

Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American College of Cardiology (San Francisco, CA, United States, March 8-12, 2013)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales del *American College of Cardiology* (San Francisco, California, Estados Unidos, 8-12 de marzo de 2013)

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Following its policy of disseminating scientific information to the cardiology community,¹⁻⁷ *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Scientific Sessions of the American American College of Cardiology (San Francisco, CA, 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.

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LATE-BREAKING CLINICAL TRIALS I

HPS2-THRIVE: Randomized Comparison of Extended-Release (ER) Niacin/Laropiprant 2 g Daily Versus Placebo in 25 673 Patients at High Risk of Occlusive Vascular Events⁸

Presented by Jane Armitage, Oxford, England.

Background. The HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) study. There is limited evidence that increasing HDL cholesterol will have positive effects on cardiovascular disease (CD) risk; therefore, this study evaluates the clinical effects of increasing HDL cholesterol with ER niacin combined with laropiprant, a drug to decrease the side effects of niacin, for patients with vascular disease and receiving LDL cholesterol lowering medication(s). The purpose of this study is to determine the role of niacin and whether adding HDL cholesterol to a statin-based treatment decreases the risk of vascular events in patients at high risk of occlusive vascular events.

Methods. 25 673 patients (M, F), 50 to 80 years old; >240 hospitals/clinics in the United Kingdom, China and Scandinavia; randomized double blind, placebo controlled study; all patients treated daily with a statin based medication; intervention group treated with the addition of the drug ER niacin/laropiprant (2 g daily); study participants had vascular disease; median follow-up 3.9 years. Primary outcomes: time to first major vascular event during scheduled treatment; non-fatal MI or coronary death, stroke, or revascularization. Secondary outcomes: major coronary events, stroke, revascularization or mortality during the scheduled treatment period.

Results. No significant benefit of ER niacin/laropiprant on the primary outcome of major vascular events when added to effective statin-based LDL-lowering therapy. There were significant excesses of serious adverse events (SAEs) due to known and unrecognized side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000. There was no clear evidence of differences in efficacy or safety in different types of patient (except for an excess of statin-related myopathy in Chinese patients).

Conclusions. Use of the ER niacin/laropiprant with a statin-based treatment does not significantly lower risk of combined occlusive vascular events (i.e., coronary deaths, non-fatal heart attacks, strokes or revascularizations) compared to only statin-based treatment. Findings are consistent with previous niacin trials. The role of ER niacin for the treatment and prevention of cardiovascular disease needs to be reconsidered.

LATE-BREAKING CLINICAL TRIALS II: INTERVENTIONAL

Early High-dose Rosuvastatin for Contrast-induced Nephropathy Prevention in Acute Coronary Syndrome⁹

Presented by Anna Toso, Milan, Italy.

Background. Anti-lipidemics with their pleiotropic properties (anti-oxidant, anti-inflammatory, anti-thrombotic) may have a nephro-protective effect improving endothelial function and reducing oxidative stress. However, the type, dose, timing, and target population are not known. The objective of the study was to assess if an early high dose of hydrophilic statin rosuvastatin, in addition to standard preventive measures (hydration and N-Acetylcystein), exert beneficial effects against CI-AKI in statin-naïve patients with NSTEMI scheduled for early invasive strategy.

Methods. All consecutive statin-naïve NSTEMI patients admitted and scheduled for early invasive strategy were enrolled between July 2010 and August 2012. A total of 543 patients were randomized to

receive rosuvastatin [40 mg load dose and 20 mg/daily (n=271)] or standard therapy (n=272) before the invasive strategy. Primary endpoint: increment of creatinine ≥ 0.5 mg/dL or $\geq 25\%$ within 72 hours of exposure. Additional endpoints: CI-AKI defined by other criteria, CI-AKI in pre-specified subgroups and adverse clinical events at 30 days. Antiplatelet treatment was ASA 300 mg load dose and 100 mg/daily and clopidogrel 600 mg load dose and 150 mg/daily. Hydration with isotonic saline as well as oral N-Acetylcystein (2400 mg/daily) were given intravenously pre- and post-contrast. Nonionic, dimeric iso-osmolar contrast medium with power injector was administered. At discharge, clopidogrel 75 mg/daily and ASA 100 mg/daily were maintained and Rosuvastatin group continued taking rosuvastatin 20 mg/daily and Control group, atorvastatin 40 mg/daily.

Results. In patients who fulfill all criteria, Rosuvastatin group (n=252) had less CI-AKI compared to controls (n=252) [$P=.001$; OR crude (95% CI): 0.41 (0.22-0.74); OR adjusted (95% CI): 0.38 (0.20-0.71); NNT=12].

Conclusions. In statin-naïve patients with NSTEMI-ACS scheduled for early invasive strategy, on-admission high-dose rosuvastatin exerts additional preventive effects against CI-AKI (with hydration and N-Acetylcystein) and is associated with better short-term clinical outcome. This study suggests that high-dose statins should be given prior to angiographic procedures to reduce renal complications after contrast medium administration.

A Randomized Evaluation of the SAPIEN XT Transcatheter Valve System in Patients with Aortic Stenosis Who Are Not Candidates for Surgery: PARTNER 2, Cohort B Outcomes¹⁰

Presented by Martin Leon, New York, United States.

Background. The PARTNER trial compared the aortic valve replacement in high-risk patients using a transcatheter valve to surgical aortic valve replacement alone. Although these patients had a reduction in 1-year mortality, transcatheter aortic valve replacement in this trial resulted in more peri-procedural strokes and paravalvular regurgitation.

Methods. Partner A randomized 699 elderly patients (mean age 84.1) with severe aortic stenosis to surgical aortic valve replacement or transcatheter aortic valve replacement in one of 26 centers in the United States, Canada, or Germany. The approach for transcatheter aortic valve replacement was transfemoral (244 patients) or transapical (104 patients).

Results. At 3 years, overall mortality was almost identical in both groups, 44.8% for surgical aortic valve replacement and 44.2% for transcatheter aortic valve replacement. In a historical analysis looking only at deaths between 1 and 3 years, 26.3% of patients in the transcatheter aortic valve replacement group who were alive at year one were dead at 3 years, compared with 24.5% of surgical aortic valve replacement patients. Stroke rates were similar at 3 years: 8.2% in the transcatheter aortic valve replacement group and 9.3% in the surgical aortic valve replacement. Death rates from all causes or all stroke were 47.1% in the transcatheter aortic valve replacement group and 45.9% in the surgical aortic valve replacement group.

Conclusions. After a 3-year follow up, the rates of stroke and all-cause mortality were similar in both groups.

One-year Outcome of a Trial Comparing Second Generation Drug-eluting Stents Using Either Biodegradable Polymer or Durable Polymer: the NOBORI™ Biolimus-eluting Versus XIENCE™/PROMUS™ Everolimus-eluting Stent Trial (NEXT)¹¹

Presented by Masahiro Natsuaki, Kyoto, Japan.

Background. The purpose of this study is to evaluate whether the biolimus-eluting stent (BES) is not inferior to the everolimus-eluting

stent (EES) in terms of the rate of target-lesion revascularization (TLR) at 1 year and death or myocardial infarction at 3 years after stent implantation in the real world clinical practice. The design of this study is all-comer, enrolling patients scheduled for percutaneous coronary intervention using drug-eluting stents without any exclusion criteria.

Methods. Multicenter, randomized, noninferiority trial comparing BES with EES. A total of 3200 patients scheduled for PCI using drug-eluting stent were included without exclusion criteria (all-comer design). They were randomized (1:1) to Nobori (BES, 1600 patients) or XIENCE V/ PROMUS (EES, 1600 patients) stenting. Follow-up was established at 1, 2, and 3 years. Imaging sub-studies were carried out at 8-12 months: Angiography (500 patients), IVUS/OCT (120 patients) and endothelial function (100 patients). Primary efficacy endpoint: Any TLR at 1 year. Primary safety endpoint: Death or myocardial infarction at 3 years.

Results. Despite the all-comers trial design, the actual study population mostly included patients with stable coronary artery disease (>80% in both arms). BES was not inferior to EES in the primary efficacy endpoint at 1 year: 4.2% (BES) vs 4.2% (EES) ($P_{\text{noninferiority}} < .0001$). Neither was inferior in terms of in-segment late loss 0.03 mm vs 0.06 mm ($P_{\text{noninferiority}} < .0001$). With respect to safety, there were no differences in total death (2.6% vs 2.5%), myocardial infarction (3.3% vs 3.1%), and definite stent thrombosis (0.25% vs 0.06%).

Conclusions. 1) In this large-scale, randomized, controlled trial, BES was demonstrated to be noninferior to EES with respect to 1-year TLR rate and 8-12 months angiographic in-segment late loss. 2) One-year clinical outcome after both BES and EES use was excellent with low rate of TLR and very low rate of stent thrombosis. 3) Long-term follow-up of the biodegradable polymer BES compared with the durable polymer EES will provide crucial implications for the future development of metallic drug-eluting stents.

Comparison of DK Crush Versus Culotte Stenting for Unprotected Distal Left Main Bifurcation Lesions: Results From a Multicenter, Randomized, Prospective DKCRUSH-III Study¹²

Presented by Junjie Zhang, Nanjing, China.

Background. The study aimed to investigate the difference in major adverse cardiac events at 1 year after double kissing crush versus culotte stenting for unprotected left main coronary artery distal bifurcation lesions. Double kissing crush and culotte stenting is reported to be effective for treatment of coronary bifurcation lesions. However, their comparative performance in unprotected left main coronary artery bifurcation lesions is not known.

Methods. A total of 419 patients with unprotected left main coronary artery bifurcation lesions were randomly assigned to double kissing (n=210) or culotte (n=209) treatment. The primary endpoint was the occurrence of a major adverse cardiac event at 1 year, including cardiac death, myocardial infarction, and target vessel revascularization. In-stent restenosis at 8 months was secondary endpoint, and stent thrombosis served as a safety endpoint. Patients were stratified by SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) and NERS (New Risk Stratification) scores.

Results. Patients in the culotte group had significant higher 1-year major adverse cardiac event rate (16.3%), mainly driven by increased target vessel revascularization (11.0%), compared with the double kissing group (6.2% and 4.3%, respectively; all $P < .05$). In-stent restenosis rate in side branch was 12.6% in the culotte group and 6.8% in the double kissing group ($P = 0.037$). Definite stent thrombosis rate was 1% in the culotte group and 0% in the double kissing group ($P = .248$). Among patients with bifurcation angle $\geq 70^\circ$, NERS score ≥ 20 , and SYNTAX score ≥ 23 , the 1-year major adverse cardiac event

rate in the double kissing group (3.8%, 9.2%, and 7.1%, respectively) was significantly different from those in the culotte group (16.5%, 20.4%, and 18.9%, respectively; all $P < .05$).

Conclusions. Culotte stenting for unprotected left main coronary artery bifurcation lesions was associated with significantly increased major adverse cardiac events, mainly due to the increased target vessel revascularization.

The Main Results of the CHAMPION PHOENIX Trial: Effect of Platelet Inhibition With Cangrelor During PCI on Ischemic Events¹³

Presented by Deepak Bhatt, Boston, Massachusetts, United States.

Background. The intensity of antiplatelet therapy during percutaneous coronary intervention (PCI) is an important determinant of PCI-related ischemic complications. Cangrelor is a potent intravenous adenosine diphosphate (ADP)-receptor antagonist that acts rapidly and has quickly reversible effects.

Methods. In a double-blind, placebo-controlled trial, we randomly assigned 11 145 patients who were undergoing either urgent or elective PCI and were receiving guideline-recommended therapy to receive a bolus and infusion of cangrelor or to receive a loading dose of 600 mg or 300 mg of clopidogrel. The primary efficacy end point was a composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization; the key secondary end point was stent thrombosis at 48 hours. The primary safety end point was severe bleeding at 48 hours.

Results. The rate of the primary efficacy end point was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (adjusted odds ratio with cangrelor, 0.78; 95% confidence interval [CI], 0.66 to 0.93; $P = .005$). The rate of the primary safety end point was 0.16% in the cangrelor group and 0.11% in the clopidogrel group (odds ratio, 1.50; 95% CI, 0.53 to 4.22; $P = .44$). Stent thrombosis developed in 0.8% of the patients in the cangrelor group and in 1.4% in the clopidogrel group (odds ratio, 0.62; 95% CI, 0.43 to 0.90; $P = .01$). The rates of adverse events related to the study treatment were low in both groups, though transient dyspnea occurred significantly more frequently with cangrelor than with clopidogrel (1.2% vs 0.3%). The benefit from cangrelor with respect to the primary end point was consistent across multiple prespecified subgroups.

Conclusions. Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding.

LATE-BREAKING CLINICAL TRIALS III: CHRONIC CAD/STABLE ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROMES

The STREAM Trial: Fibrinolysis or Primary PCI in ST-segment Elevation Myocardial Infarction¹⁴

Presented by Frans Van de Werf, Leuven, Belgium.

Background. It is not known whether prehospital fibrinolysis, coupled with timely coronary angiography, provides a clinical outcome similar to that with early primary percutaneous coronary intervention after acute ST-segment elevation myocardial infarction (STEMI).

Methods. Among 1892 patients with ST-segment elevation myocardial infarction who presented within 3 hours after symptom onset and who were unable to undergo primary percutaneous coronary intervention within 1 hour, patients were randomly

assigned to undergo either primary percutaneous coronary intervention or fibrinolytic therapy with bolus tenecteplase (amended to half dose in patients ≥ 75 years of age), clopidogrel, and enoxaparin before transport to a hospital capable of performing percutaneous coronary interventions. Emergency coronary angiography was performed if fibrinolysis failed; otherwise, angiography was performed 6 to 24 hours after randomization. The primary end point was a composite of death, shock, congestive heart failure, or reinfarction up to 30 days.

Results. The primary end point occurred in 116 of 939 patients (12.4%) in the fibrinolysis group and in 135 of 943 patients (14.3%) in the primary percutaneous coronary intervention group (relative risk in the fibrinolysis group, 0.86; 95% confidence interval, 0.68 to 1.09; $P=.21$). Emergency angiography was required in 36.3% of patients in the fibrinolysis group, whereas the remainder of patients underwent angiography at a median of 17 hours after randomization. More intracranial hemorrhages occurred in the fibrinolysis group than in the primary percutaneous coronary intervention group (1.0% vs 0.2%, $P=.04$; after protocol amendment, 0.5% vs 0.3%, $P=.45$). The rates of nonintracranial bleeding were similar in the two groups.

Conclusions. Prehospital fibrinolysis with timely coronary angiography resulted in effective reperfusion in patients with early STEMI who could not undergo primary percutaneous coronary intervention within 1 hour after the first medical contact. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding.

Early Administration of Eplerenone in Patients With Acute Myocardial Infarction Without Heart Failure: Results of the Randomized, Double-blind, Placebo-controlled REMINDER Trial¹⁵

Presented by Gilles Montalescot, Paris, France.

Background. There is increasing body of evidence supporting the use of mineralocorticoid receptor blockade in advanced and mild heart failure (HF), such as the EPHEsus and RALES trial. The objective of the study was to assess if eplerenone reduces cardiovascular mortality (CV) and morbidity in patients with acute myocardial infarction (AMI) and no HF.

Methods. Interventional, randomized, double-blind, placebo-controlled trial in patients having had an ST-elevation AMI within 24 hours and ejection fraction $>40\%$, without history of HF. Primary composite endpoint: time to first event (CV mortality, re-hospitalization or extended initial hospital stay due to diagnosis of HF, sustained ventricular tachycardia or fibrillation in the first 18 months).

Results. A total of 1012 patients were enrolled and mean follow-up was 10.5 months. Fewer events were reported in the eplerenone group (93, 18.4%) as compared to the placebo group (150, 29.6%), adjusted hazard ratio 0.571; 95% confidence interval 0.439; $P<.0001$.

Conclusions. This study strengthens the evidence in support of aldosterone blockade therapy in AMI to improve clinical outcomes.

Effects of the P-selectin Antagonist Inclacumab in the Select-acute Coronary Syndromes Trial¹⁶

Presented by Jean-Claude Tardif, Montreal, Canada.

Background. The study aimed at evaluating inclacumab for reduction of myocardial damage during percutaneous coronary intervention (PCI) in patients with non-ST segment elevation myocardial infarction (NSTEMI). P-selectin is an adhesion molecule involved in interactions between endothelial cells, platelets, and leukocytes. Inclacumab is a recombinant monoclonal antibody against P-selectin, with potential anti-inflammatory, anti-thrombotic, and anti-atherogenic properties.

Methods. Patients ($n=544$) with NSTEMI scheduled for coronary angiography and possible ad hoc PCI were randomized to receive one pre-procedural infusion of inclacumab 5 or 20 mg/kg or placebo. The primary end point, evaluated in patients who underwent PCI, received study medication, and had available efficacy data ($n=322$), was the change from baseline in troponin I (TnI) at 16 and 24 hours after PCI.

Results. There was no effect of inclacumab 5 mg/kg. Placebo-adjusted geometric mean percent changes in TnI with inclacumab 20 mg/kg were -24.4% at 24 hours ($P=.05$) and -22.4% at 16 hours ($P=.07$). Peak TnI was reduced by 23.8% ($P=.05$) and area under the curve over 24 hours by 33.9% ($P=.08$). CK-MB yielded similar results, with changes of -17.4% at 24 hours ($P=.06$) and -16.3% at 16 hours ($P=.09$). The incidence of CK-MB increases >3 times ULN within 24 hours was 18.3% and 8.9% in the placebo and inclacumab 20 mg/kg groups ($P=.05$). Placebo-adjusted changes in soluble p-selectin level were -9.5% ($P=.25$) and -22.0% ($P<0.01$) with inclacumab 5 and 20 mg/kg. There was no significant difference in adverse events between groups.

Conclusions. Inclacumab appears to reduce myocardial damage after PCI in patients with NSTEMI.

Randomized Comparison of High-dose Oral Vitamins Versus Placebo in the Trial to Assess Chelation Therapy¹⁷

Presented by Gervasio Lamas, New York, United States.

Background. Chelation therapy has been predicted to produce an improvement in symptoms, endothelial function, and major vascular events and reduction in atherosclerotic plaque. The objective was to determine the benefits and risks of the use of high doses of vitamins and minerals and chelation therapy in patients with prior myocardial infarction.

Methods. Randomized, double-blind, placebo-controlled 2x2 trial. Patients were randomized to receive 40 doses of a disodium EDTA-chelation solution vs placebo and 3 oral doses of vitamins and minerals twice daily vs placebo. The primary endpoint was a composite of all-cause mortality, myocardial infarction, stroke, coronary revascularization, and hospitalization for angina.

Results. In total, 1704 patients were included. There was only a modest reduction in cardiac events in the chelation therapy group, both in the treatment group with vitamins and minerals and in the group without them.

Conclusions. Chelation treatment with or without supplements provides a modest reduction in cardiac events compared to a placebo treatment. The use of high-dose and mineral therapy in prior MI patients in addition to standard medical therapy to reduce the occurrence of additional cardiac events is not supported by these results.

Evaluation of Ranolazine in Patients With Type 2 Diabetes Mellitus and Chronic Stable Angina: Results From the Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) Randomized Clinical Trial¹⁸

Presented by Mikhail Kosiborod, Kansas City, Missouri, United States.

Background. To examine the efficacy of ranolazine versus placebo on weekly angina frequency in subjects with type 2 diabetes, CAD, and chronic stable angina who remain symptomatic despite treatment with up to 2 antianginal agents. Patients with diabetes have more extensive coronary artery disease (CAD) than those without diabetes, and a high burden of angina. Ranolazine is not only effective in treating angina but also may improve glycemic control, thus providing several potential benefits in this high-risk group. We conducted a randomized trial to test the antianginal benefit of ranolazine in patients with diabetes and stable angina.

Methods. TERISA was an international, randomized, double-blind trial of ranolazine vs placebo in patients with diabetes, CAD, and stable angina treated with 1-2 antianginals. After a single-blind, 4-week placebo run-in, patients were randomized to 8 weeks of double-blind ranolazine (target dose 1000 mg bid) or placebo. Anginal episodes and nitroglycerin use were recorded with daily entry into a novel electronic diary. Primary outcome was the average weekly number of anginal episodes over the last 6 weeks of the study.

Results. A total of 949 patients were randomized across 104 centers in 14 countries. Mean age was 64 years, 61% were men, mean diabetes duration was 7.5 yrs, and mean baseline HbA1c was 7.3%. Electronic diary data capture was 98% in both groups. Weekly angina frequency was significantly lower with ranolazine versus placebo (3.8 [3.6-4.1] vs 4.3 [4.0-4.5] episodes, $P=.008$), as was the weekly sublingual nitroglycerin use (1.7 [1.6-1.9] vs 2.1 [1.9-2.3] doses, $P=.003$). There was no difference in the incidence of serious adverse events between groups.

Conclusions. Among patients with diabetes and chronic angina despite treatment with up to 2 agents, ranolazine reduced angina and sublingual nitroglycerin use and was well tolerated.

LATE-BREAKING CLINICAL TRIALS IV: GENERAL CARDIOLOGY

Three-year Outcomes After Transcatheter or Surgical Aortic Valve Replacement in High-risk Patients With Severe Aortic Stenosis¹⁹

Presented by Vinod Thourani, Atlanta, Georgia, United States.

Background. The PARTNER trial compared replacement of the aortic valve in high-risk patients using a transcatheter valve to surgical aortic valve replacement alone (SAVR). Although these patients had a reduction in 1-year mortality, transcatheter aortic valve replacement (TAVR) in this trial resulted in more periprocedural strokes and paravalvular regurgitation. The objective of this study was to report 3-year outcomes.

Methods. PARTNER A randomized 699 elderly patients (median age 84.1) with severe aortic stenosis to either TAVR or conventional surgery at one of 26 centers in the United States, Canada, or Germany, with patients in the TAVR group undergoing either a transfemoral procedure (244 patients) or a transapical procedure (104 patients).

Results. In the 3-year outcomes, all-cause mortality was nearly identical in both groups, at 44.8% for surgical AVR and 44.2% for TAVR. In a landmark analysis looking only at deaths between 1 and 3 years, 26.3% of TAVR patients still alive at 12 months were dead by year 3, as compared with 24.5% of SAVR-treated patients. Stroke rates were no different at 3 years: 8.2% in the TAVR group and 9.3% in the surgical-AVR group. Rates of all-cause mortality or stroke, combined, were 47.1% in the TAVR group and 45.9% in the SAVR group.

Conclusions. Rates of both stroke and all-cause mortality were similar between both groups of patients at 3 years out of follow-up.

A Randomized Trial to Compare Percutaneous Coronary Intervention Between Massachusetts Hospitals With Cardiac Surgery On-site and Community Hospitals Without Cardiac Surgery On-site²⁰

Presented by Alice Jacobs, Boston, Massachusetts, United States.

Background. Emergency surgery has become a rare event after percutaneous coronary intervention (PCI). Whether having cardiac-

surgery services available on-site is essential for ensuring the best possible outcomes during and after PCI remains uncertain.

Methods. We enrolled patients with indications for nonemergency PCI who presented at hospitals in Massachusetts without on-site cardiac surgery and randomly assigned these patients, in a 3:1 ratio, to undergo PCI at that hospital or at a partner hospital that had cardiac surgery services available. A total of 10 hospitals without on-site cardiac surgery and 7 with on-site cardiac surgery participated. The coprimary end points were the rates of major adverse cardiac events — a composite of death, myocardial infarction, repeat revascularization, or stroke — at 30 days (safety end point) and at 12 months (effectiveness end point). The primary end points were analyzed according to the intention-to-treat principle and were tested with the use of multiplicative noninferiority margins of 1.5 (for safety) and 1.3 (for effectiveness).

Results. A total of 3691 patients were randomly assigned to undergo PCI at a hospital without on-site cardiac surgery (2774 patients) or at a hospital with on-site cardiac surgery (917 patients). The rates of major adverse cardiac events were 9.5% in hospitals without on-site cardiac surgery and 9.4% in hospitals with on-site cardiac surgery at 30 days (relative risk, 1.00; 95% one-sided upper confidence limit, 1.22; $P_{\text{noninferiority}} <.001$) and 17.3% and 17.8%, respectively, at 12 months (relative risk, 0.98; 95% one-sided upper confidence limit, 1.13; $P_{\text{noninferiority}} <.001$). The rates of death, myocardial infarction, repeat revascularization, and stroke (the components of the primary end point) did not differ significantly between the groups at either time point.

Conclusions. Nonemergency PCI procedures performed at hospitals in Massachusetts without on-site surgical services were noninferior to procedures performed at hospitals with onsite surgical services with respect to the 30-day and 1-year rates of clinical events.

The German Off-pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE)²¹

Presented by Anno Diegeler, Bad Neustadt, Germany.

Background. The benefits of coronary-artery bypass grafting without cardiopulmonary bypass in the elderly are still undetermined.

Methods. We randomly assigned patients 75 years of age or older who were scheduled for elective first-time coronary-artery bypass grafting to undergo the procedure either without cardiopulmonary bypass (off-pump coronary-artery bypass grafting) or with it (on-pump coronary-artery bypass grafting). The primary end point was a composite of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy at 30 days and at 12 months after surgery.

Results. A total of 2539 patients underwent randomization. At 30 days after surgery, there was no significant difference between patients who underwent off-pump surgery and those who underwent on-pump surgery in terms of the composite outcome (7.8% vs 8.2%; odds ratio, 0.95; 95% confidence interval [CI], 0.71 to 1.28; $P=.74$) or 4 of the components (death, stroke, myocardial infarction, or new renal replacement therapy). Repeat revascularization occurred more frequently after off-pump coronary-artery bypass grafting than after on-pump coronary-artery bypass grafting (1.3% vs 0.4%; odds ratio, 2.42; 95% CI, 1.03 to 5.72; $P=.04$). At 12 months, there was no significant between-group difference in the composite end point (13.1% vs 14.0%; hazard ratio, 0.93; 95% CI, 0.76 to 1.16; $P=.48$) or in any of the individual components. Similar results were obtained in a per-protocol analysis that excluded the 177 patients who crossed over from the assigned treatment to the other treatment.

Conclusions. In patients 75 years of age or older, there was no significant difference between on-pump and off-pump coronary-

artery bypass grafting with regard to the composite outcome of death, stroke, myocardial infarction, repeat revascularization, or new renal-replacement therapy within 30 days and within 12 months after surgery.

CORONARY: The Coronary Artery Bypass Grafting Surgery Off or on Pump Revascularization Study. Results at 1 year²²

Presented by Andre Lamy, Hamilton, Ontario, Canada.

Background. Previously, we reported that there was no significant difference at 30 days in the rate of a primary composite outcome of death, myocardial infarction, stroke, or new renal failure requiring dialysis between patients who underwent coronary-artery bypass grafting performed with a beating-heart technique (off-pump) and those who underwent coronary-artery bypass grafting performed with cardiopulmonary bypass (on-pump). We now report results on quality of life and cognitive function and on clinical outcomes at 1 year.

Methods. We enrolled 4752 patients with coronary artery disease who were scheduled to undergo coronary-artery bypass grafting and randomly assigned them to undergo the procedure off-pump or on-pump. Patients were enrolled at 79 centers in 19 countries. We assessed quality of life and cognitive function at discharge, at 30 days, and at 1 year and clinical outcomes at 1 year.

Results. At 1 year, there was no significant difference in the rate of the primary composite outcome between off-pump and on-pump coronary-artery bypass grafting (12.1% and 13.3%, respectively; hazard ratio with off-pump coronary-artery bypass grafting, 0.91; 95% confidence interval [CI], 0.77 to 1.07; $P=.24$). The rate of the primary outcome was also similar in both groups in the period between 31 days and 1 year (hazard ratio, 0.79; 95% CI, 0.55 to 1.13; $P=.19$). The rate of repeat coronary revascularization at 1 year was 1.4% in the off-pump group and 0.8% in the on-pump group (hazard ratio, 1.66; 95%CI 0.95-2.89; $P=.07$). There were no significant differences between groups at 1 year in measures of quality of life or neurocognitive function.

Conclusions. At 1 year after coronary-artery bypass grafting, there was no significant difference between off-pump and on-pump coronary-artery bypass grafting with respect to the primary composite outcome, the rate of repeat coronary revascularization, quality of life, or neurocognitive function.

PRAGUE-6 Trial: Off-pump Versus On-pump Coronary Artery Bypass Graft Surgery in Patients With EuroSCORE ≥ 6 ²³

Presented Jan Hlavicka, Prague, Czech Republic.

Background. The study aimed to determine if off-pump CABG has better outcome and fewer complications than on-pump surgery in high-risk surgical patients.

Methods. The study recruited 206 high risk patients with a EuroSCORE < 6 . Patients were randomized to coronary artery bypass graft surgery with or without pump. The primary objective was the composite of death, myocardial infarction, stroke or kidney failure requiring dialysis.

Results. At 30 days of follow up, the results showed a reduction in the primary objective on the surgery on-pump group. In addition, there was a reduction in the need for transfusion and surgical re-exploration for bleeding and tamponade.

Conclusions. The short-term morbidity is lower in surgical risk patients if pump surgery is used, because the procedure is shorter. The shorter the procedure, the better, especially in older patients with more comorbidities.

LATE-BREAKING CLINICAL TRIALS V: HEART FAILURE

The St Vincent's Screening to Prevent Heart Failure Study: Impact of Natriuretic Peptide Guided Screening and Treatment on Long-term Prevalence of Left Ventricular Dysfunction, Heart Failure and Cardiovascular Events²⁴

Presented by Mark Ledwidge, Dublin, Ireland.

Background. Natriuretic peptides may be a reliable marker to diagnose the status of heart failure. The aim of the study is to analyze whether a natriuretic peptide-guided screening (PN) and shared care treatment have an impact on the long-term prevalence of left ventricular dysfunction, heart failure, and cardiovascular events.

Methods. A prospective, randomized, study with a control group of patients over 40 years with risk factors for heart failure, screened yearly for cardiovascular risk factors and plasma natriuretic peptide, treated by family physician, and an intervention group with B-Type natriuretic peptide levels over 50 pg/mL, echocardiogram and care shared between a family doctor and a specialist. Primary Endpoint: prevalence of left ventricular dysfunction and heart failure.

Results. We included a total of 1374 patients with a mean age of 64.7 years. Mean follow-up was 4.3 years. In the control group, 8.7% of patients had left ventricular dysfunction or heart failure and 40.4% were hospitalized for cardiovascular events vs 5.3% of left ventricular dysfunction /heart failure and 22.3% of hospitalizations for cardiovascular events in the intervention group.

Conclusions. Patients at risk of heart failure receiving shared care and natriuretic peptide-guided screening had a reduction in the long-term prevalence of left ventricular dysfunction and heart failure as well as the incidence rate of major cardiovascular events.

Digoxin Reduces 30-Day All-cause Hospital Admission in Ambulatory Older Patients With Chronic Heart Failure and Reduced Ejection Fraction²⁵

Presented by Ali Ahmed, Birmingham, Alabama, United States.

Background. Heart failure is a leading cause of hospital admission and readmission in older adults. The new United States healthcare reform law has created provisions for financial penalties for hospitals with higher than expected 30-day all-cause readmission rates for hospitalized Medicare beneficiaries aged ≥ 65 years with heart failure. We examined the effect of digoxin on 30-day all-cause hospital admission in older patients with heart failure and reduced ejection fraction.

Methods. In the main Digitalis Investigation Group trial, 6800 ambulatory patients with chronic heart failure (ejection fraction $\geq 5\%$) were randomly assigned to digoxin or placebo. Of these, 3405 were aged ≥ 65 years (mean age, 72 years; 25% were women; 11% were nonwhite). The main outcome in the current analysis was 30-day all-cause hospital admission.

Results. In the first 30 days after randomization, all-cause hospitalization occurred in 5.4% (92/1693) and 8.1% (139/1712) of patients in the digoxin and placebo groups, respectively, (hazard ratio [HR] when digoxin was compared with placebo, 0.66; 95% confidence interval [CI], 0.51-0.86; $P=.002$). Digoxin also reduced both 30-day cardiovascular (3.5% vs 6.5%; HR, 0.53; 95%CI, 0.38-0.72; $P<.001$) and heart failure (1.7 vs 4.2%; HR, 0.40; 95%CI, 0.26-0.62; $P<.001$) hospitalizations, with similar trends for 30-day all-cause mortality (0.7% vs 1.3%; HR, 0.55; 95% CI, 0.27-1.11; $P=.096$). Younger patients were at lower risk of events but obtained similar benefits from digoxin.

Conclusions. Digoxin reduces 30-day all-cause hospital admission in ambulatory older patients with chronic systolic heart failure. Future studies need to examine its effect on 30-day all-cause hospital readmission in hospitalized patients with acute heart failure.

The ASTRONAUT Study: Aliskiren Trial on Acute Heart Failure Outcomes²⁶

Presented by Mihai Gheorghide Chicago, Illinois, United States.

Background. To investigate whether aliskiren, a direct renin inhibitor, when added to standard therapy, would reduce the rate of cardiovascular (CV) death or HF rehospitalization among HHF patients. Hospitalizations for heart failure (HHF) represent a major health burden, with high rates of early postdischarge rehospitalization and mortality.

Methods. International, double-blind, placebo-controlled study that randomized hemodynamically stable HHF patients a median 5 days after admission. Eligible patients were 18 years or older with left ventricular ejection fraction (LVEF) 40% or less, elevated natriuretic peptides (brain natriuretic peptide [BNP] ≥ 400 pg/mL or N-terminal pro-BNP [NT-proBNP] ≥ 1600 pg/mL), and signs and symptoms of fluid overload. Patients were recruited from 316 sites across North and South America, Europe, and Asia between May 2009 and December 2011. The follow-up period ended in July 2012. All patients received 150 mg (increased to 300 mg as tolerated) of aliskiren or placebo daily, in addition to standard therapy. The study drug was continued after discharge for a median 11.3 months. Cardiovascular death or HF rehospitalization at 6 months and 12 months.

Results. In total, 1639 patients were randomized, with 1615 patients included in the final efficacy analysis cohort (808 aliskiren, 807 placebo). Mean age was 65 years; mean LVEF, 28%; 41% of patients had diabetes mellitus, mean estimated glomerular filtration rate, 67 mL/min/1.73 m². At admission and randomization, median NT-proBNP levels were 4239 pg/mL and 2718 pg/mL, respectively. At randomization, patients were receiving diuretics (95.9%), β -blockers (82.5%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (84.2%), and mineralocorticoid receptor antagonists (57.0%). In total, 24.9% of patients receiving aliskiren (77 CV deaths, 153 HF rehospitalizations) and 26.5% of patients receiving placebo (85 CV deaths, 166 HF rehospitalizations) experienced the primary end point at 6 months (hazard ratio [HR], 0.92; 95% CI, 0.76-1.12; $P=.41$). At 12 months, the event rates were 35.0% for the aliskiren group (126 CV deaths, 212 HF rehospitalizations) and 37.3% for the placebo group (137 CV deaths, 224 HF rehospitalizations; HR, 0.93; 95%CI, 0.79-1.09; $P=.36$). The rates of hyperkalemia, hypotension, and renal impairment/renal failure were higher in the aliskiren group compared with placebo.

Conclusions. Among patients hospitalized for HF with reduced LVEF, initiation of aliskiren in addition to standard therapy did not reduce CV death or HF rehospitalization at 6 months or 12 months after discharge.

Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) Trial²⁷

Presented by Margaret Redfield, Rochester, Minnesota, United States.

Background. To determine the effect of the phosphodiesterase-5 inhibitor sildenafil compared with placebo on exercise capacity and clinical status in HFPEF. Studies in experimental and human heart failure suggest that phosphodiesterase-5 inhibitors may enhance cardiovascular function and thus exercise capacity in heart failure with preserved ejection fraction (HFPEF).

Methods. Multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial of 216 stable outpatients with HF,

ejection fraction $\geq 50\%$, elevated N-terminal brain-type natriuretic peptide or elevated invasively measured filling pressures, and reduced exercise capacity. Participants were randomized from October 2008 through February 2012 at 26 centers in North America. Follow-up was through August 30, 2012. Sildenafil (n=113) or placebo (n=103) was administered orally at 20 mg, 3 times daily for 12 weeks, followed by 60 mg, 3 times daily for 12 weeks. Primary end point was change in peak oxygen consumption after 24 weeks of therapy. Secondary end points included change in 6-minute walk distance and a hierarchical composite clinical status score (range, 1-n, a higher value indicates better status; expected value with no treatment effect, 95) based on time to death, time to cardiovascular or cardiorenal hospitalization, and change in quality of life for participants without cardiovascular or cardiorenal hospitalization at 24 weeks.

Results. Median age was 69 years, and 48% of patients were women. At baseline, median peak oxygen consumption (11.7 mL/kg/min) and 6-minute walk distance (308 m) were reduced. The median E/e⁻¹ (16), left atrial volume index (44 mL/m²), and pulmonary artery systolic pressure (41 mmHg) were consistent with chronically elevated left ventricular filling pressures. At 24 weeks, median (IQR) changes in peak oxygen consumption (mL/kg/min) in patients who received placebo (-0.20 [IQR, -0.70 to 1.00]) or sildenafil (-0.20 [IQR, -1.70 to 1.11]) were not significantly different ($P=.90$) in analyses in which patients with missing week-24 data were excluded, and in sensitivity analysis based on intention to treat with multiple imputation for missing values (mean between-group difference, 0.01 mL/kg/min, [95% CI, -0.60 to 0.61]). The mean clinical status rank score was not significantly different at 24 weeks between placebo (95.8) and sildenafil (94.2) ($P=.85$). Changes in 6-minute walk distance at 24 weeks in patients who received placebo (15.0 m [IQR, -26.0 to 45.0]) or sildenafil (5.0 m [IQR, -37.0 to 55.0]; $P=.92$) were also not significantly different. Adverse events occurred in 78 placebo patients (76%) and 90 sildenafil patients (80%). Serious adverse events occurred in 16 placebo patients (16%) and 25 sildenafil patients (22%).

Conclusions. Among patients with HFPEF, phosphodiesterase-5 inhibition with administration of sildenafil for 24 weeks, compared with placebo, did not result in significant improvement in exercise capacity or clinical status.

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