

Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American College of Cardiology (San Diego, United States, March 14–16, 2015)



Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales del *American College of Cardiology* (San Diego, Estados Unidos, 14–16 de marzo de 2015)

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Article history:

Available online 30 April 2015

INTRODUCCION

Following our priority policy to reinforce continuing medical education for our readers, we present the results of the clinical trials that were presented in special sections (Late-breaking Clinical Trials) in the American College of Cardiology 2015 Congress, held in San Diego. As in previous editions,^{1,2} 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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JOINT AMERICAN COLLEGE OF CARDIOLOGY /JACC LATE-BREAKING CLINICAL TRIALS

PROMISE: Anatomic Versus Functional Diagnostic Testing Strategies in Symptomatic Patients With Suspected Coronary Artery Disease³

Presented by Pamela S. Douglas, Durham, North Carolina, United States.

Background. Many patients have symptoms suggestive of coronary artery disease (CAD) and are often evaluated with the use of diagnostic testing, although there are limited data from randomized trials to guide care.

Methods. We randomly assigned 10 003 symptomatic patients to a strategy of initial anatomical testing with the use of coronary computed tomographic angiography (CTA) or to functional testing (exercise electrocardiography, nuclear stress testing, or stress echocardiography). The composite primary end point was death, myocardial infarction, hospitalization for unstable angina, or major procedural complication. Secondary end points included invasive cardiac catheterization that did not show obstructive CAD and radiation exposure.

Results. The mean age of the patients was 60.8 ± 8.3 years, 52.7% were women, and 87.7% had chest pain or dyspnea on exertion. The mean pretest likelihood of obstructive CAD was $53.3 \pm 21.4\%$. Over a median follow-up period of 25 months, a primary end-point event occurred in 164 of 4996 patients in the CTA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (adjusted hazard ratio, 1.04; 95% confidence interval, 0.83 to 1.29; $P = .75$). CTA was associated with fewer catheterizations showing no obstructive CAD than was functional testing (3.4% vs 4.3%; $P = .02$), although more patients in the CTA group underwent catheterization within 90 days after randomization (12.2% vs 8.1%). The median cumulative radiation exposure per patient was lower in the CTA group than in the functional-testing group (10.0 mSv vs 11.3 mSv), but 32.6% of the patients in the functional-testing group had no exposure, so the overall exposure was higher in the CTA group (mean, 12.0 mSv vs 10.1 mSv; $P < .001$).

Conclusions. In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years.

PEGASUS: Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Acetylsalicylic Acid⁴

Presented by Marc Steven Sabatine, Boston, Massachusetts, United States.

Background. The potential benefit of dual antiplatelet therapy beyond 1 year after a myocardial infarction has not been established. We investigated the efficacy and safety of ticagrelor, a P2Y₁₂ receptor antagonist with established efficacy after an acute coronary syndrome, in this context.

Methods. We randomly assigned, in a double-blind 1:1:1 fashion, 21 162 patients who had had a myocardial infarction 1 to 3 years earlier to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. All the patients were to receive low-dose aspirin and were followed for a median of 33 months. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The

primary safety end point was Thrombolysis in Myocardial Infarction (TIMI) major bleeding.

Results. The two ticagrelor doses each reduced, as compared with placebo, the rate of the primary efficacy end point, with Kaplan–Meier rates at 3 years of 7.85% in the group that received 90 mg of ticagrelor twice daily, 7.77% in the group that received 60 mg of ticagrelor twice daily, and 9.04% in the placebo group (hazard ratio for 90 mg of ticagrelor vs placebo, 0.85; 95% confidence interval [CI], 0.75 to 0.96; $P = .008$; hazard ratio for 60 mg of ticagrelor vs placebo, 0.84; 95%CI, 0.74 to 0.95; $P = .004$). Rates of TIMI major bleeding were higher with ticagrelor (2.60% with 90 mg and 2.30% with 60 mg) than with placebo (1.06%) ($P < .001$ for each dose vs placebo); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively.

Conclusions. In patients with a myocardial infarction more than 1 year previously, treatment with ticagrelor significantly reduced the risk of cardiovascular death, myocardial infarction, or stroke and increased the risk of major bleeding.

JOINT AMERICAN COLLEGE OF CARDIOLOGY/JAMA LATE-BREAKING CLINICAL TRIALS

OSLER 1 and 2: Effect of the PCSK9 Inhibitor Evolocumab on Cardiovascular Outcomes⁵

Presented by Marc Steven Sabatine, Boston, Massachusetts, United States.

Background. Evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9), significantly reduced low-density lipoprotein (LDL) cholesterol levels in short-term studies. We conducted two extension studies to obtain longer-term data.

Methods. In two open-label, randomized trials, we enrolled 4465 patients who had completed 1 of 12 phase 2 or 3 studies (“parent trials”) of evolocumab. Regardless of study group assignments in the parent trials, eligible patients were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 months with assessment of lipid levels, safety, and (as a prespecified exploratory analysis) adjudicated cardiovascular events including death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure. Data from the two trials were combined.

Results. As compared with standard therapy alone, evolocumab reduced the level of LDL cholesterol by 61%, from a median of 120 mg per deciliter to 48 mg per deciliter ($P < .001$). Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol. The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group = 0.47; 95% confidence interval, 0.28 to 0.78; $P = .003$).

Conclusions. During approximately 1 year of therapy, the use of evolocumab plus standard therapy, as compared with standard therapy alone, significantly reduced LDL cholesterol levels and reduced the incidence of cardiovascular events in a prespecified but exploratory analysis.

EMBRACE-STEMI: Safety, Tolerability and Efficacy of Intravenous Bendavia™ on Reperfusion Injury in Patients Treated With Standard Therapy⁶

Presented by C. Michael Gibson, Boston, Massachusetts, United States.

Background. Although significant efforts have been made to improve ST-segment elevation myocardial infarction (STEMI) outcomes by reducing symptom-onset-to-reperfusion times, strategies to decrease the clinical impact of ischemic reperfusion injury have demonstrated limited success. Bendavia, an intravenously administered mitochondrial targeting peptide, has been shown to reduce myocardial infarct size and attenuate coronary no-reflow in experimental models when given before reperfusion. EMBRACE-STEMI is testing the hypothesis that Bendavia, in conjunction with standard-of-care therapy, is superior to placebo for the reduction of myocardial infarction size among patients with first time, acute, anterior wall STEMI who undergo successful reperfusion with primary PCI and stenting.

Methods. The EMBRACE STEMI study is a phase 2a, randomized, double-blind, placebo-controlled trial enrolling patients with a first-time anterior STEMI and an occluded proximal or mid-left anterior descending artery undergoing primary percutaneous coronary intervention (PCI) within 4 hours of symptom onset to either Bendavia 0.05 mg/kg/hr (n = 58) or placebo (n = 60). The primary end point is infarct size measured by the area under the creatine kinase-MB enzyme curve calculated from measurements from the central clinical chemistry laboratory obtained over the initial 72 hours after the primary PCI procedure, and the major secondary end point is infarct size calculated by the volume of infarcted myocardium (late contrast gadolinium enhancement) on the day 4 ± 1 cardiac magnetic resonance imaging.

Results. Patient characteristics: Mean patient age: 60 years, females 28%, diabetics 10%, ischemia time: 151 minutes, left anterior descending artery (LAD) area at risk: 85%, aspiration thrombectomy prior to percutaneous coronary intervention (PCI): 68%. The primary outcome was similar in the bendavia and placebo arms: 217.4 vs 266.6 (no significant difference, [NS]). Secondary outcomes: AUC troponin I at 6 hours, 144.6 vs 139.3 (NS); complete ST-segment resolution immediately post-PCI: 14.6% vs 22%; $P > .05$; infarct volume at day 4, 43.1 vs 48.4 (NS); left ventricular ejection fraction at day 4, 44.0% vs 41.9% (NS); infarct volume at day 30, 30.1 vs 31.5; left ventricular ejection fraction at day 30, 44.8% vs 46.1% (NS); complete ST-segment resolution immediately after PCI, 14.6% vs 22% (NS); or at 24 hours 53.6% vs 50.9% (NS); TIMI 3 flow after PCI, 88.3% vs 87.1% (NS); death/new-onset chronic heart failure rehospitalization at 30 days, 22.4% vs 28.3% (NS); and at 6 months: 25.9% vs 28.3% (NS). In the 8 hours during / following Bendavia administration, there was a trend towards reduced symptomatic heart failure (8.6% vs 18.3%; $P = .18$).

Conclusions. The results of this trial indicate that Bendavia, a novel agent to prevent mitochondrial dysfunction, and thus potentially reperfusion injury, does not reduce infarct size compared with placebo in patients with anterior STEMI due to proximal/mid occlusion of the LAD. Further phase 3 trials are ongoing. The hypothesis generating data that demonstrated a trend toward a favorable reduction in CHF symptoms in the 8 hours during/following Bendavia administration is being prospectively evaluated at comparable and higher doses in an ongoing trial of patients with systolic heart failure (HFREF).

REGULATE-PCI: Efficacy and Safety of the REG1 Anticoagulation System Compared to Bivalirudin in Patients Undergoing Percutaneous Coronary Intervention⁷

Presented by Roxana Mehran, New York City, New York, United States.

Background. The REG1 Anticoagulation System (Regado Biosciences) is a novel, aptamer-based, factor IXa inhibitor,

pegnivocogin. Coupled with the reversible agent, anivamersen, this approach was developed for patients undergoing PCI. The safety and efficacy of REG1 compared with established anticoagulants is unknown.

Methods. We conducted a Phase 3, randomized (1:1), open-label, multi-center study comparing REG1 to bivalirudin in patients undergoing PCI. The study was designed to include 13 200 patients. The main exclusion criteria were STEMI within 48 hours, contraindication for anticoagulation or high risk for bleeding, and allergy or intolerance to aspirin or all available ADP/P2Y12 inhibitors. The primary efficacy endpoint was the composite of all-cause death, myocardial infarction, stroke or unplanned target lesion revascularization at day 3 after randomization. The primary safety endpoint was a BARC 3 or 5 bleeding at day 3. Safety evaluation was conducted by an Independent Data Safety Monitoring Board. A Clinical Events Committee provided an independent and blinded key endpoints assessment.

Results. The study was terminated early due to an excess of serious allergic reactions in the REG1 arm. Final enrollment was 3232 patients from 325 centers. The 2 treatment groups were well-balanced for baseline characteristics. At 3 days there were no differences in the occurrence of the primary endpoint between REG1 and bivalirudin (6.7% vs 6.4%; odds ratio [OR] = 1.05; 95% confidence interval [95%CI], 0.80-1.39; $P = .72$). REG1 was associated with a numerically higher rate of BARC 3 or 5 bleeding (0.4% vs 0.1%; OR = 3.49; 95%CI, 0.73-16.82; $P = .09$) and a significantly higher rate of BARC 2, 3 or 5 bleeding (6.5% vs 4.1%; OR = 1.65; 95%CI, 1.19-2.25; $P = .002$) compared with bivalirudin. Serious allergic events were observed within 24 hours after drug administration in 10/1605 patients who received REG1 (0.6%), including one fatal event and 9 anaphylactic reactions. One patient who received bivalirudin had a serious allergic event (< 0.1%).

Conclusions. REG1 anticoagulation system was associated with similar rates of primary efficacy endpoint at day 3, but higher rates of bleeding and serious allergic events compared with bivalirudin.

SCOT-HEART: Computed Tomography Coronary Angiography in Patients With Suspected Angina Due to Coronary Heart Disease⁸

Presented by David E. Newby, Edinburgh, United Kingdom.

Background. The benefit of CT coronary angiography (CTCA) in patients presenting with stable chest pain has not been systematically studied. We aimed to assess the effect of CTCA on the diagnosis, management, and outcome of patients referred to the cardiology clinic with suspected angina due to coronary heart disease.

Methods. In this prospective open-label, parallel-group, multicentre trial, we recruited patients aged 18–75 years referred for the assessment of suspected angina due to coronary heart disease from 12 cardiology chest pain clinics across Scotland. We randomly assigned (1:1) participants to standard care plus CTCA or standard care alone. Randomisation was done with a web-based service to ensure allocation concealment. The primary endpoint was certainty of the diagnosis of angina secondary to coronary heart disease at 6 weeks. All analyses were intention to treat, and patients were analysed in the group they were allocated to, irrespective of compliance with scanning.

Results. Between Nov 18, 2010, and Sept 24, 2014, we randomly assigned 4146 (42%) of 9849 patients who had been referred for assessment of suspected angina due to coronary heart disease. 47% of participants had a baseline clinic diagnosis of coronary heart disease and 36% had angina due to coronary heart disease. At 6 weeks, CTCA reclassified the diagnosis of coronary heart disease in 558 (27%) patients and the diagnosis of angina due to coronary heart disease in

481 (23%) patients (standard care, 22 [1%] and 23 [1%]; $P < .0001$). Although both the certainty (relative risk [RR] = 2.56; 95% confidence interval [95%CI], 2.33–2.79; $P < .0001$) and frequency of coronary heart disease increased (RR = 1.09; 95%CI, 1.02–1.17; $P = .0172$), the certainty increased (RR = 1.79; 95%CI, 1.62–1.96; $P < .0001$) and frequency seemed to decrease (RR = 0.93; 95%CI, 0.85–1.02; $P = .1289$) for the diagnosis of angina due to coronary heart disease. This changed planned investigations (15% vs 1%; $P < .0001$) and treatments (23% vs 5%; $P < .0001$) but did not affect 6-week symptom severity or subsequent admittances to hospital for chest pain. After 1.7 years, CTCA was associated with a 38% reduction in fatal and nonfatal myocardial infarction (26 vs 42; HR = 0.62; 95%CI, 0.38–1.01; $P = .0527$), but this was not significant.

Conclusions. In patients with suspected angina due to coronary heart disease, CTCA clarifies the diagnosis, enables targeting of interventions, and might reduce the future risk of myocardial infarction.

PROMISE: Economic Comparison of Anatomic Versus Functional Diagnostic Testing Strategies in Symptomatic Patients With Suspected CAD⁹

Presented by Daniel B. Mark, Durham, North Carolina, United States.

Background. The PROMISE trial is an NHLBI-funded randomized comparative effectiveness trial that compared anatomic testing (≥ 64 detector CT angiography) versus functional testing (exercise ECG, stress nuclear, or stress echocardiography) as the initial diagnostic test in patients with new onset symptoms suspicious for coronary artery disease in whom clinicians required diagnostic testing for further evaluation. An economic substudy was conducted to assess economic outcomes and cost effectiveness from a US societal perspective.

Methods. The PROMISE study randomized 10 003 patients in the United States and Canada between 2010 and 2013. We prospectively collected detailed resource consumption data, including the initial testing strategy, along with any subsequent tests and therapies employed. Cost weights for resource consumption were derived from prospectively collected hospital billing data for US patients (with charge to cost conversion), while physician costs and outpatient testing costs were derived from Medicare fees. The primary aim of this part of PROMISE is to compare total medical costs for the two diagnostic testing arms by intention to treat. Costs have been adjusted for inflation and reported in 2014 dollars (\$).

Results. Mean age was 60.8 ± 8.3 years, and 53% were female. Cardiac risk factors include, hypertension in 65%, diabetes in 21%, dyslipidemia in 68%, obesity (BMI > 30) in 48%, peripheral or cerebrovascular disease in 6%, past or current tobacco use in 51%, and family history of premature coronary artery disease in 32%. The primary symptom was chest pain in 73% and exertional dyspnea in 15%. Among those receiving an initial functional test (4831 patients), 68% received nuclear testing, 22% stress echo and 10% exercise ECG; 29% were pharmacologic. A total of 4818 patients underwent CTA as an initial test. The cost of a CTA test was estimated to be \$404. For the functional tests, the cost of echocardiography with an exercise stress test was \$514, the cost of echocardiography with a pharmacologic stress test was \$501, the cost of a nuclear test with exercise was \$946 and a nuclear pharmacologic stress testing was estimated to be \$1132. The cost of an ECG-only stress was \$174. CTA increased the use of invasive catheterizations by 4% over functional testing, and those in the CTA arm were twice as likely to have revascularization (311 patients [6.2%] vs 158 patients [3.2%]). Fifty one percent of the CTA patients referred for catheterization underwent revascularization compared with 39% of the functionally studied patients. After looking

at the average cost of each test and subsequent follow-up testing, the net cost in the first 90 days was \$279 higher on average with CTA than with functional testing. By year 2, however, the cost differential was only \$29.

Conclusions. In stable patients with new chest pain, CTA strategy improved efficiency of use of invasive evaluation. But despite lower testing costs for CTA compared with functional tests, net effect was to drive a small ($< \$500$), statistically non-significant increase in cost.

LATE-BREAKING CLINICAL TRIALS III

PARTNER 1: Five-year Outcomes¹⁰

Presented by Michael Mack, Plano, Texas, United States.

Background. The Placement of Aortic Transcatheter Valves (PARTNER) trial showed that mortality at 1 year, 2 years, and 3 years is much the same with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for high-risk patients with aortic stenosis. We report here the 5-year outcomes.

Methods. We did this randomised controlled trial at 25 hospitals, in Canada (2), Germany (1), and the United States (23). We used a computer-generated randomisation sequence to randomly assign high-risk patients with severe aortic stenosis to either SAVR or TAVR with a balloon-expandable bovine pericardial tissue valve by either a transfemoral or transapical approach. Patients and their treating physicians were not masked to treatment allocation. The primary outcome of the trial was all-cause mortality in the intention-to-treat population at 1 year, we present here predefined outcomes at 5 years. The study is registered with ClinicalTrials.gov, number NCT00530894.

Results. We screened 3105 patients, of whom 699 were enrolled (348 assigned to TAVR, 351 assigned to SAVR). Overall mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 11.7%. At 5 years, risk of death was 67.8% in the TAVR group compared with 62.4% in the SAVR group (hazard ratio = 1.04; 95% confidence interval, 0.86–1.24; $P = .76$). We recorded no structural valve deterioration requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the SAVR group ($P < .0001$), and was associated with increased 5-year risk of mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation vs 56.6% for those with mild aortic regurgitation or less; $P = .003$).

Conclusions. Our findings show that TAVR as an alternative to surgery for patients with high surgical risk results in similar clinical outcomes.

CoreValve US Pivotal High Risk Trial. 2-Year Outcomes¹¹

Presented by Michael J. Reardon, Houston, Texas, United States.

Background. The randomized CoreValve trial demonstrated that transcatheter aortic valve replacement (TAVR) resulted in significantly lower mortality compared with surgical AVR at 1 year in patients who were at increased risk for surgery. Longer-term outcomes following TAVR with the self-expanding CoreValve are necessary to further validate this survival advantage.

Methods. We included patients with severe aortic stenosis at increased surgical risk with NYHA functional class II or greater. The primary endpoint was all-cause mortality at 2 year.

Results. Median patient follow-up of 24 (TAVR, 24.4; surgical AVR, 24.2) months. All-cause mortality (22.2% vs 28.6%; Log-rank, $P = .04$) and all stroke (10.9% vs 16.6%; Log-rank, $P = .05$) was lower in the TAVR group compared to the surgical AVR group. There were no differences in major stroke (6.8% TAVR vs 9.8% surgical AVR). MACCE was significantly lower in the TAVR group compared to the surgical AVR group (29.7% vs 38.6%; $P = .01$).

Conclusions. At 2 years for patients with symptomatic severe AS at increased risk of surgery, the superior survival seen at 1 year for TAVR over surgical AVR is maintained. All stroke was less with TAVR over surgical AVR but major stroke showed no difference and MACCE was significantly lower with TAVR compared to surgical AVR

Early Clinical and Echocardiographic Outcomes With the SAPIEN 3 Transcatheter Aortic Valve Replacement System in Inoperable, High-risk and Intermediate-risk Aortic Stenosis Patients¹²

Presented by Susheel Kodali, New York, New York, United States.

Introduction. The SAPIEN 3 TAVR system is the newest iteration of balloon-expandable valve designed with an external fabric skirt to minimize paravalvular regurgitation (PVR). Two non-randomized registries were embedded in the PARTNER II trial to evaluate valve performance.

Methods. From October 2013 to September 2014, 1661 patients with aortic stenosis (583 high-risk or inoperable [S3-HR], 1078 intermediate risk [S3-I]) were treated via the transfemoral (TF) ($n = 1450$; 87%), transapical or transaortic ($n = 211$; 13%) access route at 57 sites. Procedural outcomes and 30-day clinical events were adjudicated by an independent clinical events committee. Echocardiographic results were analyzed by a core laboratory.

Results. In the S3-HR cohort, 30 day all-cause mortality was 2.2% (TF, 1.6%); cardiac mortality was 1.4% (TF, 1.0%). Other complications included all stroke 1.5%, myocardial infarction 0.5%, major vascular complications 5%, and requirement for permanent pacemaker 13.0%. PVR was none/trace in 61.6% of patients, mild in 35.5%, and moderate in 2.9%. No patients had severe PVR. Mean gradients decreased from 45.5 mmHg at baseline to 11.1 mmHg. In the S3-I cohort, 30 day all-cause mortality was 1.1% (TF = 1.0%); cardiac mortality was 0.9%. All stroke, 2.6%, myocardial infarction 0.3%, major vascular complications 5.6%, and requirement for permanent pacemaker 10.1%.

Conclusions. The SAPIEN 3 TAVR system was associated with low 30-day complications and reduced PVR (compared with previous transcatheter valves).

DEFLECT III: Evaluation of the TriGuard™ HDH Embolic Deflection Device During Transcatheter Aortic Valve Replacement¹³

Presented by Alexandra J. Lansky, New Haven, Connecticut, United States.

Background. Clinical stroke after TAVR is frequent (4-7% at 30 days in RCTs), generally under-reported (17% after SAVR when evaluated by neurologist), confers 3- to 9-fold increased risk of mortality and 50% occurs peri-procedural. Silent stroke affects 58-100% of patients and are associated with neurocognitive decline, dementia and stroke. The safety, efficacy and performance of TriGuard (a Single-wire nitinol device for neurological protection positioned across all 3 cerebral vessels) protection compared with unprotected TAVR is assessed in DEFLECT III trial.

Methods. Multicenter prospective single-blind randomized controlled trial at 13 sites, including 86 patients (exploratory study for the design of a pivotal RCT). Primary Safety Endpoint (ITT population): In-hospital composite of death, stroke, life-threatening or disabling bleeding, AKI (2/3), and major vascular complications (VARC-2). Secondary Performance outcome: successful positioning (complete 3-vessel coverage verified by angiography) and retrieval without TAVR interference. Secondary Efficacy: Frequency, number, and average single, maximal, and total lesion volumes by DW-MRI at 4 days (range 2-6 days). Neurocognitive assessment was performed by Montreal Cognitive Assessment scores.

Results. There were not important baseline characteristic differences between both groups. CoreValve (Medtronic) was employed in about a third of patients, with a Sapien device (Edwards LifeSciences) being used in the rest. Fluoroscopy time was longer with the TriGuard (28.2 vs 18.6 minutes; $P < .001$). 29% and 34% of study and control patients, respectively, were lost to follow-up over 30 days for reasons including stroke, refusal, permanent pacemaker implantation, or death. Technical success was achieved in 87% of the study group (6 patients lost complete coverage), and TAVR success did not differ between the study arms. The primary safety endpoint and its individual components were comparable between both groups. At 30 days, 73% of the TriGuard group and 88% of controls had new lesions on diffusion-weighted MRI (4.5 and 4.0 new lesions per patient, respectively). TriGuard reduced single and maximum lesion volumes: 16% and 17%, respectively, in the intention-to-treat analysis, and 41% and 45% in the per-treatment analysis. Within the study arm, the percentage of patients with zero total lesion volume at 30 days was 21.9% in the intention-to-treat analysis and 26.9% in the per-treatment analysis. Only 12.5% of controls had zero total lesion volume. National Institutes of Health (NIH) stroke scale score, improved or stayed the same at 30 days for the majority of patients in both the study (97.4%) and control arms (87.9%). Montreal Cognitive Assessment scores improved in the TriGuard arm and worsened in the control arm.

Conclusions. In this exploratory clinical trial, use of the TriGuard was safe and provided complete cerebral coverage in 87% of cases, it increased the proportion of patients completely free of ischemic brain lesions and it reduced single and maximum lesion volume.

Outcomes of the Initial Experience With Commercial Transcatheter Mitral Valve Repair in the United States¹⁴

Presented by Paul Sorajja, Minneapolis, Minnesota, United States.

Background. Degenerative MR is common, affecting ~600 000 persons in the United States. Surgery is the standard of care, and is indicated for patients with symptoms or left ventricle (LV) dysfunction. However, there are patients in whom the risk of surgery is prohibitive. The Mitraclip system received commercial approval in October 24, 2011, being indicated for symptomatic patients with primary MR ≥ 3 and prohibitive surgical risk. Our objective was to analyze and report the initial commercial experience with the MitraClip System in the United States.

Methods. This study shows all commercial transcatheter mitral valve repair (TMVR) cases with MitraClip enrolled in the registry through August 31, 2014 for 564 participants across 61 health care centers in the United States. The in-hospital and 30-day outcomes for procedure success, complications, and device-related events, were examined. Procedure success was considered if post-implant MR grade ≤ 2 , without CV surgery and without in-hospital mortality. Other definitions were procedure complications (cardiac perforation,

major bleeding, stroke, myocardial infarction, mitral injury, or death) and device-related adverse events (single leaflet device attachment, complete clip detachment, device thrombosis, device or delivery component embolization).

Results. Clip implantation occurred in 94% of the cases, and procedural success was achieved in 91.8%. Variables related with procedural success were: smaller left ventricular end-diastolic diameters, less severe baseline mitral regurgitation, A2-P2 clip location and case volume ($\times 2$). Procedure complications and device-related adverse events rates were 7.8% and 2.7%. Mortality was 2.3% in-hospital, and 5.8% at 30-days.

Conclusions. In this first report of the US commercial experience with TMVR, procedure success, clinical outcomes, and adverse events were favourable in comparison to pre-approval studies and other national registries. These data demonstrate effectiveness and safety of TMVR with MitraClip for the treatment of prohibitive risk patients with symptomatic MR.

JOINT AMERICAN COLLEGE OF CARDIOLOGY/NEW ENGLAND JOURNAL OF MEDICINE LATE-BREAKING CLINICAL TRIALS

AATAC: Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device¹⁵

Presented by Luigi Di Biase, Austin, Texas, United States.

Background. Catheter ablation (CA) represents a valid treatment option in patients with drug-refractory symptomatic atrial fibrillation (AF). The majority of catheter ablation trials have mainly enrolled patients with preserved LVEF and paroxysmal AF. However, a significant number of patients with AF also have heart failure (HF) and rhythm control with antiarrhythmic drugs has not shown satisfactory results in randomized trials both in patients with or without HF. Whether CA is superior to amiodarone for the treatment of persistent AF in patients with HF is unknown.

Methods. This was an open-label, randomized, parallel-group, multicenter study. Patients with persistent AF, dual-chamber ICD or CRT-D, NYHA II-III and LVEF < 40% within the last 6 months were randomly assigned (1:1 ratio) to undergo CA for AF (group 1 = 102 patients) or receive amiodarone, (group 2 = 101 patients). The main goal of the ablation procedure was pulmonary vein antrum isolation. Recurrence of AF was the primary end point. Recurrence of AF was the primary endpoint.

Results. Baseline characteristics were not different between groups. At 26 \pm 8 months follow-up, 71 (70%) patients in group 1 were free of recurrences after average 1.4 \pm 0.6 procedures as compared to 34 (34%) in group 2 (log-rank, $P < .001$). Success rate of CA in the different centers after a single procedure ranged from 29% to 61%. After adjusting for covariates in multivariable model, patients on amiodarone therapy were found to be 2.5 times more likely to fail (HR = 2.5; 95% confidence interval [95%CI], 1.5-4.3; $P < .001$) compared to CA. Over the 2 year follow-up, hospitalization rate was 31% (32 patients) in group 1 and 57% (58 patients) in group 2 ($P < .001$), showing 45% relative risk reduction (RR = 0.55; 95%CI, 0.39-0.76. A significant lower mortality was observed in CA (8 [8%] versus AMIO (18 [18%]; $P = .037$).

Conclusions. This multicenter randomized study shows that CA of AF is superior to amiodarone in achieving freedom from AF at long-term follow-up and reducing hospitalization and mortality in patients with heart failure and persistent AF.

Effectiveness of Surgical Ablation of Atrial Fibrillation During Mitral Valve Surgery¹⁶

Presented by A. Gillinov, New York, New York, United States.

Background. Among patients undergoing mitral-valve surgery, 30 to 50% present with atrial fibrillation, which is associated with reduced survival and increased risk of stroke. Surgical ablation of atrial fibrillation has been widely adopted, but evidence regarding its safety and effectiveness is limited.

Methods. We randomly assigned 260 patients with persistent or long-standing persistent atrial fibrillation who required mitral-valve surgery to undergo either surgical ablation (ablation group) or no ablation (control group) during the mitral-valve operation. Patients in the ablation group underwent further randomization to pulmonary vein isolation or a biatrial maze procedure. All patients underwent closure of the left atrial appendage. The primary end point was freedom from atrial fibrillation at both 6 months and 12 months (as assessed by means of 3-day Holter monitoring).

Results. More patients in the ablation group than in the control group were free from atrial fibrillation at both 6 and 12 months (63.2% vs 29.4%; $P < .001$). There was no significant difference in the rate of freedom from atrial fibrillation between patients who underwent pulmonary-vein isolation and those who underwent the biatrial maze procedure (61.0% and 66.0%, respectively; $P = .60$). One-year mortality was 6.8% in the ablation group and 8.7% in the control group with ablation, (HR = 0.76; 95% confidence interval, 0.32 to 1.84; $P = .55$). Ablation was associated with more implantations of a permanent pacemaker than was no ablation (21.5 vs 8.1 per 100 patient-years; $P = .01$). There were no significant between-group differences in major cardiac or cerebrovascular adverse events, overall serious adverse events, or hospital readmissions (figure 2).

Conclusions. The addition of atrial fibrillation ablation to mitral-valve surgery significantly increased the rate of freedom from atrial fibrillation at 1 year among patients with persistent or long-standing persistent atrial fibrillation, but the risk of implantation of a permanent pacemaker was also increased.

LEGACY: Long-term Effect of Goal Directed Weight Management on an Atrial Fibrillation Cohort¹⁷

Presented by Rajeev K. Pathak, Adelaide, Australia.

Background. Obesity and atrial fibrillation (AF) are dual epidemics that frequently coexist. Weight-loss reduces AF burden; however, whether this is sustained, has a dose effect or is influenced by weight-fluctuation is not known. The aim was to evaluate the long-term impact of weight-loss and weight-fluctuation on rhythm control in obese individuals with atrial fibrillation.

Methods. Of 1415 consecutive patients with AF, 825 had BMI ≥ 27 kg/m² and were offered weight management. After screening for exclusion criteria, 355 were included in this analysis. To determine a dose-response, weight-loss was categorized as: Group-1 (> 10%); Group-2 (3-9%); and Group-3 (< 3%). Weight trend/fluctuation was determined by yearly follow-up. We determined the impact on AF severity scale and 7-day ambulatory monitoring.

Results. There were no differences in baseline characteristics or follow-up duration between the groups (NS). At follow-up, AF burden and symptom severity decreased more in Group-1 compared to Group-2 and 3 (p 10% resulted in a six-fold (95% confidence interval, 3.4-10.3; $P < .001$) greater probability of arrhythmia-free survival compared to other two groups. Greater than 5% weight-fluctuation partially offsets this benefit with a two-fold (95% confidence interval, 1.0-4.3; $P = .02$) increased risk of arrhythmia recurrence.

Conclusions. Long-term sustained weight-loss is associated with significant reduction of AF burden and maintenance of sinus rhythm. Weight-loss and avoidance of weight-fluctuation constitute important strategies for reducing the rising burden of AF.

ERICCA: Effect of Remote Ischemic Preconditioning on Clinical Outcomes in Patients Undergoing Coronary Artery Bypass Graft Surgery¹⁸

Presented by Derek J. Hausenloy, London, United Kingdom.

Background. There is a need of cardiac protective strategies for high risk patients undergoing cardiac surgery. Remote ischemic conditioning (RIC) supposes a simple non-invasive and low-cost intervention that may improve long-term clinical outcomes in this setting.

Methods. 1612 patients from 29 UK centers undergoing on-pump CABG with or without valve surgery, with EuroSCORE ≥ 5 were randomized to RIC consisting of 4 \times 5 min BP cuff inflations/deflations versus a sham procedure. Primary outcome was the composite of one year cardiovascular death, myocardial infarction, Stroke, or need of revascularization. Secondary endpoints were peri-operative myocardial injury, inotrope score, acute Kidney Injury, and length of ITU/ Hospital stay.

Results. There were not important baseline characteristic differences between both groups. Average EuroSCORE was 6.6 and 6.7 in RIC and control arm respectively. Approximately half of patients underwent CABG with valve surgery associated in both arms. Average cardiopulmonary bypass time was 112 min in both arms. Primary endpoint occurred at one year in 27% and 28% of patients in RIC and control arm respectively (HR = 0.96; 95% confidence interval, 0.8-1.16; $P = .66$). There were not statistical significant differences between groups in the components or primary endpoint. Peri-operative myocardial injury assessed by 72 hours AUC Trop-T in ng/h/ml was 30.1 in RIC arm and 35.7 in control arm ($P = .031$).

Conclusions. RIC did not improve long-term clinical outcomes in high-risk patients undergoing on-pump cardiac bypass surgery with blood cardioplegia.

BEST: Everolimus-eluting Stents Versus Bypass Surgery for Multivessel Coronary Artery Disease¹⁹

Presented by Seung-Jung Park, Seoul, South Korea.

Background. During primary percutaneous coronary intervention (PCI), manual thrombectomy may reduce distal embolization and thus improve microvascular perfusion. Small trials have suggested that thrombectomy improves surrogate and clinical outcomes, but a larger trial has reported conflicting results.

Methods. We randomly assigned 10732 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI to a strategy of routine upfront manual thrombectomy versus PCI alone. The primary outcome was a composite of death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within 180 days. The key safety outcome was stroke within 30 days.

Results. The primary outcome occurred in 347 of 5033 patients (6.9%) in the thrombectomy group versus 351 of 5030 patients (7.0%) in the PCI-alone group (hazard ratio in the thrombectomy group, 0.99; 95% confidence interval, 0.85 to 1.15; $P = .86$). The rates of cardiovascular death (3.1% with thrombectomy vs 3.5% with PCI alone; HR = 0.90; 95% confidence interval, 0.73 to 1.12; $P = .34$) and the

primary outcome plus stent thrombosis or target-vessel revascularization (9.9% vs 9.8%; HR = 1.00; 95% confidence interval, 0.89 to 1.14; $P = .95$) were also similar. Stroke within 30 days occurred in 33 patients (0.7%) in the thrombectomy group versus 16 patients (0.3%) in the PCI-alone group (HR = 2.06; 95%CI, 1.13 to 3.75; $P = .02$).

Conclusions. In patients with STEMI who were undergoing primary PCI, routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days but was associated with an increased rate of stroke within 30 days.

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