Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Orlando, USA, November 4-7, 2007)

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Several clinical trials were selected from the Scientific Sessions of the American Heart Association 2007 for presentation in a special sessions. These studies were chosen due to being considered particularly important and their results were communicated orally. Summaries of the reports have been published online. Following recent publishing policy,[1-4] *Revista Española de Cardiología* offers its readers a summary of these studies. The aims, methods, and results of these studies are briefly described based on what was presented. As the results of most of these studies have not yet been published as original articles, the information offered in the present article should be understood as being preliminary.

ISCHEMIC HEART DISEASE

Prasugrel Versus Clopidogrel in Patients With Acute Coronary Syndrome and Scheduled Percutaneous Coronary Intervention: The TRITONTIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) Study

Presented by Elliot M. Animan, Boston (USA).

Dual antiplatelet therapy with aspirin and a thienopyridine is the therapy of choice in preventing thrombotic complications in acute coronary syndromes and percutaneous coronary intervention.

Methods: To compare prasugrel (a new thienopyridine) with clopidogrel, 13 608 patients with moderate- to high-risk acute coronary syndrome, scheduled for percutaneous coronary intervention, were randomized to receive prasugrel (60-mg loading dose and 10-mg daily maintenance dose) or clopidogrel (300-mg loading dose and 75-mg daily maintenance dose) for 6 to 15 months. The primary efficacy endpoint was established as death due to cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The primary safety endpoint was major bleeding.

Results: The primary efficacy endpoint was observed in 12.1% of the patients receiving clopidogrel and in 9.9% of the patients receiving prasugrel (hazard ratio [HR] of prasugrel vs clopidrogrel, 0.81; 95% confidence interval [CI], 0.73-0.90; *P*<.001). There was a significant reduction in the prasugrel group in the risk of acute myocardial infarction (9.7% in the clopidogrel group vs 7.4% in the prasugrel group; *P*<.001), urgent target-vessel revascularization (3.7 vs 2.5%; *P*<.001) and stent thrombosis (2.4% vs 1.1%; *P*<.001). Major bleeding was observed in 2.4% of the patients receiving prasugrel and in 1.8% of the patients receiving clopidogrel (HR=1.32; 95% CI, 1.03-1.68; *P*=.03). The risk of life-threatening bleeding was also greater in the prasugrel group (1.4% vs 0.9%; *P*=.01), as well as nonfatal bleeding (1.1% and 0.9%; *P*=.23) and fatal bleeding (0.4% vs 0.1%; *P*=.002).

Conclusions: In patients with acute coronary syndromes and scheduled percutaneous coronary intervention, prasugrel therapy was associated with significant reductions in the risk of ischemic events, including stent thrombosis, but there was an increased risk of major bleeding, including fatal bleeding. Total mortality did not significantly differ between groups.

This study has already been published as a full-text article.[5]

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Effects of Torcetrapib in Patients at High Risk for Coronary Events. The ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) Study

Presented by Philip J. Barter, Camperdown, NSW (Australia).

The inhibition of cholesteryl ester transfer protein (CETP) has been associated with a beneficial effect on plasma lipoprotein concentrations. This study was designed to investigate if torcetrapib, a strong CETP inhibitor, could reduce the rate of major cardiovascular events. The study was prematurely stopped due to an increase in the risk of death and cardiovascular events in patients receiving the drug.

Methods: This randomized, double-blind study included 15 607 patients at high cardiovascular risk. The patients received combined torcetrapib and atorvastatin or atorvastatin alone. The primary endpoint was the time to a major cardiovascular event, defined as death due to coronary heart disease, acute non-fatal myocardial infarction, stroke, or hospitalization due to unstable angina.

Results: Compared to baseline values, there was a 72.1% increase in high-density lipoprotein cholesterol and a 24.9% decrease in low-density lipoprotein cholesterol at 12 months in the torcetrapib group ($P<.001$ for both comparisons), and a 5.4 mm Hg increase in systolic blood pressure, a decrease in serum potassium levels and an increase in sodium, bicarbonate, and aldosterone levels ($P<.001$ for all comparisons). Furthermore, there was an increase in the risk of cardiovascular events (HR=1.25; 95% CI, 1.14-2.19; $P=.006$). A post-hoc analysis showed an increased risk of death in the patients treated with torcetrapib where the decrease in potassium levels or the increase in bicarbonate levels was greater than the median of the total group.

Conclusions: Treatment with torcetrapib increases the risk of mortality and morbidity due to an unknown mechanism. Although the beneficial effect on plasma lipid levels was demonstrated, it seems that there are serious side effects associated with the use of the drug.

This study has already been published as a full text article.[6]

The EVA-AMI (Eptifibatide vs Abciximab in Primary PCI for Acute ST elevation Myocardial Infarction) Study

Presented by Uwe Zeymer, Paris (France).

The use of intracoronary stents in primary PCI during acute myocardial infarction (AMI) does not improve early reperfusion, but does reduce the reintervention rate. On the other hand, adjuvant therapy with glycoprotein (GP) IIb/IIIa inhibitors improves post-AMI reperfusion, left ventricular function, and clinical prognosis. No placebo-controlled studies have been conducted on the use of small-molecule GP IIb/IIIa inhibitors, such as eptifibatide or tirofiban, in this context. In the ESPRIT study, eptifibatide, a synthetic GP IIb/IIIa inhibitor, reduced the rate of thrombotic complications in patients undergoing elective intracoronary stent implantation. Eptifibatide is cheaper than abciximab and has the advantage of reversible binding to the receptor. Thus, it seems appropriate to compare the safety and efficacy of these drugs in the context of primary PCI with stenting.

Objectives: To evaluate the use of abciximab and eptifibatide in patients undergoing PCI for AMI.

Methods: Patients undergoing PCI in the acute phase of ST-segment elevation myocardial infarction (STEMI) were randomized to receive eptifibatide (double bolus, followed by 24-h infusion, n=226) or abciximab (bolus, followed by 12-h infusion; n=201). Electrocardiographic studies were conducted at enrollment and 1 h after the procedure to assess ST resolution.

Results: The mean time from symptom onset to drug administration was 230 min and the mean time from baseline to PCI was 30 min. There was anterior infarction in 44% of the patients. There were no between-group differences in the proportion of patients with TIMI-III flow after the procedure (82.4% vs 84.3% in the eptifibatide group and abciximab group, respectively; nonsignificant difference). Data on ST resolution was available 1 h after the procedure in approximately half of the study patients. Complete ST resolution (>70% reduction) was observed in 63.1% in the eptifibatide group and in 59.6% in abciximab group, confirming noninferiority of treatment. There were no significant differences in in-hospital events in mortality (3.5% in both groups), re-AMI (0% vs 1.5%), heart failure (6.4% vs 8.5%), or revascularization (2.7% vs 4%) in the eptifibatide and abciximab groups, respectively. Major bleeding occurred in 1.8% and 0% of the eptifibatide group and abciximab group, respectively (nonsignificant difference). No differences were observed in the rate of major bleeding.

Conclusions: Inhibition of GP IIb/IIIa with eptifibatide is not inferior to abciximab therapy in patients undergoing PCI for STEMI regarding the primary endpoint of complete ST resolution 1 h after the procedure.

Randomized Controlled Study on Metoprolol Versus Placebo in Patients Undergoing Noncardiac Surgery. The POISE (Perioperative Ischemic Evaluation Trial) Study

Presented by P.J. Devereaux, Hamilton (Canada).

The aim of the study was to assess the effect of treatment with metoprolol compared to placebo on major

cardiovascular events in patients undergoing nonheart surgery.

Methods: The patients were randomized to receive treatment with metoprolol (n=4174) or placebo (n=4177). A dose of 100 mg controlled-release metoprolol or placebo was administered 2-4 h before surgery and 0-6 h afterwards. The patients then received 200 mg of metoprolol or placebo for 30 days afterwards.

Results: At enrollment, 43% of the patients had coronary heart disease, 41%, peripheral vascular disease, and 15%, previous stroke. Vascular surgery was performed in 42% of the patients, intraperitoneal surgery in 22%, orthopedic surgery in 21%, and other types of surgery in 15%. The risk of the primary composite endpoint of cardiovascular mortality, myocardial infarction, or cardiac arrest was reduced in the metoprolol group compared to placebo (5.8% vs 6.9%; HR=0.83; 95% CI, 0.70-0.99; *P*=.04), due to a reduction in the rate of non-fatal myocardial infarction (3.6% vs 5.1%; HR=0.70; *P*=.0007). Revascularization rates (0.3% vs 0.6%; *P*=.01) and atrial fibrillation rates (2.2 vs 2.9%; *P*=.04) were also reduced. However, total mortality (3.1% vs 2.3%; HR=1.33; *P*=.03) was greater and stroke (1% vs 0.5%; HR=2.17; *P*=.005) more common in the metoprolol group. The metoprolol group also had higher rates of symptomatic hypotension (15% vs 9.7%; *P*<.0001) and bradycardia (6.6% vs 2.4%; *P*<.00001).

Conclusions: In patients undergoing non-cardiac surgery, treatment with the beta-blocker metoprolol was associated with a reduction in the risk of the primary endpoint of cardiac mortality, myocardial infarction or stroke at 30 days compared to placebo, but total mortality was greater in the metoprolol group.

The BRIEF-PCI (Abbreviated Infusion of Eptifibatide After Successful Percutaneous Coronary Intervention) Study

Presented by Anthony Fung, Vancouver (Canada).

The recommended treatment regimen with eptifibatide during PCI is a double bolus followed by an 18-h infusion. The aim of this study was to compare a brief infusion of eptifibatide with the standard 18-h infusion in patients undergoing successful PCI during which eptifibatide was used during the procedure.

Methods: After a nonemergency PCI procedure, the patients were randomized to a standard 18-h infusion regimen (n=312) or a brief infusion administered over less than 2 h (n=312). Biomarkers were measured at baseline, 8 h and 24 h after enrollment in an independent core laboratory.

Results: The principal diagnosis was stable angina in 49% of the patients, acute coronary syndrome in 37%, and STEMI within 48 h in 15%. Approximately two-thirds of the patients received a loading dose of clopidogrel. Half of the study patients had multivessel coronary heart disease with a predominance of type B2 or C lesions (63%). Two or more stents were used in 41% of the cases. The primary endpoint of periprocedural ischemic myocardial injury was observed in 30.1% of the brief-treatment group compared to 28.3% of the standard 18-h treatment group (*P*=.012, noninferiority hypothesis). The rate of AMI at 30 days was similar in the 2 groups (4.8% in the brief-treatment group vs 4.5% in the standard-treatment group; nonsignificant difference). The need for urgent target-vessel revascularization was also similar (0.6% in both groups). No patient died in either group. The general rate of major adverse events was 4.8% in the brief-treatment group and 4.5% in the standard-treatment group (nonsignificant difference). Major bleeding was less common in the brief-treatment group (1% vs 4.2%; *P*=.002). No difference was observed in the rate of minor bleeding.

Conclusions: In patients undergoing nonemergency PCI during which eptifibatide was used, an abbreviated 2-h infusion of eptifibatide is not inferior to the standard treatment of 18-h infusion regarding periprocedural myocardial ischemic injury.

Analysis of Quality of Life and Costs of the OAT (Occluded Artery Trial) Study

Presented by Daniel B. Mark, Toronto (Canada).

The OAT study compared the results of PCI with stenting to medical therapy alone after acute myocardial infarction (up to 28 days later) in high-risk patients with an occluded coronary artery and who met a high-risk criterion (ejection fraction <50% or proximal occlusion of a major coronary artery).[7] PCI did not reduce the composite endpoint of death, myocardial infarction or hospitalization due to class IV heart failure. Quality of life (QOL) and costs were secondary outcomes of the OAT study.

Methods: The quality of life battery of tests included the Duke Activity Status Index (DASI), the Medical Outcomes Study Short Form-36 (SF-36) for physical function, social function, and psychological well-being, and the Rose angina and Rose dyspnea questionnaires for cardiac symptoms. This QOL substudy included 951 patients (48% of the total included between 2000 and 2004). Data were collected at enrollment (median of 6 days after AMI) and 4, 12, and 24 months after randomization; 95% of forms were completed. Costs were calculated for all the patients from the United States of America on the basis of billing data.

Results: The OAT study QOL sample was representative of the total study population (median age, 59 years; 83% were Caucasian, and 78% were men). During the first 2 years of follow-up, the results of DASI showed that the rate of heart disease remained the same in the PCI group, whereas there was a modest reduction in the medical treatment group. The greatest difference in the DASI was observed at 4 months after enrollment (4 DASI points), but this was not clinically significant after this. On the other hand, PCI did not lead to increased psychological well-being as measured by the Mental Health Inventory SF-36. At 4 months after AMI, the Rose angina rates were greater in the medical treatment group than in the PCI group (16.5% vs 10.3%; *P*=.049), but the differences were lower and nonsignificant at 12 months and 24 months. In the 469 patients included in the United States of America, the medical costs were 9000 dollars higher in the PCI group than in the medical treatment group (*P*<.0001). The medical follow-up costs were similar in the 2 study branches. The costs to produce 1 extra quality-adjusted life-year with PCI exceeded 100 000 dollars.

Conclusions: In the OAT study, PCI with stenting was associated with a discrete transitory improvement in the angina rate and physical function at 4 months, but not afterwards. The type of PCI employed in the OAT study is not a cost-effective treatment to improve cardiovascular well-being in these patients.

Randomized Study of Angiotensin-II Receptor Antagonists (ARA-II) Versus Standard Treatment in Patients With Coronary Heart Disease and Hypertension. The HIJ-Create (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease) Study

Presented by Hiroshi Kasanuki, Tokyo (Japan).

The aim of the study was to assess treatment with candesartan compared to standard treatment without an ARA-II in patients with angiographically documented coronary heart disease and hypertension.

Methods: In this open-label study, the patients were randomized to receive candesartan without an angiotensin-converting enzyme inhibitor (n=1024) or standard treatment without an ARA-II (n=102). Target blood pressure was defined as <130/85 mm Hg.

Results: Most patients had chronic coronary heart disease (65%) and 35% were included following acute coronary syndrome. Approximately one-third of the patients had suffered a previous infarction. No differences were observed between groups in the primary endpoint of major cardiovascular events (25.8% vs 28.1%; RR=0.89; 95% CI, 0.76-1.06; *P*=.19). No differences were observed in the rate of any major cardiovascular event, but the rate of cardiovascular death or myocardial infarction in the standard treatment group was lower than other events, which were more common in the candesartan group. No differences were observed between the groups in the revascularization rate (25% vs 26.4% in the candesartan group and standard treatment group, respectively; *P*=.41). The rate of new onset diabetes mellitus was lower in the candesartan group (1.1% vs 2.9%; *P*=.027). The rate of drug-related adverse effects was lower in the candesartan group (*P*=.027), as well as the need to interrupt treatment (*P*=.001).

Conclusions: In the patients with coronary heart disease and hypertension, treatment with candesartan was not associated with a reduction in major cardiovascular events after a median follow-up of 4.2 years, compared to standard treatment without an ARA-II.

The PROVIDENCE-1 (Prospective Evaluation of Rifalazil Effect on Vascular Symptoms of Intermittent Claudication and Other Endpoints in Chlamydia Seropositive Patients) Study

Presented by Michael R. Jaff, Massachusetts (USA).

The aim of this study was to assess treatment with the antibiotic rifalazil compared to placebo in patients with intermittent claudication who had high levels of antibodies to *Chlamydia pneumoniae*.

Methods: The patients were randomized to receive rifalazil (n=153, 25 mg) or placebo (n=144), administered weekly for 8 weeks. Patients underwent exercise stress test at baseline and 2, 3, 6, and 12 months after enrollment.

Results: At the time of enrollment the ankle-brachial index was 0.63 and serological assay indicated *Chlamydia* titers ≥1:512 in 42% of the patients. Approximately 25% of the patients were diabetic. No differences were observed between groups in the primary endpoint of change in peak walking time at 6 months (20% improvement in the rifalazil group vs 16% in the placebo group; nonsignificant difference). No differences were observed in quality of life tests at 6 months using the walking impairment questionnaire (mean 35.7 vs mean 39.2 in the rifalazil group and placebo group, respectively; nonsignificant difference) or the physical function SF-36 questionnaire (51.5 vs 51.9, respectively; nonsignificant difference). There were no differences in the rate of major cardiovascular events. There was 1 death in the rifalazil group and 1 death in the placebo group.

IMAGING TECHNIQUES

Improvement in Myocardial Ischemia During Stress Testing: Differences Between Percutaneous Coronary Intervention and Optimal Medical Treatment Alone; Nuclear Substudy of the COURAGE (Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation Trial) Study

Presented by Leslee J. Shaw, Atlanta (USA).

In the COURAGE study,[8] no differences were observed in the clinical endpoints between the PCI group and optimal medical treatment group. However, no study has investigated either the value of myocardial perfusion SPECT imaging to identify the subgroup of patients with stable coronary heart disease and inducible ischemia, or changes in ischemic burden obtained with treatment.

Methods: Of the 2287 patients in the COURAGE study, 313 underwent SPECT imaging at rest and during stress at the time of enrollment and at 6-18 months after randomization. The results of SPECT imaging were analyzed blindly by an independent core laboratory that quantified total differential ischemia under stress and at rest. A 5% reduction in ischemic myocardium was considered significant. A generalized linear model adjusted for baseline ischemia was estimated.

Results: At enrollment, the groups of patients were similar regarding functional class for angina (74% of the patients in each group were in Canadian Cardiovascular Society classes I-II), ischemia under SPECT imaging (8.2% and 8.6% of the total myocardium in the PCI + medical treatment group vs medical treatment only group, respectively), and angiographically documented multivessel coronary heart disease (75% of each group). After treatment, the reduction in the percentage of ischemic myocardium was greater in the PCI + medical treatment group than in the medical treatment alone group ($P<.0001$); 33% of the patients who underwent PCI showed a significant reduction in ischemia as shown by SPECT imaging vs 19% of the patients receiving medical treatment alone ($P=.0004$). The patients with high-risk ischemia before treatment (≥10% compromised myocardium) undergoing PCI showed a significant reduction in ischemia vs the medical treatment alone group (78% vs 52%; $P=.007$).

Conclusions: In this group of patients selected from the COURAGE study, PCI combined with medical treatment was more effective in reducing ischemia than medical treatment alone. The greatest reductions in ischemic area using PCI combined with medical treatment were observed in the patients with more extensive ischemia at baseline. These data support the use of myocardial perfusion SPECT imaging to identify the patients with a greater probability of benefiting from PCI.

Evaluation of Coronary Arteries Using 64-Row Computerized Tomography. Results of an International Multicenter Study to Analyze the Diagnostic Accuracy of the Technique Compared to Angiography. The CORE-64 (Coronary Artery Evaluation Using 64-Row multidetector Computed Tomography Angiography) Study

Presented by Julie M. Miller, Baltimore (the United States).

Multi-detector spiral CT angiography (MDCTA) has been proposed as a non-invasive alternative to conventional angiography in detecting obstructive lesions in patients with suspected coronary heart disease. However, previous single-center studies have found that diagnostic accuracy varies widely with this technique which has not been compared to conventional coronary angiography (CA) in relation to predicting the likelihood of revascularization.

Methods: The CORE-64 study was the first multicenter prospective study to compare MDCTA with CA. A total of 9 centers participated that included 316 patients with calcium scores ≤600 who had been referred for CA due to clinical indications. Of this group, 291 consecutive studies of MDCTA followed by CA were analyzed by independent core laboratories. Each core laboratory had 2 independent investigators blinded to all the clinical data and to the other imaging modality. All the nonstented segments with a diameter >1.5 mm were analyzed. Stenosis was visually and quantitatively assessed, and lesions greater than 50% were considered significant when measured by standard quantitative angiography.

Results: Of the 291 patients (26% women), the median age was 59 years, body mass index, 27, and calcium score, 80. The detected prevalence of significant coronary heart disease was 56%. Compared to CA, the quantitative analysis of coronary stenosis using MDCTA showed a receiver operating characteristic curve area of 0.92 and 0.91 for some severely stenosed segments (50% and 70%, respectively). Visual analysis of the MDCTA images compared to those of quantitative angiography showed a specificity of 91% (interval, 86%-96%) and a sensitivity of 83% (78%-89%), with a positive predictive value of 92% (86%-96%) and negative predictive value of 81% (74%-87%). In the analysis by patient, no differences were found between considering the segments that could not be assessed by MDCTA as having coronary heart disease, and excluding them from the analysis. Furthermore, quantitative MDCTA demonstrated a similar capacity to that of CA to predict subsequent

revascularization, with an area under the receiver operating characteristic curve of 0.80 versus 0.79 with conventional quantitative angiography.

Conclusions: In patients with suspected coronary heart disease and a calcium score ≤600, a 64-row MDCTA can be used to detect significant coronary heart disease and the likelihood of later revascularization. The diagnostic capacity of quantitative MDCTA was higher than visual analysis (area under the curve=0.92), and thus the use of both methods is recommended.

HEART FAILURE

Rosuvastatin in Patients With Ischemic Heart Failure. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) Study

Presented by Ake Hjalmarson, Breda (The Netherlands).

As placebo-controlled clinical statin trials have excluded patients with heart failure, the potential risks and benefits of statins in patients with heart failure have not been studied. The aim of the CORONA study was to assess treatment with rosuvastatin versus placebo in older patients with systolic heart failure. The main aim was to determine if rosuvastatin (10 mg daily) reduces the number of patients with a primary composite outcome of cardiovascular mortality, nonfatal myocardial infarction or nonfatal stroke (time up to the first event). The secondary outcome was death from any cause.

Methods: The study included patients older than 60 years with chronic ischemic systolic heart failure and an ejection fraction ≤40% (in NYHA III or IV functional class) or ≤35% (in functional class II or higher). Patients already taking hypolipidemic drugs were excluded. This was an endpoint trial which terminated when the primary outcome had occurred in 1422 patients.

Results: After an initial 2-4 week phase using placebo, the patients were randomized to receive rosuvastatin (n=2514) or placebo (n=2497). The ejection fraction at inclusion was 31%. Of the total patients, 62% were in functional class III, 60% had previous infarction, 73% had previous angina, and 30% had suffered diabetes mellitus. Treatment with rosuvastatin was associated with a decrease in low-density lipoprotein cholesterol concentrations from 137 mg/dL to 76 mg/dL at 3 months, but no effect was observed in the placebo group. Similarly, there were decreases in C-reactive protein concentrations from 3.1 mg/dL to 2.1 mg/dL at 3 months in the rosuvastatin group, whereas these increased in the placebo group (from 3 mg/dL to 3.3 mg/dL at 3 months; *P*<.001 between groups). The primary composite outcome rate of cardiovascular death, myocardial infarction, or stroke was not significantly different between the 2 groups (11.4 for rosuvastatin vs 12.3 every 100 patients/year of follow-up; HR=0.92; 95% CI, 0.83-1.02; *P*=.12). No significant between-group differences were observed for the secondary outcome of mortality from any cause (HR=0.95; 95% CI, 0.86-1.05; *P*=.31) or any coronary event (HR=0.92; 95% CI, 0.82-1.04; *P*=.18). There were fewer hospitalizations due to cardiovascular causes in the rosuvastatin group than in the placebo group (HR=0.92; 95% CI, 0.85-0.99; *P*=.004 for the first event and *P*<.001 for multiple events). No between-group differences were observed in changes in NYHA functional class. No differences were observed in the rate of side effects.

Conclusions: In patients with systolic heart failure, hypolipidemic treatment with rosuvastatin is not associated with a reduction in the rate of cardiovascular mortality, acute myocardial infarction, or stroke at a median follow-up time of 32.8 months compared to placebo.

This study has already been published as a full text article.[9]

Atrial Fibrillation and Congestive Heart Failure. The AF-CHF Study

Presented by Denis Roy, Montreal (Canada).

Objective: To determine if restoring and maintaining sinus rhythm compared to a rate control strategy reduces cardiovascular mortality in patients with congestive heart failure (CHF) and atrial fibrillation.

Methods: The patients were randomized to rhythm control (n=682) or rate control (n=694). Rhythm control was performed using electrical cardioversion combined with antiarrhythmic drug therapy, including amiodarone as first-line treatment, followed, if necessary, with dofetilide and sotalol; nonpharmacological techniques were applied in refractory patients. The rate control strategy included the use of beta-blockers, digoxin, or AV nodal catheter ablation and pacemaker implantation if required. All the patients received optimal medical treatment for heart failure and anticoagulant therapy.

Results: At inclusion, 31% of the patients were in NYHA functional class III or IV. Ejection fraction was 27% and atrial fibrillation was paroxysmal in 31% of the patients and persistent in 69%. Following the study design, 82% of the patients in the rhythm control group received amiodarone, 1.8%, sotalol, and 0.4%, dofetilide. In the rate control group, 88% received beta-blockers and 75% received digoxin. During the study, 21% of patients crossed over from the rhythm control group to the rate control group and 10% of patients in the rate control

group crossed over to the rhythm control group. No differences were observed in the primary outcome of cardiovascular death between the 2 groups (26.7% in the rhythm control group vs 25.2% in the rate control group; HR=1.06; 95% CI, 0.86-1.30; *P*=.59). No differences were observed in total mortality (31.8% vs 32.9% in the rhythm control group and rate control group, respectively; *P*=.73), stroke (2.6% vs 3.6%; *P*=.32), worsening CHF (27.6% vs 30.8%; *P*=.17) or composite endpoint of cardiovascular death, stroke, or worsening CHF (42.7% vs 45.8%; *P*=.20). There were more cardioversions in the rhythm control group (39%) than in the rate control group (8%) (*P*=.0001). Bradyarrhythmias were more frequent in the rhythm control group (8.5% vs 4.9%; *P*=.0007).

Conclusions: In patients with congestive heart failure and atrial fibrillation, rhythm control was not associated with differences in cardiovascular mortality compared to a rate control strategy, after a mean follow-up of 3 years.

Atrial Fibrillation in Heart Failure Patients Candidate for a Cardiac Resynchronization Therapy Device. One-Year Results of the MASCOT (Management of Atrial Fibrillation Suppression in AF-HF COmorbitidity Therapy) Study

Presented by Luigi Padeletti, Florence (Italy).

Atrial fibrillation (AF) is associated with an increase in morbidity and mortality in heart failure patients, especially in those with left bundle branch block. Patients with heart failure, systolic dysfunction in NYHA functional class III or IV and with a wide QRS complex are candidates for cardiac resynchronization therapy (CRT) and can benefit from overdrive pacing therapy aimed at preventing the development of AF.

Methods: The MASCOT study included patients in NYHA functional class III or IV, with EF ≤35% and QRS ≥130 ms in sinus rhythm. A CRT device was implanted and patients were then randomized to receive atrial overdrive pacing (AOP) (n=197) or not (n=197) before being discharged.

Results: Mean LVEF was 25% and 86% of the patients were in NYHA functional class III. The average QRS interval was 163 ms. There was a previous history of AF in 19% of the cohort and 50% of the patients had chronic ischemic heart disease. In relation to the therapy used, atrial overdrive pacing was more common in the AOP group (80 vs 30; *P*<.0001). No differences were observed in the rates of ventricular pacing (95% in every group), but the heart rate was higher in the AOP group (72 bpm vs 67 bpm; *P*=.05). The means of heart failure severity improved at 1 year in both groups by one NYHA class (67% with AOP vs 70% without AOP; nonsignificant difference), and there were also nonsignificant improvements in LVEF (mean 33.1% vs 32.7%, respectively), and left ventricular endsystolic dimension (57 mm vs 53 mm, respectively). No differences were observed in the primary endpoint of permanent AF between the groups (7 patients in the AOP group and 6 patients in the no-AOP group). Mortality at 1 year was 7.6% in the AOP group and 11.7% in the no-AOP group.

Conclusions: In patients with heart failure with an implanted CRT device, active atrial overdrive pacing is not associated with a difference in the rate of persistent AF at 1 year compared to conventional programming.

Cardiac Resynchronization Therapy in Patients With a Narrow QRS Complex. The RethinQ (Resynchronization Therapy in Patients with Narrow QRS) Study

Presented by John F. Beshai, Chicago (USA).

Indications for CRT include patients with a QRS interval >120 ms, EF ≤35% and NYHA functional class III or IV. However, some patients with a narrow QRS complex present evidence of mechanical dyssynchrony and may also benefit from CRT.

Methods: The study included 172 patients who presented standard indications for an implantable automatic cardioverter-defibrillator. The patients received the CRT device and were randomly assigned to receive CRT (group treatment) or no CRT (control group) over 6 months. The primary endpoint was the proportion of patients with an increase in peak oxygen consumption of at least 1 mL/kg/min during cardiopulmonary exercise testing at 6 months.

Results: At 6 months, there were no significant differences between the CRT group and the control group in the proportion of patients with the primary endpoint (46% and 41%, respectively). In a prespecified subgroup of patients with a QRS interval ≥120 ms, the peak oxygen consumption increased in the CRT group (*P*=.02), but did not change in the group of patients with a QRS interval <120 ms (*P*=.45). There were 24 heart-failure events that required intravenous medication in 14 patients in the CRT group (16.1%) and 41 events in 19 patients in the control group (22.3%), but this difference was not statistically significant. There were no between-group differences in variables such as quality of life, change in the 6-min walk test, or change in ejection fraction.

Conclusions: Cardiac resynchronization therapy did not improve oxygen consumption in patients with moderate-severe heart failure, indicating that patients with a narrow QRS complex may not benefit from CRT.

This study has already been published as a full-text article.[10]

ARRHYTHMIA

The MASTER I (Microvolt T Wave Alternans Testing for Risk Stratification of Post MI Patients) Study

Presented by Theodore Chow, Cincinnati (USA).

Automatic implantable cardioverter-defibrillators (ICD) have demonstrated a reduction in mortality in patients with severe ischemic ventricular dysfunction (LVEF ≤30%). However, LVEF lacks sensitivity and specificity to predict life-threatening high-risk ventricular tachyarrhythmic events (HRVTE). Previous studies have demonstrated the capacity of T-wave alternans to predict total and arrhythmic mortality, but the capacity of this test to identify candidates for ICD implantation who are at higher risk of receiving an appropriate shock from the device due to an HRVTE has not been clarified. The primary aim of the MASTER I study was to determine if T-wave alternans predicts the incidence of HRVTE in post-AMI patients with LVEF ≤30%. A secondary aim was to investigate the value of the test in different groups of patients in relation to their QRS interval.

Methods: Multicenter study conducted in 50 centers in the USA. Patients were eligible for inclusion who met the MADIT-II indications for ICD and were not in AF. All the patients underwent T-wave alternans testing and were classified according to the standard criteria. The protocol required that indeterminate tests should be repeated. Following the tests to identify HRVTE, patients underwent ICD implantation with prespecified programming to minimize the risk of inappropriate shocks. Mean follow-up time was 2 years.

Results: The results of 575 patients were analyzed (84% males; mean age, 65 years; mean LVEF, 24%). The results of the T-wave alternans test were positive in 51% of the patients, negative in 37%, and indeterminate in 12%. The tests that initially resulted in an indeterminate outcome were repeated, with a definitive outcome in 41 of 69 cases (59%). After a mean follow-up of 2.1 years, 70 HRVTE were observed (7 arrhythmic deaths and 63 appropriate shocks). An HRVTE was recorded in 13% (6.3%/year) of the patients with a positive or indeterminate T-wave alternans test versus 10% (5%/year) in the patients with a negative test. A non-negative test was not associated with an HRVTE (HR=1.26; 95% CI, 0.76-2.09; *P*=.37). Patients with a QRS interval <120 ms and a non-negative T-wave alternans test tended have a greater likelihood of an HRVTE (HR=2.3; 95% CI, 0.92-5.76; *P*=.08).

Conclusions: Risk stratification with T-wave alternans did not predict serious ventricular tachyarrhythmic events in post-AMI patients with ischemic left ventricular dysfunction meeting criteria for ICD implantation.

Randomized Trial of Genotype-Guided Versus Standard Warfarin Dosing in Patients Initiating Oral Anticoagulation. The Couma-Gene Study

Presented by Jeffrey L. Anderson, Salt Lake City (USA).

Pharmacogenetic-guided dosing is a promising application of "personalized medicine," but remains to be suitably tested in randomized trials.

Methods: A total of 206 patients being initiated on warfarin therapy were randomized to receive pharmacogenetic-guided dosage or standard dosage. Buccal swab DNA was genotyped for *CYP2C9**2, *CYP2C9**3, and *VKORC1* C1173T by rapid assay. The standard dosage followed an empirical protocol, whereas the pharmacogenetic-guided dosage was carried out through a regression equation that included the three genetic variants, and age, sex, and weight. Prothrombin time international normalized ratio (INR) was systematically measured on days 0, 3, 5, 8, 21, 60, and 90. A research pharmacologist who was not blinded to the treatment strategy managed the dose adjustments. The patients were followed up for 3 months.

Results: The pharmacogenetic-guided doses more accurately predicted stable doses (*P*<.001), resulting in smaller (*P*=.002) and less frequent (*P*=.03) changes in dosage, as well as fewer INR fluctuations (*P*=.06). However, the primary endpoint of the study, the percentage of out-of-range INRs (30.7% vs 33.1%, pharmacogenetic-guided and standard dosing, respectively) did not significantly differ between groups. Nevertheless, a significant improvement was observed in the pharmacogenetic-guided dosage group (29% of out-of-range INRs vs 39% standard dosage; *P*=.03) following a post-hoc analysis of the primary endpoint when restricted to the wild-type carriers, who required larger doses (*P*<.001), or multiple variant genotype carriers, who required smaller doses (*P*<.001). Multiple variant allele carriers were at greater risk of an INR ≥4 (*P*=.03).

Conclusions: An algorithm guided by pharmacogenetic and clinical factors improved the accuracy and the efficiency of warfarin dosing. However, the primary endpoint of reducing the out-of-range INR rate was not achieved. In the subgroup analysis, pharmacogenetic-guided dosing appears promising for the wild-type and multiple variant genotypes.

This study has already been published as a full-text article.[11]

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