Special article

Summary of the Clinical Studies Reported in the European Society of Cardiology Congress 2013 (31 August – 4 September, 2013, Amsterdam, The Netherlands)

Resumen de estudios clínicos presentados en el Congreso de 2013 de la Sociedad Europea de Cardiología (31 de agosto-4 de septiembre de 2013, Ámsterdam, Países Bajos)

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The European Society of Cardiology held its annual congress in Amsterdam in 2013. 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, *Revista Española de Cardiología* presents a summary of these studies that 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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THROMBOSIS

The Hokusai VTE study: Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism[1]

Presented by Harry Buller (Amsterdam, The Netherlands).

Background. Whether the oral factor Xa inhibitor edoxaban can be an alternative to warfarin in patients with venous thromboembolism is unclear.

Methods. In a randomized, double-blind, noninferiority study, we randomly assigned patients with acute venous thromboembolism, who had initially received heparin, to receive edoxaban at a dose of 60 mg once daily, or 30 mg once daily (e.g., in the case of patients with creatinine clearance of 30 to 50 ml per minute or a body weight below 60 kg), or to receive warfarin. Patients received the study drug for 3 to 12 months. The primary efficacy outcome was recurrent symptomatic venous thromboembolism. The principal safety outcome was major or clinically relevant nonmajor bleeding.

Results. A total of 4921 patients presented with deep-vein thrombosis, and 3319 with a pulmonary embolism. Among patients receiving warfarin, the time in the therapeutic range was 63.5%. Edoxaban was noninferior to warfarin with respect to the primary efficacy outcome, which occurred in 130 patients in the edoxaban group (3.2%) and 146 patients in the warfarin group (3.5%) (HR=0.89; 95% confidence interval [CI], 0.70 to 1.13; *P*<.001 for noninferiority). The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group (HR=0.81; 95% CI, 0.71 to 0.94; *P*=.004 for superiority). The rates of other adverse events were similar in the two groups. A total of 938 patients with pulmonary embolism had right ventricular dysfunction, as assessed by measurement of N-terminal pro–brain natriuretic peptide levels; the rate of recurrent venous thromboembolism in this subgroup was 3.3% in the edoxaban group and 6.2% in the warfarin group (HR=0.52; 95% CI, 0.28 to 0.98).

Conclusions. Edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism.

TASTE: Thrombus Aspiration During ST-segment Elevation Myocardial Infarction. A Multicenter, Prospective, Registry Based Randomized Clinical Trial[2]

Presented by Ole Frobert (Orebro, Sweden).

Background. The clinical effect of routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with STEMI is uncertain. We aimed to evaluate whether thrombus aspiration reduces mortality.

Methods. We conducted a multicenter, prospective, randomized, controlled, open-label clinical trial, with enrollment of patients from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and end points evaluated through national registries. A total of 7244 patients with STEMI undergoing PCI were randomly assigned to manual thrombus aspiration followed by PCI or to PCI only. The primary end point was all-cause mortality at 30 days.

Results. No patients were lost to follow-up. Death from any cause occurred in 2.8% of the patients in the thrombus-aspiration group (103 of 3621), as compared with 3.0% in the PCI-only group (110 of 3623) (HR=0.94; 95% Confidence Interval [CI], 0.72 to 1.22; *P*=.63). The rates of hospitalization for recurrent myocardial infarction at 30 days

were 0.5% and 0.9% in the two groups, respectively (HR=0.61; 95% CI, 0.34 to 1.07; *P*=.09), and the rates of stent thrombosis were 0.2% and 0.5%, respectively (HR=0.47; 95% CI, 0.20 to 1.02; *P*=.06). There were no significant differences between the groups with respect to the rate of stroke or neurologic complications at the time of discharge (*P*=.87). The results were consistent across all major prespecified subgroups, including subgroups defined according to thrombus burden and coronary flow before PCI.

Conclusions. Routine thrombus aspiration before PCI as compared with PCI alone did not reduce 30-day mortality among patients with STEMI.

TAO: Otamixaban in Non-ST-segment Elevation Acute Coronary Syndrome patients Undergoing a planned Invasive Strategy[3]

Presented by Philippe Gabriel Steg (Paris Cedex, France).

Background. The optimal anticoagulant for patients with non–ST-segment elevation acute coronary syndromes (NSTEACS) managed with an invasive strategy remains controversial. The objective was to compare the clinical efficacy and safety of otamixaban, a novel intravenous direct factor Xa inhibitor, with that of unfractionated heparin plus downstream eptifibatide in patients with NSTEACS undergoing a planned early invasive strategy.

Methods. Randomized, double-blind, active-controlled superiority trial that enrolled 13 229 patients with NSTEACS and a planned early invasive strategy, at 568 active sites in 55 countries and conducted between April 2010 and February 2013. A planned interim analysis was conducted for otamixaban dose selection. Eligible participants were randomized to otamixaban (bolus and infusion, at 1 of 2 doses) or unfractionated heparin plus, at the time of PCI, eptifibatide. The otamixaban dose selected at interim analysis was an intravenous bolus of 0.080 mg/kg followed by an infusion of 0.140 mg/kg per hour. The primary efficacy outcome was the composite of all-cause death or new myocardial infarction through day 7.

Results. Rates of the primary efficacy outcome were 5.5% (279 of 5105 patients) randomized to receive otamixaban and 5.7% (310 of 5466 patients) randomized to receive unfractionated heparin plus eptifibatide (adjusted relative risk, 0.99 [95%CI, 0.85-1.16]; *P*=.93). There were no differences for the secondary end points, including procedural thrombotic complications. The primary safety outcome of Thrombosis in Myocardial Infarction major or minor bleeding through day 7 was increased by otamixaban (3.1%vs 1.5%; relative risk, 2.13 [95%CI, 1.63-2.78]; P < .001). Results were consistent across prespecified subgroups.

Conclusions. Otamixaban did not reduce the rate of ischemic events relative to unfractionated heparin plus eptifibatide but did increase bleeding. These findings do not support the use of otamixaban for patients with NSTE-ACS undergoing planned early PCI.

RE-ALIGN: Dabigatran in Patients With a Mechanical Heart Valve[4]

Presented by Frans Van de Werf (Leuven, Belgium).

Background. Dabigatran is an oral direct thrombin inhibitor that has been shown to be an effective alternative to warfarin in patients with atrial fibrillation. We evaluated the use of dabigatran in patients with mechanical heart valves.

Methods. In this phase 2 dose-validation study, we studied two populations of patients: those who had undergone aortic- or mitral-valve replacement within the past 7 days and those who had undergone such replacement at least 3 months earlier. Patients were

randomly assigned in a 2:1 ratio to receive either dabigatran or warfarin. The selection of the initial dabigatran dose (150, 220, or 300 mg twice daily) was based on kidney function. Doses were adjusted to obtain a trough plasma level of at least 50 ng per milliliter. The warfarin dose was adjusted to obtain an international normalized ratio of 2 to 3 or 2.5 to 3.5 on the basis of thromboembolic risk. The primary end point was the trough plasma level of dabigatran.

Results. The trial was terminated prematurely after the enrollment of 252 patients because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. In the as-treated analysis, dose adjustment or discontinuation of dabigatran was required in 52 of 162 patients (32%). Ischemic or unspecified stroke occurred in 9 patients (5%) in the dabigatran group and in no patients in the warfarin group; major bleeding occurred in 7 patients (4%) and 2 patients (2%), respectively. All patients with major bleeding had pericardial bleeding.

Conclusions. The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk.

PARIS: Incidence and Impact of Dual Antiplatelet Therapy Cessation On Adverse Cardiac Events Following Percutaneous Coronary Intervention: Two-Year Results from the Patterns of Non-Adherence to Antiplatelet Regimens In Stented Patients Study[5]

Presented by Roxana Mehran (New York, United States).

Background. Dual antiplatelet therapy (DAPT) cessation increases the risk of adverse events after PCI. Whether the risk changes over time, depends on the underlying reason for DAPT cessation, or both is unknown. We assessed associations between different modes of DAPT cessation and cardiovascular risk after PCI.

Methods. The PARIS (patterns of nonadherence to antiplatelet regimens in stented patients) registry is a prospective observational study of patients undergoing PCI with stent implantation in 15 clinical sites in the United States and Europe between July 1, 2009, and Dec 2, 2010. Adult patients (aged 18 years or older) undergoing successful stent implantation in one or more native coronary artery and discharged on DAPT were eligible for enrollment. Patients were followed up at months 1, 6, 12, and 24 after implantation. Prespecified categories for DAPT cessation included physician-recommended discontinuation, brief interruption (for surgery), or disruption (nonadherence or because of bleeding). All adverse events and episodes of DAPT cessation were independently adjudicated. Using Cox models with time-varying covariates, we examined the effect of DAPT cessation on major adverse events (MACE [composite of cardiac death, definite or probable stent thrombosis, myocardial infarction, or target-lesion revascularization]). Incidence rates for DAPT cessation and adverse events were calculated as Kaplan-Meier estimates of time to the first event.

Results. We enrolled 5031 patients undergoing PCI, including 5018 in the final study population. Over 2 years, the overall incidence of any DAPT cessation was 57.3%. Rate of any discontinuation was 40.8%, of interruption was 10.5%, and of disruption was 14.4%. The corresponding overall 2-year MACE rate was 11.5%, most of which (74%) occurred while patients were taking DAPT. Compared with those on DAPT, the adjusted HR for MACE due to interruption was 1.41 (95% CI 0.94–2.12; *P*=.10) and to disruption was 1.50 (1.14–1.97; *P*=.004). Within 7 days, 8 to 30 days, and more than 30 days after disruption, adjusted HRs were 7.04 (3.31–14.95), 2.17 (0.97–4.88), and 1.3 (0.97–1.76), respectively. By contrast with patients who remained on DAPT, those who discontinued had lower MACE risk (0.63 [0.46–0.86]). Results were similar after excluding patients receiving bare metal

stents and using an alternative MACE definition that did not include target lesion revascularization.

Conclusions. In a real-world setting, for patients undergoing PCI and discharged on DAPT, cardiac events after DAPT cessation depend on the clinical circumstance and reason for cessation, and attenuate over time. While most events after PCI occur in patients on DAPT, early risk for events due to disruption is substantial irrespective of stent type.

INTERVENTION AND DEVICES

PRAMI: Preventive Angioplasty in Myocardial Infarction Trial[6]

Presented by David Wald (London, Great Britain).

Background. In acute STEMI, the use of PCI to treat the artery responsible for the infarct (infarct, or culprit, artery) improves prognosis. The value of PCI in noninfarct coronary arteries with major stenoses (preventive PCI) is unknown.

Methods. From 2008 through 2013, at 5 centers in the United Kingdom, we enrolled 465 patients with acute STEMI (including 3 patients with left bundle-branch block) who were undergoing infarct-artery PCI and randomly assigned them to either preventive PCI (234 patients) or no preventive PCI (231 patients). Subsequent PCI for angina was recommended only for refractory angina with objective evidence of ischemia. The primary outcome was a composite of death from cardiac causes, nonfatal myocardial infarction, or refractory angina. An intention-to-treat analysis was used.

Results. By January 2013, the results were considered conclusive by the data and safety monitoring committee, which recommended that the trial be stopped early. During a mean follow-up of 23 months, the primary outcome occurred in 21 patients assigned to preventive PCI and in 53 patients assigned to no preventive PCI (infarct artery-only PCI), which translated into rates of 9 events per 100 patients and 23 per 100, respectively (HR in the preventive-PCI group, 0.35; 95% CI, 0.21 to 0.58; *P*<.001). The HRs for the 3 components of the primary outcome were 0.34 (95% CI, 0.11 to 1.08) for death from cardiac causes, 0.32 (95% CI, 0.13 to 0.75) for nonfatal myocardial infarction, and 0.35 (95% CI, 0.18 to 0.69) for refractory angina.

Conclusions. In patients with STEMI and multivessel coronary artery disease undergoing infarct artery PCI, preventive PCI in noninfarct coronary arteries with major stenoses significantly reduced the risk of adverse cardiovascular events, as compared with PCI limited to the infarct artery.

ACCOAST: A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pre-treatment at the Time of Diagnosis in Patients with Non-ST-elevation Myocardial Infarction[7]

Presented by Gilles Montalescot (Paris, France).

Background. Although P2Y12 antagonists are effective in patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) acute coronary syndromes, the effect of the timing of administration –before or after coronary angiography- is not known. We evaluated the effect of administering the P2Y12 antagonist prasugrel at the time of diagnosis vs administering it after the coronary angiography if PCI was indicated.

Methods. We enrolled 4033 patients with NSTEACS and a positive troponin level who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization. Patients were randomly

assigned to receive prasugrel (a 30-mg loading dose) before the angiography (pretreatment group) or placebo (control group). When PCI was indicated, an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI and 60 mg of prasugrel was given in the control group.

Results. The rate of the primary efficacy end point, a composite of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7, did not differ significantly between the two groups (HR with pretreatment, 1.02; 95% CI, 0.84 to 1.25; *P*=.81). The rate of the key safety end point of all Thrombolysis in Myocardial Infarction (TIMI) major bleeding episodes, whether related or not related to coronary-artery bypass grafting (CABG), through day 7 was increased with pretreatment (HR=1.90; 95% CI, 1.19 to 3.02; *P*=.006). The rates of TIMI major bleeding and life-threatening bleeding not related to CABG were increased by a factor of 3 and 6, respectively. Pretreatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days. All the results were confirmed at 30 days and in prespecified subgroups.

Conclusions. Among patients with NSTEACS acute coronary syndromes who were scheduled to undergo catheterization, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications.

DECAAF: Delayed Enhancement – MRI Determinant of Successful Catheter Ablation of Atrial Fibrillation: Analysis of Post Ablation Scar and Outcome[8]

Presented by Nassir Marrouche (Salt Lake City, United States).

Background. We are still debating what the best strategy is and where to ablate.

Methods. In total, 260 patients with atrial fibrillation, including 65% with paroxysmal atrial fibrillation, were included in the study. All patients underwent a preablation MRI up to 30 days before the procedure and 90 days following the ablation. Based on the degree of atrial remodeling/fibrosis, patients were classified into 4 groups: stage 1 (<10% fibrosis), stage 2 (>10% to <20% fibrosis), stage 3 (>20% to <30% fibrosis), and stage 4 (>30% fibrosis).

Results. After adjustment for multiple variables, including age, gender, hypertension, comorbidities, type of atrial fibrillation, left atrial volume, and left ventricular ejection fraction, the extent of atrial disease was the only significant predictor of atrial-fibrillation recurrence. Each 1% increase in the extent of atrial fibrosis was associated with a significant 5.8% increased risk of recurrence postablation. For patients classified with stage 1 scarring, 84.6% were free from the arrhythmia at one year compared with just 31% of patients with stage 4 fibrosis. Overall, 64% and 54% of patients with stage 2 and 3 fibrosis were arrhythmia-free at one year.

Conclusions. The extent of atrial disease was the only predictor of outcomes.

PRAGUE 14: Perioperative Ischemia Versus Perioperative Bleeding in Consecutive Cardiac Patients Undergoing Noncardiac Surgery[9]

Presented by Petr Widimsky (Prague, Czech Republic).

Background. Modern therapy of most cardiac diseases includes some form of antithrombotic therapy. Surgeons usually recommend stopping all antithrombotic medication 1 week before surgery to prevent perioperative bleeding. This strategy may increase the risk of

perioperative ischemic or thrombotic complications. This study was designed to collect data from all consecutive patients with heart disesase undergoing noncardiac surgery in order to analyze the bleeding/ischemic risk balance.

Methods. All departments performing major noncardiac surgery in a large tertiary university hospital participated: abdominal surgery, vascular surgery, oncologic surgery, trauma surgery, orthopedic surgery, urology, neurosurgery and anesthesiology. The study was designed and coordinated by the department of cardiology in the same hospital. All 1005 consecutive patients with a cardiovascular disease undergoing noncardiac surgery were enrolled. The cardiovascular diagnosis included at least one of the following: coronary artery disease (68% pts.), atrial fibrillation (32%), valvular disease (14.5%), prior stroke (10%), prior pulmonary embolism (7%), prosthetic valve (2,5%), heart failure (4%), cardiomyopathy (2%). These 1005 cardiac patients totaled 4.7% of all patients undergoing noncardiac surgery in this hospital during the study period of 2.5 years (2011 – 2013). The baseline characteristics included: (mean) age 74 ± 11 years, male sex in 58%, diabetes in 29%, hypertension in 76%, history of chronic kidney disease in 11%, chronic liver disease in 5%, chronic pulmonary disease in 13%, and current tumor in 16%. The following data were recorded: medication (prior, during, and after surgery), blood count, INR, type of surgery, type of anesthesia, perioperative bleeding, perioperative thrombotic and ischemic complications, and cause of death.

Results. Chronic medication included aspirin in 58%, thienopyridine in 5%, warfarin in 24%, and dabigatran in 0.3%. Medication was stopped median 7 (aspirin), 4 (thienopyridine) and 8 (warfarin) days before surgery. Perioperative bleeding greater than usual occurred in 10% of patients (serious bleeding in 2%), blood transfusions were used in 13%. Perioperative ischemic/thrombotic complications occurred in 4.6% and acute (or worsening) heart failure in 3.4%. In-hospital mortality of cardiac patients was 3% (versus 0.5% mortality of remaining patients without heart disease). In-hospital mortality of cardiac patients with perioperative ischemic or thrombotic complication was 24%. The most frequent cause of death was heart failure (n=16), followed by pulmonary embolism (n=4). Only 1 patient died as a direct result of bleeding. There were no significant differences in mean duration of chronic aspirin/warfarin (antithrombotic) therapy interruption between the groups with perioperative bleeding (aspirin 4.2 days and warfarin 6.5 days) vs perioperative ischemia (aspirin 3.8 days and warfarin 4.3 days). Interestingly, the mean time without antithrombotic therapy was significantly shorter (aspirin 3.8 days and warfarin 4.3 days) among patients who developed perioperative ischemia vs those without ischemia (aspirin 7 days, *P*<.001 and warfarin 8 days, *P*<.013). Preoperative dual antiplatelet therapy was used only in 24 patients; this small number did not allow statistical analysis of this subgroup.

Conclusions. Delayed (or no) interruption of antithrombotic therapy with aspirin or warfarin before major noncardiac surgery in cardiac patients does not prevent perioperative ischemic or thrombotic complications, and increases the risk of bleeding complications. The ischemic or thrombotic complications in this high-risk elderly population are surprisingly rare. Thus, the traditional strategy of 1-week interruption of antithrombotic drugs should not be changed.

LINC Study: A Multicenter Randomized Trial Comparing a Mechanical CPR Algorithm Using LUCAS Versus Manual CPR in Out-of-hospital Cardiac Arrest Patients[10]

Presented by Sten Rubertsson (Uppsala, Sweden).

Background. When performing manual chest compressions in CPR, disruption due to fatigue causes incorrect compressions depth as

well as defibrillation breaks, which could be the main factors contributing to poor performance in out-of-hospital cardiac arrest. The hypothesis is that mechanical chest compressions using the LUCAS device and defibrillation during ongoing chest compressions improve survival at 4 hours compared with manual out-of-hospital CPR.

Methods. In 6 European places, from January 2008 to August 2012, 2589 patients were randomized to out-of-hospital CPR, treatment with L-PCR (n=1300), or M-PCR according to current guidelines (n=1289). Surviving patients were followed for 6 months and neurologic outcome was assessed using the Scale Cerebral Performance Category (CPC), in which CPC 1-2 is classified as a good result.

Results. No differences in background variables between groups. In the intention-to-treat population (n=2589), survival at 4 hours was 307 patients (23.6%) with L-CPR and 305 (23.7 %) with M-CPR (risk difference -0.05%, 95% CI: -3.32 to 3.23, *P*=1.00). Survival with good neurological outcome was 108 (8.3%) vs 100 (7.8%) (*P*=.61) at hospital discharge, 105 (8.1%) vs 94 (7.3 %) (*P*=.46) in a month and 110 (8.5%) vs 98 (7.6%) (*P*=.43) at 6 months after cardiac arrest in the L-CPR and M-CPR groups, respectively.

Conclusions. There was no difference in survival in the short or long term up to 6 months for patients treated with the LUCAS concept compared with manual PCR. Neurological outcome was not good in the vast majority of survivors in both groups.

IN-TIME Study. The Influence of Implant-Based Home Monitoring on the Clinical Management of Heart Failure Patients With an Impaired Left Ventricular Function[11]

Presented by Gerhard Hindricks (Leipzig, Germany).

Background. New technology that allows transmission of diagnostic data from implanted devices to a monitoring physician or clinic, as opposed to patients being followed via in-office visits, may allow early detection of atrial or ventricular arrhythmias or specific trends in certain clinical parameters due to the rapid transmission of information.

Methods. The prospective, randomized, controlled, multicenter trial analysed 664 patients, mean age 66±9 years, with chronic heart failure lasting for 3 months or more, class II or III New York Heart Association (NYHA) symptoms, and a reduced left ventricular ejection fraction (LVEF) of ≤35%. Most patients included had ischemic heart disease (69%), mean LVEF was 26±6%, and heart failure medication: diuretics (93%), beta-blockers (91%), and ACE inhibitors or angiotensin receptor blockers (89%). The primary endpoint of IN-TIME was the modified Packer score, a clinical composite score consisting of mortality, overnight hospitalization for worsened heart failure, and NYHA class global self-assessment. A secondary endpoint of the trial was all-cause total mortality. All patients were fitted with implanted devices that had a telemonitoring function, with 58% receiving a cardiac resynchronization device (CRT-D) and 42% an implantable dual chamber. Data transmission was initiated by a time trigger (eg, 3 AM every day) or by a relevant arrhythmic or technical event, and was transmitted from the patient's implanted device to a central monitoring unit at the Leipzig Heart Centre. A run-in phase of 1 month was used to optimise patients' heart failure therapy and ensure that the device's transmission system was functioning, after which patients were randomized to either telemonitoring (n=333) or standard care (n=331). This meant that in the standard care group, telemonitoring data was still collected but was not accessible to the central monitoring unit or treating physicians until the end of the study. For these patients all treatment interventions were either patient-initiated or triggered by in-office follow-ups. In contrast, for telemonitored patients, relevant observations such as frequency of

ventricular extrasystoles or atrial and ventricular tachyarrhythmia episodes were forwarded to the patient's treating physician, which could lead to additional follow-ups, and therapy changes at the physician's discretion.

Results. The IN-TIME trial showed that at 1 year, significantly more patients randomized to telemonitoring scored better on a composite end point that included all-cause mortality and specific cardiac measures. At 12 months follow-up, significantly more patients in the control group as compared to the home monitoring group worsened according to the modified Packer score (27.5% vs 18.9%; *P*<.05). Moreover, there was a significantly lower rate of all-cause mortality as well as cardiovascular mortality in the telemonitoring arm compared to controls (3.4% vs 8.7%; *P*<.01; *P*<.012).

Conclusions. Heart failure patients have significant survival benefits when their implanted cardioverter-defibrillators (ICD) or cardiac resynchronization therapy defibrillators (CRT-D) are fitted with telemonitoring technology that alerts medical experts to potential problems, results of the IN-TIME trial reveal.

RISK FACTORS AND DIABETES

PURE: Contrasting Associations Between Risk Factor Burden, CVD Incidence and Mortality in High, Middle and Low Income Countries[12]

Presented by Salim Yusuf (Hamilton, California, United States).

Background. Over recent decades, the prevalence of noncommunicable diseases such as obesity, diabetes and CVD has increased in countries around the world. However, there are some questions to be answered: What associations exist between societal factors and CVD risk factors, event rates, and mortality?

Methods. Large-scale epidemiological study, including 155 245 participants in more than 600 communities in 17 countries of low, middle and high income. Data include medical history, lifestyle factors such as physical activity and diet, blood collection, electrocardiogram and anthropometric measures. Mean follow-up was 3.9 years. The primary endpoint was the impact of risk factors on CV disease and mortality.

Results. The highest risk factors for CVD were more prevalent in high-income countries (*P*=.0001). However, the frequency of major CVD (including fatal CVD) per 1000 person years was 4.3% in high, 5.1% in middle, and 6.4% in low-income countries (*P*=.0001). In contrast, the frequency of nonmajor CVD per 1000 person years was greater in high, intermediate in middle, and lower in low-income countries (*P*=.0001).

Conclusions. High-income countries have the highest risk factors for CVD, but less major CVD than low-income countries. Health care plays a role in risk-factor control and management of nonmajor CVD. Approaches for middle and low-income countries will be important.

EXAMINE: EXamination of CArdiovascular OutcoMes With AlogliptIN Versus Standard of CarE in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome[13]

Presented by William B White (Farmington, Connecticut, United States).

Background. To assess potentially elevated cardiovascular risk related to new antihyperglycemic drugs in patients with type 2 diabetes, regulatory agencies require a comprehensive evaluation of the cardiovascular safety profile of new antidiabetic therapies. We

assessed cardiovascular outcomes with alogliptin, a new inhibitor of dipeptidyl peptidase 4 (DPP-4), as compared with placebo in patients with type 2 diabetes who had had a recent acute coronary syndrome.

Methods. We randomly assigned patients with type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive alogliptin or placebo in addition to existing antihyperglycemic and cardiovascular drug therapy. The study design was a double-blind, noninferiority trial with a prespecified noninferiority margin of 1.3 for the HR for the primary end point of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Results. A total of 5380 patients underwent randomization and were followed for up to 40 months (median, 18 months). A primary end-point event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (HR=0.96; upper boundary of the one-sided repeated CI, 1.16; $P<.001$ for noninferiority). Glycated hemoglobin levels were significantly lower with alogliptin than with placebo (mean difference, −0.36 percentage points; $P<.001$). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo.

Conclusions. Among patients with type 2 diabetes who had had a recent acute coronary syndrome, the rates of major adverse cardiovascular events were not increased with the DPP-4 inhibitor alogliptin as compared with placebo.

SAVOR-TIMI 53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Study[14]

Presented by Deepak Bhatt (Newton, United States).

Background. The cardiovascular safety and efficacy of many current antihyperglycemic agents, including saxagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor, are unclear.

Methods. We randomly assigned 16 492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke.

Results. A primary end-point event occurred in 613 patients in the saxagliptin group and 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; HR with saxagliptin, 1.00; 95% CI, 0.89 to 1.12; $P=.99$ for superiority; $P <.001$ for noninferiority); the results were similar in the "on-treatment" analysis (HR=1.03; 95% CI, 0.91 to 1.17). The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; HR=1.02; 95% CI, 0.94 to 1.11; $P=.66$). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs 2.8%; HR=1.27; 95% CI, 1.07 to 1.51; $P=.007$). Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3% in the saxagliptin group and 0.2% in the placebo group; chronic pancreatitis, <0.1% and 0.1%, respectively).

Conclusions. DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischemic events, though the rate of hospitalization for heart failure was increased. Although saxagliptin improves

glycemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.

ASSURE: Results of the Effect of an Oral Agent Inducing Apo A-I Synthesis on Progression of Coronary Atherosclerosis Study[15]

Presented by Stephen James Nicholls (Adelaide, Australia).

Background. The aim was to investigate the experimental apolipoprotein A1 (apoA1) inducer, RVX-208 for increasing high-density lipoprotein (HDL) and reducing arterial plaque in patients with mild coronary aterosclerosis.

Methods. ASSURE was a prospective, randomized, double-blind clinical trial carried out at 60 centers. It included 323 patients with low HDL, coronary disease, and a target blood vessel for imaging with less than 50% stenosis. All patients received treatment with statins during the study and were also randomized to receive either RVX-208 100 mg (n=244) or placebo (n=80) twice daily for 26 weeks. The primary and secondary outcomes of the study were change from baseline in percent atheroma volume (PAV) and normalized total atheroma (TAV), both measures of the amount of plaque present in the coronary artery. Intravascular ultrasonography was used at baseline and the end of the study to measure these outcomes.

Results. HDL cholesterol increased by 10.9% in the RVX-280 group compared to 7.7% in the placebo group ($P=.32$), and LDL cholesterol decreased by 16.0% vs 17.6% with placebo ($P=.72$). Additionally, the impact of RVX-208 on apoA1 levels from baseline was not significantly different from placebo ($P=.18$). The levels increased by 10.6% ($P<.001$ compared with baseline) in the placebo group and 12.8% ($P<.001$ compared with baseline) in the RVX-208 group. In terms of efficacy, PAV decreased by 0.40% in the RVX-208 group compared to 0.30% in the placebo group ($P=.81$) and TAV decreased by 4.2 mm^3 vs 3.8 mm^3, respectively ($P=.86$). There were no significant differences in cardiovascular events between the groups (13.8% in the RVX-2008 group vs 7.4% in the placebo; $P=.09$). However, there were more discontinuations due to adverse events in the RVX-280 group (3.7% vs 2.5%) as well as significantly more elevations of liver enzymes at triple the normal limit or more (7.0% vs 0%, $P=.009$). All liver enzyme elevations occurred within the first 2 months of treatment with spontaneous resolution when the study drug was discontinued.

Conclusions. RVX-208 did not significantly increase HDL-C and apoA1 compared to placebo, and did not promote regression of atherosclerotic plaque.

COMPARE: Effect of Losartan on Aortic Dilatation Rate in Adults With Marfan Syndrome[16]

Presented by Barbara J.M. Mulder (Amsterdam, The Netherlands).

Background. Patients with Marfan syndrome (MFS) have an increased risk of life-threatening aortic complications, mostly preceded by aortic dilatation. Recently, treatment with losartan showed reduction of the aortic dilatation rate in a MFS mouse model. The primary aim of our study was to determine whether losartan reduces aortic dilatation rate in humans with MFS.

Methods. In this multicenter, open-label, randomized controlled trial with blinded assessments, losartan was compared with no additional treatment in 233 adults with MFS. The primary endpoint was aortic dilatation rate at any aortic level as determined by magnetic resonance imaging after 3 years of follow-up. The secondary

endpoint was the reduction of the incidence of cardiovascular mortality, aortic dissection, or prophylactic aortic surgery. The effect of losartan on aortic dilatation rate was evaluated by covariance analysis with baseline aortic dimension as covariate.

Results. A total of 233 participants (47% female) underwent randomization to either losartan (n=116) or no additional treatment (n=117). Follow-up was 3.1±0.4 years, similar in both arms.

Marfan patients on losartan demonstrated a significantly lower aortic root dilatation rate (0.77±1.36 vs 1.35±1.55 mm, *P*=.014), no significant differences in aortic dilatation rate beyond the aortic root in the total study population, and after aortic root replacement, a significantly lower dilatation rate of the aortic arch (0.50±1.26 vs 1.01±1.31 mm, *P*=.033). No significant differences in clinical endpoints were found.

Conclusions. Addition of losartan to standard of care (betablockers) in adults with Marfan syndrome reduces aortic root dilatation rate. After aortic root replacement, losartan reduces arch dilatation rate.

HEART FAILURE AND ACUTE CORONARY SYNDROME

Centenary of the Tour de France Group: Mortality of French Participants From the Tour de France 1947-2012[17]

Presented by Xavier Jouven (Paris, France).

Background. There are concerns regarding performance-enhancing techniques and the potential negative health effects of excessive high-level physical activity. Data collection on the long-term outcomes and causes of death in elite endurance cyclists is of particular interest.

Methods. The study assessed 786 French cyclists who participated at least once in the Tour de France between 1947 and 2012, and compared them to the general French male population of the same age. The cyclists had participated in a median of 2.5 Tour de France races and were followed for a median of 37.4 years. Their median age at the first race was 25 years. A standardized mortality ratio (SMR) was calculated based on the actual death rate of the cyclists compared to the death rate in the age-matched French population according to the Human Mortality Database.

Results. The study found that of the 786 cyclists, 208 (26%) had died by September 1, 2012 – an SMR of 0.59 and a mortality rate that is 41% lower than the general population. The two main causes of death for the cyclists were neoplasms (32.2%), and cardiovascular diseases (29%), both occurring less frequently than in the general public (SMRs of 0.56 and 0.67, respectively). Among cancers, the 3 main diagnoses were digestive (35%), lung (22%), and prostate (7%). For the third highest cause of death (15.8%), classified as "external" (mostly trauma-related), the SMR was 1.06 indicating about the same rate as in the general public. Other causes of death included infectious diseases (2.2%), endocrine and nutritional diseases (2.2%), neurological (2.2%), digestive system diseases (2.2%), and genitourinary disease (1.1%). The cyclists' SMR was consistent across different periods of participation, corresponding to the reported or suspected use of cocaine and amphetamines (1947-1970), androgens and anabolic steroids (1971-1990), and growth hormone and erythropoietin (1991-2012). The SMRs were also consistent across all age groups, except for the group younger than 30 years in whom a nonsignificantly higher death rate was observed (SMR 1.65) compared to the general population.

Conclusions. French participants in the Tour de France between 1947–2012 lived longer than their same-aged French counterparts.

ATOMIC-AHF: Results From the Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure Study[18]

Presented by John R. Teerlink (San Francisco, United States).

Background. Currently available inotropic agents can cause myocardial ischemia/damage, arrhythmias, hypotension, and increased morbidity and mortality. Omecamtiv mecarbil (OM) is a novel cardiac myosin activator that directly increases cardiac function with no effect on intracellular calcium or cAMP. In healthy volunteers and patients with stable heart failure (HF), OM improves echocardiographic measures of cardiac function. ATOMIC-AHF is the first study of IV OM in patients with acute heart failure (AHF) and was designed to evaluate its efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics in AHF.

Methods. ATOMIC-AHF is a multi-center, randomized, double-blind, placebo-controlled, dose-escalating study of 3 sequential cohorts (~200 subjects per cohort; median target OM plasma concentration: 115, 230, 310 ng/mL). Patients admitted for AHF with LVEF ≤40% and a history of HF were eligible if they had persisting dyspnea at rest or with minimal exertion despite IV diuretic treatment, and biomarker evidence of congestion (elevated BNP or NTproBNP). Patients were randomized 1:1 to a 48-hour infusion of placebo or OM within 24 hours of initial IV diuretic. The primary efficacy hypothesis is that at least 1 dose level of OM will improve dyspnea within 48 hours. Secondary efficacy endpoints include other symptom/well-being measures, changes in biomarkers, clinical outcomes through 30 days, and mortality through 180 days; a PK and echocardiogram substudy investigates the relationship of OM plasma concentrations to changes in cardiac function.

Results. There was no change in the primary efficacy endpoint of dyspnea response on the Likert Scale (*P*=.33). There was an improvement in dyspnea in the cohort receiving the highest dose and with higher plasma concentrations achieved (*P*=.03). In addition, there was a trend towards a reduction in episodes of WHF with escalating dose. There was the expected dose and plasma concentration-dependent increase in systolic ejection time (SET) (*P*<.0001). There was no signal for increased arrhythmic events. Indeed, there was a reduction in HR (*P*<.0001) and a small reduction in SBP (*P*=.0017) at higher doses. On the other hand, there was an increase in troponin. However, there was no increase in clinical ischaemic events.

Conclusions. This 600-patient study of a novel therapeutic class, cardiac myosin activators, is the first in patients with AHF. OM has the potential to be a safe and effective therapy to improve cardiac performance and patient outcomes. OM is also being studied as an oral formulation in chronic HF.

EchoCRT: Echocardiography-guided Cardiac Resynchronization Therapy in Patients With Narrow QRS[19]

Presented by Frank Ruschitzka (Zurich, Switzerland).

Background. Cardiac-resynchronization therapy (CRT) reduces morbidity and mortality in chronic systolic heart failure with a wide QRS complex. Mechanical dyssynchrony also occurs in patients with a narrow QRS complex, which suggests the potential usefulness of CRT in such patients.

Methods. We conducted a randomized trial involving 115 centers to evaluate the effect of CRT in patients with New York Heart Association class III or IV heart failure, a left ventricular ejection fraction of 35% or less, a QRS duration of less than 130 msec, and echocardiographic evidence of left ventricular dyssynchrony. All

patients underwent device implantation and were randomly assigned to have CRT capability turned on or off. The primary efficacy outcome was the composite of death from any cause or first hospitalization for worsening heart failure.

Results. On March 13, 2013, the study was stopped for futility on the recommendation of the data and safety monitoring board. At study closure, the 809 patients who had undergone randomization had been followed for a mean of 19.4 months. The primary outcome occurred in 116 of 404 patients in the CRT group, as compared with 102 of 405 in the control group (28.7% vs 25.2%; HR=1.20; 95% CI, 0.92 to 1.57; *P*=.15). There were 45 deaths in the CRT group and 26 in the control group (11.1% vs. 6.4%; HR=1.81; 95% CI, 1.11 to 2.93; *P*=.02).

Conclusions. In patients with systolic heart failure and a QRS duration of less than 130 msec, CRT does not reduce the rate of death or hospitalization for heart failure and may increase mortality.

AQUARIUS: Results From the Effect of the Renin Inhibitor Aliskiren on Progression of Coronary Atherosclerosis Study[20]

Presented by Stephen James Nicholls (Adelaide, Australia).

Background. Blood pressure reduction and renin-angiotensin-aldosterone system inhibition are targets for treatment of atherosclerosis. The effect of renin inhibition on coronary disease progression has not been investigated. The aim was to determine the effects of renin inhibition with aliskiren on progression of coronary atherosclerosis.

Methods. A double-blind, randomized, multicenter trial (Aliskiren Quantitative Atherosclerosis Regression Intravascular Ultrasound Study) comparing aliskiren with placebo in 613 participants with coronary artery disease, systolic blood pressure between 125 and 139 mm Hg (prehypertension range), and 2 additional cardiovascular risk factors, conducted at 103 academic and community hospitals in Europe, Australia, and North and South America (enrollment from March 2009 to February 2011; end of follow-up: January 31, 2013). Participants underwent coronary intravascular ultrasound (IVUS) imaging and were randomized to receive 300 mg of aliskiren (n=305) or placebo (n=308) taken orally daily for 104 weeks. Disease progression was measured by repeat IVUS examination after at least 72 weeks of treatment. The primary efficacy parameter was the change in percent atheroma volume (PAV) from baseline to study completion. Secondary efficacy parameters included the change in normalized total atheroma volume (TAV) and the percentage of participants with atheroma regression. Safety and tolerability were also assessed.

Results. Evaluable imaging data were available at baseline and follow-up for 458 participants (74.7%). The primary IVUS efficacy parameter, PAV, did not differ between participants treated with aliskiren (−0.33%; 95% CI, −0.68% to 0.02%) and placebo (0.11%; 95% CI, −0.24% to 0.45%) (between-group difference, −0.43% [95% CI, −0.92% to 0.05%]; P = .08). The secondary IVUS efficacy parameter, TAV, did not differ between participants treated with aliskiren (−4.1 mm³; 95% CI, −6.27 to −1.94 mm³) and placebo (−2.1 mm³; 95% CI, −4.21 to 0.07 mm³) (between-group difference, −2.04 mm³ [95% CI, −5.03 to 0.95 mm³]; *P*=.18). There were no significant differences in the proportion of participants who demonstrated regression of PAV (56.9% vs 48.9%; *P*=.08) and TAV (64.4% vs 57.5%; *P*=.13) in the aliskiren and placebo groups, respectively.

Conclusions. Among participants with prehypertension and coronary artery disease, the use of aliskiren compared with placebo did not result in improvement or slowing of progression of coronary atherosclerosis. These findings do not support the use of aliskiren for regression or prevention of progression of coronary atherosclerosis.

BIC-8: Instant Early Rule-out using Cardiac Troponin and Copeptin In Low- to Intermediate-Risk Patients With Suspected ACS: a Prospective, Randomized Multicenter Study[21]

Presented by Martin Moeckel (Berlin, Germany).

Background. Copeptin is a marker of severe hemodynamic stress and is detectable immediately in patients with acute MI. In observational studies, a combination of cardiac troponin and copeptin was shown to be a significant predictor of acute events.

Methods. BIC-8, a multicenter, open, randomized, controlled clinical trial, included 902 patients with acute chest pain at low to intermediate risk of ACS. After the initial negative troponin test, 451 patients were randomized to the experimental arm and underwent a copeptin assay. The other 451 patients were randomized to standard care, including serial cardiac troponin testing. If the copeptin test was positive, defined as >10 pmol/L, they were treated with standard ACS care. If the copeptin assay showed copeptin levels <10 pmol/L, patients were discharged into ambulant care and scheduled for an outpatient visit within 72 hours.

Results. At 30 days of follow-up, the rate of major adverse cardiovascular events (MACE) was similar in both groups (5.46% in the experimental arm vs 5.5% in the standard arm), but emergency room discharge rates were significantly higher in the experimental arm (66% vs 12%; *P*<.001).

Conclusions. The combination of a negative troponin and copeptin test seems to be safe to rule out ACS and effectively discharged patients from the emergency department. A clinical assessment of the patients is advisable before sending them home.

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