

Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Orlando, United States, November 12-16, 2011)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales de la *American Heart Association* (Orlando, Estados Unidos, 12-16 de noviembre de 2011)

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Following its policy of disseminating scientific information to the cardiology community,¹⁻⁹ *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Annual Scientific Sessions of the American Heart Association (Orlando, United States, November 12-16, 2011), 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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Lipid-Modulating Effects of Evacetrapib, a Novel CETP Inhibitor, Administered as Monotherapy or in Combination With the Most Commonly-Used Statins.

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Full English text available from: www.revescardiol.org

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ACUTE CORONARY SYNDROMES

ISAR-REACT 4: Abciximab Plus Unfractionated Heparin Versus Bivalirudin in Patients With Non-ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention¹⁰

Presenter: Adnan Kastrati, Munich, Germany.

Introduction. The combination of glycoprotein IIb/IIIa inhibitors and heparin has not been compared with bivalirudin in studies specifically involving patients with non-ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (PCI). We compared the two treatments in this patient population.

Methods. Immediately before PCI, we randomly assigned, in a double-blind manner, 1721 patients with acute non-ST-segment elevation myocardial infarction to receive abciximab plus unfractionated heparin (861 patients) or bivalirudin (860 patients). The study tested the hypothesis that abciximab and heparin would be superior to bivalirudin with respect to the primary composite end point of death, large recurrent myocardial infarction, urgent target-vessel revascularization, or major bleeding within 30 days. Secondary end points included the composite of death, any recurrent myocardial infarction, or urgent target-vessel revascularization (efficacy end point) and major bleeding (safety end point) within 30 days.

Results. The primary end point occurred in 10.9% of the patients in the abciximab group (94 patients) and in 11% in the bivalirudin group (95 patients) (relative risk with abciximab, 0.99; 95% confidence interval [CI], 0.74 to 1.32; $P=.94$). Death, any recurrent myocardial infarction, or urgent target-vessel revascularization occurred in 12.8% of the patients in the abciximab group (110 patients) and in 13.4% in the bivalirudin group (115 patients) (relative risk, 0.96; 95% CI, 0.74 to 1.25; $P=.76$). Major bleeding occurred in 4.6% of the patients in the abciximab group (40 patients) as compared with 2.6% in the bivalirudin group (22 patients) (relative risk, 1.84; 95% CI, 1.10 to 3.07; $P=.02$).

Conclusions. Abciximab and unfractionated heparin, as compared with bivalirudin, failed to reduce the rate of the primary end point and increased the risk of bleeding among patients with non-ST-segment elevation myocardial infarction who were undergoing PCI.

TRACER: The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome Trial¹¹

Presenter: Kenneth W. Mahaffey, Durham, North Carolina, United States.

Introduction. The platelet protease-activated receptor-1 (PAR-1), the main thrombin receptor, is a novel target for treatment and prevention of arterial thrombosis. The TRACER trial evaluated the efficacy and safety of vorapaxar, a first-in-class, orally active, potent, and selective PAR-1 antagonist, compared with placebo in high-risk patients with non-ST-segment elevation (NSTEMI) ACS treated with current standard of care.

Methods. TRACER is a prospective, randomized, double-blind, placebo-controlled trial in which 12 942 patients were enrolled in 37 countries. Eligible patients had ischemic symptoms within 24 hrs of hospital presentation and either elevated troponin or CK-MB or ST-segment changes on ECG, and at least 1 additional high-risk criterion: age ≥ 55 , prior MI or revascularization procedure (PCI or CABG), diabetes mellitus, or peripheral arterial disease. Vorapaxar or placebo was given as a loading dose (40 mg) followed by a maintenance dose (2.5 mg daily). The primary end point was the composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, and urgent coronary revascularization. The first 3 components of the primary composite (cardiovascular death, MI, or stroke) defined the key secondary efficacy end point. Safety-related end points included the composite of moderate and severe GUSTO bleeding and clinically significant TIMI bleeding. On January 13, 2011, prior to the scheduled completion of the trial follow-up phase, the DSMB informed the trial leadership that the trial should be closed out and that there were a sufficient number of primary and key secondary end point events for the primary analysis.

Results. For the composite primary endpoint, the trend hinting at vorapaxar benefit was driven by a significant 12% reduction in risk of MI ($P=.021$); there was no significant difference in rates for the other components of the primary endpoint. Over two years, vorapaxar was associated with significantly increased GUSTO moderate or severe bleeding (GUSTO severe bleeding went up by 35%; $P<.001$), as well as bleeding that was "clinically significant" by TIMI criteria (the risk of TIMI major bleeding went up by 53%; $P<.001$).

Conclusions. Adding vorapaxar to standard ACS therapy significantly raised the risk of major bleeding complications, including intracranial hemorrhage (ICH), over two years.

ATLAS ACS 2-TIMI 51: Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction¹²

Presenter: C. Michael Gibson, Boston, Massachusetts, United States.

Background. Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose

rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

Methods. In this double-blind, placebo-controlled trial, we randomly assigned 15 526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Results. Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; $P=.008$), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs 10.7%, $P=.02$) and the twice-daily 5-mg dose (8.8% vs 10.7%, $P=.03$). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs 4.1%, $P=.002$) and from any cause (2.9% vs 4.5%, $P=.002$), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs 0.6%, $P<.001$) and intracranial hemorrhage (0.6% vs 0.2%, $P=.009$), without a significant increase in fatal bleeding (0.3% vs 0.2%, $P=.66$) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs 0.4%, $P=.04$).

Conclusions. In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.

INTERVENTIONAL CARDIOLOGY

AIDA-STEMI: Intracoronary Compared With Intravenous Bolus Abciximab Application During Primary Percutaneous Coronary Intervention¹³

Presenter: Holger Thiele, Leipzig, Germany.

Introduction. Intracoronary (IC) abciximab bolus application during PCI results in high local drug concentration, improved perfusion, reduction of infarct size, and less microvascular obstruction in comparison to intravenous (IV) bolus application. Metaanalyses of randomized small- to medium-sized trials suggest a reduction of death and reinfarction with the IC bolus application. The hypothesis of this trial is that IC abciximab bolus in comparison to standard IV application will improve the outcome of patients undergoing primary PCI in STEMI.

Methods. The AIDA STEMI study randomized 2072 STEMI patients at 27 tertiary centers in a 1:1 fashion from July 2008 to April 2011 to either IC or IV bolus abciximab administration during primary PCI with subsequent IV infusion for 12 hours. The primary efficacy endpoint is the composite of all-cause mortality, recurrent infarction or new congestive heart failure within 90 days of randomization. Secondary clinical endpoints are each individual component of the endpoint within 90 days after randomization.

Results. Patient characteristics showed no significant differences in baseline characteristics. At 90 days, the results showed no significant difference in the primary end point. There was a suggestion that new heart failure may be reduced with the IC administration.

Conclusions. There was no benefit of giving abciximab by an IC bolus over the normal IV route.

Evidence-Based, Individualized Informed Consent Form. Testing an Evidence-Based, Individualized Informed Consent Form to Improve Patients' Experiences With PCI¹⁴

Presenter: John Spertus, Kansas City, Missouri, United States.

Introduction. Informed consent for PCI has repeatedly been shown to be deficient. In light of the Institute of Medicine's mandate for the delivery of more evidence-based, safer, cost-effective, personalized care, we implemented a novel program, PRISM, for generating individualized consent forms with patient-specific risk estimates from ACC NCDR Cath-PCI models and tested its impact on patients' experiences with PCI. The authors hypothesized that PRISM-generated consents for PCI would improve patients' experiences, knowledge transfer, and participation in shared medical decision-making.

Methods. A 9-center, pre-post test design of patients undergoing PCI. Primary outcomes included the percentage of patients who read the consent form, knowledge transfer, and patients' participation in decision-making.

Results. The authors interviewed 590 patients receiving traditional consent documents and 527 receiving PRISM consents. Across the entire sample, marked improvements in reviewing (72% for PRISM vs 45% for original consents) and understanding the consent forms were observed. Site-adjusted analyses revealed better understanding of the PRISM consents (odds ratios (ORs)=1.8-3, depending upon the outcome), but there was marked heterogeneity across sites (median relative difference (MRD) in ORs of PRISM's effect=2-3.2). Patients receiving the PRISM consents were more likely to understand the purposes and risks of the procedure (ORs=1.9-3.9, MRDs=1.1-6.2), to engage in shared decision-making (proportional OR=2.1 [95%CI=1.02-4.4], MRD=2.2) and to discuss stent options with their physicians (58% vs 31%; site-adjusted odds ratio=2.7 [95% CI=1.2, 6.3], MRD=2.6).

Conclusions. Informed consent documents, embedded with patient-specific risk estimates, can improve the process of informed consent and shared decision-making. Marked heterogeneity of benefits across hospitals highlights that consent documents are but one aspect of engaging patients in understanding and participating in treatment decisions.

CPORT E: Outcomes of Non-Primary PCI at Hospitals With and Without On-Site Cardiac Surgery: A Randomized Study¹⁵

Presenter: Thomas Aversano, Baltimore, Maryland, United States.

Introduction. It is not clear whether percutaneous coronary intervention (PCI) should only be performed at hospitals with on-site cardiac surgery.

Methods. In the CPORT (Cardiovascular Patient Outcomes Research Team) trial, 18 500 patients were randomized on a 3:1 basis to PCI centers with cardiac-surgery capabilities or hospitals without surgical backup.

Results. PCI success was >90% in both groups but lower in those randomized to hospitals without surgery on-site (success rate difference of 1.1% on a per patient basis). Emergency CABG was rare but occurred more frequently in those randomized to hospitals with surgery on-site compared with those with no surgical backup (0.2% vs 0.1%). The incidence of bleeding, vascular repair, stroke, and renal failure was similar in both groups. Mortality at 6 weeks was 0.93% in the surgical-backup group, compared with 0.91% in the no-surgical-backup group ($P=.94$).

Conclusions. Patients who had elective PCI at experienced US hospitals without on-site cardiac surgery fared no worse than those who had the same procedure at institutions with surgical backup.

ARRHYTHMIAS

ALPHEE: Double Blind Placebo Controlled Dose Ranging Study of the Efficacy and Safety of Celivarone 50, 100 or 300 mg OD With Amiodarone as Calibrator for the Prevention of ICD Interventions or Death¹⁶

Presenter: Peter R. Kowey, Wynnewood, Pennsylvania, United States.

Introduction. The development of an ideal anti-arrhythmic drug that can be used in all patients with arrhythmias has been very complicated due to use of these drugs in patients with underlying heart diseases, particularly with both arrhythmias and heart failure. Celivarone is the first experimental drug being tested for use in pharmacological anti-arrhythmic therapy. The objective of the study was to assess the efficacy of celivarone for the prevention of implantable cardioverter defibrillator (ICD) interventions or death and assess the tolerability and safety of the different dose regimens of celivarone in the selected population.

Methods. Double blind, placebo controlled dose ranging study. Visits are planned to be performed at baseline, after 5 days, after 14 days, every month for 6 months and then, every 3 months after 6 months until the end of the study. The primary endpoints were time to ventricular tachycardia or ventricular fibrillation (VT/VF), triggered ICD interventions or sudden death.

Results. Celivarone did not prevent sudden death or ICD interventions.

Conclusions. More research is needed to identify an intervention to prevent shocks in patients with an ICD.

FAST: Atrial Fibrillation Catheter Ablation versus Surgical Ablation Treatment: a Multi-center Randomized Clinical Trial¹⁷

Presenter: Lucas Boersma, Nieuwegein, Netherlands.

Introduction. The strategies of endocardial catheter ablation isolation of the pulmonary veins and minimally-invasive thorascopic surgical epicardial isolation have been in use for several years now with each reporting results as a successful strategy. The study was designed to provide more insight into the relative merits of both catheter ablation and minimally-invasive surgical ablation and which might be better and/or safer for ablation of drug-refractory atrial fibrillation.

Methods. Interventional, Randomized, Safety/Efficacy Study, Parallel Assignment, Open Label, Treatment (n=129). The primary endpoints were freedom from AF or secondary left atrial arrhythmias lasting >60 seconds and safety or adverse events.

Results. Overall efficacy favored surgical ablation over catheter ablation (65.5% vs 36.5%, $P<.01$). Major adverse events in each group were 23% in the surgical ablation group and 3.2% in the catheter ablation group.

Conclusions. Minimally invasive surgical ablation was more effective than catheter ablation to treat atrial fibrillation, but was significantly more likely to cause major complications.

MANTRA-PAF: A Randomized Multicenter Comparison of Radiofrequency Ablation and Antiarrhythmic Drug Therapy as First-Line Treatment in 294 Patients With Paroxysmal Atrial Fibrillation¹⁸

Presenter: Jens Cosedis Nielsen, Aarhus, Denmark.

Introduction. Medical treatment of atrial fibrillation is characterized by potential side effects and is often only moderately

effective. The purpose of the study was to compare medical antiarrhythmic drug therapy to radiofrequency ablation as first-line treatment in paroxysmal atrial fibrillation.

Methods. Randomized, prospective, phase 3 Scandinavian/German multicenter study, 294 patients. 7-day Holter monitor results, 2-year follow-up. The primary end point was cumulative atrial fibrillation burden (% of atrial fibrillation) over 35 days and then in follow-up.

Results. At 24 months, atrial fibrillation burden was 22/146 in the radiofrequency ablation group compared to 43/148 in the antiarrhythmic drug therapy group, $P=.004$. Atrial fibrillation symptoms were 10/146 in the radiofrequency ablation group compared to 24/148 in the antiarrhythmic drug therapy group, $P=.012$.

Conclusions. Atrial fibrillation, atrial fibrillation occurrence, and atrial fibrillation with symptoms were significantly lower in radiofrequency ablation group, but cumulative atrial fibrillation burden was not significantly different.

PALLAS: The Results of the PALLAS Study¹⁹

Presenter: Stuart J. Connolly, Hamilton, Ontario, Canada.

Introduction. Dronedronarone restores sinus rhythm and reduces hospitalization or death in intermittent atrial fibrillation. It also lowers heart rate and blood pressure and has antiadrenergic and potential ventricular anti-arrhythmic effects. We hypothesized that dronedronarone would reduce major vascular events in high-risk permanent atrial fibrillation.

Methods. We assigned patients who were at least 65 years of age with at least a 6-month history of permanent atrial fibrillation and risk factors for major vascular events to receive dronedronarone or placebo. The first coprimary outcome was stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes. The second coprimary outcome was unplanned hospitalization for a cardiovascular cause or death.

Results. After the enrollment of 3236 patients, the study was stopped for safety reasons. The first coprimary outcome occurred in 43 patients receiving dronedronarone and 19 receiving placebo (hazard ratio, 2.29; 95% confidence interval [CI], 1.34 to 3.94; $P=.002$). There were 21 deaths from cardiovascular causes in the dronedronarone group and 10 in the placebo group (hazard ratio, 2.11; 95% CI, 1 to 4.49; $P=.046$), including death from arrhythmia in 13 patients and 4 patients, respectively (hazard ratio, 3.26; 95% CI, 1.06 to 10; $P=.03$). Stroke occurred in 23 patients in the dronedronarone group and 10 in the placebo group (hazard ratio, 2.32; 95% CI, 1.11 to 4.88; $P=.02$). Hospitalization for heart failure occurred in 43 patients in the dronedronarone group and 24 in the placebo group (hazard ratio, 1.81; 95% CI, 1.10 to 2.99; $P=.02$).

Conclusions. Dronedronarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events. Our data show that this drug should not be used in such patients.

COPPS Atrial Fibrillation: Colchicine Reduces Post-Operative Atrial Fibrillation²⁰

Presenter: Massimo Imazio, Torino, Italy.

Introduction. Inflammation and pericarditis may be contributing factors for postoperative atrial fibrillation (POAF), and both are potentially affected by antiinflammatory drugs and colchicine, which

has been shown to be safe and efficacious for the prevention of pericarditis and the postpericardiotomy syndrome (PPS). The aim of the Colchicine for the Prevention of the Post-Pericardiotomy Syndrome (COPPS) POAF substudy was to test the efficacy and safety of colchicine for the prevention of POAF after cardiac surgery.

Methods. The COPPS POAF substudy included 336 patients (mean age, 65.7±12.3 years; 69% male) of the COPPS trial, a multicenter, double-blind, randomized trial. Substudy patients were in sinus rhythm before starting the intervention (placebo/colchicine 1 mg twice daily starting on postoperative day 3 followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients ≥70 kg, halved doses for patients <70 kg or intolerant to the highest dose). The substudy primary end point was the incidence of POAF on intervention at 1 month.

Results. Despite well-balanced baseline characteristics, patients on colchicine had a reduced incidence of POAF (12% vs 22%, respectively; $P=.021$; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4 ± 3.7 vs 10.3 ± 4.3 days; $P=.040$) and rehabilitation stay (12.1 ± 6.1 vs 13.9 ± 6.5 days; $P=.009$). Side effects were similar in the study groups.

Conclusions. Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.

PREVENTION

AIM-HIGH: Extended-Release Niacin Does Not Reduce Clinical Events in Patients With Established Cardiovascular Disease Whose LDL-Cholesterol is Optimally Controlled With Statin Therapy²¹

Presenter: William E. Boden, Buffalo, New York, United States.

Introduction. In patients with established cardiovascular disease, residual cardiovascular risk persists despite the achievement of target low-density lipoprotein (LDL) cholesterol levels with statin therapy. It is unclear whether extended-release niacin added to simvastatin to raise low levels of high-density lipoprotein (HDL) cholesterol is superior to simvastatin alone in reducing such residual risk.

Methods. We randomly assigned eligible patients to receive extended-release niacin, 1500 to 2000 mg per day, or matching placebo. All patients received simvastatin, 40 to 80 mg per day, plus ezetimibe, 10 mg per day, if needed, to maintain an LDL cholesterol level of 40 to 80 mg per deciliter (1.03 to 2.07 mmol per liter). The primary end point was the first event of the composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

Results. A total of 3414 patients were randomly assigned to receive niacin (1718) or placebo (1696). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy. At 2 years, niacin therapy had significantly increased the median HDL cholesterol level from 35 mg per deciliter (0.91 mmol per liter) to 42 mg per deciliter (1.08 mmol per liter), lowered the triglyceride level from 164 mg per deciliter (1.85 mmol per liter) to 122 mg per deciliter (1.38 mmol per liter), and lowered the LDL cholesterol level from 74 mg per deciliter (1.91 mmol per liter) to 62 mg per deciliter (1.60 mmol per liter). The primary end point occurred in 282 patients in the niacin group (16.4%) and in 274 patients in the placebo group (16.2%) (hazard ratio, 1.02; 95% confidence interval, 0.87 to 1.21; $P=.79$ by the log-rank test).

Conclusions. Among patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of less than 70 mg per deciliter (1.81 mmol per liter), there was no incremental clinical benefit from

the addition of niacin to statin therapy during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels.

POWER: Practice-Based Opportunities for Weight Reduction²²

Presenter: Lawrence J. Appel, Baltimore, Maryland, United States.

Introduction. Obesity and its cardiovascular complications are extremely common medical problems, but evidence on how to accomplish weight loss in clinical practice is sparse.

Methods. We conducted a randomized, controlled trial to examine the effects of two behavioral weight-loss interventions in 415 obese patients with at least one cardiovascular risk factor. Participants were recruited from six primary care practices; 63.6% were women, 41% were black, and the mean age was 54 years. One intervention provided patients with weight-loss support remotely — through the telephone, a study-specific website, and e-mail. The other intervention provided in-person support during group and individual sessions, along with the three remote means of support. There was also a control group in which weight loss was self-directed. Outcomes were compared between each intervention group and the control group and between the two intervention groups. For both interventions, primary care providers reinforced participation at routinely scheduled visits. The trial duration was 24 months.

Results. At baseline, the mean body-mass index (the weight in kilograms divided by the square of the height in meters) for all participants was 36.6, and the mean weight was 103.8 kg. At 24 months, the mean change in weight from baseline was -0.8 kg in the control group, -4.6 kg in the group receiving remote support only ($P<.001$ for the comparison with the control group), and -5.1 kg in the group receiving in-person support ($P<.001$ for the comparison with the control group). The percentage of participants who lost 5% or more of their initial weight was 18.8% in the control group, 38.2% in the group receiving remote support only, and 41.4% in the group receiving in-person support. The change in weight from baseline did not differ significantly between the two intervention groups.

Conclusions. In two behavioral interventions, one delivered with in-person support and the other delivered remotely, without face-to-face contact between participants and weight-loss coaches, obese patients achieved and sustained clinically significant weight loss over a period of 24 months.

SATURN: Comparison of the Progression of Coronary Atherosclerosis for Two High Efficacy Statin Regimens With Different HDL Effects²³

Presenter: Stephen J. Nicholls, Cleveland, Ohio, United States.

Introduction. Statins reduce adverse cardiovascular outcomes and slow the progression of coronary atherosclerosis in proportion to their ability to reduce low-density lipoprotein (LDL) cholesterol. However, few studies have either assessed the ability of intensive statin treatments to achieve disease regression or compared alternative approaches to maximal statin administration.

Methods. We performed serial intravascular ultrasonography in 1039 patients with coronary disease, at baseline and after 104 weeks of treatment with either atorvastatin, 80 mg daily, or rosuvastatin, 40 mg daily, to compare the effect of these two intensive statin regimens on the progression of coronary atherosclerosis, as well as to assess their safety and side-effect profiles.

Results. After 104 weeks of therapy, the rosuvastatin group had lower levels of LDL cholesterol than the atorvastatin group (62.6 vs 70.2 mg per deciliter [1.62 vs 1.82 mmol per liter], $P<.001$), and higher levels of high-density lipoprotein (HDL) cholesterol (50.4 vs 48.6 mg per deciliter [1.30 vs 1.26 mmol per liter], $P=.01$). The primary efficacy end point, percent atheroma volume (PAV), decreased by 0.99% (95% confidence interval [CI], -1.19 to -0.63) with atorvastatin and by 1.22% (95% CI, -1.52 to -0.90) with rosuvastatin ($P=.17$). The effect on the secondary efficacy end point, normalized total atheroma volume (TAV), was more favorable with rosuvastatin than with atorvastatin: -6.39 μ l (95% CI, -7.52 to -5.12), as compared with -4.42 μ l (95% CI, -5.98 to -3.26) ($P=.01$). Both agents induced regression in the majority of patients: 63.2% with atorvastatin and 68.5% with rosuvastatin for PAV ($P=.07$) and 64.7% and 71.3%, respectively, for TAV ($P=.02$). Both agents had acceptable side-effect profiles, with a low incidence of laboratory abnormalities and cardiovascular events.

Conclusions. Maximal doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis. Despite the lower level of LDL cholesterol and the higher level of HDL cholesterol achieved with rosuvastatin, a similar degree of regression of PAV was observed in the two treatment groups.

Lipid-Modulating Effects of Evacetrapib, a Novel CETP Inhibitor, Administered as Monotherapy or in Combination With the Most Commonly-Used Statins²⁴

Presenter Stephen J. Nicholls, Cleveland, Ohio, United States.

Introduction. Interest remains high in cholesteryl ester transfer protein (CETP) inhibitors as cardioprotective agents. Few studies have documented the efficacy and safety of CETP inhibitors in combination with commonly used statins. The aim of the study was to examine the biochemical effects, safety, and tolerability of evacetrapib, as monotherapy and in combination with statins, in patients with dyslipidemia.

Methods. Randomized controlled trial conducted among 398 patients with elevated low-density lipoprotein cholesterol (LDL-C) or low high-density lipoprotein cholesterol (HDL-C) levels from April 2010 to January 2011 at community and academic centers in the United States and Europe. Following dietary lead-in, patients were randomly assigned to receive placebo ($n=38$); evacetrapib monotherapy, 30 mg/d ($n=40$), 100 mg/d ($n=39$), or 500 mg/d ($n=42$); or statin therapy ($n=239$) (simvastatin, 40 mg/d; atorvastatin, 20 mg/d; or rosuvastatin, 10 mg/d) with or without evacetrapib, 100 mg/d, for 12 weeks. The co-primary end points were percentage changes from baseline in HDL-C and LDL-C after 12 weeks of treatment.

Results. The mean baseline HDL-C level was 55.1 (SD, 15.3) mg/dL and the mean baseline LDL-C level was 144.3 (SD, 26.6) mg/dL. As monotherapy, evacetrapib produced dose-dependent increases in HDL-C of 30 to 66 mg/dL (53.6% to 128.8%) compared with a decrease with placebo of -0.7 mg/dL (-3%; $P<.001$ for all compared with placebo) and decreases in LDL-C of -20.5 to -51.4 mg/dL (-13.6% to -35.9%) compared with an increase with placebo of 7.2 mg/dL (3.9%; $P<.001$ for all compared with placebo). In combination with statin therapy, evacetrapib, 100 mg/d, produced increases in HDL-C of 42.1 to 50.5 mg/dL (78.5% to 88.5%; $P<.001$ for all compared with statin monotherapy) and decreases in LDL-C of -67.1 to -75.8 mg/dL (-11.2% to -13.9%; $P<.001$ for all compared with statin monotherapy). Compared with evacetrapib monotherapy, the combination of statins and evacetrapib resulted in greater reductions in LDL-C ($P<.001$) but no greater increase in HDL-C ($P=.39$). Although the study was underpowered, no adverse effects were observed.

Conclusions. Compared with placebo or statin monotherapy, evacetrapib as monotherapy or in combination with statins increased HDL-C levels and decreased LDL-C levels. The effects on cardiovascular outcomes require further investigation.

Post-MI FREEE: The Impact of Full Coverage for Preventive Medications After Myocardial Infarction on Recurrent Vascular Events: The Post-MI Free Rx Event and Economic Evaluation Trial²⁵

Presenter: Niteesh K. Choudhry, Boston, Massachusetts, United States.

Introduction. Adherence to medications that are prescribed after myocardial infarction is poor. Eliminating out-of-pocket costs may increase adherence and improve outcomes.

Methods. We enrolled patients discharged after myocardial infarction and randomly assigned their insurance-plan sponsors to full prescription coverage (1494 plan sponsors with 2845 patients) or usual prescription coverage (1486 plan sponsors with 3010 patients) for all statins, beta-blockers, angiotensin-converting-enzyme inhibitors, or angiotensin-receptor blockers. The primary outcome was the first major vascular event or revascularization. Secondary outcomes were rates of medication adherence, total major vascular events or revascularization, the first major vascular event, and health expenditures.

Results. Rates of adherence ranged from 35.9 to 49% in the usual-coverage group and were 4 to 6 percentage points higher in the full-coverage group ($P<.001$ for all comparisons). There was no significant between-group difference in the primary outcome (17.6 per 100 person-years in the full-coverage group vs 18.8 in the usual-coverage group; hazard ratio, 0.93; 95% confidence interval [CI], 0.82 to 1.04; $P=.21$). The rates of total major vascular events or revascularization were significantly reduced in the full-coverage group (21.5 vs 23.3; hazard ratio, 0.89; 95% CI, 0.90 to 0.99; $P=.03$), as was the rate of the first major vascular event (11 vs 12.8; hazard ratio, 0.86; 95% CI, 0.74 to 0.99; $P=.03$). The elimination of copayments did not increase total spending (\$66,008 for the full-coverage group and \$71 778 for the usual-coverage group; relative spending, 0.89; 95% CI, 0.50 to 1.56; $P=.68$). Patient costs were reduced for drugs and other services (relative spending, 0.74; 95% CI, 0.68 to 0.80; $P<.001$).

Conclusions. The elimination of copayments for drugs prescribed after myocardial infarction did not significantly reduce rates of the trial's primary outcome. Enhanced prescription coverage improved medication adherence and rates of first major vascular events and decreased patient spending without increasing overall health costs.

HEART FAILURE

HOOPS: Pharmacist Intervention to Prevent Hospitalization and Death in Patients With Heart Failure: A Prospective Cluster Randomized Controlled Trial²⁶

Presenter: Richard Lowrie, Glasgow, United Kingdom.

Introduction. Meta-analysis of small trials suggests that pharmacist-led collaborative review and revision of medical treatment may improve outcomes in heart failure.

Methods. We studied patients with left ventricular systolic dysfunction in a cluster-randomized controlled, event driven trial in primary care. We allocated 87 practices (1090 patients) to pharmacist intervention and 87 practices (1074 patients) to usual care. The

intervention was delivered by non-specialist pharmacists working with family doctors to optimize medical treatment. The primary outcome was a composite of death or hospital admission for worsening heart failure.

Results. The median follow-up was 4.7 years. At baseline, 86% of patients in both groups were treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. In patients not receiving one or other of these medications, or receiving less than the recommended dose, treatment was started, or the dose increased, in 33.1% of patients in the intervention group and in 18.5% of the usual care group [odds ratio (OR) 2.26, 95% CI 1.64–3.10; $P<.001$]. At baseline, 62% of each group were treated with a β -blocker and the proportions starting or having an increase in the dose were 17.9% in the intervention group and 11.1% in the usual care group (OR 1.76, 95% CI 1.31–2.35; $P<.001$). The primary outcome occurred in 35.8% of patients in the intervention group and 35.4% in the usual care group (hazard ratio 0.97, 95% CI 0.83–1.14; $P=.72$). There was no difference in any secondary outcome.

Conclusions. A low-intensity, pharmacist-led collaborative intervention in primary care resulted in modest improvements in prescribing of disease-modifying medications but did not improve clinical outcomes in a population that was relatively well treated at baseline.

MISCELLANEA

ADOPT: Extended Anticoagulant Prophylaxis in Initially Hospitalized Medically Ill Patients: Apixaban Dosing to Optimize Protection From Thrombosis Trial²⁷

Presenter: Samuel Z. Goldhaber, Boston, Massachusetts, United States.

Introduction. The efficacy and safety of prolonging prophylaxis for venous thromboembolism in medically ill patients beyond hospital discharge remain uncertain. We hypothesized that extended prophylaxis with apixaban would be safe and more effective than short-term prophylaxis with enoxaparin.

Methods. In this double-blind, double-dummy, placebo-controlled trial, we randomly assigned acutely ill patients who had congestive heart failure or respiratory failure or other medical disorders and at least one additional risk factor for venous thromboembolism and who were hospitalized with an expected stay of at least 3 days to receive apixaban, administered orally at a dose of 2.5 mg twice daily for 30 days, or enoxaparin, administered subcutaneously at a dose of 40 mg once daily for 6 to 14 days. The primary efficacy outcome was the 30-day composite of death related to venous thromboembolism, pulmonary embolism, symptomatic deep-vein thrombosis, or asymptomatic proximal-leg deep-vein thrombosis, as detected with the use of systematic bilateral compression ultrasonography on day 30. The primary safety outcome was bleeding. All efficacy and safety outcomes were independently adjudicated.

Results. A total of 6528 subjects underwent randomization, 4495 of whom could be evaluated for the primary efficacy outcome — 2211 in the apixaban group and 2284 in the enoxaparin group. Among the patients who could be evaluated, 2.71% in the apixaban group (60 patients) and 3.06% in the enoxaparin group (70 patients) met the criteria for the primary efficacy outcome (relative risk with apixaban, 0.87; 95% confidence interval [CI], 0.62 to 1.23; $P=.44$). By day 30, major bleeding had occurred in 0.47% of the patients in the apixaban group (15 of 3184 patients) and in 0.19% of the patients in the enoxaparin group (6 of 3217 patients) (relative risk, 2.58; 95% CI, 1.02 to 7.24; $P=.04$).

Conclusions. In medically ill patients, an extended course of thromboprophylaxis with apixaban was not superior to a shorter course with enoxaparin. Apixaban was associated with significantly more major bleeding events than was enoxaparin.

EASE: Randomized Trial of Early Surgery Versus Conventional Treatment for Infective Endocarditis²⁸

Presenter: Duk-Hyun Kang, Seoul, Korea.

Introduction. Infective endocarditis is associated with the potential for serious complications including stroke and heart failure. The best timing and indications for surgery is not clear. The objective of the study was to compare clinical outcomes for early surgery to standard treatment for infective endocarditis.

Methods. Prospective, randomized trial; two Korean centers; 5-year follow-up. EASE randomized patients with severe left-sided native-valve infective endocarditis with at least 10 mm of vegetation to either conventional antimicrobial treatment ($n=39$) according to the guidelines or surgery ($n=37$) within 48 hours of randomization. Endocarditis was diagnosed with transesophageal echocardiography and computed tomography. The primary endpoint was the composite of in-hospital death and acute embolism over 6 weeks.

Results. Primary endpoint: early surgery (2.7%) and conventional treatment (23.1%); $P=.031$. Death for any cause, embolic events, recurrence of infective endocarditis at 6 months: 2.7% (early surgery) vs 28.2% (conventional treatment); $P=.017$.

Conclusions. In patients with large vegetations, early surgery reduced in-hospital death and embolic events.

CLEVER: Claudication Treatment Comparative Effectiveness: 6-Month Outcomes²⁹

Presenter: Alan T. Hirsch, Minneapolis, Minnesota, United States.

Introduction. Claudication is a common and disabling symptom of peripheral artery disease that can be treated with medication, supervised exercise (SE), or stent revascularization (ST).

Methods. We randomly assigned 111 patients with aortoiliac peripheral artery disease to receive 1 of 3 treatments: optimal medical care (OMC), OMC plus SE, or OMC plus ST. The primary end point was the change in peak walking time on a graded treadmill test at 6 months compared with baseline. Secondary end points included free-living step activity, quality of life with the Walking Impairment Questionnaire, Peripheral Artery Questionnaire, Medical Outcomes Study 12-Item Short Form, and cardiovascular risk factors.

Results. At the 6-month follow-up, change in peak walking time (the primary end point) was greatest for SE, intermediate for ST, and least with OMC (mean change vs baseline, 5.8 ± 4.6 , 3.7 ± 4.9 , and 1.2 ± 2.6 minutes, respectively; $P<.001$ for the comparison of SE vs OMC, $P=.02$ for ST vs OMC, and $P=.04$ for SE vs ST). Although disease-specific quality of life as assessed by the Walking Impairment Questionnaire and Peripheral Artery Questionnaire also improved with both SE and ST compared with OMC, for most scales the extent of improvement was greater with ST than SE. Free-living step activity increased more with ST than with either SE or OMC alone (114 ± 274 vs 73 ± 139 vs -6 ± 109 steps per hour), but these differences were not statistically significant.

Conclusions. SE results in superior treadmill walking performance than ST, even for those with aortoiliac peripheral artery disease. The contrast between better walking performance for SE and better patient-reported quality of life for ST warrants further study.

ELEVATE-TIMI 56: Escalating Clopidogrel by Involving a Genetic Strategy³⁰

Presenter: Jessica Mega, Brigham and Women's Hospital, Boston, Massachusetts, United States.

Introduction. Variants in the CYP2C19 gene influence the pharmacologic and clinical response to the standard 75-mg daily maintenance dose of the antiplatelet drug clopidogrel. The aim of the study was to test whether higher doses (up to 300 mg daily) improve the response to clopidogrel in the setting of loss-of-function CYP2C19 genotypes.

Methods. ELEVATE-TIMI 56 was a multicenter, randomized, double-blind trial that enrolled and genotyped 333 patients with cardiovascular disease across 32 sites from October 2010 until September 2011. Maintenance doses of clopidogrel were given for 4 treatment periods, each lasting approximately 14 days, based on genotype. In total, 247 noncarriers of a CYP2C19*2 loss-of-function allele were to receive 75 and 150 mg daily of clopidogrel (2 periods each), whereas 86 carriers (80 heterozygotes, 6 homozygotes) were to receive 75, 150, 225, and 300 mg daily. The primary endpoint were platelet function test results (vasodilator-stimulated phosphoprotein [VASP] phosphorylation and VerifyNow P2Y12 assays) and adverse events.

Results. With 75 mg daily, CYP2C19*2 heterozygotes had significantly higher on-treatment platelet reactivity than did noncarriers (VASP platelet reactivity index [PRI]: mean, 70%; 95% CI, 66%-74%, vs 57.5%; 95% CI, 55.1%-59.9%, and VerifyNow P2Y12 reaction units [PRU]: mean, 225.6; 95% CI, 207.7-243.4, vs 163.6; 95% CI, 154.4-173.9; $P < .001$ for both comparisons). Among CYP2C19*2 heterozygotes, doses up to 300 mg daily significantly reduced platelet reactivity, with VASP PRI decreasing to 48.9% (95% CI, 44.6%-53.2%) and PRU to 127.5 (95% CI, 109.9-145.2) ($P < .001$ for trend across doses for both). Whereas 52% of CYP2C19*2 heterozygotes were nonresponders (≥ 230 PRU) with 75 mg of clopidogrel, only 10% were nonresponders with 225 or 300 mg ($P < .001$ for both). Clopidogrel, 225 mg daily, reduced platelet reactivity in CYP2C19*2 heterozygotes to levels achieved with standard clopidogrel, 75 mg, in noncarriers (mean ratios of platelet reactivity, VASP PRI, 0.92; 90% CI, 0.85-0.99, and PRU, 0.94; 90% CI, 0.84-1.04). In CYP2C19*2 homozygotes, even with 300 mg daily of clopidogrel, mean VASP PRI was 68.3% (95% CI, 44.9%-91.6%) and mean PRU, 287.0 (95% CI, 170.2-403.8).

Conclusions. Among patients with stable cardiovascular disease, tripling the maintenance dose of clopidogrel to 225 mg daily in CYP2C19*2 heterozygotes achieved levels of platelet reactivity similar to that seen with the standard 75-mg dose in noncarriers; in contrast, for CYP2C19*2 homozygotes, doses as high as 300 mg daily did not result in comparable degrees of platelet inhibition.

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