Special article

Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Dallas, Texas, United States, November 16–20, 2013)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales de la *American Heart Association* (Dallas, Texas, Estados Unidos, 16-20 de noviembre de 2013)

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Following its policy of disseminating scientific information to the cardiology community[1-10], *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Scientific Sessions of the American Heart Association (Dallas, Texas, United States, November 16-20, 2013), 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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EU-PACT Warfarin Study: Genotype-guided Dosing of Warfarin vs Standard Dosing.

COAG Trial: Clarification of Optimal Anticoagulation Through Genetics.

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ACUTE CARDIOVASCULAR AND CEREBROVASCULAR CARE

NIAMI Study: Nitrites in Acute Myocardial Infarction[11]

Presented by Nishat Siddiqi, Aberdeen, United Kingdom.

Introduction and objectives. Despite reperfusion therapy for acute myocardial infarction (AMI), heart failure remains a major sequel. Reperfusion leads to further damage, described as ischemia-reperfusion-injury (IRI). This contributes up to 50% of the final infarct size. In pre-clinical models, nitrite potently protects against IRI in the heart and other organs. Intravenous (iv) sodium nitrite, administered immediately before opening of the infarct-related artery, results in significant reduction of IRI in patients with acute ST elevation MI (STEMI)

Methods. In this phase II, randomised, placebo-controlled, double-blind, multicenter trial, 220 patients with first acute STEMI and TIMI 0 or 1 flow were randomised in a double-blind fashion to 70 micromol iv sodium nitrite or matching placebo over 5 minutes immediately preceding opening of the infarct-related artery. The primary end point was the difference in infarct size between sodium nitrite and placebo groups using cardiovascular magnetic resonance imaging (CMR) at 6 to 8 days following AMI, adjusted for area at risk (AAR), diabetes status, and centre. Secondary end points comprised: *a)* infarct size (CMR) at 6 months; *b)* plasma CK and troponin I, measured until 72 hours after injection of the study medication; *c)* infarct size corrected for AAR measured using T2-weighted CMR; and *d)* left ventricular (LV) ejection fraction and LV end systolic volume index measured by CMR at 6 to 8 days and at 6 months.

Results. Infarct size at 6 to 8 days by CMR did not differ between nitrite and placebo groups (effect size -0.7% 95% confidence interval [CI] -2.2, +0.7; *P* =.34). There were no significant differences in the predefined secondary end points. There was no treatment effect in nondiabetics, but in diabetics was -4.5% (95%CI -8.8, -0.2; *P* = .041) although the interaction was not significant (*P* = .067).

Conclusions. Sodium nitrite administered intravenously immediately prior to reperfusion in patients with acute STEMI did not reduce infarct size. A potential benefit in diabetics warrants further study.

CATIS Trial: Blood Pressure Reduction Among Acute Ischemic Stroke Patients[12]

Presented by Jiang He, New Orleans, Louisiana, United States.

Introduction and objectives. Although the benefit of reducing blood pressure for primary and secondary prevention of stroke has been established, the effect of antihypertensive treatment in patients with acute ischemic stroke is uncertain. The objective was to evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 days or hospital discharge.

Methods. The China Antihypertensive Trial in Acute Ischemic Stroke, a single-blind, blinded end points randomized clinical trial, was conducted among 4071 patients with non-thrombolysed ischemic stroke within 48 hours of onset and elevated systolic blood pressure. Patients were recruited from 26 hospitals across China between August 2009 and May 2013. Patients (n = 2038) were randomly assigned to receive antihypertensive treatment (aimed at lowering systolic blood pressure by 10% to 25% within the first 24 hours after randomization, achieving blood pressure less than 140/90 mmHg within 7 days, and maintaining this level during hospitalization) or to discontinue all antihypertensive medications (control) during hospitalization (n = 2033).

Results. Primary outcome was a combination of death and major disability (modified Rankin Scale score ≥ 3) at 14 days or hospital discharge. Mean systolic blood pressure was reduced from 166.7 mmHg to 144.7 mmHg (-12.7%) within 24 hours in the antihypertensive treatment group and from 165.6 mmHg to 152.9 mmHg (-7.2%) in the control group within 24 hours after randomization (difference, -5.5% [95%CI, -4.9 to -6.1%]; absolute difference, -9.1 mmHg [95%CI, -10.2 to -8.1]; *P* < .001). Mean systolic blood pressure was 137.3 mmHg in the antihypertensive treatment group and 146.5 mmHg in the control group at day 7 after randomization (difference, -9.3 mmHg [95%CI, -10.1 to -8.4]; *P* < .001). The primary outcome did not differ between treatment groups (683 events [antihypertensive treatment] vs 681 events [control]; odds ratio, 1.00 [95%CI, 0.88 to 1.14]; *P* = .98) at 14 days or hospital discharge. The secondary composite outcome of death and major disability at 3-month posttreatment follow-up did not differ between treatment groups (500 events [antihypertensive treatment] vs 502 events [control]; odds ratio, 0.99 [95%CI, 0.86 to 1.15]; *P* = .93).

Conclusions. Among patients with acute ischemic stroke, blood pressure reduction with antihypertensive medications, compared with the absence of hypertensive medication, did not reduce the likelihood of death and major disability at 14 days or hospital discharge.

Randomized Clinical Trial of Prehospital Induction of Mild Hypothermia in Out-of-hospital Cardiac Arrest Patients Using a Rapid Infusion of 4°C Normal Saline[13]

Presented by Francis Kim, Seattle, Washington, United States.

Introduction and objectives. Hospital cooling improves outcome after cardiac arrest, but prehospital cooling immediately after return of spontaneous circulation may result in better outcomes. The objective was to determine whether prehospital cooling improves outcomes after resuscitation from cardiac arrest in patients with ventricular fibrillation (VF) and without VF.

Methods. A randomized clinical trial that assigned adults with prehospital cardiac arrest to standard care with or without prehospital cooling, accomplished by infusing up to 2 L of 4°C normal saline as soon as possible following return of spontaneous circulation. Adults in King County, Washington, with prehospital cardiac arrest and resuscitated by paramedics were eligible and 1359 patients (583 with VF and 776 without VF) were randomized between December 15, 2007, and December 7, 2012. Patient follow-up was completed by May 1, 2013. Nearly all of the patients resuscitated from VF and admitted to the hospital received hospital cooling regardless of their randomization. The primary outcomes were survival to hospital discharge and neurological status at discharge.

Results. The intervention decreased mean core temperature by 1.20°C (95%CI, −1.33°C to −1.07°C) in patients with VF and by 1.30°C (95%CI, −1.40°C to −1.20°C) in patients without VF by hospital arrival and reduced the time to achieve a temperature of less than 34°C by about 1 hour compared with the control group. However, survival to hospital discharge was similar among the intervention and control groups among patients with VF (62.7% [95%CI, 57.0-68.0] vs 64.3% [95%CI, 58.6-69.5], respectively; *P* = .69) and among patients without VF (19.2% [95%CI, 15.6-23.4] vs 16.3% [95%CI, 12.9-20.4], respectively; *P* = .30). The intervention was also not associated with improved neurological status of full recovery or mild impairment at discharge for patients with VF (57.5% [95%CI, 51.8-63.1] of cases had full recovery or mild impairment vs 61.9% [95%CI, 56.2-67.2] of controls; P = .69) or those without VF (14.4% [95%CI, 11.3-18.2] of cases vs 13.4% [95%CI, 10.4-17.2] of controls; *P* = .30). Overall, the intervention group experienced more rearrest in the field than the control group (26% [95%CI, 22-29] vs 21% [95%CI,18-24], respectively; *P* = .008), as well as increased diuretic use and pulmonary edema on first chest x-ray, which resolved within 24 hours after admission.

Conclusions. Although use of prehospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34°C, it did not improve survival or neurological status among patients resuscitated from prehospital VF or those without VF.

TTM Trial: Target Temperature Management 33°C Versus 36°C After Out-of-hospital Cardiac Arrest[14]

Presented by Niklas Nielsen, Helsingborg, Sweden.

Introduction and objectives. Unconscious survivors of out-of-hospital cardiac arrest have a high risk of death or poor neurologic function. Therapeutic hypothermia is recommended by international guidelines, but the supporting evidence is limited, and the target temperature associated with the best outcome is unknown. Our objective was to compare 2 target temperatures, both intended to prevent fever.

Methods. In an international trial, we randomly assigned 950 unconscious adults after out-of-hospital cardiac arrest of presumed cardiac cause to targeted temperature management at either 33°C or 36°C. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale.

Results. In total, 939 patients were included in the primary analysis. At the end of the trial, 50% of the patients in the 33°C group (235 of 473 patients) had died, as compared with 48% of the patients in the 36°C group (225 of 466 patients) (hazard ratio [HR] with a temperature of 33°C, 1.06; 95% CI, 0.89 to 1.28; $P = .51$). At the 180-day follow-up, 54% of the patients in the 33°C group had died or had poor neurologic function according to the CPC, as compared with 52% of patients in the 36°C group (HR = 1.02; 95%CI, 0.88 to 1.16; $P = .78$). In the analysis using the modified Rankin scale, the comparable rate was 52% in both groups (HR = 1.01; 95%CI, 0.89 to 1.14; $P = .87$). The results of analyses adjusted for known prognostic factors were similar.

Conclusions. In unconscious survivors of out-of-hospital cardiac arrest of presumed cardiac cause, hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with a targeted temperature of 36°C.

PREVENTION: FROM SCHOOLS TO COUNTRIES

Promotion of Cardiovascular Health in Preschool Children: 36-month Cohort Follow-up[15]

Presented by Jaime Céspedes, Bogotá, Colombia.

Introduction and objectives. Educational interventions in preschool children could improve dietary behavior and physical activity, and prevent unhealthy body weights in low- and middle-income countries. We have previously reported the beneficial impact of an educational intervention in preschoolers in a 6-month trial. We now report extended results after 36 months.

Methods. To evaluate the cohort of previously intervened children, baseline measurements were made in May 2009 in 14 preschool facilities in Usaquén (Bogotá, Colombia). Follow-up measurements were performed at 18 and 36 months. The primary outcome was the mean change in children's knowledge and attitudes scores regarding healthy eating and living an active lifestyle, including habits scores related to physical activity. Secondary outcomes were the change over time of children's nutritional status and the mean change in parents' knowledge, attitudes, and habits.

Results. We included 1216 children, 3 to 5 years of age, and 928 parents. After adjusting by sex and age of the children, socioeconomic status, age of parents, age and education level of teachers, we found a significant increase in mean knowledge, attitudes, and habits scores at 36 months, compared to baseline: 87.94 vs. 76.15 ($P < .001$); 86.39 vs. 57.03 ($P < .001$); and 66.29 vs. 48.72 ($P < .001$), respectively. We observed a similar increase in knowledge and attitude scores in parents: 73.45 vs. 70.01 ($P < .001$) and 78.08 vs. 74.65 ($P < .001$). The proportion of eutrophic children increased from 62.1% at baseline to 75.0% at 36 months ($P < .0001$).

Conclusions. After 36 months, the educational intervention maintained a beneficial trend toward a healthy lifestyle in children and their parents.

Randomized Trial of Social Network Lifestyle Intervention for Obesity: MICROCLINIC Intervention Results and 16-month Follow-up[16]

Presented by: Eric L Ding, Boston, Massachussetts, United States.

Introduction and objectives. Obesity has been suggested to propagate within social networks. A social network program was engineered to contagiously propagate healthy lifestyles and leverage pre-existing social networks to decrease obesity. We expand upon a 9- to 10-month intervention program with 16-month follow-up to investigate the power of social networks in the first ever long-term randomized trial.

Methods. Based in a rural Appalachian region of Kentucky, we investigate the Microclinic Social Network (MSN) Behavioral Health Intervention, a lifestyle intervention in a resource-limited but socially cohesive area with high obesity prevalence. Social clusters of 2 to 8 individuals who participated together in a program with weekly physical activity, nutrition, health education, and social activity sessions led by health educators; controls had access to standard care from the local county health department. Body weight and waist circumference were collected in follow-up waves during intervention, plus at 16 months after baseline in a 52% sample subcohort. Longitudinal analyses utilized multilevel repeated-measures mixed models, with multilevels of neighborhood center, classroom, and social cluster (ie, microclinic) to examine the change in health outcomes in program participants vs controls.

Results. Study enrolled 552 participants, comprised of 242 social clusters, among 27 classroom clusters, and from 5 neighborhood cohorts. Participants were 85.8% women, mean age 50.9 years (13.8), mean BMI 36.2 (7.6). From baseline to end of intervention period, the MSN intervention group showed decreased body weight of -6.52 lbs (95%CI: -8.57 to -4.47; $P < .001$), and improved central adiposity with decreased waist circumference of -1.24 inches (-1.85 to -0.63; $P < .001$), relative to controls. In subcohort at 16 months, decreases in weight (-4.70 lbs, -7.56 to -1.84) and waist circumference (-0.99 inches, -1.81 to -0.17) were maintained.

Conclusions. Expanded and long-term findings demonstrate the effectiveness of MSN Behavioral Health Invervention for obesity control in resource limited settings. Results hold promise for social engineering and leveraging the power of social networks interventions to propagate healthy lifestyle behaviors.

Medication Study: Medication Adherence and Secondary Prevention Measures After Acute Coronary Syndrome Hospital Discharge[17]

Presented by Michael Ho, Denver, Colorado, United States.

Introduction and objectives. Adherence to cardioprotective medication regimens in the year after hospitalization for acute coronary syndrome (ACS) is poor. The objective is to test a multifaceted intervention to improve adherence to cardiac medications.

Methods. In this randomized clinical trial, 253 patients from 4 Department of Veterans Affairs medical centers located in Denver (Colorado), Seattle (Washington); Durham (North Carolina), and Little Rock (Arkansas) admitted with ACS were randomized to the multifaceted intervention (INT) or usual care (UC) prior to discharge. The INT lasted for 1 year following discharge and comprised: *a)* pharmacist-led medication reconciliation and tailoring; *b)* patient education; *c)* collaborative care between pharmacist and a patient's primary care clinician and/or cardiologist; and *d)* 2 types of voice messaging (educational and medication refill reminder calls). The primary outcome of interest was proportion of patients adherent to medication regimens based on a mean proportion of days covered (PDC) greater than 0.80 in the year after hospital discharge using pharmacy refill data for 4 cardioprotective medications (clopidogrel, betablockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors [statins], and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [ACEI/ARB]). Secondary outcomes included achievement of blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) targets.

Results. Of 253 patients, 241 (95.3%) completed the study (122 in INT and 119 in UC). In the INT group, 89.3% of patients were adherent compared with 73.9% in the UC group (P = .003). Mean PDC was higher in the INT group (0.94 vs 0.87; P < .001). A greater proportion of INT patients were adherent to clopidogrel (86.8% vs 70.7%; P = .03), statins (93.2% vs 71.3%; P < .001), and ACEI/ARB (93.1% vs 81.7%; P = .03) but not -blockers (88.1% vs 84.8%; P = .59). There were no statistically significant differences in the proportion of patients who achieved BP and LDL-C goals.

Conclusions. A multifaceted intervention comprising pharmacist-led medication reconciliation and tailoring, patient education, collaborative care between pharmacist and patients' primary care clinician and/or cardiologist, and voice messaging increased adherence to medication regimens in the year after ACS hospital discharge without improving BP and LDL-C levels. Understanding the impact of such improvement in adherence on clinical outcomes is needed prior to broader dissemination of the program.

China Rural Health Initiative. Sodium Reduction Study: Effects of a Community-Based Sodium Reduction Program on 24hr Urinary Sodium and Blood Pressure in Rural China[18]

Presented by Nicole Li, Sydney, Australia.

Introduction and objectives. Cardiovascular diseases are the leading cause of death in rural China. High blood pressure caused by excessive sodium consumption has been identified as an important modifiable risk factor. An effective, low-cost, population-based strategy to reduce sodium intake in rural China has significant public health potential.

Methods. The study is a large-scale, cluster-randomized trial done in 5 northern provinces in China. Two counties have been selected from each province and 12 townships enrolled from each county, making a total of 120 clusters. One village from each township was selected for participation and randomized to intervention or control with stratification by county. The 60 control group villages received no intervention and simply continued with their usual practices. The 60 intervention villages received general community health education advising reduced salt intake, specific health education targeting salt reduction messages to patients at high risk of cardiovascular diseases, and a food supply strategy designed to promote the sale of a reduced sodium, added potassium salt substitute through the village convenience stores. The 60 intervention villages were further randomised into 2 equal groups, such that 30 villages had access to salt substitute at a price parity with normal salt and 30 had salt substitute available at market price (about twice the cost of normal salt). The intervention was implemented for 18 months. An age- and sex-stratified random sample of 2400 men and women from the 120 villages (20 from each village) were selected at the end of the intervention period for outcome evaluation. The primary outcome was 24-hour urinary sodium and secondary outcomes were blood pressure, 24-hour urinary potassium, urinary sodium:potassium ratio, and proportion with hypertension.

Results. There was a significant reduction in the intervention group versus the control group in urinary sodium (230 vs. 243 mmol/day; P = .03) and a significant increase in urinary potassium (51 vs. 44 mmol/day; P < .001). There was no significant change in hypertension prevalence (56% vs. 58%; P = .20).

Conclusions. A population-level sodium reduction strategy is feasible and effective. These findings have potential for impacting public health policy.

MEDICAL AND SURGICAL APPROACHES TO IMPROVING HEART FAILURE OUTCOMES

Atrial Antitachycardia Pacing and Managed Ventricular Pacing Reduce the Endpoint Composed by Death, Cardiovascular Hospitalizations, and Permanent Atrial Fibrillation Compared to Conventional Dual-chamber Pacing in Bradycardia Patients: Results of the Minerva Randomized Study[19]

Presented by Giuseppe Boriani, Bologna, Italy.

Introduction and objectives. Atrial fibrillation (AF) is a common comorbidity in bradycardia patients. The most advanced pacemakers feature atrial preventive pacing and atrial antitachycardia pacing (DDDRP), which may reduce AF occurrence and duration, and Managed Ventricular Pacing (MVP), which may minimize right ventricular pacing detrimental effects. We evaluated whether DDDRP and MVP might reduce mortality, morbidity or progression to permanent AF compared with standard dual-chamber pacing (Control DDDR).

Methods. In a randomized, parallel, single-blind, multicenter international trial, we enrolled patients with bradycardia, previous atrial tachyarrhythmias, and no history of permanent AF or third-degree atrioventricular block, in whom a DDDRP pacemaker had recently been implanted. Patients were randomly assigned in a 1:1:1 manner to Control DDDR, DDDRP + MVP or MVP. The primary outcome was the 2-year incidence of a combined end point composed of death, cardiovascular hospitalizations or permanent AF. Analysis was intention-to-treat using Kaplan-Meier estimates and log-rank test.

Results. We randomized 1166 patients, aged 74 ± 9 years, 588 (50%) males. The primary end point occurred in 102 of 385 Control DDDR patients (26.5%), in 76 of 383 DDDRP + MVP patients (19.8%) (HR = 0.74; 95%CI, 0.55-0.99; P = .04 vs Control DDDR), and in 85 of 398 MVP patients (21.4%) (HR = 0.89; 95%CI, 0.77-1.03; P = .12 vs Control DDDR), as shown in the figure. DDDRP + MVP was associated with a reduced risk of permanent AF (HR = 0.39; 95%CI, 0.21-0.75; P = .004 vs Control DDDR).

Conclusions. In patients with bradycardia and atrial tachyarrhythmias, DDDRP + MVP is superior to standard dual-chamber pacing, as it reduces the end point composed of death, cardiovascular hospitalizations, or permanent AF. The positive effect is mainly due to a decrease in the progression of atrial tachyarrhythmias to permanent AF.

ROSE AHF Trial: Renal Optimization Strategies Evaluation in Acute Heart Failure[20]

Presented by Horng H. Chen, Rochester, Minnesota, United States.

Introduction and objectives. Small studies suggest that low-dose dopamine or low-dose nesiritide may enhance decongestion and

preserve renal function in patients with acute heart failure and renal dysfunction; however, neither strategy has been rigorously tested. The objective was to test the 2 independent hypotheses that, compared with placebo, addition of low-dose dopamine (2 µg/kg/min) or low-dose nesiritide (0.005 µg/kg/min without bolus) to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.

Methods. Multicenter, double-blind, placebo-controlled clinical trial (Renal Optimization Strategies Evaluation [ROSE]) of 360 hospitalized patients with acute heart failure and renal dysfunction (estimated glomerular filtration rate of 15-60 mL/min/1.73 m^2), randomized within 24 hours of admission. Enrollment occurred from September 2010 to March 2013 across 26 sites in North America. Participants were randomized in an open, 1:1 allocation ratio to the dopamine or nesiritide strategy. Within each strategy, participants were randomized in a double-blind, 2:1 ratio to active treatment or placebo. The dopamine (n = 122) and nesiritide (n = 119) groups were independently compared with the pooled placebo group (n = 119).

Results. Coprimary end points included 72-hour cumulative urine volume (decongestion end point) and the change in serum cystatin C from enrollment to 72 hours (renal function end point). Compared with placebo, low-dose dopamine had no significant effect on 72-hour cumulative urine volume (dopamine, 8524 mL; 95%CI, 7917-9131 vs placebo, 8296 mL; 95% CI, 7762-8830; difference, 229 mL; 95%CI, −714 to 1171 mL; *P* = .59) or on the change in cystatin C level (dopamine, 0.12 mg/L; 95%CI, 0.06-0.18 vs placebo, 0.11 mg/L; 95%CI, 0.06-0.16; difference, 0.01; 95%CI, −0.08 to 0.10; *P* = .72). Similarly, low-dose nesiritide had no significant effect on 72-hour cumulative urine volume (nesiritide, 8574 mL; 95%CI, 8014-9134 vs placebo, 8296 mL; 95%CI, 7762-8830; difference, 279 mL; 95%CI, −618 to 1176 mL; *P* = .49) or on the change in cystatin C level (nesiritide, 0.07mg/L; 95%CI, 0.01-0.13 vs placebo, 0.11mg/L; 95%CI, 0.06-0.16; difference, −0.04; 95%CI, −0.13 to 0.05; *P* = .36). Compared with placebo, there was no effect of low-dose dopamine or nesiritide on secondary end points reflective of decongestion, renal function, or clinical outcomes.

Conclusions. In participants with acute heart failure and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.

CTSN SMR Trial: Mitral-valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation[21]

Presented by Michael A. Acker, Philadelphia, Pennsylvania, United States.

Introduction and objectives. Ischemic mitral regurgitation is associated with a substantial risk of death. Practice guidelines recommend surgery for patients with a severe form of this condition but acknowledge that the supporting evidence for repair or replacement is limited.

Methods. We randomly assigned 251 patients with severe ischemic mitral regurgitation to undergo either mitral-valve repair or chordal-sparing replacement in order to evaluate efficacy and safety. The primary end point was the left ventricular end-systolic volume index (LVESVI) at 12 months, as assessed with the use of a Wilcoxon rank-sum test in which deaths were categorized below the lowest LVESVI rank.

Results. At 12 months, the mean LVESVI among surviving patients was 54.6 ± 25.0 mL/m^2 of body-surface area in the repair group and 60.7 ± 31.5 mL/m^2 in the replacement group (mean change from baseline, −6.6 and −6.8 mL/m^2, respectively). The rate of death was 14.3% in the repair group and 17.6% in the replacement group (HR with repair, 0.79; 95%CI, 0.42 to 1.47; *P* = .45 by the log-rank test). There was no significant between-group difference in LVESVI after adjustment for death (z score, 1.33; *P* = .18). The rate of moderate or severe recurrence of mitral regurgitation at 12 months was higher in the repair group than in the replacement group (32.6% vs 2.3%, *P* < .001). There were no significant between-group differences in the rate of a composite of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 months

Conclusions. We observed no significant difference in left ventricular reverse remodeling or survival at 12 months between patients who underwent mitral-valve repair and those who underwent mitral-valve replacement. Replacement provided a more durable correction of mitral regurgitation, but there was no significant between-group difference in clinical outcomes.

TOPCAT Trial: Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist[22]

Presented by Marc A. Pfeffer, Boston, Massachusetts, United States.

Introduction and objectives. In the absence of a proven therapy to improve the prognosis of patients with heart failure and preserved left ventricular (LV) ejection fraction (HFpEF), treatment remains empirical. Mineralcorticoids receptor antagonists have been shown to reduce the risk of death and other major cardiovascular events in patients with reduced EF heart failure and following myocardial infarction.

Methods. NHLBI contract, international, randomized, placebo-controlled trial evaluating the effectiveness and safety of aldosterone antagonist (spironolactone: 15 mg titrated to 45 mg) compared to placebo in patients with HFpEF, using time to first event cardiovascular mortality, aborted cardiac arrest, or heart failure hospitalization as the primary end point. Inclusion criteria were informed consent, age ≥ 50 years, symptomatic HF, LVEF ≥ 45%, HF hospitalization (within 12 months, Stratum I), or an elevated BNP or NT proBNP (≥ 100 or 360 pg/mL, Stratum II). Recent stroke, coronary event, uncontrolled hypertension, eGFR < 30, and hyperkalemia (≥ 5.0 mmol/L) were some of the major exclusions. Subjects were randomized within each stratum and followed for 3.4 years on average. Safety assessments, nonfatal cardiovascular events, the development of atrial fibrillation, diabetes mellitus, and quality of life were key secondary end points.

Results. 1722 patients were randomized to the spironolactone arm, and 1723 to placebo. There were no statistically significant differences for the primary outcome (18.6% vs 20.4%, respectively; HR = 0.89; 95% CI, 0.77-1.04; *P* = .138), but there was for multiple hospitalization for HF (*P* < .01). There were no significant differences in adverse events, except more hyperkalemia with spironolactone and more hypokalemia on placebo.

Conclusions. Spironolactone did not alter the primary composite outcome, but did reduce hospitalization for HF. The use of spironolactone in these patients requires careful monitoring of potassium and creatinine.

THERAPEUTIC ADVANCES IN CORONARY AND PERIPHERAL VASCULAR DISEASE

One Year Mortality in STEMI Patients Randomized to Primary PCI or a Pharmaco-invasive Strategy. The Stream 1 Year Follow-up[23]

Presented by Peter Sinnaeve, Leuven, Belgium.

Introduction and objectives. We present one year mortality in STEMI patients randomized in the STREAM trial.

Methods. In the STREAM trial, 1892 STEMI patients presenting within 3 hours after onset of symptoms and unable to undergo

primary PCI within 1 hour were randomized to a pharmaco-invasive (PI) strategy or standard primary PCI according to local practice. The PI approach consisted of bolus tenecteplase, clopidogrel and enoxaparin with dose adjustments in the elderly.

Results. The primary combined end point of death, shock, congestive heart failure, and reinfarction at 30 days was nominally lower in PI patients (12.4% vs 14.3%; *P* = .21). The incidence of congestive heart failure (6.1% vs 7.6%; *P* = .18) and shock (4.4% vs 5.9%; *P* = .13) were also lower and more aborted infarctions (11.1% vs 6.9%; *P* < .01) were observed in PI patients, suggesting more salvage of ischemic myocardium due to earlier reperfusion (the median times between symptom onset and bolus tenecteplase or start of PCI procedure were 100 and 178 min, respectively; *P* < .001). PI patients were also more likely to undergo coronary artery bypass grafting than patients allocated to primary PCI (4.7% vs 2.1%; *P* = .002) potentially due to avoidance of urgent PCI in about one third of PI patients, whereas because of successful reperfusion, coronary angiography could be performed nonurgently in the remainder. As prespecified by protocol, 1-year mortality data were acquired in all patients surviving the first 30 days.

Conclusions. Mortality was similar independently of the reperfusion strategy.

VISTA-16 Study: Varespladib and Cardiovascular Events in Patients with an Acute Coronary Syndrome[24]

Presented by Stephen Nicholls, Adelaide, Australia.

Introduction and objectives. Secretory phospholipase A2 (sPLA2) generates bioactive phospholipid products implicated in atherosclerosis. The sPLA2 inhibitor varespladib has favorable effects on lipid and inflammatory markers; however, its effect on cardiovascular outcomes is unknown. The objective was to determine the effectsof sPLA2 inhibition with varespladib on cardiovascular outcomes.

Methods. A double-blind, randomized, multicenter trial at 362 academic and community hospitals in Europe, Australia, New Zealand, India, and North America of 5145 patients randomized within 96 hours of presentation of an acute coronary syndrome (ACS) to either varespladib (n = 2572) or placebo (n = 2573) with enrollment between June 1, 2010, and March 7, 2012 (study termination on March 9, 2012). Participants were randomized to receive varespladib (500 mg) or placebo daily for 16 weeks, in addition to atorvastatin and other established therapies.

Results. The primary efficacy measure was a composite of cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or unstable angina with evidence of ischemia requiring hospitalization at 16 weeks. Six-month survival status was also evaluated. At a prespecified interim analysis, including 212 primary end point events, the independent data and safety monitoring board recommended termination of the trial for futility and possible harm. The primary end point occurred in 136 patients (6.1%) treated with varespladib compared with 109 patients (5.1%) treated with placebo (HR = 1.25; 95%CI, 0.97-1.61; log-rank, *P* = .08). Varespladib was associated with a greater risk of MI (78 [3.4%] vs 47 [2.2%]; HR = 1.66; 95%CI, 1.16-2.39; log-rank; *P* = .005). The composite secondary end point of cardiovascular mortality, MI, and stroke was observed in 107 patients (4.6%) in the varespladib group and 79 patients (3.8%) in the placebo group (HR = 1.36; 95% CI, 1.02-1.82; *P* = .04).

Conclusions. In patients with recent ACS, varespladib did not reduce the risk of recurrent cardiovascular events and significantly increased the risk of MI. The sPLA2 inhibition with varespladib may be harmful and is not a useful strategy to reduce adverse cardiovascular outcomes after ACS.

Randomized Comparison of Endovascular Revascularization Plus Supervised Exercise Therapy Versus Supervised Exercise Therapy Only in Patients With Peripheral Artery Disease and Intermittent Claudication: Results of the Endovascular Revascularization and Supervised Exercise Trial[25]

Presented by Farzin Fakhry, Rotterdam, Netherlands.

Introduction and objectives. Intermittent claudication is the most common presentation of peripheral artery disease, associated with significant functional disability. Currently, supervised exercise therapy (SET) is being recommended as first-line treatment for intermittent claudication. However, a combination therapy of endovascular revascularization (EVR) plus SET seems more promising but has not been properly investigated in a large randomized trial. We instigated the ERASE trial to compare the clinical effectiveness of EVR plus SET versus the standard care of SET only in patients with intermittent claudication.

Methods. In a multicenter randomized controlled trial 212 patients with claudication were randomly assigned to receive either a combination therapy of EVR plus SET (n = 106) or SET only (n = 106). All patients had a clinical and quality of life assessment before intervention and at 1, 6, and 12 months follow-up. Functional performance measures including pain-free and maximum walking distance were recorded during a graded treadmill test. The VascuQol and Short-Form 36 Health Survey (SF-36) were used to assess the patient-reported health-related quality of life. Repeated measurement techniques were used to analyze the data on an intention-to-treat basis.

Results. After 12 months the completeness of follow-up was 94% in the combination therapy group and 92% in the SET group. At 12 months, compared to SET, the combination therapy was associated with 282 meters (99% CI, 60 to 505 meters; *P* =.001) greater improvement in maximum walking distance and 408 meters (99% CI, 195 to 622 meters; *P* <.001) greater improvement in pain-free walking distance. Similarly, the disease-specific VascuQol showed greater improvement in the combination therapy group (mean difference 0.62; 99% CI, 0.20 to 1.03; *P* < .001). Moreover, the SF-36 scale Physical Functioning was associated with significantly greater improvement in the combination therapy group compared to the SET group (*P* = .002).

Conclusions. After 12 months, in patients with intermittent claudication a combination therapy of EVR followed by SET resulted in significantly greater improvements in pain-free and maximum walking distance and health-related quality-of-life scores compared to the standard care of SET only.

CORAL Study: Renal Artery Stenting in Preventing Cardiovascular and Renal Events[26]

Presented by Christopher J. Cooper, Toledo, Ohio, United States.

Introduction and objectives. Atherosclerotic renal-artery stenosis is a common problem in the elderly. Despite 2 randomized trials that did not show a benefit of renal-artery stenting with respect to kidney function, the usefulness of stenting for the prevention of major adverse renal and cardiovascular events is uncertain.

Methods. We randomly assigned 947 participants who had atherosclerotic renal-artery stenosis and either systolic hypertension while taking 2 or more antihypertensive drugs or chronic kidney disease to medical therapy plus renal-artery stenting or medical therapy alone. Participants were followed for the occurrence of adverse cardiovascular and renal events (a composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy).

Results. Over a median follow-up period of 43 months (interquartile range, 31 to 55), the rate of the primary composite end point did not differ significantly between participants who underwent stenting in addition to receiving medical therapy and those who received medical therapy alone (35.1% and 35.8%, respectively; HR with stenting, 0.94; 95% CI, 0.76 to 1.17; *P* = .58). There were also no significant differences between the treatment groups in the rates of the individual components of the primary end point or in all-cause mortality. During follow-up, there was a consistent modest difference in systolic blood pressure favoring the stent group (−2.3 mm Hg; 95% CI, −4.4 to −0.2; *P* = .03).

Conclusions. Renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease.

NEW STRATEGIES FOR ATRIAL FIBRILLATION PATIENTS: RHYTHM AND THROMBOSIS

RADAR-AF Trial. A Randomized Multicenter Comparison of Radiofrequency Catheter Ablation of Drivers versus Circumferential Pulmonary Vein Isolation in Patients with Atrial Fibrillation[27]

Presented by Felipe Atienza, Madrid, Spain.

Introduction and objectives. Empiric circumferential pulmonary vein isolation (CPVI) has become the therapy of choice for drug-refractory AF. However, results are suboptimal and the outcomes of a mechanistically-based strategy aimed at targeting AF drivers is unknown. This multi-center, single blinded, randomized clinical trial was designed to compare the efficacy and safety of high frequency source ablation (HFSA) in AF.

Methods. In paroxysmal AF (PaAF), patients were randomized to undergo CPVI or HFSA only using a noninferiority design. In persistent AF (PeAF), patients were randomized to CPVI or to a combined ablation approach (CPVI + HFSA) using a superiority design. The primary end point was freedom from AF at 6 months post-first ablation procedure off antiarrhythmic medications. Secondary end points included freedom from AF and from AT/AF at 6 and 12 months post-ablation off/on antiarrhythmic medications and incidence of complications. All analyses were intention-to-treat. Patients were followed by ECG and 48-hour Holter at 3, 6, and 12 months.

Results. A total of 232 patients were included (mean age 53 ± 10 years, 186 males), PaAF (115) or PeAF (117). Baseline characteristics were similar between groups. In PaAF, HFSA was noninferior to CPVI at 12 months for freedom from AF and AT/AF end point. There was a significant reduction of the risk difference of severe adverse events in the HFSA vs. CPVI group (*P* = .03). In PeAF, there were no significant differences between treatment groups in the primary (60% vs 61%; *P* = ns) and secondary end points, and a trend towards an increase in severe adverse events rate (24% vs 10%; *P* = .08) in the combined group.

Conclusions. In PaAF patients, HFSA was not inferior to CPVI at 12 months to achieve freedom from AT/AF, with a lower incidence of severe adverse events. In PeAF, the addition of HFSA to CPVI offered no incremental value. These results offer a novel mechanistic treatment paradigm for PaAF.

EU-PACT Warfarin Study: Genotype-guided Dosing of Warfarin vs Standard Dosing[28]

Presented by Munir Pirmohamed, Liverpool, United Kingdom.

Introduction and objectives. The level of anticoagulation in response to a fixed-dose regimen of warfarin is difficult to predict during the initiation of therapy. We prospectively compared the effect of genotype-guided dosing with that of standard dosing on anticoagulation control in patients starting warfarin therapy.

Methods. We conducted a multicenter, randomized, controlled trial involving patients with AF or venous thromboembolism. Genotyping for CYP2C9*2, CYP2C9*3, and VKORC1 (−1639G A) was performed with the use of a point-of-care test. For patients assigned to the genotype-guided group, warfarin doses were prescribed according to pharmacogenetic-based algorithms for the first 5 days. Patients in the control (standard dosing) group received a 3-day loading-dose regimen. After the initiation period, the treatment of all patients was managed according to routine clinical practice. The primary outcome measure was the percentage of time in the therapeutic range of 2.0 to 3.0 for the international normalized ratio (INR) during the first 12 weeks after warfarin initiation.

Results. A total of 455 patients were recruited, with 227 randomly assigned to the genotype-guided group and 228 assigned to the control group. The mean percentage of time in the therapeutic range was 67.4% in the genotype-guided group as compared with 60.3% in the control group (adjusted difference, 7.0 percentage points; 95% CI, 3.3 to 10.6; *P* < .001). There were significantly fewer incidences of excessive anticoagulation (INR ≥ 4.0) in the genotype-guided group. The median time to reach a therapeutic INR was 21 days in the genotype-guided group as compared with 29 days in the control group (*P* < .001).

Conclusions. Pharmacogenetic-based dosing was associated with a higher percentage of time in the therapeutic INR range than was standard dosing during the initiation of warfarin therapy.

COAG Trial: Clarification of Optimal Anticoagulation Through Genetics[29]

Presented by Stephen E. Kimmel, Philadelphia, Pennsylvania, United States.

Introduction and objectives. The clinical utility of genotype-guided (pharmacogenetically based) dosing of warfarin has been tested only in small clinical trials or observational studies, with equivocal results.

Methods. We randomly assigned 1015 patients to receive doses of warfarin during the first 5 days of therapy that were determined according to a dosing algorithm that included both clinical variables and genotype data or to one that included clinical variables only. All patients and clinicians were unaware of the dose of warfarin during the first 4 weeks of therapy. The primary outcome was the percentage of time that the international normalized ratio (INR) was in the therapeutic range from day 4 or 5 through day 28 of therapy.

Results. At 4 weeks, the mean percentage of time in the therapeutic range was 45.2% in the genotype-guided group and 45.4% in the clinically guided group (adjusted mean difference, [genotype-guided group minus clinically guided group], −0.2; 95% CI, −3.4 to 3.1; *P* = .91). There also was no significant between-group difference among patients with a predicted dose difference between the 2 algorithms of 1 mg per day or more. There was, however, a significant interaction between dosing strategy and race (*P* = .003). Among black patients, the mean percentage of time in the therapeutic range was less in the genotype-guided group than in the clinically guided group. The rates of the combined outcome of any INR of 4 or more, major bleeding, or thromboembolism did not differ significantly according to dosing strategy.

Conclusions. Genotype-guided dosing of warfarin did not improve anticoagulation control during the first 4 weeks of therapy.

ENGAGE AF-TIMI 48 Primary Results[30]

Presented by Robert P. Giugliano, Boston, Massachusetts, United States.

Introduction and objectives. Edoxaban is a direct oral factor Xa inhibitor with proven antithrombotic effects. The long-term efficacy

and safety of edoxaban as compared with warfarin in patients with AF is not known.

Methods. We conducted a randomized, double-blind, double-dummy trial comparing 2 once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk AF (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

Results. The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), as compared with 1.18% with high-dose edoxaban (HR = 0.79; 97.5% CI, 0.63 to 0.99; $P < .001$ for noninferiority) and 1.61% with low-dose edoxaban (HR = 1.07; 97.5% CI, 0.87 to 1.31; $P = .005$ for noninferiority). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban vs warfarin (HR = 0.87; 97.5% CI, 0.73 to 1.04; $P = .08$) and an unfavorable trend with low-dose edoxaban vs warfarin (HR = 1.13; 97.5% CI, 0.96 to 1.34; $P = .10$). The annualized rate of major bleeding was 3.43% with warfarin vs 2.75% with high-dose edoxaban (HR = 0.80; 95% CI, 0.71 to 0.91; $P < .001$) and 1.61% with low-dose edoxaban (HR = 0.47; 95% CI, 0.41 to 0.55; $P < .001$). The corresponding annualized rates of death from cardiovascular causes were 3.17% vs 2.74% (HR = 0.86; 95% CI, 0.77 to 0.97; $P = .01$), and 2.71% (HR = 0.85; 95% CI, 0.76 to 0.96; $P = .008$), and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (HR = 0.87; 95% CI, 0.78 to 0.96; $P = 0.005$), and 4.23% (HR = 0.95; 95% CI, 0.86 to 1.05; $P = .32$).

Conclusions. Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

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