

# Summary of the Clinical Studies Reported in the 58th Scientific Session of the American College of Cardiology (Orlando, USA, March 28-31, 2009)

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In the Annual Scientific Sessions of the 58th Congress of the American College of Cardiology, 2009, the results of a number of recently concluded clinical trials of great importance were communicated in a series of special sessions (Late Breaking Clinical Trials), allowing the most important information obtained to be orally transmitted. In agreement with the editorial policy established over recent years,<sup>1-4</sup> the *Revista Española de Cardiología* here offers its readers a summary of these studies, including their aims, methods and results, as reported orally in the above special sessions. Since many of these results have not yet been fully published, the information offered here should be interpreted as preliminary. In those cases in which the full results have been published, a corresponding reference is provided.

## SUMMARY BY TOPICS

### Primary Prevention

The JUPITER study: a randomized trial on the role of rosuvastatin in the prevention of venous thromboembolism.

The TIPS study (The Indian Polycap study): effect of a "polycapsule" on the risk factors of middle-aged people without cardiovascular disease.

The AURORA study: rosuvastatin and cardiovascular events in patients subjected to hemodialysis.

A telemedicine study: continuous communication of data over the Internet by the patient compared

to follow-up via consultations for the reduction of cardiovascular risk.

### Ischemic Heart Disease

The OMEGA study: the role of omega-3 fatty acids added to current treatment for acute myocardial infarction.

The REVIVAL-3 study: erythropoietin in patients with ST elevated acute myocardial infarction subjected to percutaneous coronary intervention.

### Heart Failure

The Pre-RELAX-AHF study: the role of relaxin in the treatment of acute heart failure.

The FIX-HF-5 study: a randomized, multi-center study on the effect of electrical modulation of cardiac contractility in patients with advanced heart failure.

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### Cardiac Intervention

The PROTECT AF study: randomized study of the percutaneous closure of the left appendage compared to oral anticoagulation treatment for the prevention of ictus in patients with atrial fibrillation.

The NAPLES II study (New Approaches for Preventing or Limiting Events II): impact of a loading dose of atorvastatin before coronary intervention.

The EARLY ACS study: eptifibatide in acute coronary syndrome. A comparison of early and late, provisional administration.

Results of the NCDR-CMS registry: clinical effectiveness of coronary stents in the "real world."

### Arrhythmias

The ACTIVE A study: effect of clopidogrel combined with aspirin in patients with atrial fibrillation.

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## Heart Surgery

The STICH study (Surgical Treatment for Ischemic Heart Failure trial): coronary revascularization on its own or with ventricular reconstruction surgery.

## PRIMARY PREVENTION

### The JUPITER Study: A Randomized Trial on the Role of Rosuvastatin in the Prevention of Venous Thromboembolism

*Presented by R.J. Glynn, Boston, USA.*

**Background.** Controversy continues to surround the possibility of arterial and venous thrombosis sharing mechanisms, and debate continues with regard to what the consequences of such sharing might be. Treatments effective against one of these conditions might provide consistent benefits against the other. Several observational studies have led to variable estimates of the effect of statin treatment on the risk of thromboembolism in venous territory, but evidence from randomized controls has been lacking.

**Methods.** A total of 17 802 apparently healthy men and women with low density lipoprotein cholesterol (LDL-C) concentrations of <130 mg/dL (3.4 mmol/L) and of ultrasensitive C-reactive protein of  $\geq 2$  mg/L were randomly assigned to receive either 20 mg/day of rosuvastatin or a placebo. Follow-up was continued until the first episode of pulmonary embolism or deep vein thrombosis. Analysis proceeded on the basis of intention to treat.

**Results.** Over a median follow-up time of 1.9 (maximum 5) years, symptomatic venous thromboembolism was seen in 94 patients—34 in the rosuvastatin group and 60 in the placebo group. The rates for venous thromboembolism were 0.18 and 0.32 events for every 100 person-years of follow-up for the rosuvastatin and placebo groups respectively (hazard ratio [HR] with rosuvastatin = 0.57; 95% confidence interval [95% CI], 0.37-0.86;  $P=.007$ ). The indices for isolated venous thromboembolism (ie, produced in the absence of known neoplasm, trauma, hospitalization or surgery, were 0.10 and 0.17 (HR=0.61; 95% CI, 0.35-1.09;  $P=.09$ ), while for concomitant thromboembolism (ie, in patients with cancer, during or shortly after trauma, hospitalization, or surgery) were 0.08 and 0.16 (HR=0.52; 95% CI, 0.28-0.96;  $P=.03$ ). The rate of pulmonary embolism was 0.09 in the rosuvastatin group and 0.12 in the placebo group (HR=0.77; 95% CI, 0.41-1.45;  $P=0.42$ ), while the deep vein thrombosis rate was 0.09 and 0.20 respectively (HR=0.45; 95% CI, 0.25-0.79;  $P=.004$ ). Similar effects were seen in all subgroups examined. No significant differences

were seen between the treatment groups with regard to the incidence of hemorrhagic episodes.

**Conclusions.** In this trial, which involved apparently healthy persons, rosuvastatin significantly reduced the incidence of symptomatic venous thromboembolism.

The results of this study have been published in the form of a complete scientific paper.<sup>5</sup>

### The TIPS Study (The Indian Polycap Study): Effect of a "Polycapsule" on the Risk Factors of Middle-Aged People Without Cardiovascular Disease

*Presented by S. Yusuf, Hamilton, Canada.*

**Background.** The combination of low doses of 3 blood pressure-lowering drugs plus a statin, aspirin, and folic acid (Polycap) may reduce cardiovascular events in healthy individuals by more than 80%. The effect of Polycap treatment on blood pressure, lipid levels, heart rhythm and urinary thromboxane B<sub>2</sub> was examined, and its tolerability determined.

**Methods.** This trial, which involved 50 centers around India, enrolled 2053 people without cardiovascular disease aged between 45 and 80 years, and with only 1 risk factor. These subjects were randomized (double blind) via the use of a secure, centralized website to receive Polycap treatment, ie, a low dose of thiazide (12.5 mg), athenolol (50 mg), ramipril (5 mg), simvastatin (20 mg), and aspirin (100 mg) every day (n=412), or to receive 1 of 8 other treatments: aspirin alone, simvastatin alone, hydrochlorothiazide alone, 3 combinations of blood pressure-lowering drugs, 1 of these 3 drugs alone, or these 3 drugs plus aspirin (n=approximately 200 for all groups). The main endpoints were the LDL-C concentration (representing the effect of treatment on lipids), blood pressure (representing the effect of the anti-hypertension drugs), the heart rate (representing the effects of athenolol), urinary dehydrothromboxane B<sub>2</sub> (representing the anti-platelet effect of aspirin), and the suspension rate of each drug for safety reasons. Analysis proceeded on the basis of intention to treat.

**Results.** Compared to the groups that received no anti-hypertensives, Polycap treatment reduced systolic blood pressure by 7.4 mmHg (95% CI, 6.1-8.1) and the diastolic pressure by 5.6 mm Hg (4.7-6.4), similar to that seen in the groups that received the 3 anti-hypertensives with or without aspirin. The reduction of the blood pressure increased with the number of anti-hypertensive drugs used: 2.2/1.3 mm Hg with one drug, 4.7/3.6 mm Hg with 2, and 6.3/4.5 mm Hg with 3. Polycap treatment reduced the LDL-C concentration by 0.7 (95% CI, 0.62-0.78)

mmol/L, significantly less than that achieved with simvastatin alone (0.83 [0.72-0.93] mmol/L;  $P=.04$ ). Both reductions were greater than those seen in groups that received no simvastatin ( $P<.0001$ ). The reduction in the heart rate was similar in the Polycap group and the groups that received atenolol (7 beats/min), and in both cases was significantly greater than in the groups that received no atenolol ( $P<.0001$ ). The reduction in urinary 11-dehydrothromboxane  $B_2$  was similar in the Polycap group (283.1 ng/mmol creatinine [95% CI, 229.1-337]) and in the groups that received the 3 anti-hypertensives plus aspirin (350 ng/mmol creatinine [95% CI, 294.6-404]) or aspirin alone (348.8 ng/mmol creatinine [277.6-419.9]) compared to those that received no aspirin. The tolerability of Polycap was similar to that recorded for the other treatments; no evidence was found of poorer tolerance as the number of drugs in the capsule increased.

**Conclusions.** The Polycap formulation provides an efficient and safe way to reduce multiple risk factors and overall cardiovascular risk.

The results of this study have been published in the form of a complete scientific paper.<sup>6</sup>

### The AURORA Study: Rosuvastatin and Cardiovascular Events in Patients Subjected to Hemodialysis

*Presented by B.C. Fellström, Uppsala, Sweden.*

**Background.** Statins reduce the incidence of cardiovascular events in patients at high cardiovascular risk. However, the benefit of statins to patients subjected to hemodialysis has not been demonstrated.

**Methods.** This international, prospective, double blind, randomized, multi-center trial involved 2776 patients aged 50-80 years all of whom received maintenance hemodialysis. Patients were randomly assigned to receive either rosuvastatin 10 mg/day or a placebo. The primary endpoint was composed of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The secondary endpoints were all cause death and isolated cardiovascular events.

**Results.** After 3 months, the mean reduction in the LDL-C concentration was 43% in the patients who received rosuvastatin (base level 100 mg/dL; 2.6 mmol/L). Over a median follow-up period of 3.8 years, 396 patients of the rosuvastatin group and 408 patients of the placebo group met the conditions of the primary endpoint (9.2 events per 100 patient-years in the rosuvastatin group compared to 9.5 in the placebo group; HR=0.96; 95% CI, 0.84-1.11;

$P=.59$ ). Rosuvastatin had no effect on the individual components of the primary endpoint, neither did it have any significant effect on all cause death (13.5 compared to 14 events/100 patient-years; HR=0.96; 95% CI, 0.86-1.07;  $P=.51$ ).

**Conclusions.** In patients who required hemodialysis, rosuvastatin treatment reduced the LDL-C concentration but had no significant effect on the primary endpoint, ie, the combination of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke.

The results of this study have been published in the form of a complete scientific paper.<sup>7</sup>

### A Telemedicine Study: Continuous Communication of Data Over the Internet by the Patient Compared to Follow-up Via Consultations for the Reduction of Cardiovascular Risk

*Presented by A.A. Bove, Philadelphia, USA.*

**Background.** Telemedicine systems allow patients to inform about their blood pressure and other cardiovascular risk factors and to receive instructions based on how well they have reached the goals set out for them.

**Methods.** In this study, 388 patients trained in the sending of data via the Internet were randomly assigned to either attend a consultation with a nurse once every 4 months for 1 year, or to attend the same consultations while also sending once a week their blood pressure and other risk factor data to a central database, the provider of which replied with instructions. At the initial consultation the patients has no known cardiovascular disease and scored <10% on the Framingham 10 year cardiovascular risk scale. The primary endpoint assessed was the achievement of a 5% reduction on this scale after 1 year of follow-up.

**Results.** At 1 year of follow-up, the mean number of communications per patient in the telemedicine group was 76.2 (7.6) (6.3 per month). No significant differences were seen in the endpoint of the interventions: a 5% reduction on the cardiovascular risk scale was achieved by 10.3% (5.5%) of the patients in the consultation group and by 9.7% (6.2%) in the telemedicine group. Systolic blood pressure was reduced in both groups, but the patients with grade 1 hypertension ( $n=153$ ; 39%) who used the telemedicine service experienced a significantly greater reduction ( $P=.037$ ). The LDL-C concentration was reduced in both groups, although the telemedicine service provided no additional benefit.

**Conclusions.** The use of telemedicine for the monitoring of health variables via the sending of

patient-provider information over the Internet did not reduce overall cardiovascular risk any more than did regular consultations at the clinic. The patients in the telemedicine group with grade 1 hypertension who frequently monitored their blood pressure at home experienced significantly larger reductions in blood pressure than those who only attended periodic consultations at the clinic.

## ISCHEMIC HEART DISEASE

### The OMEGA Study: the Role of Omega-3 Fatty Acids Added to Current Treatment for Acute Myocardial Infarction

*Presented by J. Senges, Ludwigshafen, Germany.*

**Background.** Omega-3 fatty acids have been shown effective in the prevention of adverse events in different types of cardiovascular disease. The aim of the present trial was to determine whether adding omega-3 fatty acids to standard medical treatment could improve the results achieved with medical treatment alone in patients who had suffered an acute myocardial infarction.

**Methods.** A total of 1940 patients over 18 years of age were randomly assigned to receive omega-3 fatty acids plus standard medical treatment, rather than medical treatment alone, 3-14 days after suffering ST elevation acute myocardial infarction (STEMI) or no ST elevation acute myocardial infarction (NSTEMI). The primary endpoint was the incidence of sudden death of cardiac origin. The secondary endpoints were death due to any cause, a new, non-fatal myocardial infarction, stroke, arrhythmic events, and the need for coronary revascularization.

**Results.** The total number of patients randomized to one group or the other was 3851; the mean age was 64 years. Some 26% of the patients were women, 66% of the patients suffered hypertension, 50% had hypercholesterolemia, 27% suffered diabetes mellitus, and 37% were smokers. Fifty nine percent had suffered STEMI while 41% had suffered NSTEMI. Coronary angiography was performed on 94% of the patients, percutaneous coronary intervention on 78%, and 8% received thrombolysis. Concomitant medication at discharge included aspirin in 95% of patients, clopidogrel in 88%, angiotensin converting enzyme inhibitors in 83%, beta-blockers in 94%, and statins in 94%. At 1 year, the primary endpoint (sudden cardiac death) was reached in 1.5% of the omega-3 group compared to 1.5% in the control group ( $P=.84$ ). Mortality due to all causes was 4.6% compared to 3.7%, the incidence of myocardial infarction was 4.5% compared to 4.1%, that of

stroke 1.4% compared to 0.7%, and revascularization was needed in 27.2% compared to 29.1%. The total number of arrhythmia events was 1.1% compared to 0.7%. During follow-up, the triglyceride concentration was 121 mg/dL compared to 127 mg/dL. None of these differences was significant.

**Conclusions.** Among patients with STEMI or NSTEMI, additional treatment with omega-3 fatty acids appears to be of no benefit. This treatment did not reduce the incidence of the primary endpoint (sudden cardiac death) nor any of the studied cardiovascular complications in isolation. Neither did it have any effect on the triglyceride concentration during follow-up. The present results do not support the use of omega-3 fatty acids in the treatment of acute coronary syndrome.

### The REVIVAL-3 Study: Erythropoietin in Patients With ST Elevated Acute Myocardial Infarction Subjected to Percutaneous Coronary Intervention

*Presented by I. Ott, Munich, Germany.*

**Background.** The aim of this work was to assess the effect of high doses of erythropoietin compared to a placebo following primary percutaneous coronary intervention (PCI) in patients with STEMI.

**Methods.** Following primary angioplasty, patients with STEMI were randomly assigned to receive either intravenous erythropoietin ( $n=68$ ) or a placebo ( $n=70$ ). The final erythropoietin dose was 100 000 U over 3 injections: at PCI and at 24 and 48 h after revascularization. The main endpoint was the left ventricular ejection fraction (LVEF) measured by cardiac magnetic resonance at 6 months. The secondary endpoints were the change in infarction size during follow-up, the change in LVEF during follow-up, the volumes of the left ventricle, serious clinical complications (death, myocardial infarction, stroke, and the need for coronary revascularization), hemorrhage during hospitalization, thrombotic events or embolisms, and the need for a blood transfusion.

**Results.** A total of 138 patients were randomized to receive intravenous erythropoietin ( $n=68$ ) or placebo ( $n=70$ ). The mean age of the patients was 59 years, 18% of the patients were women, 16% had diabetes, the mean LVEF value was 46%, and 93% of patients received a drug-eluting stent. The mean time elapsed between the onset of symptoms and presentation was 168 min, and that between admission and PCI was 84 min. The results for the main endpoint (LVEF at 6 months) was 52% in the erythropoietin group and 52% in placebo group ( $P=.91$ ). The values for the secondary endpoints for the 2 groups were: end-



diastolic left ventricular volume 81 mL/m<sup>2</sup> versus 82 mL/m<sup>2</sup> (ie, erythropoietin group vs placebo group); end-systolic left ventricular volume 40 mL/m<sup>2</sup> versus 40 mL/m<sup>2</sup>; size of infarction 22% versus 20%; and the increase in LVEF 3% versus 2%. With respect to serious complications, the incidence of death was 1.5% versus 2.9%, of myocardial infarction 2.9% versus 1.4%, of stroke 1.5% versus 0%, and of revascularization 2.9% versus 2.9%. None of the differences recorded was significant.

**Conclusions.** In patients with STEMI who receive primary PCI, high doses of erythropoietin appear to provide no benefit. They did not improve the main endpoint (LVEF at 6 months), nor did they help reduce the size of the infarction. No significant differences were seen between the treatments in terms of the incidence of complications in this relatively small study.

## HEART FAILURE

### The Pre-RELAX-AHF Study: the Role of Relaxin in the Treatment of Acute Heart Failure

*Presented by J.R. Teerlink, San Francisco, USA.*

**Background.** The majority of patients admitted for acute heart failure have normal or high blood pressure. Relaxin is a natural human peptide involved in a number of metabolic vascular control pathways; it may therefore be associated with mechanisms that could be of benefit to such patients. The dose-response relationship of relaxin was determined with respect to the improvement of symptoms, other clinical outcomes, and safety.

**Methods.** This study involved 54 centers in 8 countries. The initial 234 patients included suffered acute heart failure, dyspnea, congestion in chest x-rays, and an increase in type-B natriuretic peptide (BNP) or in the N terminal of the propeptide (NT-proBNP), mild to moderate kidney failure, and a systolic blood pressure of >125 mm Hg. All patients were enrolled in the study within 16 h of presentation. The patients were randomized (double blind) via an interactive telephone answering system to receive either standard treatment plus 48 h of intravenous transfusion of a placebo (n=62) or relaxin 10 µg/kg (n=40), 30 µg/kg (n=43), 100 µg/kg (n=39), or 250 µg/kg (n=50) per day. A number of clinical endpoints were chosen to determine whether the effect of intravenous relaxin should be assessed with respect to acute heart failure in larger clinical trials, to identify the optimum dose, and to help in the selection of evaluation criteria and sample size

determination. Analysis proceeded on the basis of modified intention to treat.

**Results.** In the modified intent-to-treat populations, 61 patients in the placebo group were assessed, 40 in the relaxin 10 µg/kg day group, 42 in the relaxin 30 µg/kg day group, 37 in the relaxin 100 µg/kg day group, and 49 in the relaxin 250 µg/kg day group. An improvement in dyspnea was seen in the relaxin 30 µg/kg day group compared to the placebo group; this was observed both on the Likert scale—17 (40%) of the 42 patients improved moderately or notably at 6, 12, and 24 h compared to 14 (23%) of 61 patients ( $P=.044$ )—and on the visual analogue scale until day 14 (8214 [8712] compared to 4622 [9003] mm/h;  $P=.053$ ). Hospitalization lasted 10.2 (6.1) days for the patients treated with relaxin compared to 12 (7.3) days for those who received the placebo, and post-discharge survival was 47.9 (10.1) days compared to 44.2 (14.2) days. Relaxin reduced the number of cardiovascular deaths and re-admissions due to heart or kidney failure at 60 days (2.6% [95% CI, 0.4-16.8] compared to 17.2% [9.6-29.6];  $P=.053$ ). The number of serious adverse events was similar in both groups.

**Conclusions.** When administered to patients with acute heart failure who show normal or elevated blood pressure, relaxin is associated with an improvement in dyspnea and other clinical variables. Its safety profile is acceptable.

The results of this study have been published in the form of a complete scientific paper.<sup>8</sup>

### The FIX-HF-5 Study: a Randomized, Multi-Center Study on the Effect of Electrical Modulation of Cardiac Contractility in Patients With Advanced Heart Failure

*Presented by W.T. Abraham, Columbus, USA.*

**Background.** Cardiac contractility modulation (CCM) signals are non-excitatory electrical signals emitted during the refractory period that increase contractility. Earlier studies in experimental animals and humans have shown that CCM signals normalize the phosphorylation of key proteins and the expression of genes coding for proteins that regulate the cell calcium cycle and contractility. Based on the hypothesis that CCM might be able to improve cardiac function variables without affecting patient safety, the aim of the present work was to assess the value of CCM plus optimum medical treatment compared to optimum medical treatment alone in patients with advanced heart failure.

**Methods.** Patients with heart failure (NYHA class III-IV, LVEF ≥35% and narrow QRS wave)

were randomly assigned to receive either CCM plus optimum medical treatment or optimum medical treatment alone. The main safety endpoint was composed of death by any cause and hospitalization for any cause. The main effectiveness endpoint was the change in the anaerobic threshold during ergospirometry. The secondary endpoints were maximum oxygen consumption ( $\text{VO}_{2\text{max}}$ ) and quality of life measures.

**Results.** The initial number of patients randomized was 428 patients; 215 received CCM plus optimum medical treatment and 213 received optimum medical treatment alone. The mean age of the patients was 58 years; 91% fell into NYHA class III, 27% were women, 65% were ischemic, the mean LVEF was 26%, the mean duration of the QRS wave was 102 ms, and the mean  $\text{VO}_{2\text{max}}$  during ergospirometry was 14.7 mL/kg/min. At the beginning of the study, 91% of the patients received angiotensin converting enzyme inhibitors or an angiotensin II receptor site blocker, 94% received beta-blockers, and 44% an aldosterone inhibitor.

The improvement in the primary effectiveness endpoint, the anaerobic threshold (for those who finished), was 17.6% in the treatment group and 11.7% in the control group ( $P=.093$ ). In addition, the  $\text{VO}_{2\text{max}}$  improved by 0.65 mL/kg/min ( $P=.024$ ) and quality of life by -9.7 points ( $P<.0001$ ) in the treatment group. The incidence of the main safety endpoint at 50 weeks was 52% for the treatment group and 48% for the control group (no inferiority;  $P=.03$ ). The improvements seen with the addition of CCM treatment were most pronounced among patients in NYHA class III and with an LVEF  $\leq 25\%$ .

**Conclusions.** In patients with advanced heart disease (NYHA classes III or IV), reduced LVEF ( $\leq 35\%$ ) and a narrow QRS wave, the use of CCM did not improve the main effectiveness endpoint, ie, the anaerobic threshold. However, it did improve the  $\text{VO}_{2\text{max}}$  and quality of life. The safety results for the treatment were no poorer than those of the control group. In subgroup analysis, the anaerobic threshold was found to improve for patients in NYHA class III and with a LVEF of  $\leq 25\%$ ; the improvements seen in  $\text{VO}_{2\text{max}}$  and quality of life were more pronounced and were maintained at 12 months.

### The PRIMA Study: Can Treatment Guided by NT-proBNP Improve the Morbidity/Mortality Associated With Heart Failure?

*Presented by L. Eurlings, Maastrich, The Netherlands.*

**Description.** The treatment of heart failure guided by the concentration of natriuretic

peptides could be more effective in the prevention of mortality and morbidity than standard treatment guided by clinical objectives. The aim of the present work was to compare the results obtained when management was guided by the serum concentration of the N-terminal of type-B natriuretic peptide (NT-proBNP) and those achieved when guided by clinical monitoring in patients with heart failure.

**Methods.** This study involved patients hospitalized for decompensated heart failure with elevated concentrations of NT-proBNP at admission that then fell by at least 10%. The patients were randomly assigned to NT-proBNP-guided treatment or standard treatment. The main endpoint was the number of days the patient lived following discharge. The secondary endpoints included cardiovascular mortality, hospitalization due to heart failure, cardiovascular reasons and all causes, and the combination death plus hospitalization. An evidence-based analysis of the use of medication for heart failure, and the analysis of the subgroup that saw no reduction in NT-proBNP during initial admission, was also performed.

**Results.** A total of 345 patients were randomized, 174 to NT-proBNP-guided treatment, and 171 to treatment based on clinical criteria. The mean age of the patients was 71 years; 45% were women, the mean LVEF was 31%, 37% had a background of myocardial infarction, and the median serum NT-proBNP concentration at admission was 8034 pmol/L. The results for the main endpoint, ie, the number of days patients survived after discharge, was 685 days with NT-proBNP-guided treatment and 664 for standard treatment ( $P=.49$ ). Total mortality was 26.5 compared to 33% ( $P=.20$ ). No significant differences were seen between the groups with respect to any of the secondary endpoints. Among the patients who maintained their serum NT-proBNP concentrations within the established range, the number of days survived after discharge was 721 compared to 664 in the control group ( $P<.01$ ), and mortality was 10.9% compared to 33.3% ( $P<.001$ ) respectively.

**Conclusions.** For patients admitted for decompensated heart failure, NT-proBNP-guided treatment did not improve the number of days survived after discharge, nor total mortality. The patients who maintained their NT-proBNP concentrations within the range established achieved better results. This study shows that NT-proBNP-guided treatment in patients with heart failure may not be any better than normal treatment, although their NT-proBNP concentration would appear to provide important prognostic information.

## CARDIAC INTERVENTION

### The PROTECT AF Study: Randomized Study of the Percutaneous Closure of the Left Appendage Compared to Oral Anticoagulation Treatment for the Prevention of Ictus in Patients With Atrial Fibrillation

*Presented by David Holmes, Scottsdale, USA.*

**Background.** Oral anticoagulation is the normal treatment for the prevention of thromboembolic complications in patients with atrial fibrillation. However, this treatment has its drawbacks, such as hemorrhagic complications, and is contraindicated in certain patients. The aim of the PROTECT AF trial was to assess the role of percutaneous closure of the left atrial appendage compared to warfarin treatment in patients with non-valvular atrial fibrillation.

**Methods.** Patients with non-valvular atrial fibrillation, all over 18 years of age and with a CHADS2 index score of at least 1, were randomly assigned to receive either (ratio, 2:1) percutaneous closure of the left appendage followed by the suspension of warfarin treatment for 45 days, or maintained oral anticoagulation treatment. The main effectiveness endpoint was composed of ischemic or hemorrhagic cerebrovascular accident, cardiovascular death or systemic embolism. The main safety endpoint was composed of embolization of the device or pericardial hemorrhage requiring intervention, intracranial or gastrointestinal hemorrhage, or hemorrhage of any kind requiring a transfusion.

**Results.** A total of 707 patients were included; 463 underwent closure of the left appendage with a Watchman device, while 224 received continued warfarin treatment. The 2 groups were well matched in terms of baseline characteristics. The mean age of the patients was 72 years; 30% were women, and the mean left ventricular ejection fraction was 57%. Two thirds of the patients had a CHADS2 score of 1 or 2. In the appendage closure group, warfarin treatment was suspended for 45 days in 87% of patients. The incidence of the main effectiveness endpoint (cardiovascular death, ictus, or systemic embolism) was 3.4 events/100 patient-years in the appendage closure group, and 5 events/100 patient-years in the control group ( $P<.05$ ; no inferiority). The incidence of ictus was 3.4 events/100 patient years compared to 3.6/100 patient-years ( $P<.05$ ; no inferiority). One hemorrhagic ictus event was recorded for the appendage closure group compared to 6 in the control group ( $P<.05$ ; superiority). The results for the main safety endpoint were 8.7 events/100 patient years in the appendage closure group compared to

4.2/100 patient-years in the control group ( $P<.05$ ; no superiority). The difference was mainly due to complications (pericardial hemorrhage) in implanting the device.

**Conclusions.** In patients with non-valvular atrial fibrillation, the Watchman device for the closure of the left appendage was not found to be inferior to warfarin treatment with respect to the incidence of cardiovascular death, ictus, or systemic embolism. The overall rate of ictus (ischemic and hemorrhagic) was similar in both treatment groups, but many fewer hemorrhagic ictus events were seen in the appendage closure group. The rate of complications was much higher in this group due to a high incidence of pericardial hemorrhage.

### The NAPLES II Study (New Approaches for Preventing or Limiting Events II): Impact of a Loading Dose of Atorvastatin Before Coronary Intervention

*Presented by C. Briguori, Naples, Italy.*

**Background.** Statins are associated with a series of beneficial effects independent of their lipid-lowering action. The ARMYDA study showed atorvastatin administered seven days before percutaneous coronary intervention (PCI) to be effective in reducing the incidence of post-intervention infarction. The aim of the NAPLES II study was to assess the possible benefit of a loading dose of atorvastatin in patients never before treated with statins who were to be subjected to PCI.

**Methods.** Patients with coronary artery disease who had been programmed to undergo PCI and who had received no prior treatment with statins, were randomly assigned to receive either a loading dose of 80 mg of atorvastatin in the 24 h prior to their intervention, or to receive no statin treatment. All patients received 100 mg of aspirin and 300 mg of clopidogrel the day before their procedures, plus intravenous heparin during PCI. Upon discharge the recommended treatment was aspirin (325 mg/day), clopidogrel (75 mg/day) and atorvastatin (20 mg/day). The main endpoint was an elevation of the CK-MB or troponin I concentration to  $>3$  times the normal upper limit at 6 h and 12 h post-PCI. The secondary endpoints included in-hospital death, myocardial infarction or the renewed need for coronary revascularization.

**Results.** The study involved 668 patients. The mean age was 64 years; 21% were women; the mean ejection fraction was 56%. Three hundred and thirty eight patients were assigned to receive 80 mg of atorvastatin before PCI, and 330 to receive no statin. Some 88% of the patients were symptomatic

before PCI; 62% had multi-vessel disease. The rate of angiographic complications was low (6%). The incidence of post-intervention myocardial infarction (defined by the mentioned enzymatic criterion) was significantly lower among the atorvastatin group (9.5% compared to 15.8% in the control group; 95% CI, 0.35-0.89; OR=0.56;  $P=.01$ ). The incidence of the troponin I concentration exceeding three times the normal upper limit was significantly lower in the atorvastatin group (26.6% compared to 39.1%; 95% CI, 0.40-0.78; OR=0.56;  $P<.001$ ). Subgroup analysis showed the benefit of the atorvastatin loading dose was greater among patients with elevated concentrations of C-reactive protein. The incidence of death, non-planned revascularization and stent thrombosis was low; no significant differences were seen between the 2 arms of the study.

**Conclusions.** The results of the NAPLES II trial indicate that a loading dose of atorvastatin given 24 h before PCI is an effective method for reducing the incidence of post-intervention myocardial infarction. It remains to be seen whether a loading dose given 7 days before PCI (the ARMYDA strategy) is superior. Nonetheless, the NAPLES II results indicate that a single loading dose could be a good strategy to follow in patients who have never before received statin treatment but who are programmed for elective PCI.

### The EARLY ACS Study: Eptifibatide in Acute Coronary Syndrome. A Comparison of Early and Late, Provisional Administration

*Presented by L.K. Newby, Durham, USA.*

**Background.** Glycoprotein IIb/IIIa inhibitors are indicated in patients with ACS who undergo PCI. The optimum moment for beginning this therapy is, however, unknown.

**Methods.** A strategy of early, fixed administration of eptifibatide was compared with a late, transitory strategy in 9492 patients with no ST elevation ACS, in whom invasive management was indicated. The patients were randomly assigned to receive early eptifibatide (2 boluses of 80 µg/kg body weight each, administered with an interval of 10 min, plus standard infusion 12 h before coronary angiography), or a similar infusion of a placebo with provisional use of eptifibatide after coronary angiography (late eptifibatide). The main effectiveness endpoint was composed of death, myocardial infarction, recurrent ischemia requiring urgent revascularization, and PCI thrombotic complications (thrombotic rescue) in the 96 h post-intervention. An important secondary endpoint was composed of myocardial infarction in the first 30 days. The main safety endpoints were

hemorrhage and the need for a blood transfusion in the first 120 h following randomization.

**Results.** The incidence of the main endpoint was 9.3% in the early eptifibatide group compared to 10% in the late group (OR=0.92; 95% CI, 0.80-1.06;  $P=.23$ ). At thirty days the rate of death or myocardial infarction was 11.2% in the early group and 12.3% in the late group (OR=0.89; 95% CI, 0.79-1.01;  $P=.08$ ). Early treatment was associated with a significantly higher rate of hemorrhaging and the need for the transfusion of red blood cell concentrates. No significant differences were seen between the groups in terms of serious hemorrhaging or serious non-hemorrhaging adverse events.

**Conclusions.** In patients with no ST elevation ACS, the use of eptifibatide 12 h or more before coronary angiography was not superior to the late, provisional use of the drug after coronary angiography. The early use of eptifibatide was associated with a greater risk of non-fatal hemorrhages and the need for transfusion.

The results of this study have been published in the form of a complete scientific paper.<sup>9</sup>

### Results of the NCDR-CMS Registry: Clinical Effectiveness of Coronary Stents in the "Real World"

*Presented by P.S. Douglas, Durham, USA.*

**Background.** The comparative effectiveness of drug-eluting stents (DES) compared to conventional stents (CS) has not been completely established. The aim of this work was to compare the clinical evolution of elderly patients who received either DES or CS.

**Methods.** An analysis was made of the evolution of 262 700 patients from 650 centers belonging to the National Cardiovascular Data Registry (2004 to 2006) using the data for the procedures requested by the Medicare company for follow-up. Events, including death, myocardial infarction (MI), revascularization, major hemorrhages, ictus, death or MI, death or MI or revascularization, and death or MI or ictus, were compared using estimated rates of accumulated incidence employing inverse probability weighted estimators and Cox proportional hazard ratios.

**Results.** DES were implanted in 217 675 patients and CS in 45 025. At 30 months, the patients implanted with DES had lower non-adjusted death (12.9% compared to 17.9%), MI (7.3% compared to 10%) and revascularization (23% compared to 24.5%) rates; no differences were seen in terms of ictus or hemorrhages. After adjusting for different variables, the DES patients had lower rates of death



(13.5% compared to 16.5%; HR=0.75; 95% CI, 0.72-0.79;  $P<.001$ ) and MI (7.5% compared to 8.9%; HR=0.77; 95% CI, 0.72-0.81;  $P<.001$ ); minimum differences were seen in the rates of revascularization (23.5% compared to 23.4%; HR=0.91; 95% CI, 0.87-0.96), ictus (3.1% compared to 2.7%; HR=0.97; 95% CI, 0.88-1.07) and hemorrhage (3.4% compared to 3.6%; HR=0.91; 95% CI, 0.84-1). DES were associated with survival benefits in all the subgroups analyzed, persisting at 30 months.

**Conclusions.** In this effectiveness study, the largest of its kind to date in the “real world” (rather than involving selected patients in clinical trials), patients treated with DES showed significantly better clinical evolution than those treated with CS, with no increase in associated ictus or hemorrhages over a 30-month follow-up period. Similar results were obtained in all subgroups analyses.

## ARRHYTHMIAS

### The ACTIVE A Study: Effect of Clopidogrel Combined With Aspirin in Patients With Atrial Fibrillation

*Presented by S.J. Connolly, Hamilton, Canada.*

**Background.** The antagonists of vitamin K reduce the risk of stroke in patients with atrial fibrillation, but are considered inadequate for many patients, who instead are normally treated with aspirin. This work tests the hypothesis that adding clopidogrel to aspirin treatment might reduce the risk of vascular complications in patients with atrial fibrillation.

**Methods.** This study involved 7554 patients with atrial fibrillation and an elevated risk of stroke, for whom treatment with vitamin K antagonists was considered inappropriate. These were randomly assigned to receive either clopidogrel (75 mg) or a placebo once per day in addition to aspirin. The main endpoint was the combination of stroke, myocardial infarction, peripheral embolism, or death of cardiovascular cause.

**Results.** The median follow-up time was 3.6 years. Major vascular complications were seen in 832 patients of the clopidogrel group (6.8% per year) compared to 924 patients in the placebo group (7.6% per year) (RR with clopidogrel = 0.89; 95% CI, 0.81-0.98;  $P=.01$ ). The difference was mainly due to a reduction in the rate of stroke with clopidogrel. Stroke was recorded in 296 patients in the clopidogrel group (2.4% per year) and in 408 patients in the placebo group (3.3% per year) (RR=0.72; 95% CI, 0.62-0.83;  $P<.001$ ). Myocardial infarction was recorded in 90 patients of the clopidogrel group (0.7% per year) and in 115 in the placebo group (0.9% per

year) (RR=0.78; 95% CI, 0.59-1.03;  $P=.08$ ). Serious hemorrhaging was recorded in 251 patients of the clopidogrel group (2% per year) and in 162 patients of the placebo group (1.3% per year) (RR=1.57; 95% CI, 1.29-1.92;  $P<.001$ ).

**Conclusions.** In patients with atrial fibrillation in whom treatment with vitamin K antagonist is not adequate, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially cerebrovascular events, and increased the risk of major hemorrhages.

## HEART SURGERY

### The STICH Study (Surgical Treatment for Ischemic Heart Failure Trial): Coronary Revascularization on Its Own or With Ventricular Reconstruction Surgery

*Presented by R.H. Jones, Durham, USA.*

**Background.** Reconstruction or ventricular remodeling surgery is a procedure specifically designed to reduce the volume of the left ventricle in patients with heart failure caused by coronary artery disease. This work investigated whether ventricular reconstruction surgery in addition to coronary revascularization (CABG) could reduce the death or hospitalization rate for cardiac causes compared to CABG only.

**Methods.** Between September 2002 and January 2006, 1000 patients with an LVEF  $\leq 35\%$ , coronary artery disease susceptible to CABG and dysfunction predominantly of the anterior region of the left ventricle treatable by ventricular reconstruction surgery, were randomly assigned to undergo either CABG ( $n=499$ ) or CABG plus ventricular reconstruction surgery ( $n=501$ ). The main endpoint was composed of death by any cause and hospitalization due to cardiac cause. The median follow-up time was 48 months.

**Results.** Surgical ventricular reconstruction reduced the end-diastolic volume index by 19% compared to 6% by CABG alone. In both groups, cardiac symptoms and tolerance to exercise improved with respect to the baseline situation. No significant difference was seen in the main endpoint results, with 292 patients (59%) affected in the CABG group and 289 (58%) in the CABG plus ventricular reconstruction surgery group (HR=0.99; 95% CI, 0.84-1.17;  $P=.90$ ).

**Conclusions.** The addition of ventricular reconstruction surgery to conventional surgical revascularization achieved a greater reduction of the left ventricular volume. However, this anatomical change was associated with no improvement in symptoms or tolerance to exercise,

nor with a reduction in the cardiac-cause death or hospitalization rate.

The results of this study have been published in the form of a complete scientific paper.<sup>10</sup>

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