

Summary of the Clinical Studies Reported in the 57th Scientific Session of the American College of Cardiology (Chicago, USA, March 30 - April 2 2008)

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In the 57th Annual Scientific Session of the American College of Cardiology, corresponding to 2008, the results from several late breaking clinical trials were presented orally in special sessions dedicated to trials of particular importance that have recently been completed.

In accordance with the established editorial policy of recent years,¹⁻⁴ *Revista Española de Cardiología* offers its readers a summary of those studies in which the objectives, methods, and results presented are briefly covered. Given that many of these trials have not yet been published in their final version, the information offered here should be considered preliminary. If the findings of a given study have already been published in full, the corresponding reference will be provided at the end of the summary to help our readers find it.

SUMMARY BY TOPICS

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HYVET trial: treatment of hypertension in patients aged over 80 years old.

ONTARGET trial: telmisartan, ramipril, and the combination of both in patients at high risk of cardiovascular disease.

PERISCOPE trial: comparison of the effect of pioglitazone versus glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes.

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ISAR-REACT 3 trial: bivalirudin versus unfractionated heparin in low-risk troponin-negative patients undergoing percutaneous coronary interventions after pretreatment with clopidogrel.

A-F trial: evaluation of a distal embolization protection device in percutaneous coronary interventions in non ST-elevation acute coronary syndrome.

ABSORB trial: bioabsorbable everolimus-eluting stent for de novo coronary artery lesions.

Heart Failure

REVERSE trial: 12 months of follow-up of cardiac resynchronization study in patients with mild systolic heart failure.

PROTECT PILOT trial: effect of rolofylline, an adenosine A₁ receptor antagonist, on the outcome of patients with acute heart failure.

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Heart Failure Home Care trial: clinical and economic results of a computer-based telephone monitoring system in older patients with heart failure.

Arrhythmias

HAT trial: use of automated external defibrillators for cardiac arrest at home.

CARISMA trial: detection of cardiac arrhythmias with an implantable loop recorder and risk stratification after myocardial infarction.

Noncoronary Intervention

ASTRAL trial: assessment of percutaneous intervention in renal artery stenosis.

PRIMARY AND SECONDARY PREVENTION

The ENHANCE Trial (Simvastatin With or Without Ezetimibe in Familial Hypercholesterolemia)

Presented by J.J. Kastelein, Amsterdam, The Netherlands

Background: Ezetimibe, a cholesterol-absorption inhibitor, reduces the concentrations of low-density lipoprotein cholesterol (LDL-C) when added to statin therapy. However, the effect of ezetimibe on the progression of atherosclerosis remains to be determined.

Methods: The investigators carried out a double-blind, randomized trial with 24-month follow-up to compare the effect of daily treatment with 80 mg of simvastatin combined with either placebo or ezetimibe 10 mg in 720 patients with familial hypercholesterolemia. Patients underwent a 2-dimensional ultrasound examination to quantify the intima-media thickness of the carotid and femoral arteries. The primary outcome measure was the change in the carotid intima-media thickness, defined as the average of the measurements of wall thickness the furthest away from the transducer of the left and right common carotid arteries, carotid bulbs, and internal carotid arteries.

Results: The primary outcome measure, the mean (SD) change in the intima-media thickness of the carotid artery was 0.0058 (0.0037) mm in the simvastatin-placebo group compared to 0.0111 (0.0038) mm in the simvastatin-ezetimibe group (combined treatment) ($P=.29$). The secondary outcome measures (all related to the intima-media thickness of the carotid and femoral arteries) showed no differences between groups. At the end of the study, the mean LDL-C was 192.7 (60.3) mg/dL (4.98 [1.56] mmol/L) in the simvastatin group and 141.3 (52.6) mg/dL (3.65 [1.36] mmol/L) in the combined treatment group (group difference, 16.5%; $P<.01$). The differences

between groups in the reduction of triglyceride and C reactive protein concentrations were 6.6% and 25.7%, respectively, with larger reductions in the combined treatment group ($P<.01$ for both comparisons). The adverse effects and the safety profile were similar in both groups.

Conclusions: In patients with familial hypercholesterolemia, combined therapy with ezetimibe and simvastatin did not lead to any significant differences in the changes in intima-media thickness compared to simvastatin alone, even though larger decreases in LDL-C and C reactive protein occurred.

The study has already been published as a full text article.⁵

HYVET Trial (Hypertension in the Very Elderly Trial)

Presented by Nigel S. Beckett, London, United Kingdom

Background: It has not been completely established whether treatment for hypertension in patients over 80 years is beneficial. It has been suggested that treatment for hypertension can reduce the risk of stroke despite a possible increase in overall mortality.

Methods: The investigators randomized 3845 patients aged 80 years or older from Europe, China, Australasia, and Tunisia who had blood pressure persistently ≥ 160 mm Hg to receive the diuretic indapamide (1.5 mg in a sustained-release tablet) or matching placebo. If necessary, in order to achieve the target blood pressure of 150/80 mm Hg, an angiotensin converting enzyme (ACE) inhibitor perindopril (2 or 4 mg) or matching placebo was added. The primary outcome measure of the study was incidence of fatal or nonfatal stroke.

Results: The active-treatment group (1933 patients) and the placebo group (1912 patients) had similar characteristics (mean age, 83.6 years; mean blood pressure while sitting, 173/90.8 mm Hg); 11.8% had a history of cardiovascular disease. The median follow-up period was 1.8 years. At 2 years, the mean blood pressure while sitting was 15/6.1 mm Hg lower in the active-treatment group compared to placebo. In the intention-to-treat analysis, active treatment was associated with a 30% decrease in the incidence of fatal or nonfatal stroke compared to the placebo-treated group (95% confidence interval [CI], -1% to 51%; $P=.06$), a 39% reduction in the mortality rate or rate of strokes (95% CI, 1-62; $P=.05$), a 21% reduction in all-cause mortality (95% CI, 4-35; $P=.02$), a 23% reduction in the rate of cardiovascular mortality (95% CI, -1 to 40; $P=.06$), and a 64% reduction in the rate of heart failure (95% CI, 42-78; $P<.001$). Fewer adverse events were reported in the active-treatment group (358 vs 448 in the placebo group; $P=.001$).

Conclusions: The results provide evidence of the benefit of indapamide (sustained release) with or without added perindopril in patients aged 80 years or more.

The study has already been published in the form of a full text article.⁶

ON-TARGET Trial (Ongoing Telmisartan Alone and in Combination With Ramipril Global End-Point Trial)

Presented by S. Yusuf, Hamilton, Canada

Background: In patients with vascular disease or high-risk diabetes but without heart failure, ACE inhibitors decrease cardiovascular mortality and morbidity, but the role of angiotensin II receptor antagonists (ARA-II) is not known. The investigators compared ramipril, an ACE inhibitor, the ARA-II telmisartan, and a combination of the 2 drugs in patients with vascular disease or high-risk diabetes.

Methods: After a 3-week single-blind run-in period, the patients were randomized in a double-blind design; 8576 were assigned to receive ramipril 10 mg/d, 8542 to receive telmisartan 80 mg/d, and 8502 to receive both drugs (combined therapy). The primary clinical outcome measure was a composite of cardiovascular death, myocardial infarction, stroke, and admission to hospital for heart failure.

Results: The mean blood pressure decreased to a greater extent in the telmisartan group (0.9/0.6 mm Hg lower than in the ramipril group) and in the combined therapy group (2.4/1.4 mm Hg lower than in the enalapril group). At a mean follow-up of 56 months, the primary endpoint was reached in 1412 patients (16.5%) in the ramipril group compared to 1423 (16.7%) in the telmisartan group (relative risk [RR], 1.01; 95% CI, 0.94-1.09). In comparison with the ramipril group, the patients treated with telmisartan had a lower rate of cough (1.1% vs 4.2%; $P<.001$) and angioedema (0.1% vs 0.3%; $P=.01$), and a greater incidence of hypotensive symptoms (2.6% vs 1.7%; $P<.001$); the incidence of syncope was similar in both groups (0.2%). In the combination-therapy group, the primary endpoint was met in 1386 patients (16.3%; RR, 0.99; 95% CI, 0.92-1.07); in comparison with the ramipril group, there was a higher incidence of hypotensive symptoms (4.8% vs 1.7%; $P<.001$), syncope (0.3% vs 0.2%; $P=.03$), and renal failure (13.5% vs 10.2%; $P<.001$).

Conclusions: Telmisartan was equivalent to ramipril in patients with vascular disease and those with high-risk diabetes, and was associated with a lower incidence of angioedema. The combination of the 2 drugs was associated with a higher rate of adverse events without increased benefit.

The study has already been published in the form of a full text article.⁷

PERISCOPE Trial (Comparison of Pioglitazone vs Glimpiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes)

Presented by S. Nissen, Cleveland, United States of America

Background: No antidiabetic therapy has proved able to reduce the progression of coronary atherosclerosis. One of the most widely used types of glucose-lowering agents are the sulfonylureas, which stimulate insulin secretion, and thiazolidinediones, which are insulin sensitizers. The aim of this study was to compare the effects of pioglitazone, an insulin sensitizer, with those of glimepiride, an insulin secretagogue, on the progression of coronary atherosclerosis in patients with type 2 diabetes.

Methods: This was a multicenter, randomized, double-blind study conducted in 97 university and public hospitals in North America and South America, with recruitment between August 2003 and March 2006. In total, 543 patients with type 2 diabetes and coronary artery disease were included. All patients underwent an intravascular ultrasound (IVUS) examination at baseline and were then randomized to receive 1 to 4 mg of glimepiride or 15 to 45 mg of pioglitazone for 18 months, with dose titration up to the maximum tolerated dose. Progression of atherosclerosis was determined by means of repeat IVUS examinations in 360 patients at study completion. The primary outcome measure was change in percent atheroma volume (PAV) from the baseline IVUS study to study completion.

Results: Least squares mean PAV increased by 0.73% (95% CI, 0.33-1.12) with glimepiride and decreased by 0.16% (95% CI, -0.57 to 0.25) with pioglitazone ($P=.002$). An alternative analysis imputing values for patients who did not complete the study according to baseline characteristics showed an increase in PAV of 0.64% (95% CI, 0.23-1.05) for glimepiride and a decrease of 0.06% (-0.47% to 0.35%) for pioglitazone ($P=.02$ for between-group comparison). The mean (SD) levels of glycated hemoglobin were 7.4% (1%) in both groups, and these decreased during the course of the treatment by, on average, 0.55% (95% CI, -0.68 to -0.42) with pioglitazone and by 0.36% (-0.48 to -0.24) with glimepiride ($P=.03$ for between-group comparison). In the pioglitazone group, compared to glimepiride, high density lipoprotein cholesterol (HDL-C) increased by 5.7 mg/dL (95% CI, 4.4-7 mg/dL; 16%) vs 0.9 mg/dL (-0.3 to 2.1 mg/dL; 4.1%), and the mean triglyceride levels decreased by 16.3 mg/dL (95% CI, -27.7 to -11.0 mg/dL; 15.3%) compared to an increase of 3.3 mg/dL (-10.7 to 11.7 mg/dL; 0.6%; $P<.001$ for both comparisons). The median fasting insulin concentrations decreased with pioglitazone and increased with glimepiride ($P<.001$). Hypoglycemia was more common

in the glimepiride group, whereas in the pioglitazone group there were more edemas and fractures and lower hemoglobin concentrations.

Conclusions: In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone was associated with a lower rate of progression of coronary atherosclerosis than with glimepiride.

The study has already been published in the form of a full text article.⁸

STRADIVARIUS Trial (Effect of Rimonabant on the Progression of Atherosclerosis in Patients with Abdominal Obesity and Coronary Artery Disease)

Presented by S. Nissen, Cleveland, United States of America

Background: Abdominal obesity is associated with metabolic abnormalities and an increased risk of atherosclerotic heart disease. However, no strategy for reducing obesity has been shown to be able to slow the progression of coronary artery disease. The aim of this trial was to determine whether weight loss and the metabolic effects of rimonabant, a selective cannabinoid type 1 receptor antagonist, reduce the progression of coronary artery disease in patients with abdominal obesity and metabolic syndrome.

Methods: This randomized, double-blind, placebo-controlled trial with 2 parallel groups (with recruitment between December 2004 and December 2005), compared rimonabant with placebo in 839 patients from 112 centers throughout North America, Europe, and Australia. The patients received dietary counseling and were then randomized to receive rimonabant 20 mg/d or matching placebo. Patients underwent intracoronary ultrasound examination at baseline (n=839) and on completing the study (n=676). The primary efficacy outcome measure was the change in percent coronary atheroma volume (PCAV) and the secondary outcome measure was change in total coronary atheroma volume (TCAV).

Results: PCAV increased by 0.25% (95% CI, -0.04 to 0.54) in the rimonabant group compared to 0.51% (0.22%-0.8) in the placebo group ($P=.22$), whereas the TCAV decreased by 2.2 (-4.09 to 0.24) μL in the rimonabant group compared to an increase of 0.88 (-1.03 to 2.79) μL in the placebo group ($P=.03$). In the rimonabant group, imputing the results according to baseline characteristics of the patients who did not complete the study, it is estimated that PCAV increased by 0.25% (-0.04% to 0.55%) compared to 0.57% (0.29%-0.84%) in the placebo group ($P=.13$) and TCAV decreased by 1.95 (-3.8 to -0.1) μL in the rimonabant group, compared to an increase of 1.19 (-0.73 to 3.12) μL with placebo ($P=.02$). The patients treated with rimonabant

experienced greater weight loss (4.3 [-5.1 to -3.5] kg compared to 0.5 [-1.3 to 0.3] kg) and greater reduction in waist circumference (4.5 [-5.4 to -3.7] cm compared to 1 [-1.9 to -0.2] cm; $P<.001$ for both comparisons). HDL-C levels increased by 5.8 mg/dL (22.4%; 95% CI, 4.9-6.8) in the rimonabant group compared to 1.8 mg/dL (6.9%; 95% CI, 0.9-2.7) in the placebo group ($P<.001$), and median triglycerides decreased by 24.8 mg/dL (20.5%; 95% CI, -35.4 to -17.3) with rimonabant, compared to 8.9 mg/dL (6.2%; 95% CI, -14.2 to -1.8) in the placebo group ($P<.001$). The patients in the rimonabant group showed larger decreases in high-sensitivity C-reactive protein (1.3 mg/dL [50.3%; -1.7 to -1.2] compared to 0.9 mg/dL [30.9%; -1.4 to -0.5]) and a smaller increase in glycated hemoglobin (0.11% [0.02%-0.2%] compared to 0.4% [0.31%-0.49%]; $P<.001$ for both comparisons). Psychiatric adverse events were more frequent in the rimonabant group (43.4% vs 28.4%; $P<.001$).

Conclusions: After 18 months of treatment, the study did not show a favorable effect of rimonabant on the progression of atherosclerotic disease quantified according to the primary outcome measure (PCAV) but it did it was beneficial in terms of the secondary outcome measure (TCAV). To demonstrate the possible utility of rimonabant, further clinical trials are needed with both imaging and clinical outcomes. Such trials are currently ongoing.

The study has already been published in the form of a full text article.⁹

ASTEROID Trial (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden)

Presented by C.M. Ballantyne, Houston, United States of America

Background: Previous studies with quantitative intracoronary ultrasound have shown that statins slow the progression of coronary stenosis in proportion to the mean LDL-C concentrations during therapy. However, no large studies have shown that statins in monotherapy are able to stop progression or achieve angiographic regression of the disease. The objective of the ASTEROID study was to evaluate whether rosuvastatin can cause regression of coronary disease assessed by intracoronary ultrasound and by quantitative coronary angiography.

Methods: Within the ASTEROID study, 507 patients with coronary artery disease were treated with 40 mg/d of rosuvastatin for 24 months. An analysis was carried out by means of quantitative coronary angiography of the percent diameter stenosis and minimum lumen

diameter in up to 10 segments of coronary arteries and major branches with >25% diameter stenosis in the baseline angiogram. For each patient, the mean of all lesions studied was calculated at baseline and on study completion. In total, the investigators studied 292 patients and 613 lesions.

Results: Rosuvastatin reduced the mean LDL-C level by 53.3%, with a final concentration of 61.1 (20.3) mg/dL, and increased HDL-C by 13.8%, with a final concentration of 48.3 (12.4) mg/dL. The mean (SD) of the percent diameter stenosis decreased from 37.3% (8.4%) (median, 35.7%; range, 26%-73%) to 36% (10.1%) (median, 34.5%; range, 8%-74%; $P<.001$). The minimum lumen diameter increased from 1.65 (0.36) mm (median, 1.62 mm; range, 0.56-2.65 mm) to 1.68 (0.38) mm (median, 1.67 mm; range, 0.76-2.77 mm) ($P<.001$).

Conclusions: Therapy for 24 months with rosuvastatin attained mean LDL-C values clearly below 70 mg/dL, and significantly increased HDL-C, and led to a regression in coronary lesions as demonstrated by the reduction in the percent lumen stenosis and the increase in the minimum lumen diameter measured by quantitative angiography.

The study has already been published in the form of a full text article.¹⁰

CARDIOVASCULAR RISK

Cardiovascular Risk of Celecoxib in 6 Randomized, Placebo-Controlled Trials: Cross-Trial Safety Analysis

Presented by S.D. Solomon, Boston, United States of America

Background: Observational studies and randomized trials have shown an increase in cardiovascular risk associated with the use of cyclooxygenase 2 inhibitors. Previous placebo-controlled randomized, trials had a limited ability to determine whether the cardiovascular risk of celecoxib was related to the dose of celecoxib itself or to the prior cardiovascular status of the patients. The aim of the investigators was to determine the cardiovascular risk associated with 3 different regimens of administration of celecoxib and assess the association between baseline cardiovascular risk and the effect of celecoxib on cardiovascular events.

Methods: The investigators carried out a pooled analysis of the data attributed to the drug from 7950 patients included in 6 placebo-controlled of celecoxib, administered for conditions other than arthritis, with a projected follow-up of at least 3 years. The patients received celecoxib at 3 different doses: 400 mg as a single daily dose, 200 mg every 12 hours, and 400 mg every 12 hours. From the pooled data, the investigators calculated the hazard ratios for each particular dose and

for all the possible dose combinations. The primary clinical outcome was a composite of cardiovascular death, myocardial infarction, stroke, heart failure, and thromboembolic events.

Results: With 16 070 patient-years of follow-up, the hazard ratio for the primary outcome measure for the group of patients treated with celecoxib was 1.6 (95% CI, 1.1-2.3). Risk increased with dose ($P=.0005$) and was lowest for the single daily dose of 400 mg (hazard ratio, 1.1; 95% CI, 0.6-2), intermediate for the 200 mg dose every 12 hours (hazard ratio, 1.8; 95% CI, 1.1-3.1), and greatest for the 400 mg dose every 12 hours (hazard ratio, 3.1; 95% CI, 1.5-6.1). Patients with highest baseline cardiovascular risk showed a disproportionately greater risk of presenting complications associated with celecoxib ($P=.034$ for the interaction).

Conclusions: The investigators uncovered evidence of different cardiovascular risk according to the regimen of administration of celecoxib and the baseline cardiovascular risk. This study extends the understanding of the cardiovascular risk of celecoxib such that it may help guide treatment decisions for patients in whom selective cyclooxygenase 2 inhibitors are indicated.

The study has already been published in the form of a full text article.¹¹

PERCUTANEOUS CORONARY INTERVENTION

Subanalysis of the TRITON-TIMI 38 Study on the Effect of Intensive Oral Antiplatelet Treatment on the Reduction of Ischemic Complications, Including Stent Thrombosis, in Patients With Acute Coronary Syndromes Who Undergo Percutaneous Coronary Intervention and Stenting

Presented by S.T. Wiviott, Boston, United States of America

Background: Compared to balloon angioplasty, intracoronary stenting improves the outcomes of percutaneous coronary interventions in patients with acute coronary syndrome, but it may increase the incidence of thrombotic complications, including stent thrombosis. The TRITON-TIMI 38 trial has shown that prasugrel, a potent thienopyridine, may reduce coronary events compared to standard therapy with clopidogrel. Therefore, the investigators analyzed the rates of ischemic events as well as their outcome and prevention in patients treated with prasugrel or clopidogrel after undergoing stenting in the TRITON-TIMI 38 study.

Methods: This substudy included patients who had received at least one coronary stent for treatment of moderate to high-risk acute coronary syndrome after

randomization in the TRITON-TIMI 38 study. Patients were then subdivided into groups according to the type of stent received. The patients were randomized 1:1 to receive as early as possible a loading dose of platelet inhibitor (prasugrel 60 mg or clopidogrel 300 mg), followed by the standard maintenance dose (10 mg/d of prasugrel and 75 mg/d of clopidogrel). All patients received treatment with aspirin. The randomized treatment was administered for a minimum of 6 months and a maximum of 15 months. The randomization was not stratified according to the type or number of stents implanted. The primary clinical outcome measure was a composite of cardiovascular death, myocardial infarction, and nonfatal or fatal stroke. The criteria used to define stent thrombosis were those of the Academic Research Consortium, and the data presented correspond to the intention-to-treat analysis. The TRITON-TIMI 38 trial is registered with Clinical-Trials.gov, number NCT00097591.

Results: Of the 12 844 patients with at least 1 stent implanted, 5743 received drug-eluting stents and 6461 received bare-metal stents. Prasugrel reduced the incidence of events including in the primary outcome measure (9.7% vs 11.9%; HR=0.81; $P=.0001$) in patients with any type of stent and in patients with drug-eluting stents (9% vs 11.1%; HR=0.82; $P=.019$) and in patients with bare-metal stents (10% vs 12.2%; HR=0.8; $P=.003$). Stent thrombosis was reported in 89% of the patients who died or suffered acute myocardial infarction (186/210). Prasugrel reduced the incidence of stent thrombosis in the overall patient group (1.13% vs 2.35%; HR=0.48; $P=.0001$), in patients with drug-eluting stents (0.84% vs 2.31%; HR=0.36; $P=.0001$), and in patients with bare-metal stents (1.27% vs 2.41%; HR=0.52; $P=.0009$).

Conclusions: Intensive antiplatelet therapy with prasugrel was associated with a lower incidence of ischemic complications than standard treatment with clopidogrel. This finding proved very statistically robust for all types of stent used and corroborates the importance of intensive antiplatelet therapy in patients with intracoronary stents.

The study has already been published in the form of a full text article.¹²

TAPAS Study (Thrombus Aspiration During Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction)

Presented by F. Zijlstra, Zwolle, the Netherlands.

Background: Primary percutaneous coronary intervention (PCI) is effective in opening the infarct-related artery in patients with acute myocardial infarction with ST elevation. However, embolization of

atherothrombotic debris induces microvascular obstruction and reduces myocardial perfusion.

Methods: The investigators conducted a randomized trial to assess whether manual aspiration of the thrombus was superior to conventional primary PCI. A total of 1071 patients were assigned to the thrombus-aspiration group or to the conventional-PCI group before the angiographic images were viewed. Aspiration was considered successful when histopathologic evidence of atherothrombotic material was found in the aspirate. Angiographic and electrocardiographic signs of myocardial reperfusion were recorded as well as the clinical outcome. The primary outcome measure was myocardial blush grades 0 or 1 (defined as absence of myocardial perfusion or minimal myocardial perfusion, respectively).

Results: Myocardial blush grades 0 or 1 were reported in 17.1% of patients in the thrombus-aspiration group and in 26.3% of patients in the conventional-PCI group ($P<.001$). Complete resolution of ST-segment elevation occurred in 56.6% and 44.2% of the patients, respectively ($P<.001$). The beneficial effect was not evenly distributed among the different baseline levels of prespecified covariates. At 30 days, the mortality rates in patients with myocardial blush grades 0 or 1, 2, and 3 were 5.2%, 2.9%, and 1%, respectively ($P=.003$), and the rates of adverse events were 14.1%, 8.8%, and 4.2%, respectively ($P<.001$). The histopathological examination showed aspiration of atherothrombotic debris in 72.9% of the patients.

Conclusions: Thrombus aspiration is applicable in a large number of patients with ST-elevation myocardial infarction and produces better reperfusion and a smaller number of clinical complications than conventional PCI, irrespective of the baseline clinical and angiographic characteristics.

The study has already been published in the form of a full text article.¹³

MULTISTRATEGY Study (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction)

Presented by L. Valgimigli, Ferrara, Italy

Background: Abciximab infusion and placement of bare-metal stents is a complementary strategy aimed at reducing major complications in patients who undergo angioplasty for ST-elevation acute myocardial infarction (STEMI). It is not known whether replacing abciximab with a high-dose bolus of tirofiban might yield similar benefit. In addition, the use of drug-eluting stents is discouraged in these patients both in view of the conflicting results of randomized trials of

efficacy and of safety concerns arising from analysis of registries. The aim of the trial was to assess the effect of a high-dose bolus of tirofiban and sirolimus-eluting stents in comparison with abciximab infusion and placement of bare-metal stents in patients undergoing primary percutaneous coronary intervention for STEMI.

Methods: An open-label 2 by 2 factorial trial was undertaken in 745 patients with STEMI or new-onset left bundle branch block in 16 centers in Italy, Spain, and Argentina between October 2004 and April 2007. The primary outcome variables were, for comparison of the drugs, at least 50% resolution of the ST-segment elevation 90 minutes after the intervention, with a prespecified noninferiority margin of 9% difference (RR=0.89); for comparison of stents, the rate of major cardiac events, which included all-cause mortality, reinfarction, and revascularization of the target lesion due to ischemia at 8 months were studied.

Results: ST-segment resolution occurred in 302 out of 361 patient who had received abciximab (83.6%) compared to 308 out of 361 (85.3%) who received a high-dose bolus of tirofiban (RR=1.02; 97.5% CI, 0.958-1.086; $P<.001$ in the noninferiority test). At 8 months, 54 patients in the bare-metal stent group had suffered a major cardiac event (14.5%) compared to 29 of those treated with a sirolimus-eluted stent (7.8%; $P=.004$ for the comparison), due mainly to a reduction in the rate of revascularization (10.2% vs 3.2%). The incidence of stent thrombosis was similar in both stent groups.

Conclusions: In patients with STEMI who underwent primary percutaneous coronary intervention, tirofiban was noninferior to abciximab in producing the ST-segment resolution at 90 minutes after the intervention, and sirolimus-eluting stents were associated with a relatively smaller risk of major cardiac complications compared to bare-metal stents at 8 months of follow-up.

The study has already been published in the form of a full text article.¹⁴

ISAR-REACT 3 Study (Bivalirudin Versus Unfractionated Heparin in Troponin-Negative Patients Undergoing Percutaneous Coronary Interventions After Pretreatment With Clopidogrel)

Presented by Adnan Kastrati, Munich, Germany

Background: In trials that did not use glycoprotein IIb/IIIa inhibitors, bivalirudin demonstrated better results than unfractionated heparin (UFH) in conjunction with PCI. It is not known whether bivalirudin is superior to UFH in terms of efficacy (ischemic events) and safety (hemorrhagic events) in patients without troponin elevation submitted to PCI after pretreatment with clopidogrel. The aim of the present trial was to investigate this question.

Methods: A total of 4570 patients with ischemic heart disease (82% with stable angina and 18% with unstable angina) and without troponin elevation were randomized, after administration of clopidogrel 600 mg and at least 325 mg of aspirin, to receive UFH (140 IU/kg bolus followed by placebo infusion; n=2281) or bivalirudin (0.75 mg/kg bolus followed by an infusion of 1.75 mg/kg/h; n=2289). The mean ejection fraction was 58% and 80% of the patients had multivessel disease. Most of the patients (83%) received drug-eluting stents. Double antiplatelet therapy continued with aspirin and clopidogrel according to the standard regimen. The primary outcome measure of the study was a composite of death, myocardial infarction (troponin elevation greater than 2 times the upper limit of normal), urgent target vessel revascularization, or major bleeding at 30 days of follow-up. The secondary outcome measure was a composite of death, myocardial infarction, or revascularization of the target vessel.

Results: The primary outcome measure, a composite of death, myocardial infarction, urgent revascularization, and major bleeding, was similar in both arms (8.3% with bivalirudin vs 8.7% with unfractionated heparin, respectively; $P=.57$). The incidence of death, myocardial infarction, and urgent target vessel revascularization was 0.1% versus 2.2% ($P=.7$); 5.6% versus 4.8% ($P=.24$), and 0.8% versus 0.7% ($P=.75$) for bivalirudin compared to UFH, respectively. The secondary outcome measure of incidence of death, myocardial infarction, or urgent revascularization was 5.9% with bivalirudin and 5% with UFH (RR=1.16; 95% CI, 0.91-1.49; $P=.23$). The incidence of major bleeding was significantly reduced by 33% with bivalirudin (3.1% vs 4.6% with UFH; $P=.008$). Likewise, the incidence of minor bleeding was also significantly reduced with bivalirudin ($P=.0001$). The need for transfusions and the incidence of thrombocytopenia was similar in both groups.

Conclusions: In patients without troponin elevation who undergo PCI after pretreatment with 600 mg clopidogrel, bivalirudin is not superior to UFH in reducing mortality, myocardial infarction, or urgent target vessel revascularization, although the incidence of major and minor bleeding was significantly reduced. The dose of UFH used in the study was somewhat greater than that used in other studies of PCI, and may have affected the incidence of events, particularly bleeding.

A-F Study (Vascular Protection in High-Risk Non-ST-Elevation Acute Coronary Syndromes: The Angioplasty Balloon-Associated Coronary Debris and the EZ Filterwire)

Presented by Mark Webster, Auckland, New Zealand

Background: The use of a protection device against distal embolization of plaque debris did not show any benefit in the DEDICATION study, which included

patients with primary PCI for STEMI. The objective of the A-F study was to evaluate whether the EZ filter could improve the outcomes of coronary interventions with stent placement in patients with non-ST-elevation acute coronary syndromes (NSTEMI).

Methods: In total, 151 patients with NSTEMI and an increased risk of distal embolization according to their clinical findings (dynamic ECG changes, resting angina, or elevated cardiac enzymes) or angiographic findings (visible thrombus, ulceration, eccentric lesion, irregular or abrupt lesion edges, length >20 mm) were randomized to receive a stent with a distal protection device (n=77) or a stent alone (n=74). The primary outcome measure was the incidence of major cardiac events (MACE): death, acute myocardial infarction, and urgent target vessel revascularization during admission to hospital. The secondary outcome measures were incidence of the same MACEs at 30 days, change in creatinine kinase MB fraction (CK-MB) and troponins at 6 hours and 12 hours after PCI, the success rate with use of the device, the rate of recovery of embolic debris, and TIMI flow after PCI.

Results: The Filterware was used successfully in 97% of the cases, with no complications related to the device. Embolic debris was recovered from 42% of the patients. The primary outcome measure occurred in 11.7% of the patients of the distal filter group compared to 9.5% of the control group. At 30 days, a MACE had occurred in 12% and 11%, respectively. The increase in cardiac enzymes was similar in both groups: peak CK-MB was 5.1 compared to 4.1, and peak troponin T was 0.4 compared to 0.4, respectively. TIMI III flow was reported after PCI in 94% of the patients in both groups. There were no differences derived from use of the distal filter in any of the subgroups analyzed: patients treated with glycoprotein IIb/IIIa inhibitor, diabetic patients, patients pretreated with clopidogrel, or patients who had already undergone thrombolytic therapy.

Conclusions: The results of this trial add to the conclusions of the recent DEDICATION study: the use of embolic protection devices is feasible in practice but it does not seem to provide any benefit in terms of improving myocardial perfusion or reducing clinical events in patients with different types of acute coronary syndromes. It seems that these devices may have an application essentially in PCI in lesions of the saphenous vein graft lesions.

ABSORB Study (Bioabsorbable Everolimus-Eluting Coronary Stent System for Patients With Single De Novo Coronary Artery Lesions: A Prospective Open-Label Trial)

Presented by J.A. Ormiston, Auckland, Australia

Background: The theoretical advantages of a completely resorbable drug-eluting stent lie in the

scaffolding of the coronary wall when necessary, during the moment of the acute PCI, and the subsequent disappearance once the phase of acute recoil and constrictive remodeling has passed. The bioabsorbable everolimus-eluting stent (BVS) has a “backbone” of poly-L-lactic acid that provides mechanical support, and a coating of poly-D,L-lactic acid that contains and releases in controlled fashion the antiproliferative agent everolimus. This study evaluated the feasibility and safety of placement of a BVS.

Methods: In this prospective and open-label study, the investigators included 30 patients with stable or unstable angina, or silent ischemia, with a single de novo coronary artery lesion suitable for treatment with a single stent measuring 3×12 mm or 3×18 mm. The patients were recruited from 4 university hospitals in Auckland, Rotterdam, Krakow, and Skejby. The primary outcome measure of the study was a composite of cardiac death, myocardial infarction, and target lesion revascularization due to ischemia. Quantitative information was obtained from the angiogram in 28 cases and from intravascular ultrasound in 24 patients. The clinical outcomes were evaluated in 30 patients at 6 and 12 months. In a subgroup of 13 patients, optical coherence tomography was done at baseline and at follow-up. The analysis was by intention to treat.

Results: Procedural success was reported in all patients (30/30), and success of the device in 94% (29/31 attempts at stent implantation). At 1 year, the rate of major adverse cardiac events was 3.3%, with a single non-Q-wave infarction in 1 patient, and no need for target lesion revascularization. No late stent thromboses were observed. At 6 months of follow-up, late luminal loss according to angiography was 0.44 (0.35) mm and was due essentially to a decrease in the stent area (–11.8%) as measured by intravascular ultrasound. The neointimal area was small (0.3 [0.44] mm²), with a minimal percent area obstruction of 5.5%.

Conclusions: This study demonstrates the feasibility of implantation of bioabsorbable everolimus-eluting stents, with an acceptable in-stent late loss, minimal intrastent neointimal hyperplasia, and little obstruction of the stent area.

The study has already been published in the form of a full text article.¹⁵

HEART FAILURE

REVERSE Study (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction: 12-Month Follow-up)

Presented by Cecilia Linde, Stockholm, Sweden

Background: Cardiac resynchronization therapy (CRT) could improve left ventricular remodeling in

patients with mild symptoms of heart failure. The objective of this study was to assess the effect of CRT compared to optimum medical treatment in patients with severe systolic left ventricular dysfunction in NYHA (New York Heart Association) functional class I-II.

Methods: After implantation of a CRT device, the investigators randomized 610 patients with an ejection fraction $\leq 40\%$ and QRS duration ≥ 120 ms who were in functional class I (18%) or II (82%) to receive treatment with active CRT (CRT ON, n=419) or inactive CRT (CRT OFF, n=191), along with optimal medical treatment. The primary outcome measure of the study was the percentage of patients with worsening disease (a composite of death, hospitalization for heart failure, need to switch to another group due to worsening heart failure, deterioration in functional class, and patient score on questionnaire with double blinding). As a secondary outcome measure, the end-diastolic left ventricular volume was studied.

Results: The CRT device was successfully implanted in 97% of the patients, and the rate of complications associated with implantation was 9.5%. The primary outcome measure of the study, the percentage of patients with worsening disease, occurred in 16% with CRT ON and 21% with CRT OFF ($P=.1$). On analysis of the overall distribution of patients who improved, remained stable, and worsened, there was a benefit in favor of the CRT ON group ($P=.004$). The left ventricular end-diastolic volume decreased from 18.4 mL/m² in the CRT group, compared to 1.3 mL/m² in the medical treatment group ($P<.0001$). The risk of hospitalization for heart failure was less in the CRT ON group ($P=.03$).

Conclusions: Use of CRT in patients with mildly symptomatic heart failure due to systolic dysfunction did not reduce the proportion of patients with worsening disease, but it did reduce the risk of hospitalization for heart failure. The treatment also improved the end-diastolic left ventricular volume; however, further studies are necessary to assess the effect of CRT on major clinical events.

PROTECT PILOT Study (Effects of Rolofylline, a New Adenosine A₁ Receptor Antagonist, on Symptoms, Renal Function, and Outcomes in Patients With Acute Heart Failure)

Presented by Barry Massie, Boston, United States of America

Background: Rolofylline, an adenosine A₁ receptor antagonist, may improve the outcome of patients with acute heart failure (AHF), as well as contribute to preserving renal function. The aim of this study was to assess the role of rolofylline as compared to placebo in patients with AHF.

Methods: In total, 301 patients with AHF of more than 2 weeks duration who had required intravenous diuretic treatment in the previous 24 hours, with an estimated glomerular filtration rate between 20 and 80 mL/h, systolic blood pressure >95 mmHg, and significant elevation of natriuretic peptides (BNP >250 pg/mL or NTproBNP >1000 pg/mL) were randomized to receive rolofylline at different doses (30 mg/d [n=74]; 20 mg/d [n=75], and 10 mg/d [n=74]) or placebo (n=78). The primary outcome measure of the study was the distribution of patients in 3 mutually exclusive categories: improvement of dyspnea on the second and third days, treatment failure (death or readmission for AHF in the first 7 days, worsening of heart failure, creatinine elevations >0.3 mg/dL on Day 7 and confirmed on Day 14), or stability (neither of the previous groups). The secondary outcome measures included changes in creatinine at 14 days, mortality at 60 days, and readmission for AHF at 60 days.

Results: Baseline creatinine was 1.4 mg/dL in the 30 mg/d rolofylline group, 1.7 mg/dL in the 20 mg/d rolofylline group, 1.5 mg/dL in the 10 mg/d rolofylline group, and 1.5 mg/dL in the placebo group. In the rolofylline 30 mg/d group, a smaller proportion of patients showed a significant increase in creatinine (>0.3 mg/dL) compared to the placebo group ($P<.05$). The rates of death and rehospitalization for AHF were 19%, 24%, 32%, and 33% in the rolofylline 30 mg/d, 20 mg/d, 10 mg/d, and placebo groups, respectively. None of the pairwise group differences were statistically significant. The incidence of adverse events was similar in the active treatment groups and the placebo group. Convulsions were not reported in any of the groups.

Conclusions: In patients with uncompensated AHF, the use of rolofylline at doses of 30 mg/d was associated with a smaller deterioration in renal function. There was also a favorable tendency in terms of decrease in death and rehospitalization for AHF in the 30 mg/d group. No adverse effects associated with rolofylline were reported.

Heart Failure Home Care Study (Societal Cost and Cost to MediCare for Enhanced Monitoring Using a Computer Based Monitoring System in Older Patients With Heart Failure)

Presented by Ozlem Soran, Pittsburgh, United States of America

Background: Previous studies had shown that specific management programs for heart failure may be effective for improving clinical outcomes and controlling costs. It is not known whether such programs may reduce health costs and whether they can be adapted to primary health care. This study was designed to evaluate the impact of

a computer-based home care program for heart failure on clinical and economic outcomes when applied to women and men of nonwhite race who had recently been hospitalized for heart failure and who were referred to their family physician for follow-up.

Methods: Multicenter, randomized, controlled study that compared a telephone follow-up according to the computer program (HFMS) with contact at 30 days and at 3 months of randomization with standard follow-up (baseline visit and then a visit every 6 months). A total of 315 patients with MediCare insurance were randomized (women and male Afro-Americans or Hispanics aged more than 65 years) with symptomatic heart failure due to systolic dysfunction despite optimal medical treatment and with hospitalization in the previous 6 months. Of these patients, 304 had insurance data available, and so it was possible to estimate the expenses for the insurance policy and the societal costs. The primary outcome measure of the study included cardiovascular death or rehospitalization for heart failure, duration of hospital stay in days, and total cost per patient and cost for the Medi-Care insurance at 6 months of inclusion in the study.

Results: The composite outcome measure of cardiovascular death and admission for heart failure occurred in 28.8% of the patients with standard follow-up and 21.2% of the patients in the HFMS group ($P=.15$). The mean duration of hospital stay was 9.3 (12.2) days with standard follow-up and 10 (7.3) days in the HFMS group ($P=.22$). The costs for the MediCare insurance and the societal costs were significantly greater for the HFMS group than for the standard group.

Conclusions: Our study indicates that, in women and non-Caucasian men aged more than 65 years who had recently been hospitalized for heart failure, educating the patients and follow-up by family physicians according to the standard method is as effective as a sophisticated system of home care with an interactive computer program and significantly less expensive.

ARRHYTHMIAS

HAT Study (Home Use of Automated External Defibrillators for Sudden Cardiac Arrest)

Presented by G.H. Bardy, Seattle, United States of America.

Background: The most likely out-of-hospital location to suffer a sudden cardiac arrest is the patient's home. This makes it difficult for the emergency medical services to arrive early enough to apply treatment. Therefore, the possibility of having an automated external defibrillator (AED) at home might improve survival of patients at risk.

Methods: The investigators randomized 7001 patients with previous anterior myocardial infarction

who were not candidates to receive an implantable cardioverter-defibrillator to have one of these 2 types of response to cardiac arrest at home: control group, based on a call to the local emergency medical services to apply the normal cardiopulmonary resuscitation (CPR) techniques and a group that used an AED, followed by a call to the emergency services and CPR techniques. The primary outcome measure was all-cause mortality.

Results: The median age of the patients was 62 years, and 17% were women. The mean follow-up period was 37.3 months. In total, 450 patients died: 228 (6.5%) out of 3506 in the control group and 222 (6.4%) out of 3495 patients in the AED group (HR=0.97; 95% CI, 0.81-1.17; $P=.77$). Mortality did not differ significantly in any of the major prespecified subgroups in the study analysis. Only 160 deaths (35.6%) were attributed to sudden cardiac arrest or tachyarrhythmia. Of these deaths, 117 occurred at home and 58 were witnessed by others; AEDs were used by 32 patients. Of these, 14 received an appropriate shock and 4 survived until they were discharged from hospital. No inappropriate shocks were reported.

Conclusions: In patients with a history of anterior-wall myocardial infarction who were not candidates for an implantable cardioverter-defibrillator, having an AED did not improve survival in the experimental group compared to the strategy based on conventional resuscitation methods.

The study has already been published in the form of a full text article.¹⁶

CARISMA Study (Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction)

Presented by PE Bloch Thomsen, Copenhagen, Denmark

Background: Implantable loop recorders (ILRs) have an automatic function for detecting arrhythmias that may be limited by the inappropriate detection of episodes. The objective of this study was 2-fold: first, to evaluate the predictive value of arrhythmias recorded by the ILRs for detecting potentially fatal tachyarrhythmias in patients who have survived an acute myocardial infarction with an ejection fraction ≤ 0.4 , and second, to document the incidence and evaluate the prognostic value of the different cardiac arrhythmias recorded by the ILRs.

Methods: An ILR was implanted in 297 patients at 5 to 21 days after a myocardial infarction after determining that the ejection fraction was ≤ 0.4 , and the mean duration of follow-up was 1.9 years. Sinus bradycardia was defined as sinus rhythm at at least 30 beats/min for 8 seconds or more; sinus arrest lasting more than 5 seconds; atrioventricular block (of second or third degree), of more than 8 seconds with ventricular frequency ≤ 30 beats/min;

nonsustained ventricular tachycardia (NSVT), which has at least 16 beats at a frequency of ≥ 125 beats/min; sustained ventricular tachycardia (SVT), which lasted at least 30 seconds at a frequency of ≥ 125 beats/min. Atrial fibrillation was defined as when the ventricular frequency was ≥ 125 beats/min.

Results: In 137 patients (46%), at least one of the prespecified arrhythmias was recorded. Of these, 86% were asymptomatic. Twenty-seven percent of the patients had new-onset atrial fibrillation; 17% had high-grade atrioventricular block or sinus bradycardia, and a further 17% had NSVT or SVT/ventricular fibrillation. In the univariate analysis of the factors associated with cardiac death, atrioventricular block was associated with a 7-fold higher risk ($P=.0004$); sinus bradycardia with a RR of 5.8 ($P=.004$); and NSVT with a RR of 3.4 ($P=.025$). The multivariate analysis showed that high-grade atrioventricular block was the only independent predictor of cardiac death (RR=4.8; 95% CI, 2-11.5; $P<.001$).

Conclusions: The study demonstrated the feasibility of ILR implantation in patients with reduced ejection fraction after an acute myocardial infarction and the prognostic value of the arrhythmias detected. High-grade atrioventricular block was the only variable that was an independent predictor of cardiac death.

NONCORONARY INTERVENTION

ASTRAL Study (Angioplasty and Stenting for Renal Artery Lesions)

Presented by Phillip Kalra, Birmingham, United Kingdom

Background: The effect of percutaneous revascularization of stenotic renal arteries is uncertain. The hypothesis of this study was that percutaneous revascularization of stenotic renal arteries is more effective at preventing progressive deterioration in renal function than medical treatment.

Methods: The investigators randomized 806 patients with significant stenosis of the renal arteries to receive treatment with percutaneous arterial revascularization along with medical treatment (n=403) or medical treatment alone (n=403). The primary outcome measure of the study was the comparison between the rate of worsening of renal function in both groups after a mean follow-up of 27 months. The secondary outcome measures were blood pressure control, incidence of acute renal failure or the need for dialysis, and mortality or major vascular complications.

Results: At baseline, the mean stenosis of the renal artery was 76%, serum creatinine was 179 $\mu\text{mol/L}$ (2.02 mg/dL), the estimated glomerular filtration rate was 40 mL/min, the mean number of antihypertensive drugs was 2.8 per patient, and the blood pressure was 151/76

mm Hg. Among the study population, 54% were ex-smokers, 30% had diabetes, and 40% had a history of peripheral vascular disease. Percutaneous revascularization was done in 4.4% of the patients assigned initially to medical treatment and the revascularization procedure was successful in 82% of the patients in that group. The use of medication in the percutaneous revascularization group compared to the medical treatment only group was as follows: diuretics, 70% versus 67%; calcium antagonists, 61% versus 68%; beta-blockers, 46% versus 52%; ACE inhibitors or ARA-II, 47% versus 38%; alpha-blockers, 40% versus 37%; aspirin, 91% versus 93%; and statins, 96% versus 95%, respectively.

There were no differences between the 2 groups for changes in serum creatinine, systolic blood pressure, time to first renal complication, mortality, or vascular complications during follow-up.

Conclusions: This study showed no evidence of benefit of percutaneous revascularization of stenotic renal arteries. The intervention did not improve serum creatinine, systolic blood pressure, incidence of renal complications (such as acute renal failure or need for dialysis), mortality, or overall vascular complications. It remains to be determined whether renal vascularization can be of benefit in certain subgroups, such as patients with acute renal failure and critical stenosis of the renal artery or those who present with sudden acute pulmonary edema.

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