

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American College of Cardiology (Atlanta, GA, USA, March 14-16, 2010)

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Following its policy of disseminating scientific information to the cardiology community,¹⁻⁷ the *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Scientific Sessions of the American College of Cardiology 2010 in Atlanta (Georgia, USA), specifically, the *Late Breaking Clinical Trials*.

A summary of each selected study is presented, briefly outlining the objectives, methods, and results based on what was presented orally or simultaneously published in scientific journals in electronic format. Given that most of these studies have yet not been published in their final version, the information offered should be interpreted as preliminary.

SUMMARY BY TOPIC

Primary Prevention

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CABANA pilot study: catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation.

RACE II study: lenient heart-rate control versus strict control in patients with atrial fibrillation.

EXPLORE-Xa study: randomized clinical trial of 3 doses of betrixaban, a long-acting oral factor Xa inhibitor in patients with atrial fibrillation.

Cardiac Intervention

CILON-T study: cilostazol-based triple antiplatelet therapy for ischemic complications after drug-eluting stent implantation.

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5-year outcomes of the MAINCOMPARE registry: long-term efficacy and safety of coronary stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease.

DES-LATE study: duration of dual antiplatelet therapy after drug-eluting stent implantation.

Results of Trials on New Stents

ISAR-TEST-2 trial: angiographic results and intracoronary stenting. Efficacy trial of 3 drug-eluting stents.

SORT OUT III trial: efficacy and safety of zotarolimus-eluting stents and sirolimus-eluting stents in daily clinical practice: randomized superiority trial.

PERSEUS trial: first report on the PERSEUS randomized trial of a novel platinum-chromium thin-strut TAXUS stent versus the TAXUS Express stent in de novo coronary stenoses.

JETSTENT trial: comparison of AngioJet rheolytic thrombectomy before direct stenting to direct stenting alone in patients with acute myocardial infarction.

PASSION trial: paclitaxel-eluting stents compared to bare-metal stents for ST-segment elevation acute myocardial infarction. Follow-up at 5 years.

DEDICATION trial: drug-eluting stents compared to bare-metal stents in patients with ST-segment elevation acute myocardial infarction: 8-month follow-up in drug elution and distal protection in acute myocardial infarction.

PRIMARY PREVENTION

ACCORD lipid study⁹: Effects of combination lipid therapy in type 2 diabetes mellitus

Presented by Henry Ginsberg

Background. Combination therapy with a statin plus a fibrate was compared to statin monotherapy, to investigate whether it would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus (DM2) who were at a high risk of this disease.

Methods. A total of 5518 patients with DM2 who were under treatment with open-label simvastatin were randomized to receive masked fenofibrate or placebo. The primary endpoint was the first appearance of nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes. The mean follow-up time was 4.7 years.

Results. The annual rate of the primary endpoint was 2.2% in the fenofibrate group and 2.4% in the placebo group (fenofibrate group, hazard ratio

[HR] = 0.92; 95% confidence interval [CI], 0.79-1.08; $P=.32$). In addition, there were no significant differences between the 2 groups regarding secondary endpoints. The annual death rates were 1.5% in the fenofibrate group and 1.6% in the placebo group (HR=0.91; 95% CI, 0.75-1.1; $P=.33$). The prespecified subgroup analyses indicated heterogeneity in the treatment effect depending on sex, with a benefit for men and potential harm for women ($P=0.01$ for interaction), and a possible interaction according to lipid subgroup, with a potential benefit for patients with a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol ($P=0.057$ for interaction).

Conclusions. The combination of simvastatin and fenofibrate did not reduce the rates of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared to simvastatin alone. These results do not support the routine use of combination therapy with simvastatin and fenofibrate to reduce cardiovascular risk in most high-risk patients with DM2.

ACCORD BP study⁹: effects of intensive blood pressure control on type 2 diabetes mellitus

Presented by William Cushman

Background. Evidence from randomized trials does not support a strategy of lowering systolic blood pressure below 135 mmHg to 140 mmHg in patients with DM2. Therapy targeting normal systolic pressure (ie, <120 mmHg) was investigated to ascertain whether major cardiovascular events were reduced in participants with DM2 and at high risk of cardiovascular events.

Methods. A total of 4733 participants with DM2 were randomly assigned to intensive therapy or standard therapy, with the respective targets of systolic pressure <120 mmHg and systolic pressure <140 mmHg. The primary composite endpoint was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up time was 4.7 years.

Results. After 1 year, the mean systolic blood pressure was 119.3 mmHg in the intensive-therapy group and 133.5 mmHg in the standard-therapy group. The annual rate of the primary endpoint was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (intensive therapy, HR=0.88; 95% CI, 0.73-1.06; $P=.20$). The annual rates of all-cause death were 1.28% and 1.19%, respectively (HR=1.07; 95% CI, 0.85-1.35; $P=.55$). The annual rates of stroke, a prespecified secondary endpoint, were 0.32% and 0.53%, respectively (HR=0.59; 95% CI, 0.39-

0.89; $P=.01$). Severe adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and in 30 of the 2371 participants in the standard-therapy group (1.3%) ($P<.001$).

Conclusions. In the patients with DM2 and at high risk of cardiovascular events, obtaining a systolic blood pressure <120 mmHg compared to <140 mm Hg did not reduce the rate of the composite endpoint of fatal and nonfatal cardiovascular events.

NAVIGATOR Nateglinide study¹⁰: effect of nateglinide on the incidence of diabetes mellitus and cardiovascular events

Presented by Robert Califf

Background. The potential of short-acting insulin secretagogues to reduce the risk of DM and cardiovascular events in patients with impaired glucose tolerance remains unknown.

Methods. In a double-blind clinical trial, 9306 participants with glucose intolerance and cardiovascular disease or cardiovascular risk factors were randomly assigned to receive nateglinide (up to 60 mg 3 times a day) or placebo, using a 2×2 factorial design with valsartan or placebo, in addition to participation in a lifestyle modification program. Mean follow-up time was 5 years for incident DM (and a median of 6.5 years for vital status). The effect of nateglinide was assessed on 3 primary endpoints: *a*) the development of DM; *b*) a primary cardiovascular endpoint composed of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure; and *c*) an extended cardiovascular endpoint composed of the individual components of the primary composite cardiovascular endpoint, hospitalization for unstable angina, or arterial revascularization.

Results. After adjustment for multiple testing, nateglinide, compared to placebo, did not significantly reduce the cumulative incidence of DM—36% and 34%, respectively (HR=1.07; 95% CI, 1.00-1.15; $P=.05$)—the primary composite cardiovascular endpoint—7.9% and 8.3%, respectively; HR=0.94; 95% CI, 0.82-1.09; $P=.43$)—or the extended composite cardiovascular endpoint—14.2% and 15.2%, respectively; HR=0.93, 95% CI, 0.83-1.03; $P=.16$). However, nateglinide increased the risk of hypoglycemia.

Conclusions. Among patients with glucose intolerance and established cardiovascular disease or cardiovascular risk factors, treatment with nateglinide for 5 years did not reduce the incidence of DM or the primary composite cardiovascular endpoint.

NAVIGATOR Valsartan study¹¹: effect of valsartan on the incidence of diabetes mellitus and cardiovascular events

Presented by Robert Califf

Background. It remains unknown if renin-angiotensin system blockers reduce the risk of DM and cardiovascular events in patients with glucose intolerance.

Methods. In this double-blind clinical trial using a 2×2 factorial design, 9306 patients with glucose intolerance and established cardiovascular disease or cardiovascular risk factors were randomly assigned to receive valsartan (up to 160 mg/d) or placebo (and nateglinide or placebo), in addition to lifestyle modification. The median follow-up time was 5 years for the development of DM (6.5 years for vital status). The effects of valsartan were assessed on 3 primary endpoints: *a*) the development of DM; *b*) a composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, arterial revascularization or hospitalization for heart failure or for unstable angina; and *c*) an extended cardiovascular endpoint that excluded unstable angina and revascularization.

Results. The cumulative incidence of DM was 33.1% in the valsartan group compared to 36.8% in the placebo group (valsartan group, HR=0.86; 95% CI, 0.8-0.92; $P<.001$). Valsartan, compared to placebo, did not significantly reduce the incidence of the extended cardiovascular endpoint—14.5% vs 14.8% (HR=0.96; 95% CI, 0.86-1.07; $P=.43$)—or the primary cardiovascular endpoint—8.1% versus 8.1% (HR=0.99; 95% CI, 0.86-1.14; $P=.85$).

Conclusions. Among patients with glucose intolerance and cardiovascular disease or risk factors, the use of valsartan for 5 years combined with lifestyle modification, led to a relative reduction of 14% in the incidence of DM, but did not reduce the rate of cardiovascular events.

ISCHEMIC HEART DISEASE

The FIR collaboration trial¹²: long-term outcome of a routine invasive strategy versus a selective strategy in patients with non-ST elevation acute coronary syndrome: first metaanalysis of 5-year outcomes based on individual patient data

Presented by Keith A Fox

Background. The management strategy for patients with acute coronary syndrome with non-

ST-elevation myocardial infarction (NSTEMI) is a matter of strong debate. The ACC/AHA 2007 guidelines recommend early risk stratification with tools such as the TIMI or GRACE score and the possibility of an early invasive strategy for patients at high risk. Although the majority of trials support an early invasive strategy for patients at high risk, trials such as ICTUS support a selective invasive strategy. Furthermore, although an earlier metaanalysis of NSTEMI trials supported an early invasive strategy, data on long-term follow-up are scarce.

Methods. The present study is a combined analysis that uses individual patient data from the 3 NSTEMI trials with 5-year follow-up (FRISC-II, ICTUS, and RITA-3) to determine the long-term benefit of a routine invasive strategy vs a selective invasive strategy. The primary endpoint was cardiovascular death or nonfatal myocardial infarction, as defined in each trial. The patients were classified in 3 groups depending on their baseline risk as determined by Cox regression using predictors of the primary endpoint.

Results. The analysis included a total of 5467 patients from the 3 trials (FRISC-II, $n=2457$; ICTUS, $n=1810$, and RITA-3, $n=1200$). The mean age was 63 years and approximately 30% were women. At 5-year follow-up, the routine invasive therapy group had fewer primary endpoints—14.7% versus 17.9% (HR=0.81; 95% CI, 0.71-0.93; $P=.002$)—fewer myocardial infarctions—10% versus 12.9% (HR=0.77; 95% CI, 0.65-0.9; $P=.001$)—and a trend toward fewer cardiovascular deaths—6.8% versus 8.1% (HR=0.83; 95% CI, 0.68-1.01; $P=.068$)—than the selective invasive therapy group. There were no statistically significant differences in all-cause death between the routine invasive therapy group and the selective group—11.7% versus 10.6% (HR=0.9; 95% CI, 0.77-1.05; $P=.19$). Other independent predictors of the primary endpoint were age, DM, previous acute myocardial infarction, presentation with depressed ST-segment, hypertension, and a low or high body mass index. These variables were used to derive an integer-based risk scoring system to classify the patients into 3 risk groups: low (0-4), intermediate (5-8), and high (≥ 9). The effect of the treatment strategy (routine invasive therapy vs selective) on the primary endpoint was greatest among the patients at high risk (risk difference of 11%) compared with those at intermediate and low risk (risk difference of 3.8% and 2%). The Kaplan-Meier curve for cardiovascular death or myocardial infarction shows that the 2 treatment groups began to diverge in the first 3 months and remained separate at 5 years. It seems that the patients in the high-risk group are those who predominantly drive this effect.

Conclusions. At 5 years, a routine invasive strategy was associated with decreased cardiovascular death and myocardial infarction in patients with NSTEMI, particularly among those with a higher underlying risk.

HEART FAILURE

DOSE study¹³: evaluation of diuretic optimization strategies in acute heart failure

Presented by Gary Michael Felker

Background. Although intravenous diuretics (IV) are routinely used in clinical practice, the optimal dose and administration route remain uncertain. Furthermore, observational studies have demonstrated worsening creatinine and clinical outcomes with high-dose furosemide. Thus, the DOSE study assessed the safety and efficacy of different strategies for diuretic (furosemide) use in patients with acute decompensated heart failure (ADHF): *a*) administration route (Q12 bolus vs continuous infusion); and *b*) dosing ($\times 1$ oral dose [low intensification] vs $\times 2.5$ oral dose [high intensification].)

Methods. Using a 2×2 factorial design, the patients were randomized to Q12 h bolus versus continuous infusion or $\times 1$ oral dose furosemide (low intensification) versus $\times 2.5$ oral dose furosemide (high intensification). Some 48 hours after randomization, the patients could be changed over to oral diuretics, continued on the same strategy or undergo a 50% increase in dose, at the discretion of the physician. Concomitant medication: angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin-II receptor antagonists (ARA-II) (64%), beta-blockers (83%), aldosterone antagonists (28%).

Results. A total of 308 patients were randomly assigned using a 2×2 factorial design. The mean ejection fraction was 35% (18%), with a baseline furosemide dose of 131 mg/d. In total, 57% of the patients had ischemic heart disease, 53% had atrial fibrillation or atrial flutter and 51% had DM. Mean systolic blood pressure was 119 mmHg, with a mean heart rate of 78 bpm. Mean sodium concentration was 138 mg/dL and mean creatinine concentration was 1.6 mg/dL. Mean N-terminal brain natriuretic peptide (NT-pro-BNP) was 7439 pg/mL. On the visual analog scale (VAS) area under the curve (AUC), there were no differences between the Q12 dose and continuous furosemide infusion (4236 vs 4373; $P=.47$). Changes in creatinine concentrations were similar (0.05 mg/dL vs 0.07 mg/dL; $P=.45$). The secondary endpoints, such as net volume loss (4237 mL vs 4249 mL; $P=.89$), treatment failure (38% vs

39%; $P=.88$), weight changes at 72 h (-6.8 lb vs 8.1 lb; $P=.2$), dyspnea at 72 h (VAS AUC, 4456 vs 4699; $P=.36$) and length of stay (5 days vs 5 days; $P=.97$), were similar between the 2 groups. The incidence of the composite endpoint of death, rehospitalization, or emergency department visit was similar between the 2 groups (HR=1.19; 95% CI, 0.86-1.66; $P=.3$). For the low and high intensification of furosemide dosing analysis, there were no differences in the VAS AUC (4171 vs 4430; $P=.06$). The change in creatinine concentration was similar (0.04 mg/dL vs 0.08 mg/dL; $P=.21$). The secondary endpoints, such as net volume loss (3575 mL vs 4899 mL; $P=.001$), weight changes at 72 h (-6.1 lb vs 8.7 lb; $P=.011$) and dyspnea at 72 h (VAS AUC, 4478 vs 4688; $P=.04$), were significantly worse in the low intensification group than in the high intensification group. Other outcomes, such as length of stay (6 days vs 5 days; $P=.55$) and treatment failure (37% vs 40%; $P=.56$), were similar between the 2 groups. The percentage of patients with an increase in creatinine concentration >0.3 mg/dL within 72 h was lower in the low intensification group (14% vs 23%; $P=.04$). However, this was transient, because there was no overall change in creatinine or cystatin C concentrations between the 2 groups. Neither were there differences between the 2 groups in serum creatinine concentration during 60-day follow-up. The incidence of the composite of death, rehospitalization, or emergency department visit was similar in both groups (HR=0.83; 95% CI, 0.6-1.16; $P=.28$).

Conclusions. The results of the DOSE trial demonstrate that there is no difference in overall symptom relief, as assessed by VAS AUC, or any change in renal function with a Q12 dose versus continuous infusion, or low intensification dosing versus high intensification dosing with furosemide. In addition, continuous dosing was not associated with an improvement in any of the secondary endpoints assessed, which included net diuresis, weight loss, or treatment failure. On the other hand, high intensification ($\times 2.5$ the oral dose) of furosemide was associated with a significant improvement of net diuresis, weight loss, and symptom relief, compared to low intensification. The changes in creatinine concentrations in the high intensification group were transient.

CARDIAC SURGERY

EVEREST II study¹⁴: catheter-based edge-to-edge mitral valve repair study

Presented by Ted Feldman

Background. The aim of the trial was to assess treatment with the catheter-based MitraClip

device compared to surgical repair or mitral valve replacement in patients with severe mitral regurgitation. Hypothesis: catheter-based mitral valve repair is not inferior in efficacy and is superior in safety.

Methods. Patients with severe mitral regurgitation (grade 3/4 or 4/4) were randomly assigned to catheter-based mitral valve repair with MitraClip ($n=184$) or to surgical repair or mitral valve replacement ($n=95$).

Results. A total of 279 patients were included. The characteristics of the catheter-based treatment group were as follows: mean age, 67 years; 63% were men; 34% had atrial fibrillation; mean ejection fraction was 60%; 8% had DM; 73% had a degenerative mitral valve; and 27% suffered from functional mitral regurgitation. The only different baseline characteristic between the groups was congestive heart failure, which was present in 91% of the catheter-based treatment group and in 78% of the control group ($P<.01$). In the per-protocol analysis, the procedure was unsuccessful in 41 patients in the catheter-based treatment group and analysis was discontinued. Adverse events at 30 days occurred in 9.6% of the catheter-based treatment group vs 57% of the control group ($P<.0001$ for superiority). This outcome was due to a greater need for blood transfusion in the control group. The clinical success rate at 12 months was 72% versus 88% ($P=.0012$ for noninferiority). In intention-to-treat analysis, adverse events at 30 days occurred in 15% of the catheter-based treatment group and 48% of the control group ($P<.0001$ for superiority). The clinical success rate at 12 months was 67% versus 74% ($P=.0005$ for noninferiority). In the protocol group, 82% achieved mitral regurgitation of $+2$ or less versus 97% of the control group. At follow-up, 98% of the catheter-based treatment group and 88% of the control group were in New York Heart Association (NYHA) class I or II.

Conclusions. Mitral valve repair with a catheter-based clip is feasible in patients with severe mitral regurgitation. This treatment has been shown to be safer at 30 days versus surgery, mainly because it reduces the need for blood transfusion. Catheter-based repair of the mitral valve was not inferior in efficacy at 12 months.

VA-CABG Cooperative study¹⁵: radial artery grafts versus saphena vein grafts in coronary artery bypass surgery

Presented by Steven Goldman

Background. The aim of the study was to assess coronary artery bypass surgery (CABG) with radial

artery grafts compared to saphena vein grafts in patients with stable coronary heart disease. Hypothesis: CABG with radial artery grafts would be more effective in improving the long-term patency of the graft.

Methods. All the patients with stable coronary heart disease received a left internal mammary artery grafted to the left anterior descending coronary artery whenever possible. The next best vessel was randomly assigned to a radial artery graft (n=366) or saphena vein graft (n=367).

Results. A total of 733 patients were randomly included. Total mortality was 2%; operative mortality, 0.7%; myocardial infarction, 1%, and stroke, 2%. The primary endpoint, graft patency at 1 year, was 89% for radial artery grafts vs 89% for the saphena vein grafts (nonsignificant differences). Graft patency was similar between the 2 groups when grafting the following locations: left anterior descending artery (83% vs 88%), circumflex (93% vs 89%) and right coronary artery (86% vs 88%). High-grade disease (string sign) was observed in the radial artery graft in 8% and in the saphena vein 1% ($P<.001$). Endoscopic harvesting did not lead to differences in the patency of the radial artery grafts (100% vs 89%); however, it lowered the patency of saphena vein grafts (78% vs 91%; $P=.009$).

Conclusions. Among patients undergoing elective CABG, the use of radial artery grafts was not superior to saphena vein grafts. Angiographic graft patency at 1 year was similar between groups. Endoscopic harvesting of the saphena vein graft appeared to lower patency.

STICH trial¹⁶: surgical treatment for ischemic heart failure: hypothesis 2

Presented by Robert E. Miller

Background. The aim of the trial was to assess medical treatment compared to surgical treatment in patients with chronic obstructive coronary disease and congestive heart failure. Hypothesis: coronary artery bypass graft (CABG) plus surgical ventricular reconstruction (SVR) in patients with anteroapical left ventricular dysfunction would be superior to CABG alone in reducing mortality and hospitalization for cardiac causes and would improve quality of life.

Methods. The patients with coronary artery disease and anteroapical left ventricular dysfunction were assigned randomly to CABG (n=499) or CABG + SVR (n=501). Concomitant medication: the CABG and CABG + SVR groups received, respectively, beta blockers (85% and 87%), ACE inhibitors (80% and 82%), digoxin (17% and 14%), diuretics (69% and 66%), aspirin (77% and 77%), and statins (79% and 75%).

Results. There were no significant differences in the baseline clinical characteristics between the groups. However, more arterial conduits were used in the patients who underwent CABG alone. Surgical ventricular reconstruction added a mean of 27 min of cardiopulmonary bypass to the procedure. There was a greater reduction of the left ventricular end-systolic volume index in the SVR group (19% less vs 6% less; $P<.001$). However, there were no significant differences in the primary endpoint of death and cardiac hospitalization (58% vs 59%; $P=.9$). There was no improvement in NYHA heart failure classification or Canadian Cardiovascular Society heart failure classification with SVR plus CABG. There were no significant differences between the 2 groups in quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire, the Seattle Angina Questionnaire and the Center for Epidemiologic Studies Depression Scale. In the US cohort, the medical costs were greater with CABG + SVR than with CABG alone (\$70 717 vs \$56 122; $P=.004$). In a subgroup of 595 patients in whom left ventricular end-systolic volume index could be measured, the patients with a baseline index ≤ 90 mL/m² had significantly reduced mortality with CABG + SVR versus CABG alone (HR=0.59; 95% CI, 0.35-1; $P=.05$). However, there was no significant difference between the 2 groups in patients with an index >90 mL/m² (HR=1.24; 95% CI, 0.75-2.06; $P=.41$).

Conclusions. The STICH trial was the first multicenter randomized study of CABG + SVR in patients with coronary heart disease. Although it was shown that SVR reduces the left ventricular end-systolic volume index more than CABG only, this result did not entail an improvement in cardiovascular morbidity and mortality in this study. Based on these results, SVR should not be routinely conducted at the same time as CABG. Although it appears that mortality improved in patients with an index <90 mL/m² (normal index, around 25 mL/m²), the results are provisional and should be confirmed in future studies. The hypothesis 1 substudy of the STICH trial, which is comparing medical treatment alone to medical treatment + CABG, is currently in progress.

ARRHYTHMIAS

STOP-AF study¹⁷: cryoballoon ablation of pulmonary veins in patients with paroxysmal atrial fibrillation

Presented by Douglas Packer

Background. Although it has been shown that radiofrequency ablation (RFA) after pulmonary

vein (PV) isolation for atrial fibrillation (AF) is associated with a reduction in symptomatic AF, particularly paroxysmal AF, multiple ablations are often required and can be accompanied by complications. Furthermore, treatment with antiarrhythmic drugs (AAD) can be accompanied by significant morbidity and mortality. Thus, the aim was to assess the safety and efficacy of a new ablation technique, ie, cryoablation with a balloon catheter designed to achieve PV isolation with a continuous cryolesion. Hypothesis: cryoballoon ablation would be safe and effective in the treatment of symptomatic AF.

Methods. The patients were randomized in a 2:1 ratio to PV isolation by cryoablation or to treatment with AAD. The cryoablation balloon-catheter was available in 2 sizes, 23 mm and 28 mm. This was a double balloon catheter implanted using a 14 Fr sheath with a steerable balloon. The PV was isolated without any type of ablation line.

Results. In total, 245 patients were included and randomly assigned to cryoablation (163) and AAD (82). The 2 groups had similar baseline characteristics. Most of the patients were highly symptomatic, with a mean of 23 symptomatic episodes in the 2 months prior to inclusion. In total, 22% of the patients had early persistent AF, the rest had paroxysmal AF and 45% had a background of atrial flutter. The patients had previously failed one or more AAD (36% flecainide, 47% propafenone, 29% sotalol). The mean CHADS₂ score was 0.06 and the mean left atrial diameter was 4.1 cm. Pulmonary vein isolation with balloon alone was achieved in 90.8% of the patients and acute procedural success (isolation of 3 or more PV) was achieved in 98.2%. The number of applications ranged from 2.9 to 3.4. The mean ablation time ranged between 196 s and 230 s, with a fluoroscopy time of 62.8 min. The temperature of the cryoballoon ranged between -49°C and -54°C. In total, 40% of the patients also underwent ablation of the cavotricuspid isthmus. Furthermore, 19% of the patients required a repeat cryoablation procedure during the blanking period. A large number of patients also crossed over from the AAD group to the cryoablation group. The primary efficacy endpoint of treatment success was significantly better in the cryoablation group than in the AAD group (69.9% vs 7.3%; $P<.001$). In 60.1% of the patients, only a single ablation procedure was needed to achieve success. Furthermore, 57.7% of the patients in the cryoablation group did not receive any AAD treatment at the end of follow-up and 12.3% received one or more AAD. In total, 95% of the patients in the cryoablation

group were taking warfarin at the beginning of the study, but this fell to only 24% at 12 months. Symptomatic AF in the cryoablation group was reduced from 100% at the beginning of the study to 19.6%. The incidence of new atrial flutter was greater in the AAD group (3.7% vs 15.9%). The total rate of complications during the cryoballoon ablation procedure was 6.3%, which was less than the projected rate of 14.8%. The incidence of composite AF events (related to the disease and the procedure) was 3.1% vs 8.5% in the cryoablation and AAD groups, respectively ($P<.001$). The combined incidence of procedure-related events and major AF adverse events was similar in both groups (6.1% vs 8.5%; $P=.6$). Cryoablation-related complications included PV stenosis (3.1% vs 2.4%) and phrenic nerve palsy (13.5% vs 7.3%). Of the 11.2% of patients with postprocedural phrenic nerve palsy, only 4 (13.8%) had persistent paralysis at 12 months.

Conclusions. The results of the STOP-AF trial indicate that cryoballoon ablation is safe and effective for the treatment of symptomatic AF compared to AAD treatment only. A significant percentage of the patients in the cryoablation group no longer required AAD and warfarin at 12 months as compared to the initial period.

CABANA pilot study¹⁸: catheter ablation versus antiarrhythmic drug therapy for atrial fibrillation

Presented by Douglas Packer

Background. The recently published ThermoCool AF study demonstrated the superiority of catheter ablation with PV isolation vs antiarrhythmic drugs for the treatment of patients with symptomatic atrial fibrillation (AF) who had failed at least 1 antiarrhythmic drug. The CABANA pivotal trial will test the hypothesis that primary catheter ablation for AF elimination is superior to state-of-the-art drug therapy to reduce recurrent AF in high-risk patients. Hypothesis: catheter ablation is superior to medical management for treating recurrent AF in high-risk patients.

Methods. Catheter ablation was conducted via the percutaneous route and 4 PV were isolated. Additional linear or circumferential ablation was also performed if needed. The patients in the medical treatment group could receive rhythm control therapy (16%), rate control therapy (13%) or both (71%).

Results. In total, 60 patients were randomly assigned to catheter ablation (29 patients) or medical treatment (31 patients). Baseline

characteristics were very similar between the 2 groups. Approximately 80% had hypertension; 18% had DM; and 17% had underlying cardiomyopathies. A total of 35% had coronary artery disease and 36% had class II or III heart failure. Paroxysmal AF was found in 32%, and 68% had persistent AF or long-standing persistent AF. In total, 30% had received prior antiarrhythmic treatment, with 25% having failed at least 1 AAD. There was a family history of atrial flutter in 23% and 39% had a CHADS₂ score ≥ 2 . Freedom from symptomatic AF after trial completion was significantly greater in the catheter ablation group than in the AAD group (65% vs 41%; HR=0.46; 95% CI, 0.21-0.99; $P=.03$). However, the incidence of any AF, atrial flutter, or atrial tachycardia was similar between the 2 groups (66% vs 72%; HR=0.69; 95% CI, 0.37-1.32; $P=.26$). Crossover from drug treatment to catheter ablation occurred in 13% of the patients during follow-up, and 21% of the patients in the catheter ablation group required at least 1 reablation procedure. Adverse events after catheter ablation included moderate PV stenosis in 1 patient. There were no cases of severe PV stenosis. Furthermore, 2 patients had an atrioventricular fistula or a pseudoaneurysm, with no atrial fistulas to the esophagus.

Conclusions. The results of the CABANA pilot study indicate that catheter ablation is associated with reduced symptomatic AF in high-risk patients compared to treatment with AAD. In this small group of patients, there was no significant difference in the incidence of AF, atrial flutter or atrial tachycardia atrial between the 2 groups. The adverse event rate was low, including the incidence of PV stenosis. The results of the CABANA pilot study will be used in the design of the CABANA pivotal study.

RACE II study¹⁹: lenient heart rate control versus strict control in patients with atrial fibrillation

Presented by Isabelle C. Van Gelder

Background. Rate control is often the treatment of choice for atrial fibrillation. Strict rate control is recommended in the guidelines, but this is not based on clinical evidence. Hypothesis: lenient rate control is not inferior to strict rate control to prevent cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

Methods. A total of 614 patients with permanent atrial fibrillation were assigned randomly to a lenient control strategy (resting heart rate <110

bpm) or to a strict control strategy (resting heart rate <80 bpm and heart rate during moderate exercise <110 bpm). The primary endpoint was a composite of death from cardiovascular causes, hospitalization for heart failure and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. Follow-up ranged between 2 years and 3 years.

Results. The estimated cumulative incidence of the primary endpoint at 3 years was 12.9% in the lenient control group and 14.9% in the strict control group, with an absolute difference regarding the lenient control group of -2 percentage points (90% CI, -7.6 to 3.5; $P<.001$ for the prespecified noninferiority margin). The frequency of the components of the primary endpoint was similar in both groups. More patients in the lenient control group reached the target cardiac rate (304 [97.7%] vs 203 [67%] in the strict control group; $P<.001$) with fewer total visits (75 [median, 0] vs 684 [median, 2]; $P<.001$). The frequencies of symptoms and adverse events were similar in the 2 groups.

Conclusions. In the patients with permanent atrial fibrillation, lenient control of the cardiac rate is as effective as strict control and is easier to achieve.

EXPLORE-Xa study²⁰: randomized clinical trial of 3 doses of betrixaban, a long-acting oral factor Xa inhibitor, in patients with atrial fibrillation

Presented by Michael Ezekowitz

Background. The aim of the phase trial 2 was to assess treatment with 3 doses of betrixaban, a long-acting oral direct factor Xa inhibitor, versus warfarin in patients with nonvalvular atrial fibrillation. Hypothesis: betrixaban is superior for preventing major bleeding events.

Methods. A total of 508 patients with nonvalvular atrial fibrillation were randomly assigned to 1 of 3 doses of betrixaban (40 mg, n=127; 60 mg, n=127; 80 mg, n=127) or warfarin, with an INR of 2-3 (n=127).

Results. Mean age was 74 years; 54% had an estimated glomerular filtration rate 70 mL/min; mean CHAD₂ score was 2.2; and 33% were women. At 3 months, there was 1 severe or clinically relevant bleeding event with betrixaban in the 40 mg group, 4 in 60 mg group, 5 in the 80 mg group, and 4 in the warfarin group. There were 0, 1, 1, and 0 stroke events and 1, 0, 0 and 1 deaths in each group, respectively. Taking into account the duration of follow-up, the lowest risk for the primary endpoint was found in the 40 mg group; intermediate risk, in the 60 mg and 80 mg groups; and the highest risk in the

warfarin group ($P=.35$, for the betrixaban groups vs warfarin group). Alanine aminotransferase (ALT) concentrations were twice the upper limit of normal in 2.4% of the betrixaban groups and in 2.4% of the warfarin group. Vomiting, nausea and diarrhea were more frequent among the betrixaban group.

Conclusions. Among the patients with atrial fibrillation, the 3 doses of betrixaban tested were well tolerated. The incidence of bleeding events appeared to be lower in the 40 mg group than at higher doses of betrixaban or with warfarin. The efficacy and safety of the betrixaban will be established in larger clinical trials.

CARDIAC INTERVENTION

CILON-T study²¹: cilostazol-based triple anti-platelet therapy for ischemic complications after drug-eluting stent implantation

Presented by Hyo-Soo Kim

Background. Several studies have recently demonstrated that limited response or nonresponse to clopidogrel are associated with adverse clinical outcomes after percutaneous coronary intervention (PCI). Cilostazol is a phosphodiesterase-3 enzyme inhibitor which has been shown to reduce clinical events in small studies of patients undergoing PCI. The current trial investigated whether triple anti-platelet therapy (TAT) with cilostazol, aspirin, and clopidogrel is superior to dual anti-platelet therapy (DAT) to reduce clinical events in patients undergoing PCI. In addition, cilostazol was assessed regarding its efficacy to overcome limited responses or nonresponse. Hypothesis: triple anti-platelet therapy would be superior to DAT in reducing poor response or nonresponse to clopidogrel (as assessed in the VerifyNow trial), as well as in reducing clinical events in patients undergoing PCI.

Methods. Patients were randomly assigned to receive TAT with aspirin, clopidogrel, and cilostazol or DAT with aspirin and clopidogrel during a 6-month period after PCI. Aspirin was administered in a dose of 100-200 mg/d; clopidogrel was administered in a loading dose of 300-600 mg followed by 75 mg/d as maintenance therapy. Cilostazol was administered in a loading dose of 200 mg, followed by 100 mg twice a day as maintenance therapy. Concomitant medication: statins (99%), beta-blockers (52%), ACE inhibitors (41%), and proton pump inhibitors (2.5%).

Results. A total of 915 patients were randomly assigned to TAT ($n=457$) and DAT ($n=458$). Baseline characteristics were similar between the 2 groups. In total, 33% of the patients had DM, 7.5% had undergone prior PCI, and 2% had undergone CABG. In total, 40% had stable angina and 10.3% had suffered myocardial infarction. Ostial lesions were observed in 24% of the patients and bifurcation lesions in 30%. Around 8% of patients presented thrombi on initial angiography. Mean lesion length was 21.1 mm and the mean reference vessel diameter was 2.95 mm. The mean number of stents per lesion was 1.2 and 35% of the patients underwent multiple-vessel PCI. Most of the stents used were paclitaxel-eluting stents (PES) (49.5%) or zotarolimus-eluting stents (ZES) (44%). The mean P2Y₁₂ reaction unit (PRU) values, as assessed with the VerifyNow assay, was significantly reduced with TAT compared to DAT, both at discharge (206.6 vs 232.1) and at 6 months (210.7 vs 255.7) ($P<.001$ for both groups). The primary outcome of cardiovascular death, nonfatal myocardial infarction, ischemic stroke and target vessel revascularization (TVR) was similar in the TAT and DAT groups (8.5% vs 9.2%; $P=.73$). The secondary endpoints of all-cause mortality (0.9% vs 1.3%; $P=.75$), myocardial infarction (0.9% vs 0.7%; $P=.73$), ischemic stroke (1.1% vs 0.9%; $P=.75$), TVR (6.6% vs 7.2%; $P=.79$), and stent thrombosis (0.7% vs 1.1%; $P=.73$) were similar in the TAT and DAT groups. Bleeding complications, including major bleeding events (0.4% vs 0.2%) and minor bleeding events (0.2% vs 0%) were similar in both groups ($P=.51$). Drug discontinuation was significantly greater in the TAT group (6.6% vs 0.7%; $P<.001$). Trials on platelet reactivity studies have demonstrated that, despite reduced PRU values with cilostazol, there are still a significant proportion of patients with a limited response or nonresponse, as demonstrated by increased PRU values. These patients had a greater rate of clinical events, regardless of the antiplatelet regime.

Conclusions. The results of this trial indicate that TAT with cilostazol, aspirin, and clopidogrel is not superior to DAT with aspirin and clopidogrel in reducing clinical events at 6 months after PCI, even though TAT is associated with significantly reduced PRU values as compared to DAT. However, this study demonstrates that platelet reactivity testing after PCI can be used in routine practice, since patients with higher PRU values had more clinical events, regardless of the anti-platelet strategy used. In clinical trials, other strategies (higher loading dose, clopidogrel twice a day), and other agents (prasugrel) appear promising in reducing PRU values and clinical events.

5-year outcomes of the MAINCOMPARE registry²²: long-term safety and efficacy of coronary stenting vs coronary artery bypass grafting for unprotected left main coronary artery disease

Presented by Seung-Jung Park

Background. In selected patients with unprotected left main coronary artery disease (LMCA), percutaneous coronary intervention (PCI) has been demonstrated to have similar mortality and myocardial infarction rates, but higher rates of repeat revascularization than coronary artery bypass grafting (CABG), according to registry data and the randomized SYNTAX trial. The 2009 ACC/AHA clinical practice guidelines on PCI recommend a class IIb indication for unprotected left main coronary artery disease PCI (formerly class III). MAINCOMPARE is a registry study comparing PCI to CABG in patients with unprotected LMCA disease. At 3 years, the composite endpoint of death, Q-wave myocardial infarction or stroke was similar between the patients treated with PCI and those treated with CABG. However, the target vessel revascularization (TVR) rate was significantly higher in the PCI group than in the CABG group. The current analysis included 5-year data.

Methods. In total, 2240 patients with unprotected LMCA disease treated with CABG were followed up for a median of 5.2 (3-9) years. Percutaneous coronary revascularization was performed in 1102 patients (bare-metal stents were used in 318 patients and drug-eluting stents in 784); CABG was performed in 1138 patients. Treatment selection bias was reduced by propensity score matching. Outcome measures included death, Q-wave myocardial infarction, stroke and TVR.

Results. In total, 542 pairs of propensity score matched patients were analyzed. The risk of death (HR=1.13; 95% CI, 0.88-1.44; $P=.35$) and the composite of risk of death, Q-wave myocardial infarction or stroke (HR=1.07; 95% CI, 0.84-1.37; $P=.59$) were similar between the patients treated with PCI and those treated with CABG. The TVR rate was significantly higher in the PCI group (HR=5.11; 95% CI, 3.52-7.42; $P<.001$). The type of stent (bare-metal or drug-eluting) did not significantly change the outcomes.

Conclusions. At 5 year follow-up, PCI for unprotected LMCA disease yielded similar rates of death, myocardial infarction or stroke compared with CABG, but was associated with more repeat revascularizations.

DES-LATE study²³: duration of dual antiplatelet therapy after drug-eluting stent implantation

Presented by Seung-Jung Park

Background. The potential benefits and risks of dual antiplatelet therapy beyond a 12-month period in patients with drug-eluting stents have not been clearly established.

Methods. In 2 trials, a total of 2701 patients with drug-eluting stents and who had been free from major adverse cardiac or cerebrovascular events and major bleeding for at least 12 months were randomly assigned to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was the composite of myocardial infarction or death from cardiac causes. The data from both trials were combined for analysis.

Results. Mean follow-up time was 19.2 months. The cumulative risk of the primary endpoint at 2 years was 1.8% with dual antiplatelet therapy vs 1.2% with aspirin alone (HR=1.65; 95% CI, 0.8-3.36; $P=.17$). There were no significant differences between groups in individual risk of myocardial infarction, stroke, stent thrombosis, need for revascularization, severe bleeding, and all-cause death. However, in the dual-therapy group, compared to the aspirin group, there was a nonsignificant increase in the composite risk of myocardial infarction, stroke, or all-cause death (HR=1.73; 95% CI, 0.99-3; $P=.051$) and in the composite risk of myocardial infarction, stroke, or death from cardiac causes (HR=1.84; 95% CI, 0.99-3.45; $P=.06$).

Conclusions. Dual antiplatelet therapy for more than 12 months in patients with drug-eluting stents was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction or death from cardiac causes. Larger randomized clinical trials with longer follow-up are needed to confirm or reject these Results.

RESULTS OF TRIALS ON NEW STENTS

ISAR-TEST-2 trial²⁴: angiographic results and intracoronary stenting. Efficacy trial of 3 limus-eluting stents

Presented by Robert Byrne

Drugs and procedures. A total of 1007 patients were randomized: 333 to dual drug-eluting stents (DES), 335 to sirolimus-eluting stents (SES), and 339 to zotarolimus-eluting stents (ZES). Patients undergoing PCI with dual DES, SES, or ZES

were randomized in a 1:1:1 ratio. The results of the ISAR-TEST-2 trial indicate that outcomes with a dual DES—incorporating the antirestenotic drugs probucol and sirolimus on a polymer-free platform—are similar to those with a sirolimus/SES and superior to those with ZES, both of which are based on permanent polymers. These results are similar to those of the ISARTEST and ISAR-TEST-3 trials, which demonstrated the noninferiority of the same dual DES as compared to the results obtained with paclitaxel-eluting stents (PES) and SES, which are both based on polymers.

SORT OUT III trial²⁵: efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care: a randomized superiority trial

Presented by Michael Maeng

The zotarolimus-eluting stent (ZES) has been shown to reduce restenosis rates without increasing the risk of stent thrombosis in low-risk patients. The efficacy and safety of the ZES vs the sirolimus-eluting stent (SES) was compared in patients with coronary artery disease who were receiving routine clinical care without direct follow-up. The SES is superior to the ZES in patients who are receiving routine clinical care.

PERSEUS trial²⁶: first report of the randomized comparison trial of a novel platinum-chromium thin-strut TAXUS stent versus the TAXUS Express stent in de novo coronary stenoses

Presented by Dean J. Kereiakes

The TAXUS Element is a new paclitaxel-eluting stent (PES) that incorporates a thinner strut than the TAXUS Express (81 µm vs 132 µm, respectively) and a platinum-enriched metal alloy platform (as compared to the stainless steel used in the TAXUS Express). It is designed for greater radiopacity (density, 9.9 g/mL vs 8 g/mL of the TAXUS Express) and improved deliverability. The PERSEUS study included 1262 patients (942 for TAXUS Elements and 320 for TAXUS Express) from 90 sites. The TAXUS Element appears to have an efficacy similar to that of the TAXUS Express DES in common lesions and may be superior to the TAXUS Express bare-metal stent in small vessels. There is no evidence of safety issues in these relatively small studies.

JETSTENT trial²⁷: comparison of AngioJet rheolytic thrombectomy before direct stenting to direct stenting alone in patients with acute myocardial infarction

Presented by David Antoniucci

The aim of the study was to compare AngioJet rheolytic thrombectomy prior to stenting to direct stenting alone in patients with acute myocardial infarction (AMI). Hypothesis: AngioJet thrombectomy would prove to be superior in improving myocardial perfusion and clinical outcomes. The use of rheolytic thrombectomy was beneficial in patients with ST elevation myocardial infarction (STEMI). The device improved myocardial reperfusion and major adverse cardiac events (MACE) at 6 months. Rheolytic thrombectomy increased procedural times. However, its use did not appear to be associated with increased procedural complications, such as the need for pacing or vessel perforation. The thrombectomy group required fewer stents per patient and the stents used were shorter. It should be highlighted that there was no increase in stroke.

DEDICATION stent trial^{28,29}: drug elution and distal protection in acute myocardial infarction

Presented by Peter Clemmensen

The aim of the trial was to assess the use of a drug-eluting stent (DES) as compared to a bare-metal stent (BMS) among patients with AMI undergoing PCI. The patients undergoing primary PCI were randomly assigned to a DES (n=313) or BMS (n=313). The choice of DES remained at the discretion of the researcher. Angiographic follow-up was conducted at 8 months. Among the patients with AMI undergoing primary PCI, the use of a DES was associated with a reduction in late lumen loss at 8 months compared to the use of a BMS, but cardiac mortality tended to increase. At 3 years, there was a significant reduction of MACE, mainly driven by a significant reduction of target lesion revascularization in the DES group as compared to the BMS group.

PASSION trial³⁰: paclitaxel-eluting stents vs bare-metal stents for ST-segment-elevation myocardial infarction. 5-year follow-up

Presented by Martín Vink

The aim of the trial was to assess treatment with paclitaxel-eluting stents (PES) vs bare-metal stents

in patients undergoing primary PCI for STEMI. The patients undergoing primary PCI were randomly assigned to an Express2 PES (n=309) or to bare-metal stents (n=310) with an Express2 or Liberte platform. Among the patients undergoing primary PCI for STEMI, the use of PES was not associated with a significant difference in the composite primary endpoint at 1 year as compared to bare-metal stents.

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