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Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American College of Cardiology (Washington D.C., United States, March 29-31, 2014)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales del *American College of Cardiology* (Washington D.C., Estados Unidos, 29-31 de marzo de 2014)

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Following its policy of disseminating scientific information to the cardiology community,[1-19] *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Scientific Sessions of the American College of Cardiology (Washington D.C., United States), 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 not yet been published in their final version, the information offered should be interpreted as preliminary.

SUMMARY BY TOPIC

STABILITY: Effect of Inhibition of Lipoprotein-associated Phospholipase A_2 With Darapladib on Ischemic Events in Patients With Chronic Coronary Heart Disease.[20]

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Negative High-sensitive Troponins in the Emergency Department and Risk of Myocardial Infarction.[30]

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A Large International Trial Assessing the Effects of Clonidine on Major Arterial Events in Patients Having Noncardiac Surgery.[32]

SIRS: Steroids in Cardiac Surgery Trial.[33]

GIPS-III: Metformin in Acute Myocardial Infarction.[34]

STAMPEDE: Effect of Bariatric Surgery vs Intensive Medical Therapy on Long-term Glycemic Control and Complications of Diabetes: 3-Year Trial Results.[35]

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Effect of Inhibition of Lipoprotein-associated Phospholipase A_2 With Darapladib on Ischemic Events in Patients With Chronic Coronary Heart Disease: The STABILITY Trial[20]

Presented by Harvey D. White, Auckland, New Zealand.

Background. Elevated lipoprotein-associated phospholipase A_2 activity promotes the development of vulnerable atherosclerotic plaques, and elevated plasma levels of this enzyme are associated with an increased risk of coronary events. Darapladib is a selective oral inhibitor of lipoprotein-associated phospholipase A_2.

Methods. In a double-blind trial, we randomly assigned 15 828 patients with stable coronary heart disease to receive either once-daily darapladib (at a dose of 160 mg) or placebo. The primary end point was the time to cardiovascular death, myocardial infarction, or stroke. Secondary end points included the components of the primary end point as well as major coronary events (death from coronary heart disease, myocardial infarction, or urgent coronary revascularization for myocardial ischemia) and total coronary events (death from coronary heart disease, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization).

Results. During a median follow-up period of 3.7 years, the primary end point occurred in 769 of 7924 patients (9.7%) in the darapladib group and 819 of 7904 patients (10.4%) in the placebo group (hazard ratio [HR] in the darapladib group = 0.94; 95% confidence interval [CI], 0.85 to 1.03; $P = .20$). There were also no significant between-group differences in the rates of the individual components of the primary end point or in all-cause mortality. Darapladib, as compared with placebo, reduced the rate of major coronary events (9.3% vs 10.3%; HR = 0.90; 95%CI, 0.82- 1.00; $P = .045$) and total coronary events (14.6% vs 16.1%; HR, 0.91; 95% CI, 0.84-0.98; $P = .02$).

Conclusions. In patients with stable coronary heart disease, darapladib did not significantly reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke.

CoreValve: Transcatheter Aortic-valve Replacement With a Self-expanding Prosthesis[21]

Presented by David H. Adams, New York, New York, United States.

Background. We compared transcatheter aortic-valve replacement (TAVR), using a self-expanding transcatheter aortic-valve bioprosthesis, with surgical aortic-valve replacement in patients with severe aortic stenosis and an increased risk of death during surgery.

Methods. We recruited patients with severe aortic stenosis who were at increased surgical risk as determined by the heart team at each study center. Risk assessment included the Society of Thoracic Surgeons Predicted Risk of Mortality estimate and consideration of other key risk factors. Eligible patients were randomly assigned in a 1:1 ratio to TAVR with the self-expanding transcatheter valve (TAVR group) or to surgical aortic-valve replacement (surgical group). The primary end point was the rate of death from any cause at 1 year, evaluated with the use of both noninferiority and superiority testing.

Results. A total of 795 patients underwent randomization at 45 centers in the United States. In the as-treated analysis, the rate of death from any cause at 1 year was significantly lower in the TAVR group than in the surgical group (14.2% vs 19.1%), with an absolute reduction in risk of 4.9 percentage points (upper boundary of the 95%CI, −0.4; $P < .001$ for noninferiority; $P = .04$ for superiority). The results were similar in the intention-to-treat analysis. In a hierarchical testing procedure, TAVR was noninferior with respect to echocardiographic indexes of valve stenosis, functional status, and quality of life. Exploratory analyses suggested a reduction in the rate of major adverse cardiovascular and cerebrovascular events and no increase in the risk of stroke.

Conclusions. In patients with severe aortic stenosis who are at increased surgical risk, TAVR with a self-expanding transcatheter aortic-valve bioprosthesis was associated with a significantly higher rate of survival at 1 year than surgical aortic-valve replacement.

The Low-density Lipoprotein Cholesterol Assessment With PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy - 2 Trial: A Phase 3, Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia - (LAPLACE-2)[22]

Presented by Jennifer Robinson, Thousand Oaks, California, United States.

Background. Elevated low-density lipoprotein (LDL) cholesterol levels are associated with increased atherosclerotic cardiovascular disease risk. Statins are currently the first-line treatment for patients who would benefit from lowering LDL-cholesterol and atherosclerotic cardiovascular disease risk, though some high-risk patients have a less-than-anticipated response or are intolerant to statin therapy. Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9, such as evolocumab, have been shown to decrease LDL-cholesterol in phase 2 clinical trials. Does treatment with evolocumab every 2 weeks or every month effectively lower LDL-cholesterol when combined with statin therapy in patients with hypercholesterolemia?

Methods. Randomized, double-blind, placebo- and ezetimibe-controlled, multicenter study; N = 1896. Randomization: 1 of 24 arms comparing subcutaneous evolocumab (140 mg every 2 weeks or 420 mg every month) vs subcutaneous placebo (every 2 weeks or every month) vs ezetimibe (10 mg daily) when added to different daily statin doses. Physical exam with collection of AEs/SAEs and cardiovascular events on day 1 and weeks 2, 8, 10, and 12 for the primary end point: Percentage LDL-cholesterol change from baseline to the mean of weeks 10 and 12.

Results. LDL-cholesterol reduction vs placebo: Evolocumab every 2 weeks, 66%-75%; Evolocumab every month, 63%-75%; Ezetimibe, 19%-32%.

Conclusions. The combination of evolocumab and a statin significantly lowered LDL-cholesterol levels in patients with hypercholesterolemia compared to statin therapy with ezetimibe ($P < .001$) or statin therapy alone ($P < .001$). Evolocumab dosing of 140 mg every 2 weeks and 420 mg every month were clinically equivalent.

Evaluation of the Dual PPAR-α/γ Agonist Aleglitazar to Reduce Cardiovascular Events in Patients With Acute Coronary Syndrome and Type 2 Diabetes Mellitus: the AleCardio Trial[23]

Presented by A. Michael Lincoff, Cleveland, Ohio, United States.

Background. No therapy directed against diabetes has been shown to unequivocally reduce the excess risk of cardiovascular complications. Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and favorable effects on lipid profiles. The objective of the study was to determine whether the addition of aleglitazar to standard medical therapy reduces cardiovascular morbidity and mortality among patients with type 2 diabetes mellitus and a recent acute coronary syndrome.

Methods. AleCardio was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted in 720 hospitals in 26 countries throughout North America, Latin America, Europe, and Asia-Pacific regions. The enrollment of 7226 patients hospitalized for acute coronary syndrome (myocardial infarction or unstable angina) with type 2 diabetes occurred between February 2010 and May 2012; treatment was planned to continue until patients were followed-up for at least 2.5 years and 950 primary end point events were positively adjudicated. Patiernts were randomized in a 1:1 ratio to receive aleglitazar 150 µg or placebo daily. The primary efficacy end point was time to cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Principal safety end points were hospitalization due to heart failure and changes in renal function.

Results. The trial was terminated on July 2, 2013, after a median follow-up of 104 weeks, upon recommendation of the data and safety monitoring board due to futility for efficacy at an unplanned interim analysis and increased rates of safety end points. A total of 3.1% of patients were lost to follow-up and 3.2% of patients withdrew consent. The primary end point occurred in 344 patients (9.5%) in the aleglitazar group and 360 patients (10.0%) in the placebo group (HR = 0.96; 95%CI, 0.83-1.11; *P* = .57). Rates of serious adverse events, including heart failure (3.4% for aleglitazar vs 2.8% for placebo, *P* = .14), gastrointestinal hemorrhages (2.4% for aleglitazar vs 1.7% for placebo, *P* = .03), and renal dysfunction (7.4% for aleglitazar vs 2.7% for placebo, *P* < .001) were increased.

Conclusions. Among patients with type 2 diabetes and recent acute coronary syndrome, use of aleglitazar did not reduce the risk of cardiovascular outcomes. These findings do not support the use of aleglitazar in this setting with a goal of reducing cardiovascular risk.

A Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: The CHOICE Trial[24]

Presented by Mohamed Abdel-Wahab, Bad Segeberg, Germany.

Background. Transcatheter aortic valve replacement (TAVR) is an effective treatment option for high-risk patients with severe aortic stenosis. Different from surgery, transcatheter deployment of valves requires either a balloon-expandable or self-expandable system. A randomized comparison of these 2 systems has not been performed. The objective is to determine whether the balloon-expandable device is associated with a better success rate than the self-expandable device.

Methods. The CHOICE study was an investigator-initiated trial in high-risk patients with severe aortic stenosis and an anatomy suitable for the transfemoral TAVR procedure. One hundred twenty-one patients were randomly assigned to receive a balloon-expandable valve (Edwards Sapien XT) and 120 were assigned to receive a self-expandable valve (Medtronic CoreValve). Patients were enrolled between March 2012 and December 2013 at 5 centers in Germany. The primary end point was device success, which is a composite end point including successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only 1 valve implanted in the proper anatomical location. Secondary end points included cardiovascular mortality, bleeding and vascular complications, postprocedural pacemaker placement, and a combined safety end point at 30 days, including all-cause mortality, major stroke, and other serious complications.

Results. Device success occurred in 116 of 121 patients (95.9%) in the balloon-expandable valve group and 93 of 120 patients (77.5%) in the self-expandable valve group (relative risk [RR] = 1.24, 95%CI, 1.12-1.37; *P* < .001). This was attributed to a significantly lower frequency of residual more-than-mild aortic regurgitation (4.1% vs 18.3%; RR = 0.23; 95%CI, 0.09-0.58; *P* < .001) and the less frequent need for implanting more than 1 valve (0.8% vs 5.8%, *P* = .03) in the balloon-expandable valve group. Cardiovascular mortality at 30 days was 4.1% in the balloon-expandable valve group and 4.3% in the self-expandable valve group (RR = 0.97; 95% CI, 0.29-3.25; *P* = .99). Bleeding and vascular complications were not significantly different, and the combined safety end point occurred in 18.2% of those in the balloon-expandable valve group and 23.1% of the self-expandable valve group (RR = 0.79; 95%CI, 0.48-1.30; *P*=.42). Placement of a new permanent pacemaker was less frequent in the balloon-expandable valve group (17.3% vs 37.6%; *P* = .001).

Conclusions. Among patients with high-risk aortic stenosis undergoing TAVR, the use of a balloon-expandable valve resulted in a greater rate of device success than use of a self-expandable valve.

Anti-PCSK9 Antibody Effectively Lowers Cholesterol in Patients With Statin Intolerance: The GAUSS-2 Randomized, Placebo-controlled Phase 3 Clinical Trial of Evolocumab[25]

Presented by Erik S.G. Stroes, Thousand Oaks, California, United States.

Background. Statin intolerance, predominantly due to muscle-related side effects, is reported in up to 10% or 20% of patients. Evolocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, demonstrated marked reductions in plasma LDL cholesterol in a phase 2 study in statin-intolerant patients. The objective was to evaluate the efficacy and safety of subcutaneous evolocumab compared with oral ezetimibe in hypercholesterolemic subjects unable to tolerate effective statin doses.

Methods. The Goal Achievement after Utilizing an anti-proprotein convertase subtilisin/kexin type 9 antibody in Statin Intolerant Subjects (GAUSS-2), a 12-week, double-blind study, randomized patients (2:2:1:1) to evolocumab 140 mg biweekly or evolocumab 420 mg monthly both with daily oral placebo; or subcutaneous placebo biweekly or monthly both with daily oral ezetimibe 10 mg. Co-primary end points were percent change from baseline in LDL cholesterol at week 12 and at the mean of weeks 10 and 12.

Results. A total of 307 patients (mean [SD] age 62 [10], LDL-cholesterol 193 [59] mg/dL) were randomized. Evolocumab reduced LDL-cholesterol from baseline by 53% to 56%, corresponding to treatment differences vs ezetimibe of 37% to 39% (*P* <.001). Muscle adverse events occurred in 12% of evolocumab- and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.

Conclusions. Robust efficacy combined with favorable tolerability makes evolocumab a promising therapy for addressing the large unmet clinical need in high-risk patients with elevated cholesterol who are statin intolerant.

Efficacy and Safety of Colchicine in Patients With Multiple Recurrences of Pericarditis: Results of a Multicenter, Double-blind, Placebo-controlled, Randomized Study (CORP-2 Trial)[26]

Presented by Massimo Imazio, Turin, Italy.

Background. Colchicine is effective for the treatment of acute pericarditis and first recurrences. However, conclusive data are lacking for the efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis.

Methods. We did this multicentre, double-blind trial at four general hospitals in northern Italy. Adult patients with multiple recurrences of pericarditis (≥ 2) were randomly assigned (1:1) to placebo or colchicine (0.5 mg twice daily for 6 months for patients weighing > 70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg)

in addition to conventional anti-inflammatory treatment with aspirin, ibuprofen, or indometacin. Permuted block randomization (size 4) was done with a central computer-based automated sequence. Patients and all investigators were masked to treatment allocation. The primary outcome was recurrent pericarditis in the intention-to-treat population.

Results. A total of 240 patients were enrolled and 120 were assigned to each group. The proportion of patients who had recurrent pericarditis was 26 (21.6%) of 120 in the colchicine group and 51 (42.5%) of 120 in the placebo group (RR = 0.49; 95%CI, 0.24–0.65; *P* = .0009; number needed to treat 5). Adverse effects and discontinuation of study drug occurred in much the same proportions in each group. The most common adverse events were gastrointestinal intolerance (9 patients in the colchicine group vs 9 in the placebo group) and hepatotoxicity (3 vs 1, respectively). No serious adverse events were reported.

Conclusions. Colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with multiple recurrences. Taken together with results from other randomized controlled trials, these findings suggest that colchicine probably should be regarded as a first-line treatment for either acute or recurrent pericarditis in the absence of contraindications or specific indications.

The Global SYMPLICITY Registry: Safety and Effectiveness of Renal Artery Denervation in Real World Patients With Uncontrolled Hypertension[27]

Presented by Michael Böhm, Homburg Saar, Germany.

Background. The Symplicity HTN-1 and -2 trials demonstrated that renal denervation offered safe blood pressure reductions in patients with blood pressure that was not controlled on multiple antihypertensive medications. The aim of this study was to evaluate the longer-term results for renal denervation in real-world hypertensive patients.

Methods. This is an observational, prospective, multi-center, single-arm, non-interventional, open-label registry. A total of 1000 patients with uncontrolled hypertension who were treated with the Symplicity Catheter System (Medtronic, Mountain View, CA) at 231 international sites in 37 countries were enrolled. The key measures were office systolic blood pressure and ambulatory systolic blood pressure at 6 months.

Results. The change of systolic blood pressure at 6 months was as follows: Office systolic blood pressure drop of 11.9 mmHg in all patients and of 19.8 mmHg in patients with baseline systolic blood pressure ≥160 mmHg; ambulatory systolic blood pressure drop of 7.9 mmHg in patients with baseline systolic blood pressure ≥140 mmHg and of 9.2 mmHg in patients with baseline systolic blood pressure ≥160 mmHg. Renal denervation proved safe at 6 months with low rates of cardiovascular death (0.2%), stroke (0.9%), hospitalization for new onset heart failure (0.7%) or atrial fibrillation (0.9%), hypertensive crisis/emergency (1.0%), and myocardial infarction (0.6%). There were 5 procedure-related events.

Conclusions. Following renal denervation, significant real-world drops in blood pressure at 6 months were measured in patients with uncontrolled hypertension.

One Year Follow-up of the Melody Transcatheter Pulmonary Valve Multicenter Post-approval Study[28]

Presented by Aimee K. Armstrong, Ann Arbor, Michigan, United States.

Background. The aim of the study was to confirm that short-term hemodynamic effectiveness of the Melody Transcatheter Pulmonary Valve (TPV) achieved by real-world providers is equivalent to the historical results established in the 5-center Investigational Device Exemption (IDE) trial in the United States. This study assessed hemodynamic function in patients with congenital defects (RV–PA conduits) who received a Melody TPV.

Methods. A prospective, nonrandomized, 10-center study enrolled 120 patients (mean age 19.9 years; mean weight 59.4 kg) with a stenotic and/or regurgitant conduit from July 2010 to July 2012. Ultimately 99 patients were implanted with the Melody TPV (Medtronic, Minneapolis, MN) for at least 24 hours. The primary end point was the presence of acceptable hemodynamic function at 6 months post-implant.

Results. Mean (standard deviation) RVOT gradient fell from 33.3 (14.1) mmHg at baseline to 16.3 (7.1) mmHg at discharge and 15.0 (9.9) mmHg at 6 months. Most patients (84.8%) had severe or moderate pulmonary regurgitation at baseline, but no evidence of this persisted at discharge or during follow-up. At 6 months, 96.7% of the implanted cohort with evaluable data (n = 90) had acceptable hemodynamic function (primary end point). Most of the implanted cohort overall (87.9%) also met the primary end point (*P* < .01). At 1-year hemodynamic function remained high at 94.3% for the implanted cohort with evaluable data and 82.8% for the overall group.

Conclusions. This study confirms the strong performance of the Melody TPV achieved by real-world providers with results comparable to the IDE trial.

Long-term Survival With Cardiac Resynchronization Therapy in Patients With Mild Heart Failure (MADIT-CRT)[29]

Presented by Ilan Goldenberg, Rochester, New York, United States.

Background. The Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) showed that early intervention with CRT with a defibrillator in patients with an electrocardiographic pattern showing left bundle-branch block was associated with a significant reduction in heart-failure events over a median follow-up of 2.4 years, as compared with defibrillator therapy alone.

Methods. We evaluated the effect of a defibrillator on long-term survival in the MADIT-CRT population. Post-trial follow-up over a median period of 5.6 years was assessed among all 1691 surviving patients (phase 1) and subsequently among 854 patients who were enrolled in post-trial registries (phase 2). All reported analyses were performed on an intention-to-treat basis.

Results. At 7 years of follow-up after initial enrollment, the cumulative rate of death from any cause among patients with left bundle-branch block was 18% in the group randomly assigned to CRT with defibrillator, as compared with 29% in those randomly assigned to defibrillator therapy alone (adjusted HR in the defibrillator group = 0.59; 95%CI, 0.43-0.80; *P* < .001). The long-term survival benefit of a defibrillator in patients with left bundle-branch block did not differ significantly according to sex, cause of cardiomyopathy, or QRS duration. In contrast, the defibrillator was not associated with any clinical benefit and possibly with harm in patients without left bundle branch block (adjusted HR for death from any cause = 1.57; 95%CI, 1.03-2.39; *P* = .04; *P* < .001 for interaction of treatment with QRS morphologic findings).

Conclusions. Our findings indicate that in patients with mild heart-failure symptoms, left ventricular dysfunction, and left bundle-branch block, early CRT intervention with defibrillator was associated with a significant long-term survival benefit.

Negative High-sensitive Troponins in the Emergency Department and Risk of Myocardial Infarction[30]

Presented by Nadia Bandstein, Stockholm, Sweden.

Background. The objective was to evaluate if an undetectable (< 5 ng/L) high-sensitivity cardiac troponin T (hs-cTnT) level and an electrocardiogram without signs of ischemia can rule out myocardial infarction in the emergency department. Chest pain is a common symptom often associated with benign conditions, but may be a sign of myocardial infarction. Since there is no rapid way to rule out myocardial infarction, many patients are admitted to hospital.

Methods. All patients who sought medical attention for chest pain, and had at least one hs-cTnT analyzed, during two years at the Karolinska university hospital in Stockholm, Sweden, were included. We calculated the negative predictive values of an undetectable hs-cTnT and electrocardiogram without ischemia for myocardial infarction and death within 30 days.

Results. We included 14 636 patients of whom 8907 (61%) had an intial hs-cTnT of <5 ng/L, 21% had 5 to 14 ng/L, and 18% had >14 ng/L. During 30 days of follow-up, 39 (0.44%) patients with undetectable hs-cTnT had a myocardial infarction, of whom 15 (0.17%) had no ischemic electrocardiogram changes. The negative predictive value for myocardial infarction within 30 days in patients with undetectable hs-cTnT, and no ischemic electrocardiogram changes was 99.8% (95%CI, 99.7-99.9). The negative predictive value for death was 100% (95%CI, 99.9-100).

Conclusions. All patients with chest pain who have an initial hs-cTnT level < 5 ng/L and no signs of ischemia on electrocardiogram have a minimal risk of myocardial infarction or death within 30 days and can be safely discharged directly from the emergency department.

POISE-2: Perioperative Ischemic Evaluation-2 Trial[31]

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

Background. There is substantial variability in the perioperative administration of aspirin in patients undergoing noncardiac surgery, both among patients who are already on an aspirin regimen and among those who are not.

Methods. Using a 2-by-2 factorial trial design, we randomly assigned 10 010 patients who were preparing to undergo noncardiac surgery and were at risk for vascular complications to receive aspirin or placebo and clonidine or placebo. The results of the aspirin trial are reported here. The patients were stratified according to whether they had not been taking aspirin before the study (initiation stratum, with 5628 patients) or were already on an aspirin regimen (continuation stratum, with 4382 patients). Patients started taking aspirin (at a dose of 200 mg) or placebo just before surgery and continued it daily (at a dose of 100 mg) for 30 days in the initiation stratum and for 7 days in the continuation stratum, after which patients resumed their regular aspirin regimen. The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days.

Results. The primary outcome occurred in 351 of 4998 patients (7.0%) in the aspirin group and in 355 of 5012 patients (7.1%) in the placebo group (HR in the aspirin group = 0.99; 95%CI, 0.86-1.15; P = .92). Major bleeding was more common in the aspirin group than in the placebo group (230 patients [4.6%] vs 188 patients [3.8%]; HR = 1.23; 95%CI, 1.01-1.49; P = .04). The primary and secondary outcome results were similar in both aspirin strata.

Conclusions. Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding.

A Large International Trial Assessing the Effects of Clonidine on Major Arterial Events in Patients Having Noncardiac Surgery[32]

Presented by Daniel I. Sessler, Cleveland, Ohio, United States.

Background. Marked activation of the sympathetic nervous system occurs during and after noncardiac surgery. Low-dose clonidine, which blunts central sympathetic outflow, may prevent perioperative myocardial infarction and death without inducing hemodynamic instability.

Methods. We performed a blinded, randomized trial with a 2-by-2 factorial design to allow separate evaluation of low-dose clonidine versus placebo and low-dose aspirin versus placebo in patients with, or at risk for, atherosclerotic disease who were undergoing noncardiac surgery. A total of 10 010 patients at 135 centers in 23 countries were enrolled. For the comparison of clonidine with placebo, patients were randomly assigned to receive clonidine (0.2 mg per day) or placebo just before surgery, with the study drug continued until 72 hours after surgery. The primary outcome was a composite of death or nonfatal myocardial infarction at 30 days.

Results. Clonidine, as compared with placebo, did not reduce the number of primary-outcome events (367 and 339, respectively; HR with clonidine = 1.08; 95%CI, 0.93-1.26; P = .29). Myocardial infarction occurred in 329 patients (6.6%) assigned to clonidine and in 295 patients (5.9%) assigned to placebo (HR = 1.11; 95%CI, 0.95-1.30; P = .18). Significantly more patients in the clonidine group than in the placebo group had clinically important hypotension (2385 patients [47.6%] vs 1854 patients [37.1%]; HR = 1.32; 95%CI, 1.24-1.40; P < .001). Clonidine, as compared with placebo, was associated with an increased rate of nonfatal cardiac arrest (0.3% vs 0.1%; HR = 3.20; 95%CI, 1.17-8.73; P = .02).

Conclusions. Administration of low-dose clonidine in patients undergoing noncardiac surgery did not reduce the rate of the composite outcome of death or nonfatal myocardial infarction; it did, however, increase the risk of clinically important hypotension and nonfatal cardiac arrest.

SIRS: Steroids in Cardiac Surgery Trial[33]

Presented by Richard Whitlock, Hamilton, Canada.

Background. The goal of the trial was to evaluate treatment with steroids compared with placebo among patients undergoing cardiac surgery with cardiopulmonary bypass. The hypothesis was that steroids will reduce perioperative adverse events.

Methods. Randomized, parallel study with a total of 7507 patients undergoing cardiac surgery with cardiopulmonary bypass. Duration of follow-up: 30 days. Primary end points: Coprimary outcome of death, myocardial infarction, stroke, renal failure, or respiratory failure. Patients undergoing surgery were randomized to methylprednisolone 500 mg IV (n = 3755) vs placebo (n = 3752).

Results. Overall, 7507 patients were randomized. The coprimary outcome of death occurred in 4.1% of the steroid group vs 4.7% of the placebo group (P = 0.23). The coprimary outcome of death, myocardial infarction, stroke, renal failure, or respiratory failure occurred in 24.3% of the steroid group vs 23.3% of the placebo group (P = 0.31). Myocardial infarction: 13.5% vs 11.2% (P = 0.001), respectively. Stroke: 1.9% vs 2.1% (P = 0.51), respectively. Renal failure: 2.8% vs 3.0% (P = 0.62), respectively. Respiratory failure: 9.1% vs 10.0% (P=0.20), respectively.

Conclusions. Among patients undergoing cardiac surgery with cardiopulmonary bypass, the use of methylprednisolone did not reduce death or major morbidity at 30 days. In fact, methylprednisolone was associated with an increase in myocardial

infarction. The prophylactic use of steroids before cardiac surgery is not recommended.

GIPS-III: Metformin in Acute Myocardial Infarction[34]

Presented by Chris PH Lexis, Amsterdam, The Netherlands.

Background. Metformin treatment is associated with improved outcome after myocardial infarction in patients with diabetes. In animal experimental studies, metformin preserves left ventricular function. The objective was to evaluate the effect of metformin treatment on preservation of left ventricular function in patients without diabetes presenting with ST-segment elevation myocardial infarction (STEMI).

Methods. Double-blind, placebo-controlled study conducted among 380 patients who underwent primary percutaneous coronary intervention for STEMI at the University Medical Center, Groningen, the Netherlands, between January 1, 2011, and May 26, 2013. Metformin hydrochloride (500 mg) (n = 191) or placebo (n = 189) twice daily for 4 months.

Results. The primary efficacy measure was left ventricular ejection fraction after 4 months, assessed by magnetic resonance imaging. A secondary efficacy measure was the N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration after 4 months. The incidence of major adverse cardiac events (MACE; the combined end point of death, reinfarction, or target-lesion revascularization) was recorded until 4 months as a secondary efficacy measure. At 4 months, all patients were alive and none were lost to follow-up. Left ventricular ejection fraction was 53.1% (95%CI, 51.6%-54.6%) in the metformin group (n = 135), compared with 54.8% (95%CI, 53.5%-56.1%) (P = .10) in the placebo group (n = 136). NT-proBNP concentration was 167ng/L in the metformin group (interquartile range, 65-393 ng/L) and 167 ng/L in the placebo group (interquartile range, 74-383 ng/L) (P = .66). MACE were observed in 6 patients (3.1%) in the metformin group and in 2 patients (1.1%) in the placebo group (P = .16). Creatinine concentration (79 µmol/L [interquartile range, 70-87 µmol/L] vs 79 µmol/L [interquartile range, 72-89 µmol/L], P = .61) and glycated hemoglobin (5.9% [interquartile range, 5.6%-6.1%] vs 5.9% [interquartile range, 5.7%-6.1%]; P = .15) were not significantly different between both groups. No cases of lactic acidosis were observed.

Conclusions. Among patients without diabetes presenting with STEMI and undergoing primary percutaneous coronary intervention, the use of metformin compared with placebo did not result in improved left ventricular ejection fraction after 4 months. The present findings do not support the use of metformin in this setting.

Effect of Bariatric Surgery vs Intensive Medical Therapy on Long-term Glycemic Control and Complications of Diabetes: 3-Year STAMPEDE Trial Results[35]

Presented by Philip Raymond Schauer, Cleveland, Ohio, United States.

Background. In short-term randomized trials (duration, 1 to 2 years), bariatric surgery has been associated with improvement in type 2 diabetes mellitus.

Methods. We assessed outcomes 3 years after the randomization of 150 obese patients with uncontrolled type 2 diabetes to receive either intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary end point was a glycated hemoglobin level of 6.0% or less.

Results. The mean (standard deviation) age of the patients at baseline was 48 (8) years, 68% were women, the mean baseline glycated hemoglobin level was 9.3 (1.5%), and the mean baseline body-mass index (the weight in kilograms divided by the square of the height in meters) was 36.0 (3.5). A total of 91% of the patients completed 36 months of follow-up. At 3 years, the criterion for the primary end point was met by 5% of the patients in the medical-therapy group, as compared with 38% of those in the gastric-bypass group (P < .001) and 24% of those in the sleeve-gastrectomy group (P = .01). The use of glucose-lowering medications, including insulin, was lower in the surgical groups than in the medical-therapy group. Patients in the surgical groups had greater mean percentage reductions in weight from baseline, with reductions of 24.5 (9.1%) in the gastric-bypass group and 21.1 (8.9%) in the sleeve-gastrectomy group, as compared with a reduction of 4.2 (8.3%) in the medical-therapy group (P < .001 for both comparisons). Quality-of-life measures were significantly better in the two surgical groups than in the medical-therapy group. There were no major late surgical complications.

Conclusions. Among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery resulted in glycemic control in significantly more patients than did medical therapy alone. Analyses of secondary end points, including body weight, use of glucose-lowering medications, and quality of life, also showed favorable results at 3 years in the surgical groups, as compared with the group receiving medical therapy alone.

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