

Special article

# Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Chicago, United States, November 13-17, 2010)

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## INTRODUCTION

Following its policy of disseminating scientific information to the cardiology community,<sup>1-9</sup> *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Annual Scientific Sessions of the American Heart Association (Chicago, United States, November 13-17, 2010), 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.

## SUMMARY BY TOPIC

### Heart failure

RAFT: Cardiac resynchronization therapy for mild-to-moderate heart failure.

EMPHASIS: Eplerenone in patients with systolic heart failure and mild symptoms.

Evaluation of the HeartWare<sup>®</sup> HVAD left ventricular assist device system for the treatment of advanced heart failure: results of the ADVANCE bridge to transplant trial.

ASCEND-HF: Acute study of clinical effectiveness of nesiritide in decompensated heart failure trial.

SMART-AV: A randomized trial comparing empirical echocardiography-guided and algorithmic atrioventricular delay programming in cardiac resynchronization therapy.

### Prevention

DEFINE: Safety of anacetrapib in patients with or at high risk for coronary heart disease.

ASCOT: Testing C-Reactive Protein at baseline and on-treatment as an independent predictor of cardiovascular outcomes.

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Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation.

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CLOSURE I: A prospective, multicenter, randomized controlled trial to evaluate the safety and efficacy of the STARFlex<sup>®</sup> septal closure system versus best medical therapy in patients with a stroke or transient ischemic attack due to presumed paradoxical embolism through a patent foramen ovale.

GRAVITAS trial: Standard versus high-dose clopidogrel according to platelet function testing after PCI.

BASKET PROVE trial: Late cardiac death and myocardial infarction associated with late stent thrombosis in large vessel stenting after 1<sup>st</sup> or 2<sup>nd</sup> generation drug-eluting compared to bare-metal stents.

### Hypertension

Symplcity HTN-2: International, multicenter, prospective, randomized, controlled trial of endovascular selective renal sympathetic denervation for the treatment of hypertension.

### Miscellanea

TAMARIS trial: NV1FGF Gene therapy on amputation-free survival in critical limb ischemia - Phase 3 randomized double-blind placebo-controlled trial.

ACT trial: A pragmatic multicenter randomized trial to evaluate the efficacy of acetylcysteine for the prevention of renal outcomes in patients undergoing coronary and vascular angiography.

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## HEART FAILURE

### RAFT: Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure<sup>10</sup>

*Presented by Anthony S. Tang, Ottawa, Ontario, Canada*

**Background.** Cardiac-resynchronization therapy (CRT) benefits patients with left ventricular systolic dysfunction and a wide QRS complex. Most of these patients are candidates for an implantable cardioverter-defibrillator (ICD). The aim of the study was to evaluate whether adding CRT to an ICD and optimal medical therapy might reduce mortality and morbidity among such patients.

**Methods.** Patients with New York Heart Association (NYHA) class II or III heart failure, a left ventricular ejection fraction of 30% or less, and an intrinsic QRS duration of 120 msec or more or a paced QRS duration of 200 msec or more, were randomly assigned to receive either an ICD alone or an ICD plus CRT. The primary outcome was death from any cause or hospitalization for heart failure.

**Results.** A total of 1798 patients were followed up (mean of 40 months). The primary outcome occurred in 297 of 894 patients (33.2%) in the ICD-CRT group and 364 of 904 patients (40.3%) in the ICD group (hazard ratio in the ICD-CRT group, 0.75; 95% confidence interval [CI], 0.64 to 0.87;  $P < .001$ ). In the ICD-CRT group, 186 patients died, as compared with 236 in the ICD group (hazard ratio, 0.75; 95% CI, 0.62 to 0.91;  $P = .003$ ), and 174 patients were hospitalized for heart failure, as compared with 236 in the ICD group (hazard ratio, 0.68; 95% CI, 0.56 to 0.83;  $P < .001$ ). However, at 30 days after device implantation, adverse events had occurred in 124 patients in the ICD-CRT group, as compared with 58 in the ICD group ( $P < .001$ ).

**Conclusions.** Among patients with NYHA class II or III heart failure, a wide QRS complex, and left ventricular systolic dysfunction, the addition of CRT to an ICD reduced rates of death and hospitalization for heart failure. This improvement was accompanied by more adverse events.

### EMPHASIS: Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms<sup>11</sup>

*Presented by Faiez Zannad, Nancy, France.*

**Background.** Mineralocorticoid antagonists improve survival among patients with chronic severe systolic heart failure and heart failure after myocardial infarction. We evaluated the effects of eplerenone in patients with chronic systolic heart failure and mild symptoms.

**Methods.** In this randomized, double-blind trial, 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

**Results.** The trial was stopped prematurely, according to prespecified rules, after a median follow-up period of 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio, 0.63; 95% confidence interval [CI], 0.54 to 0.74;  $P < .001$ ). A total of 12.5% of patients receiving eplerenone and 15.5% of those receiving placebo died (hazard ratio, 0.76; 95% CI, 0.62 to 0.93;  $P = .008$ ); 10.8% and 13.5%, respectively, died of cardiovascular causes (hazard ratio,

0.76; 95% CI, 0.61 to 0.94;  $P = .01$ ). Hospitalizations for heart failure and for any cause were also reduced with eplerenone. A serum potassium level exceeding 5.5 mmol per liter occurred in 11.8% of patients in the eplerenone group and 7.2% of those in the placebo group ( $P < .001$ ).

**Conclusions.** Eplerenone, as compared with placebo, reduced both the risk of death and the risk of hospitalization among patients with systolic heart failure and mild symptoms.

### Evaluation of the HeartWare® HVAD Left Ventricular Assist Device System for the Treatment of Advanced Heart Failure: Results of the ADVANCE Bridge to Transplant Trial<sup>12</sup>

*Presented by Keith D. Aaronson, Ann Arbor, Michigan, USA*

**Background.** Improved outcomes with ventricular assist devices have been demonstrated in continuous flow pumps utilizing axial flow technology compared to older pulsatile designs. The HeartWare HVAD is a small, durable, centrifugal flow pump implanted directly in the left ventricular apex and contained within the pericardial space. The centrifugal flow pattern combined with the smaller size and no space requirement may result in improved clinical outcomes. The aim of the study was to report the outcomes of ADVANCE, a multicenter prospective trial in advanced heart failure patients listed for transplantation who have failed medical therapy.

**Methods.** The study hypothesis is that the primary composite end point, the proportion of patients alive, transplanted or explanted for recovery and without device replacement at 180 days, will be noninferior to that of a contemporaneous control group undergoing bridge to transplant (BTT) with commercially available left ventricular assist devices and enrolled in the INTERMACS Registry. With a noninferiority margin of 15%, the trial design and sample sizes provide >90% power to test the primary hypothesis at the one-sided 0.05 significance level.

**Results.** 140 adults (28%F, 72%M; 43% ischemic) listed for transplant as UNOS status 1A or 1B, with BSA  $\geq 1.2$  cm, received HVADs as BTT at 30 sites. Baseline characteristics for HVAD patients included (mean  $\pm$  SD): age 53.5  $\pm$  10.3 (range 22–70) years, BSA 2.1  $\pm$  0.3 m<sup>2</sup>, LVEF 17.9  $\pm$  7.0%, CI 2.0  $\pm$  0.7 L/min/m<sup>2</sup>, mean BP 76.6  $\pm$  12.6 mmHg, PCW 22.3  $\pm$  8.8 mmHg, PA systolic 51.1  $\pm$  15.5 mmHg. Over 85% of patients were receiving one or more intravenous inotropes and 25% were supported with an IABP at HVAD implantation.

**Conclusions.** The primary end point and survival will be compared between HVAD patients and contemporaneous control patients from INTERMACS. Adverse events, operative times and transfusion requirements will also be reviewed. In addition, we will present quality of life and functional outcomes for the HVAD patients. As the first FDA pivotal trial to incorporate a comparison against controls from the NIH-sponsored INTERMACS Registry, ADVANCE's novel design provides a model for investigation of future devices.

### ASCEND-HF: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial<sup>13</sup>

*Presented by Adrian F Hernandez, Durham, North Carolina, USA.*

**Background.** Nesiritide is a recombinant intravenous formulation of human B-type natriuretic peptide known to reduce dyspnea and

intracardiac filling pressures within 3 hours of administration in patients with acute decompensated heart failure (ADHF).

However, the effect of nesiritide on dyspnea at 6 or 24 hours is unknown. Moreover, no clinical outcome trial exists that provides a reliable estimate of the effect of nesiritide on morbidity and mortality.

**Methods.** In a prospective, double-blind randomized trial, ADHF patients within 24 hours of hospitalization were randomly assigned to receive either intravenous nesiritide or matching placebo for 24 hours to 7 days. The 2 co-primary end points are (1) assessment of acute dyspnea at 6 or 24 hours, and (2) death or rehospitalization for HF within 30 days.

**Results.** Enrolment will end in August 2010 with the prespecified >7000 subjects from approximately 400 sites worldwide. Current baseline characteristics show that the median age is 68 years (25th/75th interquartile range (IQR): 57 yrs-77yrs) and 34% of subjects are female. Ischemic heart disease is present in 60% and the median ejection fraction is 30% (25th/75th IQR: 20%, 37%); 22% have an ejection fraction >40%. Treatment pre-randomization included loop diuretics in 95.3%, inotropes in 4.4%, and vasodilators in 14.8%. A bolus of study drug was used in 61.3% of patients and the median duration of study drug infusion was 42.2 hours (25th/75th IQR: 24.1, 48.6 hrs). Last 30-day follow-up visit will occur in September 2010.

**Conclusions.** The data from the ASCEND-HF trial will evaluate whether nesiritide safely improves acute dyspnea at 6 or 24 hours as well as all-cause mortality and rehospitalization for heart failure at 30 days.

#### SMART-AV: A Randomized Trial Comparing Empirical Echocardiography-Guided and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy<sup>14</sup>

*Presented by Kenneth A. Ellenbogen, Richmond, Virginia, USA.*

**Background.** A number of small non-randomized studies have suggested optimization of the atrioventricular (AV) interval may improve response to CRT therapy. There are no large prospective randomized trials comparing the clinical and echocardiographic outcomes after AV interval optimization. Approximately 30% of patients who receive a CRT device experience a limited benefit in heart failure (HF) symptoms and/or reverse left ventricular (LV) remodeling. One variable that may influence cardiac resynchronization therapy response is the programmed atrioventricular (AV) delay. The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial prospectively randomized patients to a fixed empirical AV delay (120 milliseconds), echocardiographically optimized AV delay, or AV delay optimized with SmartDelay, an electrogram-based algorithm.

**Methods.** A total of 1014 patients (68% men; mean age, 66±11 years; mean left ventricular ejection fraction, 25±7%) who met enrolment criteria received a cardiac resynchronization therapy defibrillator, and 980 patients were randomized in a 1:1:1 ratio. All patients were programmed (DDD-60 or DDDR-60) and evaluated after implantation and 3 and 6 months later. The primary end point was left ventricular end-systolic volume. Secondary end points included New York Heart Association class, quality-of-life score, 6-minute walk distance, left ventricular end-diastolic volume, and left ventricular ejection fraction.

**Results.** The medians (quartiles 1 and 3) for change in left ventricular end-systolic volume at 6 months for the SmartDelay, echocardiography, and fixed arms were -21 mL (-45 and 6 mL),

-19 mL (-45 and 6 mL), and -15 mL (-41 and 6 mL), respectively. No difference in improvement in left ventricular end-systolic volume at 6 months was observed between the SmartDelay and echocardiography arms ( $P = .52$ ) or the SmartDelay and fixed arms ( $P = .66$ ). Secondary end points, including structural (left ventricular end-diastolic volume and left ventricular ejection fraction) and functional (6-minute walk, quality of life, and New York Heart Association classification) measures, were not significantly different between arms.

**Conclusions.** Neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 milliseconds. The routine use of AV optimization techniques assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to cardiac resynchronization therapy.

#### PREVENTION

##### DEFINE: Safety of Anacetrapib in Patients With or at High Risk for Coronary Heart Disease<sup>15</sup>

*Presented by Christopher P. Cannon, Boston, USA*

**Background.** Anacetrapib is a cholesteryl ester transfer protein inhibitor that raises high-density lipoprotein (HDL) cholesterol and reduces low-density lipoprotein (LDL) cholesterol.

**Methods.** We conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy and safety profile of anacetrapib in patients with coronary heart disease or at high risk for coronary heart disease. Eligible patients who were taking a statin and who had an LDL cholesterol level consistent with that recommended in guidelines were assigned to receive 100 mg of anacetrapib or placebo daily for 18 months. The primary end points were the percent change from baseline in LDL cholesterol at 24 weeks (HDL cholesterol level was a secondary end point) and the safety and side-effect profile of anacetrapib through 76 weeks. Cardiovascular events and deaths were prospectively adjudicated.

**Results.** A total of 1623 patients underwent randomization. By 24 weeks, the LDL cholesterol level had been reduced from 81 mg per deciliter (dL) (2.1 mmol per liter (L)) to 45 mg/dL (1.2 mmol/L) in the anacetrapib group, as compared with a reduction from 82 mg/dL (2.1 mmol/L) to 77 mg/dL (2.0 mmol/L) in the placebo group ( $P < .001$ ) – a 39.8% reduction with anacetrapib beyond that seen with placebo. In addition, the HDL cholesterol level increased from 41 mg/dL (1.0 mmol/L) to 101 mg/dL (2.6 mmol/L) in the anacetrapib group, as compared with an increase from 40 mg/dL (1.0 mmol/L) to 46 mg/dL (1.2 mmol/L) in the placebo group ( $P < .001$ ) – a 138.1% increase with anacetrapib beyond that seen with placebo. Through 76 weeks, no changes were noted in blood pressure or electrolyte or aldosterone levels with anacetrapib as compared with placebo. Prespecified adjudicated cardiovascular events occurred in 16 patients (2.0%) treated with anacetrapib and 21 patients (2.6%) receiving placebo ( $P = .40$ ). The prespecified Bayesian analysis indicated that this event distribution provided a predictive probability (confidence) of 94% that anacetrapib would not be associated with a 25% increase in cardiovascular events, as seen with torcetrapib.

**Conclusions.** Treatment with anacetrapib had robust effects on LDL and HDL cholesterol, had an acceptable side-effect profile, and, within the limits of the power of this study, did not result in the adverse cardiovascular effects observed with torcetrapib.

### The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): Testing C-Reactive Protein at Baseline and On-treatment as an Independent Predictor of Cardiovascular Outcomes<sup>16</sup>

Presented by Peter S. Sever, Glasgow, UK.

**Background.** Lowering high-sensitivity C-reactive protein (hsCRP) by statins has been shown to independently predict cardiovascular (CV) outcomes. In a nested case-control study, we explore the relationship between biomarkers prior to, and in-trial, with blood pressure and lipid lowering therapy, and CV outcomes.

**Methods.** In UK and Ireland, ASCOT randomised 9098 hypertensive adults to either calcium channel blocker or beta blocker-based treatment; 4853 patients with total cholesterol <6.5 mmol/L (250 mg/L) were further randomised to atorvastatin or placebo. Over 5.5 years, 485 CV cases (fatal coronary heart disease, non-fatal MI, coronary revascularization, fatal and non-fatal stroke), were age and sex matched with 1367 controls. Conditional logistic regression models were used to evaluate the association between CV events and LDL-cholesterol (LDL-c) and hsCRP.

**Results.** Baseline LDL-c and hsCRP were significantly correlated ( $r = 0.11$ ,  $P < .0001$ ) and predicted CV events (odds ratio [OR] 1.31 [CI 1.10–1.56,  $P < .002$ ], and OR 1.19 [CI 1.05–1.34,  $P < .006$ ]) respectively. Both ORs per 1-SD increase in log-transformed data. However, inclusion of hsCRP into the Framingham risk model only minimally improved prediction of CV events. At 6 months, atorvastatin reduced LDL-c by 40.3% and median hsCRP by 27.4%. In those randomised to atorvastatin, lower in-trial LDL-c <median (2.1 mmol/L) at 6 months was associated with a highly significant reduction in CV events (OR 0.41 [CI 0.22–0.75,  $P < .004$ ] compared with those with  $\geq$ median LDL-c, in a fully adjusted model incorporating other baseline risk factors. By contrast, in those randomized to atorvastatin, in the fully adjusted model, lower hsCRP at 6 months was not associated with CV events (OR 0.86 [0.49–1.51,  $P = 0.60$ ]) when comparing those with < median (1.83 mg/L) and those with  $\geq$  median hsCRP levels. Consequently, addition of on-treatment hsCRP to on-treatment LDL-c did not improve prediction of statin efficacy.

**Conclusion.** These analyses do not support the hypothesis that hsCRP usefully improves risk factor prediction or indeed that a reduction in hsCRP associated with statin therapy is an independent predictor of CV outcomes.

### Results of the First Major Clinical Trial of an Oral Agent Inducing Apo A1 Synthesis: A New Approach to HDL Raising and CV Risk Modification<sup>17</sup>

Presented by Stephen J. Nicholls, Cleveland, Ohio, USA.

**Background.** High-density lipoproteins (HDL) and reverse cholesterol transport remains a major focus in the development of new anti-atherosclerotic therapies. While the optimal therapeutic approach to promote HDL functionality remains uncertain, there is considerable consensus that the ability to increase synthesis of its major protein, apolipoprotein A1 (apoA1), represents a highly promising approach. The aim of this study was to evaluate the efficacy and safety of the first oral agent that induces synthesis of apoA1 (RVX-208) in patients with stable coronary artery disease.

**Methods.** A double-blind, randomized controlled trial of patients with stable coronary artery disease, on a stable dose of statin therapy for at least 30 days, treated for 12 weeks with RVX-

208 (i) 100 mg/daily, (ii) 200 mg/daily, (iii) 300 mg/daily or (iv) placebo. Sample Size: Of 360 patients screened, 299 patients were randomized in 35 centers in the United States between January and February 2010. The primary end point is the percentage change in apoA1 levels in patients treated with RVX-208 compared to placebo. Additional objectives include characterizing the dose and time response relationships for apoA1, major lipid parameters, and HDL subclasses and the safety and tolerability of RVX-208 over the 12-week treatment period. It was estimated that 70 patients would be required in each treatment group to provide 80% power to detect an 8% increase in apoA1 compared to placebo, assuming a standard deviation of 15%.

**Results.** The median increase in apoA-1 levels from baseline over the three months of the study was 0.9% in the placebo group, 0.1% for the patients on the 100-mg/daily dose of RVX-208 ( $P = .09$  compared with placebo), 3.8% for the 200-mg/daily-dose patients ( $P = .10$  compared with placebo), and 5.6% for the 300-mg/daily-dose group ( $P = .06$  compared with placebo). Also, the 200-mg patients and the 300-mg patients showed a 6.3% and 8.3% increase in HDL-c levels, respectively, vs. no change in the placebo group ( $P < .05$  and  $P < .01$ ). The 200-mg and 300-mg groups also showed a significant increase in large HDL particles, 20.2% and 21.1%, respectively ( $P < .01$  and  $P < .001$ ), and significant increases in the larger 1 HDL particles of 8.0% and 8.8%, respectively ( $P < .05$  and  $P < .05$ ).

**Conclusion.** The last patient received the final dose of treatment in May 2010. The initial efficacy and safety data will be available during the summer and ready for full presentation soon thereafter. This study provides the first opportunity to characterize the early experience of apoA1 induction therapy in statin-treated patients with coronary artery disease.

### ARRHYTHMIAS

#### ROCKET AF: Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation<sup>18</sup>

Presented by Kenneth Mahaffey, Durham, North Carolina, USA.

**Background.** Anticoagulation with warfarin prevents ischemic stroke in patients with nonvalvular atrial fibrillation (AF), but routine coagulation monitoring, dose adjustments, and bleeding risk limit its overall use. The oral direct Factor Xa inhibitor rivaroxaban represents a potential alternative anticoagulant. The aim of the study was to establish whether rivaroxaban is noninferior to dose-adjusted warfarin within a risk ratio margin of 1.46 for the prevention of all stroke and systemic embolic events.

**Methods.** Patients with AF and a history of stroke or at least 2 stroke risk factors ( $n = 14\ 269$ ) were randomized at 1215 participating sites in 45 countries to receive either rivaroxaban, 20 mg daily, or dose-adjusted warfarin (target INR 2.5, range 2.0–3.0) double-blind. The primary efficacy end point was all adjudicated strokes (ischemic and hemorrhagic) and systemic embolic events. The primary analysis was based on establishing noninferiority in the per-protocol population.

**Results.** These data are preliminary, as final follow-up and database closure is underway. The median patient age was 73 years; 40% were female, 63% had heart failure, 90% hypertension, 40% diabetes, and 55% a prior stroke or TIA. The intrinsic stroke risk of enrolled patients was high (90% had a CHADS<sub>2</sub> score  $>3$ ). Overall, rivaroxaban was noninferior to warfarin in terms of the



primary end point, a composite of stroke and non-CNS embolism, and as noted, was superior to warfarin when analyzing the risk of stroke and non-CNS embolism in patients who remained on treatment over the course of the 40-month trial. It was not superior to warfarin in the stricter intention-to-treat analysis. In terms of bleeding, the rates of the composite major and nonmajor clinically relevant bleeding were comparable in the rivaroxaban- and warfarin-treatment arms, with less fatal bleeding and intracranial hemorrhage observed among those treated with the new anticoagulant. Major bleeding occurred in 395 patients, a rate of 3.60 per 100 patient-years, in the warfarin-treated patients, and in 386 patients, a rate of 3.45 per 100 patient-years, in rivaroxaban-treated patients ( $P = .576$ ).

**Conclusion.** Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with nonvalvular AF.

### Efficacy and Safety of Prescription Omega-3 Fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation<sup>19</sup>

*Presented by Peter R. Kowey, Wynnewood, Pennsylvania, USA.*

**Background.** Atrial fibrillation (AF) is common, yet there remains an unmet medical need for additional treatment options. Current pharmacological treatments have limited efficacy and significant adverse events. Limited data from small trials suggest omega-3 polyunsaturated fatty acids may provide a safe, effective treatment option for AF patients. The aim of the study was to evaluate the safety and efficacy of prescription omega-3 fatty acids (prescription omega-3) for the prevention of recurrent symptomatic AF.

**Methods.** This is a prospective, randomized, double-blind, placebo-controlled, parallel-group multicenter trial involving 663 US outpatient participants with confirmed symptomatic paroxysmal ( $n = 542$ ) or persistent ( $n = 121$ ) AF, with no substantial structural heart disease, and in normal sinus rhythm at baseline, recruited from November 2006 to July 2009 (final follow-up was January 2010). Prescription omega-3 (8 g/d) or placebo was given for the first 7 days; prescription omega-3 (4 g/d) or placebo thereafter through week 24. The primary end point was symptomatic recurrence of AF (first recurrence) in participants with paroxysmal AF. Secondary analyses included first recurrence in the persistent stratum and both strata combined. Participants were followed up for 6 months.

**Results.** At 24 weeks, in the paroxysmal AF stratum, 129 of 269 participants (48%) in the placebo group and 135 of 258 participants (52%) in the prescription group had a recurrent symptomatic AF or flutter event. In the persistent AF stratum, 18 participants (33%) in the placebo group and 32 (50%) in the prescription group had documented symptomatic AF or flutter events. There was no difference between treatment groups for recurrence of symptomatic AF in the paroxysmal stratum (hazard ratio [HR], 1.15; 95% confidence interval [CI], 0.90-1.46;  $P = .26$ ), in the persistent stratum (HR, 1.64; 95% CI, 0.92-2.92;  $P = .09$ ), and both strata combined (HR, 1.22; 95% CI, 0.98-1.52;  $P = .08$ ). Secondary end points were supportive of the primary result. A total of 5% of those receiving placebo and 4% of those receiving prescription omega-3 discontinued due to adverse events. Eicosapentaenoic and docosahexaenoic acid blood levels were significantly higher in the prescription group than in the placebo group at weeks 4 and 24.

**Conclusion.** Among participants with paroxysmal AF, 24-week treatment with prescription omega-3 compared with placebo did not reduce recurrent AF over 6 months.

## INTERVENTIONAL CARDIOLOGY

### CLOSURE I: A Prospective, Multicenter, Randomized Controlled Trial to Evaluate the Safety and Efficacy of the STARFlex® Septal Closure System versus Best Medical Therapy in Patients With a Stroke or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale<sup>20</sup>

*Presented by Anthony Furlan, Cleveland, Ohio, USA*

**Background.** Some strokes with unknown etiology (cryptogenic) may be the result of paradoxical embolism traversing through a patent foramen ovale (PFO). The utility of percutaneous devices for secondary prevention in patients with cryptogenic stroke or transient ischemic attack (TIA) and PFO compared to medical therapy alone is not known. CLOSURE I is the first completed randomized controlled trial comparing the safety and efficacy of percutaneous PFO closure to medical therapy alone for secondary TIA and stroke prevention in patients with PFO. The main results of CLOSURE I will be presented. The primary objective of CLOSURE I is to determine whether percutaneous PFO closure utilizing the STARFlex® Septal Closure System in combination with medical therapy is superior to medical therapy alone for the prevention of recurrent TIA, stroke, and mortality in patients with cryptogenic TIA or stroke and PFO.

**Methods.** CLOSURE I is a prospective, multicenter, randomized, open-label, two-arm superiority trial. The study population includes patients with a cryptogenic TIA or stroke and PFO documented by TEE, with or without atrial septal aneurysm, within 6 months of randomization. Between June 23, 2003 and October 24, 2008, 910 patients age 18–60 were randomized at 87 sites in the USA and Canada to either medical therapy (aspirin 325 mg daily or warfarin target INR 2.0–3.0 or a combination of the two) or percutaneous PFO closure utilizing STARFlex® plus medical therapy (clopidogrel 75 mg for 6 months and aspirin 325 mg for two years). Follow up visits were at 1 month (phone), 6 months, 12 months, and 24 months. The primary end point is the 2-year rate of stroke or TIA, all-cause mortality for the first 30 days, and neurological mortality  $\geq 31$  days.

**Results.** At two years, the composite primary end point, as well as rates of stroke or TIA alone, were no different between groups. An analysis of outcomes according to baseline characteristics, including shunt size or presence/absence of atrial shunts, also found no differences between groups. Both major vascular complications and atrial fibrillation, mostly periprocedural, were significantly more common in the intervention group, but other safety end points were no different between study arms. Procedural and technical success rates (no or trace residual leaking) were high, with 86.7% percent of PFOs closed at one year.

**Conclusions.** In patients with a cryptogenic TIA or stroke and PFO, CLOSURE I found no differences in the primary end point of stroke or TIA at two years, all-cause mortality at 30 days, and neurological mortality between 31 days and 2 years when comparing medical therapy and percutaneous PFO closure utilizing STARFlex® plus medical therapy.

### Results of the GRAVITAS Trial: Standard versus High-Dose Clopidogrel According to Platelet Function Testing After PCI<sup>21</sup>

*Presented by Matthew J. Price, La Jolla, CA, USA*

**Background.** Observational, single-center studies have suggested an association between high residual platelet reactivity on clopidogrel

therapy and cardiovascular events after percutaneous coronary intervention.

**Methods.** In this multicenter, blinded, placebo-controlled, randomized trial, we compared high-dose clopidogrel (additional loading dose, 150 mg daily thereafter) with standard-dose clopidogrel (no additional loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events after percutaneous coronary intervention with drug-eluting stents in 2,214 patients with high residual platelet reactivity according to the VerifyNow P2Y12 Test (Accumetrics, San Diego, California), measured 12 to 24 hours after the procedure. A cohort of 586 patients without high residual platelet reactivity selected at random were also enrolled and treated in a blinded fashion with standard-dose clopidogrel (75-mg daily). The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stent thrombosis at 6-month follow-up.

**Results.** At 6 months of follow-up, the composite end point of cardiovascular death/myocardial infarction/stent thrombosis was identical in both groups, at 2.3%. Stent thrombosis occurred in 0.5% of the high-dose group and 0.7% of the standard-dose group, a non-significant difference. There was also no difference in bleeding rates.

**Conclusions.** GRAVITAS is the first large-scale clinical trial designed to examine whether adjustment of antiplatelet therapy on the basis of platelet function testing with a point-of-care assay improves outcomes after PCI with DES. In post-PCI patients with low-risk clinical presentations, a treatment strategy of high-dose clopidogrel for high residual reactivity on platelet-function testing is not warranted.

#### **BASKET PROVE: Late Cardiac Death and Myocardial Infarction Associated With Late Stent Thrombosis in Large Vessel Stenting After 1<sup>st</sup> or 2<sup>nd</sup> Generation Drug-eluting Compared to Bare-metal Stents: The BASKET PROspective Evaluation Examination<sup>22</sup>**

*Presented by Christoph A. Kaiser, Basel, Switzerland*

**Background.** Recent data have suggested that patients with coronary disease in large arteries are at increased risk for late cardiac events after percutaneous intervention with first-generation drug-eluting stents, as compared with bare-metal stents. We sought to confirm this observation and to assess whether this increase in risk was also seen with second-generation drug-eluting stents.

**Methods.** We randomly assigned 2314 patients needing stents that were 3.0 mm or more in diameter to receive sirolimus-eluting, everolimus-eluting, or bare-metal stents. The primary end point was the composite of death from cardiac causes or nonfatal myocardial infarction at 2 years. Late events (occurring during months 7 to 24) and target-vessel revascularization were the main secondary end points.

**Results.** The rates of the primary end point were 2.6% among patients receiving sirolimus-eluting stents, 3.2% among those receiving everolimus-eluting stents, and 4.8% among those receiving bare-metal stents, with no significant differences between patients receiving either drug-eluting stent and those receiving bare-metal stents. There were also no significant between-group differences in the rate of late events or in the rate of death, myocardial infarction, or stent thrombosis. Rates of target-vessel revascularization for reasons unrelated to myocardial infarction were 3.7% among patients receiving sirolimus-eluting

stents, 3.1% among those receiving everolimus-eluting stents, and 8.9% among those receiving bare-metal stents. The rate of target-vessel revascularization was significantly reduced among patients receiving either drug-eluting stent, as compared with a bare-metal stent, with no significant difference between the two types of drug-eluting stents.

**Conclusions.** In patients requiring stenting of large coronary arteries, no significant differences were found among sirolimus-eluting, everolimus-eluting, and bare-metal stents with respect to the rate of death or myocardial infarction. With the two drug-eluting stents, similar reductions in rates of target-vessel revascularization were seen.

#### **HYPERTENSION**

#### **Symlicity HTN-2: International, Multicenter, Prospective, Randomized, Controlled Trial of Endovascular Selective Renal Sympathetic Denervation for the Treatment of Hypertension<sup>23</sup>**

*Presented by Murray Esler, Melbourne, Australia*

**Background.** Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

**Methods.** In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more ( $\geq 150$  mm Hg for patients with type 2 diabetes), despite taking 3 or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness end point was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months.

**Results.** Of 190 patients screened for eligibility, 106 (56%) were randomly allocated to renal denervation ( $n = 52$ ) or control ( $n = 54$ ) groups between June 9, 2009, and Jan 15, 2010. At 6 months, 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary end point. Office-based blood pressure measurements in the renal denervation group were reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg,  $P < .0001$ ), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg,  $P = .77$  systolic and  $P = .83$  diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg ( $P < .0001$ ). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls ( $P < .0001$ ). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

**Conclusion.** Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

## MISCELLANEA

**TAMARIS: NV1FGF Gene Therapy on Amputation-Free Survival in Critical Limb Ischemia - Phase 3 Randomized Double-Blind Placebo-Controlled Trial**<sup>24</sup>

Presented by William R. Hiatt, Denver, Colorado, USA.

**Background.** Patients with critical limb ischemia (CLI) and skin lesions unsuitable for revascularization have a high rate of amputation and mortality. Local gene therapy using non-viral plasmid DNA-encoding acidic fibroblast growth factor (riferminogene pectaplasmid, also known as NV1FGF) demonstrated positive phase 2 results on both amputation and mortality in CLI. The TAMARIS phase 3 trial tested the hypothesis that intramuscular injection of NV1FGF would confirm the benefit on amputation-free survival in CLI.

**Methods.** This was a large international trial involving 170 sites in 30 countries, enrolling 525 patients (523 treated) with CLI unsuitable for revascularization who had stable ischemic skin lesions. Patients were included who had a lower extremity ischemic ulcer and met hemodynamic criteria of an ankle pressure <70 mmHg and/or a toe pressure <50 mmHg or a transcutaneous oxygen pressure ≤30 mmHg in the treated leg. Patients were randomized double-blind to receive 8 intramuscular injections on the same leg of either 2.5 ml NV1FGF at 0.2 mg/ml or placebo on Days 1, 15, 29, and 43. The primary end point was the reduction of major amputation or death, whichever came first, at 1 year analyzed with a log rank test using a multivariate Cox proportional hazard model. The sample size was based on an assumed annual event rate of 51.5% on placebo and 33.2% on NV1FGF (90% power, alpha 5%).

**Results.** Patients had a mean age of 70±10 years, 70% were male, 53% had diabetes, 61% had a history of smoking, and 54% had a history of coronary artery disease. The results demonstrated no benefit of the treatment on the primary end point or components of the primary. During the conduct of the trial there were no major safety concerns (ischemic heart disease, malignant neoplasms, proliferative retinopathy and renal impairment).

**Conclusions.** Intramuscular injection of NV1FGF has failed to show a significant benefit in CLI patients unsuitable for revascularization.

**Acetylcystein for the Prevention of Contrast-Induced nephropathy (ACT) Trial: A Pragmatic Multicenter Randomized Trial to Evaluate the Efficacy of Acetylcystein for the Prevention of Renal Outcomes in Patients Undergoing Coronary and Vascular Angiography**<sup>25</sup>

Presented by Otavio Berwanger, Sao Paulo, Brazil

**Background.** Acetylcystein has been evaluated in several small trials as a means of reducing the risk of contrast-induced nephropathy (CIN) in patients undergoing coronary angiographic procedures; however, systematic reviews of these studies do not provide reliable answers. Thus, we planned the ACT Trial, the largest randomized clinical trial (RCT) testing the hypothesis that acetylcystein reduces the risk of CIN in at-risk patients undergoing an intravascular angiography conducted to date.

**Methods.** ACT is a RCT of acetylcystein versus matching placebo in patients at risk for CIN undergoing an intravascular angiographic procedure. The randomization list was concealed (central web based randomization) and all analysis followed the intention-to-treat principle. The study drugs (acetylcystein 1200 mg or placebo) were administered orally twice daily, two doses before and two doses

after the procedure. The primary outcome was the occurrence of CIN, defined as a 25% elevation of serum creatinine above baseline between 48 and 96 hours after angiography.

**Results.** A total of 2308 patients have been included in 46 centers in Brazil. Sixty seven percent of the procedures were coronary diagnostic angiographies, 29% were percutaneous coronary interventions and 4% were vascular procedures. Mean age was 68±10 years, 15.7% had a baseline serum creatinine >1.5 mg/dL, and 60.4% were diabetics. Compliance to study drugs was over 95% and intravenous hydration was given to 98% of the patients. The incidence of CIN was 12.7% in the acetylcystein group and 12.7% in the control group (relative risk 1.00; 95% CI 0.81-1.25). Other clinical outcomes were also similar in the two groups (duplication of serum creatinine, all cause mortality or need for dialysis at 30 days, cardiovascular mortality).

**Conclusion.** Acetylcystein does not reduce the risk of CIN nor other clinically relevant outcomes. These results may help to inform clinical practice and to update current guidelines.

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