

Summary of the Clinical Studies Reported in the European Society of Cardiology Congress 2010 (August 28-September 1, 2010, Stockholm, Sweden)

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The European Society of Cardiology held its annual congress in Stockholm in 2010. The results of a selection of recently concluded clinical trials of outstanding importance were presented in special sections (Hot Lines).

Following recently established publishing policy,¹⁻⁷ the *Revista Española de Cardiología* presents for the second time a summary of these studies which briefly outlines their objectives, methods, and results in line with the oral presentations. In view of the fact that many of these studies have still to be published in their final version, the information we offer should be considered preliminary. When a specific study has been published, its citation is given at the end of the summary to facilitate referencing.

SUMMARY BY SUBJECT

Primary and Secondary Prevention

INNOVATE PCI study: a phase II safety and efficacy study of PRT060128 (elinogrel), a novel intravenous and oral P2Y₁₂ inhibitor, in non-urgent percutaneous coronary intervention (PCI).

AVERROES study: apixaban versus acetylsalicylic acid (ASA) to prevent strokes.

EINSTEIN DVT study: oral rivaroxaban versus standard therapy in the initial treatment of symptomatic deep vein thrombosis and long-term prevention of recurrent venous thromboembolism.

RESPONSE study: effect of a nurse-coordinated prevention program on cardiovascular risk after an acute coronary syndrome: main results of the RESPONSE trial.

Acute Coronary Syndrome

ATOLL study: an international, randomized trial comparing i.v. enoxaparin with i.v. unfractionated heparin in primary PCI for ST-elevation myocardial infarction (MI).

E5555 study: double-blind, placebo-controlled, phase II studies of E5555 in Japanese patients with acute coronary syndrome (ACS) and coronary artery disease (CAD).

ALPHA OMEGA study: effect of low doses of n-3 fatty acids on cardiovascular disease in post-MI patients.

HEBE III study: a single dose of erythropoietin in ST-elevation myocardial infarction.

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STAR Heart study: acute and long-term effect of intracoronary stem-cell transplantation in 191 patients with chronic heart failure.

PEARL HF study: multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study to evaluate the effects of RLY5016 in heart failure patients.

SHIFT study: effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction.

Arrhythmia

DANPACE study: the Danish multicenter randomised trial on single-lead atrial versus dual-chamber pacing in sick sinus syndrome.

ANTIPAF study: angiotensin II antagonists in paroxysmal atrial fibrillation trial.

Surgery

ART study: randomised trial to compare survival following bilateral versus single internal mammary (IMA) grafting in coronary revascularization.

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Interventional Cardiology

LESSON I study: long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization.

ISAR REACT 3A study: a trial of reduced doses of unfractionated heparin in patients undergoing PCI.

FUTURE OASIS 8 study: randomised trial comparing two regimens of adjunctive intravenous unfractionated heparin during PCI in high-risk patients with non-STEACS treated with fondaparinux.

PRIMARY AND SECONDARY PREVENTION

INNOVATE PCI study: a phase II safety and efficacy study of PRT060128 (elinogrel), a novel intravenous and oral P2Y₁₂ inhibitor, in non-urgent percutaneous coronary intervention (PCI)⁸

Presented by S. Rao (United States of America)

Introduction and objectives: The currently available options for oral antiplatelet therapy are limited by the variability of response or increased risk of major bleeding. Elinogrel is a novel oral and intravenous (i.v.) P2Y₁₂ inhibitor that does not require metabolic activation and provides reversible, competitive, intense and rapid platelet inhibition.

Methods: A randomized, double-blind, triple dummy, active-controlled, parallel-group, dose-ranging phase II trial was conducted to assess the safety and tolerability of i.v. and oral elinogrel in 652 patients undergoing non-urgent PCI. Patients were assigned to receive pre-PCI clopidogrel 300 mg or 600 mg followed by 75 mg once daily or elinogrel 80 mg i.v. bolus followed by 50 mg, 100 mg, or 150 mg of oral elinogrel twice daily. The trial was not statistically powered to assess any specific endpoint, and a range of clinical and biological endpoints was examined. The efficacy parameters included short-term and intermediate-term death, myocardial infarction, ischemic stroke, urgent target vessel revascularization, stent thrombosis, or urgent rescue using glycoprotein IIb/IIIa inhibitors (anti-GPIIb/IIIa). The biological efficacy endpoints were the proportion of patients presenting any troponin elevation or troponin elevation more than twice the normal upper limit after PCI. The safety endpoints were short-term and intermediate-term bleeding, defined as clinically relevant major, minor, or minimal bleeding, and TIMI major and minor bleeding and bleeding requiring medical attention (BRMA). Pharmacodynamic studies

were conducted using a subset of patients. Short-term outcomes were assessed at 24 hours post-PCI or at hospital discharge, whichever occurred first. The patients were initially followed up for 60 days, but the protocol was modified to extend follow-up to 120 days. In addition, the Data and Safety Monitoring Committee (DSMC) recommended discontinuing enrollment into the 50-mg oral dose arm and increasing the i.v. dose of elinogrel to 120 mg as described in the protocol. The enrollment of patients into the 50 mg oral dose arm of elinogrel was discontinued after 116 patients had been enrolled. The i.v. dose of elinogrel was increased up to 120 mg after 177 patients had been enrolled. A total of 590 patients were followed up for 60 days and 328 patients for 120 days.

Results: The median of age of the patients was 61 years and 77% were men. Approximately 30%-40% of the patients presented diabetes mellitus and 46% received maintenance treatment with clopidogrel at the time of inclusion. Pharmacodynamic data were available on 52 patients, 75% of whom were receiving maintenance treatment with clopidogrel at the time of inclusion. Using light transmittance aggregometry and 5 micromolar ADP, i.v. and oral elinogrel led to greater platelet inhibition than clopidogrel in the peri-PCI phase and at 30-day assessment. There was no excess of TIMI major or minor bleeding with elinogrel at either 24-hour assessment or 120-day assessment. There was a dose-dependent increase in BRMA among the elinogrel arms, which mainly occurred during the periprocedural period. There were no significant differences in efficacy endpoints at either 24-hours or 120-days between elinogrel and clopidogrel. Adverse events were similar in the patients treated with elinogrel and with clopidogrel, with the exception of dyspnea, which was more frequent in patients assigned to elinogrel. Furthermore, there were more cases of liver transaminase elevation, predominantly occurring within 60 days of inclusion, in the elinogrel arms with a possible dose-response relationship, but there were no cases in which Hy's law was fulfilled.

Conclusions: The results of the INNOVATE-PCI phase II trial show that, despite greater platelet inhibition observed with elinogrel compared with standard-dose clopidogrel, there was no some increase in TIMI major or minor bleeding in the peri-PCI period or during follow-up. Although the trial was not designed with the statistical power needed for efficacy, there were no significant differences in clinical or biological efficacy endpoints among the various treatment arms. These data support conducting more studies on this novel compound in patients with ischemic heart disease.

AVERROES Study: Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Strokes⁹

Presented by S. Connolly (Canada)

Introduction and objectives: Patients with atrial fibrillation (AF) are at increased risk of stroke. Vitamin K antagonists (VKA), such as warfarin, are effective in reducing stroke but are associated with an increased risk of bleeding. Furthermore, the management of VKA therapy is complex and requires frequent monitoring due to genetic variability and multiple interactions between drugs and diet. Many patients with AF cannot be maintained effectively with AVK therapy, others have experienced complications, and some patients reject the treatment. Among patients unsuitable for VKA therapy, the only alternative treatment is ASA, which is only moderately effective. Apixaban is an oral anticoagulant undergoing research that selectively inhibits factor Xa. Studies on venous thromboembolism prophylaxis have shown that apixaban is effective and has a favorable risk benefit relationship compared with low-molecular-weight heparin. The aim of the AVERROES study was to assess apixaban for the prevention of stroke or systemic embolism in patients with AF and at risk of stroke who are unsuitable for VKA therapy. Apixaban was compared to the standard treatment (ASA) of these patients.

Methods: The AVERROES study was a double-blind, randomized and active-controlled trial in which apixaban was compared to ASA. Patients with documented AF and at least one risk factor for stroke who are also unsuitable for VKA therapy were randomized 1:1 to receive either apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) or ASA (81 mg-324 mg per day). The study was conducted in 520 centers throughout the world and the recruitment of 5600 patients was completed in December 2009. Based on the overwhelming evidence of efficacy against stroke or systemic embolism, as well as an excellent safety profile, the Data Monitoring Committee recommended terminating the study so that all the patients could receive open-label apixaban. This recommendation was accepted by the Steering Committee and the sponsors of the study.

Results: The preliminary results are briefly described. The treatment groups were well balanced regarding all baseline factors. The mean age was 70 years. The mean CHADS2 score was 2. A total of 75% of the patients were receiving ASA therapy at the time of inclusion in the study, and 15% were receiving oral anticoagulants. A

total of 40% had previously received a vitamin K antagonist. The annual rate of stroke or systemic embolism (the primary endpoint) was 4% per year with ASA therapy and 1.7% per year with apixaban (hazard ratio [HR] = 0.43; 95% confidence interval [CI], 0.3-0.62; $P < .001$). The rate of major bleeding was 1.2% per year with ASA and of 1.5% per year with apixaban (HR=1.26; 95% CI, 0.79-2; $P = .33$). The rate of hemorrhagic stroke was 0.2% per year in both treatment groups (HR=1.15; 95% CI, 0.42-3.17; $P = .79$). There was no evidence of liver toxicity or other major adverse events.

Conclusions: In the patients with AF and at risk of stroke who are unsuitable for AVK therapy, apixaban reduces the risk of stroke or systemic embolism by 57%, without significantly increasing the risk of major bleeding. Apixaban has an important advantage over ASA for preventing stroke in these patients.

RESPONSE Study: Effect of a Nurse-Coordinated Prevention Program on Cardiovascular Risk After an Acute Coronary Syndrome: Main Results of the RESPONSE Trial¹⁰

Presented by R. Peters (Netherlands)

Introduction and objectives: There is a considerable gap between the guidelines on the secondary prevention of cardiovascular disease and their real application. In the RESPONSE study, we quantified the impact of a hospital-based, nurse-coordinated prevention program on the risk of future complications in patients with an established coronary artery disease.

Methods: The RESPONSE study was a randomized clinical trial conducted in 11 hospitals in the Netherlands. Patients aged 18 years-80 years admitted for an acute clinical coronary complication within 8 weeks prior to inclusion were eligible for inclusion in the study. Patients were randomly assigned to the nurse-coordinated prevention program in combination with standard care (intervention group) or to standard care alone (control group). The intervention included up to 4 outpatient visits to a nurse during the first 6 months following inclusion. The nursing protocol was based on current guidelines and focused on lifestyle issues (quitting smoking, appropriate physical exercise and suitable weight/fat distribution), biometric risk factors (blood pressure control, lipid control, screening for diabetes and blood glucose control in diabetic patients), and adherence to medication. The data were collected independently at baseline and

at 6 months and 12 months after inclusion. The primary endpoint of the study was the SCORE 10-year cardiovascular risk estimation, assessed at 12 months (6 months after the last visit), that includes data on age, sex, total cholesterol, systolic blood pressure, and smoking habit. A secondary endpoint was the proportion of patients classified as having good control of the risk factors, defined as having at least 7 of 9 risk factors established at target levels.

Results: A total of 754 participants were randomly assigned to the intervention group (n=377) or to the control group (n=377). At 12 months, SCORE estimation was 4.5% in the patients in the intervention group and 5.4% in those in the control group, which corresponds to a reduction of 16.9 in relative risk ($P=.029$). In 35% of the patients in the intervention group compared with 25% of the control group, risk factor control at 12 months was classified as good (27% increase; $P=.006$). Adherence to medication was excellent in both groups and there were no significant differences.

Conclusions: A nursing intervention lasting 6 months leads to significant and enduring reductions in cardiovascular risk due to improved control of risk factors. These programs can be easily implemented in clinical practice.

ACUTE CORONARY SYNDROME

ATOLL Study: an International, Randomized Trial Comparing i.v. Enoxaparin With i.v. Unfractionated Heparin in Primary PCI for ST-Elevation Myocardial Infarction¹¹

Presented by G. Montalescot (France)

Introduction and objectives: Intravenous (i.v.) low molecular weight heparin enoxaparin (0.5 mg/kg) has been associated with a 57% reduction in the relative risk of major bleeding compared to unfractionated heparin (UFH) in a large randomized study conducted in elective PCI. To date, primary PCI (pPCI) for ST-elevation myocardial infarction (STEMI) has been traditionally supported by UHF. Intravenous enoxaparin can lead to better outcomes when used for pPCI. The objective of this study was to directly compare enoxaparin and UFH in patients undergoing pPCI for STEMI. Patients were selected at first medical contact and randomized and treated mostly before hospital admission.

Methods: Patients over 18 years, without an upper age limit, referred for pPCI of STEMI within 12 hours of symptom onset, were eligible for randomization. Patients who had received

any type of anticoagulant therapy before randomization were excluded. In both groups, the use of other concomitant drugs, including anti-GPIIb/IIIa, was left to the discretion of the researchers. The primary endpoint was net clinical benefit, assessed by the composite of death, MI complications, procedural failure and major bleeding unrelated to coronary artery bypass grafting, at 30 days. The main safety endpoint was major bleeding during hospitalization (according to STEEPLE definitions). The main ischemic endpoint (secondary) was the composite of death, recurrent ACS or urgent revascularization.

Results: A total of 910 patients underwent randomization. In the enoxaparin group, the median age was 59 years, 22% were women, 14% had diabetes, 4% had previous shock or cardiac arrest before the intervention, the time elapsed between symptom onset and randomization was 2.33 hours, the radial approach was used in 69% of patients, stents were implanted in 96% and an anti-GPIIb/IIIa was used in 71%. The primary endpoint was reached in 28% of the patients in the enoxaparin group and in 34% in the UFH group ($P=.07$). For secondary endpoints, the composite of death, ACS, and revascularization occurred in 5.1% vs 8.5% ($P=.04$); death, MI complications, and major bleeding occurred in 10.2% vs 15% ($P=.03$); death and MI complications occurred in 7.8% vs 12.4% ($P=.02$); all-cause mortality occurred in 3.8% vs 6.3% ($P=.08$); and death or resuscitated cardiac arrest occurred in 4% vs 7% ($P=.049$). Major bleeding unrelated to coronary artery bypass grafting occurred in 4.5% vs 4.9% (without reaching statistical significance [NS]), and TIMI major bleeding occurred in 2.9% vs 2.4% (NS).

Conclusions: In patients with STEMI, the use of enoxaparin compared to UFH during pPCI is a feasible option. Enoxaparin did not reduce the primary endpoint rate, although the secondary ischemic endpoints were reduced; bleeding was similar in both groups. The benefit observed in the primary endpoints should be explored in future larger studies with more standardized definitions of ischemic and bleeding events.

E5555 study: double-blind, placebo-Controlled, phase II studies of E5555 in Japanese patients with acute coronary syndrome (ACS) and coronary artery disease (CAD)¹²

Presented by S. Goto (Japan)

Introduction and objectives: A multicenter, randomized, double-blind, placebo-controlled, phase II study assessed the safety and efficacy

of oral protease-activated receptor 1 (PAR-1) antagonist E5555 in combination with standard therapy in Japanese patients with ACS or high-risk CAD.

Methods: Patients with ACS (n=241) or high-risk CAD (n=263) received E5555 therapy (50 mg, 100 mg or 200 mg) or placebo once a day for 12 weeks (ACS patients) or 24 weeks (CAD patients).

Results: The incidence of TIMI major, minor and minimal bleeding requiring medical care was similar in the placebo group and the combined E5555 therapy group (atopaxar) (ACS group: 6.6% with placebo vs 5% with E5555; CAD group: 1.5% with placebo vs 1.5% with E5555). There were no major TIMI bleeding events and 3 CURE major bleeding events (2 with placebo; 1 with 100 mg E5555). There was a numerical increase in the total of "any" TIMI bleeding event with the 200 mg dose of E5555 (ACS group: 16.4% with placebo vs 23% with E5555; $P=.398$; CAD group: 4.5% with placebo vs 13.2% with E5555; $P=.081$). There were no differences between the combination E5555 group and placebo group in major adverse cardiac events rate (ACS group: 6.6% with placebo vs 5% with E5555; $P=.73$; CAD group: 4.5% with placebo vs 1% with E5555; $P=.066$). There was a statistically significant, dose-dependent increase in liver function abnormalities and in the Fridericia correction formula (QTcF) with E5555. At the time of minimum concentrations, in both populations, mean inhibition of platelet aggregation was >90% with 100 mg and 200 mg of E5555 and 20%-60% with 50 mg of E5555.

Conclusions: Treatment with E5555 (50 mg, 100 mg and 200 mg) did not increase clinically significant bleeding, although there was an increased rate in the total of any TIMI bleeding with the 2 higher doses. All the doses investigated achieved a significant level of platelet inhibition. A significant dose-dependent increase was observed in liver function abnormalities and in QTcF. Although further studies are needed, PAR-1 antagonism could provide a new pathway for platelet inhibition that could be added to current standard therapy.

ALPHA OMEGA trial: effect of low doses of n-3 fatty acids on cardiovascular disease in post-MI patients¹³

Presented by D. Kromhout (Netherlands)

Introduction and objectives: The results of prospective cohort studies and randomized controlled trials have provided evidence of a protective effect of n-3 fatty acids on cardiovascular disease. We examined the effect of n-3 fatty acids

eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and plant-derived alpha-linolenic acid (ALA) on cardiovascular events in post-MI patients.

Methods: In a multicenter, double-blind, and placebo-controlled trial, we studied 4837 patients aged between 60 years and 80 years (78% were men) who had experienced a myocardial infarction and were receiving antihypertensive, antithrombotic, and lipid modifying drugs according to current guidelines. Patients were randomly assigned to 1 of the 4 margarines investigated in the trial for 40 months: a margarine enriched with EPA and DHA (with the aim of the additional daily consumption of 400 mg of EPA-DHA); a margarine enriched with ALA (with the aim of the additional daily consumption of 2 g of ALA); a margarine enriched with EPA-DHA and ALA; or a placebo margarine. The primary endpoint was the major cardiovascular event rate that included fatal and non-fatal cardiovascular events and cardiac procedures. Data were analyzed on an intention to treat basis using Cox proportional hazards models.

Results: The patients consumed an average of 18.8 g of margarine per day, which entailed an additional consumption of 226 mg of EPA with 150 mg of DHA, 1.9 g of ALA, or all of these in the active treatment groups. During the follow-up period, major cardiovascular events developed in 671 patients (13.9%). The primary endpoint was not reduced by either EPA-DHA or ALA (EPA-DHA, HR=1.01; 95% CI, 0.87-1.17; $P=.93$; ALA, HR=0.91; 95% CI, 0.78-1.05; $P=.2$). In the prespecified subgroup of women, the use of ALA vs placebo or EPA-DHA alone was associated with a borderline statistically significant reduction in the major cardiovascular event rate (HR=0.73; 95% CI, 0.51-1.03; $P=.07$). There were no significant differences between study groups in the adverse event rate.

Conclusions: Supplements of low doses of EPA-DHA or ALA do not significantly reduce the major cardiovascular event rate in post-MI patients who were receiving antihypertensive, antithrombotic and lipid modifying drugs according to the current guidelines.

HEBE III study: single-doses of erythropoietin in ST-elevation myocardial infarction¹⁴

Presented by A. Voors (Netherlands)

Introduction and objectives: The cardioprotective effects of erythropoietin (EPO) have been demonstrated in experimental and small clinical studies. We conducted a prospective,

multicenter, randomized trial to assess the effects of a single high dose of EPO after PCI for ST-elevation myocardial infarction (STEMI).

Methods: Patients treated successfully with PCI for a first STEMI were randomly assigned to receive standard medical treatment alone or in combination with a single bolus of 60 000 IU of EPO-alpha i.v. within 3 h of PCI. The primary endpoint was left ventricular ejection fraction (LVEF) after 6 weeks, as assessed by planar radionuclide ventriculography. The prespecified secondary endpoints were enzymatic infarct size and major cardiovascular events.

Results: A total of 529 patients were included (EPO, n=263; control, n=266). At baseline (before EPO administration), the groups were well-balanced for all relevant characteristics. After a mean of 6.5±2 weeks, LVEF was 0.53±0.1 in the EPO group and 0.52±0.11 in the control group ($P=.41$). The median area under the curve [interquartile range] after 72 h for the creatine kinase was 50 136 [28 212-76 664] U/L/72 h in the EPO group and 53 510 [33 973-90 486] U/L/72 h in the control group ($P=.058$). There were more major cardiac events in the control group than in the EPO group (19 vs 8; $P=.032$).

Conclusions: A single high dose of EPO after successful PCI for STEMI did not improve LVEF after 6 weeks. However, the use of EPO was associated with fewer major cardiovascular events and a favorable clinical safety profile.

HEART FAILURE

STAR Heart study: acute and long-term effect of intracoronary stem-cell transplantation in 191 patients with chronic heart failure¹⁵

Presented by B.E. Strauer (Germany)

Introduction and objectives: Despite accumulated evidence that intracoronary bone marrow cell (BMC) therapy can be of benefit in AMI, current data on the effectiveness of BMC in chronic heart failure are still limited. The objective of this study was to quantitatively investigate ventricular hemodynamics, geometry and contractility and the long-term clinical results of BMC therapy in patients with reduced LVEF due to chronic ischemic cardiomyopathy.

Methods: Patients with chronic heart failure (n=391; LVEF ≤35%) due to ischemic cardiomyopathy were included in the study. Of these, 191 patients (mean NYHA class, 3.22) received intracoronary BMC therapy. The control group (mean NYHA class, 3.06) was composed of 200 patients with a comparable LVEF. The assessment

of hemodynamics at rest and during exercise, quantitative ventriculography, spiroergometry, 24-hour Holter ECG, late potentials and heart rate variability were analyzed.

Results: Between 3 months and 5 years after intracoronary BMC therapy there was a significant improvement in hemodynamics (eg, LVEF, cardiac index), exercise capacity, oxygen uptake and left ventricular contractility. Attention should be drawn to the fact that there was a significant reduction in long-term mortality in the patients treated with BMC compared to the control group.

Conclusions: Intracoronary BMC therapy improves ventricular function, quality of life and survival in patients with heart failure. These effects were present when BMC were administered in addition to standard treatment regimens. No adverse side effects were observed.

EARL HF study: multicenter, randomized, double-Blind, placebo-Controlled, parallel-Group, multiple-Dose study to evaluate the effects of RLY5016 in heart failure patients¹⁶

Presented by B. Pitt (United States of America)

Introduction and objectives: Despite the efficacy of aldosterone antagonists (AA) in heart failure, the use of AA has been limited by the onset or fear of hyperkalemia (HK). Relypsa's K⁺-binding polymer (RLY5016) is a nonabsorbed, oral, potassium-binding polymer with some unique characteristics and that is being developed as a serum potassium (K⁺) management tool. The use of RLY5016 will prevent hyperkalemia in patients with heart failure and chronic kidney disease (CKD) receiving AA therapy.

Methods: A total of 105 patients with chronic heart failure who were clinically indicated to receive spironolactone therapy underwent randomization. Of these patients, 104 were assessable: 55 patients assigned to RLY5016 and 49 to placebo. The study included patients with a serum K⁺ of 4.3-5.1 mEq/L, and CKD (GFR <60 mL/min) receiving 1 or more heart failure therapies (angiotensin-converting enzyme inhibitors [ACEI], angiotensin II receptor antagonists [ARA-II], or β-blockers [BB]) or with a documented history of hyperkalemia within the last 6 months which led to the discontinuation of therapy with AA, ACEI, ARB or BB. They received spironolactone 25 mg-50 mg per day and were randomly assigned to 30 g/d of RLY5016 or placebo for 4 weeks. The primary endpoint was a change in K⁺ serum between baseline and the end of the double-blind treatment period

based on the last observation carried forward imputation method. Efficacy also was evaluated by the proportion of patients with hyperkalemia ($K^+ > 5.5$ mEq/L) and the proportion of patients in whom the dose of spironolactone could be increased. Efficacy was assessed in the subgroup of patients with GFR < 60 mL/min. Safety was evaluated by adverse events and clinical laboratory findings.

Results: The baseline characteristics were similar in both treatment groups. At baseline, mean K^+ serum was 4.69 ± 0.06 mEq/L in the RLY5016 group and 4.65 ± 0.07 mEq/L in the placebo group. The mean change in baseline K^+ serum was -0.22 mEq/L and $+0.23$ mEq/L in the patients treated with RLY5016 and placebo, respectively ($P < .001$). Treatment with RLY5016 significantly reduced the incidence of HK compared to placebo (7% vs 25%; $P = .015$) and increased the proportion of patients in whom the spironolactone dose could be increased (91% vs 74%; $P = .019$). It appeared that patients with a GFR < 60 mL/min had a more pronounced treatment effect than those with a documented history of hyperkalemia. Treatment with RLY5016 was well tolerated. Withdrawal from the study because of adverse events was 7% with RLY5016 and 6% with placebo, and there were no drug-associated serious adverse events.

Conclusions: Treatment with RLY5016 may allow the use of RAAS blocking agents in patients with heart failure and CKD who are at high risk of HK. However, new studies using multiple doses will be required before its clinical application.

SHIFT study: effects of ivabradine on cardiovascular events in patients with moderate to severe chronic heart failure and left ventricular systolic dysfunction¹⁷

Presented by M. Komajda (France)

Introduction and objectives: Chronic heart failure is associated with a high morbidity and mortality.

An elevated resting heart rate is a risk factor for adverse clinical outcomes. The objective of this study was to assess the effects of a reduction of heart rate obtained by using the selective sinus node inhibitor ivabradine on clinical outcomes in heart failure.

Methods: Patients were eligible for inclusion in this randomized, double-blind, placebo-controlled, parallel-group study if they had symptomatic heart failure and an LVEF $\leq 35\%$, were in sinus rhythm with a heart rate of 70 beats/min or higher, had been hospitalized for heart failure in the previous

year and had received stable background therapy that included a BB if it was well tolerated. Patients were randomly assigned by a computer-generated allocation schedule to ivabradine therapy titrated to a maximum of 7.5 mg twice a day or to an identical placebo. Patients and investigators were masked to treatment allocation. The primary endpoint was the composite of cardiovascular death or hospitalization for worsening heart failure. The analysis was conducted on an intention-to-treat basis.

Results: A total of 6558 patients were randomly assigned to the treatment groups (3268 to ivabradine, 3290 to placebo). Data were available for the analysis of 3241 patients in the ivabradine group and of 3264 patients assigned to placebo. Median follow-up time was 22.9 [18-28] months. A total of 793 (24%) patients in the ivabradine group and 937 (29%) of those receiving placebo presented a primary endpoint event (HR=0.82; 95% CI, 0.75-0.9; $P < .0001$). The effects were mainly due to hospital admissions for worsening heart failure (672 [21%] placebo vs 514 [16%] ivabradine; HR=0.74; 95% CI, 0.66-0.83; $P < .0001$) and deaths due to heart failure (151 [5%] vs 113 [3%]; HR=0.74; 95% CI, 0.58-0.94; $P = .014$). There were fewer severe adverse events in the ivabradine group (3388 events) than in the placebo group (3847; $P = .025$). A total of 150 (5%) patients in the ivabradine group presented symptomatic bradycardia compared with 32 (1%) in the placebo group ($P < .0001$). Visual side effects (phosphenes) were reported by 89 (3%) of the patients receiving ivabradine and by 17 (1%) of those receiving placebo ($P < .0001$).

Conclusions: Our results support the importance of reducing the heart rate with ivabradine to improve clinical outcomes parameters in heart failure and confirm the important role played by heart rate in the pathophysiology of this disorder.

ARRHYTHMIA

DANPACE study: the Danish multicenter randomised trial on single-lead atrial versus dual-chamber pacing in sick sinus syndrome¹⁸

Presented by J.C. Nielsen (Denmark)

Introduction and objectives: In patients with sick sinus node syndrome (SSS), bradycardia can be treated with any pacemaker. The use of a pacemaker in the right ventricle may cause harm, but it has not been established whether rate-adaptive single lead atrial (AAIR) pacing is preferable to rate-adaptive dual-chamber (DDDR) pacing.

Methods: Eligible consecutive patients presenting SSS, with normal QRS width and

without atrioventricular block, referred for primary pacemaker implantation were included in the study. They were randomly assigned to AAIR or DDDR pacing and followed up at 3 months and every year up to 10 years. Randomization was computer-based. Analysis was performed on an intention-to-treat basis.

Results: A total of 1415 patients (age, 73 ± 11.3 years; 64.5% women) with SSS were randomly assigned to AAIR (n=707) or DDDR (n=708) pacing, and were followed up for a mean of 5.4 ± 2.6 (1.2-10.5) years. A total of 96.1% were treated as randomized, 93.4% in the AAIR group and 98.9% in the DDDR group. No patients were lost to follow-up. All-cause mortality was 29.6% (209/707) in the AAIR group and 27.3% (193/708) in the DDDR group (HR=0.94; 95% CI, 0.77-1.14; $P=.53$). The incidence of paroxysmal atrial fibrillation (AF) was lower in the DDDR group than in the AAIR group (HR=0.79; 95% CI, 0.64-0.97; $P=.024$), even after correcting for relevant baseline variables. The incidence of chronic atrial fibrillation, stroke and heart failure was not different between groups. There were significantly fewer patients in the DDDR group than in the AAIR group who underwent reintervention follow-up (HR=0.5; 95% CI, 0.39-0.66; $P<.001$).

Conclusions: All-cause mortality did not differ between patients with SSS treated with AAIR or DDDR pacing. The use of DDDR should be the preferred mode of pacing in patients with SSS to reduce AF and reintervention.

ANTIPAF study: angiotensin II antagonists in atrial paroxysmal fibrillation trial¹⁹

Presented by A. Goette (Germany)

Introduction and objectives: In contrast to antiarrhythmic drugs, the safety and beneficial effects of angiotensin II receptor antagonists (ARA-II) in patients with structural heart disease are well established. Up to the present, the clinical efficacy of ARA-II to prevent the atrial fibrillation (AF) has only been demonstrated in patients with structural heart disease. We present the results of the primary endpoint of the ANTIPAF trial, which investigated the effect of olmesartan medoxomil compared to placebo on AF burden in patients presenting paroxysmal AF in the absence of structural heart disease.

Methods: The ANTIPAF trial was a prospective, randomized, placebo-controlled, multicenter study in which the primary endpoint was AF burden (percentage of days with documented paroxysmal AF episodes) during 12-month follow-up. A total of 430 patients with documented paroxysmal

AF and without structural heart disease were randomly assigned to treatment with placebo or 40 mg of olmesartan per day. Concomitant treatment with ARA-II, angiotensin-converting enzyme inhibitors or antiarrhythmic drugs was prohibited. The patients were followed up using daily transtelephonic ECG (tele-ECG) recordings, independent of symptoms.

Results: A total of 425 patients were included in the intention-to-treat population (211 in the placebo group and 214 in the olmesartan group). A total of 87 818 tele-ECG recordings were analyzed in these patients during follow-up (44 888 ECG in the placebo group and 42 930 ECG in the olmesartan group). Thus, a mean of 207 tele-ECG per patient were provided, with a mean of 1.12 tele-ECG per patient and day of follow-up. The primary endpoint (AF burden) did not differ between the 2 groups ($P=.77$). Secondary outcome parameters, including the quality of life, also did not differ between the 2 groups. Specifically, the time to the first recurrence of AF, the time to persistent AF, and the number of hospitalizations were identical in the 2 groups. The time to the prescription of recovery medication (amiodarone) was the only parameter that differed between groups, with an earlier prescription of amiodarone in the placebo group ($P=.0365$).

Conclusions: Treatment with ARA-II alone does not reduce the number of AF episodes in patients with documented paroxysmal AF and without structural heart disease. Thus, ARA-II cannot be recommended as first-line treatment for paroxysmal AF if their use is not indicated for other reasons.

SURGERY

ART study: a randomised trial to compare survival following bilateral versus single internal mammary (IMA) grafting in coronary revascularisation²⁰

Presented by D. Taggart (United Kingdom)

Introduction and objectives: Observational data indicate that the use of both internal mammary arteries (BIMA) during coronary artery bypass grafting may provide superior revascularization than that obtained with single internal mammary artery (SIMA) grafting, but remaining concerns over safety have impeded the widespread application of BIMA. The Arterial Revascularization Trial (ART) is a randomized trial of BIMA vs SIMA with the primary endpoint of survival at 10 years. Outcomes at 1 year are reported for mortality, morbidity, and the use of resources.

Methods: Patients undergoing coronary artery bypass grafting in 28 hospitals in 7 countries were included in the study. A total of 3102 patients were randomly assigned to receive SIMA (n = 1554) or BIMA (n = 1548).

Results: The mean number of grafts was 3 in each group. In total, 40% and 42% of the SIMA and BIMA procedures, respectively, were performed offpump. 30-day mortality was 18/1548 (1.2%) with SIMA and 19/1537 (1.2%) with BIMA, and 1-year mortality was 36/1540 (2.3%) and 38/1529 (2.5%), respectively. The rates of stroke, myocardial infarction and repeat revascularization were all $\leq 2\%$ at 1 year and were similar in both groups. Sternal wound reconstruction was needed in 0.6% and 1.9% of the patients in the SIMA and BIMA groups, respectively.

Conclusions: The ART study demonstrates similar outcomes using SIMA and BIMA in clinical endpoints at 1 year, but BIMA grafts are associated with a small absolute increase (1.3%) in the need for sternal wound reconstruction. The results indicate that using BIMA grafting is feasible on a routine basis. The 10-year outcomes of the ART study will confirm whether the use of BIMA grafts leads to decreased mortality and the need for repeat interventions.

INTERVENTIONAL CARDIOLOGY

LESSON I study: long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularisation²¹

Presented by S. Windecker (Switzerland)

Introduction and objectives: Everolimus-eluting stents (EES) have improved clinical outcomes than paclitaxel-eluting stents. However, it remains unclear whether there are differences in safety and efficacy between EES and sirolimus-eluting stents (SES) during long-term follow-up.

Methods: Consecutive patients undergoing percutaneous coronary intervention (PCI) using EES (n=1601) or SES (n=1532) between May 2004 and March 2009 were identified. Propensity score matching was used to compare the clinical outcomes obtained in 1342 pairs of patients treated with EES or SES.

Results: The primary endpoint was the composite of death, myocardial infarction and target vessel revascularization. The median follow-up time was 1.5 years and the results are presented up to 3 years. The hazard ratios (HR) for comparing EES and SES were calculated by Cox regression analysis. The median duration of prescribed dual

antiplatelet therapy was 12 months in both groups. Primary endpoint episodes occurred in 14.9% of the patients in the EES group and in 18% in the SES group up to 3 years (HR=0.83; 95% CI, 0.68-1; $P=.056$). All-cause mortality (6% vs 6.5%; $P=.59$) was similar, whereas the risk of myocardial infarction (3.3% vs 5%; $P=.017$) and target vessel revascularization (7% vs 9.6%; $P=.039$) was lower with EES than with SES. Cases of definite stent thrombosis (HR=0.30; 95% CI, 0.12-0.75, $P=.01$) and definite or probable stent thrombosis (HR=0.64; 95% CI, 0.41-0.98, $P=.041$) were less frequent among patients treated with EES. The lower rate of myocardial infarction with EES was partly explained by the decreased risk of definite stent thrombosis and the corresponding reduction in the events associated with stent thrombosis (HR=0.25; 95% CI, 0.08-0.75; $P=.013$).

Conclusions: The unrestricted use of EES appears to be associated with an improvement in long-term clinical outcomes compared to SES. Differences in favor of EES are partly due to a decreased risk of myocardial infarction associated with stent thrombosis.

ISAR REACT 3A: a trial of reduced doses of unfractionated heparin in patients undergoing PCI²²

Presented by S. Schulz (Germany)

Introduction and objectives: Although a dose of 140 U/kg unfractionated heparin (UFH) was comparable to bivalirudin in net clinical outcome in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 3, its use was associated with an increased risk of bleeding. We designed this study to determine whether reducing the UFH dose from 140 U/kg to 100 U/kg is associated with an improvement in net clinical outcome.

Methods: A total of 2505 patients with negative biomarkers undergoing PCI following pretreatment with clopidogrel who received a single bolus of 100 U/kg of UFH were studied. The primary endpoint was the net clinical outcome (quadruple endpoint of death, myocardial infarction, urgent target-vessel revascularization within 30 days and in-hospital major bleeding defined according to REPLACE 2 criteria). The main comparison was performed with the historical UFH comparison group of the ISAR-REACT 3 trial (2281 patients). In a second analysis, we confirmed noninferiority versus the historical bivalirudin comparison group of the ISAR-REACT 3 trial (2289 patients).

Results: The incidence of the primary endpoint was 7.3% in the lower UFH dose group compared

with 8.7% in the higher UFH dose group (HR=0.81; 95% CI, 0.67-1; $P=.045$). The incidence of major bleeding was 3.6% in the lower UFH dose group and 4.6% in the higher UFH dose group (HR=0.79; 95% CI, 0.59-1.05; $P=.11$). The lower UFH dose met the criterion of noninferiority compared with bivalirudin ($P<.001$).

Conclusions: In patients with negative biomarkers undergoing PCI after receiving loading doses of clopidogrel, a reduced dose of 100 U/kg of UFH led to a net clinical benefit compared to the historical control group receiving 140 U/kg of HNF in the ISAR-REACT 3 trial. The beneficial effect was mainly due to the reduction in bleeding.

FUTURA OASIS 8 study: a randomised trial comparing two regimens of adjunctive intravenous unfractionated heparin during PCI in high-risk patients with non-STEACS treated with fondaparinux²³

Presented by S. Jolly (Canada)

Introduction and objectives: The optimal UFH regimen for PCI in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) receiving fondaparinux remains unclear. The objective of this study was to compare the safety of 2 UFH regimens during PCI in high-risk patients with NSTEACS initially receiving fondaparinux.

Methods: This was a double-blind, randomized, parallel-group trial conducted in 179 hospitals in 18 countries, which included 2026 patients undergoing PCI within a 72-hour period, nested within a cohort

of 3235 high-risk patients with NSTEACS who were initially treated with fondaparinux and included in the study between February 2009 and March 2010. The patients received low-dose UFH, 50 U/kg i.v., regardless of anti-GPIIb/IIIa use, or standard-dose UFH, 85 U/kg (60 U/kg with anti-GPIIb/IIIa), adjusted according to activated clotting time (ACT) using a blinded design. The main outcome measures were the composite of major bleeding events, minor bleeding or major access site complications up to 48 h after PCI. The key secondary endpoints were the composite of major bleeding up to 48 h, together with death, myocardial infarction or target vessel revascularization within 30 days.

Results: There were primary outcome events in 4.7% of the patients in the low-dose group compared with 5.8% in the standard-dose group (odds ratio [OR] = 0.8; 95% CI, 0.54-1.19; $P=.27$). The rates of major bleeding did not differ, but the rates of minor bleeding were lower in the low-dose group (0.7%) than in the standard-dose group (1.7%) (OR=0.4; 95% CI, 0.16-0.97; $P=.04$). For the key secondary endpoint, the rates were 5.8% in the low-dose group compared with 3.9% in the standard-dose group (OR=1.51; 95% CI, 1-2.28; $P=.05$), whereas the rate for death, myocardial infarction or target vessel revascularization were 4.5% in the low-dose group vs 2.9% in the standard-dose group (OR=1.58; 95% CI, 0.98-2.53; $P=.06$). The rates of catheter thrombosis were very low (0.5% in the low-dose group and 0.1% in the standard-dose group; $P=.15$).

Conclusions: The use of low-dose UFH compared to standard-dose UFH did not reduce major periprocedural PCI bleeding or vascular access site complications.

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