

Summary of the Clinical Studies Reported in the 54th Scientific Session of the American College of Cardiology (Orlando, Florida, USA, 6-10 March 2005)

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At the Annual Scientific Sessions of the 54th Congress of the American College of Cardiology in 2005, late breaking clinical trials were presented in sessions whose purpose to allow quick dissemination of findings from recent studies of particular importance.

We briefly summarize the objectives, methods, and findings of these studies, as presented orally in these sessions. Many of them have not been published in written form in full; therefore, the information presented here should be considered as preliminary. When the studies summarized have been published in full, we refer the reader to the original publication.

PRIMARY AND SECONDARY PREVENTION

Aspirin in Primary Prevention in Women (WHS Aspirin Study: Women's Health Study—Low-Dose Aspirin in Primary Prevention)

Presented by Dr Paul M. Ridker, Boston, USA

Background. Randomized studies in men have shown that low-dose aspirin reduces the risk of a first myocardial infarction but has little effect on the risk of ischemic stroke. Data on a possible effect in women are limited.

Methods. A total of 39 876 initially healthy women aged 45 years or older were randomized to receive 100 mg of aspirin or placebo. Study subjects were followed for 10 years to detect the incidence of major cardiovascular disease (essentially nonfatal acute myocardial infarction, nonfatal stroke, or cardiovascular death).

Results. During follow-up, 477 major cardiovascular events were reported in the aspirin group compared to 522 in the placebo group, corresponding to a nonsignificant risk reduction of 9% with aspirin treatment (relative risk [RR]=0.91; 95% confidence interval (CI), 0.80-1.03; $P=.13$). A breakdown of the secondary endpoints showed a reduction of 17% in the risk of stroke in the aspirin group (RR=0.83; 95% CI, 0.69-0.99; $P=.04$), corresponding to a 24% decrease in the risk of ischemic stroke (RR=0.76; 95% CI, 0.63-0.93; $P=.009$) and a nonsignificant increase in the risk of hemorrhagic stroke (RR=1.24; 95% CI, 0.82-1.87; $P=.31$). Aspirin did not have a significant effect on the risk of fatal or nonfatal infarction (RR=1.02; 95% CI, 0.84-1.25; $P=.83$) or

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cardiovascular death (RR=0.95; 95% CI, 0.74-1.22; $P=.68$) compared to placebo. Gastrointestinal bleeding requiring transfusion was more common in the aspirin group than the placebo group (RR=1.40; 95% CI, 1.07-1.83; $P=.02$). Subgroup analysis showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction in women aged 65 years or older.

Conclusions. In this large study of primary prevention in women, aspirin reduced the risk of stroke without affecting the risk of myocardial infarction or cardiovascular death. Therefore, significant differences in the overall primary study endpoint were not found.

Vitamin E in Primary Prevention in Women (WHS Vitamin E Study: Women's Health Study—Vitamin E in Primary Prevention)

Presented by Dr Julie E. Buring, Boston, USA

Background. Researchers have suggested that vitamin E, an antioxidant, might reduce the risk of cardiovascular disease and epithelial tumors, though its effect in women is not known. Vitamin E was compared to placebo in a very large sample of women to investigate a possible effect.

Methods. A total of 39 876 initially healthy women aged 45 years or more were randomized to receive 600 IU of vitamin E or placebo every other day in a 2×2 factorial design that also evaluated the effect of low-dose aspirin. Follow-up lasted for 10.1 years, during which time major cardiovascular complications (nonfatal acute myocardial infarction, nonfatal stroke, or cardiovascular death), and neoplastic disease of epithelial origin were reported. The events were reviewed by a panel of investigators who were blinded to patient assignment.

Results. During follow-up, 482 major cardiovascular events were reported in the vitamin E group compared to 517 in the placebo group (relative risk [RR]=0.93; 95% confidence interval [CI], 0.82-1.05; $P=.26$). No differences were found in the individual components of the cardiovascular endpoint such as fatal or nonfatal myocardial infarction (196 AMI in the vitamin E group vs 195 in the placebo group; RR=1.01, $P=.96$). There were no differences for overall stroke (241 strokes in the vitamin E group vs 246 in the placebo group; RR=0.98; $P=.82$), ischemic stroke (194 in the vitamin E group vs 197 in the placebo group; RR=0.99, $P=.88$), or hemorrhagic stroke (44 in the vitamin E group vs 48 in the placebo group; RR=0.92; $P=.68$). The incidence of fatal and nonfatal strokes was also similar. The incidence of cardiovascular death was significantly lower in the vitamin E group (106 deaths vs 140 in the placebo group; RR=0.76; 95% CI, 0.59-0.98; $P=.03$),

whereas there were no differences in all-cause mortality (636 deaths vs 615 in the placebo group; RR=1.04; $P=.53$). The findings for the composite endpoint remained unchanged in subgroup analysis by degree of treatment compliance, hormone replacement therapy, or postmenopausal state. Adverse events showed no difference between the 2 groups, with an incidence of gastrointestinal bleeding of 4.2% in the vitamin E group and of 4.1% in the placebo group ($P=.77$).

Conclusions. Vitamin E treatment in healthy women was not associated with a significantly lower incidence of major cardiovascular events compared to placebo after a mean follow-up of 10 years. The significant reduction in the number of cardiovascular deaths requires a detailed analysis, as there were no significant differences with respect to fatal myocardial infarction or fatal stroke. A lower incidence of sudden death in patients treated with vitamin E might explain this difference, though specific data were not presented.

Intensive Lipid-Lowering Treatment in Patients with Ischemic Heart Disease (TNT: Treating to New Targets study)

Presented by Dr John C. La Rosa, New York, USA

Background. Previous clinical studies have shown that decreases in low-density lipoprotein cholesterol (LDL-C) to below levels recommended in current guidelines are beneficial for patients with acute coronary syndromes. This study prospectively analyzed the efficacy and safety of lowering LDL-C levels to below 100 mg/dL (2.6 mmol/L) in patients with stable coronary heart disease (CHD).

Methods. Overall, 10 001 patients with clinical evidence of CHD and LDL-C levels below 130 mg/dL (3.4 mmol/L) were randomized in this double-blind study to receive 10 mg or 80 mg of atorvastatin a day. Patients were followed for a mean of 4.9 years. The primary endpoint was occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal nonprocedural-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

Results. Mean levels of LDL-C were 77 mg/dL (2.0 mmol/dL) in the group treated with 80 mg/day of atorvastatin and 101 mg/dL (2.6 mmol/L) in the 10 mg/day group. The incidence of persistent transaminase elevation was 0.2% in the group on 10 mg/day of atorvastatin and 1.2% in the group who received 80 mg/day ($P<.001$). A primary endpoint event was reported in 434 patients (8.7%) in the 80 mg/day dose group compared to 548 patients (10.9%) in the group treated with 10 mg of atorvastatin, corresponding to an

absolute reduction in the incidence of major cardiovascular events of 2.2%, and a reduction of 22% in the relative risk (hazard ratio [HZ]=0.78; 95% CI, 0.69-0.89; $P<.001$). Overall mortality was similar for both groups.

Conclusion. Intensive lipid-lowering treatment with 80 mg of atorvastatin a day in patients with stable CHD provides significant additional benefits compared to the benefit obtained from treatment with 10 mg of atorvastatin a day. This effect was accompanied by a higher incidence of transaminase elevations.

Rimonabant in the Treatment of Obesity (RIO-EUROPE Study: Rimonabant In Obesity Europe Study)

Presented by Dr Luc van Gaal, Amberes, Belgium

Background. Rimonabant, a cannabinoid type 1 receptor antagonist, can help treat the most important cardiovascular risk factors such as obesity, smoking, dyslipidemia, and metabolic syndrome. Many therefore think use of this drug may be beneficial in populations with these risk factors. The objective of the RIO-Europe study was to compare 3 regimens (low-dose and high-dose rimonabant and placebo) in overweight or obese patients over a 2-year treatment period.

Methods. A total of 1507 nondiabetic patients—mainly white women—with central obesity (mean body mass index, 36.6 kg/m²; waist circumference, 110 cm) were included. They were assigned to 3 groups: placebo, rimonabant 5 mg/day, and rimonabant 20 mg/day. All patients included in the study were recommended to reduce their calorie intake by 600 kcal/day.

Results. After 2 years of follow-up, patients on high-dose rimonabant had lost a mean of 8.7 kg, that is, 4.3 kg more than those on placebo ($P<.001$). In the patients treated with rimonabant 20 mg/day, 32% of the patients lost more than 10% of their body weight compared to only 10.9% in the placebo group ($P<.001$). In addition, waist circumference decreased by 5.7 cm in those treated with 20 mg/day of rimonabant compared to 1.8 cm in the placebo group. High-density lipoprotein cholesterol (HDL-C) increased by 22.6% and triglycerides decreased by 4.1% in the patients who completed 2 years of treatment with rimonabant 20 mg/day, compared to a reduction of 12.6% in HDL-C and an increase of 10% in triglyceride levels in the placebo group ($P<.001$). Patients treated with high doses of rimonabant were more sensitive to insulin than those in the placebo group ($P<.001$). After 1 year of treatment with rimonabant 20 mg/day, the 50% decrease in the number of pa-

tients who met the criteria for metabolic syndrome was maintained after 2 years, in contrast to placebo ($P<.001$). A significant reduction was also observed in small dense low-density lipoprotein cholesterol (LDL-C) particles compared to patients in the placebo group. The most common adverse events at high doses of rimonabant were gastrointestinal (nausea: 13.7% vs 5.2% with placebo; vomiting: 5.2% vs 1.6% with placebo; dizziness: 9.3% vs 5.2% with placebo; and diarrhea: 8.2% vs 4.6% with placebo). The discontinuation rate after 2 years was 13.1% at high doses of rimonabant, 10.9% at low doses, and 8.9% for placebo.

Conclusion. This study confirms the results of previous studies in which the addition of rimonabant at doses of 20 mg/day to a low-calorie diet increased weight loss and improved the lipid profile compared to placebo in obese patients. The drug also contributed to a decrease in the prevalence of different components of the metabolic syndrome and had a favorable adverse events profile.

ISCHEMIC HEART DISEASE

Clopidogrel in Acute Myocardial Infarction (CLARITY-TIMI 28 Study: Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28 Study)

Presented by Dr Marc Sabatine, Boston, USA

Background. A substantial number of patients who receive thrombolytic therapy for ST-segment elevation acute myocardial infarction either do not achieve adequate reperfusion or experience reocclusion of the infarct-related artery. This increases the risk of death and complications.

Methods. In this study, 3491 patients between 18 and 75 years old presenting with ST-segment elevation myocardial infarction within 12 hours of the onset of symptoms were randomized to receive clopidogrel (loading dose of 300 mg followed by 75 mg/day) or placebo. Patients were treated with a fibrinolytic agent, aspirin, and heparin (adjusted for body weight) when necessary. They were scheduled for coronary angiography between 48 and 192 hours after starting the study drug. The primary efficacy endpoint was a composite of occluded infarct-related artery (defined as TIMI flow 0 or 1) in the coronary angiograph, and incidence of death or recurrent infarction before the coronary angiograph.

Results. The primary endpoint of the study was reached in 21.7% of the patients in the placebo group and in 15.0% in the clopidogrel group, corresponding to an absolute reduction of 6.7% and a reduction in the relative risk of 36% with clopidogrel (95% CI, 24%-47%; $P<.001$). At 30 days, treatment with

clopidogrel reduced the risk of occurrence of the composite endpoint of cardiovascular death, recurrent myocardial infarction, or reinfarction leading to emergency revascularization by 20% (from 14.1% to 31.6%, $P=.03$). The incidence of major bleeding and intracranial hemorrhage was similar in both groups.

Conclusion. The addition of clopidogrel to aspirin and fibrinolytic therapy in patients aged up to 75 years old for treatment of ST-segment elevation myocardial infarction improves the patency rates of the infarct-related artery and reduces ischemic complications.

Clopidogrel in Acute Myocardial Infarction (COMMIT/CCS2: Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study)

Presented by Dr Zhenming Chen, Oxford, United Kingdom

Background. The effect of the addition of clopidogrel to other thrombolytic therapies used in myocardial infarction is not known, so a study to investigate this strategy was designed in collaboration between the Clinical Trials Unit of Oxford University (United Kingdom) and researchers of more than 1000 hospitals throughout China. The role of early administration of metoprolol in myocardial infarction was also investigated in the same study.

Methods. The study randomized 45 852 patients who had been transferred to hospital within 24 hours of onset of a myocardial infarction (defined as signs and symptoms indicative of ST-segment changes or left-bundle-branch block) to receive clopidogrel treatment (75 mg/day) or placebo. No age limit was imposed by the inclusion criteria, and all patients received 162 mg/day of aspirin. Patients who underwent primary angioplasty and those with a high risk of hemorrhage were excluded from the study. The primary endpoint was a composite of death, reinfarction, or stroke while in hospital.

Results. Twenty-six percent of the patients were older than 70 years, 67% of them presented within 12 hours of the onset of symptoms, and 49% received thrombolytic treatment. The remaining coadjutant treatments for infarction were those used in current practice—anticoagulants were being taken by 75% of the patients, and angiotensin converting enzyme inhibitors by 68%.

The primary endpoint of the study occurred in 10.1% of the patients in the placebo group and in 9.3% in the clopidogrel group, corresponding to a 9% reduction in relative risk in favor of clopidogrel ($P=.002$). The group treated with clopidogrel also showed a significant reduction in all-cause mortality (8.1% in the placebo group and 7.7% in the clopido-

grel group; 7% reduction in relative risk; $P=.03$) and in the incidence of reinfarction (2.4% in the placebo group vs 2.1% in the clopidogrel group; 13% reduction in relative risk; $P=.02$). No significant differences in incidence of major hemorrhages or strokes (whether hemorrhagic or some other type) were seen between the 2 groups.

The benefit from clopidogrel was already evident after 24 hours of follow-up, and in the subgroup analysis, it was similar regardless of whether the patients were older than 70 years or not and regardless of sex. The benefit was more apparent in patients who arrived at hospital sooner after onset, and did not depend on whether fibrinolytic therapy had been used.

Conclusion. In this study, administration of clopidogrel in addition to other thrombolytic treatments commonly used in myocardial infarction was associated with a decrease in the incidence of death and reinfarction, without causing an increase in the rate of hemorrhages or stroke.

Intravenous Metoprolol in Acute Myocardial Infarction (COMMIT/CCS2 Study: Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study)

Presented by Dr Rory Collins, Oxford, United Kingdom

Background. The net effect of beta-blocker treatment in myocardial infarction is not known. Although treatment seems to reduce the incidence of reinfarction and severe arrhythmia, cases of infarction with heart failure or hemodynamic instability might be aggravated. The objective of the COMMIT/CCS2 study, done jointly between investigators in China and the United Kingdom, was to investigate administration of clopidogrel to the same patients but with a different randomization.

Methods. A total of 45 852 patients who were transferred to hospital within 24 hours of onset of a myocardial infarction (defined by ST-segment changes or left-bundle-branch block in the electrocardiogram) were randomized to receive metoprolol (15 mg by intravenous route for 15 minutes followed by oral treatment at a dose of 200 mg/day) or matching placebo. Patients in shock and those with systolic blood pressure below 100 mm Hg, heart rate below 50 beats/min, or second or third degree atrioventricular block were excluded.

Fibrinolytic therapy was used in approximately half the patients, who accounted for 85% of those who arrived within 12 hours of onset of symptoms. The 2 primary endpoints of this study were all-cause mortality and a composite endpoint of death, reinfarction, ventricular fibrillation, or cardiac arrest in hospital or

within 4 weeks of randomization. Follow-up corresponded to the time spent in hospital—mean follow-up time was 16 days.

Results. Metoprolol showed no appreciable effects on either of the primary endpoints (mortality was 7.8% with placebo and 7.7% with metoprolol; $P>.1$; the composite endpoint was reached in 9.9% of patients on placebo and 9.5% of those treated with metoprolol; $P>.1$). A significant reduction was seen in the risk of reinfarction (2.5% with placebo vs 2.0% with metoprolol; $P=.002$) and ventricular fibrillation (absolute reduction of 6 cases per 1000 treated; $P<.001$). However, the risk of cardiogenic shock increased by 11 cases per 1000 patients treated ($P<.00001$).

Conclusion. In this study, early administration of metoprolol to patients who arrived at hospital within 24 hours of myocardial infarction was not associated with a significant benefit in terms of decreased mortality or incidence of a composite set of major cardiac events. The significant reduction in the rate of reinfarction and ventricular fibrillation episodes associated with metoprolol was compensated by an increase in the incidence of cardiogenic shock. Future studies should investigate whether certain subgroups of patients with myocardial infarction might benefit from the advantages of beta-blockers without an increase in adverse events. Further studies should also clarify whether administration of the beta-blockers later after infarction can avoid the undesired effects observed in this study.

Metalloproteinase Inhibitors in Infarction (PREMIER Study: PREvention of MI Early Remodeling)

Presented by Dr Douglas Weaver, Detroit, USA

Background. Ventricular remodeling after myocardial infarction is accompanied by an increased ventricular volume that is associated with the development of heart failure, serious arrhythmias, and greater mortality. Metalloproteinases (MP) play a fundamental part in remodeling, and MP inhibitors have been shown to reduce remodeling in animal studies. This pilot study was designed to evaluate whether the metalloproteinase inhibitor PG-116800 could reduce postinfarction remodeling of the myocardium in humans.

Methods. In total, 250 patients with ST-segment elevation myocardial infarction were randomized to receive PG-116800 or placebo 48 hours after undergoing a reperfusion intervention (90% by percutaneous coronary intervention, and 5% by thrombolytic therapy). An echocardiogram was done at baseline and 90 days postinfarction. The primary study endpoint was

change in ventricular end-diastolic volume at 90 days postinfarction.

Results. No differences were seen between the 2 groups for the primary study endpoints or for clinical events observed during follow-up. The extent of remodeling showed large variations among individuals—60% of the patients had ventricular dilation whereas 8% had a decrease in volume with respect to baseline. The study drug was generally well tolerated, and did not cause any significant bone or muscular side effects (which have been described for other MP inhibitors) but was associated with mild arthralgia and gastrointestinal upsets.

Conclusion. Administration of MP PG-116800 in this study did not reduce the extent of postinfarction ventricular remodeling or clinical events associated with this process. Given the encouraging results in previous animal experiments and the good clinical tolerance observed, further studies would be appropriate, either in a population at higher risk of clinical events or at higher doses.

Late “Primary” Angioplasty in Acute Myocardial Infarction (BRAVE-2 Study: Beyond 12 Hours Reperfusion Alternative Evaluation Study)

Presented by Dr Adnan Kastrati, Munich, Germany

Background. A high percentage of patients with myocardial infarction present to the emergency room more than 12 hours after the onset of symptoms. Previous studies have shown that use of thrombolytics after this time is of limited or no benefit, and so these drugs are not recommended. However, the usefulness of percutaneous coronary intervention in this situation has not been assessed in randomized studies.

Methods. Patients with myocardial infarction (defined as a chest pain lasting more than 20 minutes with ST-segment elevation or new Q-waves) who presented between 12 and 24 hours after onset were enrolled. Medical treatment included clopidogrel (300-600 mg), aspirin (500 mg), and heparin (70 U/kg). After receiving this medication, patients were randomized to receive invasive treatment (coronary angiography with or without percutaneous coronary intervention and abciximab) or conventional medical treatment. Revascularized patients received 75 mg/day of clopidogrel for at least 1 month and 200-325 mg/day of aspirin indefinitely. The primary study endpoint was infarct size measured by technetium sestamibi scintigraphy (SPECT) at 5 to 10 days after randomization. The secondary endpoint was a composite of all-cause death, reinfarction, or stroke within 30 days of randomization.

Results. The population comprised 365 randomized patients with a mean baseline ejection fraction

of 50%. The infarct-related artery was the left anterior descending coronary artery in 38%. In the invasive treatment arm, the infarct-related artery was completely occluded in 57% of the patients who underwent coronary angiography. After the procedure, done 1.5 h after randomization, 87% of the patients had normal coronary blood flow (TIMI 3); 87% of the patients received a stent. The primary endpoint (infarct size, expressed as a percentage of left-ventricular size) was significantly lower in the invasive arm (8% vs 13% in the medical treatment arm; $P < .0002$). The rates of death and/or reinfarction were similar for both groups, and the secondary composite endpoint also showed no differences at 30 days. Percutaneous coronary intervention was done in 33% of the patients assigned to conservative treatment, generally because of recurrent ischemia, hemodynamic instability, severe heart failure, or mechanical complications.

Conclusion. Early percutaneous coronary intervention in patients who arrive at hospital more than 12 hours after the onset of the infarction can reduce infarct size. This improvement did not translate into a significant reduction in short-term cardiovascular events, but the findings of this study nevertheless suggest that an invasive intervention is a valid alternative to medical treatment of patients who arrive late at the emergency room after myocardial infarction.

PERCUTANEOUS CORONARY INTERVENTION

Comparison of Paclitaxel-Eluting Stent and Sirolimus-Eluting Stent in the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease (ISAR-DIABETES Study: Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease)

Presented by Dr Adnan Kastrati, Munich, Germany

Background. Diabetic patients are at higher risk of cardiovascular disease and, moreover, are at higher risk of restenosis and thrombotic events after angioplasty than nondiabetic patients. Both sirolimus-eluting stents (Cypher) and the paclitaxel-eluting stents (Taxus) have been shown to be effective at reducing restenosis, but it is not clear whether there are differences between the 2 when used in a high-risk population such as diabetic patients.

Methods. The ISAR-DIABETES study was designed as a "noninferiority" study, whose hypothesis

was that the Taxus stent would be less effective than Cypher at preventing restenosis in diabetic patients. Diabetic patients with angina pectoris and/or positive stress test in the presence of lesions of more than 50% in a native coronary artery were included in the study. The prospectively defined criterion of noninferiority was that the margin of difference in late lumen loss between the 2 groups should be less than 0.16 mm. The investigators chose angiographic restenosis at 6 months, binary (yes/no) restenosis, and need for new revascularization of a target lesion as secondary study endpoints.

Results. Two-hundred-and-fifty patients were randomized to receive Taxus or Cypher stents. The clinical and angiographic characteristics of the patients were similar. Most patients (71% in the Taxus group vs 63% in the Cypher group) did not require insulin treatment to control their diabetes.

After 9 months of follow-up, there were no differences in the incidence of death (4.8% in the Taxus group vs 3.2% in the Cypher group, $P = \text{NS}$) or myocardial infarction (2.4% in the Taxus group vs 4.0% in the Cypher group, $P = \text{NS}$). However, the primary study endpoint, late lumen loss, was greater with the Taxus stent measured both in-segment (0.67 mm in the Taxus group vs 0.43 mm in the Cypher group; $P = .002$) and in-stent (0.45 mm in the Taxus group vs 0.19 mm in the Cypher group; $P = .001$). The rate of angiographic restenosis was significantly greater in the Taxus arm (16.5% vs 6.9% in the Cypher group; $P = .03$), but there were no differences in need for revascularization of the target lesion (12% vs 6.4%; $P = .13$).

Conclusion. The stents assessed in this study reduced the risk of restenosis compared to previous studies of bare-metal stents in diabetic patients. The sirolimus-eluting stent (Cypher) was more effective than the taxol-eluting stent (Taxus) at preventing restenosis in diabetic patients.

Paclitaxel-Eluting Stents Versus Sirolimus-Eluting Stents in Unselected Lesions (SIRTAX Study: Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization)

Presented by Dr Stephan Windecker, Bern, Switzerland

Background. It is not proven whether clinical efficacy differs between sirolimus-eluting stents (Cypher) and Taxol-eluting stents in the treatment of patients with coronary artery lesions not selected according to clinical considerations or anatomical characteristics of the lesions such as site, complexity or length. Therefore, the SIRTAX study aimed to extend our knowledge of the 2 types of stent, investigating whether

sirolimus-eluting stents achieved a greater reduction in the incidence of major cardiac events compared to Taxol-eluting stents.

Methods. The study randomized 1012 patients with stent-treatable coronary artery disease to undergo placement of one of the 2 types of drug-eluting stent. No limitations were imposed by site, number, complexity, or length of lesions. A subgroup of 600 patients was prospectively established to undergo angiographic follow-up at 8 months. The main endpoint of the study was major cardiac events, including cardiac death, myocardial infarction, and target lesion revascularization. The study was done in a single center without external economic support. The patients received unfractionated heparin during the procedure and aspirin and clopidogrel as thrombolytic therapies during follow-up.

Results. A total of 1401 lesions were treated in 1012 patients, with an average of 1.2 stents per target lesion. The clinical and angiographic characteristics of the patients and target lesions were similar in both groups. In total, 49% of the patients had stable angina, whereas the remaining 51% underwent treatment for acute coronary syndrome. Overall, 22% of the patients treated had ST-segment elevation myocardial infarction. The percutaneous coronary intervention was successful in 99% of the patients. The incidence of major cardiac events included in the primary endpoint of the study was lower in the group who received sirolimus-eluting stents than in the group who received Taxol-eluting stents (6.2% vs 10.8%; RR=1.8; 95% CI, 1.16-2.8; $P=.009$). The incidence of individual components of the primary outcome measure at 9 months was as follows: cardiac death (1% with Cypher vs 2.2% with Taxus; $P=NS$), myocardial infarction (2.8% vs 3.5%; $P=.148$), and target lesion revascularization (4.8% vs 8.3%; RR=1.77; $P=.025$). The secondary endpoint of target vessel failure occurred in 7.0% of the patients in the group treated with sirolimus-eluting stents compared to 11.6% in the other group ($P=.012$). There were no differences in the incidence of stent thrombosis (2.0% with Cypher vs 1.6% with Taxus). In the subgroup analysis, the benefit of treatment with the sirolimus-eluting stent was particularly notable among diabetic patients (RR=3.27; $P=.013$) compared to nondiabetic patients (RR=1.51; $P=.11$). Late lumen loss during follow-up of the prospectively defined subgroup was lower in the Cypher group than in the Taxus group measured both in-segment (0.19 vs 0.32; $P=.001$) and in-stent (0.13 vs 0.25; $P<.001$) segments. Likewise, restenosis according to the binary definition was lower in the group treated with sirolimus-eluting stents (6.7% vs 11.9% for the in-segment measurement; $P=.02$, and 3.2% vs 7.6% in the in-stent measurement; $P=.013$).

Conclusion. In this study, which included patients with no limitations on the coronary lesions, the sirolimus-eluting stent was associated with a lower number of major cardiac events after 9 months. Most of this difference was due to a lower rate of revascularization of the target lesion. This type of stent also had a lower incidence of infarction.

Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent in Unselected Lesions (REALITY Study: Prospective, Randomized, Multicentre Head-to-Head Comparison of Cypher and Taxus Stent Systems)

Presented by Dr Marie-Claude Morice, Massy, France

Background. The objective of this study was to compare sirolimus-eluting stents with Taxol-eluting stents in the treatment of unselected *de novo* coronary artery lesions.

Methods. A total of 1353 patients with *de novo* coronary artery lesions were randomized to placement of one of the 2 types of drug-eluting stent. Direct stent placement and treatment of ostial and bifurcation lesions were allowed. All patients underwent angiography after 8 months of follow-up.

Results. In the study, 1911 lesions in 1353 patients were treated, with an average of 1.94 stents per patient. The clinical and angiographic characteristics of the patients and the target lesions were similar in the 2 groups. Diabetic patients accounted for 28% of the total population. The target lesions were relatively complex—86.4% of the lesions were type BII or C, 27.6% of them were longer than 20 mm, and 5.2% were bifurcation lesions. The initial procedure was successful in 95% of the cases in both groups. In the angiographic followup at 8 months, patients who received sirolimus-eluting stents had a greater minimal lumen diameter (2.0 mm vs 1.85 mm), lower late lumen loss (0.09 mm vs 0.31 mm), and a lower percentage of patients with stenosis (23.1% vs 26.7%). All comparisons were significant ($P<.0001$). However, the primary endpoint, binary restenosis, showed no differences (9.6% with the sirolimus-eluting stent and 11.1% with the paclitaxel-eluting stent; $P=.32$). At 8 months of follow-up, the incidence of major cardiac events did not differ between groups (9.2% in the group treated with sirolimus-eluting stents vs 10.6% in the group treated with the paclitaxel-eluting stent; $P=.41$). The incidences of the individual components of the primary endpoint were as follows: cardiac death—1.8% with Cypher vs 1.2% with Taxus ($P=.50$); myocardial infarction—4.8% vs 5.5%, respectively ($P=.62$); and revascularization of the target lesion—5.0% vs 5.4%, respectively ($P=.81$). The

incidence of stent thrombosis after 30 days was greater in the paclitaxel group (1.8% with Taxus vs 0.4% with Cypher; $P=.0196$ in the analysis by stent used, and 1.6% with Taxus vs 0.6% with Cypher; $P=.0723$ in the intention-to-treat analysis).

Conclusion. In patients with de novo coronary artery lesions, the sirolimus-eluting stent was not associated with a greater incidence of binary restenosis at 8 months when compared with the paclitaxel-eluting stent.

Sirolimus-Eluting Stents in Multivessel Disease Susceptible to Bypass Surgery (ARTS II Study: Arterial Revascularization Therapies Study Part II. Sirolimus-Eluting Stents Versus PCI and CABG at 1 Year)

Presented by Dr Patrick Serruys, Rotterdam, Netherlands

Background. The aim of this study was to compare the results of sirolimus-eluting stents in patients with multivessel coronary artery disease with the results of the 2 techniques assessed in the preceding ARTS I study (coronary artery bypass graft in 605 patients and coronary angioplasty with bare-metal stents in 600 patients).

Methods. The registry was conducted to collect the endpoints from a single group of patients treated with sirolimus-eluting stents. The primary study endpoint was a composite of all-cause mortality, cerebrovascular accident, myocardial infarction, and any type of repeat intervention for coronary revascularization. Patients could be included if they had findings of myocardial ischemia and lesions in at least 2 main vessels, including the left anterior descending artery. For better matching with the population of the ARTS I study, patients were stratified such that the mean number of diseased vessels was 2.7.

Results. A higher prevalence of diabetes, hypertension, and hypercholesterolemia was found in the 607 patients included in this registry than in those of the ARTS I study, but fewer patients were smokers. The number of lesions per patient was greater in this registry (3.6 vs 2.8 in the 2 arms of the ARTS I study), and the average number of stents used in each patient was 3.7 ± 1.5 compared to 2.8 ± 1.3 bare-metal stents in the PCI arm of ARTS I. Patients in the ARTS II study had more complex lesions, but the procedure duration and length of stay in hospital were shorter than in the 2 arms of the ARTS I study.

Subacute stent occlusion rates at 30 days were lower in the ARTS II study compared to bare-metal stent arm of the ARTS I study (0.8 vs 2.8%; $P=.009$). Mortality, stroke, and myocardial infarction at 30 days were very low in the ARTS II registry, and the incidence of

major events, including revascularization, at 30 days was 3.1%.

After 1 year of follow-up, only 1 additional case of late stent occlusion occurred, giving a total incidence of 1.1%. Furthermore, the rate of death/stroke/myocardial infarction at 1 year of follow-up was significantly less than in the 2 arms of the ARTS I registry ($P<.001$ for comparison with the bypass surgery group). Patients in the ARTS II registry always compared favorably with patients from the bare-metal stent group of the ARTS I registry in the breakdown by the individual components of the composite endpoint. No significant differences were found in the primary composite endpoint in the comparison of the endpoints at 1 year for the bypass surgery group of the ARTS I registry and the patients of the ARTS II registry (11.6% with bypass surgery vs 10.4% in the ARTS II; $P=.46$). This is due to the greater number of revascularization procedures in the ARTS II registry (8.5% vs 4.1%; $P=.003$). The incidence of the remaining events (death/stroke/myocardial infarction) was lower in the patients of the ARTS II registry than in the bypass surgery group of the ARTS I registry.

Conclusion. The use of sirolimus-eluting stents for revascularization of patients with multivessel disease showed clear advantages over use of bare-metal stents in terms of short and long-term clinical events. The findings from this registry with drug-eluting stents are not inferior to those obtained for bypass surgery group in the ARTS I registry, which included patients with more favorable baseline characteristics.

Paclitaxel-Eluting Stent in Complex Lesions (TAXUS-V De Novo Study: Clinical and Angiographic Results of the Taxus Stent in Complex Lesions)

Presented by Dr Gregg Stone, New York, USA

Background. As part of the TAXUS series of clinical studies to assess the safety and efficacy of paclitaxel-eluting stents, this study compared this drug-eluting stent with a bare-metal stent in the treatment of complex de novo lesions, defined as those measuring 10 to 46 mm in length in vessels 2.25 to 4.0 mm in diameter.

Methods. In this double-blind study, 1172 patients with complex de novo coronary artery lesions were randomized to treatment with Taxus stents or bare-metal stents. The primary study endpoint was target vessel revascularization at 9 months of follow-up. A prospectively defined subgroup analysis was performed by stent size, and by whether patients had overlapping stents. Analysis was by intention-to-treat.

Results. The complexity of the lesions is reflected by their mean length (17±9 mm), the small vessel diameter (2.69 mm), and the fact that more than 75% of the lesions were type BII-C and that 30% of the patients had diabetes. Baseline and lesion characteristics were similar in both groups. At 30 days, major cardiac events showed no significant differences between groups, although, at 9 months, the rates of target vessel revascularization (12.1% vs 17.3%; $P=.018$) and of major cardiac events (15.0% vs 21.2%; $P=.008$) were significantly lower in the Taxus stent arm. Stent thrombosis occurred in 4 patients in each subgroup of the study (0.7%). In-stent late lumen loss (0.49 ± 0.61 mm vs 0.9 ± 0.62 mm; $P<.0001$) and binary restenosis rates (18.9% vs 33.9%; $P=.0001$) were significantly lower in the Taxus group. In the subgroup analysis, differences in favor of the Taxus group were particularly marked among patients who received multiple stents.

Conclusion. For very complex lesions, Taxus stents provided better clinical and angiographic endpoints than conventional bare-metal stents in the overall population and the different subgroups analyzed. The results for taxus stents are worse than those previously obtained in studies that included less complex lesions.

Comparison of 2 Loading Doses of Clopidogrel Before Percutaneous Coronary Intervention (ARMYDA-2 Study: Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty Study)

Presented by Dr Germano Di Sciascio, Rome, Italy

Background. Aggressive inhibition of platelet function is crucial to help reduce myocardial damage and the incidence of early cardiac complications after percutaneous coronary intervention. The findings of observational studies suggest that pretreatment with a high loading dose of clopidogrel can be more effective than conventional doses, but this has not been assessed in a randomized study.

Methods. A total of 255 patients awaiting elective percutaneous coronary intervention were randomized to receive a loading dose of 600 mg or 300 mg of clopidogrel, administered 4 to 8 hours before the intervention and 8 and 24 hours afterwards. The primary endpoint was the incidence of death, myocardial infarction, and target vessel revascularization at 30 days postintervention.

Results. The primary endpoint was reached in 4% of patients treated with the 600 mg loading dose of clopidogrel, compared to in 12% of the patients in the group who received the conventional loading dose ($P=.041$), the difference being due entirely to

periprocedural infarctions. Peak levels of myocardial necrosis markers were significantly lower in the high loading dose group ($P\leq.038$). Adverse events were similar in both arms of the study. Multivariate analysis showed that the loading dose of 600 mg was associated with a 50% reduction in the incidence of myocardial infarction (RR=0.48; 95% CI, 0.15-0.97; $P=.044$). Additional benefit (risk reduction of 80%) was observed in patients randomized to the 600 mg loading dose of clopidogrel who received statin treatment.

Conclusion. Treatment with a 600 mg loading dose of clopidogrel administered 4 to 8 hours before percutaneous coronary intervention is a safe method which significantly reduces the incidence of myocardial infarction associated with the procedure compared to the conventional dose of 300 mg. These findings might lead to changes in routine antiplatelet treatment regimens currently administered before percutaneous coronary intervention.

HEART FAILURE

Cardiac Resynchronization in Heart Failure (CARE-HF Study: Cardiac Resynchronization Heart Failure Study)

Presented by Dr John G. Cleland, Kingston, United Kingdom

Background. Cardiac resynchronization ameliorates symptoms and improves left ventricular function in many patients with heart failure due to left-ventricular systolic dysfunction and dyssynchrony. In this study, we assess the effects of cardiac resynchronization on morbidity and mortality.

Methods. Patients with heart failure due to left-ventricular systolic dysfunction and cardiac dyssynchrony were randomized to receive medical treatment alone or accompanied by cardiac resynchronization. All patients were in New York Heart Association functional class III or IV, and they were receiving standard treatment for heart failure. The primary endpoint was time-to-death of any cause or unplanned hospitalization for a major cardiovascular event. The most important secondary endpoint was all-cause mortality.

Results. A total of 813 patients were included in the study. They were followed for a mean of 29.4 months. The primary endpoint was reached by 159 patients in the cardiac resynchronization group, compared to 224 patients in the medical treatment group (39% vs 55%, respectively; RR=0.63; 95% confidence interval [CI], 0.51-0.77; $P<.001$). Eighty-two deaths occurred in the cardiac resynchronization group compared to 120 in the medical treatment group (20% vs 30%; RR=0.64; 95% CI, 0.48-0.85; $P<.002$). Compared to medical

treatment, cardiac resynchronization shortened inter-ventricular mechanical delay and reduced end-diastolic volume and the mitral regurgitation area, but increased the left ventricular ejection fraction and improved functional class and quality of life ($P < .01$ for all cases).

Conclusions. Cardiac resynchronization improves functional class and quality of life, and reduces complications and risk of death in patients with advanced heart failure and dyssynchrony. These benefits are additive with those provided by standard pharmacological treatment. Placement of cardiac resynchronization devices should be routinely considered in the treatment of these patients.

Tezosentan in Acute Heart Failure (VERITAS: Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Studies)

Presented by Dr John Teerlink, San Francisco, USA, and Dr John Mc Murray, Glasgow, United Kingdom

Background. Previous studies have failed to demonstrate that administration of tezosentan, an endothelin-1 receptor inhibitor, to patients with acute heart failure is accompanied by significant clinical or hemodynamic improvement. The objective of this study was to definitively assess the role of tezosentan in the treatment of these patients.

Methods. The VERITAS program comprised 2 parallel clinical trials, and pooled data from both were presented. The studies randomized 1435 patients with acute heart failure to receive placebo ($n=708$) or tezosentan ($n=727$), with an initial loading dose of 2.5 mg in 30 minutes followed by perfusion at 1 mg/h for 24 to 72 hours. Randomization was stratified according to whether right-heart catheterization was done.

Results. The baseline characteristics of the patients were similar in both groups. The mean ejection fraction was 29%, and 68% of the patients had ischemic heart disease. Intravenous diuretics were being taken by 99%, angiotensin antagonists by 62%, and beta-blockers by 42%. The study was interrupted by the Data and Safety Monitoring Board due to lack of beneficial effect when 75% of the planned number of patients had been recruited. The investigators found no differences in the degree of dyspnea after 24 hours of treatment or in the composite endpoint of death and worsening heart failure after 7 days (26.4% with placebo and 26.3% with tezosentan; $P=.95$). Likewise, after 30 days, no differences were seen in the composite endpoint (33.2% with placebo and 31.9% with tezosentan; $P=.61$). Major adverse events were reported in

42.4% of the patients on placebo and in 20.4% of those in the tezosentan arm ($P=.95$). Hemodynamic parameters improved in the tezosentan group, with a decrease in systolic blood pressure of 6 mm Hg compared to placebo and some improvement in the cardiac index after 72 hours. There was no difference in survival between the 2 groups at 6 months.

Conclusion. In the study population of patients with acute heart failure, treatment with tezosentan did not improve dyspnea at 24 hours or the composite endpoint of death and worsening heart failure at 7 days. Although no increase in adverse events was observed, the study was terminated early in view of the lack of effect. The absence of clinical improvement occurred despite significant improvements in hemodynamic parameters such as systolic blood pressure and the cardiac index.

Continuous Monitoring of Pulmonary Artery Pressure in the Management of Heart Failure (COMPASS-HF Study: Chronicle Offers Management to Patients with Advanced Symptoms and Signs of Heart Failure)

Presented by Dr Robert Bourge, Birmingham, USA

Background. The Chronicle system is an implantable device to continuously measure intracardiac pressure. The device comprises a monitor the size of a pacemaker and a lead with a pressure-sensor placed in the right ventricular outflow tract such that the device can permanently record and store hemodynamic information and transmit it intermittently to a network for review by the treating physicians. The system is implanted in a similar way to a pacemaker. The COMPASS-HF study was designed to assess the possible benefit of the system in patients with heart failure.

Methods. In the study, 274 patients with chronic heart failure (New York Heart Association functional class III-IV) were randomized. The device was implanted in all patients, who then received medical treatment according to conventional standards or guided with data provided by the Chronicle system. Treating physicians had full access to the data collected by the system in the first group of patients, but could not consult these data in the control group. The primary endpoint of the study was a composite of major cardiac events requiring hospitalization or visits to the emergency room at 6 months of follow-up.

Results. In the group of patients whose clinical management was guided by information from the device, the RR decreased by 22% for major cardiac events ($P=.27$). The risk of hospitalization decreased by 21% and there was a 33% reduction in the per-

centage of patients with worsening heart failure ($P=.03$). Among patients in functional class III, who formed the biggest subgroup by functional class (85% of the total population), the number of events related to heart failure decreased by 41% ($P=.03$). No significant adverse events due to implantation of the device were reported.

Conclusion. The use of a device to continuously monitor intracardiac pressure led to a decrease in the number of admissions to hospital and the number of patients with worsening functional class in a population with chronic advanced heart disease, particularly among those in functional class III.

HYPERTENSION

New Agents for Lowering Blood Pressure Compared to Traditional Ones in the Treatment of Hypertension (ASCOT-BPLA: Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm)

Presented by Dr Björn Dahlöf, Gotheborg, Sweden, and Peter S. Sever, London, United Kingdom

Background. The objective of the hypotensor treatment arm of the ASCOT study was to evaluate whether hypertension treatment with calcium antagonist with or without an angiotensin converting enzyme (ACE) inhibitor was more effective than traditional treatment with a beta-blocker with or without a diuretic to prevent ischemic heart disease in hypertense patients with relatively low levels of cholesterol. Additionally, the study evaluated whether use of a statin could further reduce the incidence of ischemic heart disease in this population, when compared to the effect due to placebo.

Methods. The blinded study had a 2×2 factorial design, in which 19 257 patients were randomized to 4 groups defined as “modern” treatment (amlodipine with or without perindopril) or “traditional” treatment (atenolol with or without bendroflumethiazide) for high blood pressure, and the use of statins versus placebo. According to one of the inclusion criteria, patients had to have untreated systolic blood pressure greater than 160 mm Hg and untreated diastolic blood pressure of greater than 100 mm Hg or greater than 140/90 mm Hg if treated at baseline. Furthermore, total cholesterol had to be below 250 mg/dL, and triglycerides below 400 mg/dL. No patient had a history of ischemic heart disease on enrollment. The primary endpoint was mortality due to ischemic heart disease or nonfatal myocardial infarction. Secondary endpoints included total mortality and major cardiovascular events. Follow-up lasted a mean of 5.4 years.

Results. The findings were presented as preliminary, pending complete data collection which was expected for May 2005. For patients randomized to receive atenolol, 73% of the patients stayed on the medication; for thiazide, 67% did so; for amlodipine, 78% did so; and for perindopril, 63% did so. Systolic blood pressure at the end of the study was slightly lower in the amlodipine/perindopril arm (135.5 mm Hg vs 136.3 mm Hg). The study was terminated early by the Data and Safety Monitoring Board because of differences in efficacy and adverse events between the 2 treatment arms. A nonsignificant reduction in the primary endpoint of the study was observed in the amlodipine/perindopril group (HR with respect to “traditional” treatment, 0.90; 95% confidence interval [CI], 0.78-1.03; $P=.12$). However, several adverse effects of treatment, which had been initially defined as secondary endpoints, occurred significantly less often in the amlodipine/perindopril group, including all-cause mortality (hazard ratio [HR]=0.86; 95% CI, 0.78-0.96; $P=.005$), overall coronary events (HR, 0.86; $P=.0048$), complications and cardiovascular procedures in general (HR, 0.84; $P=.0001$), cerebrovascular accident (RR=0.77; $P=.0007$), and cardiovascular mortality (HR=0.76; $P=.0017$). In addition, the appearance of newly diagnosed diabetes mellitus was lower in the amlodipine/perindopril group (HR=0.68; $P=.0048$).

Conclusion. In the study population—hypertense patients with relatively low levels of cholesterol—the approach of starting treatment with amlodipine and adding perindopril when necessary was associated with a lower incidence of multiple secondary endpoints, including all-cause mortality, when compared with a strategy based on initial treatment with atenolol, to which thiazide was added as necessary. This led to early termination of the study to allow a change in antihypertensive treatment in patients randomized to the “traditional” treatment group.

CELL THERAPY STUDIES

Study of the University of Leuven

Presented by Dr Stefan Janssens, Leuven, Belgium

This randomized study is the only one of its type. The study compared intracoronary transplantation of bone marrow cells (BMC) with placebo in patients with acute myocardial infarction with ST-segment elevation greater than or equal to 6 mm who had been symptomatic for at least 2 hours. For all patients, primary angioplasty was successfully completed and BMC could be obtained. Twenty-four hours later, BMC or placebo were infused into the heart by intracoronary route under a double blind.

After 4 months of follow-up, the authors found no differences from baseline for ejection fraction, whereas significant differences were reported for decrease in the left ventricular mass index or infarct size. The beneficial effect of treatment on patients who received BMC was greater in those who underwent primary angioplasty within 6 hours of infarction and in those with larger infarct sizes. Notably, the decrease in infarct size was associated with a smaller loss of end-diastolic thickness of the ventricular wall. This may have implications in the prevention of subsequent ventricular remodeling. The adverse effects of treatment were similar in both groups; 6 patients in the BMC group had supraventricular tachycardias compared to 5 in the placebo group. All 3 cases of ventricular tachycardia occurred in the placebo group. In conclusion, intracoronary treatment of the reperfused myocardium after percutaneous coronary intervention within 6 hours of infarction with autologous BMC seems to reduce infarct size but does not improve left-ventricular systolic function. The technique showed an excellent safety profile.

Arizona Heart Institute Study

Presented by Dr Nabil Dib, Phoenix, USA

Autologous myoblasts were implanted by direct injection during coronary artery bypass surgery in 24 patients with substantial ventricular dysfunction—all had a left ventricular ejection fraction (LVEF) of less than 40%, and half had LVEF less than 30%. Mean follow-up lasted 11 to 45 months. After 1 year, patients showed significant improvement in New York Heart Association functional class, but after 2 years, the improvement was no longer apparent. Significant increases in LVEF were reported after 1 year and 2 years of follow-up, and end-diastolic volume also decreased. Positron emission tomography done at baseline and after 6 months showed an increase in myocardial viability. The authors concluded that isolation and subsequent injection and expansion of autologous myoblasts in the myocardium are technically feasible and safe, and could increase the extent of viable myocardium.

BioHEART-Thoraxcenter Study

Presented by Dr Patrick Serruys, Rotterdam, Netherlands

The study included 15 patients with chronic heart failure and a 4 to 6-year history of myocardial infarction. Patients received a percutaneous endocardial injection under fluoroscopic guidance of autologous skeletal myoblasts at regions of myocardial

scarring. One of the first 6 patients included in the study died and a further 2 presented ventricular tachycardia, which prompted the Data and Safety Monitoring Board to recommend inclusion of patients with a cardioverter defibrillator. Such patients were originally excluded by the study protocol. Additionally, the board advised defibrillator placement in patients already included. After 12 months of follow-up, 2 patients had died, both within 2 weeks of the procedure. Of the remaining patients, all of whom had defibrillators, 3 had ventricular arrhythmias that triggered defibrillation. The wall motion score index at rest in surviving patients improved slightly and significantly with respect to baseline. However, parameters such as left ventricular ejection fraction and end-diastolic volume showed no differences after 1 year of follow-up.

The authors concluded that injection of skeletal myoblasts as a stand-alone technique is feasible, and that the findings of this pilot study were favorable for potential efficacy. The technique should be investigated in randomized trials with a larger number of patients under close surveillance to detect and treat potentially serious arrhythmias.

HEART SURGERY

Study of the Complications of the Cyclooxygenase 2 Inhibitors Parecoxib and Valdecoxib After Heart Surgery (COX-2 Inhibitors After Cardiac Surgery)

Presented by Dr Andrew A. Whelton, Baltimore, USA

Background. Valdecoxib and its intravenous pro-drug, parecoxib, are used for treating postoperative pain, but their use after coronary artery bypass grafting may involve risk of adverse events. A randomized study was performed to assess the safety of these drugs after coronary artery bypass grafting.

Methods. In this randomized, double-blind study with 10 days of treatment and 30 days of follow-up, 1671 patients were randomized to receive intravenous parecoxib for at least 3 days, followed by oral valdecoxib until Day 10, or intravenous placebo followed by oral valdecoxib or placebo for 10 days. All patients could use their normal opiate analgesics as needed. The primary endpoint was frequency of predefined adverse events, including cardiovascular events, renal impairment or failure, gastroduodenal ulcer, or surgical wound-healing complications.

Results. Compared to the placebo-only group, both the parecoxib plus valdecoxib and the placebo plus valdecoxib groups have a higher percentage of patients with at least one adverse event confirmed as drug-related (7.4% for these 2 groups vs 4% in the

placebo-only group; relative risk [RR] for each of the comparisons, 1.9; 95% confidence interval [CI], 1.1-3.2; $P=.02$ for both comparisons with placebo-only group). Cardiovascular events in particular (including myocardial infarction, cardiac arrest, stroke, and pulmonary embolism) were more frequent in patients who received parecoxib and valdecoxib compared to those who received placebo (2.0% vs 0.5%; RR=3.7; 95% CI, 1.0-13.5; $P=.03$).

Conclusions. The use of parecoxib and valdecoxib after heart surgery is associated with an increase

in the incidence of cardiovascular events. This raises suspicions about the use of these drugs in such cases.

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