

## SPECIAL ARTICLE

# Summary of the Clinical Studies Reported in the Annual Scientific Sessions of the American College of Cardiology (New Orleans, March 24-27, 2007)

Javier Segovia,<sup>a</sup> Javier Bermejo,<sup>a</sup> and Fernando Alfonso<sup>b</sup>

<sup>a</sup>Associate Editors, *Revista Española de Cardiología*

<sup>b</sup>Editor in Chief, *Revista Española de Cardiología*

In the 56th Annual Scientific Sessions of the American College of Cardiology, corresponding to 2007, some late breaking clinical trials were presented in special sessions with a view to facilitating rapid dissemination of studies of particular importance whose results have only recently become available.

The following is a brief summary of the objectives, methods, and findings of these studies, as given in the oral presentations. Given that many have not been published in their final version yet, the information offered here should be considered preliminary. In the event that a given study has been published in full by the time these summaries reach the reader, we provide the reference to the original publication, which will usually be written in English.

## SUMMARY BY TOPICS

### Primary and Secondary Prevention

Aliskiren and valsartan in the treatment of arterial hypertension.

VALIDD study: valsartan in diastolic dysfunction of the left ventricle.

ERASE study: effect of infusion of high-density lipoproteins on the size of coronary atheromatous plaque.

RADIANCE 1 study: effect of torcetrapib combined with atorvastatin in carotid atherosclerosis in patients with heterozygous familial hypercholesterolemia.

ILLUSTRATE study: effect of torcetrapib on the size of coronary lesions.

METEOR study: effect of rosuvastatin on carotid atherosclerosis.

### Ischemic Heart Disease

MERLIN TIMI 36 study: clinical effect of ranolazine in patients with non-ST-elevation acute coronary syndrome.

ARISE study: long-term effect of succinobucol administration after acute coronary syndrome.

DELTA MI study: inhibition of  $\Delta$  protein kinase C to limit the extent of acute myocardial infarction.

TRIUMPH study: effect of tilarginine, a nitric oxide synthase inhibitor, on patients with cardiogenic shock following myocardial infarction.

### Heart Failure

EVEREST study: effect of tolvaptan, a vasopressin antagonist, on long-term outcomes of patients admitted to hospital for heart failure.

FUSION II study: medium-term effect of serial infusions of nesiritide in an outpatient setting in patients with heart failure.

SPICE study: effect of the *Crataegus* extract on long-term outcome in patients with moderate systolic heart failure.

### Arrhythmias

ALPHA study: usefulness of studying T-wave alternans to predict serious arrhythmic events in patients with heart failure due to systolic dysfunction.

### Percutaneous Coronary Intervention

COURAGE study: coronary intervention compared to medical treatment in stable angina.

Correspondence: *Revista Española de Cardiología*.

Sociedad Española de Cardiología.

Nuestra Señora de Guadalupe, 5-7. 28028 Madrid. España.

E-mail: rec@secardiologia.es

ARMYDA-ACS study: effect of treatment with atorvastatin prior to percutaneous coronary intervention in patients with acute coronary syndrome.

DEDICATION study: effect of a distal protection device in primary percutaneous coronary intervention for myocardial infarction.

SPIRIT III study: comparison of everolimus-eluting stent with paclitaxel-eluting stent in de novo coronary lesions.

ISAR-PEACE study: effect of adding estradiol to an everolimus-eluting stent for treatment of coronary lesions.

ABSORB study: first clinical study in humans with bioabsorbable drug-eluting stents.

### Cell Therapy

Mesenchymal stem cell transplantations after myocardial infarction.

## PRIMARY AND SECONDARY PREVENTION

### Aliskiren and Valsartan in the Treatment of Arterial Hypertension

*Presented by Suzanne Oparil, Birmingham, Alabama, United States*

**Background:** Aliskiren is a new renin inhibitor that can be administered orally. The aim of this study was to assess the effect of treatment with aliskiren, valsartan, or the 2 drugs in combination, compared to placebo in patients with mild or moderate hypertension.

**Methods:** After a washout period of 1 to 2 weeks and a run-in treatment period of 3 to 4 weeks, the patients were randomized in to receive aliskiren (150 mg/day, n=437), valsartan (160 mg/day, n=455), a combination of the two (n=446), or placebo (n=459) in a double-blind design. Treatment was administered for 4 weeks, whereupon the dose was doubled and administration continued for a further 4 weeks. Blood pressure was assessed at baseline, and after 4 and 8 weeks.

**Results:** Blood pressure at baseline was 154/100 mm Hg. After 8 weeks of follow-up, diastolic blood pressure (DBP) decreased by 4.1 mm Hg in the placebo group, 9.0 mm Hg in the aliskiren group, 9.7 mm Hg in the valsartan group, and 12.2 mm Hg in the combined treatment group ( $P<.001$  for the combination vs the other groups). Likewise, systolic blood pressure (SBP) decreased by 4.6 mm Hg in the placebo group, 13.0 mm Hg in the aliskiren group,

12.8 mm Hg in the valsartan group, and 17.2 mm Hg in the combined treatment group ( $P<.001$  for the combination versus the other groups). The blood pressure response rate was greater in the combined treatment group (65.8% vs 19.9% with placebo, 53.5% with aliskiren, and 55.2% with valsartan;  $P<.05$  for comparison of the combination with each of the other groups) and similar findings were reported for the extent of blood pressure control (49.3% vs 16.5% with placebo, 37.4% with aliskiren, and 33.8% with valsartan). The frequency of adverse events was similar in all groups (36.7% with placebo, 34.1% with aliskiren, 36.7% with valsartan, and 35.0% in the combined treatment group).

**Conclusions:** In patients with mild–moderate hypertension, aliskiren, valsartan, and the combination of the 2 was associated with a decrease in blood pressure after 8 weeks compared to placebo. The most marked decrease was observed in the combined treatment group, and so the hypotensive effect of the 2 drugs appears to be additive.

### Valsartan in Diastolic Dysfunction (VALIDD) Study

*Presented by Scott D. Solomon, Boston, United States*

**Background:** The aim of this study was to assess how well blood pressure is controlled with valsartan compared to treatment without an inhibitor of the renin–angiotensin–aldosterone system (RAAS) in hypertensive patients with diastolic dysfunction.

**Methods:** After diagnosis of diastolic dysfunction, characterized by the presence of reduced mitral annular relaxation velocities in cardiac Doppler, patients were randomized to receive antihypertensive treatment with valsartan (320 mg/day, n=386) or antihypertensive treatment without an RAAS inhibitor (n=198) for 38 weeks in a double-blind design. The treatment goal was to reduce blood pressure to below 135/80 mm Hg in both groups. To achieve these goals, other common antihypertensive agents such as diuretics,  $\beta$ -blockers, and calcium antagonists were used.

**Results:** The mean baseline blood pressure was 144/86 mm Hg and the ejection fraction was 57%. Prior to enrollment, 76% of the patients were receiving antihypertensive treatment. At baseline, 12% had diabetes and less than 4% had left ventricular hypertrophy.

The systolic blood pressure decreased in both groups compared to baseline (13 mm Hg in the valsartan group vs 10 mm Hg in the control group) with no significant

differences between the 2 groups. The primary outcome measure, change in the myocardial relaxation rate at 9 months, changed significantly in both groups (0.60 in the valsartan group vs 0.44 in the control group) but there were no differences between groups ( $P=.30$ ). The left ventricular mass index decreased by 3.9 in the valsartan group and by 3.8 in the control group ( $P=.84$  for the group comparison).

**Conclusions:** In patients with diastolic dysfunction, treatment of hypertension based on valsartan did not lead to any different effects on the myocardial relaxation velocity at 38 weeks of follow-up compared to antihypertensive treatment without an RAAS inhibitor. Both treatment groups obtained similar benefit in terms of change from baseline myocardial relaxation velocity. In the study population, hypertension was very mild and few patients had left ventricular hypertrophy; it is not known what the effect of RAAS inhibitors might be in patients with more severe hypertension or left ventricular hypertrophy.

### Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Study

*Presented by Jean-Claude Tardif, Montreal, Canada*

See full publication in: JAMA 2007, March 26 [Epub ahead of print].

**Introduction:** High density lipoprotein cholesterol (HDL-C) is an inverse predictor of coronary atherosclerosis. Preliminary data suggest that infusions of high density lipoprotein (HDL) can induce regression of atherosclerosis. The aim of this study was to investigate the effects of reconstituted HDL on plaque load, assessed by intravascular ultrasound (IVUS).

**Methods:** Between July 2005 and October 2006, a randomized study was performed in 17 centers in Canada. In total, 183 patients were included. All patients underwent IVUS at baseline and 2 to 3 weeks after the last treatment infusion. Overall, 145 patients had repeat IVUS studies at 6 weeks. Sixty patients were randomized to receive 4 weekly injections of placebo (saline), 111 to receive 40 mg/kg of reconstituted HDL (CSL-111), and 12 to receive 80 mg/kg of CSL-111. The main efficacy outcome measure was change in percent atheromatous plaque volume. Other predefined endpoints were absolute changes in plaque volume and change in normalized atheromatous plaque volume by IVUS, as well as the coronary score in quantitative coronary angiography.

**Results:** Patients in the treatment group with a high dose of CSL-111 were withdrawn prematurely from the study due to abnormal liver function test findings. The percentage change in atheroma volume was  $-3.4\%$  with CSL-111 and  $-1.6\%$  for placebo ( $P=.48$  between groups;  $P<.001$  compared to baseline values in the CSL-111 group). The absolute change in atheroma volume was  $-5.3 \mu\text{L}$  with CSL-111 and  $-2.3 \mu\text{L}$  for placebo ( $P=.39$  between groups;  $P<.001$  compared to baseline values in the CSL-111 group). Mean changes in the normalized plaque volume estimated by IVUS ( $-0.0097$  with CSL-111 and  $0.0128$  for placebo) and the mean changes in the coronary score in quantitative coronary angiography ( $-0.039$  mm with CSL-111 and  $-0.071$  mm for placebo) were significantly different between groups ( $P=.01$  and  $P=.03$ , respectively). Administration of 40 mg/dL of CSL-111 caused a mild and self-limiting transaminase elevation, but it was clinically well tolerated.

**Conclusions:** Reconstituted HDL administered in short infusions led to nonsignificant percent decreases in atheromatous plaque volume and absolute changes in plaque volume with respect to placebo, but it did significantly improve the normalized plaque volume and the coronary score in quantitative coronary angiography. Raising LDL levels remains a valid goal in the treatment of vascular disease, and further studies on intravenous infusion of HDL with clinical outcomes would seem to be warranted.

### Rating Atherosclerotic Disease Change by Imaging With a New CETP Inhibitor 1 (RADIANCE-1) Study

*Presented by John J. Kastelein, Amsterdam, the Netherlands*

**Background:** The objective of the study was to assess the effect of torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP), added to atorvastatin, and to compare the effect with that of atorvastatin alone on atherosclerotic progression in patients with heterozygous familial hypercholesterolemia.

**Methods:** After an initial run-in phase of 6 to 14 weeks in which all patients were treated with atorvastatin with doses titrated up to target concentrations recommended by the National Cholesterol Education Program, the patients were randomized to receive torcetrapib (60 mg;  $n=450$ ) added to atorvastatin, or atorvastatin alone plus placebo ( $n=454$ ). Carotid ultrasound imaging was done before randomization and every 6 months for the 24 months of follow-up.

**Results:** The mean lipid concentrations were as follows: HDL, 52 mg/dL; low density lipoprotein (LDL), 138 mg/dL; total cholesterol, 213 mg/dL, and triglycerides, 97 mg/dL. The mean atorvastatin dose in the study was 56.5 mg.

At the end of the study, HDL had increased to 81.5 mg/dL in the torcetrapib group but remained at 52 mg/dL in the group receiving atorvastatin monotherapy ( $P<.001$ ). Likewise, the decrease in LDL was greater in the torcetrapib group (final LDL, 115.1 mg/dL vs 143.2 mg/dL in the atorvastatin monotherapy group;  $P<.001$ ). The other lipid parameters also favored the torcetrapib group. There were no differences in the primary outcome measure: comparison of the annual change in the carotid intima-media thickness in 12 carotid segments in the 2 treatment groups (0.0053 mm/year in the torcetrapib group vs 0.0047 mm/year in the atorvastatin monotherapy group;  $P=.87$ ). The change in maximum carotid intima-media thickness at the 4 points measured in the common carotid artery showed disease progression in the torcetrapib group and regression in the atorvastatin monotherapy group (0.0040 vs  $-0.0042$  mm/year;  $P=.02$ ). Similarly, the change in mean carotid intima-media thickness at each of the 4 points measured in the common carotid artery also showed progression (0.0038 mm/year vs  $-0.0014$  mm/year;  $P=.005$ ).

The incidence of serious adverse events was greater in the torcetrapib group (12.4% vs 8.6%) and the incidence of serious cardiovascular events was also greater in this group (5.3% vs 2.4%). The final systolic blood pressure was 2.8 mm Hg greater in the torcetrapib group compared to the atorvastatin monotherapy group (121.7 mm Hg vs 119.0 mm Hg).

**Conclusions:** In patients with heterozygous familial hypercholesterolemia, treatment with torcetrapib added to atorvastatin was not associated with decreased disease progression or disease regression compared to atorvastatin monotherapy after 2 years of treatment.

### Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) Study

Presented by Steven E. Nissen, Cleveland, United States

See full publication in *N Engl J Med*. 2006;356:1304-16.

**Background:** Levels of high-density lipoprotein cholesterol (HDL-C) are inversely proportional to

cardiovascular risk. Torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP), increases HDL-C levels, but the functional effects associated with this mechanism remain unclear.

**Methods:** The investigators performed intravascular ultrasound studies on 1188 patients with coronary artery disease. After treatment with atorvastatin to lower low-density lipoprotein cholesterol (LDL-C) levels to below 100 mg/dL (2.59 mmol/L), patients were randomly assigned to receive either atorvastatin monotherapy or atorvastatin plus 60 mg of torcetrapib a day. After 24 months, disease progression was determined by repeating the intravascular ultrasound study in 910 patients (77% of all patients).

**Results:** After 24 months, the effect of torcetrapib and atorvastatin compared to atorvastatin monotherapy was a relative increase in HDL-C of approximately 61% and a relative decrease of 20% in LDL-C. The ratio of LDL-C to HDL-C was therefore less than 1.0. Torcetrapib also produced an increase of 4.6 mm Hg in systolic blood pressure. The percent atheroma volume (the primary efficacy outcome measure) increased 0.19% in the group receiving atorvastatin monotherapy and 0.12% in the group that received torcetrapib plus atorvastatin ( $P=.72$ ). A secondary outcome measure, the variation in normalized atheroma volume, showed a slightly favorable effect for torcetrapib ( $P=.02$ ), but significant differences were not observed in the variation of atheroma volume of the diseased vessel segment.

**Conclusions:** The CETP inhibitor torcetrapib caused a substantial increase in HDL-C and a decrease in LDL-C. It was also associated with increased blood pressure, without a significant decrease in the progression of coronary atherosclerosis. This lack of efficacy could be linked to the mechanism of action of this class of drugs or to specific adverse effects of the molecule.

### Measuring Effects of Intima-Media Thickness an Evaluation of Rosuvastatin (METEOR) Study

Presented by John R. Crouse III, Winston-Salem, United States

See the full publication in *JAMA*. 2007;297:1344-53.

**Background:** The arteriosclerotic process is often in advanced stages when clinical symptoms appear, and it is not known whether preventative treatment is beneficial in patients with a low Framingham cardiovascular risk score and mild-moderate subclinical

arteriosclerosis. The aim of this study was to assess whether treatment with statins can slow progression and/or induce regression in the carotid intima-media thickness at 2 years.

**Methods:** A total of 984 individuals were recruited for this randomized, prospective, double-blind, placebo-controlled study. The only risk factors for cardiovascular disease were age (mean, 57 years) or 10-year Framingham cardiovascular risk score of 10%. Patients had a slight increase in carotid intima-media thickness (from 1.2 to 3.2 mm) and elevated LDL-C (mean, 154 mg/dL). The study was performed in 61 primary care facilities in the United States and Europe between August 2002 and May 2006.

Patients were randomized to receive either 40 mg/day of rosuvastatin or placebo. The primary outcome measure was rate of change of carotid intima-media thickness (assessed by 2-dimensional ultrasound) in 12 carotid sites. Secondary outcome measures included changes in maximum carotid intima-media thickness in the common carotid artery, the carotid bulb, and the internal carotid artery, and mean carotid intima-media thickness in the common carotid artery. Regression of carotid intima-media thickness was only assessed in the rosuvastatin group.

**Results:** In patients in the rosuvastatin group, mean (SD) baseline LDL-C was 155 (24.1) mg/dL. This level declined to 78 (27.5) mg/dL (mean reduction of 49%,  $P<.001$  with respect to placebo). The change in maximum carotid intima-media thickness in 12 carotid sites was  $-0.0014$  mm/year (95% confidence interval [CI],  $-0.0041$  to  $0.0014$ ) in the rosuvastatin group and  $0.0131$  mm/year (95% CI,  $-0.0087$  to  $0.0174$ ) in the placebo group ( $P<.001$ ). In the rosuvastatin group, the change in maximum carotid intima-media thickness in the common carotid was  $-0.0038$  mm/year (95% CI,  $-0.0064$  to  $-0.0013$ ;  $P<.001$ ),  $0.0040$  mm/year (95% CI,  $-0.0090$  to  $0.0010$ ) in the carotid bulb ( $P<.001$ ), and  $0.0039$  mm/year (95% CI,  $-0.0090$  to  $0.0088$ ;  $P<.02$ ) in the internal carotid artery. The mean change in carotid intima-media thickness in the rosuvastatin group in the common carotid artery was  $0.0004$  mm/year (95% CI,  $-0.0011$  to  $0.0019$ ;  $P<.001$ ). All  $P$  values reflect comparisons with the placebo group. Overall, rosuvastatin was well tolerated and the adverse effects were infrequent (6 participants [0.86%] had 8 events [1.1%] during 2 years of follow-up).

**Conclusions:** In middle-aged adults with Framingham cardiovascular risk scores less than 10% with evidence of subclinical arteriosclerosis, rosuvastatin yielded statistically significant reductions in the rate of progression of maximum carotid intima-media thickness compared to placebo during the 2-year follow-up. Rosuvastatin did not induce disease regression. Larger studies with long-term follow-up are needed to determine the clinical implications of these findings.

## ISCHEMIC HEART DISEASE

### Metabolic Efficiency With Ranolazine for Less Ischemia in NSTEMI (MERLIN TIMI) 36 Study

Presented by David Morrow, Boston, United States

**Background:** Ranolazine has been used to treat angina in patients with chronic angina, but its effect in acute coronary syndrome (ACS) remains unknown. The aim of this study was to assess the safety and efficacy of long-term treatment with ranolazine compared to placebo in patients with non-ST-elevation ACS (nSTEMI-ACS).

**Methods:** Patients were randomized in a double-blind design to receive ranolazine ( $n=3279$ ) or matching placebo ( $n=3281$ ). Ranolazine was administered intravenously at a loading dose of 200 mg for 1 hour followed by an intravenous infusion of 80 mg/h, with a subsequent long-term oral treatment phase with ranolazine (1000 mg every 12 h) or placebo during follow-up (median, 348 days). During the first week of treatment, continuous outpatient electrocardiographic (ECG) monitoring was performed.

**Results:** Overall, 51% of the patients presented non-ST-elevation acute myocardial infarction (AMI). The median time from onset of symptoms until randomization was 24 hours. A third of the patients had a history of diabetes and a third had a history of prior AMI. Coronary angiography was done in 59% of the patients during their initial stay in hospital.

The primary outcome measure, a composite of cardiovascular death, AMI, and recurrent ischemia, was reached in 21.8% of the patients treated with ranolazine and 23.5% of placebo patients (hazard ratio [HR], 0.92; 95% CI, 0.83-1.02;  $P=.011$ ). Among the individual components of the composite endpoint, there were no differences in the incidence of cardiovascular death or AMI (10.4% vs 10.4%; HR, 0.99;  $P=.87$ ), but recurrent ischemia was less frequent in the ranolazine group (17.3% vs 20.0%; HR, 0.87;  $P=.03$ ). The incidence of cardiovascular death, AMI, severe recurrent ischemia, or positive Holter findings at 30 days was 23.1% among the patients treated with ranolazine and 25.1% in the placebo group ( $P=.055$ ). Fewer patients in the ranolazine group required higher doses of angina treatment (10% vs 12.2%;  $P=.006$ ). Likewise, progressive angina was reported less often in the ranolazine group (4.2% vs 5.9%;  $P=.023$ ).

All-cause death was similar for both groups (HR, 0.99;  $P=.91$ ), as was the composite endpoint of death and cardiovascular hospitalization (HR, 0.98;  $P=.67$ ). Symptomatic arrhythmias were documented in 99 patients in the ranolazine group and 102 in the placebo group ( $P=.84$ ). Clinically significant arrhythmias were less common in the ranolazine group (73.7% vs 83.1%;

$P < .001$ ). Syncope was more common in the ranolazine group (3% vs 2%;  $P = .01$ ).

**Conclusions:** In patients with nSTE-ACS, treatment with ranolazine was not associated with differences with respect to placebo in the incidence of the composite endpoint of cardiovascular death, AMI, and recurrent ischemia, after a median follow-up of 1 year.

## Aggressive Reduction of Inflammation Stops Events (ARISE) Study

*Presented by Jean-Claude Tardif, Montreal, Canada*

**Background:** The aim of this study was to compare the effect of treatment with the new antioxidant succinobucol with placebo in high-risk patients with recent acute coronary syndrome (ACS).

**Methods:** In this prospective, randomized, double-blind, placebo-controlled study, patients were randomized to receive succinobucol (300 mg/day,  $n = 3078$ ) or placebo ( $n = 3066$ ) after a 14-day run-in treatment phase with placebo. The primary outcome measure was a composite of cardiovascular death, cardiac arrest, AMI, stroke, unstable angina, and coronary revascularization at 2 years.

**Results:** On enrollment, 72% of the patients had suffered prior AMI and 83% had undergone some type of coronary revascularization. Overall, 37% of the patients had been diagnosed with diabetes. At baseline, mean LDL-C was 88 mg/dL and mean HDL-C was 45 mg/dL. In the group treated with succinobucol, LDL-C increased and HDL-C decreased, whereas the group assigned to placebo did not show changes in these parameters.

There were no differences in the primary composite endpoint of the study (17.2% with succinobucol vs 17.3% with placebo; hazard ratio [HR], 1.00;  $P = .985$ ). The secondary endpoint, a composite of cardiovascular death, cardiac arrest, AMI, or stroke occurred less frequently in the active treatment group (6.7% with succinobucol vs 8.2% with placebo; HR, 0.81;  $P = .028$ ). The incidence of newly diagnosed diabetes was lower in the succinobucol group (1.6% vs 4.2% with placebo;  $P = .0001$ ). The incidence of heart failure was greater in the succinobucol group ( $n = 107$  vs  $n = 83$ ). The incidence of serious adverse events was similar in both groups (31% with succinobucol vs 29% with placebo).

**Conclusions:** In high-risk patients with recent ACS, treatment with the new antioxidant succinobucol was not associated with differences in the incidence of the primary outcome composite measure of cardiovascular death, cardiac arrest, AMI, stroke, unstable angina, and coronary revascularization after 2 years of follow-up. Whereas some secondary endpoints, such as incidence of newly diagnosed diabetes or the composite endpoint of

cardiovascular death, cardiac arrest, AMI, or stroke occurred less frequently in the succinobucol group, others such as the incidence of heart failure or unstable angina were more common with succinobucol. Moreover, the increase in LDL-C and the decrease in HDL-C in patients treated with succinobucol were unexpected findings whose impact on the incidence of atherosclerotic events should be assessed.

## Direct Inhibition of D Protein Kinase C Enzyme to Limit Total Infarct Size in Acute MI (DELTA MI) Study

*Presented by Matthew T. Roe, Durham, United States*

**Background:** The objective of this study was to assess treatment with the new  $\Delta$ -protein kinase C inhibitor KAI-9803 in comparison with placebo in patients with ST-elevation acute myocardial infarction (AMI) undergoing primary percutaneous intervention (PCI).

**Methods:** The investigators randomized 154 patients 2:1 to receive KAI-9803 ( $n = 102$ ) at one of 4 increasing doses (0.05, 0.5, 1.25, and 5 mg) or placebo ( $n = 52$ ). The drug was administered in 2 intracoronary injections, one before and one after PCI.

**Results:** The median area under curve of creatine kinase MB isoenzyme (CK-MB) was always less than placebo in all the KAI-9803 dose groups (0.05 mg, 4.001 vs 4.858 ng/mL; 0.5 mg, 5.226 vs 6.934 ng/mL; 1.25 mg, 5.740 vs 7.352 ng/mL; 5.0 mg, 6.662 vs 8.230 ng/mL). However, these differences were not statistically significant. The infarct size in the single photon emission computed tomography (SPECT) at 14 days was smaller, although not significantly so, in the 0.5 mg and 1.25 mg dose groups compared to placebo (23% vs 29.5% and 32.5% vs 43%, respectively), but was no different to placebo in the lowest dose group (25.5% vs 33.5%) or the highest dose group (45.5% vs 30%). Likewise, TIMI myocardial perfusion score of 3 after PCI was most frequent in the KAI-9803 0.5 and 1.25 mg dose groups compared to placebo (72.2% vs 53.8% and 69.6% vs 45.4%, respectively), but was no different to placebo in the low-dose group (60.0% vs 72.7%) or the high-dose group (48.0% vs 61.5%).

After 6 months of follow-up, there were no differences in the incidences of mortality or heart failure. The frequency of serious adverse events was similar between KAI-9803 groups and placebo. All patients received both injections of study medication.

**Conclusions:** In patients with ST-elevation AMI who undergo primary PCI, treatment with the new  $\Delta$ -protein kinase C inhibitor KAI-9803 by intracoronary injection appeared to be associated with lower levels of CK-MB

compared to placebo, although the differences were not statistically significant. There were no unfavorable findings in the safety analysis, although much larger studies would be necessary to fully evaluate the safety profile.

### **Tilarginine Acetate in a Randomized International Study in Unstable Patients With Cardiogenic Shock (TRIUMPH) Study**

*Presented by Judith S. Hochman, New York, United States*

**Background:** In the SHOCK-2 study, the nitric oxide synthase (NOS) inhibitor tilarginine showed beneficial hemodynamic effects in patients with cardiogenic shock as a result of acute myocardial infarction (AMI). The aim of this study was to assess the impact on mortality of treatment with tilarginine in comparison with placebo in patients in shock due to AMI.

**Methods:** Patients were randomized in a double-blind design to receive treatment with tilarginine (1 mg/kg bolus followed by 5-hour infusion; n=206) or placebo (n=190).

**Results:** The study was stopped early after a futility analysis. At the time of enrollment in the study, the median ejection fraction was 27% in both groups. The median time between AMI and shock was 4.6 hours, and the time from shock until reperfusion was 1.4 hours. The culprit artery was the left anterior descending artery in 58% of the patients and the left coronary artery in 12%. Balloon counterpulsation was used in 90% of the patients, and 12% received assist device support.

There were no differences between groups in terms of the primary outcome measure, 30-day mortality (48% with tilarginine vs 42% with placebo, risk ratio [RR], 1.14;  $P=.24$ ) or 6-month mortality (58% vs 59%;  $P=.80$ ). The incidence of heart failure at 30 days was 48% in the tilarginine group and 51% in the placebo group ( $P=.51$ ) and recurrence of AMI was 4.0% and 3.9%, respectively ( $P=.95$ ). Similarly, there were no differences in the frequency of resolution of shock (66% vs 61%;  $P=.31$ ) or shock duration (median duration, 156 h with tilarginine vs 190 hours with placebo;  $P=.16$ ). The change in systolic blood pressure at 2 hours was greater in the tilarginine group compared to placebo (increase of 12.0/5.0 vs 7.0/1.0 mm Hg).

**Conclusions:** In patients with cardiogenic shock after AMI, treatment with the NOS inhibitor tilarginine was not associated with differences in 30-day mortality in comparison with placebo. Prognosis in patients with shock after AMI continues to have poor prognosis with limited therapeutic options.

## **HEART FAILURE**

### **Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Study**

*Presented by Marvin A. Konstam, Boston, United States*

See the full publication in JAMA. 2007;297:1319-31.

**Introduction:** Vasopressin is a mediator of fluid retention in heart failure. Tolvaptan, a vasopressin V2-receptor blocker, could be a useful drug in the treatment of heart failure. The aim of this study was to investigate the effects of tolvaptan in patients admitted to hospital for heart failure.

**Methods:** The EVEREST study was a randomized, double-blind, placebo-controlled study in which the events occurring during follow-up were reported. The study population comprised 4133 patients hospitalized for heart failure who were initially included in 2 studies with short-term follow-up, randomized in 359 centers in North America, South America, and Europe between October 2003 and February 2006. In this study, patients continued treatment with long-term follow-up. Patients were randomized within 48 hours of admission to receive tolvaptan, 30 mg/day orally (n=2072) or placebo (n=2061) for at least 60 days in addition to the normal medication. There were 2 primary outcome measures: all-cause mortality (superiority and non inferiority analysis) and cardiovascular death plus hospitalization for heart failure (superiority analysis only). The secondary criteria included changes in the degree of dyspnea, body weight, and edema.

**Results:** During mean follow-up of 9.9 months, 537 patients died in the tolvaptan group (25.9%) compared to 543 in the placebo group (26.3%) (hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.87-1.11;  $P=.68$ ). The upper confidence interval for the difference in mortality was within the predefined limit of 1.25 for noninferiority ( $P<.001$ ). The composite endpoint of cardiovascular death or hospitalization occurred in 871 patients in the tolvaptan group (42.0%) and in 829 patients in the placebo group (40.2%; HR, 1.04; 95% CI, 0.95-1.14;  $P=.55$ ). The single-event secondary endpoints of cardiovascular death and hospitalization, and the extent of deterioration in heart failure also showed no differences. Tolvaptan significantly improved secondary criteria such as subjective dyspnea on the first day of treatment, body weight on day 1, and edema at 7 days. In patients with hyponatremia, sodium levels increased significantly. The overall score on the Kansas City Cardiomyopathy Questionnaire had not improved in the week after discharge from hospital, but the effect of tolvaptan

on sodium concentrations and weight loss persisted for a long time after discharge. Tolvaptan caused an increased sensation of thirst and dry mouth, but the frequency of serious adverse events was similar in both groups.

**Conclusion.** Use of tolvaptan in the initial treatment of patients hospitalized for heart failure had no effect on long-term mortality or cardiovascular death.

### Follow-Up Serial Infusions of Nesiritide for the Management of Patients With Heart Failure (FUSION II) Study

*Presented by Clyde W. Yancy, Dallas, United States*

**Background:** Nesiritide, a natriuretic peptide B analogue, is approved in the United States for treating acute heart failure but not chronic heart failure. The results of previous studies have generated uncertainty about the safety of the drug, particularly in terms of kidney failure and mortality. The aim of this study was to assess outpatient treatment with repeated doses of nesiritide compared to placebo.

**Methods:** In this randomized, double-blind study, patients were randomized 2:1 to receive nesiritide in an outpatient setting 1 or 2 days a week (2 µg/kg boluses followed by an infusion of 0.01 µg/kg/min for 4–6 h; n=605) or placebo (n=306) for 12 weeks. After 12 weeks of active treatment, patients entered a 4-week phase of progressive dose reduction and finally an additional 8-week follow-up phase. The patients also received standard treatment for heart failure at the discretion of their treating physician.

**Results:** At the time of enrollment in the study, 47% of the patients were in functional class III and 53% in class IV. The etiology of heart failure was ischemic heart disease in 64% of the patients. The mean baseline left ventricular ejection fraction (LVEF) was 25%, 39% of the patients were carriers of implantable cardioversion defibrillators (ICDs), and 74% had a history of coronary artery disease. Diabetes had been diagnosed in 51%.

There were no differences in the primary outcome measure — a composite of all-cause mortality and hospitalization for cardiovascular or renal disease (36.7% with nesiritide vs 36.8% with placebo; hazard ratio, 1.03;  $P=.79$ ). Among the components of this composite endpoint, there were no differences in mortality (9.5% with nesiritide vs 9.6%;  $P=.98$ ) or hospitalizations for cardiovascular or renal disease (32.9% vs 33.9%;  $P=.95$ ). The mean number of hospitalizations was 1.0 in the nesiritide group and 0.8 in the placebo group. There were no differences in the measures of quality of life.

Drug-related adverse events were reported more frequently in the nesiritide group (42.0% vs 27.5%;  $P<.01$ ), essentially because of hypotension, but there were no differences in the incidence of serious drug-related adverse events (8.0% vs 8.2%). The frequency of creatinine elevations greater than 0.5 mg/dL was smaller in the nesiritide group compared to placebo (32% vs 39%;  $P<.05$ ).

**Conclusions:** In patients with chronic decompensated heart failure, treatment with serial infusions of nesiritide in an outpatient setting for 12 weeks was not associated with differences in the incidence of the primary outcome measure of death and hospitalization for cardiovascular or renal disease in comparison with placebo.

### Survival and Prognosis: Investigation of *Crataegus* Extract WS 1442 in Congestive Heart Failure (SPICE) Study

*Presented by Christian J.F. Holubarsch, Vad Krozingen, Germany*

**Background:** The extract of *Crataegus* (commonly known as hawthorn) contains 17% to 20% of oligomeric procyanidins, compounds with proven relaxing effect on the smooth muscle of the vascular wall. This product (WS-1442), used in traditional medicine in eastern European countries, improved the functional parameters of patients with mild forms of heart disease according to initial studies although this benefit was not confirmed in the HERB-CHF study reported in 2004. The aim of this study was to assess the effect of the *Crataegus* extract on the survival of patients with moderate heart failure due to left ventricular systolic dysfunction.

**Methods:** In total, 2681 patients with heart failure in functional class II to III and a left ventricular ejection fraction (LVEF) less than or equal to 0.35 were randomized to receive 900 mg/day of WS-1442 or placebo for 2 years. All patients also received standard treatment for heart failure, which included diuretics in 85%, angiotensin converting enzyme (ACE) inhibitors in 83%, β-blockers in 64%, digitalis derivatives in 57%, and aldosterone antagonists in 39%. The primary outcome measure was a composite of cardiac mortality, AMI, and hospitalization for heart failure.

**Results:** The primary outcome measure at 2 years was reached in 28% of the patients with active treatment and in 29% of the control group ( $P=NS$ ). However, cardiac mortality at 6 and 18 months showed a significant decrease in the group treated with WS-1442 (relative reductions of 41% [ $P=.009$ ] and 20% [ $P=.046$ ], respectively). In contrast, after 12 and 24 months of follow-up, the decrease in mortality of 18% and 10%, respectively, was not



significant. In the prospectively defined subgroup analysis according to ejection fraction and etiology of the heart disease, the beneficial effect was found to be limited to those patients with the worst ejection fractions (25%-35%) and to the 70% of patients with ischemic heart disease.

In the safety analysis, the number of adverse events and serious adverse events did not differ in the 2 study groups (overall, 68% had adverse events and 40% serious adverse events).

**Conclusions:** In patients with mild—moderate heart failure due to left ventricular systolic dysfunction, the *Crataegus* extract did not show a beneficial effect on the primary outcome measure of the study, a composite of cardiac death, AMI, and hospitalization for heart failure. WS-1442 administered concomitantly with standard treatment for heart failure showed a favorable safety profile.

## ARRHYTHMIAS

### T-Wave Alternans in Patients With Heart Failure (ALPHA) Study

*Presented by Gaetano M. de Ferrari, Pavia, Italy*

**Background:** Although implantable cardioverter defibrillators (ICDs) have been shown to be effective at preventing mortality due to serious ventricular arrhythmias, the selection criteria for candidates for this very costly treatment are still not well defined. Specifically, it is necessary to better identify which patients with heart failure are at greatest risk of serious ventricular arrhythmias. The objective of this study was to assess the predictive role of the presence of abnormal T-wave alternans in patients with nonischemic cardiomyopathy through comparison with the group without abnormal T-wave alternans.

**Methods:** The study included patients with nonischemic cardiomyopathy in functional class II to III and an ejection fraction less than 40%. Serious arrhythmias and death were reported during follow-up, which lasted for 18 to 24 months. The patients did not have a prior history of life-threatening ventricular arrhythmias.

**Results:** Abnormal T-wave alternans were found in 65% of the 446 patients included (200 patients were negative for T-wave abnormalities and, in 92, intermediate findings were considered pathological). At the time of enrollment, the duration of heart disease was 4 years. The patients with abnormal T-wave alternans were older (60 years vs 57 years), had a slightly lower LVEF (29% vs 31%), greater incidence of left bundle branch block

(LBBB) in the ECG, and were more frequently in functional class III.

The primary outcome measure, a composite of cardiac death or serious arrhythmias, was more frequent in the patients with T-wave abnormalities compared to those with normal T-wave findings (hazard ratio [HR], 4.01; 95% CI, 1.41-11.41;  $P=.002$ ). The negative predictive value of normal T-wave alternans findings was 97.3% at 18 months for the primary outcome measure. Likewise, overall mortality was also greater in patients with abnormal T-wave alternans ( $n=25$  vs  $n=3$ ; HR, 4.60; 95% CI, 1.39-1.25;  $P=.002$ ). Similar findings were reported for the composite of arrhythmia-related death or serious ventricular arrhythmias (HR, 5.53; 95% CI, 1.29-23.65;  $P=.004$ ). Given that the populations compared were different—patients in the group with abnormal T-wave alternans had more severe heart failure—an adjusted multivariate model was constructed for the clinical variables associated with greatest risk (age, LVEF, LBBB, class III functional status), and the presence of abnormal T-wave alternans was still associated with a 3-fold greater risk of cardiac death or serious ventricular arrhythmias.

**Conclusions:** In patients with nonischemic cardiomyopathy, the presence of abnormal T-wave alternans was associated with greater risk (4-fold higher in the unadjusted analysis and 3-fold higher in the adjusted one) of cardiac death or life-threatening arrhythmias in the 2-year follow-up, compared to a population with normal T-wave alternans. T-wave alternans provides additional information which is independent of that provided by other risk markers in the prediction of serious arrhythmic events in this group of patients.

## PERCUTANEOUS CORONARY INTERVENTION

### Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Study

*Presented by William E. Boden, Buffalo, United States*

See the full publication in *N Engl J Med.* 2007;356:1503-16.

**Background:** In patients with stable coronary artery disease, it is still not clear whether the therapeutic strategy of performing percutaneous coronary intervention (PCI) plus optimal medical treatment with intensive pharmacotherapy and lifestyle interventions is better than optimal medical treatment alone in terms of decreasing the risk of cardiovascular events.

**Methods:** A randomized trial was done in which 2287 patients with objective signs of myocardial ischemia and significant coronary artery disease participated in 50 centers in the United States and Canada. Between 1999 and 2004, we assigned 1149 patients to undergo PCI along with optimal medical treatment (PCI group) and a further 1138 to receive optimal medical treatment alone (medical treatment group). The primary outcome measure was a composite of all-cause mortality and nonfatal myocardial infarction during a follow-up period of between 2.5 and 7.0 years (median, 4.6 years).

**Results:** Overall, 211 events corresponding to the primary outcome measure were reported in the PCI group compared to 202 in the medical therapy group. The cumulative rate of events after 4.6 years was 19.0% in the PCI group and 18.5% in the medical therapy group (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87-1.27;  $P=.62$ ). No significant differences were observed between the PCI group and the group receiving medical therapy according to the composite outcome measure of death, myocardial infarction, and stroke (20% vs 19.5%; hazard ratio, 1.05; 95% CI, 0.87-1.27;  $P=.62$ ); hospitalization for acute coronary syndrome (12.4% vs 11.8%; hazard ratio, 1.07; 95% CI, 0.84-1.37;  $P=.56$ ), or myocardial infarction (13.2% vs 12.3%; hazard ratio, 1.13; 95% CI, 0.89-1.43;  $P=.33$ ).

**Conclusions:** As an initial therapeutic strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other serious cardiovascular events when used in combination with optimal medical therapy in comparison with medical therapy alone.

### Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes (ARMYDA-ACS) Study

*Presented by Germano di Sciascio, Rome, Italy*

See the full publication in *J Am Coll Cardiol*. 2007;49:1272-8.

**Background:** Randomized studies have shown that administration of atorvastatin in patients with stable angina who undergo elective percutaneous coronary intervention (PCI) reduces the incidence of acute myocardial infarction (AMI) during the intervention. It is not known whether this treatment is also effective in patients with acute coronary syndrome (ACS). The aim of this study was to investigate the possible protective effect of atorvastatin in patients with PCI due to ACS.

**Methods:** In total, 171 patients with non-ST-elevation ACS was randomized to receive treatment with

atorvastatin from before PCI (80 mg 12 hours before, followed by 40 mg immediately before the procedure;  $n=86$ ) or placebo ( $n=85$ ). All patients received loading doses of clopidogrel 600 mg, and all received subsequent long-term treatment with atorvastatin (40 mg/day). The primary outcome measure of the study was incidence of major cardiac events (death, AMI, or unplanned revascularization) at 30 days.

**Results:** The primary endpoint was met in 5% of the patients treated with atorvastatin compared to 17% in the placebo group ( $P=.01$ ); this difference was due mainly to a lower incidence of myocardial infarction (5% vs 15%;  $P=.04$ ). Elevation of CK-MB and troponin I after the procedure also occurred significantly less frequently in the atorvastatin group (7% vs 27%,  $P=.001$ ; and 41% vs 58%,  $P=.039$ , respectively). In the multivariate analysis, prior treatment with atorvastatin was associated with a decrease in risk of 88% for major adverse cardiac events at 30 days (hazard ratio, 0.12; 95% CI, 0.05-0.50;  $P=.004$ ).

**Conclusions:** The ARMYDA-ACS study showed that treatment prior to PCI, even when administered for a very short period, can improve the outcomes of patients with acute coronary syndrome treated with an early invasive strategy. These results suggest that systematic use of high doses of statins before PCI may be beneficial in patients with ACS.

### Distal-Protection Trial in Primary Percutaneous Coronary Intervention (DEDICATION) Study

*Presented by Leif Thuesen, Skejby, Denmark*

**Background:** Previous studies of distal protection devices in primary angioplasty in the setting of acute myocardial infarction (AMI) such as the EMERALD and PROMISE studies, have reported a limited effectiveness, with no evidence of decreased infarct size. The aim of this study was to evaluate treatment with the filterwire distal protection device in comparison with conventional intervention in patients with ST-elevation AMI who had undergone percutaneous coronary intervention (PCI). Another objective of the study was to compare PCI using drug-eluting stents and using conventional stents.

**Methods:** We randomly assigned 626 patients with primary PCI for AMI for placement of the filterwire distal protection device ( $n=312$ ) or no device placement ( $n=314$ ). The patients were then randomized once again to receive a drug-eluting stent or a conventional stent (data not presented).

**Results:** Overall, 62% of the patients had single-vessel disease. Glycoprotein IIb/IIIa inhibitors were used in 96% of the cases. Almost two thirds of the patients (62%)

had coronary artery occlusion. Only 10% of the patients were diagnosed with diabetes. In the subgroup randomized to receive the filterwire device, success was achieved in 81% of the procedures.

There were no differences in the rate of resolution of ST-segment elevation greater than or equal to 70% at 90 minutes after PCI in continuous ECG monitoring in the distal protection group compared to the group with no protection (76% vs 72%;  $P=.29$ ). Similarly, there were no differences in the time elapsed until resolution of the ST-segment elevation (mean of 26 minutes in both groups). There were also no differences in peak CK-MB (236 vs 238  $\mu\text{g/L}$ ) or troponin T (6.72 vs 6.69  $\mu\text{g/L}$ ). TIMI flow after PCI was slight, but significantly greater in the distal protection group (95% vs 88% with TIMI>II;  $P=.01$ ). There were no differences in the wall-motion index (1.6 in both groups) or LVEF at the time of discharge. The incidence of major adverse cardiac events at 30 days was 5.4% in the group with distal protection and 3.2% in the convention PCI group ( $P=.17$ ).

**Conclusions:** In patients with ST-elevation AMI who underwent PCI, use of the filterwire distal protection device did not show any benefit in terms of ST-segment resolution or peak cardiac enzymes compared to conventional PCI.

### Comparison of Everolimus-Eluting Stent With Paclitaxel-Eluting Stent in Percutaneous Coronary Intervention (SPIRIT III) Study

*Presented by Gregg W. Stone, New York, United States*

**Background:** The aim of this study was to assess treatment with an everolimus-eluting stent (EES) compared to treatment with a paclitaxel-eluting stent (PES) in patients undergoing percutaneous coronary intervention (PCI) for de novo coronary lesions.

**Methods:** Patients were randomized 2:1 to receive EES ( $n=669$ ) or PES ( $n=333$ ). In a subgroup of 564 patients, scheduled angiographic follow-up was done after 8 months. Of these patients, 240 were studied by intravascular ultrasound. Aspirin was administered at a loading dose of  $\geq 300$  mg and then  $\geq 80$  mg/day, along with clopidogrel at a loading dose of  $\geq 300$  mg followed by 75 mg/day for 6 months.

**Results:** Stents were implanted in a single lesion in 84% of the patients and in 2 lesions in 16%. The lesion was located in the left anterior descending artery in 42% of the patients. One fourth of the patients had diabetes. The minimum lumen diameter before the procedure was 0.82 mm in the EES group and 0.83 mm in the PES group. On average, 1.3 stents were implanted per patient.

The primary outcome measure, in-stent late lumen loss at 8 months, was lower in the EES group than in the PES group (0.14 vs 0.28 mm;  $P<.001$  for the noninferiority analysis and  $P=.004$  for the superiority analysis). The minimum lumen diameter of the stented segment was 2.22 mm in the EES group and 2.12 mm in the PES group ( $P=.08$ ). Binary restenosis occurred in 4.7% of the lesions treated with EES and in 8.9% of those treated with PES ( $P=.07$ ). In the intravascular ultrasound study, the volume of neointimal hyperplasia was 10.1 in the EES group and 20.9 in the PES group. There were no differences in the rate of incomplete apposition at 8 months (25.6% with EES and 16.3% with PES;  $P=.27$ ) or the lack of late-acquired incomplete apposition (1.1% vs 2.3%, respectively;  $P=.54$ ).

There were no differences in the secondary outcome measures, such as failure of target vessel (cardiac death, AMI, or revascularization of the target vessel) at 9 months (7.2% in the EES group and 9.0% in the PES group;  $P<.001$  for the noninferiority analysis and  $P=.31$  for the superiority analysis). Among the individual components of failure in the treated vessel in the EES and PES groups, cardiac death was reported in 0.5% and 0.6%, respectively ( $P=.67$ ), AMI in 2% versus 2.5%, respectively ( $P=.64$ ), and revascularization of the target vessel in 5.3% versus 6.5%, respectively ( $P=.47$ ). Revascularization of the target lesion at 9 months was reported in 2.6% of the EES group compared to 5.0% of the PES group ( $P=.053$ ). Stent thrombosis at 9 months occurred in 0.5% of the patients in the EES group and in no patients in the PES group.

**Conclusions:** In patients undergoing elective PCI for de novo coronary lesions, treatment with EES was associated with decreased late lumen loss at 8 months in the angiographic follow-up compared to PES.

### Intracoronary Stenting and Angiographic Restenosis: Promote Endothelial Cells With Estradiol (ISAR-PEACE) Study

*Presented by Julinda Mehilli, Munich, Germany*

See the full publication in *J Am Coll Cardiol*. 2007;49:1265-71.

**Background:** Estradiol favors rapid endothelialization of coronary stents in animal models, but it is not known whether the combination of this drug with rapamycin represents an advance in the technology of drug-eluting stents in terms of lower lumen loss. The aim of this study was to assess the efficacy of a rapamycin-eluting stent and 17- $\beta$ -estradiol compared to a rapamycin-eluting stent in patients with coronary disease.

**Methods:** In total, 502 patients with de novo lesions in native coronary arteries were randomized to treatment with a polymer-free estradiol plus rapamycin eluting

stent (ERES, n=252) or treatment with a rapamycin-eluting stent (RES, n=250). The primary outcome measure was in-stent late lumen loss in the angiographic follow-up. The secondary outcome measures were binary angiographic restenosis, revascularization of the culprit lesion, combined incidence of death and myocardial infarction, and incidence of stent thrombosis in the year after randomization. The study was designed to test the hypothesis of superiority of ERES compared to RES in terms of in-stent late lumen loss.

**Results:** Late lumen loss (0.52 [0.58] vs 0.51 [0.58] mm;  $P=.83$ ), incidence of binary angiographic restenosis (17.6% vs 16.9%;  $P=.85$ ), incidence of revascularization of the culprit lesion (14.3% vs 13.2%;  $P=.72$ ), combined incidence of death and infarction (7.9% vs 8.0%;  $P=.98$ ), and the incidence of stent thrombosis (0.8% vs 1.2%;  $P=.99$ ) were not significantly different between the ERES and RES groups.

**Conclusions:** Addition of estradiol to a RES did not provide any apparent benefit during the 1-year follow-up after the intervention.

### Bioabsorbable Drug-Eluting Stents for Percutaneous Coronary Intervention (ABSORB) Study

*Presented by Patrick W. Serruys, Rotterdam, the Netherlands*

**Background:** The aim of this study was to assess the usefulness of bioabsorbable stents as a platform for drug elution in patients who had undergone percutaneous coronary intervention (PCI) for treatment of a de novo coronary lesions.

**Methods:** This nonrandomized study reports the first clinical experience in humans with a bioabsorbable stent platform for drug elution. The stent releases everolimus and is designed to be reabsorbed with time. The bioabsorbable structure of the stent is made from polylactic acid, a biodegradable polyester derivative of lactic acid. The patients will be followed for 5 years and coronary angiography and intravascular ultrasound (IVUS) will be done at 180 days and 2 years.

**Results:** Of the 30 patients included initially in the study, 3 were excluded because they required a conventional stent to resolve a poor outcome of the procedure and 1 because of device failure. The baseline lesions had a minimum lumen diameter (MLD) of 1.10 mm, percent stenosis of 59%, and a length of 8.66 mm. Half the lesions treated were located in the left anterior descending artery, and 65% were of type B1. The MLD after the intervention was 2.33 mm and the mean percent stenosis was 16%.

In the angiographic follow-up at 6 months, late lumen loss was 0.44 mm, MLD was 1.88 mm, and percent

stenosis was 27%. In-stent neointimal hyperplasia in the IVUS revealed an obstruction of 5.54% with a volume of 4.26  $\mu$ L. Incomplete apposition of the stent was observed in 6 of the 26 patients (23.1%) at 6 months, and later in 7 of 26 (26.9%). The only clinical event during follow-up was non-Q-wave AMI (3.3%). There were no deaths or need for revascularization of the target lesions due to ischemia or stent thrombosis at 6 months.

**Conclusions:** This nonrandomized study of the first-in-human use of bioabsorbable everolimus-eluting stents in patients undergoing elective PCI for de novo coronary lesions shows that the procedure is feasible. Conclusions about the safety and efficacy cannot be drawn due to the small number of patients included and the short follow-up. Large-scale studies with several years follow-up will be needed to determine the role of these devices in clinical practice.

## CELL THERAPY

### Mesenchymal Stem Cell Therapy Following Acute MI

*Presented by Joshua Hare, Miami, United States*

**Background:** The aim of this study was to assess the efficacy and safety of administration of different doses of mesenchymal stem cells (MSCs) obtained from allogeneic bone marrow in comparison with placebo in patients with recent acute myocardial infarction (AMI).

**Methods:** The study included hemodynamically stable patients aged between 21 and 85 years, with a first AMI between 1 and 10 years prior to randomization, a patent culprit artery, and variable degrees of left ventricular systolic dysfunction, LVEF of 30% to 60%, hemodynamic stability in the 24 hours prior to randomization, elevations of more than 2 times the upper limit of normal of CK-MB or troponin during the index AMI, and Karnofsky score of 60 or more. Between 3 and 10 days after the AMI, patients were randomized to receive 3 increasing doses of MSCs (0.5, 1.6, or  $5 \times 10^6$  MSC/kg; n=34) or placebo (n=19). The patients were monitored continuously by ECG during the study.

**Results:** The mean baseline LVEF was 50%. Half the patients included had anterior AMI. In total, 23.5% of the patients treated with MSCs compared to 31.6% of those in the placebo group required at least one readmission to hospital. The mean number of readmissions to hospital was 0.26 in the MSC group and 0.37 in the placebo group. The mean number of adverse events was 5.3 in the MSC group and 7.0 in the placebo group. Arrhythmias were reported in 8.8% of the patients in the MSC group compared to 36.8% of those in the

placebo group. The mean number of ventricular premature beats per day and the number of patients with more than 10 ventricular premature beats was lower in the MSC group. In the spirometry tests, an improvement in the forced expiratory volume in 1 second ( $FEV_1$ ) was observed more often in the MSC-treated group. At 6 months, there were no differences in mean  $FEV_1$  in the group treated with MSCs compared to placebo. There was no relationship between cell dose and effect in the groups treated with different doses of MSCs.

**Conclusions:** In patients with recent AMI, infusion of MSCs isolated from allogeneic bone marrow was not associated with an increased number of adverse events compared to placebo. The safety profile of infusion of MSCs appears to be acceptable, with no increased incidence of arrhythmias or other types of complication, and with improved spirometric parameters. These findings justify planning similar studies on a larger scale to assess the efficacy of treatment with MSCs.