

Special article

# Summary of the Clinical Studies Reported in the European Society of Cardiology Congress 2014 (August 30 – September 3, 2014, Barcelona, Spain)



Resumen de estudios clínicos presentados en el Congreso de 2014 de la Sociedad Europea de Cardiología (30 de agosto-3 de septiembre de 2014, Barcelona, España)

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One of the main objectives of the current editorial team<sup>1-2</sup> has been to reinforce continuing medical education and provide the reader with frequent educational material. Apart from the "Update" section<sup>3-5</sup> and the editorial articles,<sup>6-11</sup> we have developed new headings like "Focus on,"<sup>12-13</sup> comments to the ESC guidelines, editor videos, and, more recently, the ECG contest.

Another classic academic section in *Revista Española de Cardiología* is the summary of the clinical studies reported in the main cardiology congresses. This time we present the results of a selection of recently concluded clinical trials of outstanding importance that were presented in special sections (Hot Lines) in the European Society of Cardiology congress held in Barcelona in 2014. As in previous editions,<sup>14-21</sup> we briefly outline the main objective, methods, and results, in line with the oral presentations. The information we offer should be considered preliminary because many of these studies have not yet been published in their final version.

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## CARDIOVASCULAR DISEASE: NOVEL THERAPIES

### PARADIGM-HF: Prospective Comparison of Angiotensin Receptor-neprilysin Inhibitor (ARNI) With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial<sup>22</sup>

*Presented by Milton Packer (Dallas, United States).*

**Background.** We compared the angiotensin receptor-neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

**Methods.** In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

**Results.** The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (HR in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87;  $P < .001$ ). A total of 711 patients (17.0%) receiving LCZ696 and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93;  $P < .001$ ); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (HR = 0.80; 95% CI, 0.71 to 0.89;  $P < .001$ ). As compared with enalapril, LCZ696 also reduced the risk of hospitalization for heart failure by 21% ( $P < .001$ ) and decreased the symptoms and physical limitations of heart failure ( $P = .001$ ). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

**Conclusions.** LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure.

### NECTAR-HF: Vagal Stimulation for the Treatment of Systolic Heart Failure: Neural Cardiac Therapy for Heart Failure<sup>23</sup>

*Presented by Faiez Zannad (Vandoeuvre Les Nancy, France).*

**Background.** The NECTAR-HF (NEural Cardiac TherApy foR Heart Failure) was a randomized sham-controlled trial designed to evaluate whether a single dose of vagal nerve stimulation (VNS) would attenuate cardiac remodeling, improve cardiac function, and increase exercise capacity in symptomatic heart failure patients with severe left ventricular (LV) systolic dysfunction despite guideline recommended medical therapy.

**Methods.** Patients were randomized in a 2:1 ratio to receive therapy (VNS ON) or control (VNS OFF) for a 6-month period. The primary endpoint was the change in left ventricular end systolic diameter (LVESD) at 6 months for control vs therapy, with secondary endpoints of other echocardiography measurements, exercise capacity, quality-of-life assessments, 24-hour Holter, and circulating biomarkers.

**Results.** Of the 96 implanted patients, 87 had paired data sets for the primary endpoint. Change in LVESD from baseline to 6 months was -0.04 (0.25) cm in the therapy group compared with -0.08 (0.32) cm in the control group ( $P = .60$ ). Additional echocardiographic parameters of LVEDD, LVESV, LVEDV, LVEF, peak  $\text{VO}_2$  and NT-proBNP failed to show superiority compared to sham treatment. There were

statistically significant improvements in quality of life for the MLHFQ ( $P = .049$ ), NYHA class ( $P = .032$ ), and the SF-36 Physical Component ( $P = .016$ ) in the therapy group.

**Conclusions.** VNS as delivered in the NECTAR-HF trial failed to demonstrate a significant effect on primary and secondary endpoint measures of cardiac remodeling and functional capacity in symptomatic HF patients.

### POPE-2: Colchicine for Postoperative Pericardial Effusion<sup>24</sup>

*Presented by Philippe Meurin, (Villeneuve-St.-Denis, France).*

**Background.** The objective of this prospective, double-blind, randomized, multicenter study was to assess the efficacy of colchicine in reducing pericardial effusion volume and the incidence of postoperative cardiac tamponades. After cardiac surgery, the incidence of pericardial effusion is high (50% to 85%). Cardiac tamponade occurs in 1% to 2% of patients. Early tamponade (during the first 7 days postoperatively) is due to surgical bleeding and accounts for about one third of all cases of tamponade. Early tamponades are usually easily diagnosed and treated because they occur while the patient is still in the intensive care unit. However, most tamponades occur more than 7 days after surgery and may develop slowly without clear-cut symptoms. This is a concern because by this time patients have often been discharged from the hospital. Growing evidence suggests that colchicine may be useful to treat acute pericarditis and to prevent -not treat- postpericardiotomy syndrome (PPS). However, PPS is a rare inflammatory postinjury syndrome that usually includes chest pain and fever and has little in common with asymptomatic postoperative pericardial effusion. Thus, colchicine efficacy in this latest setting remains unknown.

**Methods.** This was a prospective, double-blind, randomized study conducted in 10 cardiac rehabilitation centers comparing colchicine vs placebo to reduce pericardial effusion in patients who underwent cardiac surgery within the previous 30 days. In total, 172 patients (86 in each group) were needed for 80% power to detect a significant difference between colchicine and placebo. We prospectively screened 8140 consecutive postoperative patients; 252 met the inclusion criteria: moderate to large pericardial effusion (grade 2, 3 or 4 on a scale of 0 to 4 as measured by echocardiography) persisting 7 to 30 days after cardiac surgery, which indicated high risk of cardiac tamponade within the next 2 weeks. Among these 252 patients, 197 could be included (see flow chart in the PDF file). Patients were randomly assigned to receive colchicine, 1 mg daily ( $n = 98$ ), or a matching placebo ( $n = 99$ ) for 14 days. The primary endpoint was change in pericardial effusion grade after 14-day treatment. A secondary endpoint was incidence of cardiac tamponade.

**Results.** Patients were 64 years old on average, and 86% were male. Surgeries performed (total > 100 due to combined operations) were CABG ( $n = 110$ , 56%), aortic valve replacement ( $n = 82$ , 42%), mitral valve replacement ( $n = 12$ , 4%), mitral valve repair ( $n = 14$ , 7%), and ascending aorta replacement ( $n = 30$ , 15%). The initial mean pericardial effusion grade was 2.9 (0.8) and 3.0 (0.8) in the placebo and colchicine groups, respectively ( $P = .46$ ). The placebo and the colchicine groups showed similar pericardial effusion grade reduction after treatment (-1.1 [1.3] vs -1.3 [1.3] grade, respectively;  $P = .23$ ). In all, 13 cases of cardiac tamponade (6.6%) occurred during the 14-day treatment (7 and 6 in the placebo and colchicine groups, respectively;  $P = .80$ ). At 6-month follow-up, a total of 22 patients (11.2%) had required pericardial drainage, without significant difference between the 2 groups.

**Conclusions.** We confirm that persisting moderate to large pericardial effusion at 7 to 30 days after cardiac surgery is a severe condition. In these patients, the administration of colchicine did not

reduce the volume of effusion or prevent the occurrence of cardiac tamponade.

### COPPS-2: Colchicine for Prevention of the Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation<sup>25</sup>

*Presented by Massimo Imazio (Torino, Italy).*

**Background.** Postpericardiotomy syndrome, postoperative atrial fibrillation (AF), and postoperative effusions may be responsible for increased morbidity and health care costs after cardiac surgery. Postoperative use of colchicine prevented these complications in a single trial. The objective is to determine the efficacy and safety of perioperative use of oral colchicine in reducing postpericardiotomy syndrome, postoperative AF, and postoperative pericardial or pleural effusions.

**Methods.** Investigator-initiated, double-blind, placebo-controlled, randomized clinical trial among 360 consecutive candidates for cardiac surgery enrolled in 11 Italian centers between March 2012 and March 2014. At enrollment, mean age of the trial participants was 67.5 years (SD, 10.6 years), 69% were men, and 36% had valve surgery planned. Main exclusion criteria were absence of sinus rhythm at enrollment, cardiac transplantation, and contraindications to colchicine. Patients were randomized to receive placebo ( $n = 180$ ) or colchicine (0.5 mg twice daily in patients  $\geq 70$  kg or 0.5 mg once daily in patients  $< 70$  kg;  $n = 180$ ) starting between 48 and 72 hours before surgery and continued for 1 month after surgery.

**Results.** The primary endpoint was the occurrence of postpericardiotomy syndrome within 3 months; main secondary study end points were postoperative AF and pericardial or pleural effusion. The primary end point of postpericardiotomy syndrome occurred in 35 patients (19.4%) assigned to colchicine and in 53 (29.4%) assigned to placebo (absolute difference, 10.0%; 95% CI, 1.1%–18.7%; number needed to treat = 10). There were no significant differences between the colchicine and placebo groups for the secondary end points of postoperative AF (colchicine, 61 patients [33.9%]; placebo, 75 patients [41.7%]; absolute difference, 7.8%; 95% CI, –2.2% to 17.6%) or postoperative pericardial/pleural effusion (colchicine, 103 patients [57.2%]; placebo, 106 patients [58.9%]; absolute difference, 1.7%; 95% CI, –8.5% to 11.7%), although there was a reduction in postoperative AF in the prespecified on-treatment analysis (placebo, 61/148 patients [41.2%]; colchicine, 38/141 patients [27.0%]; absolute difference, 14.2%; 95% CI, 3.3%–24.7%). Adverse events occurred in 21 patients (11.7%) in the placebo group vs 36 (20.0%) in the colchicine group (absolute difference, 8.3%; 95% CI, 0.76%–15.9%; number needed to harm = 12), but discontinuation rates were similar. No serious adverse events were observed.

**Conclusions.** Among patients undergoing cardiac surgery, perioperative use of colchicine compared with placebo reduced the incidence of postpericardiotomy syndrome but not of postoperative AF or postoperative pericardial/pleural effusion. The increased risk of gastrointestinal adverse effects reduced the potential benefits of colchicine in this setting.

## CORONARY ARTERY DISEASE AND LIPIDS

### SOLID-TIMI 52: The Stabilization of Plaques Using Darapladib<sup>26</sup>

*Presented by Michelle O'Donoghue (Boston, United States).*

**Background.** Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been hypothesized to be involved in atherogenesis through

pathways related to inflammation. Darapladib is an oral, selective inhibitor of the Lp-PLA2 enzyme. The objective was to evaluate the efficacy and safety of darapladib in patients after an acute coronary syndrome (ACS) event.

**Methods.** SOLID-TIMI 52 was a multinational, double-blind, placebo-controlled trial that randomized 13 026 participants within 30 days of hospitalization with an ACS (non-ST-elevation or ST-elevation myocardial infarction [MI]) at 868 sites in 36 countries. Patients were randomized to either once-daily darapladib (160 mg) or placebo on a background of guideline-recommended therapy. Patients were followed up for a median of 2.5 years between December 7, 2009, and December 6, 2013. The primary end point (major coronary events) was the composite of coronary heart disease (CHD) death, MI, or urgent coronary revascularization for myocardial ischemia. Kaplan-Meier event rates are reported at 3 years.

**Results.** During a median duration of 2.5 years, the primary end point occurred in 903 patients in the darapladib group and 910 in the placebo group (16.3% vs 15.6% at 3 years; HR = 1.00 [95% CI, 0.91–1.09];  $P = .93$ ). The composite of cardiovascular death, MI, or stroke occurred in 824 in the darapladib group and 838 in the placebo group (15.0% vs 15.0% at 3 years; HR = 0.99 [95% CI, 0.90–1.09];  $P = .78$ ). There were no differences between the treatment groups for additional secondary end points, for individual components of the primary end point, or in all-cause mortality (371 events in the darapladib group and 395 in the placebo group [7.3% vs 7.1% at 3 years; HR = 0.94 [95% CI, 0.82–1.08];  $P = .40$ ). Patients were more likely to report an odor-related concern in the darapladib group vs the placebo group (11.5% vs 2.5%) and also more likely to report diarrhea (10.6% vs 5.6%).

**Conclusions.** In patients who experienced an ACS event, direct inhibition of Lp-PLA2 with darapladib added to optimal medical therapy and initiated within 30 days of hospitalization did not reduce the risk of major coronary events.

### SIGNIFY: Ivabradine in Patients With Stable Coronary Artery Disease Without Clinical Heart Failure<sup>27</sup>

*Presented by Kim Fox (London, Great Britain).*

**Background.** An elevated heart rate is an established marker of cardiovascular risk. Previous analyses have suggested that ivabradine, a heart-rate-reducing agent, may improve outcomes in patients with stable coronary artery disease, left ventricular dysfunction, and a heart rate of 70 beats per minute or more.

**Methods.** We conducted a randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19 102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more (including 12 049 patients with activity-limiting angina [class  $\geq$  II on the Canadian Cardiovascular Society scale, which ranges from I to IV, with higher classes indicating greater limitations on physical activity owing to angina]). We randomly assigned patients to placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction.

**Results.** At 3 months, the mean (standard deviation) heart rate of the patients was 60.7 (9.0) beats per minute in the ivabradine group versus 70.6 (10.1) beats per minute in the placebo group. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; HR = 1.08; 95% confidence interval, 0.96 to 1.20;  $P = .20$ ), nor were there significant differences in the incidences of death from cardiovascular causes and

nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina ( $P = .02$  for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs 2.3%,  $P < .001$ ).

**Conclusions.** Among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes.

### ODYSSEY COMBO II: Efficacy and Safety of Alirocumab in High Cardiovascular Risk Patients With Inadequately Controlled Hypercholesterolemia on Maximally Tolerated Daily Statin<sup>28</sup>

*Presented by Christopher Paul Cannon (Boston, United States).*

**Background.** Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is currently being investigated for the treatment of hypercholesterolemia and for the reduction of cardiovascular (CV) events.

**Methods.** ODYSSEY COMBO II is a Phase 3, randomized, double-blind, multicenter, 104-week study in patients with history of CVD and low-density lipoprotein cholesterol (LDL-C)  $\geq 1.81$  mmol/L ( $\geq 70$  mg/dL), or no history of CVD but with other risk factors and LDL-C  $\geq 2.59$  mmol/L ( $\geq 100$  mg/dL), and who were receiving a maximally tolerated daily statin dose (stable for at least 4 weeks prior to screening); other lipid-lowering therapies were not permitted. Patients were randomized 2:1 to either alirocumab 75 mg subcutaneously (SC) every 2 weeks (Q2W) or ezetimibe 10 mg daily. At Week 12, the dose of alirocumab was increased to 150 mg Q2W if Week 8 LDL-C was  $\geq 1.81$  mmol/L. Alirocumab (75/150 mg) and placebo injections were administered as a single 1 mL using a prefilled pen. This prespecified analysis includes the primary endpoint (% change in LDL-C from baseline to Week 24, intent-to-treat analysis), efficacy up to Week 52, and safety analysis up to Week 52-102, including all data collected after the last patient completed Week 52 visit.

**Results.** Mean (standard deviation) baseline LDL-C levels were 2.8 (0.9) mmol/L [108.6 (36.5) mg/dL] in the alirocumab arm ( $N = 479$ ) and 2.7 (0.9) mmol/L [104.6 (34.1) mg/dL] in the ezetimibe arm ( $N = 241$ ). Only 18.4% of alirocumab patients required a dose increase to 150 mg Q2W at Week 12. At Week 24, LS mean (SE) reductions from baseline were 50.6(1.4)% and 20.7(1.9)% for alirocumab and ezetimibe, respectively (both on a background of maximally tolerated statin), for a difference of -29.8 (2.3)% ( $P < .0001$ ); 77% of alirocumab and 46% of ezetimibe patients achieved LDL-C  $< 1.81$  mmol/L ( $< 70$  mg/dL) ( $P < .0001$ ). Achieved LS mean (SE) LDL-C levels at Week 24 were 1.34 (0.04) mmol/L [51.6 (1.4) mg/dL] with alirocumab and 2.14 (0.05) mmol/L [82.5 (2.0) mg/dL] with ezetimibe. These differences were maintained to Week 52. At 52 weeks, 84.8% and 85.5% of patients in the alirocumab and ezetimibe groups, respectively, were continuing study treatments. Treatment-emergent adverse events (TEAEs) occurred in 71.2% ( $N=341$ ) of alirocumab patients and 67.2% ( $N = 162$ ) of ezetimibe patients. TEAEs led to discontinuation in 7.5% ( $N = 36$ ) of alirocumab and 5.4% ( $N = 13$ ) of ezetimibe patients. The most common TEAEs (occurring in  $\geq 5\%$  of patients from either treatment arm) were upper respiratory tract infection, accidental overdose, dizziness, and myalgia.

**Conclusions.** In this population of high CV risk patients unable to achieve targets with maximal statin use, a "treat to target" approach with alirocumab, in which approximately 80% did not require an increase in dose to 150 mg Q2W, achieved significantly greater (~30% absolute) reductions in LDL-C vs ezetimibe after 24 and 52 weeks of treatment. At Week 24, >75% of alirocumab-treated patients achieved

LDL-C  $< 1.81$  mmol/L ( $< 70$  mg/dL). The frequency of TEAEs was similar between the alirocumab and ezetimibe groups.

### ODYSSEY FH I and FH II: Efficacy and Safety of Alirocumab in Patients With Heterozygous Familial Hypercholesterolaemia Not Adequately Controlled With Current Lipid-lowering Therapy<sup>29</sup>

*Presented by Michel Farnier (Dijon, France).*

**Background.** FH I and FH II (NCT01623115; NCT01709500) are Phase 3 studies in the ODYSSEY programme evaluating long-term efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, exclusively in patients with heterozygous familial hypercholesterolaemia (heFH) inadequately controlled on their current statin and other lipid-lowering therapy (LLT).

**Methods.** ODYSSEY FH I and FH II are ongoing randomised, 78-week, double-blind, placebo-controlled trials being conducted in North America, Europe, and South Africa. Patients with heFH inadequately controlled on maximally tolerated stable statin therapy with or without other LLT were randomised in a 2:1 ratio to receive alirocumab 75 mg or placebo every 2 weeks (Q2W) for 78 weeks via 1-mL subcutaneous injection using a prefilled pen. If LDL-C at Week 8 was  $\geq 1.81$  mmol/L (70 mg/dL), the alirocumab dose was increased to 150 mg Q2W (also 1 mL volume) at Week 12. In this prespecified analysis we report the primary efficacy endpoint (the % change in LDL-C from baseline to Week 24, by intent-to-treat [ITT] analysis), efficacy to Week 52, and safety data to Week 52-78 (including all data collected after last patient completed Week 52 visit).

**Results.** Alirocumab produced significant reductions in LDL-C at Week 24 in both studies vs placebo, which were maintained to Week 52. Treatment-emergent adverse events (TEAEs) across both studies occurred in a similar proportion of patients on alirocumab (74.8% [ $N = 366$ ]) and placebo (75.4% [ $N = 184$ ]), leading to study discontinuation in 3.1% [ $N = 15$ ] and 3.7% [ $N = 9$ ] of patients, respectively. Most common TEAEs (occurring in  $\geq 5\%$  of patients from either treatment arm) included injection site reactions, nasopharyngitis, influenza, and headache.

**Conclusions.** Alirocumab demonstrated significantly greater LDL-C lowering vs placebo after 24 weeks treatment in a large cohort of heFH patients with poorly controlled LDL-C despite maximally-tolerated statin therapy and other LLT. A majority of patients treated with alirocumab reached prespecified lipid goals at Week 24. As were generally comparable between groups.

### ODYSSEY LONG TERM: Long-term Safety, Tolerability, and Efficacy of Alirocumab Versus Placebo in High Cardiovascular Risk Patients<sup>30</sup>

*Presented by Jennifer Robinson, (Iowa City, United States).*

**Background.** Monoclonal antibodies to proprotein convertase subtilisin/kexin type 9 (PCSK9) represent a new class of drug with potential for lipid lowering and CV risk reduction. As for any new class, extensive long-term evaluation of efficacy and safety in a large patient population is required. ODYSSEY LONG TERM (NCT01507831) assessed safety, tolerability, and efficacy of alirocumab in 2,341 patients at high CV risk (including 17.7% of patients with heFH) for 18 months.

**Methods.** This phase 3, randomised, double-blind, placebo-controlled, parallel-group, multinational study enrolled patients with either heterozygous familial hypercholesterolaemia (determined by genotyping or clinical criteria) or coronary heart disease (CHD) or CHD risk equivalent. All patients had LDL-C  $\geq 1.81$  mmol/L (70 mg/dL)



and were receiving a maximally tolerated stable statin dose with/without other lipid-lowering therapy (LLT) for  $\geq 4$  weeks prior to screening. Patients were randomised 2:1 to either alirocumab 150 mg or placebo subcutaneously every two weeks for 78 weeks. This prespecified analysis includes the primary efficacy endpoint (% change in LDL-C from baseline to Week 24, intent-to-treat analysis), efficacy to Week 52, and safety results to 52-78 weeks (52 weeks for all patients continuing treatment, and 817 patients exposed for at least 76 weeks [543 on alirocumab, 274 on placebo]).

**Results.** Treatment-emergent adverse events (TEAEs) occurred in 78.6% (1218 of 1550) alirocumab and 80.6% (635 of 788) of placebo patients. TEAEs led to discontinuation in 6.2% and 5.5% of alirocumab and placebo patients, respectively. No marked imbalance was observed in the frequency of TEAEs. Treatment-emergent cardiovascular (CV) events were positively adjudicated in 4.0% and 4.4% of the alirocumab and placebo patients, respectively. In a posthoc analysis, the rate of adjudicated major CV events (cardiac death, myocardial infarction, ischemic stroke, and unstable angina requiring hospitalization) was 1.4% for alirocumab vs 3.0% for placebo (nominal  $P = .0089$ ), HR = 0.46 (95% CI: 0.26 to 0.82). Mean [standard deviation] baseline LDL-C levels were 3.2 [1.1] mmol/L (122.7 [42.6] mg/dL) in the alirocumab group and 3.2 [1.1] mmol/L (121.9 [41.4] mg/dL) in the placebo group. At Week 24, LS mean [SE] changes from baseline were -61.0 [0.7]% and +0.8 [1.0]% for alirocumab and placebo, respectively, for a difference in LDL-C % change from baseline to Week 24 of -61.9 [1.3]%, alirocumab vs placebo ( $P < .0001$ ); 81% of the alirocumab-treated patients reached prespecified LDL-C treatment levels according to their level of CVD risk. Achieved LS mean [SE] LDL-C levels at Week 24 were 1.25 [0.02] mmol/L (48.3 [0.9] mg/dL) with alirocumab and 3.08 [0.03] mmol/L (118.9 [1.2] mg/dL) with placebo. LDL-C reduction with alirocumab was maintained to Week 52.

**Conclusions.** In the largest double-blind phase 3 study of a PCSK9 inhibitor with the longest follow-up to date, alirocumab demonstrated safety generally comparable with maximally tolerated statin therapy with/without other LLT and produced significant reductions in LDL-C, with a majority of alirocumab-treated patients reaching prespecified LDL-C treatment levels at Week 24.

## HEART FAILURE: DEVICES AND INTERVENTIONS

### Comparison of an Ultrathin Strut Biodegradable Polymer Sirolimus-eluting Stent With a Durable Polymer Everolimus-eluting Stent for Percutaneous Coronary Revascularization<sup>31</sup>

*Presented by Thomas Pilgrim (Bern, Switzerland).*

**Background.** Refinements in stent design affecting strut thickness, surface polymer, and drug release have improved clinical outcomes of drug-eluting stents. We aimed to compare the safety and efficacy of a novel, ultrathin strut cobalt-chromium stent releasing sirolimus from a biodegradable polymer with a thin strut durable polymer everolimus-eluting stent.

**Methods.** We did a randomised, single-blind, non-inferiority trial with minimum exclusion criteria at nine hospitals in Switzerland. We randomly assigned (1:1) patients aged 18 years or older with chronic stable coronary artery disease or acute coronary syndromes undergoing percutaneous coronary intervention to treatment with biodegradable polymer sirolimus-eluting stents or durable polymer everolimus-eluting stents. Randomisation was via a central web-based system and stratified by centre and presence of ST segment elevation myocardial infarction. Patients and outcome assessors were masked to treatment allocation, but treating physicians were not. The primary endpoint, target lesion failure, was a composite of cardiac

death, target vessel myocardial infarction, and clinically-indicated target lesion revascularisation at 12 months. A margin of 3.5% was defined for non-inferiority of the biodegradable polymer sirolimus-eluting stent compared with the durable polymer everolimus-eluting stent. Analysis was by intention to treat.

**Results.** Between Feb 24, 2012, and May 22, 2013, we randomly assigned 2119 patients with 3139 lesions to treatment with sirolimus-eluting stents (1063 patients, 1594 lesions) or everolimus-eluting stents (1056 patients, 1545 lesions). 407 (19%) patients presented with ST-segment elevation myocardial infarction. Target lesion failure with biodegradable polymer sirolimus-eluting stents (69 cases; 6.5%) was non-inferior to durable polymer everolimus-eluting stents (70 cases; 6.6%) at 12 months (absolute risk difference -0.14%, upper limit of one-sided 95% CI 1.97%,  $p$  for non-inferiority  $< .0004$ ). No significant differences were noted in rates of definite stent thrombosis (9 [0.9%] vs 4 [0.4%]; RR = 2.26, 95% CI 0.70–7.33,  $P = .16$ ). In pre-specified stratified analyses of the primary endpoint, biodegradable polymer sirolimus-eluting stents were associated with improved outcome compared with durable polymer everolimus-eluting stents in the subgroup of patients with ST-segment elevation myocardial infarction (7 [3.3%] vs 17 [8.7%]; RR = 0.38, 95% CI, 0.16–0.91;  $P = .024$ ,  $P$  for interaction = .014).

**Conclusions.** In a patient population with minimum exclusion criteria and high adherence to dual antiplatelet therapy, biodegradable polymer sirolimus-eluting stents were non-inferior to durable polymer everolimus-eluting stents for the combined safety and efficacy outcome target lesion failure at 12 months. The noted benefit in the subgroup of patients with ST-segment elevation myocardial infarction needs further study.

### ANTHEM HF: Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms<sup>32</sup>

*Presented by Inder Anand (Minneapolis, United States).*

**Background.** ANTHEM-HF evaluated a novel autonomic regulation therapy (ART) via either left or right vagus nerve stimulation (VNS) in patients with heart failure (HF) and reduced ejection fraction (HFrEF).

**Methods.** Sixty subjects (NYHA class II-III, LVEF  $\leq 40\%$ , LVEDD  $\geq 50$  mm and  $< 80$  mm) receiving optimal pharmacological therapy were randomized at 10 sites. VNS systems were randomly implanted on the left ( $n = 31$ ) or right side ( $n = 29$ ). All patients were successfully implanted and 59 were titrated over 10 weeks to a well-tolerated chronic intermittent stimulation (10 Hz, 250  $\mu$ s, 14 sec on, 66 s off). The current amplitude was titrated to prevent side effects and acute HR changes (average up-titrated output current was 2.0 [0.6] mA). One patient died 3 days after an embolic stroke that occurred during implant. Common device-related adverse events after VNS titration were transient mild dysphonia, cough, and oropharyngeal pain, similar for left- and right-sided VNS.

**Results.** After 6 months of ART, in the combined population, absolute LVEF improved by 4.5% [95% CI, 2.4 to 6.6], LVESV improved by -4.1 mL [-9.0 to 0.8], and LVESD improved by -1.7 mm [-2.8 to -0.7]. The adjusted left-right differences in LVEF, end-systolic volume (LVESV), and end-systolic diameter (LVESD) were 0.2% [-4.4 to 4.7], 3.7 mL [-7.0 to 14.4], and 1.3 mm [-0.9 to 3.6], respectively. Heart rate variability improved by 17 ms [6.5 to 28] with minimal left-right difference. Six-minute walk distance improved an average of 56 m [37 to 75]; however, improvement was greater for right-sided ART (77 m [49 to 105]). NYHA class improved in 77% of patients (baseline to 6 months).

**Conclusions.** Chronic, low-amplitude ART via left- or right-sided VNS is feasible and well-tolerated in HFrEF patients. Safety assessment does not raise concerns; efficacy measures are encouraging and warrant further study.

## Comparison of Right Ventricular Septal Pacing and Right Ventricular Pacing in Patients Receiving a CRT-D<sup>33</sup>

Presented by Christophe Leclercq (Rennes, France).

**Background.** Cardiac resynchronization therapy (CRT) is a recommended therapeutic strategy in the treatment of symptomatic heart failure patients with depressed left ventricular ejection fraction (LVEF) and wide QRS. The location of the right ventricular lead, septal versus apical, impacting biventricular pacing is still a matter of debate. We conducted a prospective randomized European multicenter (25 centers) non inferiority trial comparing the septal RV pacing to the apical RV pacing on the LV reverse remodeling in CRT defibrillator (CRT-D) patients.

**Methods.** Patients included in the trial fulfilled the ESC guidelines for CRT. They were all in sinus rhythm at implant and were randomly assigned in a 1:1 ratio to septal RV pacing or to apical RV pacing. The RV lead location was assessed using predefined anatomical and electrical parameters. The LV lead was positioned on the lateral LV wall whenever possible. The primary endpoint was to demonstrate that RV septal pacing was not inferior to RV apical pacing in terms of changes in LV end systolic volume (LVESV) between baseline and 6 months at echocardiography. The primary endpoint of non-inferiority was defined with a safety margin of 20 ml for the LVESV. The main secondary objective was to assess the percentage of "echo-responders" defined by a > 15% reduction in the LVESV between baseline and 6 months. All echocardiographic analyses were performed on the PP population according to implanted sites. All echocardiographic recordings were analyzed by an independent core lab.

**Results.** A total of 182 patients (mean age, 63.3 [9.8]; 73% male; LVEF = 0.30 [0.08], 69% non-ischemic cardiomyopathy, 88% in NYHA class III), were randomized (90 septal, 92 apex). The QRS duration was 160 [22] ms. RV implant success rate fulfilling the pre-required anatomical lead position and electrical parameters, including one defibrillation test at 21J, was not statistically different in both groups. The non-inferiority of septal vs apical pacing was reached with a difference of -4.72 ml (95% CI = -16.54; 7.10). Changes in LVESV are given in the table. The percentage of "echo-responders" was similar in both groups (50%). During a 11.7 months mean follow-up, the proportion of patients experiencing  $\geq 1$  major adverse event (MAE), including deaths from all causes, cardiac and procedure-related or device-related MAE was not different ( $P = .437$ ) between RV septal pacing (37.8%) and the RV apical pacing (31.5%).

**Conclusions.** This first randomized prospective trial comparing RV apical and RV septal pacing in CRT-D recipients demonstrates the non-inferiority of RV septal pacing when compared to conventional RV apical pacing.

## STAR AF 2: Optimal Method and Outcomes of Catheter Ablation of Persistent Atrial Fibrillation<sup>34</sup>

Presented by Atul Verma (Newmarket, Canada).

**Background.** Ablation of persistent atrial fibrillation (AF) is challenging. The optimal catheter ablation strategy for persistent AF is unknown. Guidelines suggest that additional substrate modification in addition to pulmonary vein isolation (PVI) is required. The STAR AF 2 (Substrate and Trigger Ablation for Reduction of AF) trial compared 3 strategies of ablation: PVI, PVI plus complex fractionated electrograms (CFE), and PVI plus linear ablation (LINES).

**Methods.** Patients undergoing a first ablation procedure for drug-refractory persistent AF (defined as episodes lasting more than 7 days) were randomized 1:4:4 to each of the three strategies at 48 sites in 12 countries. For PVI ( $n = 67$ ), all PV antra were isolated

guided by a circular mapping catheter with confirmed entrance and exit block. For PVI+CFE ( $n = 263$ ), PVI was followed by AF induction and total elimination of electrograms demonstrating complex activity (or until AF terminated to sinus). For PVI+LINES ( $n=259$ ), PVI was followed by linear ablation along the left atrial roof and along the mitral isthmus with confirmation of bidirectional block. Repeat procedures using the identical strategy as first ablation were allowed between 3 and 6 months. Patients were followed up at 3, 6, 9, 12, and 18 months with a visit and 48-hour Holter. Weekly and symptomatic transtelephonic monitoring was performed for 18 months. The primary endpoint was time to first documented AF > 30 seconds after a single ablation procedure.

**Results.** A total of 589 patients with persistent AF were included (79% male, age 60 [9] years, LA size 45 [6] mm). Most patients (76%) were continuously in AF for > 6 months pre-ablation (median duration of continuous AF 2.2 years, IQR 0.9-4.8). At the time of ablation, 79% of patients were in spontaneous AF. Successful PVI was achieved in 97% of all patients with no differences between groups. For PVI+CFE, CFE were successfully mapped and ablated in 80% (11% could not be mapped because AF was noninducible after PVI); for PVI+LINES, 74% had successful lines with bidirectional block. Acute AF termination occurred in 45% of PVI+CFE, 22% of PVI+LINES and 8% of PVI ( $P < .0001$ ). Procedure time was significantly shorter for PVI (167 [55] min) compared to PVI+CFE (229 [83] min) and PVI+LINES (223 [89] min) ( $P < .0001$ ). After 18 months, 59% of patients randomized to PVI were free from any documented AF after a single ablation compared to 48% for PVI+CFE and 44% for PVI+LINES ( $P = .15$ ). When atrial flutter and tachycardia recurrences were counted in addition to AF, there was still no difference between the 3 arms after a single procedure. Repeat ablation was performed in 29% of all patients with no significant difference between groups. Complications included tamponade (0.2%), TIA (0.5%), and 1 atrio-esophageal fistula.

**Conclusions.** Catheter ablation with PVI achieves reasonable outcomes in persistent AF. The addition of further substrate ablation with either CFE or LINES increases procedural time, but offers no additional benefit over PVI alone.

## EuroEco: A Provider Perspective on Follow-Up Costs and Net Financial Impact of Remote Monitoring in Six European Countries<sup>35</sup>

Presented by Hein Heidebuchel (Leuven, Belgium).

**Background.** Remote follow-up (FU) of implantable cardiac defibrillators (ICDs) allows for fewer in-office visits in combination with earlier detection of relevant findings. Its implementation requires investment and reorganisation of care. Providers (physicians or hospitals) are unsure about the financial impact. The primary endpoint of this randomised prospective multicentre health economic trial was the total FU related cost for providers, comparing home monitoring facilitated FU (HM ON) to regular in-office FU (HM OFF) during the first two years after ICD implantation. Also the net financial impact on providers (taking national reimbursement into account) and costs from a healthcare payer perspective were evaluated.

**Methods.** A total of 312 patients with VVI- or DDD-ICD implants from 17 centres in six EU countries were randomized to HM ON or OFF, of which 303 were eligible for data analysis. For all contacts (in-office, calendar- or alert-triggered web-based review, discussions, calls) time-expenditure was tracked. Country-specific cost parameters were used to convert resource use into monetary values. Remote FU equipment itself was not included in the cost calculations. Given only two patients from Finland (1 per group), a monetary valuation analysis was not performed for Finland.

**Results.** Average patient age was 62.4 [13.1] years, 81% were male, 39% received a DDD system, and 51% had a prophylactic ICD. Resource use with HM ON was clearly different: remote FU was associated with less FU visits (3.79 [1.67] vs 5.53 [2.32];  $P < .001$ ) despite a small increase of unscheduled visits (0.95 [1.50] vs 0.62 [1.25];  $P < .005$ ), more non-office based contacts (1.95 [3.29] vs 1.01 [2.64];  $P < .001$ ), more Internet sessions (11.02 [15.28] vs 0.06 [0.31];  $P < .001$ ) and more in-clinic discussions (1.84 [4.20] vs 1.28 [2.92];  $P < .03$ ), but with numerically fewer hospitalizations (0.67 [1.18] vs 0.85 [1.43];  $P = .23$ ) and shorter length-of-stay (6.31 [15.5] vs 8.26 [18.6];  $P = .27$ ), albeit not significant. For the whole study population, the total FU cost for providers was not different for HM ON vs OFF (mean [95% CI]: €204 [169-238] vs €213 [182-243]; range for difference [€-36 to 54], NS). From a payer perspective, FU-related costs were similar while the total cost per patient (including other physician visits, examinations, and hospitalizations) was numerically (but not significantly) lower. There was no difference in the net financial impact on providers (profit of €408 [327-489] vs €400 [345-455]; range for difference [€-104 to 88], NS), but there was heterogeneity among countries, with less profit for providers in the absence of specific remote FU reimbursement (Belgium, Spain, Netherlands) and maintained or increased profit in cases where such reimbursement exists (Germany and UK). Nevertheless, even in countries where remote monitoring reimbursement is available, the total costs for healthcare payers over 2 years of follow-up did not increase, in line with the fewer hospitalisations and shorter length-of-stay. Quality of life (as measured by SF-36) was not different.

**Conclusions.** For all patients as a whole, FU related costs for providers are not different for FU based on remote monitoring vs purely in-office FU, despite clearly reorganised care. However, disparity in the impact on provider budget among different countries illustrates the need for proper reimbursement to ensure effective remote FU implementation.

## MYOCARDIAL INFARCTION

### ATLANTIC: In-ambulance Versus In-cath Lab Administration of Ticagrelor in STEMI Patients Transferred for Primary PCI<sup>36</sup>

*Presented by Gilles Montalescot (Paris, France).*

**Background.** The direct-acting platelet P2Y<sub>12</sub> receptor antagonist ticagrelor can reduce the incidence of major adverse cardiovascular events when administered at hospital admission to patients with ST-segment elevation myocardial infarction (STEMI). Whether prehospital administration of ticagrelor can improve coronary reperfusion and the clinical outcome is unknown.

**Methods.** We conducted an international, multicenter, randomized, double-blind study involving 1862 patients with ongoing STEMI of less than 6 hours' duration, comparing prehospital (in the ambulance) versus in-hospital (in the catheterization laboratory) treatment with ticagrelor. The coprimary end points were the proportion of patients who did not have a 70% or greater resolution of ST-segment elevation before percutaneous coronary intervention (PCI) and the proportion of patients who did not have Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related artery at initial angiography. Secondary end points included the rates of major adverse cardiovascular events and definite stent thrombosis at 30 days.

**Results.** The median time from randomization to angiography was 48 minutes, and the median time difference between the two treatment strategies was 31 minutes. The two coprimary end points did not differ significantly between the prehospital and in-hospital groups. The absence of ST-segment elevation resolution of 70% or

greater after PCI (a secondary end point) was reported for 42.5% and 47.5% of the patients, respectively. The rates of major adverse cardiovascular events did not differ significantly between the two study groups. The rates of definite stent thrombosis were lower in the prehospital group than in the in-hospital group (0% vs 0.8% in the first 24 hours; 0.2% vs 1.2% at 30 days). Rates of major bleeding events were low and virtually identical in the two groups, regardless of the bleeding definition used.

**Conclusions.** Prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion.

### The British Heart Foundation Fractional Flow Reserve Versus Angiography in Guiding Management to Optimise Outcomes in Non-ST-segment Elevation Myocardial Infarction<sup>37</sup>

*Presented by Robert Anthony Henderson (Nottingham, United Kingdom).*

**Background.** We assessed the management and outcomes of non-ST segment elevation myocardial infarction (NSTEMI) patients randomly assigned to fractional flow reserve (FFR)-guided management or angiography-guided standard care.

**Methods.** We conducted a prospective, multicentre, parallel group, 1 : 1 randomized, controlled trial in 350 NSTEMI patients with  $\geq 1$  coronary stenosis  $\geq 30\%$  of the lumen diameter assessed visually (threshold for FFR measurement). Enrolment took place in six UK hospitals from October 2011 to May 2013. Fractional flow reserve was disclosed to the operator in the FFR-guided group ( $n = 176$ ). Fractional flow reserve was measured but not disclosed in the angiography-guided group ( $n = 174$ ). Fractional flow reserve  $\leq 0.80$  was an indication for revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). The median (IQR) time from the index episode of myocardial ischaemia to angiography was 3 (2, 5) days.

**Results.** For the primary outcome, the proportion of patients treated initially by medical therapy was higher in the FFR-guided group than in the angiography-guided group [40 (22.7%) vs 23 (13.2%), difference 95% (95% CI: 1.4%, 17.7%);  $P = .022$ ]. Fractional flow reserve disclosure resulted in a change in treatment between medical therapy, PCI or CABG in 38 (21.6%) patients. At 12 months, revascularization remained lower in the FFR-guided group [79.0 vs 86.8%, difference 7.8% (-0.2%, 15.8%);  $P = .054$ ]. There were no statistically significant differences in health outcomes and quality of life between the groups.

**Conclusions.** In NSTEMI patients, angiography-guided management was associated with higher rates of coronary revascularization compared with FFR-guided management. A larger trial is necessary to assess health outcomes and cost-effectiveness.

### MITOCARE: Effect of Intravenous TRO40303 as an Adjunct to Primary Percutaneous Coronary Intervention for Acute ST-elevation Myocardial Infarction<sup>38</sup>

*Presented by Dan Atar (Oslo, Norway).*

**Background.** The MITOCARE study evaluated the efficacy and safety of TRO40303 for the reduction of reperfusion injury in patients undergoing revascularization for ST-elevation myocardial infarction (STEMI).

**Methods.** Patients presenting with STEMI within 6 h of the onset of pain randomly received TRO40303 ( $n = 83$ ) or placebo ( $n = 80$ ) via intravenous bolus injection prior to balloon inflation during primary percutaneous coronary intervention in a double-blind manner. The



primary endpoint was infarct size expressed as area under the curve (AUC) for creatine kinase (CK) and for troponin I (TnI) over 3 days. Secondary endpoints included measures of infarct size using cardiac magnetic resonance (CMR) and safety outcomes.

**Results.** The median pain-to-balloon time was 180 min for both groups, and the median (mean) door-to-balloon time was 60 (38) min for all sites. Infarct size, as measured by CK and TnI AUCs at 3 days, was not significantly different between treatment groups. There were no significant differences in the CMR-assessed myocardial salvage index (1-infarct size/myocardium at risk) (mean 52 vs 58% with placebo,  $P = .1000$ ), mean CMR-assessed infarct size (21.9 g vs 20.0 g, or 17 vs 15% of LV-mass) or left ventricular ejection fraction (LVEF) (46 vs 48%), or in the mean 30-day echocardiographic LVEF (51.5 vs 52.2%) between TRO40303 and placebo. A greater number of adjudicated safety events occurred in the TRO40303 group, for unexplained reasons.

**Conclusions.** This study in STEMI patients treated with contemporary mechanical revascularization principles did not show any effect of TRO40303 in limiting reperfusion injury of the ischemic myocardium.

## CORONARY ARTERY DISEASE AND ATRIAL FIBRILLATION

### X-VERT: Oral Rivaroxaban Once Daily Versus Dose-adjusted Vitamin K Antagonists in Patients With Nonvalvular Atrial Fibrillation Undergoing Elective Cardioversion<sup>39</sup>

*Presented by Riccardo Cappato (San Donato Milanese, Italy).*

**Background.** X-Vert is the first prospective randomized trial of a novel oral anticoagulant in patients with atrial fibrillation undergoing elective cardioversion.

**Methods.** We assigned 1504 patients to rivaroxaban (20 mg once daily, 15 mg if creatinine clearance was between 30 and 49 mL/min) or dose-adjusted vitamin K antagonists (VKAs) in a 2:1 ratio. Investigators selected either an early (target period of 1–5 days after randomization) or delayed (3–8 weeks) cardioversion strategy. The primary efficacy outcome was the composite of stroke, transient ischemic attack, peripheral embolism, myocardial infarction and cardiovascular death. The primary safety outcome was major bleeding. The primary efficacy outcome occurred in 5 (2 strokes) of 978 patients (0.51%) in the rivaroxaban group and in 5 (2 strokes) of 492 patients (1.02%) in the VKA group (HR = 0.50; 95% confidence interval [CI], 0.15–1.73).

**Results.** In the rivaroxaban group, 4 patients experienced primary efficacy events following early cardioversion (0.71%) and 1 following delayed cardioversion (0.24%).

In the VKA group, 3 patients had primary efficacy events following early cardioversion (1.08%) and 2 following delayed cardioversion (0.93%). Rivaroxaban was associated with a significantly shorter time to cardioversion compared with VKAs ( $P < .001$ ). Major bleeding occurred in 6 patients (0.6%) in the rivaroxaban group and 4 patients (0.8%) in the VKA group (HR = 0.76; 95% CI, 0.21–2.67).

**Conclusions.** Oral rivaroxaban appears to be an effective and safe alternative to VKAs and may allow prompter cardioversion.

### AMIOCAT: Recurrence of Arrhythmia Following Short-term Oral Amiodarone After Catheter Ablation for Atrial Fibrillation: A Double-blind, Randomized, Placebo-controlled Study<sup>40</sup>

*Presented by Stine Darkner (Copenhagen, Denmark).*

**Background.** Patients undergoing catheter ablation for atrial fibrillation (AF) often experience recurrent arrhythmias within the

first few months post ablation. We aimed to investigate whether short term use of amiodarone to prevent early arrhythmias following radiofrequency ablation for AF could reduce later recurrence.

**Methods.** In a 2-center, randomized, double-blind, placebo-controlled study, we randomized a total of 212 patients undergoing AF ablation. Patients were stratified according to type of AF (paroxysmal/persistent) and history of previous AF ablation and randomly assigned to 8 weeks of oral amiodarone therapy or matched placebo following catheter ablation. Patients were followed for 6 months. Analyses were performed according to the intention-to-treat principle.

**Results.** Of 212 enrolled patients (median age 61 [IQR 54–66], 83% male, 50% paroxysmal, 29% with history of previous ablation), 206 patients were available for analysis of the primary endpoint which was any documented atrial tachyarrhythmia lasting >30 seconds following a blanking period of 3 months. This was observed in 42/107 (39%) in the amiodarone group versus 48/99 (48%) in the placebo group ( $P = .18$ ). Among the secondary endpoints, the amiodarone group showed significantly lower rate of atrial tachyarrhythmia related hospitalizations (rate ratio = 0.43; 95% CI = 0.23–0.77;  $P = .006$ ) and cardioversions (rate ratio = 0.36; 95% CI 0.20–0.62,  $P = .0004$ ) within the blanking period.

**Conclusions.** Short term oral amiodarone treatment following ablation for paroxysmal or persistent AF did not significantly reduce recurrence of atrial tachyarrhythmias at 6 months follow-up, but it more than halved atrial arrhythmia-related hospitalization and cardioversion rates during the blanking period.

### IBIS-4: High-intensity Statin Therapy and Atherosclerosis in Patients With ST-elevation Myocardial Infarction<sup>41</sup>

*Presented by Lorenz Raber (Bern, Switzerland).*

**Background.** The effect of long-term high-intensity statin therapy on coronary atherosclerosis among patients with acute ST-segment elevation myocardial infarction (STEMI) is unknown. The aim of this study was to quantify the impact of high-intensity statin therapy on plaque burden, composition, and phenotype in non-infarct-related arteries of STEMI patients undergoing primary percutaneous coronary intervention (PCI).

**Methods.** Between September 2009 and January 2011, 103 STEMI patients underwent intravascular ultrasonography (IVUS) and radiofrequency ultrasonography (RF-IVUS) of the two non-infarct-related epicardial coronary arteries (non-IRA) after successful primary PCI. Patients were treated with high-intensity rosuvastatin (40 mg/day) throughout 13 months and serial intracoronary imaging with the analysis of matched segments was available for 82 patients with 146 non-IRA. The primary IVUS end-point was the change in percent atheroma volume (PAV).

**Results.** 13 months, low-density lipoprotein cholesterol (LDL-C) had decreased from a median of 3.29 to 1.89 mmol/L ( $P < .001$ ), and high-density lipoprotein cholesterol (HDL-C) levels had increased from 1.10 to 1.20 mmol/L ( $P < .001$ ). PAV of the non-IRA decreased by  $-0.9\%$  (95% CI:  $-1.56$  to  $-0.25$ ;  $P = .007$ ). Patients with regression in at least one non-IRA were more common (74%) than those without (26%). Per cent necrotic core remained unchanged ( $-0.05\%$ , 95% CI:  $-1.05$  to  $0.96\%$ ;  $P = .93$ ), as did the number of RF-IVUS defined thin cap fibroatheromas (124 vs 116;  $P = .15$ ).

**Conclusions.** High-intensity rosuvastatin therapy over 13 months is associated with regression of coronary atherosclerosis in non-infarct-related arteries without changes in RF-IVUS defined necrotic core or plaque phenotype among STEMI patients.



## IMPI Steroid Study: A Trial of Adjunctive Prednisolone in Tuberculous Pericarditis<sup>42</sup>

Presented by Bongani Mawethu Mayosi (Cape Town, South Africa).

**Background.** The Investigation of the Management of Pericarditis (IMPI) trial was a multicenter, randomized, double-blind, placebo-controlled, 2-by-2 factorial study. Eligible patients were randomly assigned to receive oral prednisolone or placebo for 6 weeks and Mycobacterium indicus pranii injection or placebo for 3 months. The primary outcome was the first occurrence of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. The secondary outcome was safety of immunomodulatory treatment measured by effect on opportunistic infections and malignancy and impact on measures of immunosuppression and the incidence of immune reconstitution disease. Tuberculous (TB) pericarditis affects a million individuals in Africa and the morbidity and mortality are very high despite anti-TB therapy. We evaluated the effectiveness and safety of adjunctive corticosteroids and *Mycobacterium indicus pranii* in patients with tuberculous pericarditis treated with anti-TB drugs, especially in those with concomitant human immunodeficiency virus (HIV) infection.

**Methods.** We randomized 1400 people (mean age, 38.7 years) with definite or probable tuberculous pericardial effusion to receive adjunctive prednisolone for 6 weeks or placebo, and to receive Mycobacterium indicus pranii immunotherapy or placebo for 3 months with the use of a 2-by-2 factorial design. The primary outcome was a composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. The secondary safety outcomes were the occurrence of opportunistic infection and malignancy (in all patients), and immunosuppression measured by CD4+ T cell count and immune reconstitution disease (in HIV positive patients).

**Results.** In the prednisolone comparison, the median follow-up was 636.5 days (interquartile range, 317.5 to 1085.5 days); at study end, the primary-outcome status was known for 1371 participants (97.9%). In the Mycobacterium indicus pranii comparison, the median follow-up was 720.5 days (interquartile range, 368.0 to 1095.0); at study end, the primary-outcome status was known for 1223 participants (97.8%). There was no significant difference between prednisolone and placebo (23.8% vs 24.8%; hazard ratio, 0.95; 95% confidence interval [CI], 0.77 to 1.18;  $P = .66$ ), or between Mycobacterium indicus pranii immunotherapy and placebo (25.0% vs 24.3%; HR = 1.03; 95% CI, 0.82 to 1.29;  $P = .81$ ) with respect to the primary outcome. Prednisolone was associated with a significant reduction in constrictive pericarditis (4.4% vs 7.8%; HR = 0.56; 95% CI, 0.36 to 0.85;  $P = .009$ ) and hospitalizations (20.7% vs 25.2%; HR = 0.79; 95% CI, 0.63 to 0.99;  $P = .04$ ). Prednisolone and Mycobacterium indicus pranii were associated with a significant increase in malignancy (1.8% vs 0.6%; HR = 3.27; 95% CI, 1.07 to 10.03;  $P = .03$ ; and 1.8% vs 0.5%; HR = 3.69; 95% CI, 1.03 to 13.24;  $P = .03$ , respectively), mainly due to an increase in HIV-associated malignancies. There was no difference in median CD4+ T cell count during the study and in the occurrence of immune reconstitution disease between the two groups for the two comparisons in HIV infected individuals.

**Conclusions.** In patients with tuberculous pericarditis, neither prednisolone nor Mycobacterium indicus pranii had a significant effect on the composite of death, cardiac tamponade or constrictive pericarditis. Both therapies were associated with an increased risk of HIV-associated malignancies. However, use of adjunctive steroids reduced the incidence of pericardial constriction and hospitalization. The beneficial effects of prednisolone on constriction and hospitalization were similar in HIV-positive and HIV-negative patients.

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