.6% for the whole population; range, 53.9% for ≥3 risk factors to 85.6% for coronary artery disease), and other evidence-based risk-reduction therapies. Current smokers accounted for a substantial proportion of patients with vascular disease (14.4%). Undertreated hypertension (50.0% with high blood pressure at baseline), undiagnosed hyperglycemia (4.9%), and high fasting glucose concentrations (36.5% in patients not previously diagnosed as diabetics) were also common. Among those with symptomatic atherosclerosis, 15.9% had symptomatic disease in multiple vascular territories.

Conclusions. This large and up-to-date international database shows that the traditional cardiovascular risk factors are consistent for and common to all countries, that they are widely undertreated, and that these factors are largely uncontrolled in many parts of the world.

PRIMARY AND SECONDARY PREVENTION

HOPE-2 (Heart Outcomes Prevention Evaluation) Study

Presented by Eva M. Lonn, Hamilton, Canada

See full publication in Can J Cardiol. 2006;22:47-53.

Background. The results of epidemiological studies have suggested that homocysteine is a risk marker for cardiovascular diseases. Treatment with folic acid and vitamin Bs reduces the concentration of homocysteine by 25% to 30%. The objective of the HOPE-2 study was to evaluate the long-term effects of treatment with vitamins on the incidence of cardiovascular events in patients with previous cardiovascular disease or diabetes.

Methods. Between January and December 2000, a total of 5522 patients (28% women), aged 55 years or more, with preexisting cardiovascular disease and/or diabetes, along with other risk factors, were randomized to receive daily treatment with a combination of folic acid (2.5 mg), vitamin B_6 (50 mg), and vitamin B_{12} (1 mg), or placebo. Mean follow-up lasted for 5 years. The primary outcome was a composite of cardiovascular death, myocardial infarction, and stroke.

Results. At the time of inclusion in the study, the mean age of patients was 69 years, 83% had a history of cardiovascular disease, 15% had prior cerebral stroke or transient ischemic attack, 55% had hypertension, 40% had diabetes, 64% had dyslipidemia, and 10% were current smokers. The median baseline concentration of homocysteine was 11.2 µmol/L (interquartile range, 9.3-13.8 µmol/L), although this concentration varied from region to region. The mean decrease in homocysteine after 2 years was 3.8 µmol/L. The main results corresponding to 95% of the assigned events with 99% of the data completed are shown in Table.

Conclusions. Despite reducing the concentration of homocysteine by approximately 25%, no apparent benefit was observed in the treatment with folic acid and vitamin Bs, except for a significant reduction in the incidence of stroke. Subsequent studies should aim to verify the effect observed for cerebrovascular accident. Treatment had no effect on cancer rates or mortality.

These results are in line with those of the Norwegian Vitamin Trial (NORVIT), which also failed to detect any significant effect on cardiovascular events despite achieving a reduction in the concentrations of homocysteine in patients with ST-elevation myocardial infarction.

TABLE. **Main Findings of the HOPE-2 Study***

Outcome	Active Group (n=2758)	Placebo Group (n=2764)	Relative Risk (95% CI)	*P*
Myocardial infarction, stroke, and cardiovascular death	509 (18.5%)	541 (19.6%)	0.94 (0.83-1.06)	.32
Myocardial infarction	333 (12.1%)	348 (12.6%)	0.96 (0.83-1.12)	.61
Stroke	115 (4.2%)	150 (5.4%)	0.77 (0.60-0.98)	.03
Cardiovascular death	261 (9.5%)	282 (10.2%)	0.93 (0.79-1.10)	.39
All-cause mortality	461 (16.7%)	473 (17.1%)	0.98 (0.86-1.11)	.73
Cancer	320 (11.6%)	306 (11.1%)	1.05 (0.90-1.23)	.55
Death due to cancer	79 (2.9%)	80 (2.9%)	0.99 (0.73-1.35)	.95

*CI indicates confidence interval.

ASTEROID (A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden)

Presented by Steven E. Nissen, Cleveland, United States of America

See full publication in JAMA. 2006;295:1556-65.

Background. Previous studies with intravascular ultrasound (IVUS) have shown that statins can slow or block progression of coronary atherosclerosis, but it has not been convincingly shown that they are able to induce regression through lowering the percent atheroma volume (PAV), the most rigorous measure of progression, or regression of the disease as measured by IVUS. The aim of this study was to determine whether intensive lipid lowering with statin therapy could induce regression of coronary atherosclerosis assessed by IVUS.

Methods. This was a prospective study, with open-label administration of the drug, and blinded assessment of the endpoints, carried out in 53 centers in the United States of America, Canada, Europe, and Australia. The study used IVUS with motorized pullback to quantify the coronary atheroma burden at baseline and after 2 years of treatment. For analysis of each IVUS measurement pair (baseline and follow-up), the investigator was blinded to the treatment assigned. Between November 2002 and December 2003, 507 patients with coronary artery disease who had undergone a baseline IVUS and received at least one dose of active drug were included in the study. After 24 months, 349 patients had evaluable IVUS available for both baseline and follow-up. All of them had received intensive treatment with 40 mg/day of rosuvastatin. Two primary efficacy endpoints were defined, namely, PAV change and change in nominal volume of the atheroma in the 10-mm subsegment with greatest disease severity. A secondary efficacy endpoint was established. Change in normalized total atheroma volume in the artery was defined as a secondary efficacy endpoint.

Results. The mean ± SD baseline concentration of low-density lipoprotein cholesterol (LDL-C) was 130.4±34.3 mg/dL. This dropped to 60.8±20.0 mg/dL during follow-up, corresponding to a mean decrease of 53.2% (*P*<.001). The mean concentration of high-density lipoprotein cholesterol (HDL-C) increased from 43.1±11.1 mg/dL to 49.0±12.6 mg/dL, corresponding to an increase of 14.7% (*P*<.001). The mean PAV change for the whole vessel was -0.98% (3.15%), with a median of -0.79% (97.5% confidence interval [CI], -1.21 to -0.53; *P*<.001 with respect to baseline volume). The mean change in atheroma volume in the 10-mm subsegment with greatest disease severity was -6.1±10.1 μL, with a median of –5.6 μL (97.5% CI, -6.8 to –4.0; *P*<.001 compared to baseline). The change in total atheroma volume showed a mean absolute decrease of –14.7±25.7 μL and a median decrease of –12.5 μL (95% CI, –15.1 to –10.5 μL; *P*<.001 with respect to baseline volume). Adverse events were uncommon, with a similar incidence to that reported in studies with other statins.

Conclusions. Intensive treatment with statins through administration of 40 mg/day of rosuvastatin achieved mean concentrations of LDL-C of 60.8 mg/dL and increased HDL-C by 14.7%, causing a significant regression in coronary atherosclerosis in the 3 prospectively defined outcome measures of total atherosclerotic burden. Concentrations of LDL-C below the current recommendations are accompanied by a significant increase in HDL-C concentrations, which may induce regression of atheroma in patients with coronary artery disease. Further studies are required to determine the effect of the changes observed on the clinical outcomes of these patients.

CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management Avoidance) Study

Presented by Deepak L. Bhatt, Ohio, United States of America

See full publication in N Engl J Med. 2006;354: 1706-17.

Background. Dual antiplatelet therapy with clopidogrel plus aspirin has not been studied in a large population of stable patients at a high risk of atherothrombotic events.

Methods. We randomized 15 603 patients with clinically documented cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 mg to 162 mg per day) or placebo plus aspirin at low doses. Clinical follow-up lasted a median of 28 months. The primary efficacy endpoint of the study was a composite of cardiovascular death, myocardial infarction, and cerebrovascular accident.

Results. The incidence of the primary endpoint was 6.8% in patients treated with clopidogrel plus aspirin and 7.3% in those on placebo plus aspirin (relative risk [RR]=0.93; 95% confidence interval, 0.83-1.05; *P*=.22). The percentage of patients reaching the secondary study endpoint, comprising admission to hospital for ischemic disease, was 16.7% versus 17.9% (RR=0.92; 95% CI, 0.86-0.995; *P*=.04), and rate of severe bleeding was 1.7% versus 1.3% (RR=1.25; 95% CI, 0.97-1.61; *P*=.09). In the subgroup

of patients with multiple risk factors, the incidence of the primary endpoint was 6.6% with clopidogrel and 5.5% with placebo (RR=1.2; 95% CI, 0.91-1.59; *P*=.20), and cardiovascular mortality was also greater with clopidogrel (3.9% vs 2.2%; *P*=.01). In the subgroup with clinically documented atherothrombosis, cardiovascular mortality was 6.9% with clopidogrel and 7.9% with placebo (RR=0.88; 95% CI, 0.77-0.998; *P*=.046).

Conclusions. The results of the study point to the benefit of treatment with clopidogrel in patients with symptomatic atherothrombosis, whereas in those with multiple risk factors, the effect seems to be negative. Taken together, the combination of aspirin and clopidogrel in stable patients with symptomatic atherothrombosis was no more effective than aspirin alone at reducing acute myocardial infarction, cerebrovascular accident, or cardiovascular death.

ISCHEMIC HEART DISEASE

ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy Trial)

Presented by Dr. Gregg W. Stone, New York, United States of America

Background. A combination of aspirin, clopidogrel, heparin (both unfractionated and low-molecular weight), and glycoprotein IIb/IIIa inhibitors (GPI), along with early coronary angiography and percutaneous revascularization as appropriate, is the treatment of choice in patients with acute coronary syndromes (ACS) of moderate and high risk. Despite therapy, these patients still present a significant risk of death or myocardial infarction, and the intensive pharmacologic regimens used cause a high rate of bleeding. Some pilot studies suggest than bivalirudin, a specific thrombin antagonist, could improve clinical outcome after ACS.

Methods. An international, prospective, randomized, controlled study was conducted in 448 centers in 17 countries. The study included patients with ACS of moderate-to-high risk. The patients were assigned 1:1:1 to one of the following 3 regimens after admission to the emergency room: heparin (unfractionated or enoxaparin) in combination with GPI, bivalirudin combined with GPI, or bivalirudin alone (GPI could be used for clinical reasons when the response was suboptimal). In the first 2 groups, a second randomization was undertaken to assign patients to receive the GPI from admission or when the coronary intervention took place (in all patients, coronary angiography was done within 72 hours of admission). The inclusion criteria included symptoms indicative of angina lasting more than 10 minutes in the last 24 hours and one of the following criteria: elevated enzymatic markers, dynamic changes in the ECG, documented coronary artery disease, or score of 4 or more on the TIMI scale for unstable angina. The primary endpoint of the study was net clinical benefit after 30 days, comprising adverse ischemic events (death, myocardial infarction, or unplanned revascularization) and major bleeding. The secondary endpoints included events related to ischemia and major bleeding separately. The sample size was calculated to demonstrate first noninferiority and second superiority of the new treatment for both the primary and secondary endpoints.

Results. In total, 13 819 patients were included, 30% of whom were women. The mean age was 63 years. Baseline cardiac enzymes were elevated in 58% of the patients, 33% had dynamic ST-segment changes, and 28% had diabetes. The clinical strategy chosen after coronary angiography was percutaneous coronary intervention in 56%, medical treatment in 33%, and coronary artery bypass surgery in 11%. The median time between study entry and angiography was 5.5 hours.

The primary endpoint of percentage of patients with net clinical benefit was significantly greater in the bivalirudin group alone compared to the heparin plus GPI group (10.1% vs 11.7%; *P*=.015 in the analysis of superiority). The bivalirudin plus GPI group met the noninferiority criterion for comparison with heparin plus GPI (11.8% vs 11.7%; *P*=.015 in the noninferiority analysis). The composite endpoint of ischemic events showed noninferiority in the bivalirudin alone group (7.8%; *P*=.01) and bivalirudin plus GPI group (7.7%; *P*=.007) versus the group treated with heparin plus GPI (7.3%), but none of the 3 treatments were superior to the others. The incidence of major bleeding was significantly lower in the bivalirudin group alone versus the group of heparin plus GPI (3.0% vs 5.7%; *P*=.001 in the superiority analysis), but it was neither significantly superior nor inferior in the bivalirudin plus GPI group versus the heparin plus GPI group (5.3% vs 5.7%; *P*=.001 in the noninferiority analysis). The results were similar for the comparison of incidence of major bleeding according to TIMI criteria (1.8% for heparin plus GPI, 1.6% for bivalirudin plus GPI, and 0.9% for bivalirudin alone; *P*<.001 for the analysis of the superiority of bivalirudin versus heparin plus GPI).

Conclusions. In patients with ACS, treatment with bivalirudin alone is associated with better clinical outcomes compared to treatment with heparin plus GPI, due essentially to a decrease in the incidence of bleeding. In addition, it was observed that the clinical benefit of bivalirudin plus GPI was not inferior to the combination of heparin plus GPI.

ACUITY Timing Trial (Acute Catheterization and Urgent Intervention Triage Strategy Timing Trial)

Presented by Dr. Gregg W. Stone, New York, United States of America

Background. Glycoprotein IIb/IIIa inhibitors (GPI) reduce serious cardiac complications in patients with acute coronary syndrome (ACS) who undergo coronary angiography followed by percutaneous coronary intervention (PCI) or who receive other measures (pharmacologic treatment or coronary artery bypass surgery), as indicated. Currently, it is not known whether it is preferable to start systematic treatment with GPI on admission of moderate-to-high risk patients with ACS to the emergency room, or only administer GPI in the catheterization laboratory to patients undergoing PCI.

Methods. To analyze the optimum time for administration of GPI to patients with ACS scheduled for invasive treatment, a prospective study was performed. A large number of patients with ACS of moderate-to-high risk were randomized to receive fixed doses of GPI from arrival in the emergency room or only when they underwent PCI after the diagnostic coronary angiography. Patients had been previously randomized to receive treatment with heparin plus GPI or bivalirudin plus GPI (the first 2 groups described in the previous summary). The aim was, with the same study, to compare the effects of: *a)* heparin versus bivalirudin, and *b)* systematic initiation of GPI (both eptifibatide and tirofiban) versus treatment with selective administration of these inhibitors (eptifibatide or abciximab) in the catheterization laboratory in patients undergoing PCI. For this analysis of the ideal timing for administration of GPIs, groups of patients treated with heparin or bivalirudin were pooled (and an interaction test carried out). The primary endpoint was incidence of severe cardiac complications (death, myocardial infarction, or unplanned revascularization) at 30 days. The secondary endpoints included hemorrhagic complications and the cost-effectiveness ratio.

Results. The median age of the 9016 patients included was 63 years, 30% were women, and 28% had diabetes mellitus. After coronary angiography, the primary strategy was percutaneous coronary intervention in 57%, coronary artery bypass grafting in 11%, and pharmacologic treatment in 32% of the patients. In the group treated immediately with GPIs, 99% of the patients received treatment, whereas in the group with deferred administration, GPIs were given to 56% of the patients (96% of the patients with PCI). Angiography was done on average 6.2 hours after randomization, and the administration of GPIs was done before angiography in 94.5% of the patients assigned to the group treated immediately with GPIs, and in 5.8% of the patients assigned to the deferred treatment group.

The primary endpoint of percentage of patients with net clinical benefit was not inferior in the group treated immediately with GPIs versus deferred treatment (11.7% in both groups; $P<.001$ in the noninferiority analysis). The composite endpoint comprising 3 ischemic events did not meet the criterion of noninferiority (7.1% for immediate treatment versus 7.9% for deferred treatment; P=NS for noninferiority and P=.13 for superiority). The incidence of major bleeding was significantly lower in the deferred treatment group (4.9% vs 6.1%; P=.009). No differences were found when major hemorrhages were compared according to TIMI criteria (1.9% vs 1.5%; P=.20), but minor bleeding according to TIMI criteria occurred less frequently in the deferred treatment group (5.4% vs 7.2%; $P<.001$). There were no differences in mortality (1.3% for immediate treatment vs 1.5% for deferred treatment) or the incidence of acute myocardial infarction (4.9% vs 5.0%), but unplanned revascularization for ischemia was less frequent in the immediate treatment group (2.1% vs 2.8%; P=.03 for superiority). In the cohort of patients who underwent PCI (n=5170), the composite endpoint of ischemic events was reached less often in the group treated immediately with GPI (8.0% vs 9.5%; P=.05).

Conclusions. In patients with ACS, according to the endpoint of net clinical benefit, immediate treatment with GPI was not inferior to deferred administration of GPI, but noninferiority was not demonstrated for the composite endpoint of ischemic events.

The joint conclusion of the last 2 summaries could be that in patients with a medium-high risk ACS, whose revascularization strategy is determined by coronary angiography, administration of bivalirudin alone makes administration of GPIs unnecessary. If GPIs are used, their administration can be deferred until the PCI is done, although their use should be avoided in patients who are scheduled for other types of treatment.

OASIS 6 (Organization to Assess Strategies for Ischemic Syndromes-6) Study

Presented by Dr. Salim Yusuf, Cleveland, United States of America

See full publication in JAMA. 2006;295:1579-90.

Background. Despite numerous therapeutic advances, mortality in patients with ST-segment

elevation myocardial infarction (STEMI) remains high. The role of new antithrombotic agents added to standard treatment is not known, especially in patients who do not receive reperfusion treatment. The objective of this study was to assess the effect of fondaparinux, a selective factor Xa inhibitor, started early and maintained for up to 8 days, compared to traditional treatment (placebo in patients for whom unfractionated heparin is not indicated [group 1] or unfractionated heparin treatment for 48 hours plus placebo up to 8 days in the remaining patients with STEMI [group 2]).

Methods. This was a randomized double-blind study that compared fondaparinux 2.5 mg once a day (initial dose administered intravenously with subsequent subcutaneous doses for 8 days) or placebo in 12 092 patients with STEMI selected from 447 hospitals in 41 countries between September 2003 and January 2006. Between days 3 and 9, all patients received fondaparinux or placebo in accordance with their assignment in the randomization. The primary endpoint of the study was a composite of death and reinfarction at 30 days. The secondary endpoints included the same events determined at 9 days and at the end of follow-up (3 to 6 months).

Results. The incidence of the primary endpoint at 30 days was reduced significantly to 677/6056 patients (11.2%) in the control group and to 585/6036 patients (9.7%) in the fondaparinux group (hazard ratio [HR]=0.86; 95% confidence interval [CI], 0.77-0.96; *P*=.008; absolute risk reduction, 1.5%; 95% CI, 0.4-2.6). This benefit was also observed after 9 days (537 [8.9%] with placebo vs 444 [7.4%] with fondaparinux; HR=0.83; 95% CI, 0.73-0.94; *P*=.003) and at the end of follow-up (857 [14.8%] with placebo vs 756 [13.4%] with fondaparinux; HR=0.88; 95% CI, 0.79-0.97; *P*=.008). Mortality was significantly reduced during the study. There was no difference in the benefit from fondaparinux in the 2 groups stratified by the prospectively defined indication for treatment with heparin. However, no benefit was observed in patients who underwent primary angioplasty. In the remaining patients of group 2, fondaparinux was superior to unfractionated heparin in the prevention of death or reinfarction at 30 days (HR=0.82; 95% CI, 0.66-1.02; *P*=.08) and at the end of the study (HR=0.77; 95% CI, 0.64-0.93; *P*=.008). Significant benefit was observed both in patients who received thrombolytic therapy (HR=0.79; *P*=.003) and in those who did not receive any reperfusion treatment (HR=0.80; *P*=.03). There was a tendency towards a smaller incidence of severe bleeding with fondaparinux (79 with placebo vs 61 with fondaparinux; *P*=.13) and a significantly smaller incidence of cardiac tamponade (48 vs 28; *P*=.02) after 9 days of follow-up.

Conclusions. In patients with STEMI, and particularly in those who do not undergo primary angioplasty, fondaparinux significantly reduces mortality and the rate of reinfarction without increasing the incidence of bleeding or cerebrovascular accidents.

ExTRACT-TIMI 25 (Enoxaparin Versus Unfractionated Heparin With Fibrinolysis for ST-Elevation Myocardial Infarction) Study

Presented by Elliot M. Antman, Boston, United States of America

See full publication in N Engl J Med. 2006;354: 1477-88.

Background. Unfractionated heparin is often used to complement fibrinolytic therapy in patients with ST-elevation acute myocardial infarction (STEMI). Enoxaparin, a low molecular weight heparin, was compared with unfractionated heparin for this indication.

Methods. In total, 20 506 patients with STEMI scheduled to receive fibrinolytic treatment were randomized to receive enoxaparin or else unfractionated heparin during the initial stay in hospital in weight-dependent doses for at least 48 hours. The main efficacy endpoint was incidence of death or nonfatal reinfarction at 30 days.

Results. The incidence of the primary endpoint was 12.0% in the patients in the group treated with unfractionated heparin and 9.9% in the group who received enoxaparin (reduction in relative risk of 17%; *P*<.001). Nonfatal reinfarction occurred in 4.5% of the patients who received unfractionated heparin and in 3.0% of those treated with enoxaparin (reduction in relative risk of 33%; *P*<.001); 7.5% of the patients who received unfractionated heparin died compared to 6.9% of those who received enoxaparin (*P*=.11). The composite endpoint of death, nonfatal reinfarction, or emergency revascularization occurred in 14.5% of the patients treated with unfractionated heparin and in 11.7% of those treated with enoxaparin (*P*<.001); severe bleeding occurred in 1.4% and 2.1%, respectively (*P*<.001). The composite endpoint of death, nonfatal reinfarction, and nonfatal intracranial bleeding (a measure of net clinical benefit) occurred in 12.2% of the patients who received unfractionated heparin and in 10.1% of those treated with enoxaparin (*P*<.001).

Conclusions. In patients who received fibrinolytic therapy for STEMI, treatment with enoxaparin during the initial period in hospital was superior to treatment with unfractionated heparin for 48 hours, but it is associated with an increase in major bleeding. These

results should be interpreted in the context of net clinical benefit.

ISAR-REACT 2 (Prospective, Randomized, Double-blind, Placebo Controlled Trial of Glycoprotein IIb/IIIa Inhibition With Abciximab in Patients With Acute Coronary Syndromes Undergoing Stenting After Pretreatment With a High Loading Dose of Clopidogrel)

Presented by Adnan Kastrati, Munich, Germany

See full publication in JAMA. 2006;295:1531-8.

Background. No studies have been specifically designed to assess the role of abciximab, a glycoprotein IIb/III inhibitor, in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) undergoing percutaneous coronary intervention after pretreatment with 600 mg of clopidogrel. This trial aims to evaluate whether abciximab provides clinical benefit in patients with high-risk NSTE-ACS.

Methods. Between March 2003 and December 2005, an international, multicenter, randomized, double-blind, placebo-controlled study was conducted in 2022 patients (mean age, 66 years) with NSTE-ACS submitted to percutaneous coronary intervention. These patients were randomized to receive abciximab (bolus of 0.25 mg/kg body weight, followed by a 12-hour infusion of 0.125 µg/kg/min [maximum, 10 µg/min]; plus heparin, 70 U/kg of body mass), or placebo (bolus of placebo and 12-hour infusion plus bolus of heparin, 140 U/kg). All patients received 600 mg of clopidogrel at least 2 hours before the procedure, as well as 500 mg of aspirin given orally or intravenously. The primary outcome measure of the study was a composite of the incidence of death, myocardial infarction, and emergency revascularization of the target vessel at 30 days after randomization. The secondary endpoints included incidence of major and minor in-hospital bleeding.

Results. Of the 2022 patients, 1012 were randomized to abciximab and 1010 to placebo. The primary endpoint occurred in 90 patients (8.9%) assigned to abciximab compared to 120 patients (11.9%) assigned to placebo, with a risk reduction of 25% with abciximab (relative risk [RR]=0.75; 95% confidence interval [CI], 0.58-0.97; *P*=.03). For patients without high concentrations of troponin, there were no differences in the incidence of the primary endpoint in the group treated with abciximab (23/499 patients [4.6%]) and the placebo group (22/474 patients [4.6%]) (RR=0.99; 95% CI, 0.56-1.76; *P*=.98), whereas for patients with elevated troponin levels, the incidence of events was significantly lower in the abciximab group (67/513 patients; 13.1%) than in the placebo group (98/536 patients; 18.3%), which corresponded to a relative risk of 0.71 (95% CI, 0.54-0.95; *P*=.02; *P*=.07 for the interaction). There were no significant differences between the 2 groups with respect to the risk of major or minor bleeding, or with respect to the need for transfusion.

Conclusions. Abciximab reduces the risk of adverse effects in patients with NSTE-ACS who undergo percutaneous coronary intervention after pretreatment with 600 mg of clopidogrel. The benefits of abciximab appear to be limited to patients with an elevated concentration of troponin.

HEART FAILURE

UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) Study

Presented by María Rosa Costanzo, Naperville, United States of America

See full publication in Eur J Heart Fail. 2006;8: 326-9.

Background. Standard treatment with intravenous diuretics in patients with acute decompensated heart failure is associated with moderate weight loss and a high rate of readmission to hospital. In these patients, mechanical ultrafiltration is able to rapidly remove fluids.

Methods. The study was performed according to a randomized multicenter design in which ultrafiltration (Aquadex System 100, CHF-Solutions Minneapolis MN, USA) was compared with intravenous diuretics in patients with acute decompensated heart failure. The primary outcome measures of the study were weight loss (kg) and dyspnea at 48 hours after randomization (efficacy); and changes in creatinine, electrolytes, and hypotensive events (safety). The secondary outcome measures were net fluid loss at 48 hours, NYHA functional class, 6-minute walk test, changes in Minnesota test scores, duration of stay in hospital, percentage of patients readmitted to hospital for acute decompensated heart failure, days in hospital for this heart failure, and unscheduled visits for the same event. Patients with acute decompensated heart failure with 2 or more signs of congestion were included in the study. Exclusion criteria were creatinine greater than 3.0 mg/dL; systolic blood pressure at baseline equal or less than 90 mm Hg; lack of venous access; and prior use of vasoactive drugs.

The assessments were done on admission to the study, during treatment, on discharge from hospital, and after 10, 30, and 90 days. The intravenous diuretic doses at 48 hours after randomization were equal or greater than 2 times the prior daily oral dose. Patients in the other group underwent venovenous ultrafiltration at a rate of 500 mL/h or less.

Results. In total, 200 patients (aged 63 [15] years, 69% men, 54% Caucasian, 71% with left ventricular ejection fraction ≤40%) were randomized to receive ultrafiltration or standard treatment. After 48 hours, the weight loss was greater in the ultrafiltration group (5.0 [3.1] kg vs 3.1 [3.5] kg; *P*<.001) and the net loss of fluids was also greater in this group (4.6 L vs 3.3 L; *P*<.001). After 48 hours, fewer patients in the ultrafiltration group required vasoactive drugs (3 [3%] vs 12 [13%]; *P*=.015). Potassium concentrations less than 3.5 mEq/L were reported in 1 patient (1%) in the ultrafiltration group and in 9 patients (12%) in the standard treatment group (*P*=.018). Dyspnea, creatinine, basal blood pressure, duration of hospital stay, and NHYA class were similar. After 90 days, fewer patients were readmitted to hospital for acute decompensated heart failure in the ultrafiltration group (16 [18%] vs 28 [32%]; *P*=.022). In this group, there were also fewer readmissions to hospital (0.22 [0.58] vs 0.46 [0.76]; *P*=.009), fewer number of days in hospital (1.4 [4.2] days vs 3.8 [8.5] days; *P*=.01), and fewer unscheduled visits for this reason (17 [26.2%] vs 31 [47%]; *P*=.011). Nine deaths were reported in the ultrafiltration group and 11 in the standard treatment group.

Conclusions. *a)* Ultrafiltration is associated with greater weight loss and loss of fluid than intravenous diuretics in patients with acute decompensated heart failure, with no treatment effect on renal function; *b)* ultrafiltration significantly reduces the percentage of patients who require readmission to hospital for acute decompensated heart failure and unscheduled visits for this reason; and *c)* in acute decompensated heart failure, symptoms and weight loss are not related to one another.

ARRHYTHMIAS

APAF (Ablation for Paroxysmal Atrial Fibrillation) Study

Presented by Dr. Carlo Pappone, Milan, Italy

Background. Circumferential pulmonary vein ablation has been undertaken safely and effectively in more than 8000 patients with atrial fibrillation. However, the safety and effectiveness of this technique have never been compared with conventional treatment with antiarrhythmic drugs in a randomized controlled study.

Methods. A total of 198 patients (age 57 [10] years, 66% men) with paroxysmal atrial fibrillation (PAF) (duration 5 [5] years; 3.3 episodes/month; left atrial diameter, 39 [5] mm) were randomized to undergo circumferential pulmonary vein ablation (n=99) or to receive antiarrhythmic agents (n=99). The agents administered were flecainide (n=33), sotalol (n=33), and amiodarone (n=33). The ablation procedure was performed on all 4 pulmonary veins, and 3 additional lines were ablated to prevent atrial tachycardia. For the procedure, either an 8-mm catheter (n=49) or a 3.5-mm irrigated-tip catheter (n=49) was used, under guidance from either the CARTO (n=49) or NavX (n=49) mapping systems. After selection, both groups started a 1-month phase to titer up the antiarrhythmic agents to the maximum dose. The patients then received the assigned therapy, that is, they either continued with pharmacologic treatment or underwent circumferential pulmonary vein ablation (i.e., in this group, the antiarrhythmic agents were discontinued after 1 month). Follow-up for all patients lasted 12 months. The ECG results were collected by daily transtelephonic transmissions. In addition, patients underwent 48-hour monitoring with a Holter recorder, and transthoracic echocardiography was done at 3, 6, and 12 months. Crossover from the initial treatment group was allowed after 3 months.

Results. The results from the first 150 patients with a follow-up of 9 months were reported. These patients had a mean PAF duration of 6 years, and 52 episodes of PAF per year in the ablation group and 30 episodes per year in the control group (*P*=.05). After 9 months of follow-up, 87% of the patients in the group undergoing circumferential pulmonary vein ablation and 29% of control subjects were free of atrial fibrillation or tachycardia (the antiarrhythmic agents had been withdrawn in all patients in the ablation group, *P*<.001). The ablation procedure was repeated in 3 patients in the group undergoing circumferential pulmonary vein ablation due to recurrent atrial fibrillation (1 patient with PAF recurrence) and atrial tachycardia (2 patients). There was a significant decrease in the left atrial diameter at 12 months in patients randomized to circumferential pulmonary vein ablation (–8%; *P*<.01), but not in those who received pharmacologic treatment. Among the events attributable to circumferential pulmonary vein ablation were transient ischemic attack and pericardial effusion.

Conclusions. In this randomized, controlled study that compared circumferential pulmonary vein ablation with therapy, antiarrhythmic, ablation was associated with significantly fewer recurrences of PAF. The findings from 1 year of follow-up for the entire

cohort are still awaited but these preliminary results are highly encouraging.

ARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmias After Cardiac Surgery) Study

Presented by Giuseppe Patti, Rome, Italy

Background. Episodes of atrial fibrillation after heart surgery are associated with an increased risk of cardiovascular complications. Inflammatory mechanisms could be implicated in the pathophysiology of postoperative atrial fibrillation. Treatment with statins could reduce the incidence of this complication because of the antiinflammatory of effects of this class of compound. The aim of this study was to assess the effect of atorvastatin compared to placebo on the incidence of postoperative atrial fibrillation after elective heart surgery.

Methods. This was a randomized, prospective, double-blind, placebo-controlled study, in which 200 patients were included. The patients had undergone heart surgery, had received no prior statin treatment, and had no history of atrial fibrillation. The patients were randomized to atorvastatin (40 mg/day, n=101) or placebo (n=99), with treatment starting 7 days before surgery. Concentrations of C-reactive protein were measured systematically before the operation and every 24 hours thereafter until the patient was discharged from hospital. The primary endpoint was incidence of postoperative atrial fibrillation.

Results. The mean age of the patients was 60 years, and 69% were men. The baseline ejection fraction was 52%, and 97% of the patients had multivessel disease. Atrial fibrillation had a significantly lower incidence in the statin group (35%) than in the placebo group (57%; *P*=.003). No differences were found in the time of appearance (51 h vs 50 h, respectively) or the duration of episodes of arrhythmia after surgery (24 h in both groups). The length of stay in hospital was shorter in the atorvastatin group (6.3 days vs 6.9 days; *P*=.001). At 30 days, 2 deaths and 3 myocardial infarctions were reported in each group. Stroke was reported in 1 patient in the placebo group and no patient required repeat revascularization. The maximum concentration of C-reactive protein after the operation was significantly lower in the patients without atrial fibrillation than in those with atrial fibrillation (*P*≤.025), regardless of treatment group. According to the multivariate analysis, treatment with atorvastatin was associated with a decrease in the risk of postoperative atrial fibrillation of 60% (odds ratio, 0.39; 95% CI, 0.18-0.85; *P*=.017).

Conclusions. Pretreatment with 40 mg/day of atorvastatin for 7 days significantly reduces the incidence of postoperative atrial fibrillation compared to placebo in patients who undergo heart surgery. The antiinflammatory effects of the treatment with statins could contribute to this clinical benefit. Should this be confirmed, the results of this study might influence pharmacologic therapeutic regimens administered prior to heart surgery.

PC-Trial (Physical Counterpressure Maneuver)

Presented by Nynke van Dijk, Amsterdam, Holland

Background. Current treatment of vasovagal syncope includes providing the patient with information about the condition and advice on lifestyle changes. It has been shown that physical counterpressure maneuvers (PCM) consisting of crossing the legs, flexing the muscles of the legs and arms, and clenching the fists to increase blood pressure can control or prevent vasovagal episodes in laboratory conditions. In this study, the effectiveness of these maneuvers is examined in daily life.

Methods. The PC-trial is a multicenter, prospective, randomized, single-blind study that included 199 patients aged from 16 years to 70 years with recurrent vasovagal syncope and recognizable prodromic symptoms. The patients were randomized to receive optimal conventional therapy and training in PCM through biofeedback techniques.

Results. Ninety-eight patients were randomized to receive conventional therapy along with PCM training and 101 patients were randomized to receive conventional therapy only. Recurrence of syncope occurred less often in the PCM group compared to controls (32% vs 51%; *P*<.01). The annual syncope rate during follow-up was significantly lower in the group trained in PCM (median, 0.0; interquartile range, 0.0-0.7) than in the control group (median, 0.6; interquartile range, 0.0-1.3; *P*=.004). The actuarial recurrence-free survival was greater in the group assigned to the PCM intervention (hazard ratio [HR]=0.59; log-rank test, *P*=.018). There were no differences in recurrence of presyncope (82.7% with PCM vs 74% in controls; *P*=.12). No adverse effects were reported.

Conclusions. Training in physical counterpressure maneuvers with biofeedback techniques, in addition to conventional therapy, is an effective and risk-free method in patients with vasovagal syncope and recognizable prodromic symptoms, and so this approach should be recommended as the treatment of choice in such patients.

PERCUTANEOUS CORONARY INTERVENTION

TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Angioplasty)

Presented by Christian Spaulding, Hesperion, Switzerland

Background. It has been shown that sirolimus-eluting stents reduce restenosis, the need for repeat procedures, and clinical events compared to bare-metal stents. However, the efficacy and safety of sirolimus-eluting stents were not demonstrated in patients with ST-elevation myocardial infarction in a large randomized study with clinical outcomes. This was the objective of the present study.

Methods. This was a multicenter, randomized, single-blind study that enrolled patients with acute myocardial infarction (defined as prolonged chest pain with ST-elevation) lasting at least 12 hours and with angiographic evidence of a target lesion for stent placement in the native coronary artery. The exclusion criteria were prior myocardial infarction, Killip class greater than 2, bifurcation lesion with need for treatment in the affected branch, lesion affecting more than 50% of the unprotected left descending coronary artery, significant stenosis (>50%) proximal or distal to the culprit lesion in the artery in which the revascularization is assessed and multivessel coronary disease in nontarget lesions that require coronary artery bypass surgery. After imaging of the culprit lesion, the patients were randomized to receive a sirolimus-eluting stent (Cypher™ or Cypher Select™) or a bare-metal stent. The primary outcome measure was failure in the target vessel at 1 year after the procedure, defined as target vessel revascularization, recurrent myocardial infarction, or cardiac death that could not clearly be attributed to a vessel other than the target one. The secondary endpoints included incidence of major cardiac complications during hospitalization and at 1, 6, and 12 months. A substudy with angiographic follow-up at 8 months was planned in 200 patients at selected centers.

Results. Between October 2003 and September 2004, 715 patients were selected with a mean age of 59 (12) years. Of these, 78% were men. The infarct was anterior in 45% of the cases and IIb/IIIa platelet inhibitors were used in 71% of the patients. The mean door-to-balloon time was 60 minutes. The primary endpoint of failure of the target vessel occurred less often in the group treated with sirolimus-eluting stents compared to the conventional stent (7.3% vs 14.3%; *P*=.0036), essentially because of mainly due to a lower rate of target vessel revasculatization (3.7% vs 12.6%; *P*<.001). No differences were found in the incidence of death or acute myocardial infarction. Likewise, there were no group differences with respect to stent thrombosis (3.4% vs 3.6%, respectively, *P*=NS), but the overall incidence of this complication was high.

In the cohort that underwent angiographic follow-up (n=184), the in-stent late luminal loss was much lower with the sirolimus-eluting stent compared to the conventional stent (0.13 mm vs 0.83 mm; *P*<.0001).

Conclusions. Use of the sirolimus-eluting stent in patients who received primary angioplasty due to acute myocardial infarction was associated with a decrease in the incidence of the primary endpoint of the study, namely, failure of the target vessel at 1-year of follow-up, in comparison with the conventional stent. The difference was essentially due to a decrease in the incidence of of the target vessel revascularization.

PASSION (Paclitaxel-Eluting Stent Versus Bare-Metal Stent in STEMI) Study

Presented by Maurits T. Dirksen, Amsterdam, Holland

Background. It has been shown that drug-eluting stents, including those that elute paclitaxel, lower the incidence of restenosis in several subgroups of patients, thus limiting the need for repeat coronary interventions. This potential advantage has still not been established for primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction (STEMI). This was the objective of the PASSION study, a prospective, randomized study done in 2 centers in patients who underwent percutaneous coronary intervention (PCI) for STEMI.

Methods. The results at 6 and 12 months were compared for 619 patients who underwent primary PCI with stenting for STEMI. The patients were randomized to receive paclitaxel-eluting stents (BSX Taxus) or conventional stents (BSX Express2 or Liberté). Permissive inclusion and exclusion criteria were applied so that the final study population would reflect the "real-life" situation and so have greater clinical relevance. Patients were administered aspirin (80-100 mg/day) and clopidogrel (loading dose of 300 mg followed by 75 mg/day for 6 months) as antiplatelet therapy.

Results. The time from onset of symptoms to artery patency was 3.1 hours. The culprit artery was the left anterior descending artery in 50% of the cases, and 45% had multivessel lesions. Angiographic success was achieved in 96% of the cases in both groups. A mean of 1.3 stents were placed per patient in both study groups. The incidence of the primary endpoint of death, reinfarction, or revascularization of the target vessel at 1 year of follow-up showed no differences

between groups (8.7% for the paclitaxel-releasing stent vs 12.6% for the conventional stent group, risk ratio =0.68; *P*=.12). The incidence of death or reinfarction was 4.8% in the first group compared to 6.5% in the second (*P*=.39). There were no differences in revascularization of the target vessel (6.2% vs 7.4%; *P*=.23). Three cases of in-stent thrombosis were reported in each group (1%).

Conclusions. In patients who undergo PCI for STEMI, the use of paclitaxel-eluting stents is not associated with differences in the incidence of the events included in the primary endpoint after 1 year of follow-up in comparison with conventional stents.

TAXUS-V ISR (Paclitaxel-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis Within Bare-Metal Stents) Study

Presented by Gregg W. Stone, New York, United States of America

See full publication in JAMA. 2006;295:1307-9.

Background. Restenosis of bare-metal stents is often treated with repeat percutaneous coronary interventions, even though the subsequent rate of recurrence is high. To date the best outcomes were achieved with vascular brachytherapy. The effectiveness of drug-eluting stents in this situation is still unknown. The objective of this study was to investigate the safety and efficacy of polymer-coated stents for slow release of paclitaxel in patients with restenotic lesions after previous placement of a conventional stent in a native coronary artery.

Methods. This was a prospective, multicenter, randomized study, done between June 6, 2003 and July 16, 2004, in 396 patients with in-stent restenosis in a previously placed bare-metal stent (vessel diameter of 2.5-3.75 mm, lesion length ≤46 mm). Patients were randomly assigned to undergo angioplasty followed by vascular brachytherapy with a beta radiation source (n=201) or implantation of a paclitaxel-eluting stent (n=195). Clinical and angiographic follow-up was scheduled at 9 months for all patients. The primary endpoint of the study was revascularization of the target vessel after 9 months.

Results. Diabetes mellitus was present in 139 patients (35.1%). The median reference vessel diameter was 2.65 mm and the median lesion length was 15.3 mm. In the vascular brachytherapy group, new stents were placed in 22 patients (10.9%), and in the paclitaxel-eluting stent group, 57 patients (29.2%) needed multiple stents, with a median stent length of 24 mm. Follow-up at 9 months was carried out for 194 patients in the vascular brachytherapy group and for 191 patients in the paclitaxel-eluting stent group (96.5% and 97.9%, respectively). The number of events and the rate of target lesion revascularization at 9 months was 27 (13.9%) versus 12 (6.3%) (relative risk [RR], 0.45; 95% confidence interval [CI], 0.24-0.86; *P*=.01) in the vascular brachytherapy group and the paclitaxed-eluting stent group, respectively. The incidence the target vessel resvaculatization directed by ischemia was 34 (17.5%) versus 20 (10.5%), respectively (RR=0.60; 95% CI, 0.36-1.00; *P*=.046). For major cardiac complications, the respective incidences were 39 (20.1%) versus 22 (11.5%) (RR=0.57; 95% CI, 0.35-0.93; *P*=.02), with similar rates of cardiac death or myocardial infarction (10 [5.2%] vs 7 [3.7%]; RR=0.71; 95% CI, 0.28-1.83; *P*=.48) and target vessel thrombosis (5 [2.6%] vs 3 [1.6%]; RR=0.61; 95% CI, 0.15-2.50; *P*=.72). The incidence of angiographic restenosis at 9 months was 31.2% (53 out of 170 patients) with vascular brachytherapy and 14.5% (25 out of 172 patients) with paclitaxel-eluting stents (RR=0.47; 95% CI, 0.30-0.71; *P*<.001).

Conclusions. Treatment of restenosis of conventional stents with paclitaxel-eluting stents decreases the rate of clinical and angiographic restenosis at 9 months and improves event-free survival compared to angioplasty followed by brachytherapy.

PROGRESS-I Study (Coronary Results of the First Absorbable Metal Stent)

Presented by Raimund Erbel, Essen, Germany

Background. Conventional coronary stents are implanted to provide scaffolding for the vessel wall after angioplasty. They also prevent early luminal loss during the healing process and reduce the rate of restenosis, making them unnecessary after the healing phase. The permanent presence of stent material has been associated with late luminal loss in the long term. Thus, it has been postulated that a reabsorbable metal stent could provide the short-term benefits of preventing early luminal loss while avoiding the long-term disadvantages of a permanent implant. The PROGRESS-I study is the first study in humans to assess the safety of a reabsorbable metal stent system used for the treatment of coronary stenosis.

Methods. The PROGRESS-I study is a multicenter nonrandomized study with consecutive recruitment of patients. The study included 63 patients from 9 centers with a single de novo lesion of a native coronary artery susceptible to percutaneous coronary intervention. The angiographic inclusion criteria were a lesion length

less than or equal to 13 mm, a vessel diameter between 3.0 and 3.5 mm, and 50% to 99% stenosis. At 4-month follow-up, coronary angiography and intravascular echography were performed and adverse events were recorded.

Results. The preliminary findings showed that, the proportion of women of was 30%, and 17% of the patients were diabetic. Overall, 82% of the patients had stable angina and 10% had unstable angina. The target lesion was located in the left anterior descending artery in 35% of the patients, in the left circumflex artery in 29%, and in the right coronary artery in 37%. In all cases, predilatation was performed with a balloon at a pressure of 9 Bar. Reabsorbable metal stents of different sizes were implanted: 3.0×10 mm, 3.0×15 mm, 3.5×10 mm, and 3.5×15 mm, with an average of 1.1 stents per patient. Postimplantation inflation was performed in 67% of the cases. Elastic recoil was 7%. The initial success of the procedure was 100%. During the 4 months of follow-up, no in-stent thrombosis events, myocardial infarctions, or deaths were reported. Repeat ischemia-driven target lesion revascularization was done in 28.5% of the cases, and the total number of patients with target lesion revascularization was 38.1%. Late luminal loss at 4 months was 1.09 mm. The mean percentage extent of stenosis was 62% before the intervention, 12% immediately afterwards, and 48% at 4 months. The minimum luminal diameter was 1.05 mm, 2.46 mm, and 1.37 mm, respectively.

Conclusions. In patients with a single *de novo* lesion in the native coronary artery, the use of reabsorbable stents was safe, with no associated deaths or myocardial infarctions, and the rate of ischemia-driven target lesion revascularization was moderate at 4 months, and greater than that for drug-eluting stents. In addition, the mean percentage extent of stenosis at 4 months was relatively high. Therefore, a larger randomized, controlled study is needed to more clearly establish the usefulness of this reabsorbable stent.

STENT (Strategic Transcatheter Evaluation of New Therapies) Registry

Presented by Charles A. Simonton, Charlotte, United States of America

Background. Paclitaxel- and sirolimus-eluting stents inhibit restenosis by different cellular mechanisms, and so may have different clinical outcomes in high-risk patients, such as those with diabetes. This study reports the outcomes with both types of stent after 9 months of follow-up in a large unselected population of diabetic patients.

Methods. The STENT project is the first prospective multicenter registry of drug-eluting stents in the United States of America. It started collecting data in 2003. All the patients, originating from 8 centers, gave their consent for information on the procedure, hospital stay, and 9-month follow-up to be used in a centralized database. This database was subject to regular audits and assignment of the key clinical events was made by medical experts.

Results. Since 2003, only drug-eluting stents (paclitaxel or sirolimus) have been used in a total of 1680 patients with diabetes who underwent percutaneous revascularization. Insulin was being administered to 498 of these patients (30%). Of these patients receiving insulin, 235 (47%) received a paclitaxel-eluting stent and 263 (53%) a sirolimus-eluting stent. Of the remaining 1182 noninsulin-dependent patients (70%), 570 (48%) were revascularized with paclitaxel-eluting stents and 612 (52%) with sirolimus-eluting stents. The clinical characteristics and the characteristics of the baseline lesions were similar for both treatment groups, except for a higher proportion of high-risk clinical factors, longer lesions, and vessels less than 3 mm in diameter among those who received a paclitaxel-eluting stent.

The results at 9 months showed no differences attributable to the type to stent used in the group of diabetic patients as a whole. Major cardiac complications were uncommon, but the investigators found that cardiac events were less frequent in the insulin-dependent patients who received a paclitaxel-eluting stent than in those who received a sirolimus-eluting stent. More specifically, paclitaxel-eluting stents were associated with a lower incidence of death (2.1% vs 5.7%), myocardial infarction (1.3% vs 1.9%), restenosis or new severe stenosis of the target vessel (3.4% vs 4.2%), and all types of major cardiac event (5.9% vs 10.6%). After adjusting for differences between the 2 types of stent, the relative risk of major cardiac complication in the group of patients treated with insulin was 52% smaller in the group receiving paclitaxel stents than in the one receiving sirolimus-eluting stent, although the differences between treatment groups were not statistically significant.

Conclusions. In this multicenter group of unselected diabetic patients, similar outcomes were found for paclitaxel-eluting stents and sirolimus-eluting stents in terms of the incidence of a range of clinical events. However, in insulin-dependent diabetic patients, paclitaxel-eluting stents seem to be associated with a lower incidence of major cardiac complications than sirolimus-eluting stents. This finding could provide the rationale for conducting a randomized trial to definitively clarify the possible differences between the 2 types of stent.

NONCORONARY INTERVENTION

MIST (Migraine Intervention With Starflex Technology) Study

Presented by Dr. Peter Wilmshurst, Andrew NMT, Matrix Contract Research, United States of America

Background. Observational studies in patients with stroke and decompression illness have shown that closure of a patent foramen ovale (PFO) can resolve migraine in 65% to 90% of patients. The MIST study aimed to investigate whether closure of the PFO could reduce the incidence of migraines in patients with PFO who present with this type of headache.

Methods. Patients with frequent migraine (with aura) who had been shown to be resistant to 2 or more classes of preventative medication were selected. After confirming by contrast transthoracic echocardiography that a PFO was present and also that it was susceptible to percutaneous closure, the patients were randomized to closure of the PFO with a Starflex Starflex Septal Repair® percutaneous device or to a simulated procedure. Unlike the treating cardiologist, the patients and their neurologists were blinded to randomization during a 180-day follow-up period. The patients received dual antiplatelet therapy with aspirin and clopidogrel for 3 months, and they filled out daily diaries in which they recorded the frequency, duration, and intensity of headaches.

Results. The study screened 432 migraine sufferers, who underwent an examination to determine whether PFO was present. Of the 260 (60.2%) who had atrial shunting, 163 (37.7%) had a large PFO and 16.7% a small PFO (previous epidemiological studies had shown that 27% of the general population have a PFO, and of these, 7% are large). The mean PFO diameter was 9.21 mm. Of these patients, 16 refused to enter the study or were rejected for medical reasons before randomization. After randomization, 73 patients were assigned to the simulated procedure and 74 to closure with the Starflex Septal Repair® device.

There were no differences between groups in terms of the primary endpoint of complete disappearance of migraine. This occurred in only 3 patients in each group. Decrease by more than 50% in the number of days with migraine occurred more frequently in the group with percutaneous closure (42% vs 23%; *P*=.038). The reduction in the total headache burden, defined as a frequency × headache duration was greater in the group with PFO closure (from a baseline burden of 136.1 to 86.06 at the end of follow-up; *P*=.033; in the control group, the burden dropped from 116.8 to 96.32; *P*=NS).

Conclusions. The prevalence of PFO in patients with migraine was much higher than in the general population. In patients with migraine, closure of the PFO was not associated with more frequent disappearance of the migraine than in the simulated procedure. However, there was a significant reduction in the frequency and duration of headaches with closure of the PFO. This finding could be useful in the treatment of these patients. The MIST-II study, which is already underway with a longer follow-up, will test the hypothesis that most of the benefit from closure of the PFO could become evident after longer periods have elapsed.

CELL THERAPY

PROTECT-CAD (Prospective Randomized Trial of Direct Endomyocardial Implantation of Bone Marrow Cells for Therapeutic Angiogenesis in Coronary Artery Diseases)

Presented by Hung-Fat Tse, Hong Kong, China

Background. Some nonrandomized pilot studies have suggested that direct implantation of mononuclear bone-marrow cells may be feasible and safe in patients with severe coronary disease.

Methods. This was a randomized controlled study to assess the effects of intramyocardial implantation of mononuclear bone-marrow cells in 28 patients with severe coronary disease and myocardial ischemia documented by computed tomography. The patients were not candidates for conventional revascularization and had Canadian Cardiovascular Society (CCS) class III or IV angina. Bone marrow cells (50 mL, CD34+ cells; 3.86% [0.72%]) were collected from all patients, who were then randomized to receive a low dose (1×10^6 cells/0.1 mL, n=9) or high dose (2×10^6 cells/0.1 mL, n=10) of mononuclear bone-marrow cells, or they were assigned to the control group (plasma, n=9). The cells were injected directly into the endomyocardium under guidance by electromechanical mapping. The primary outcome measure was the exercise time on a treadmill at 6 months. The secondary objectives included functional angina class (CSS), functional dyspnea class (NYHA), weekly episodes of angina, extent of perfusion, and myocardial function assessed by computed tomography and magnetic resonance imaging.

Results. The baseline characteristics of the 3 groups were similar, with a mean age of 66.4 [1.5] years, and 82% were men. Overall, 68% of the patients had undergone coronary revascularization, 61% percutaneous coronary intervention, 50% were diabetic, and 71% were hypertensive. A total of 422 injections were done (mean of 14.6 [0.7] per patient) of 0.1 mL each in 41 target regions, without any acute complications. At 6 months, the exercise time on the

treadmill was significantly greater in patients who had received mononuclear bone-marrow cells (464 [45] s vs 393 [31] s; *P*=.048) in comparison with the reference values, but not in the controls (439 [61] s vs 404 [81] s; *P*=.23). However, both the patients who received mononuclear bone-marrow cell injections and those who received plasma experienced a significant improvement in angina and dyspnea functional class, and fewer episodes of angina compared to reference values (all *P*<.05). Magnetic resonance imaging at 6 months showed significant improvement in the left ventricular ejection fraction of patients who received mononuclear bone-marrow cells (56% [2%] vs 52% [2%]; *P*=.037) compared to reference values, but no improvement was observed in controls (49% [3%] vs 48% [3%]; *P*=.89).

Conclusions. Direct endomyocardial implantation of mononuclear bone-marrow cells significantly improves exercise time and the left ventricular ejection fraction in patients with severe coronary artery disease.

CARDIAC SURGERY

PRIMOCABG II (Pexelizumab for the Reduction of Infarction and Mortality in Coronary Artery Bypass Graft Surgery II) Study

Presented by Peter K.Smith, Durham, United States of America

Background. Local and systemic complement activation during coronary artery bypass grafting with extracorporeal circulation contributes to myocardial damage and could be related to postoperative complications. This multicenter, randomized, double-blind, placebo-controlled study aimed to evaluate whether administration of pexelizumab, a terminal complement inhibitor, is associated with a decrease in the incidence of death and myocardial infarction at 30 days in patients undergoing coronary artery bypass grafting with extracorporeal circulation.

Methods. Patients undergoing coronary artery bypass grafting, with or without associated valve replacement, and with at least 2 prospectively defined risk factors (diabetes mellitus, prior heart surgery, emergency intervention, female sex, history of neurological events, or congestive heart failure and 2 or more previous myocardial infarctions or one recent one) were randomly assigned to receive pexelizumab (bolus of 2.0 mg/kg plus 0.05 mg/kg per hour for 24 h) or placebo immediately before the surgical procedure. The primary endpoint was incidence of death or myocardial infarction at 30 days in all study patients. The secondary endpoints included all-cause mortality up until day 90 after the operation and the appearance or worsening of heart failure during the hospital stay or readmission to hospital for this reason up until day 30 of follow-up. The definition of myocardial infarction included both Q-wave and non-Q-wave episodes. The presence and type of myocardial infarction was determined by a panel of experts who were blinded to the history of each patient. The adverse effects were recorded in all patients up until day 30.

Results. An emergency operation was performed in 72% of the patients, 60% had diabetes and 40% had a history of heart disease. The incidence of the primary endpoint of death or AMI at 30 days was 15.2% of the patients in the pexelizumab group and 16.3% in the placebo group (relative risk reduction, 6.7%; *P*=.201), and mortality was 3.8% and 4.6%, respectively (relative risk reduction, 17%; *P*=.177). The subgroups of the primary composite endpoint showed similar results. There were no differences in the incidence of major complications (31.2% with pexelizumab vs 32.5% with placebo). The incidence of sepsis was lower in the pexelizumab group (2.1% vs 3.1%).

Conclusions. Treatment with pexelizumab was not associated with a reduction in mortality or myocardial infarction at 30 days in patients who underwent coronary artery bypass grafting with extracorporeal circulation.

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