Rev Esp Cardiol. 2011;64(11):1011.e1-e8

Special article

Summary of the Clinical Studies Reported in the European Society of Cardiology Congress 2011 (August 27-30, 2011, Paris, France)

Resumen de estudios clínicos presentados en el Congreso de 2011 de la *European Society of Cardiology* (27-30 de agosto de 2011, París, Francia)

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Article history:
Available online 14 October 2011

The European Society of Cardiology held its annual congress in Paris in 2011. 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,[1-6] *Revista Española de Cardiología* presents a summary of these studies which briefly outlines their objectives, methods, and results in line with the oral presentations. The information we offer should be considered preliminary because many of these studies have not yet been published in their final version.

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CARDIOVASCULAR RISK AND COMPLICATIONS

PURE: The Prevention Gaps in 17 low, Middle and High Income Countries Involving Over 150 000 PEOPLE[7]

Presented by S. Yusuf (Canada).

Introduction. Although most cardiovascular disease occurs in low-income and middle-income countries, little is known about the use of effective secondary prevention medications in these communities. We aimed to assess use of proven effective secondary preventive drugs (antiplatelet drugs, β blockers, angiotensin-converting-enzyme [ACE] inhibitors or angiotensin-receptor blockers [ARBs], and statins) in individuals with a history of coronary heart disease or stroke.

Material and methods. In the Prospective Urban Rural Epidemiological (PURE) study, we recruited individuals aged 35-70 years from rural and urban communities in countries at various stages of economic development. We assessed rates of previous cardiovascular disease (coronary heart disease or stroke) and use of proven effective secondary preventive drugs and blood-pressure-lowering drugs with standardised questionnaires, which were completed by telephone interviews, household visits, or on patient's presentation to clinics. We report estimates of drug use at national, community, and individual levels.

Results. We enrolled 153 996 adults from 628 urban and rural communities in countries with incomes classified as high (3 countries), upper-middle (7), lower-middle (3), or low (4) between January, 2003, and December, 2009. 5650 participants had a self-reported coronary heart disease event (median 5 years previously [IQR 2—10]) and 2292 had stroke (4 years previously [2-8]). Overall, few individuals with cardiovascular disease took antiplatelet drugs (25.3%), β blockers (17.4%), ACE inhibitors or ARBs (19.5%), or statins (14.6%). Use was highest in high-income countries (antiplatelet drugs 62%, β blockers 40%, ACE inhibitors or ARBs 49.8%, and statins 66.5%), lowest in low-income countries (8.8%, 9.7%, 5.2%, and 3.3%, respectively), and decreased in line with reduction of country economic status (*P* trend<0.0001 for every drug type). Fewest patients received no drugs in high-income countries (11.2%), compared with 45.1% in upper middle-income countries, 69.3% in lower middle-income countries, and 80.2% in low-income countries. Drug use was higher in urban than rural areas (antiplatelet drugs 28.7% urban vs 21.3% rural, β blockers 23.5% vs 15.6%, ACE inhibitors or ARBs 22.8% vs 15.5%, and statins 19.9% vs 11.6%; all *P*<.0001), with greatest variation in poorest countries (*P* interaction <.0001 for urban vs rural differences by country economic status). Country-level factors (eg, economic status) affected rates of drug use more than did individual-level factors (eg, age, sex, education, smoking status, body-mass index, and hypertension and diabetes statuses).

Conclusions. Because use of secondary prevention medications is low worldwide (especially in low-income countries and rural areas), systematic approaches are needed to improve the long-term use of basic, inexpensive, and effective drugs.

HCS: Prospective Evaluation Pf Post-Prandial Triglycerides And Cardiovascular Events In Patients With Coronary Artery Disease[8]

Presented by U. Laufs (Germany).

Introduction. Risk prediction with fasting serum triglycerides (TG) in high cardiovascular risk patients with normal and impaired glucose tolerance remains uncertain. The role of postprandial serum triglycerides as a risk modifier in secondary prevention is unknown.

Material and methods. An oral triglyceride and glucose tolerance test was developed to obtain standardized measurements of postprandial TG kinetics in 514 consecutive patients with angiographically confirmed coronary artery disease. Follow-up was 18 months and the primary outcome was the composite of cardiovascular death and cardiovascular hospitalization.

Results. Postprandial TG kinetics depended on glucose tolerance: Patients with normal glucose tolerance had lower fasting TG (N=126, 108±42 mg/dl) and a lower absolute postprandial TG increase compared to patients with pathologic glucose metabolism (N=388, fasting TG 172±157 mg/dl) whereas the mean relative TG increase was similar. In the total cohort and in patients with impaired glucose tolerance, postprandial TG did not correlate with the number of primary endpoint events. Fasting TG were predictive in univariate- but not in multivariable analysis. In patients with normal glucose metabolism, fasting TG as well as postprandial TG kinetics (area under the curve and the relative postprandial increase) predicted the occurrence of the primary outcome. They remained independent predictors after adjustment for baseline characteristics, metabolic parameters and cardiovascular risk factors (fasting TG >150 mg/dl vs. <106 mg/dl: HR 3.10 (CI 1.06-9.06), *P*=.04; relative postprandial TG increase >210% vs. <171%: HR 4.45 (CI 1.33-14.91), *P*=.02).

Conclusions. Fasting and postprandial triglyceride values independently predict cardiovascular events in patients with coronary artery disease and normal glucose tolerance.

dal-VESSEL: Efficacy and Safety of Dalcetrapib in Patients With or at Risk of Coronary Heart Disease[9]

Presented by T.F. Lüscher (Switzerland).

Introduction. Dalcetrapib increases high-density lipoprotein cholesterol (HDL-C) levels through effects on cholesteryl ester transfer protein (CETP). As part of the dalcetrapib dal-HEART clinical trial program, the dal-VESSEL study assessed the efficacy and safety of dalcetrapib in coronary heart disease (CHD) patients.

Material and methods. Men and women with CHD or CHD risk equivalent, with HDL-C levels <50 mg/dL were recruited for a 36-week, double-blinded, placebo-controlled trial. After a pre-randomization phase of up to 8 weeks, patients received dalcetrapib 600 mg/day or placebo in addition to their existing treatments. Brachial flow-mediated dilatation (FMD) measured by B-mode ultrasound represents endothelial function and is a validated marker for early atherosclerosis and cardiovascular disease risk. The primary efficacy endpoint was change from baseline in brachial FMD after 12 weeks. The primary safety endpoint was 24-hour ambulatory blood pressure monitoring assessed at week 4. Patients were treated for 36 weeks.

Results. Phase 2 multi-center trial evaluating the feasibility of using FMD and assessment of risk markers. Dalcetrapib reduced CETP activity by almost 50% and increased HDL-C levels by 31% without changing nitric-oxide-dependent endothelial function or markers of inflammation and oxidative stress. No safety signals were observed during the study period; 23 prespecified positively adjucated events occurred, with an even distribution in both treatment arms (11 with dalcetrapib and 12 with placebo).

Conclusions. Dalcetrapib does not worsen endothelial function nor does it raise blood pressure.

ARISTOTLE: Efficacy and Safety of Apixaban Compared to Warfarin for Prevention of Stroke and Systemic Embolism in 18 202 Patients With Atrial Fibrillation: Primary Results[10]

Presented by C.B. Granger (United States).

Introduction. Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several

limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

Material and methods. In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18 201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

Results. The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.6% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; *P*<.001 for noninferiority; *P*=.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; *P*<.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; *P*=.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; *P*<.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; *P*=.42).

Conclusions. In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

CORP: COlchicine for Recurrent Pericarditis (CORP). A Multicenter, Double-Blind, Randomized, Controlled Trial[11]

Presented by M. Imazio (Italy).

Introduction. Recurrences are the most common complications of pericarditis affecting up to 50% of patients (mean 20% to 30%). Aim of the COlchicine for REcurrent pericarditis (CORE) study is to evaluate the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis.

Material and methods. The study is a prospective, randomized, double-blind, placebo-controlled, multicenter trial. We enrolled 120 patients with a first episode of recurrent pericarditis from 4 general hospitals in Italian urban areas. Patients were randomized to receive placebo or colchicine on top of conventional treatment.

Colchicine was given at the dose of 1.0-2.0 mg for the first day followed by a maintenance dose of 0.5-1.0 mg daily for 6 months. The primary study end point was the recurrence rate at 18 months. Secondary end points were symptom persistence at 72 hours, remission rate at 1 week, number of recurrences, time to first recurrence, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis rates.

Results. At 18 months actuarial recurrence rate was 24% in the colchicine group and 55% in the placebo group (absolute risk reduction [ARR], 31%; 95% confidence interval [CI], 13% to 46%; relative risk reduction [RRR], 56%; 95% CI, 27% to 73%; number needed to treat [NNT]=3; 95% CI, 2 to 7). Colchicine reduced the symptoms persistence at 72 hours (ARR, 30%; 95% CI, 13% to 45%; RRR, 56%; 95% CI, 27% to 74%), and the mean number of recurrences, increasing the remission rate at 1 week and prolonging the time to subsequent recurrence. The rate of side effects and drug withdrawal were similar in the study groups.

Conclusions. When added to empiric anti-inflammatory therapy, colchicine appears to be an in-expensive and safe means to hasten symptoms resolution, improve remission rates by 1 week, and reduce recurrences following an initial episode of recurrent pericarditis.

FRONTIERS IN INTERVENTIONAL AND DEVICE TREATMENTS

EVATEL: Remote Follow-up of Patients Implanted With an ICD[12]

Presented by P. Mabo (France).

Introduction. According to manufactor guidelines, a telemetric control of implanted ICD has to be performed every 3 months. Now, device follow-up (FU) may be performed either during in-office visit or by analysing remote data transmitted to implant centre. The aim of the study was to evaluate safety and efficiency of ICD remote FU as compared to conventional in-office FU.

Material and methods. EVATEL is a prospective, randomized, non-inferiority trial, with 2 parallel groups ("control group" with in-office FU and "remote group" with remote FU, conducted in patients with a first single or dual chamber ICD implantation. All commercially available devices with remote features may be implanted. A device FU was performed every 3 months either during in-office visit or remotely according to the randomization arm during an overall 1 year period. The primary endpoint was a composite endpoint: death, cardiovascular hospitalization, inappropriate or ineffective device therapy. A cost-effectiveness evaluation was also planned as a secondary end-point.

Results. 1501 patients were included in 30 French centres from January 2008 to January 2010, the last FU being performed in January 2011. The mean age of pts was 59±13 years with a majority of males (84.9%). The indication for ICD implant was predominantly primary prevention (971 patients, 64.7%). An underlying cardiomyopathy was observed in 1380 patients (92.2%), of ischemic origin in 67.5%. The NYHA class was I or II in 85.7% of patients. All the baseline characteristics were comparable between the 2 groups excepted for history of atrial fibrillation (23.8% vs 18.9%, *P*=.020) and heart failure hospitalisation within the year before inclusion (23.8% vs 18.9%, *P*=.018) more frequently observed in the remote group. Switch from remote to control group before validation of the primary endpoint was observed in 46 patients mainly due to non compatible phone connexion. On per protocol analysis, the primary endpoint was validated in 210 patients (28.5%; 95% CI 25.2 – 31.7) in the control group (n= 738) and in 214 patients (30.2%; 95% CI 26.8 – 33.6) in the remote group (n=696). As the 95% CI of the difference of the event rate was from -3.0 to 6.4% the non inferiority hypothesis with a safety margin of 5% between the 2 groups is not validated. Nevertheless a difference between groups on the primary endpoint has not been demonstrated. The time to occurrence of the first primary endpoint (*P*=.71) and the actuarial survival rate between the 2 groups (p=0.31) did not show any significant difference. The number of inappropriate therapies was lower in the remote group (n=33; 4.7%) as compared to the control group (n=55; 7.5%) (*P*=.03).

Conclusion. Even if the non inferiority hypothesis with a strict safety margin of 5% was not validated, remote FU may be proposed as an alternative for ICD FU as no significant differences were observed between the 2 groups on the primary composite endpoint and on overall mortality. In addition less inappropriate therapies were delivered in the remote group. The cost/effectiveness analysis is still ongoing.

ECOST: Safety of Implantable Cardioverter Defibrillator Follow-up Using Remote Monitoring: A Randomized Controlled Trial[13]

Presented by S. Kacet (France).

Introduction. Implantable cardioverter defibrillators (ICD) remote monitoring, using transmission of clinical and technical data and intracardiac electrograms to a central receiving station, attracts attention from cardiologists as a way to improve quality of care and reduce costs. However, we have limited information on the safety of the system.

Material and methods. The ECOST randomized, multicenter, non-inferiority trial examined the safety of long-term remote monitoring of ICD. Between January 2007 and April 2008, 433 patients were randomly assigned to remote monitoring follow-up (active group) versus standard care (control group). Patients assigned to active group underwent automatic daily remote monitoring and were seen in the ambulatory department at yearly intervals, unless an anomalous ICD function or an event of clinical concern was reported by remote monitoring, requiring an ambulatory visit. Patients assigned to the control group, were followed in the ambulatory department at 6-month intervals. The overall follow-up duration was 27 months. The primary objective was to confirm that the proportion of patients experiencing at least 1 major adverse event (MAE), including all-cause mortality, major cardiac adverse events and major device related adverse events, was not higher in the active than in the control group. Number of delivered shocks and battery longevity were compared in both groups.

Results. The characteristics of the study groups were similar (88% male, 62±13 years, 53.6% primary prevention ICD indication, 30.3% dual chamber implants, 85.3% first implantation, 34.9±13.3% left ventricular ejection fraction). Over a follow-up of 24.2±7.3 months, 38.5% of patients in the active and 41.5% in the control group experienced at least 1 MAE (P<.05 for non-inferiority). The total number of delivered shocks (193 vs. 657) was significantly reduced in the active compared to the control group (P<.05). The total number of inappropriate shocks (28 vs. 283) was also reduced, with a number of patients suffering from inappropriate shocks lower in the active group (11 vs. 22) P<.05. At the end of the study, the battery longevity was greater in the active group because of a number of capacitor charges significantly reduced (499 vs. 2081).

Conclusions. Our results are consistent with, and extend, previous findings by definitively showing that long term remote ICD monitoring is not less safe than conventional follow-up in terms of all cardiac or device related major adverse events and all cause deaths. Moreover it can significantly lower the number of delivered shocks.

EMPHASIS-HF: The Effect of Eplerenone Versus Placebo on Cardiovascular Mortality or Heart Failure Hospitalization in Subjects With NYHA Class II Chronic Systolic Heart Failure: An Analysis of the High-Risk Groups in the Study Population[14]

Presented by B. Pitt (United States).

Introduction. In chronic moderate-to-severe HF and post MI CHF with LVSD, aldosterone antagonists have been shown to improve survival. More recently the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF) demonstrated a reduction of the primary endpoint which was a composite of death from cardiovascular causes and hospitalization for heart failure (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.54 to 0.74; P<.001) in patients with chronic systolic HF in NYHA class II. It is not known however whether eplerenone can improve outcomes in mildly symptomatic patients, especially in the high risk groups defined as age ≥75 years, LVEF<30%, eGFR<60 ml/min/1.73 m^2, diabetes and patients with low BP (<median).

Material and methods. We randomly assigned 2737 patients with New York Heart Association class II heart failure and an ejection fraction of no more than 35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy and analyzed prespecified subgroups of patients with high risk. After the premature stopping of enrollment into the trial due to efficacy (mean FU 21 months) patients had an additional follow-up of up to 7 months.

Results. In the subgroup of patients ≥75 years the HR for the primary endpoint was 0.66 (95% CI, 0.49-0.88; P=.0044). In patients with a LVEF<30% the HR was 0.65 (95% CI, 0.53-0.78; P<.0001); in those with type-2 diabetes the HR was 0.54 (95% CI, 0.42-0.70; P<.0001), in patients with a eGFR <60 ml/min/1.73 m^2 the HR was 0.62 (95% CI, 0.49-0.79; P<.0001) and in patients with a systolic BP < the median of 123 mmHg the HR was 0.62 (95% CI, 0.51-0.79; P<.0001). Additionally, in these five sub-groups, the secondary endpoints of all-cause hospitalization and HF hospitalization achieved statistically significant relative risk reductions for the eplerenone group compared to the placebo group (P<.01). In each of the high risk sub-groups evaluated, patients receiving eplerenone had a significant increase in the incidence of hyperkalemia (K+>5.5 mmol/l). However, there was no significant increase in serious hyperkalemia (K+>6.0 mmol/l), hyperkalemia leading to drug discontinuation, hospitalization for hyperkalemia, or hospitalization for worsening renal function. The beneficial effect of eplerenone on the primary endpoint of the EMPHASIS trial (death from cardiovascular causes and hospitalization for heart failure) remained significant over an additional follow-up of up to 7 months (HR 0.66; 95% CI, 0.57-0.77; P<.0001).

Conclusions. The consistency of the efficacy and safety of eplerenone in addition to standard therapy on pre-specified high-risk subgroups and the persistence of a significant beneficial effect on the primary endpoint (cardiovascular mortality or hospitalization for heart failure) over an additional up-to 7 months of follow-up on double-blind therapy in conjunction with prior beneficial results from EPHESUS presents compelling evidence for the use of eplerenone in patients with systolic heart failure and mild symptoms.

RESET: One-year Outcome of the Randomized Evaluation of Sirolimus-Eluting Versus Everolimus-Eluting Stent Trial[15]

Presented by T. Kimura (Japan).

Introduction. Everolimus-eluting stent (EES) as compared with paclitaxel-eluting stent consistently demonstrated superior clinical outcomes in previous randomized controlled trials. Several recent randomized trials suggested similar one-year clinical outcomes between EES and sirolimus-eluting stent (SES). However, none of these trials was adequately powered to evaluate the efficacy outcomes after stent implantation such as target-lesion revascularization (TLR) or target-vessel revascularization (TVR).

Material and methods. Randomized Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial (RESET) is a prospective randomized multicenter open label trial comparing EES with SES in daily clinical practice in Japan. Patients scheduled for percutaneous coronary intervention using drug-eluting stents were enrolled without any exclusion criteria. Randomization was performed at any time before attempt of stent implantation and was stratified by center, diabetes, and participation in the imaging sub-studies (angiography, intravascular ultrasound, optical coherence tomography, and coronary endothelial function). Primary efficacy endpoint was defined as any TLR. The trial was a sequential non-inferiority and superiority study, which was powered for non-inferiority on the

primary efficacy endpoint at 1 year after the index procedure. Primary safety endpoint was defined as a composite of death or myocardial infarction at 3 years after the index procedure. Lesions treated at the index PCI procedure were regarded as the target lesions, while lesions treated at the scheduled staged procedures were not included in the target lesions.

Results. Between February and July 2010, a total of 3206 patients were enrolled in the trial among 100 participating centers. Excluding 9 patients who withdrew consent, 3197 patients with 3927 lesions were randomly assigned to receive either EES (1597 patients with 1967 lesions) or SES (1600 patients with 1960 lesions). The study population included large proportions of patients with advanced age, diabetes, and prior PCI. However, mean SYNTAX scores were relatively low (EES: 11.3 ± 7.4, and SES: 11.1 ± 7.1, *P*=.6), suggesting inclusion of patients with less complex coronary anatomy. The two groups of patients were well balanced in terms of baseline clinical, angiographic and procedural characteristics. EES was non-inferior to SES with respect to the primary clinical endpoint, which occurred in 4.3% and 5.0% of patients, respectively (*P*<.0001 for non-inferiority, and *P*=.34 for superiority). There were no significant between-group differences in the rate of death, myocardial infarction, clinically-driven TLR, TVR, and a composite of death or myocardial infarction. The rate of stent thrombosis (definite or probable) was very low in both groups (EES: 0.39%, and SES: 0.38%, *P*=1.0). Among the pre-specified subgroup analyses, EES as compared with SES was associated significantly lower rate of TLR in the subgroup of insulin-treated diabetes (EES [N=175]: 5.4%, and SES [N=163]: 12.3%, *P*=.03). EES was also non-inferior to SES with respect to the primary angiographic endpoint (0.07±0.38 mm versus 0.03±0.46 mm, *P*<.0001 for non-inferiority, and *P*=.26 for superiority).

Conclusions. In this large scale randomized controlled trial comparing EES with SES, EES was demonstrated to be non-inferior to SES with respect to TLR rate at 1 year and angiographic in-segment late loss at 8-12 months. One-year clinical outcome after both EES- and SES-use was excellent with low rate of TLR and very low rate of stent thrombosis. Longer-term follow-up is important to address whether EES could positively affect the late adverse events beyond 1 year reported after SES implantation such as late restenosis and very late stent thrombosis.

Comparison of Three-Year Outcome After PCI and CABG Stratified by the SYNTAX Score in Patients With Triple Vessel Coronary Artery Disease: An Observation From the CREDO-Kyoto PCI/CABG REGISTRY COHORT-2[16]

Presented by H. Shiomi (Japan).

Introduction. Long-term outcome of percutaneous coronary intervention (PCI) compared with coronary artery bypass grafting (CABG) in patients with triple vessel coronary artery disease (TVD) remains to be elucidated. The aim of the study was to compare long-term outcome after PCI and CABG in TVD patients stratified by the SYNTAX score.

Material and methods. We identified 2981 patients with TVD (PCI: N=1825, CABG: N=1156) among 15 263 patients with first coronary revascularization enrolled in the CREDO-Kyoto PCI/CABG registry cohort-2. Main outcome measure of the current analysis is a composite of death/myocardial infarction (MI)/stroke .

Results. PCI as compared with CABG was associated with higher 3-year risk for the primary endpoint (adjusted hazard ratio [HR]=1.47; 95% confidence interval [CI], 1.13-1.92; *P*=.004), and MI (HR=2.39 [95%CI, 1.31-4.36; *P*=.004]). Although the risk for all-cause death was significantly higher after PCI (HR=1.62; 95%CI, 1.16-2.27; *P*=.005), risk for cardiac death was not significantly different (HR=1.30; 95%CI, 0.81-2.07; *P*=.28]). Cumulative incidence of the primary endpoint was not different between the PCI and CABG groups in patients with low (<23, N=874 and N=257) and intermediate SYNTAX score (23-32, N=638 and N=388), while in patients with high SYNTAX score (≥ 33, N=280 and N=375), it was markedly higher after PCI than after CABG (15.8% and 12.5%, P=.25, 18.8% and 16.7%, P=.24, and 27.0% and 16.4%, P=.004, respectively). However, the adjusted risk of PCI relative to CABG for the primary endpoint was HR=1.66 (95% CI, 1.04-2.65; *P*=.03) in the low-score category, HR=1.24 (95% CI, 0.83-1.85; *P*=.29) in the intermediate-score category, and HR=1.59 (95% CI, 0.998-2.54; *P*=.051) in the high-score category, respectively.

Conclusions. PCI as compared with CABG was associated with significantly higher risk for serious adverse events in TVD patients. Further studies are warranted to investigate whether PCI could be a viable option in TVD patients with less complex coronary anatomy.

ACUTE CORONARY SYNDROMES

PRODIGY: Randomized Comparison of 6 Versus 24 Months Clopidogrel Therapy After Balancing Anti-Intimal Hyperplasia Stent Potency in all Comer Patients Undergoing Percutaneous Coronary Intervention. Results of the PRODIGY Trial[17]

Presented by M. Valgimigli (Italy).

Introduction. Data suggest that a certain patient population may benefit from prolonged dual antiplatelet therapy. The aim of the study was to evaluate the efficacy and safety of prolonged antiplatelet therapy in patients with coronary disease.

Material and methods. PRODIGY study is a 4-by-2 randomized, 3-center open-label clinical trial. In total, 2013 patients (74% with acute coronary syndromes and 26% with stable angina) were scheduled for elective, urgent, or emergency coronary angioplasty and randomly assigned in a 1:1:1:1 fashion to one of 4 stent types: everolimus-eluting stent, paclitaxel-eluting stent, zotarolimus-eluting stent, or third-generation thin-strut bare metal stent. At 30 days, patients in each stent group were then further randomized to either 6 or 24 months of dual antiplatelet treatment (clopidogrel plus aspirin). The primary objective of the study was to assess whether 24-month dual antiplatelet treatment, consisting of clopidogrel and aspirin after coronary stenting, was associated with a lower cumulative incidence of all-cause mortality, non-fatal myocardial infarction, or cerebrovascular accident (the primary outcome) than 6-month dual therapy at 2-year follow up.

Results. The cumulative risk of the primary outcome at 2 years was 10.1% with the 24-month treatment, and 10.0% with the 6-month treatment (HR=0.98; 95% CI, 0.74-1.29; *P*=.91). The individual risks of death, myocardial infarction, cerebrovascular accident, or stent thrombosis did not differ between groups. Among the patients receiving long-term dual antiplatelet therapy, there was a roughly 2-fold greater risk of type 5, 3, or 2 bleeding events (HR=2.17; 95% CI, 1.44-3.22; *P* = .00018) as well as type 5 or 3 bleeding events (HR=1.78; 95% CI, 1.02-3.13; *P* = .037) according to the Bleeding Academic Research Consortium classification. The risks of TIMI-defined major bleeding and red blood cell transfusion were also increased in the 24-month clopidogrel group.

Conclusions. Prolonging therapy with clopidogrel beyond 6 months after coronary stenting is not only associated with no clinical benefit but also with a significant increase in actionable bleeding events requiring rehospitalizations and multiple diagnostic and therapeutic resources.

The RUBY-1 Trial: Safety, Tolerability and Efficacy of YM150, an Oral Factor Xa Inhibitor, in Secondary Prevention of Ischaemic Vascular Events in Patients Following a Acute Coronary Syndrome[18]

Presented by P.G. Steg (France).

Introduction. The aim of the study was to establish the safety, tolerability and most promising regimen of darexaban (YM150), a novel, oral, direct factor Xa inhibitor, for prevention of ischaemic events in acute coronary syndrome (ACS).

Material and methods. In a 26-week, multi-centre, double-blind, randomized, parallel-group study, 1279 patients with recent high-risk non-ST-segment or ST-segment elevation ACS received one of six darexaban regimens: 5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d., or 60 mg o.d. or placebo, on top of dual antiplatelet treatment. Primary outcome was incidence of major or clinically relevant non-major bleeding events. The main efficacy outcome was a composite of death, stroke, myocardial infarction, systemic thromboembolism, and severe recurrent ischaemia.

Results. Bleeding rates were numerically higher in all darexaban arms vs. placebo (pooled HR= 2.275; 95% CI, 1.13-4.60, *P*=.022). Using placebo as reference (bleeding rate 3.1%), there was a dose-response relationship (*P*=.009) for increased bleeding with increasing darexaban dose (6.2, 6.5, and 9.3% for 10, 30, and 60 mg daily, respectively), which was statistically significant for 30 mg b.i.d. (*P*=.002). There was no decrease (indeed a numerical increase in the 30 and 60 mg dose arms) in efficacy event rates with darexaban, but the study was underpowered for efficacy. Darexaban showed good tolerability without signs of liver toxicity.

Conclusions. Darexaban when added to dual antiplatelet therapy after ACS produces an expected dose-related two- to four-fold increase in bleeding, with no other safety concerns but no signal of efficacy. Establishing the potential of low-dose darexaban in preventing major cardiac events after ACS requires a large phase III trial.

The EXAMINATION Trial: A Randomized Comparison Between Everolimus-Eluting Stent and Bare Metal Stent in Patients With ST-Segment Elevation Myocardial Infarction[19]

Presented by M. Sabaté (Spain).

Introduction. The use of drug-eluting stents in the acute phase of ST-segment elevation myocardial infarction (STEMI) is still controversial. First generation drug-eluting stents (DES) have demonstrated to be efficacious and safe in randomized controlled trials with strict inclusion and exclusion criteria. No data have been generated so far by the use of currently available second generation DES in STEMI. The aim of this study is to assess, in a multicenter randomized controlled trial with an "all-comers" design, the safety and performance of the Everolimus-Eluting Stent (EES) versus a cobalt chromium bare metal stent (BMS) in the setting of percutaneous coronary intervention (PCI) for treatment of patients presenting with STEMI.

Material and methods. The Evaluation of Xience-V™ stent in Acute Myocardial INfArcTION (EXAMINATION) trial randomly assigned (1:1) either EES or BMS to patients fulfilling any of the following inclusion criteria: STEMI <12 hours after the onset of symptoms; rescue PCI after failed thrombolysis; PCI indicated early (<24 h) after effective thrombolysis; and, ST-elevation myocardial infarction (>12 h-48 h) after the onset of symptoms ("latecomers"). The main clinical exclusion criteria were patients suffering from stent thrombosis as a cause of STEMI and patients receiving anti-vitamin K therapy. The only angiographic exclusion criterion was a vessel size <2.25 mm or >4.0 mm (visual estimate). The primary endpoint was the composite of all-cause death, any myocardial infarction and any revascularization at 1 year (patient-oriented endpoint according to ARC definitions). Secondary endpoints included the individual components of the primary endpoint, stent thrombosis according to ARC definitions and bleeding.

Results. Between December 2008 and May 2010 a total of 1,498 patients have been included in this trial (EES group, 751; BMS group, 747). This figure represents up to 70% of the total number of patients suffering from STEMI during the recruitment period. Mean age was 61.2±12.4 years; 83% male. Main coronary risk factors included: smoking (72.2%); hypertension (48.4%); diabetes (17.2%); dyslipidemia (43.8%); and, family history (16.4%). Most of patients were included as STEMI <12 hours (84.6%). Rescue PCI involved 6.5% of patients, PCI early after successful thrombolysis 2.3% and, latecomers 6.5%. Most of patients were in Killip class I (89.6%). Target lesion was most often located in the right coronary artery (43.6%), followed by left anterior descending artery (40.6%). Antithrombotic regimen included unfractioned heparin (78%); low molecular weight heparin (9.1%) and bivalirudin (7.1%). Overall, IIb/IIIa inhibitors were administered in 53% of patients. Manual thrombectomy was used in 65.4% of patients. At 1-year clinical follow-up the rate of the primary endpoint was 13.9% for BMS group and 11.9% for the EES group (*P*=.3). All cause death rate accounted for 3.5% in each group; any myocardial infarction rate was 2.0% in BMS versus 1.3% in EES (*P*=.3). Any revascularization rate was 10.3% in BMS vs. 8 in EES (*P*=.1). The rates of definitive and definitive/probable stent thrombosis were significantly lower in the EES group (0.5% and 0.9% vs. 1.9% and 2.5%, respectively; both *P*=.01).

Conclusions. The use of EES in the setting of STEMI resulted in a numerically (not significantly) reduced primary endpoint at the expense of a trend in reduction the repeat revascularization rate. The significant reduction observed in the definite and definite/probable stent thrombosis rates suggest an excellent safety profile of the EES in this high risk patients presenting with STEMI. The results of this "all-comer" randomized trial are highly representative of the real world population.

Newer Generation Everolimus-Eluting Stents Eliminate the Risk of Very Late Stent Thrombosis Compared With Early Generation Sirolimus-Eluting and Paclitaxel-Eluting Stents[20]

Presented by L. Räber (Switzerland).

Introduction. Early generation drug-eluting stents (DES) releasing sirolimus (SES) or paclitaxel (PES) are associated with an increased risk of very late stent thrombosis (VLST). It is unknown whether the risk of VLST persists with newer generation DES releasing everolimus (EES).

Material and methods. A cohort of 12,339 patients treated with the unrestricted use of DES (3,819 SES, 4,308 PES, 4,212 EES) at two academic institutions between 2002 and 2009 were followed for a median of 2.9 years. The primary endpoint was ARC definite ST through 4 years. Results are reported as cumulative incidence per 100 person-years (CIR) and hazards are weighted using inverse probability of treatment weight to adjust for group differences.

Results. During follow-up to 4 years, the overall CIR of definite ST was lower with EES (1.4%) compared with SES (2.9%; hazard ratio [HR]=0.41; 95% CI, 0.27-0.62, *P*<.0001) and PES (4.4%; HR=0.33; 95% CI, 0.23-0.48; *P*<.0001). The CIR of early, late, and VLST amounted to 0.6%, 0.1%, and 0.6% among EES, 1.0%, 0.3%, and 1.6% among SES, and 1.3%, 0.7%, and 2.4% among PES treated patients, respectively. Differences in favour of EES were most pronounced during the very late period with a 67% (EES vs SES *P*=.006) and 76% (EES vs PES *P*<.0001) risk reduction, respectively. There was a trend towards a lower risk of cardiac death or MI with EES compared with SES

(HR=0.88; 95%CI, 0.75-1.02, *P*=.09) and a significant reduction with EES compared with PES (HR= 0.67; 95% CI, 0.58-0.77; *P*<.0001), which was directly related to the lower risk of ST associated events (EES vs. SES: HR=0.46; 95% CI, 0.26-0.81; EES vs. PES, HR=0.36; 95% CI, 0.23-0.57).

Conclusions. Newer generation EES reduce the risk of definite ST compared with early generation DES during long-term follow-up. The near elimination of VLST with the unrestricted use of EES overcomes the principal limitation of early generation DES and constitutes an important advance in DES safety.

CRISP AMI: A Multi-Center, Randomized, Controlled Study of Mechanical Left Ventricular Unloading With Counterpulsation to Reduce Infarct Size Pre-PCI for Acute Myocardial Infarction: Rationale and Design of the CRISP AMI Trial[21]

Presented by M. Patel (United States).

Introduction. Intra-aortic balloon counterpulsation (IABC) is an adjunct to revascularization in patients with cardiogenic shock and reduces infarct size when placed prior to reperfusion in animal models. The aim of the study was to determine if routine IABC placement prior to reperfusion in patients with anterior ST-segment elevation myocardial infarction (STEMI) without shock reduces myocardial infarct size.

Material and methods. An open, multicenter, randomized controlled trial, the Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP AMI) included 337 patients with acute anterior STEMI but without cardiogenic shock at 30 sites in 9 countries from June 2009 through February 2011. IABC was initiated before primary percutaneous coronary intervention (PCI) and continued for at least 12 hours (IABC plus PCI) vs primary PCI alone. The primary endpoint was measurement of infarct size expressed as a percentage of left ventricular (LV) mass, measured by cardiac magnetic resonance imaging performed 3 to 5 days after PCI. Secondary end points included all-cause death at 6 months and vascular complications and major bleeding at 30 days.

Results. The median time from first contact to first coronary device was 77 minutes (interquartile range, 53 to 114 minutes) for the IABC plus PCI group vs 68 minutes (interquartile range, 40 to 100 minutes) for the PCI alone group (P =0.04). The mean infarct size was not significantly different between the patients in the IABC plus PCI group and in the PCI alone group (42.1% [95% CI, 38.7% to 45.6%] vs 37.5% [95% CI, 34.3% to 40.8%], respectively; difference of 4.6% [95% CI, −0.2% to 9.4%], *P*=.06; imputed difference of 4.5% [95% CI, −0.3% to 9.3%], *P*=.07) and in patients with proximal left anterior descending Thrombolysis in Myocardial Infarction flow scores of 0 or 1 (46.7% [95% CI, 42.8% to 50.6%] vs 42.3% [95% CI, 38.6% to 45.9%], respectively; difference of 4.4% [95% CI, −1.0% to 9.7%], *P*=.11; imputed difference of 4.8% [95% CI, −0.6% to 10.1%], *P*=.08). At 30 days, there were no significant differences between the IABC plus PCI group and the PCI alone group for major vascular complications (n=7 [4.3%; 95% CI, 1.8% to 8.8%] vs n=2 [1.1%; 95% CI, 0.1% to 4%], respectively; *P*=.09) and major bleeding or transfusions (n=5 [3.1%; 95% CI, 1% to 7.1%] vs n=3 [1.7%; 95% CI, 0.4% to 4.9%]; *P*=.49). By 6 months, 3 patients (1.9%; 95% CI, 0.6% to 5.7%) in the IABC plus PCI group and 9 patients (5.2%; 95% CI, 2.7% to 9.7%) in the PCI alone group had died (*P*=.12).

Conclusions. Among patients with acute anterior STEMI without shock, IABC plus primary PCI compared with PCI alone did not result in reduced infarct size.

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