

## Special article

# Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American Heart Association (Los Angeles, CA, United States, november 3-7, 2012)

Resumen de los ensayos clínicos presentados en las Sesiones Científicas Anuales de la *American Heart Association* (Los Ángeles, California, Estados Unidos, 3-7 de noviembre de 2012)

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### Article history:

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Following its policy of disseminating scientific information to the cardiology community,<sup>1-8</sup> *Revista Española de Cardiología* offers a selection of the most relevant studies presented at the Scientific Sessions of the American Heart Association (Los Angeles, California, United States, November 3-7, 2012), 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

### Practice Implications for Coronary Artery Disease and Venous Thromboembolism

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A Randomized Trial of Bedside Platelet-Function Monitoring to Adjust Antiplatelet Therapy versus Standard of Care in Patients Undergoing Drug-Eluting Stent Implantation: The ARCTIC Study.

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### Treatments for Prevention of Cardiovascular Events: a Population Perspective

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Fish Oil for the Prevention of Post-operative Atrial Fibrillation: The Omega-3. Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) Trial

A Randomized Trial of a Multivitamin in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study II.

Use of a Multidrug Pill in Reducing Cardiovascular Events (UMPIRE).

### Novel Treatments for Managing Lipids Disorders

Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD): Interim Results from a Phase 2, Randomized, Double-blind, Placebo-Controlled Trial.

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E-mail address: [rec@revespcardiol.org](mailto:rec@revespcardiol.org) (P. Avanzas).

Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS): Interim Results from a Randomized, Double-blind, Placebo-Controlled Study.

Effects of 12 Weeks of Treatment with RN316 (PF-04950615), a Humanized IgG2 $\Delta$ a Monoclonal Antibody Binding Proprotein Convertase Subtilisin Kexin Type 9, in Hypercholesterolemic Subjects on High- and Maximal Dose Statins.

Effects of the Cholesteryl Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome.

### Cell-based Therapies for Myocardial Regeneration

Results of the Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction (Swiss AMI) Trial.

The Effect of Timing of Stem-cell Delivery Following Acute Myocardial Infarction: The NHLBI and CCTRN TIME Trial.

Randomized Comparison of Allogeneic versus Autologous Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy.

Effect of Cardiac Stem Cells in Patients With Ischemic Cardiomyopathy: Interim Results of the SCPIO Trial Up to 2 Years After Therapy.

### Management of Left Ventricle Dysfunction: Devices and Drugs

MADIT Randomized Trial to Reduce Inappropriate Therapy (MADIT-RIT).

Biventricular versus Right Ventricular Pacing in Patients With Left Ventricular Dysfunction and Atrioventricular Block (BLOCK HF Study).

Pilot Trial of Two Levels of Hypothermia in Comatose Survivors of Out-of-hospital Cardiac Arrest.

The Relaxin in Acute Heart Failure (RELAX-AHF) Trial.

Cardiorenal Rescue Study in Acute Decompensated Heart Failure: Results of CARRESS-HF, for the Heart Failure Clinical Research Network.

### PRACTICE IMPLICATIONS FOR CORONARY ARTERY DISEASE AND VENOUS THROMBOEMBOLISM

#### Aspirin for the Prevention of Recurrent Venous Thromboembolism After a First Unprovoked Event: Results of the ASPIRE Randomized Controlled Trial<sup>9</sup>

Presenter: Tim Brighton, Sydney, Australia.

**Background.** Patients who have had a first episode of unprovoked venous thromboembolism have a high risk of recurrence after anticoagulants are discontinued. Aspirin may be effective in preventing a recurrence of venous thromboembolism.

**Methods.** We randomly assigned 822 patients who had completed initial anticoagulant therapy after a first episode of unprovoked venous thromboembolism to receive aspirin, at a dose of 100 mg daily, or placebo for up to 4 years. The primary outcome was a recurrence of venous thromboembolism.

**Results.** During a median follow-up of 37.2 months, venous thromboembolism recurred in 73 of 411 patients assigned to placebo and in 57 of 411 assigned to aspirin (a rate of 6.5% per year vs 4.8% per year; hazard ratio [HR] with aspirin, 0.74; 95% confidence interval [CI], 0.52 to 1.05;  $P=.09$ ). Aspirin reduced the rate of the two prespecified secondary composite outcomes: the rate of venous thromboembolism, myocardial infarction (MI), stroke, or cardiovascular death was reduced by 34% (a rate of 8% per year with placebo vs 5.2% per year with aspirin; HR with aspirin, 0.66; 95% CI, 0.48 to 0.92;  $P=.01$ ), and the rate of venous thromboembolism, MI,

stroke, major bleeding, or death from any cause was reduced by 33% (HR=0.67; 95% CI, 0.49 to 0.91;  $P=.01$ ). There was no significant between-group difference in the rates of major or clinically relevant nonmajor bleeding episodes (rate of 0.6% per year with placebo vs 1.1% per year with aspirin,  $P=.22$ ) or serious adverse events.

**Conclusions.** In this study, aspirin, as compared with placebo, did not significantly reduce the rate of recurrence of venous thromboembolism but resulted in a significant reduction in the rate of major vascular events, with improved net clinical benefit. These results substantiate earlier evidence of a therapeutic benefit of aspirin when it is given to patients after initial anticoagulant therapy for a first episode of unprovoked venous thromboembolism.

#### A Randomized Trial of Bedside Platelet Function Monitoring to Adjust Antiplatelet Therapy versus Standard of Care in Patients Undergoing Drug Eluting Stent Implantation: The ARCTIC Study<sup>10</sup>

Presenter: Gilles Montalescot, Paris, France.

**Background.** Patients' responses to oral antiplatelet therapy are subject to variation. Bedside monitoring offers the opportunity to improve outcomes after coronary stenting by individualizing therapy.

**Methods.** We randomly assigned 2440 patients scheduled for coronary stenting at 38 centers to a strategy of platelet-function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy, or to a conventional strategy without monitoring and drug adjustment. The primary end point was the composite of death, MI, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation. For patients in the monitoring group, the VerifyNow P2Y12 and aspirin point-of-care assays were used in the catheterization laboratory before stent implantation and in the outpatient clinic 2 to 4 weeks later.

**Results.** In the monitoring group, high platelet reactivity in patients taking clopidogrel (34.5% of patients) or aspirin (7.6%) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure. The primary end point occurred in 34.6% of the patients in the monitoring group, as compared with 31.1% of those in the conventional-treatment group (HR=1.13; 95% CI, 0.98 to 1.29;  $P=.10$ ). The main secondary end point, stent thrombosis or any urgent revascularization, occurred in 4.9% of the patients in the monitoring group and 4.6% of those in the conventional-treatment group (HR=1.06; 95% CI, 0.74 to 1.52;  $P=.77$ ). The rate of major bleeding events did not differ significantly between groups.

**Conclusions.** This study showed no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting, as compared with standard antiplatelet therapy without monitoring.

#### First Large-scale Platelet-function Evaluation in an Acute Coronary Syndromes Trial: The TRILOGY ACS Platelet-function Sub-study<sup>11</sup>

Presenter: Paul A. Gurbel, Baltimore, Maryland, United States.

**Background.** The relationship of platelet function testing measurements with outcomes in patients with acute coronary syndromes (ACS) initially managed medically without revascularization is unknown. The objective of the study was to characterize the differences and evaluate clinical outcomes associated

with platelet reactivity among patients with ACS treated with clopidogrel or prasugrel.

**Methods.** Patients with medically managed unstable angina or non-ST-segment elevation MI were enrolled in the TRILOGY ACS trial (2008 to 2011) comparing clopidogrel versus prasugrel. Of 9326 participants, 27.5% were included in a platelet function substudy: 1286 treated with prasugrel and 1278 treated with clopidogrel. Aspirin with either prasugrel (10 or 5 mg/d) or clopidogrel (75 mg/d) was given. Patients aged 75 or older, or those younger than 75 but who weighed less than 60 kg, received a maintenance dose of prasugrel (5 mg). The main outcome was platelet reactivity, measured in P2Y12 reaction units (PRUs) at baseline, at 2 hours, and at 1, 3, 6, 12, 18, 24, and 30 months after randomization. The primary efficacy end point was a composite of cardiovascular death, MI, or stroke through 30 months.

**Results.** Among participants younger than 75 years and weighing 60 kg or more, the median PRU values at 30 days were 64 (interquartile range [IQR], 33-128) in the prasugrel group versus 200 (IQR, 141-260) in the clopidogrel group ( $P<.001$ ), a difference that persisted through all subsequent time points. For participants younger than 75 years and weighing less than 60 kg, the median 30-day PRU values were 139 (IQR, 86-203) for the prasugrel group versus 209 (IQR, 148-283) for the clopidogrel group ( $P<.001$ ), and for participants 75 years or older, the median PRU values were 164 (IQR, 105-216) for the prasugrel group versus 222 (IQR, 148-268) for the clopidogrel group ( $P<.001$ ). At 30 months the rate of the primary efficacy end point was 17.2% (160 events) in the prasugrel group versus 18.9% (180 events) in the clopidogrel group ( $P=.29$ ). There were no significant differences in the continuous distributions of 30-day PRU values for participants with a primary efficacy end point event after 30 days ( $n=214$ ) compared with participants without an event ( $n=1794$ ;  $P=.07$ ) and no significant relationship between the occurrence of the primary efficacy end point and continuous PRU values (adjusted HR [HR] for increase of 60 PRUs, 1.03; 95% CI, 0.96-1.11;  $P=.44$ ). Similar findings were observed with 30-day PRU cut points used to define high on-treatment platelet reactivity—PRU more than 208 (adjusted HR, 1.16; 95% CI, 0.89-1.52,  $P=.28$ ) and PRU more than 230 (adjusted HR, 1.20; 95% CI, 0.90-1.61;  $P=.21$ ).

**Conclusions.** Among patients with ACS, without ST-segment elevation, and initially managed without revascularization, prasugrel was associated with lower platelet reactivity than clopidogrel, irrespective of age, weight, and dose. Among those in the platelet substudy, no significant differences existed between prasugrel versus clopidogrel in the occurrence of the primary efficacy end point through 30 months and no significant association existed between platelet reactivity and occurrence of ischemic outcomes.

### Results of the Trial to Assess Chelation Therapy<sup>12</sup>

Presenter: Gervasio A. Lamas, Miami, Florida, United States.

**Background.** According to reports from the CDC, the use of chelation therapy with disodium ethylene diamine tetra acetic acid (EDTA) therapy to treat atherosclerosis is increasing in the United States. Whether or not it is safe or effective cannot be determined based on current clinical data. The purpose of the study was to evaluate the safety and effectiveness of an EDTA chelation solution versus placebo in post-MI patients.

**Methods.** This randomized study included 1708 post-MI patients ( $\geq 6$  weeks post-MI) who also received standard care, aged  $\geq 50$  years with an average follow-up of 4 years. The intervention consisted of 40 infusions of an EDTA-chelation solution and of an oral, high-dose, multivitamin and mineral supplement versus placebo. The primary composite end point was mortality (all-cause), MI, stroke, coronary

revascularization, or angina hospitalization. Secondary end points were composite CV death, nonfatal MI, nonfatal stroke

**Results.** Composite endpoints: 18% reduction EDTA versus placebo ( $P=.035$ ); Analysis by subgroups: Diabetes: 39% reduction in composite endpoints versus placebo ( $P=.002$ ); Nondiabetics: 0.04% reduction versus placebo ( $P=.725$ ); Anterior MI: 37% reduction versus placebo.

**Conclusions.** Post-MI patients who received chelation therapy had fewer clinical events compared to placebo. Two groups benefited most: diabetics and those who had experienced an anterior MI. Additional research is needed to confirm these findings and to understand the mechanisms of action for the benefits seen in this trial.

### Main Results of the Future Revascularization Evaluation in Patients With Diabetes mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial<sup>13</sup>

Presenter: Valentin Fuster, New York, United States.

**Background.** In some randomized trials comparing revascularization strategies for patients with diabetes, coronary-artery bypass grafting (CABG) has had a better outcome than percutaneous coronary intervention (PCI). We sought to discover whether aggressive medical therapy and the use of drug-eluting stents could alter the revascularization approach for patients with diabetes and multivessel coronary artery disease (CAD).

**Methods.** In this randomized trial, we assigned patients with diabetes and multivessel CAD to undergo either PCI with drug-eluting stents or CABG. The patients were followed for a minimum of 2 years (median among survivors, 3.8 years). All patients were prescribed currently recommended medical therapies for the control of low-density lipoprotein cholesterol, systolic blood pressure (BP), and glycated hemoglobin. The primary outcome measure was a composite of death from any cause, nonfatal MI, or nonfatal stroke.

**Results.** From 2005 through 2010, we enrolled 1900 patients at 140 international centers. The patients' mean age was  $63.1 \pm 9.1$  years, 29% were women, and 83% had 3-vessel disease. The primary outcome occurred more frequently in the PCI group ( $P=.005$ ), with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was driven by differences in rates of both MI ( $P<.001$ ) and death from any cause ( $P=.049$ ). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group and 5.2% in the CABG group ( $P=.03$ ).

**Conclusions.** For patients with diabetes and advanced CAD, CABG was superior to PCI in that it significantly reduced rates of death and MI, with a higher rate of stroke.

### HEALTH ECONOMICS AND QUALITY OF LIFE IN CONTEMPORARY TRIALS

#### Prospective Evaluation of Outcomes With Stress Perfusion Imaging Versus Stress Wall Motion Imaging During Dobutamine or Exercise Echocardiography<sup>14</sup>

Presenter: Thomas R. Porter, Omaha, Nebraska, United States.

**Background.** Retrospective studies examining real-time myocardial contrast echocardiography (RTMCE) during an intravenous (iv) microbubble infusion have improved the detection of CAD during exercise or pharmacologic stress echocardiography (SE). These studies

were performed with experienced reviewers in selected patients. The purpose of this study was to prospectively compare the predictive value of RTMCE with conventional stress echo (CSE), where contrast is used only for the Food and Drug Administration indication of left ventricular opacification.

**Methods.** A total of 2063 patients with intermediate pre-test probability undergoing either dobutamine or exercise SE were prospectively randomized to either RTMCE or CSE as their imaging modality during SE. A continuous infusion of Definity (Lantheus Medical) was used for all RTMCE studies to examine for both myocardial perfusion and wall motion, while Definity was used for CSE only when endocardial border delineation was inadequate (46% of all studies). RTMCE was performed with real-time pulse sequence schemes (mechanical index <0.25; frame rate 20–25 Hz). Studies were interpreted immediately by either an experienced reviewer (R1; n=1257) in perfusion imaging, or 4 Level III reviewers with basic training in perfusion imaging (R2; n=806).

**Results.** Follow-up was available in 2014 patients (median follow up 2.5 years). Mean age was 59±13 years (53% women). Patients randomized to RTMCE had slightly lower ejection fraction and higher frequency of prior revascularization (both  $P<.005$ ). Abnormal RTMCE studies were more frequent than abnormal CSE ( $P<.001$ ), and more frequently abnormal in a multivessel territory ( $P<.005$ ). Overall event-free survival (EFS) in those with positive or negative studies was not different between CSE and RTMCE. The predictive value of a positive study for both CSE and RTMCE was significant for R1 but not for R2 reviewers.

**Conclusions.** Abnormal studies are more frequently detected with RTMCE. Although the predictive value of SE with contrast is improved with experienced contrast users, the overall positive or negative predictive value of a dobutamine or exercise SE, when performed with RTMCE versus CSE in general practice, is not different.

### Economic Outcomes of Percutaneous Coronary Intervention Performed at Sites With and Without On-site Cardiac Surgery<sup>15</sup>

Presenter: Eric L. Eisenstein, Durham, North Carolina, United States.

**Background.** The aim was to compare costs of PCI between centers without and with on-site cardiac surgery.

**Methods.** The study groups consisted of 14 149 (no on-site surgery centers) and 4718 patients (on-site surgery centers). Cost data were collected from inpatient bills and estimated the costs for outpatient cardiac procedures, inpatient stays, emergency-department visits, physician visits, and ambulance transportation costs.

**Results.** Patients undergoing PCI at centers with cardiac surgery on-site had slightly lower average costs over 9 months than similar patients treated at centers without surgery, but the difference in cost was statistically nonsignificant. The costs of the procedures at the centers without surgery were statistically sensitive to variations in annual PCI volume, with higher-volume centers generally incurring lower per-procedure costs. Most important, the study requirement that PCI patients at the nonsurgery centers be treated in the intensive-care unit after their procedure had a “dramatic” effect on the costs, even though patients treated at the nonsurgery centers had a shorter length of hospitalization on average. Periprocedural costs were greater in the low-volume centers than at high-volume centers, especially among the centers with no on-site cardiac surgery. These differences were related not to differences in implant costs but to the total costs in the cath lab. No patients at centers with on-site surgery were required to receive postprocedural care in an ICU or CCU.

**Conclusions.** Although PCI costs slightly less in centers with cardiac-surgery capabilities than in centers without them, the

difference appears to be related to center volume rather than the direct benefits of on-site emergency surgical backup.

### Quality-of-life Outcomes in the Trial to Assess Chelation Therapy (TACT)<sup>16</sup>

Presenter: Daniel B. Mark, Durham, North Carolina, United States.

**Background.** This study examined quality of life outcomes in the Trial to Assess Chelation Therapy (TACT).

**Methods.** This is a NIH-funded, randomized, double-blind, placebo-controlled, 2 × 2 factorial trial comparing 40 infusions of an ethylene diamine tetra-acetic (EDTA)-chelation solution with placebo in patients with CAD. In a random sample of the 50% of patients in TACT (n=911 of a total 1708 patients), quality of life was assessed at baseline and at 6, 12, and 24 months. The quality-of-life tests included the Medical Outcomes Study Short Form-36 (SF-36), including its Mental Health Inventory-5 (MHI-5) component that assessed anxiety and depression. The MHI-5 along with the Duke Activity Status Index (DASI), a measure of cardiac functional status, were “co-principal end points” for the analysis. Also included were the Seattle Angina Questionnaire (SAQ) Anginal Frequency and Quality of Life subscales.

**Results.** Chelation therapy had almost no effect on standard measurements of quality of life, compared to placebo. The exception was slight improvement in self-reported anginal symptoms with chelation therapy at 1 year ( $P=.016$ ). However, according to the SAQ, about 80% of the patients had no anginal symptoms at baseline, so it was a small minority of the total population.

**Conclusions.** Obtained improvements in quality of life were very small and not associated with chelation. The quality-of-life results do not support clinical results.

### Cost-effectiveness of Percutaneous Coronary Intervention With Drug-eluting Stents versus Bypass Surgery for Patients With Diabetes and Multivessel Coronary Artery Disease: Results From the FREEDOM Trial<sup>17</sup>

Presenter: Elizabeth A. Magnuson, Kansas City, Missouri, United States.

**Background.** Although earlier studies have suggested that PCI could be more cost-effective than CABG, there has not been a study that compares the cost-effectiveness of PCI with drug-eluting stents (DES-PCI) to CABG in diabetic patients having multivessel revascularization. The purpose of the study was to evaluate cost-effectiveness of CABG versus DES-PCI for diabetic patients having multivessel revascularization. These results will compliment the clinical results of the FREEDOM trial.

**Methods.** Diabetic patients (n=1900) with multivessel CAD were randomized to either DES-PCI or CABG. Follow-up: 5 years. The primary endpoint was incremental cost-effectiveness ratio (ICER), or cost per quality-adjusted life year gained (QALY).

**Results.** Initial costs: CABG cost \$8622/patient more than DES-PCI ( $P<.001$ ). Five-year costs: CABG cost \$3641/patient and yielded 0.031 QALY improvement and a ICER gain of \$116 699/QALY. Lifetime cost-effectiveness ratio: 0.66 gain in QALY, CABG costs of \$5392 /patient (ICER gain of \$8132/QALY for CABG).

**Conclusions.** For diabetic patients with multivessel disease, initial costs were higher for CABG than for PCI because of hospital stay and early complications. Total 5-year costs for CABG were also higher, but the follow-up costs for PCI were greater. However, based on lifetime projections, CABG was found to be more cost-effective compared to DES-PCI.

## TREATMENTS FOR PREVENTION OF CARDIOVASCULAR EVENTS: A POPULATION PERSPECTIVE

### Omega-3 fatty Acids for the Prevention of Recurrent Symptomatic Atrial Fibrillation: Results of a Double-blind Randomized Clinical Trial (FORWARD)<sup>18</sup>

Presenter: *Alejandro Macchia, Santa Maria Imbaro, Italy.*

**Background.** Atrial fibrillation (AF) is associated with increased risk of death, thromboembolic complications, and decreased quality of life. Despite this burden, pharmacologic agents for prevention of AF in patients who achieved normal sinus rhythm are of limited utility, mostly because of serious and frequent side effects. Thus, the availability of safer and more effective drugs may reduce the burden of disease. The aim of the study was to test the efficacy of pharmacologic supplementation with 1 g daily of n-3 fatty acids (PUFA) for the maintenance of normal sinus rhythm in patients with previous AF.

**Methods.** FORWARD randomized patients with at least 2 symptomatic episodes of documented AF in the past 6 months or successful electrical or pharmacological cardioversion for persistent AF performed in the previous 3 to 90 days to 1 g daily of fish oil (n=289) or placebo (n=297). Patients were recruited from January 2008 to March 2011 and followed for 12 months or time to death or recurrent AF. The primary end point was the time to first recurrence of symptomatic or asymptomatic AF documented by 12-lead ECG.

**Results.** At 12 months, 18.9% of patients on placebo had a recurrence of AF compared with 24.0% of those who took fish oil (HR=1.28, *P*=.17). There was no difference between treatment with fish oil and placebo for any other prespecified end points.

**Conclusions.** Pharmacologic supplementation with 1 g of PUFA does not reduce AF recurrence in patients with previous AF who have recovered normal sinus rhythm.

### Fish Oil for the Prevention of Post-Operative Atrial Fibrillation: The Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) Trial<sup>19</sup>

Presenter: *Roberto Marchioli, Santa Maria Imbaro, Italy.*

**Background.** Postoperative AF or flutter is one of the most common complications of cardiac surgery and significantly increases morbidity and health care utilization. A few small trials have evaluated whether long-chain n-3-PUFA reduce postoperative AF, with mixed results. The aim was to determine whether perioperative n-3-PUFA supplementation reduces postoperative AF.

**Methods.** The Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) double-blind, placebo-controlled, randomized clinical trial. A total of 1516 patients scheduled for cardiac surgery in 28 centers in the United States, Italy, and Argentina were enrolled between August 2010 and June 2012. Inclusion criteria were broad; the main exclusions were regular use of fish oil or absence of sinus rhythm at enrollment. Patients were randomized to receive fish oil (1-g capsules containing  $\geq 840$  mg n-3-PUFA as ethyl esters) or placebo, with preoperative loading of 10 g over 3 to 5 days (or 8 g over 2 days) followed postoperatively by 2 g/d until hospital discharge or postoperative day 10, whichever came first. The main outcome measure was the occurrence of postoperative AF lasting longer than 30 seconds. Secondary end points were postoperative AF lasting longer than 1 hour, resulting in symptoms, or treated with cardioversion; postoperative AF excluding atrial flutter; time to first postoperative AF; number of AF episodes per patient; hospital

utilization; and major adverse CV events, 30-day mortality, bleeding, and other adverse events.

**Results.** At enrollment, mean age was 64 (SD, 13) years; 72.2% of patients were men and 51.8% had planned valvular surgery. The primary end point occurred in 233 (30.7%) patients assigned to placebo and 227 (30.0%) assigned to n-3-PUFAs (odds ratio, [OR]=0.96; 95% CI, 0.77-1.20; *P*=.74). None of the secondary end points were significantly different between the placebo and fish oil groups, including postoperative AF that was sustained, symptomatic, or treated (231 [30.5%] vs 224 [29.6%]; *P*=.70) or number of postoperative AF episodes per patient (1 episode, 156 [20.6%] vs 157 [20.7%]; 2 episodes, 59 [7.8%] vs 49 [6.5%];  $\geq 3$  episodes, 18 [2.4%] vs 21 [2.8%]); (*P*=.73). Supplementation with n-3-PUFA was generally well tolerated, with no evidence for increased risk of bleeding or serious adverse events.

**Conclusion.** In this large multinational trial among patients undergoing cardiac surgery, perioperative supplementation with n-3-PUFA, compared with placebo, did not reduce the risk of postoperative AF.

### A Randomized Trial of a Multivitamin in the Prevention of Cardiovascular Disease in Men: The Physicians' Health Study II<sup>20</sup>

Presenter: *Howard D. Sesso, Boston, Massachusetts, United States.*

**Background.** Although multivitamins are used to prevent vitamin and mineral deficiency, there is a perception that multivitamins may prevent cardiovascular disease (CVD). Observational studies have shown inconsistent associations between regular multivitamin use and CVD, with no long-term clinical trials of multivitamin use. The objective was to determine whether long-term multivitamin supplementation decreases the risk of major cardiovascular events among men.

**Methods.** The Physicians' Health Study II, a randomized, double-blind, placebo-controlled trial of a common daily multivitamin, began in 1997 with continued treatment and follow-up through June 1, 2011. A total of 14 641 male US physicians initially aged 50 years or older (mean, 64.3 [SD, 9.2] years), including 754 men with a history of CVD at randomization, were enrolled. Patients were randomized to daily multivitamin or placebo. The main outcome measures were the composite end point of major cardiovascular events, including nonfatal MI, nonfatal stroke, and CVD mortality. Secondary outcomes included MI and stroke individually.

**Results.** During a median follow-up of 11.2 [interquartile range, 10.7-13.3] years, there were 1732 confirmed major cardiovascular events. Compared with placebo, there was no significant effect of a daily multivitamin on major cardiovascular events (11 and 10.8 events per 1000 person-years for multivitamin vs placebo, respectively; HR=1.01; 95%CI, 0.91-1.10; *P*=.91). Further, a daily multivitamin had no effect on total MI (3.9 and 4.2 events per 1000 person-years; HR=0.93; 95% CI, 0.80-1.09; *P*=.39), total stroke (4.1 and 3.9 events per 1000 person-years; HR= 1.06; 95% CI, 0.91-1.23; *P*=.48), or CVD mortality (5.0 and 5.1 events per 1000 person-years; HR=0.95; 95% CI, 0.83-1.09; *P*=.47). A daily multivitamin was also not significantly associated with total mortality (HR=0.94; 95% CI, 0.88-1.02; *P*=.13). The effect of a daily multivitamin on major cardiovascular events did not differ between men with or without a baseline history of CVD (*P*=.62 for interaction).

**Conclusions.** Among this population of US male physicians, taking a daily multivitamin did not reduce major cardiovascular events, MI, stroke, and CVD mortality after more than a decade of treatment and follow-up.

### Use of a Multidrug Pill In Reducing Cardiovascular Events (UMPIRE)<sup>21</sup>

Presenter: Simon A. Thom, London, United Kingdom.

**Background.** Preventive therapies that address multiple CV risk factors are limited. Novel approaches are needed. A CVD preventive strategy consisting of a combination of aspirin, a statin, and 2 BP-lowering agents is one option that may reduce CV events. The objective of the study was to test the polypill compared to usual medications in patients with established CVD and those who are at high risk to increase adherence to guideline-indicated therapy and improve BP and LDL-cholesterol (LDL-C) in people at high risk.

**Methods.** This study randomized 2004 subjects from India and Europe to a polypill strategy, fixed-dose combination (FDC) or usual care (UC). Two versions were applied: *a*) aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg and atenolol 50 mg, or *b*) hydrochlorothiazide 12.5 mg instead of atenolol. The primary outcome was adherence to indicated medications, based on self-report.

**Results.** Adherence was 86% on FDC, 65% on UC with 1.22 treatment effect (95% CI, 1.24-1.41).

**Conclusions.** Improvement in adherence occurs with FDC, including antiplatelet, statin and BP-lowering drugs. Both BP and cholesterol also improved in patients with CVD and a 33% increase in adherence in 15 months was reported.

### NOVEL TREATMENTS FOR MANAGING LIPIDS DISORDERS

#### Reduction of Low-density Lipoprotein Cholesterol With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD): Interim Results From a Phase 2, Randomized, Double-blind, Placebo-controlled Trial<sup>22</sup>

Presenter: Frederick Raal, Johannesburg, South Africa.

**Background.** Despite statin treatment, many patients with heterozygous familial hypercholesterolemia do not reach desired low-density lipoprotein cholesterol (LDL-C) targets. AMG145, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease, demonstrated significant reductions in LDL-C in phase 1 studies. This phase 2, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study evaluated the efficacy and safety of AMG145 in heterozygous familial hypercholesterolemia patients.

**Methods.** Patients with heterozygous familial hypercholesterolemia diagnosed by Simon Broome criteria with LDL-C  $\geq 2.6$  mmol/L (100 mg/dL) despite statin therapy with or without ezetimibe were randomized 1:1:1 to AMG145 350 mg, AMG145 420 mg, or placebo-administered subcutaneously every 4 weeks. The primary end point was percentage change from baseline in LDL-C at week 12.

**Results.** Of 168 patients randomized, 167 received investigational product and were included in the full analysis set, with mean [SD] age, 50 [13] years; 47% female; 89% white; mean [SD] baseline LDL-C, 4.0 [1.1] mmol/L (156 [42] mg/dL). At week 12, LDL-C reduction measured by preparative ultracentrifugation (least squares mean [standard error (SE)]) was 43 (3)% and 55 (3)% with AMG145 350 mg and 420 mg, respectively, compared with 1 (3)% increase with placebo ( $P < .001$  for both dose groups). Serious adverse events (not considered treatment-related) occurred in 2 patients on AMG145.

**Conclusions.** AMG145 administered every 4 weeks yielded rapid and substantial reductions in LDL-C in heterozygous familial hypercholesterolemia patients despite intensive statin use, with or without ezetimibe, with minimal adverse events and good tolerability.

#### Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS): Interim Results From a Randomized, Double-blind, Placebo-controlled Study<sup>23</sup>

Presenter: Evan Stein, Cincinnati, Ohio, United States.

**Background.** An estimated 10% to 20% of patients cannot tolerate statins or adequate doses to achieve treatment goals. Plasma proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipoprotein (LDL) receptors, promoting their degradation and increasing LDL cholesterol levels. In phase 1 studies, a human monoclonal antibody to PCSK9, AMG145, was well tolerated and reduced LDL cholesterol levels. The objective of the study was to assess the efficacy and tolerability of AMG145 in patients with statin intolerance due to muscle-related side effects.

**Methods.** This is a 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, dose-ranging study conducted between July 2011 and May 2012 in statin-intolerant adult patients at 33 international sites. Patients were randomized equally to 1 of 5 groups: AMG145 alone at doses of 280 mg, 350 mg, or 420 mg; AMG145 at 420 mg plus 10 mg of ezetimibe; or 10 mg of ezetimibe plus placebo. AMG145 or placebo was administered subcutaneously every 4 weeks. The primary end point was percentage change from baseline to week 12 in ultracentrifugation-measured LDL cholesterol. Other end points included measures of safety and tolerability of different doses of AMG145 and AMG145 plus ezetimibe.

**Results.** Of 236 patients screened, 160 were randomized (mean age, 62 years; 64% female; mean baseline LDL cholesterol, 193 mg/dL); all patients had intolerance to 1 or more statins because of muscle-related events. At week 12, mean changes in LDL cholesterol levels were -67 mg/dL (-41%; 95% CI, -49% to -33%) for the AMG145, 280-mg, group; -70 mg/dL (-43%; 95% CI, -51% to -35%) for the 350-mg group; -91 mg/dL (-51%; 95% CI, -59% to -43%) for the 420-mg group; and -110 mg/dL (-63%; 95% CI, -71% to -55%) for the 420-mg/ezetimibe group compared with -14 mg/dL (-15%; 95% CI, -23% to -7.0%) for the placebo/ezetimibe group ( $P < .001$ ). Four serious adverse events were reported with AMG145 (CAD, acute pancreatitis, hip fracture, syncope). Myalgia was the most common treatment-emergent adverse event during the study, occurring in 5 patients (15.6%) in the 280-mg group (n=32); 1 patient (3.2%) in the 350-mg group (n=31), 1 patient (3.1%) in the 420-mg group (n=32), 6 patients (20%) receiving 420-mg AMG145/ezetimibe, and 1 patient (3.1%) receiving placebo/ezetimibe.

**Conclusions.** In this phase 2 study in statin-intolerant patients, subcutaneous administration of a monoclonal antibody to PCSK9 significantly reduced LDL cholesterol levels and was associated with short-term tolerability.

#### Effects of 12 Weeks of Treatment With RN316 (PF-04950615), a Humanized IgG2a Monoclonal Antibody Binding Proprotein Convertase Subtilisin Kexin Type 9, in Hypercholesterolemic Subjects on High and Maximal Dose Statins<sup>24</sup>

Presenter: Barry Gumbiner, San Diego, California, United States.

**Background.** Proprotein convertase subtilisin kexin type 9 (PCSK9) binds to LDL-C receptors preventing LDL-C clearance, therefore increasing LDL-C levels in the blood. RN316, a humanized monoclonal antibody, binds to PCSK9 preventing down-regulation of the LDL-C receptors, which has been shown to improve LDL-C clearance, and therefore reducing LDL-C levels. The objective of the study was to evaluate effects of RN316 on LDL-C levels in patients on high-to-maximal doses of atorvastatin, rosuvastatin, or simvastatin.

**Methods.** In this Phase 2, double-blind, randomized, placebo-controlled study, 135 patients already undergoing statin treatment

were randomized to 1 of 5 treatment arms: placebo, 0.25 mg/kg, 1.0 mg/kg, 3.0 mg/kg, or 6.0 mg/kg of RN316 administered every 4 weeks for 12 weeks with an 8-week follow-up period.

**Results.** LDL-C levels were significantly decreased with 3 mg/kg and 6 mg/kg dose of RN316 in addition to high- or maximal-dosage statin treatment. Total cholesterol was also reduced and levels of HDL-C increased. No significant changes were observed in triglycerides across any of the 5 treatment arms. Very few drug-related adverse events were observed. Those that did occur were mild and resolved with no intervention. The effect on LDL-C persisted for 4 weeks posttreatment.

**Conclusions.** RN316 significantly lowered LDL-C in addition to high or maximal statin dosage and was generally safe and well tolerated.

### Effects of the Cholesteryl Ester Transfer Protein Inhibitor Dalcetrapib in Patients With Recent Acute Coronary Syndrome<sup>25</sup>

Presenter: Gregory G. Schwartz, Denver, Colorado, United States.

**Background.** In observational analyses, higher levels of high-density lipoprotein (HDL) cholesterol have been associated with a lower risk of coronary heart disease events. However, whether raising HDL cholesterol levels therapeutically reduces CV risk remains uncertain. Inhibition of cholesteryl ester transfer protein (CETP) raises HDL cholesterol levels and might therefore improve CV outcomes.

**Methods.** We randomly assigned 15 871 patients who had a recent ACS to receive the CETP inhibitor dalcetrapib at a dose of 600 mg daily or placebo, in addition to the best available evidence-based care. The primary efficacy end point was a composite of death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.

**Results.** At the time of randomization, the mean HDL cholesterol level was 42 mg per deciliter (1.1 mmol per liter), and the mean low-density lipoprotein (LDL) cholesterol level was 76 mg per deciliter (2 mmol per liter). Over the course of the trial, HDL cholesterol levels increased from baseline by 4% to 11% in the placebo group and by 31% to 40% in the dalcetrapib group. Dalcetrapib had a minimal effect on LDL cholesterol levels. Patients were followed for a median of 31 months. At a prespecified interim analysis that included 1135 primary end-point events (71% of the projected total number), the independent data and safety monitoring board recommended termination of the trial for futility. As compared with placebo, dalcetrapib did not alter the risk of the primary end point (cumulative event rate, 8.0% and 8.3%, respectively; HR with dalcetrapib, 1.04; 95% confidence interval, 0.93 to 1.16;  $P=.52$ ) and did not have a significant effect on any component of the primary end point or total mortality. The median C-reactive protein level was 0.2 mg/L higher and the mean systolic BP was 0.6 mm Hg higher with dalcetrapib, compared with placebo ( $P<.001$  for both comparisons).

**Conclusions.** In patients with a recent ACS, dalcetrapib increased HDL cholesterol levels but did not reduce the risk of recurrent CV events.

### CELL-BASED THERAPIES FOR MYOCARDIAL REGENERATION

#### Results of the Swiss Multicenter Intracoronary Stem Cells Study in Acute Myocardial Infarction (Swiss AMI) Trial<sup>26</sup>

Presenter: Daniel Sürder, Lugano, Switzerland.

**Background.** Recent studies report that intracoronary administration of autologous bone marrow mononucleated cells

(BM-MNCs) may improve remodeling of the left ventricle after acute myocardial infarction (AMI). Subgroup analysis suggests that early treatment between days 4 and 7 after AMI is probably most effective; however, the optimal time point of intracoronary cell administration has never been addressed in clinical trials. Furthermore, reliable clinical predictors are lacking for the identification of patients who are thought to benefit most from cellular therapy.

**Methods.** In a multicenter trial, 200 patients with AMI successfully treated by PCI of the infarct-related artery were randomized in a 1:1:1 pattern to 1 control and 2 BM-MNC treatment groups. The control group was treated with state-of-the-art medical management. The treatment groups received intracoronary administration of autologous BM-MNC at 5 to 7 days or 3 to 4 weeks after the initial event, respectively. Left ventricular function as well as scar size, transmural extension, and regional wall motion score were assessed by cardiac magnetic resonance (CMR) studies at baseline and after 4 and 12 months. The primary end point was the change in global left ventricular (LV) ejection fraction by CMR at 4 months as compared to baseline. Secondary end points included change in LV volumes, infarct size (DE CMR) and regional myocardial thickening. MACE (death, MI, coronary revascularization, stroke) and predictors for efficacy (time to reperfusion, transmural, microvascular obstruction) were assessed.

**Results.** Intracoronary infusion of BM-MNC, either 5-7 d or 3-4 weeks after primary PCI for STEMI, did not improve LV function as assessed by CMR at 4 months compared with control. Subgroup analysis indicates potential benefit of intracoronary BM-MNC in patients with early reperfusion (within 4.5 h from the onset of pain)

**Conclusions.** Intracoronary infusion of BM-MNC did not improve left ventricular function as assessed by MRI compared with controls either at 1 week or 4 weeks after primary PCI for ST-elevation MI. However, subgroup analysis suggests this approach may offer some benefit in patients reperfused within 4.5 hours of the onset of chest pain.

#### The Effect of Timing of Stem Cell Delivery Following Acute Myocardial Infarction: The NHLBI and CTRN TIME Trial<sup>27</sup>

Presenter: Jay H. Traverse, Minneapolis, Minnesota, United States.

**Background.** While the delivery of cell therapy after ST-segment elevation myocardial infarction (STEMI) has been evaluated in previous clinical trials, the influence of the timing of cell delivery on the effect on left ventricular function has not been analyzed. The objective of the study was to determine the effect of intracoronary autologous bone marrow mononuclear cell (BMC) delivery after STEMI on recovery of global and regional left ventricular function and whether timing of BMC delivery (3 days vs 7 days after reperfusion) influences this effect.

**Methods.** A randomized, 2 × 2 factorial, double-blinded, placebo-controlled trial, Timing In Myocardial Infarction Evaluation (TIME) enrolled 120 patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤45%) after successful primary PCI of anterior STEMI between July 17, 2008, and November 15, 2011, as part of the Cardiovascular Cell Therapy Research Network sponsored by the National Heart, Lung, and Blood Institute. The intervention consisted of intracoronary infusion of 150 × 10<sup>6</sup> BMCs or placebo (randomized 2:1) within 12 hours of aspiration and cell processing administered at day 3 or day 7 (randomized 1:1) after treatment with PCI. The primary end points were change in global (LVEF) and regional (wall motion) left ventricular function in infarct and border zones at 6 months measured by cardiac magnetic resonance imaging and change in left ventricular function as affected by timing of treatment on day 3 versus day 7. The secondary end points included major adverse CV events as well as changes in left ventricular volumes and infarct size.

**Results.** The mean (SD) patient age was 56.9 (10.9) years and 87.5% of participants were male. At 6 months, there was no significant increase in LVEF for the BMC group (45.2% [95% CI, 42.8% to 47.6%] to 48.3% [95% CI, 45.3% to 51.3%]) versus the placebo group (44.5% [95% CI, 41.0% to 48.0%] to 47.8% [95% CI, 43.4% to 52.2%]) ( $P=.96$ ). There was no significant treatment effect on regional left ventricular function observed in either infarct or border zones. There were no significant differences in change in global left ventricular function for patients treated at day 3 ( $-0.9\%$  [95% CI,  $-6.6\%$  to  $4.9\%$ ],  $P=.76$ ) or day 7 ( $1.1\%$  [95% CI,  $-4.7\%$  to  $6.9\%$ ],  $P=.70$ ). The timing of treatment had no significant effect on regional left ventricular function recovery. Major adverse events were rare among all treatment groups.

**Conclusions.** Among patients with STEMI treated with primary PCI, the administration of intracoronary BMCs at either 3 days or 7 days after the event had no significant effect on recovery of global or regional left ventricular function compared with placebo.

### Randomized Comparison of Allogeneic Versus Autologous Mesenchymal Stem Cells in Patients With Ischemic Cardiomyopathy<sup>28</sup>

Presenter: Joshua M. Hare, Miami, Florida, United States.

**Background.** Mesenchymal stem cells (MSCs) are under evaluation as a therapy for ischemic cardiomyopathy (ICM). Both autologous and allogeneic MSC therapies are possible; however, their safety and efficacy have not been compared. The objective was to test whether allogeneic MSCs are as safe and effective as autologous MSCs in patients with left ventricular (LV) dysfunction due to ICM.

**Methods.** A phase 1/2 randomized comparison (POSEIDON study) in a US tertiary-care referral hospital of allogeneic and autologous MSCs in 30 patients with LV dysfunction due to ICM between April 2, 2010, and September 14, 2011, with 13-month follow-up. Twenty million, 100 million, or 200 million cells (5 patients in each cell type per dose level) were delivered by transcatheter stem cell injection into 10 LV sites. Main outcome measures were 30-day postcatheterization incidence of predefined treatment-emergent serious adverse events (SAEs). Efficacy assessments included 6-minute walk test, exercise peak VO<sub>2</sub>, Minnesota Living with Heart Failure Questionnaire (MLHFQ), New York Heart Association class, LV volumes, ejection fraction (EF), early enhancement defect (EED; infarct size), and sphericity index.

**Results.** Within 30 days, 1 patient in each group (treatment-emergent SAE rate, 6.7%) was hospitalized for heart failure, less than the prespecified stopping event rate of 25%. The 1-year incidence of SAEs was 33.3% ( $n=5$ ) in the allogeneic group and 53.3% ( $n=8$ ) in the autologous group ( $P=.46$ ). At 1 year, no ventricular arrhythmia SAEs were observed among allogeneic recipients compared with 4 patients (26.7%) in the autologous group ( $P=.10$ ). Relative to baseline, autologous but not allogeneic MSC therapy was associated with an improvement in the 6-minute walk test and the MLHFQ score, but neither improved exercise VO<sub>2</sub> max. Allogeneic and autologous MSCs reduced mean EED by  $-33.21\%$  (95% CI,  $-43.61\%$  to  $-22.81\%$ ;  $P<.001$ ) and sphericity index but did not increase EF. Allogeneic MSCs reduced LV end-diastolic volumes. Low-dose concentration MSCs (20 million cells) produced greatest reductions in LV volumes and increased EF. Allogeneic MSCs did not stimulate significant donor-specific alloimmune reactions.

**Conclusions.** In this early-stage study of patients with ICM, transcatheter injection of allogeneic and autologous MSCs without a placebo control were both associated with low rates of treatment-emergent SAEs, including immunologic reactions. In aggregate, MSC injection favorably affected patient functional capacity, quality of life, and ventricular remodeling.

### Effect of Cardiac Stem Cells In Patients With Ischemic Cardiomyopathy: Interim Results of the SCIPIO Trial Up to 2 Years After Therapy<sup>29</sup>

Presenter: Roberto Bolli, Louisville, Kentucky, United States.

**Background.** The aim was to evaluate the usefulness of cardiac stem-cell (CSC), instead of cells derived from bone marrow, in heart-failure patients.

**Methods.** This is a phase 1, randomized, open-label trial of c-KIT-positive CSCs in patients with left ventricular dysfunction (LVEF  $<40\%$ ) following an MI. In the trial, the cells were harvested from the patient's right atrial appendage, isolated and expanded, and then infused to repair an infarction during coronary bypass surgery.

**Results.** Echocardiography showed the average LVEF in the 18 patients treated with the CSC infusion increased from 29.0% before infusion to 36.0% ( $P<.001$ ) 4 months after the procedure. During that period, LVEF improved only from 29.2% to 29.4% in 13 control patients. The benefits seen in the treated group grew relative to the control group at 1-year and 2-year follow-up. The average LVEF grew insignificantly from 30.3% at baseline to 31.7% at 1 year post-procedure in the 12 control patients followed that long. In 17 patients in the CSC-treatment group at 1-year follow-up, LVEF increased to 37.8% from a baseline average of 29.7%. At 2 years, 5 control patients still showed no significant change in LVEF, while average LVEF rose to 41.7% in the 12 CSC-treated patients who had reached the 2-year follow-up. Global wall-motion scores declined slightly in the control group over 24 months but improved from  $-2.50$  to  $-3.92$  ( $P=.006$ ) in the treatment group.

Cardiac MRI showed that the CSC-treated patients had statistically significant improvements in mass of nonviable myocardial tissue and the percentages of viable tissue within the infarcted region. Minnesota Heart Failure Scores improved significantly in the CSC-treated patients while remaining almost flat in the control group. No adverse effects attributable to CSCs have been reported in the trial out to 2 years.

**Conclusions.** CSC is a useful treatment in patients with left ventricular dysfunction. Further studies are required to evaluate its potential.

### MANAGEMENT OF LEFT VENTRICLE DYSFUNCTION: DEVICES AND DRUGS

#### MADIT Randomized Trial to Reduce Inappropriate Therapy (MADIT-RIT)<sup>30</sup>

Presenter: Arthur J. Moss, Rochester, New York, United States.

**Background.** The implantable cardioverter-defibrillator (ICD) is highly effective in reducing mortality among patients at risk for fatal arrhythmias, but inappropriate ICD activations are frequent, with potential adverse effects.

**Methods.** We randomly assigned 1500 patients with a primary-prevention indication to receive an ICD with 1 of 3 programming configurations. The primary objective was to determine whether programmed high-rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of  $\geq 200$  beats per minute) or delayed therapy (with a 60-second delay at 170 to 199 beats per minute, a 12-second delay at 200 to 249 beats per minute, and a 2.5-second delay at  $\geq 250$  beats per minute) was associated with a decrease in the number of patients with a first occurrence of inappropriate antitachycardia pacing or shocks, as compared with conventional programming (with a 2.5-second delay at 170 to 199 beats per minute and a 1.0-second delay at  $\geq 200$  beats per minute).



**Results.** During an average follow-up of 1.4 years, high-rate therapy and delayed ICD therapy, as compared with conventional device programming, were associated with reductions in a first occurrence of inappropriate therapy (HR with high-rate therapy vs conventional therapy, 0.21; 95% CI, 0.13 to 0.34;  $P<.001$ ; HR with delayed therapy vs conventional therapy, 0.24; 95% CI, 0.15 to 0.40;  $P<.001$ ) and reductions in all-cause mortality (HR with high-rate therapy vs conventional therapy, 0.45; 95% CI, 0.24 to 0.85;  $P=.01$ ; HR with delayed therapy vs conventional therapy, 0.56; 95% CI, 0.30 to 1.02;  $P=.06$ ). There were no significant differences in procedure-related adverse events among the 3 treatment groups.

**Conclusions.** Programming of ICD therapies for tachyarrhythmias of 200 beats per minute or higher or with a prolonged delay in therapy at 170 beats per minute or higher, as compared with conventional programming, was associated with reductions in inappropriate therapy and all-cause mortality during long-term follow-up.

### Biventricular Versus Right Ventricular Pacing in Patients With Left Ventricular Dysfunction and Atrioventricular Block (BLOCK HF Study)<sup>31</sup>

Presenter: Anne B. Curtis, Buffalo, New York, United States.

**Background.** The objective of the study was to evaluate if biventricular (BiV) pacing can prevent progression of heart failure and its clinical and economic consequences in patients with AV block.

**Methods.** Eligibility criteria were a) AV block necessitating pacing; b) LVEF <50%; c) NYHA class I, II or III; d) absence of a class I indication for CRT; and e) no previous pacemaker or ICD. Echocardiography was performed at randomization, 6, 12, 18 and 24 months. The primary end point was the composite of all-cause mortality, heart failure-related urgent care or increase in LV end-systolic volume.

**Results.** A total of 691 patients were randomized; 349 were allocated to BiV pacing and 342 to RV pacing. Average follow-up was more than 36 months in both groups. The primary endpoint was reached more frequently in the RV pacing group (HR=0.74; 95%CI, 0.6-0.8).

**Conclusions.** In patients with AV block and LV systolic dysfunction, BiV pacing compared to RV pacing leads to a significant 26% reduction in the combined end point of mortality, heart failure related urgent care and increase in LV end systolic volume.

### Pilot Trial of Two Levels of Hypothermia in Comatose Survivors From Out-of-hospital Cardiac Arrest<sup>32</sup>

Presenter: Esteban Lopez-de-Sa, Madrid, Spain.

**Background.** It is recommended that comatose survivors of out-of-hospital cardiac arrest should be cooled to 32° to 34°C for 12 to 24 hours. However, the optimal level of cooling is unknown. The aim of this pilot study was to obtain initial data on the effect of different levels of hypothermia. We hypothesized that deeper temperatures will be associated with better survival and neurological outcome.

**Methods.** Patients were eligible if they had a witnessed out-of-hospital cardiac arrest from March 2008 to August 2011. Target temperature was randomly assigned to 32°C or 34°C. Enrollment was stratified on the basis of the initial rhythm as shockable or asystole. The target temperature was maintained during 24 hours followed by 12 to 24 hours of controlled rewarming. The primary outcome was survival free from severe dependence (Barthel Index score  $\geq 60$  points) at 6 months.

**Results.** Thirty-six patients were enrolled in the trial (26 shockable rhythm, 10 asystole), with 18 assigned to 34°C and 18 to 32°C. Eight of

18 patients in the 32°C group (44.4%) met the primary end point compared with 2 of 18 in the 34°C group (11.1%) (log-rank  $P=.12$ ). All patients whose initial rhythm was asystole died before 6 months in both groups. Eight of 13 patients with initial shockable rhythm assigned to 32°C (61.5%) were alive free from severe dependence at 6 months compared with 2 of 13 (15.4%) assigned to 34°C (log-rank  $P=.029$ ). The incidence of complications was similar in both groups except for the incidence of clinical seizures, which was lower (1 versus 11;  $P=.0002$ ) in patients assigned to 32°C compared with 34°C. On the contrary, there was a trend toward a higher incidence of bradycardia (7 versus 2;  $P=.054$ ) in patients assigned to 32°C. Although potassium levels decreased to a greater extent in patients assigned to 32°C, the incidence of hypokalemia was similar in both groups.

**Conclusions.** The findings of this pilot trial suggest that a lower cooling level may be associated with a better outcome in patients surviving out-of-hospital cardiac arrest secondary to a shockable rhythm. The benefits observed here merit further investigation in a larger trial in out-of-hospital cardiac arrest patients with different presenting rhythms.

### The Relaxin in Acute Heart Failure (RELAX-AHF-1) Trial<sup>33</sup>

Presenter: John R. Teerlink, San Francisco, California, United States.

**Background.** Serelaxin, recombinant human relaxin-2, is a vasoactive peptide hormone with many biological and haemodynamic effects. In a pilot study, serelaxin was safe and well tolerated with positive clinical outcome signals in patients with acute heart failure. The RELAX-AHF trial tested the hypothesis that serelaxin-treated patients would have greater dyspnoea relief compared with patients treated with standard care and placebo.

**Methods.** RELAX-AHF was an international, double-blind, placebo-controlled trial, enrolling patients admitted to hospital for acute heart failure who were randomly assigned (1:1) via a central randomisation scheme blocked by study centre to standard care plus 48-h intravenous infusions of placebo or serelaxin (30 µg/kg per day) within 16 h from presentation. All patients had dyspnoea, congestion on chest radiograph, increased brain natriuretic peptide (BNP) or N-terminal prohormone of BNP, mild-to-moderate renal insufficiency, and systolic BP greater than 125 mm Hg. Patients, personnel administering study drug, and those undertaking study-related assessments were masked to treatment assignment. The primary endpoints evaluating dyspnoea improvement were change from baseline in the visual analogue scale area under the curve (VAS AUC) to day 5 and the proportion of patients with moderate or marked dyspnoea improvement measured by Likert scale during the first 24 h, both analysed by intention to treat.

**Results.** 1161 patients were randomly assigned to serelaxin (n=581) or placebo (n=580). Serelaxin improved the VAS AUC primary dyspnoea endpoint (448 mm × h, 95% CI 120–775;  $P=.007$ ) compared with placebo, but had no significant effect on the other primary endpoint (Likert scale; placebo, 150 patients [26%]; serelaxin, 156 [27%];  $P=.70$ ). No significant effects were recorded for the secondary endpoints of cardiovascular death or readmission to hospital for heart failure or renal failure (placebo, 75 events [60-day Kaplan-Meier estimate, 13.0%]; serelaxin, 76 events [13.2%]; Hazard ratio [HR]=1.02 [95% CI, 0.74-1.41],  $P=.89$ ) or days alive out of the hospital up to day 60 (placebo, 47.7 [12.1] days; serelaxin, 48.3 [11.6];  $P=0.37$ ). Serelaxin treatment was associated with significant reductions of other prespecified additional endpoints, including fewer deaths at day 180 (placebo, 65 deaths; serelaxin, 42; HR=0.63; 95% CI, 0.42-0.93;  $P=.019$ ).

**Conclusions.** Treatment of acute heart failure with serelaxin was associated with dyspnoea relief and improvement in other clinical outcomes, but had no effect on readmission to hospital. Serelaxin

treatment was well tolerated and safe, supported by the reduced 180-day mortality.

### Cardiorenal Rescue Study in Acute Decompensated Heart Failure: Results of CARESS-HF, for the Heart Failure Clinical Research Network<sup>24</sup>

Presenter: Bradley A. Bart, Minneapolis, Minnesota, United States.

**Background.** Ultrafiltration is an alternative strategy to diuretic therapy for the treatment of patients with acute decompensated heart failure. Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function.

**Methods.** We randomly assigned a total of 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients). The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days.

**Results.** Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrollment ( $P=.003$ ), owing primarily to an increase in the creatinine level in the ultrafiltration group. At 96 hours, the mean change in the creatinine level was  $-0.04 \pm 0.53$  mg/dL ( $-3.5 \pm 46.9$   $\mu$ mol/L) in the pharmacologic-therapy group, as compared with  $+0.23 \pm 0.70$  mg/dL ( $20.3 \pm 61.9$   $\mu$ mol/L) in the ultrafiltration group ( $P=.003$ ). There was no significant difference in weight loss 96 hours after enrollment between patients in the pharmacologic-therapy group and those in the ultrafiltration group (a loss of  $5.5 \pm 5.1$  kg [ $12.1 \pm 11.3$  lb] and  $5.7 \pm 3.9$  kg [ $12.6 \pm 8.5$  lb], respectively;  $P=.58$ ). A higher percentage of patients in the ultrafiltration group than in the pharmacologic-therapy group had a serious adverse event (72% vs 57%,  $P=.03$ ).

**Conclusions.** In a randomized trial involving patients hospitalized for acute decompensated heart failure, worsened renal function, and persistent congestion, the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 hours, with a similar amount of weight loss with the 2 approaches. Ultrafiltration was associated with a higher rate of adverse events.

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