Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Chicago, Illinois, United States, November 15-19, 2014)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales de la *American Heart Association* (Chicago, Illinois, Estados Unidos, 15-19 de noviembre de 2014)

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Following our priority policy to reinforce continuing medical education for our readers,[1-14] we present the results of the clinical trials that were presented in special sections (Late-Breaking Clinical Trials) in the American Heart Association 2014 Congress, held in Chicago. As in previous editions,[15-20] we briefly outline the main objective, methods, and results, in line with the oral presentations. The information we offer should be considered preliminary because many of these studies have not yet been published in their final version.

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RISK AND BENEFIT OF DUAL ANTIPLATELET THERAPY

Increased Risk of Ischemic Events Upon Discontinuation of Prasugrel After 12 or 30 Months of Therapy Following Placement of the Taxus Liberté Paclitaxel-eluting Coronary Stent[21]

Presented by Kirk N Garratt, New York, New York, United States.

Background. The TAXUS Liberte-Post Approval Study (TL-PAS) contributed patients treated with TAXUS Liberté paclitaxel-eluting stent and prasugrel to the Dual Antiplatelet Therapy Study (DAPT) that compared 12 and 30 months of thienopyridine plus aspirin therapy after drug-eluting stents.

Methods. Outcomes for 2191 TL-PAS patients enrolled into DAPT were assessed.

Results. The DAPT coprimary composite end point (death, myocardial infarction [MI], or stroke) was lower with 30 vs 12 months prasugrel treatment (3.7% vs 8.8%; hazard ratio [HR] = 0.407; $P < .001$). Rates of death and stroke were similar between groups, but MI was significantly reduced with prolonged prasugrel treatment (1.9% vs 7.1%; HR = 0.255; $P < .001$). The DAPT coprimary end point, stent thrombosis, was also lower with longer therapy (0.2 vs 2.9%; HR = 0.063; $P < .001$). MI related to stent thrombosis (0 vs 2.6%; $P < .001$) and occurring spontaneously (1.9 vs 4.5%; HR = 0.407; $P = .007$) were both reduced with prolonged prasugrel. MI rates increased within 90 days of prasugrel cessation after both 12 and 30 months treatment. Composite Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) moderate or severe bleeds were modestly increased (2.4 vs 1.7%; HR = 1.438; $P = .234$) but severe bleeds were not more frequent (0.3 vs 0.5%; HR = 0.549; $P = .471$) in the prolonged treatment group.

Conclusions. Prasugrel and aspirin continued for 30 months reduced ischemic events for the TAXUS Liberté paclitaxel-eluting stent patient subset from DAPT, through reductions in MI and stent thrombosis. Withdrawal of prasugrel was followed by an increase in MI after both 12 and 30 months therapy. The optimal duration of dual antiplatelet therapy with prasugrel after TAXUS Liberté paclitaxel-eluting stent remains unknown, but appears to be > 30 months.

ISAR-SAFE: Randomized, Double Blind Trial of 6 vs 12 Months of Dual Antiplatelet Therapy After DES-Implantation[22]

Presented by Stefanie Schüpke, Munich, Germany.

Background. Current guidelines recommend that dual antiplatelet therapy (DAPT) with aspirin and an ADP receptor inhibitor be continued for a minimum of 12 months following drug-eluting stent (DES) percutaneous coronary intervention (PCI). The optimal duration, however, remains unclear. This trial sought to investigate whether 6 months of DAPT was superior to 12 months in patients undergoing DES PCI. The hypothesis was that 6 months of DAPT would be noninferior to 12 months of therapy in patients undergoing DES PCI.

Methods. Patients with DES PCI received 6 months of open-label DAPT with aspirin and clopidogrel. At 6 months, they were randomized in a 1:1 fashion to receive an additional 6 months of DAPT or aspirin alone. The trial was terminated early due to a lower than anticipated event rate. At this time, a total of 4005 patients were randomized, 2007 to 12 months of DAPT and 1998 to 6 months of therapy.

Results. Baseline characteristics were fairly similar between the two arms. Approximately 24% had diabetes mellitus and 15% were smokers. Indication for PCI was stable angina in 48%, ST-segment elevation myocardial infarction (STEMI) in 8%, and NSTE-acute coronary syndrome (NSTEACS) in 32%. Multivessel disease was observed in 62%, with the target vessel being left anterior descending in 40% and right coronary artery in 33%. The mean number of lesions treated was 1.7, with approximately 1.45 stents/patient. Reference vessel diameter was 3.0 mm. Stent type was everolimus-eluting stent (EES) in 49%, zotarolimus-eluting stent (ZES) in 15%, biolimus in 8%, newer-generation sirolimus-eluting stent (SES) in 16%, and bare-metal stent (BMS) in 0.4%. The primary major adverse cardiac event (MACE) end point was similar between the 6- and 12-month DAPT arms (1.5 vs 1.6%, P for noninferiority < .001). The composite of death, MI, stroke, and stent thrombosis was also similar (1.3 vs 1.5%; $P = .59$). Individual end points including mortality (0.4 vs 0.6%; $p = 0.37$), MI (0.7 vs 0.7%; $P = .85$), stent thrombosis (0.3 vs 0.2%; $p = 0.74$), and stroke (0.4 vs 0.3%; $P = .57$) were similar between the two arms, respectively. TIMI major or minor bleeding was numerically lower, with 6 months of DAPT (0.3 vs 0.7%; $P = 0.12$), wherease BARC ≥ class 2 bleeding was significantly reduced (1 vs 2%; $P = 0.01$).

Conclusions The results of the ISAR-SAFE trial indicate that 6 months of DAPT may be noninferior to 12 months of DAPT in patients undergoing DES PCI, with a trend toward lower bleeding. However, this trial had to be terminated early due to a significantly lower event rate than anticipated (actual: 1.6%; anticipated: 10%); thus, the results must be viewed within this context.

ITALIC: Six-month vs 24-month Dual Antiplatelet Therapy After Implantation of Drug-eluting Stents in Patients Nonresistant to Aspirin[23]

Presented by Martine Gilard, Brest Cedex, France.

Background. The currently recommended duration of dual antiplatelet therapy (DAPT) in drug-eluting stent (DES) recipients is 12 months, to reduce the risk of late stent thrombosis, particularly in acute coronary syndrome. It was hypothesized that antiplatelet treatment with DAPT for 6 months may be noninferior to DAPT for 24 months in aspirin-sensitive patients.

Methods. A multicenter, randomized study assigned patients undergoing implantation of Xience V (Abbott Vascular) to receive 6- or 24-month DAPT with confirmed nonresistance to aspirin. The primary end point was a composite of death, myocardial infarction, urgent target vessel revascularization, stroke, and major bleeding at 12 months poststenting.

Results. In total, 2031 patients were enrolled in 70 European and Middle East centers. The trial was prematurely terminated due to problems with recruitment: 941 patients were randomized to 24-month DAPT and 953 to 6-month DAPT; 137 patients were resistant to aspirin. The two treatment groups had similar baseline and procedural characteristics. There was no significant difference between the 2 treatment groups regarding the primary end point (1.5 vs. 1.6%; $P = .85$), even in high-risk (ACS) patients. Noninferiority was demonstrated for 6-month vs 24-month DAPT, with an absolute risk difference of 0.11% (95% CI: -1.04 to 1.26; P for noninferiority = .0002). There were no significant differences in stent thrombosis and in bleeding complications. In the 792 (44%) high-risk patients with ACS, primary and secondary end points did not significantly differ: 1.7% [95% CI: 0.519 to 6.057; $P = .361$]. Interaction between DAPT duration and ACS was nonsignificant ($P = .305$).

Conclusion: The ITALIC trial showed that rates of bleeding and of thrombotic events were not significantly different according to 6- versus 24-month DAPT after PCI with new-generation DES in good aspirin responders.

DAPT: Risk and Benefit of Prolonged Dual Antiplatelet Therapy After Drug-eluting Coronary Stents: Primary End Point Results[24]

Presented by Laura Mauri, Boston, Massachusetts, United States.

Background. Dual antiplatelet therapy is recommended after coronary stenting to prevent thrombotic complications, yet the benefits and risks of treatment beyond 1 year are uncertain.

Methods. Patients were enrolled after they had undergone a coronary stent procedure in which a drug-eluting stent was placed. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months; all patients continued receiving aspirin. The coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months. The primary safety end point was moderate or severe bleeding.

Results. A total of 9961 patients were randomly assigned to continue thienopyridine treatment or to receive placebo. Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio = 0.29; 95% confidence interval (CI), 0.17 to 0.48; $P < .001$) and major adverse cardiovascular and cerebrovascular events (4.3% vs 5.9%; hazard ratio = 0.71; 95%CI, 0.59 to 0.85; $P < .001$). The rate of myocardial infarction was lower with thienopyridine treatment than with placebo (2.1% vs 4.1%; hazard ratio = 0.47; $P < .001$). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (hazard ratio = 1.36; 95%CI, 1.00 to 1.85; $P = .05$). The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs 1.6%; $P = .001$). An elevated risk of stent thrombosis and myocardial infarction was observed in both groups during the 3 months after discontinuation of thienopyridine treatment.

Conclusions. Dual antiplatelet therapy beyond 1 year after placement of a drug-eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events but was associated with an increased risk of bleeding.

ANTILIPID THERAPY AND PREVENTION OF CARDIOVASCULAR DISEASE

Low-dose Aspirin for Primary Prevention of Cardiovascular Events in Elderly Patients With Multiple Atherosclerotic Risk Factors[25]

Presented by Kazuyuki Shimada, Tochigi, Japan.

Background. Prevention of atherosclerotic cardiovascular diseases is an important public health priority in Japan due to an aging population. The objective was to determine whether daily, low-dose aspirin reduces the incidence of cardiovascular events in older Japanese patients with multiple atherosclerotic risk factors.

Methods. The Japanese Primary Prevention Project (JPPP) was a multicenter, open-label, randomized, parallel-group trial. Patients (N = 14 464) were aged 60 to 85 years, presenting with hypertension, dyslipidemia, or diabetes mellitus and recruited by primary care physicians at 1007 clinics in Japan between March 2005 and June 2007, and were followed up for up to 6.5 years, with last follow-up in May 2012. A multidisciplinary expert panel (blinded to treatment assignments) adjudicated study outcomes. Patients were randomized 1:1 to enteric-coated aspirin 100mg/d or no aspirin in addition to ongoing medications. Composite primary outcome was death from cardiovascular causes (myocardial infarction, stroke, and other cardiovascular causes), nonfatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and nonfatal myocardial infarction. Secondary outcomes included individual end points.

Results. The study was terminated early by the data monitoring committee after a median follow-up of 5.02 years (interquartile range, 4.55–5.33) based on likely futility. In both the aspirin and no aspirin groups, 56 fatal events occurred. Patients with an occurrence of nonfatal stroke totaled 114 in the aspirin group and 108 in the no aspirin group; of nonfatal myocardial infarction, 20 in the aspirin group and 38 in the no aspirin group; of undefined cerebrovascular events, 3 in the aspirin group and 5 in the no aspirin group. The 5-year cumulative primary outcome event rate was not significantly different between the groups (2.77% [95%CI, 2.40%-3.20%] for aspirin vs 2.96% [95%CI, 2.58%-3.40%] for no aspirin; hazard ratio [HR] = 0.94 [95%CI, 0.77-1.15]; $P = .54$). Aspirin significantly reduced incidence of nonfatal myocardial infarction (0.30 [95%CI, 0.19-0.47] for aspirin vs 0.58 [95%CI, 0.42-0.81] for no aspirin; HR = 0.53 [95%CI, 0.31-0.91]; $P = .02$) and transient ischemic attack (0.26 [95%CI, 0.16-0.42] for aspirin vs 0.49 [95%CI, 0.35-0.69] for no aspirin; HR = 0.57 [95%CI, 0.32-0.99]; $P = .04$), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95%CI, 0.67-1.11] for aspirin vs 0.51 [95%CI, 0.37-0.72] for no aspirin; HR = 1.85 [95%CI, 1.22-2.81]; $P = .004$).

Conclusions. Once-daily, low-dose aspirin did not significantly reduce the risk of the composite outcome of cardiovascular death, nonfatal stroke, and nonfatal myocardial infarction among Japanese patients 60 years or older with atherosclerotic risk factors.

FACTOR-64: Screening for Asymptomatic Obstructive Coronary Artery Disease Among High-risk Diabetic Patients Using Coronary CT Angiography[26]

Presented by Joseph B Muhlestein, Murray, Utah, United States.

Background. Coronary artery disease (CAD) is a major cause of cardiovascular morbidity and mortality in patients with diabetes mellitus, yet CAD often is asymptomatic prior to myocardial infarction (MI) and coronary death. The objective was to assess whether routine screening for CAD by coronary computed tomography angiography (CCTA) in patients with type 1 or type 2 diabetes deemed to be at high cardiac risk, followed by CCTA-directed therapy, would reduce the risk of death and nonfatal coronary outcomes.

Methods. The FACTOR-64 study was a randomized clinical trial in which 900 patients with type 1 or type 2 diabetes of at least 3 to 5 years' duration and without symptoms of CAD were recruited from 45 clinics and practices of a single health system (Intermountain Healthcare, Utah), enrolled at a single-site coordinating center, and randomly assigned to CAD screening with CCTA (n = 452) or to standard national guidelines–based optimal diabetes care (n = 448) (targets: glycated hemoglobin level < 7.0%, low-density lipoprotein cholesterol level < 100 mg/dL, systolic blood pressure < 130 mmHg). All CCTA imaging was performed at the coordinating center. Standard therapy or aggressive therapy (targets: glycated hemoglobin level < 6.0%, low-density lipoprotein cholesterol level < 70 mg/dL, high-density lipoprotein cholesterol level > 50 mg/dL [women] or > 40 mg/dL [men], triglycerides level < 150 mg/dL, systolic blood pressure < 120 mmHg), or aggressive therapy with invasive coronary angiography, was recommended based on CCTA findings. Enrollment occurred between July 2007 and May 2013, and follow-up extended to August 2014. The primary outcome was a composite of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization; the secondary outcome was ischemic major adverse cardiovascular events (composite of CAD death, nonfatal MI, or unstable angina).

Results At a mean follow-up time of 4.0 (SD, 1.7) years, the primary outcome event rates were not significantly different between the CCTA and the control groups (6.2% [28 events] vs 7.6% [34 events]; hazard ratio, 0.80 [95%CI, 0.49-1.32]; *P* = .38). The incidence of the composite secondary end point of ischemic major adverse cardiovascular events also did not differ between groups (4.4 [20 events] vs 3.8% [17 events]; hazard ratio, 1.15 [95%CI, 0.60-2.19]; *P* = .68).

Conclusions. Among asymptomatic patients with type 1 or type 2 diabetes, use of CCTA to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization at 4 years. These findings do not support CCTA screening in this population.

ODYSSEY ALTERNATIVE: Efficacy and Safety of the Proprotein Convertase Subtilisin/kexin Type 9 Monoclonal Antibody, Alirocumab, vs Ezetimibe, in Patients With Statin Intolerance as Defined by a Placebo Run-in and Statin Rechallenge Arm[27]

Presented by Patrick M Moriarty, Kansas City, Kansas, United States.

Background. Statin intolerance (SI) limits many patients from taking statins and achieving LDL-C goals. Ezetimibe (EZE) is a recommended option for patients with SI. ODYSSEY ALTERNATIVE (NCT01709513) compared alirocumab (ALI) vs EZE in patients with history of SI due to muscle symptoms (inability to tolerate = 2 statins, 1 at lowest approved starting dose). The novel study design included a placebo (PBO) run-in period and statin rechallenge arm to document SI.

Methods. The SI patients (with CHD/other CV risk factors) first received single-blind subcutaneous and oral PBO for 4 weeks (W), and were excluded if muscle-related adverse events (AEs) were reported with PBOs. Continuing patients were randomized (2:2:1 ratio) to ALI 75 mg self-administered via 1mL pre -filled pen every 2 weeks (Q2W) or EZE 10 mg/day or atorvastatin (ATV) 20 mg/day for 24 weeks. ALI dose was increased to 150 mg Q2W (also 1-mL) at W12 depending on CV risk and W8 LDL-C level. Primary end point was % change in LDL-C from baseline to W24 (intent-to-treat analysis). Patients could enter an open-label extension (OLE) and receive ALI 75/150 mg Q2W.

Results. PBO run-in was completed by 87.0% (314/361) patients; 6.9% (25) discontinued due to muscle AE. Baseline mean LDL-C levels were 191-194 mg/dL, 15% of patients had HeFH. ALI produced significant LDL-C reductions vs EZE at W24. Although treatment-emergent adverse events (TEAEs) were generally comparable between groups, the rate of skeletal muscle-related TEAEs was significantly lower for ALI vs ATV (*P* < .05). Myalgia was the most common TEAE in all groups. In total, 89.5% of randomized patients entered the OLE.

Conclusions. ALI demonstrated significantly greater LDL-C lowering vs EZE after 24 weeks in an SI population with very high baseline LDL-C levels and was well tolerated, with significantly lower rates of musculoskeletal TEAEs than ATV. ALI may be considered a good alternative therapy in patients with a history of SI.

IMPROVE-IT Trial: Ezetimibe/Simvastatin versus Simvastatin Monotherapy on Cardiovascular Outcomes After Acute Coronary Syndromes[28]

Presented by Christopher P Cannon, Boston, Massachusetts, United States.

Background. Although low-density lipoprotein (LDL) lowering has been the mainstay of therapy for primary and secondary cardiovascular (CV) prevention, the data have been primarily for statins. Other nonstatin agents such as fibrates, niacin, and high-density lipoprotein (HDL)-raising agents have all failed to show a clinical benefit when added to statins. The current trial sought to study the safety and efficacy of ezetimibe/simvastatin compared with simvastatin alone in reducing CV events in patients at high risk. The hypothesis was that ezetimibe/simvastatin would be superior to simvastatin alone in reducing CV events in patients with recent acute coronary syndrome (ACS).

Methods. Patients with recent ACS were randomized in a 1:1 fashion to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg. A total of 18 144 patients were randomized at 1158 sites in 39 countries, 9067 to ezetimibe/simvastatin and 9077 to simvastatin alone.

Results. Baseline characteristics were fairly similar between the two arms. Approximately 27% had diabetes mellitus and 21% had a history of prior myocardial infarction (MI). Presentation was ST-segment elevation MI (STEMI) in 29%, NSTEMI in 47%, and unstable angina (UA) in 24%. Nearly 88% underwent diagnostic angiography and 70% underwent percutaneous coronary intervention. Uptitration to 80 mg simvastatin occurred in 27% of the simvastatin arm and 6% of the ezetimibe/simvastatin arm. Premature discontinuation was observed in 42% of patients in both arms. Baseline LDL cholesterol (LDL-C) levels were 95 mg/dl in both arms; the median follow-up average was 53.7 mg/dL vs 69.5 mg/dL in the ezetimibe/simvastatin and simvastatin arms, respectively. LDL lowering was observed as early as 1 month, and appeared sustained over the duration of follow-up. At 1 year, triglycerides were also lowered by 16.7 mg/dL in the combination arm, while HDL was increased by 0.6 mg/dL. The primary end point of CV death/MI/UA/coronary revascularization beyond 30 days/stroke was significantly lower in the ezetimibe/simvastatin arm compared with the simvastatin arm over the duration of follow-up (32.7% vs. 34.7%; hazard ratio [HR] = 0.94, 95% confidence interval [CI] 0.89-0.99; *P* = 0.016). This corresponded to a number needed to treat (NNT) of 50 patients to prevent one event. Other end points including MI (13.1 vs 14.8%; *P* = .002), stroke (4.2 vs 4.8%; *P* = .05), ischemic stroke (3.4% vs. 4.1%; *P* = .008), and CV death/MI/stroke (20.4 vs 22.2%; *P* = .003) were all significantly lower in the ezetimibe/simvastatin arm; no differences were noted for all-cause mortality (15.4 vs 15.3%; *P* = .78), CV mortality (6.9 vs 6.8%; *P* = .99) and need for coronary revascularization (21.8 vs 23.4%; *P* = .11). On subgroup analysis, patients with diabetes had a greater benefit with ezetimibe/simvastatin (HR = 0.86, *p* for interaction = .023). On-treatment analysis confirmed and further embellished the primary intention-to-treat analyses; the primary end point was significantly reduced in the ezetimibe/simvastatin arm compared with placebo (29.8 vs 32.4%, HR = 0.92; 95%CI, 0.87-0.98; *P* = .012; NNT = 38). No differences were observed in cancer incidence (10.2 vs 10.2%; *P* = .57), myopathy (0.2 vs 0.1%; *P* = .32), or transaminitis (2.5 vs 2.3%; *P* = .43).

Conclusions. The results of the landmark IMPROVE-IT trial indicate that in patients posthigh-risk ACS, ezetimibe 10 mg/simvastatin 40 mg is superior to simvastatin 40 mg alone in reducing CV events. This is the first study powered for clinical outcomes to show a benefit with a nonstatin agent when added to a statin.

TREATMENT OF STRUCTURAL HEART DISEASE

Randomized Trial of Atenolol Versus Losartan in Children and Young Adults With Marfan Syndrome[29]

Presented by Ronald V Lacro, Boston, Massachusetts, United States.

Background. Aortic-root dissection is the leading cause of death in Marfan syndrome. Studies suggest that with regard to slowing

aortic-root enlargement, losartan may be more effective than beta-blockers, the current standard therapy in most centers.

Methods. We conducted a randomized trial comparing losartan with atenolol in children and young adults with Marfan syndrome. The primary outcome was the rate of aortic root enlargement, expressed as the change in the maximum aortic-root-diameter z score indexed to body-surface area (hereafter, aortic-root z score) over a 3-year period. Secondary outcomes included the rate of change in the absolute diameter of the aortic root; the rate of change in aortic regurgitation; the time to aortic dissection, aortic-root surgery, or death; somatic growth; and the incidence of adverse events.

Results. From January 2007 through February 2011, a total of 21 clinical centers enrolled 608 participants, 6 months to 25 years of age (mean [SD, standard deviation] age, 11.5 (SD, 6.5) years in the atenolol group and 11.0 (SD, 6.2) years in the losartan group), who had an aortic-root z score greater than 3.0. The baseline-adjusted rate of change (SE) in the aortic-root z score did not differ significantly between the atenolol group and the losartan group (−0.139 [0.013] and −0.107 [0.013] standard-deviation units per year, respectively; $P = .08$). Both slopes were significantly less than zero, indicating a decrease in the degree of aortic-root dilatation relative to body-surface area with either treatment. The 3-year rates of aortic-root surgery, aortic dissection, death, and a composite of these events did not differ significantly between the 2 treatment groups.

Conclusions. Among children and young adults with Marfan syndrome who were randomly assigned to losartan or atenolol, we found no significant difference in the rate of aortic-root dilatation between the 2 treatment groups over a 3-year period.

INHERIR: A Randomized Trial of Losartan in Hypertrophic Cardiomyopathy[30]

Presented by Anna Axelsson, Copenhagen, Denmark.

Background. Animal models have demonstrated a favorable effect of angiotensin-receptor blockers (ARBs) on left ventricular (LV) mass and myocardial fibrosis in patients with hypertrophic cardiomyopathy (HCM). The current study sought to study the efficacy of losartan in improving LV morphology in patients with HCM. Hypothesis: Losartan would be superior to placebo in improving LV morphology in patients with HCM.

Methods. Patients with HCM were randomized in a 1:1 fashion to either losartan 100 mg daily or matching placebo. The primary end point was the change in LV mass between baseline and 12 months.

Results. A total of 133 patients were randomized, 64 to losartan and 69 to placebo. Concomitant medications were beta-blockers (57%) and calcium channel blockers (14%). Baseline characteristics were fairly similar between the 2 arms. About 20% had undergone prior septal reduction therapy, 10% had treated hypertension, and 10% had suffered previous cardiac arrest/sustained ventricular tachycardia (VT)/appropriate implantable cardioverter-defibrillator (ICD) shock. Genetic testing was performed in > 80%, and a disease-specific gene was identified in 43% of patients. Baseline LV mass was 107 g/m^2 with a mean maximal wall thickness of 23 mm. LV fibrosis was observed in 85% on cardiac magnetic resonance. The primary end point was similar between the losartan and placebo arms (difference 1 g/m^2, 95% confidence interval -3 to 6 g/m^2; $P = .6$). Change in maximal wall thickness (1 vs 1 mm; $P = .26$), peak LV outflow gradient during Valsalva (7 vs 2 mmHg; $P = .47$), and % LV fibrosis (2 vs 3%; $P = .62$) were similar between the two arms. Peak V02 max was also similar ($P = .08$). No differences were noted in clinical events such as sudden cardiac death (0 vs. 2), angioedema (1 vs 0), and hyperkalemia (1 vs 0); ($P > .05$ for all).

Conclusions. The results of the INHERIT trial indicate that losartan is not superior in reducing LV mass and thickness, compared with placebo, in patients with HCM. There have been other smaller studies in this patient population, including with other angiotensin-receptor blockers (ARBs) such as candesartan, showing a possible improvement in LV geometry in HCM patients. Other studies are needed to assess the role of ARBs in this patient population. The magnitude of blood pressure lowering was not available in this trial, and will also need to be factored into future studies in these patients.

The Incidence of Infective Endocarditis in England is Increasing: An Assessment of the Impact of Cessation of Antibiotic Prophylaxis Using Population Statistics[31]

Presented by Martin H Thornhill, Sheffield, United Kindom.

Background. Antibiotic prophylaxis given before invasive dental procedures in patients at risk of developing infective endocarditis has historically been the focus of infective endocarditis prevention. Recent changes in antibiotic prophylaxis guidelines in the USA and Europe have substantially reduced the number of patients for whom antibiotic prophylaxis is recommended. In the UK, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommended complete cessation of antibiotic prophylaxis for prevention of infective endocarditis in March, 2008. We aimed to investigate changes in the prescribing of antibiotic prophylaxis and the incidence of infective endocarditis since the introduction of these guidelines.

Methods. We did a retrospective secular trend study, analysed as an interrupted time series, to investigate the effect of antibiotic prophylaxis vs no prophylaxis on the incidence of infective endocarditis in England. We analysed data for the prescription of antibiotic prophylaxis from Jan 1, 2004, to March 31, 2013, and hospital discharge episode statistics for patients with a primary diagnosis of infective endocarditis from Jan 1, 2000, to March 31, 2013. We compared the incidence of infective endocarditis before and after the introduction of the NICE guidelines using segmented regression analysis of the interrupted time series.

Results. Prescriptions of antibiotic prophylaxis for the prevention of infective endocarditis fell substantially after introduction of the NICE guidance (mean, 10 900 prescriptions per month [Jan 1, 2004, to March 31, 2008] vs 2236 prescriptions per month [April 1, 2008, to March 31, 2013]; $P < .0001$). Starting in March, 2008, the number of cases of infective endocarditis increased significantly above the projected historical trend, by 0.11 cases per 10 million people per month (95% CI 0.05–0.16; $P < .0001$). By March, 2013, 35 more cases per month were reported than would have been expected had the previous trend continued. This increase in the incidence of infective endocarditis was significant both for individuals at high risk of infective endocarditis and those at lower risk.

Conclusions. Although our data do not establish a causal association, prescriptions of antibiotic prophylaxis have fallen substantially and the incidence of infective endocarditis has increased significantly in England since introduction of the 2008 NICE guidelines.

The Surgical Treatment of Moderate Ischemic Mitral Regurgitation: A Randomized Clinical Trial From The Cardiothoracic Surgical Trials Network[32]

Presented by Robert E Michler, New York, New York, United States.

Background. Ischemic mitral regurgitation is associated with increased mortality and morbidity. For surgical patients with moderate regurgitation, the benefits of adding mitral valve repair to coronary-artery bypass grafting (CABG) are uncertain.

Methods. We randomly assigned 301 patients with moderate ischemic mitral regurgitation to CABG alone or CABG plus mitral-valve repair (combined procedure). The primary end point was the left ventricular end-systolic volume index (LVESVI), a measure of left ventricular remodeling, at 1 year. This end point was assessed with the use of a Wilcoxon rank-sum test in which deaths were categorized as the lowest LVESVI rank.

Results. At 1 year, the mean (standard deviation) LVESVI among surviving patients was 46.1 (22.4) mL per square meter of body-surface area in the CABG-alone group and 49.6 (31.5) mL per square meter in the combined-procedure group (mean change from baseline, −9.4 and −9.3 mL per square meter, respectively). The rate of death was 6.7% in the combined-procedure group and 7.3% in the CABG-alone group (hazard ratio with mitral-valve repair, 0.90; 95% confidence interval, 0.38 to 2.12; $P = .81$). The rank-based assessment of LVESVI at 1 year (incorporating deaths) showed no significant between-group difference (z score, 0.50; $P = .61$). The addition of mitral-valve repair was associated with a longer bypass time ($P < .001$), a longer hospital stay after surgery ($P = .002$), and more neurologic events ($P = .03$). Moderate or severe mitral regurgitation was less common in the combined-procedure group than in the CABG-alone group (11.2 vs 31.0%, $P < .001$). There were no significant between-group differences in major adverse cardiac or cerebrovascular events, deaths, readmissions, functional status, or quality of life at 1 year.

Conclusions. In patients with moderate ischemic mitral regurgitation, the addition of mitral-valve repair to CABG did not result in a higher degree of left ventricular reverse remodeling. Mitral-valve repair was associated with a reduced prevalence of moderate or severe mitral regurgitation but an increased number of untoward events. Thus, at 1 year, this trial did not show a clinically meaningful advantage of adding mitral-valve repair to CABG. Longer-term follow-up may determine whether the lower prevalence of mitral regurgitation translates into a net clinical benefit.

ISCHEMIC HEART DISEASE: DRUGS, DEVICES, AND SYSTEMS OF CARE

BASKET-PROVE II: Long-term Outcome of Biodegradable Compared to Durable Polymer Drug-eluting Stents and Bare Metal Stents[33]

Presented by Christoph A Kaiser, Basel, Switzerland.

Background. Biodegradable-polymer drug-eluting stents (BP-DES) were developed to be as effective as second-generation durable-polymer drug-eluting stents (DP-DES) and as safe > 1 year as bare-metal stents (BMS). Thus, very late stent thrombosis (VLST) attributable to durable polymers should no longer appear.

Methods. To address these early and late aspects, 2291 patients presenting with acute or stable coronary disease needing stents ≥ 3.0 mm in diameter between April 2010 and May 2012 were randomly assigned to biolimus-A9–eluting BP-DES, second-generation everolimus-eluting DP-DES, or thin-strut silicon-carbide–coated BMS in 8 European centers. All patients were treated with aspirin and risk-adjusted doses of prasugrel. The primary end point was combined cardiac death, myocardial infarction, and clinically indicated target-vessel revascularization within 2 years. The combined secondary safety end point was a composite of VLST, myocardial infarction, and cardiac death.

Results. The cumulative incidence of the primary end point was 7.6% with BP-DES, 6.8% with DP-DES, and 12.7% with BMS. By intention-to-treat, BP-DES were noninferior (predefined margin, 3.80%) compared with DP-DES (absolute risk difference, 0.78%; −1.93% to 3.50%; P for noninferiority = .042; per protocol $P = .09$) and superior to BMS (absolute risk difference, −5.16; −8.32 to −2.01; $P = .0011$). The 3 stent groups did not differ in the combined safety end point, with no decrease in events > 1 year, particularly VLST with BP-DES.

Conclusions. In large-vessel stenting, BP-DES appeared barely noninferior compared with DP-DES and more effective than thin-strut BMS, but without evidence for better safety nor lower VLST rates > 1 year. Findings challenge the concept that durable polymers are key in VLST formation.

EVOLVE II: A Prospective Randomized Investigation of a Novel Bioabsorbable Polymer-coated, Everolimus-eluting Coronary Stent[34]

Presented by Dean J. Kereiakes, Cincinnati, Ohio, United States.

Background. The goal of the trial was to evaluate treatment with a bioabsorbable-polymer drug-eluting stent compared with a durable-polymer drug-eluting stent among participants with obstructive coronary artery disease. The hypothesis was that a bioabsorbable-polymer drug-eluting stent will be noninferior to a durable-polymer drug-eluting stent.

Methods. Participants with obstructive coronary artery disease were randomized to a bioabsorbable-polymer everolimus-eluting stent (n = 846) vs durable-polymer everolimus-eluting stent (n = 838). Concomitant medications were P2Y12 inhibitor for 6 months. The primary outcome was target lesion failure at 12 months.

Results. Overall, 1684 patients were randomized. The mean age was 64 years, 27% were women, 22% were current smokers, 29% had a prior myocardial infarction (MI), and 31% had diabetes. Dual antiplatelet therapy at 12 months was 89.7% of the bioabsorbable-polymer group, compared with 87.3% of the durable-polymer group. At 12 months, the primary outcome occurred in 6.7% of the bioabsorbable-polymer group vs 6.5% of the durable-polymer group (P for noninferiority = .0005); cardiac death, 0.5% vs 0.9% ($P = .34$); target vessel MI, 4.3% vs. 4.7% ($P = .71$); clinically indicated target lesion revascularization, 2.6% vs. 1.7% ($P = .221$); definite/probable stent thrombosis (< 30 days), 0.4% vs. 0.6% ($P = .50$); definite/probable stent thrombosis (≥ 30 days), 0% vs 0% for all comparisons, respectively.

Conclusions. Among patients with obstructive coronary artery disease, the bioabsorbable-polymer drug-eluting stent was noninferior to the durable-polymer drug-eluting stent. Noninferiority was achieved on the composite outcome of target lesion failure at 12 months. Stent thrombosis was low with both stent designs, with no events beyond 30 days.

AVOID Study: Randomized Controlled Trial of Oxygen Therapy in Acute ST-segment Elevation Myocardial Infarction[35]

Presented by Dion Stub, Vancouver, Canada.

Background. Oxygen is commonly administered to patients with ST-elevation myocardial infarction (STEMI) despite previous studies suggesting a possible increase in myocardial injury due to coronary vasoconstriction and heightened oxidative stress.

Methods. We conducted a multicenter, prospective, randomized, controlled trial comparing oxygen (8 L/min) with no supplemental oxygen in patients with STEMI diagnosed on paramedic 12-lead electrocardiogram. Of 638 patients randomized, 441 were confirmed STEMI patients who underwent primary end point analysis. The primary end point was myocardial infarct size as assessed by cardiac enzymes, troponin (cTnI), and creatine kinase (CK). Secondary end

points included recurrent myocardial infarction, cardiac arrhythmia, and myocardial infarct size assessed by cardiac magnetic resonance (CMR) imaging at 6 months.

Results. There was a significant increase in mean peak CK in the oxygen group compared to the no oxygen group (1948 U/L vs 1543 U/L; means ratio, 1.27; 95%CI, 1.04 to 1.52; *P* = .01). Mean peak troponin was similar in the oxygen and no oxygen groups (57.4 µg/L vs 48.0 µg/L; ratio, 1.20; 95% confidence interval [CI], 0.92 to 1.56; *P* = .18). There was an increase in the rate of recurrent myocardial infarction in the oxygen group compared to the no oxygen group (5.5 vs 0.9%; *P* = .006) and an increase in frequency of cardiac arrhythmia (40.4 vs 31.4%; *P* = .05). At 6 months, the oxygen group had an increase in myocardial infarct size on CMR: n = 139; 20.3g vs 13.1g; *P* = .04).

Conclusions. Supplemental oxygen therapy in patients with STEMI but without hypoxia increased early myocardial injury and was associated with larger myocardial infarct size assessed at 6 months.

STEMI ACCELERATOR: Developing Regional STEMI Systems of Care: Final Results[36]

Presented by Matthew W Sherwood , Durham, North Carolina, United States.

Background. Current guidelines recommend implementation of regional systems of care to improve the timely reperfusion for STEMI patients. While door-to-device times are generally excellent in primary PCI centers, the new standards of EMS first medical contact (FMC) to device and transfer times remain suboptimal.

Methods. We intervened in 16 large United States metropolitan regions involving 171 PCI hospitals and over 200 non-PCI hospitals and 1253 EMS agencies. We required PCI hospitals to participate in a common database, organized local regional leadership and coordination, and established STEMI protocols for EMS activation and inter-hospital transfer, with ongoing measurement and feedback through Mission: Lifeline regional quarterly reports containing blinded hospital comparison reports. Primary outcomes were first medical contact (FMC) to device times, and first door to device (as well as door-in to door-out times in emergency departments) for transfer patients for hospitals implementing protocols. Results are compared from baseline to 1 year later and stratified according to the adoption of specific process interventions from final survey data.

Results. In 16 regions across the US for the baseline quarter of involvement (Q3 2012), 3538 STEMI patients were admitted to participating sites, 2727 of which directly presented to a PCI center, 811 transferred from a non-PCI (age 61years, 30% female, 7.7% cardiogenic shock). For those presenting directly to PCI centers, median FMC to device time was 85 min (interquartile range 68, 107). For patients transferred for primary PCI, median FMC to device time was 132 min with a median door-in to door-out time of 63 min. Coordination with EMS was highly correlated with better survival (ED wait time / mortality: ≤ 30 min / 2.3%; 30-45 min / 7.7%; > 45 min / 11.2%, *P* = .0001).

Conclusions. In a diverse group of cities and states across the United States, baseline data show important opportunities to improve timely reperfusion therapy beginning at the new standard, first medical contact. The importance of collaboration between the EMS team and the hospitals was seen in these study results, with improved survival as one of the outcomes.

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