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The 2003 Congress of the European Society of Cardiology (ESC) in Vienna, Austria, was attended by 25,463 people, including 18,932 physicians. The program included 2,652 abstract presentations, 170 symposia or clinical seminars, and 5 Hotline and Clinical Trial Update sessions. In this report we review some of the key presentations. A detailed content, including the abstracts, can be found in the Virtual Congress Space on the ESC Website: http://www.escardio.org.

CLINICAL STUDIES

Treatment of chronic heart failure: a comparison of carvedilol and metoprolol—COMET. The Carvedilol Or Metoprolol European Trial (COMET) compares the effects of carvedilol and metoprolol on mortality and morbidity in patients with class II to IV chronic heart failure and left ventricular (LV) ejection fraction (EF) <35% (1). The study was presented by P. A. Poole-Wilson (London, United Kingdom). A total of 3,029 patients were randomized and followed for a mean of 58 months. The primary end points were all-cause mortality, and the composite end point was all-cause mortality and all-cause hospital admission. A significant reduction occurred in all-cause mortality with carvedilol as compared to metoprolol (34% vs. 40%, p = 0.0017). No significant difference existed between the groups in the composite end point of all-cause mortality and all-cause hospital admission. Therefore, the benefits of carvedilol were driven by the reduction in mortality.

The doses used in COMET aimed for comparable reductions in resting heart rate in the two groups. Initially, heart rate decreased more in the carvedilol-treated than in the metoprolol-treated patients, after four months by 13.3 beats/min in the carvedilol group and by 11.7 beats/min in the metoprolol group. After 16 months, heart rates did not differ.

Carvedilol was superior to metoprolol in this trial. However, the mechanism of the different responses to carvedilol and metoprolol was not elucidated. Therefore, it is difficult to exclude that a small difference in degree of beta-blockade may play a role.

Treatment of chronic heart failure: cardiac resynchronization therapy—COMPANION. The Comparison of Medical Resynchronization, Pacing, and Defibrillation Ther-

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potassium to 6.0 mmol/l or above in 2% of the candesartan-treated patients as compared to 1% in the placebo group (p = 0.017). The average serum potassium increased by 0.14 mmol/l in the candesartan group, while there was no overall change in the placebo group (p < 0.0001). Creatinine doubled in 6% of the candesartan-treated patients and in 4% of the placebo-treated patients (p = 0.002). Blood pressure decreased more in the candesartan group, by 5.2 mm Hg in systolic and by 3.0 mm Hg in diastolic pressure (p < 0.001). A small increase in fatal cancer likely resulted from the play of chance. The incidence of nonfatal neoplasms detected during the study was similar in the treatment groups. Angioedema recurred in only 3 of 39 patients with previous angioedema or anaphylaxis on ACE inhibitors. In these 3 patients the angioedema was mild and not life-threatening.

The CHARM-Added trial showed that in patients with reduced EF, the addition of candesartan to an ACE inhibitor caused a significant reduction in cardiovascular death and hospital admission (3). Importantly, the benefits of candesartan came on top of beta-blocker treatment.

The CHARM-Alternative trial showed that in patients intolerant to ACE inhibitors, candesartan was well tolerated and reduced cardiovascular mortality and morbidity (4). The magnitude of the reductions was comparable to those previously reported for ACE inhibitors. The CHARM-Preserved trial showed no significant difference between the candesartan and placebo groups in terms of cardiovascular death (5). However, candesartan had a moderate positive effect on hospital admissions.

The CHARM program provides strong support for the use of angiotensin-receptor blockers in addition to ACE inhibitors and beta-blockers in patients with chronic heart failure and reduced EF, and as an alternative to ACE inhibitors in patients with intolerance to the latter class of drugs. However, higher rates of withdrawals for renal dysfunction and hyperkalemia when an ACE inhibitor is combined with angiotensin-receptor blockers indicate a necessity for close monitoring of renal function and serum potassium. There is also need for further studies in the group of patients with heart failure and preserved EF, and such studies should include objective measures of diastolic function.

**Treatment of stable coronary artery disease: ACE inhibition by perindopril—EUROPA.** The ACE inhibitors have proved very effective therapy for hypertension and heart failure. The Heart Outcomes Prevention Evaluation (HOPE) trial established its benefits in patients at high risk of cardiovascular events, including diabetics. This was strongly suggestive of benefits beyond treatment of hypertension or heart failure. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) was presented by W. J. Remme (Rhoon, The Netherlands) and K. Fox (London, United Kingdom) (6). The study was established to test the ability of perindopril to reduce cardiovascular death, myocardial infarction (MI), and cardiac arrest in patients with stable coronary artery disease (CAD) and without heart failure or hypertension. A total of 13,655 subjects were registered with either previous MI (64%), angiographic evidence of CAD (61%), prior coronary revascularization (55%), or a positive stress test only (5%). After a run-in period of four weeks, patients were randomly assigned to either perindopril (8 mg once daily) or matching placebo. At baseline, more than 90% of the patients were on platelet inhibitors, 58% on lipid-lowering therapy, and 62% on beta-blockers.

After a mean follow-up of 4.2 years, patients randomly assigned to perindopril had a 20% reduction of the composite of cardiovascular death, nonfatal MI, and cardiac arrest with successful resuscitation (from 9.9% to 8.0%, p = 0.0003). This benefit started to appear after one year and gradually increased throughout the trial. This was associated with a consistent benefit on secondary end points, notably the composite of total mortality, nonfatal MI, unstable angina, and cardiac arrest with successful resuscitation (14.8% vs. 17.1%, p = 0.0009). Most of the benefit appeared to be driven by a reduction in fatal and nonfatal MI. The clinical benefit was consistent in most predefined subgroups, including men, women, elderly and young patients, diabetic patients, and patients with and without hypertension. Importantly, the benefits were seen on top of high usage of aspirin, beta-blockers, and lipid-lowering drugs.

Treatment with perindopril was well tolerated, with 10% of the patients who did not continue therapy after the open-label run-in phase, and a similar withdrawal rate in both treatment arms during the blinded treatment period. The reduction in systolic blood pressure by perindopril was on average 5.2 mm Hg. With respect to the primary end point of the trial, approximately 50 patients must be treated for four years to prevent one major cardiovascular event. It was concluded that after EUROPA, strong consideration should be given to adding the ACE inhibitor perindopril to the standard therapy of all patients with stable CAD.

**Treatment of acute MI: facilitated percutaneous coronary intervention (PCI) with tenecteplase plus enoxaparin—GRACIA.** Facilitated angioplasty refers to the combination of primary angioplasty for acute MI preceded by pharmacologic therapy “en route” to the catheterization laboratory to facilitate intervention and specifically to achieve recanalization in some patients prior to mechanical intervention. To explore the value of such a strategy, Spanish and Portuguese investigators in the Grupo de Analisis de la Cardiopatia Isquemica Aguda (GRACIA)-2 trial randomized 212 patients in 15 centers with ST-segment elevation acute MI to either a strategy of “facilitated intervention” (i.e., tenecteplase + enoxaparin, followed within 3 to 12 h by revascularization using stents or coronary artery bypass surgery) or to a strategy of optimal primary PCI of the infarct-related artery, using stents and abciximab. The end points of the trial were three-fold: 1) infarct size measured by c-troponinT and creatine kinase-MB mass release; 2) the percentage of patients with...
of the trial was the Thrombolyis In Myocardial Infarction (TIMI) flow grade 3 at initial angiography, as it was hoped that prehospital administration might result in a higher patency rate before PCI, which in turn is usually correlated with higher success rates for primary mechanical intervention and improved clinical outcomes. Secondary end points included TIMI flow in the infarct-related vessel, presence of thrombus in the infarct artery at initial angiography, and success rates for primary PCI. Approximately 500 patients were randomized to early versus late initiation of tirofiban. All patients received unfractionated heparin (5,000 IU) and aspirin (500 mg IV bolus) before PCI. After PCI, all patients were treated with weight-adjusted low molecular weight heparin for 48 h, clopidogrel 300 mg loading and 75 mg for 30 days, and aspirin, beta-blocker, ACE inhibitors, and statins. Tirofiban was given as a first bolus of 10 μg/kg, followed by a 0.15 μg/kg/min infusion lasting 24 h. Females younger than 50, and all patients older than 80 years, or in Killip class III or IV, or on treatment with oral anticoagulation, or treated with fibrinolysis <24 h, in hemodialysis, or with contraindications to the use of GP IIb/IIIa inhibitors were not included. After randomization (41% in the ambulance) patients were immediately taken to a PCI center rather than to the nearest hospital. Mean age was 62 years; 10% of patients were diabetics, 46% had anterior infarction, and 16% were in Killip class 2.

Patient-related delay was 94 min, and the time from diagnosis to randomization was 25 min. Interhospital transportation required 33 min, the door-to-angiography time was 25 min, and finally the time from angiography to angioplasty was 15 min. The early group received initiation of tirofiban in non-PCI centers (51%), in the prehospital setting (41%), or in the emergency room of a PCI center (8%) before going to the catheterization laboratory. The median difference in delay to tirofiban administration between the two treatment arms was 59 min. On initial angiography, assessed by a central core laboratory, TIMI flow grade 3 in the infarct vessel was seen in 19% versus 15% of the early and late patients, respectively (p = 0.22), and combined TIMI flow grade 2 or 3 in 43% versus 34% (p = 0.04). Thrombus was seen in 25% versus 32% of the infarct vessels in the early and late groups and fresh occlusion in 35% versus 41% (p = 0.20). The combined incidence of thrombus and fresh occlusion was seen overall in 60% versus 73% (p = 0.002). There was no difference as to the final PCI result: TIMI flow grade 3 was 89% in the early group versus 91% in the late group (p = 0.56), myocardial blush grade 3: 51% versus 53% (p = 0.87), and corrected TIMI frame count 27 ± 17 versus 26 ± 15 (p = 0.56). At 30 days, 11 patients died (2.2%) and only 5 had reinfarction (1%); 1 patient had fibrinolysis-related stroke and 19 had major bleeding (3.7%).

Thus, the ON-TIME trial showed a modest improvement in patency rates with prehospital initiation of tirofiban prior to primary PCI, compared to catheterization laboratory initiation. There was a borderline reduction in angio-
graphic evidence of thrombus. Given the relative safety of this therapy, it deserves further study for early “facilitation” of primary PCI on top of heparin and aspirin in patients with acute MI transferred to undergo mechanical reperfusion therapy. The study discussant, F. Ribichini (Novara, Italy), commented that ON-TIME shows that the optimal medical treatment to facilitate PCI in ST-segment elevation MI is still not defined. The TIMI flow grade 3 reported by the investigators is similar to that obtained with the pre-PCI administration of abciximab in the Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADIMIRAL) trial (17%), and lower than the TIMI flow grade 3 rate obtained with a half dose of tissue-type plasminogen activator (t-PA) in the Plasminogen activator Angioplasty Compatibility Trial (PACT) (33%).

The most remarkable finding of ON-TIME is not related to the study drug, but to the very short time of patient-delay and health-care system reaction. Indeed, patient-related delay is almost half of that seen in the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) V trial, and door-to-balloon time is <50 min. This indicates that pretreatment times can be largely reduced, and this is expected to translate into clinical benefit. Enhancing the awareness of patients about the significance of symptoms and the health-care network about the importance of shortening intervention times will likely maximize the mortality benefit eventually obtainable with any therapy.

**PCI after MI: effect of late recanalization—DECOPI.**

The value of late recanalization of the occluded infarct artery remains both unsettled and a controversial topic. Though a host of experimental and observational clinical data exist to suggest the benefit of late recanalization of the infarct artery beyond the time window compatible with myocardial salvage (the “open artery hypothesis”), current evidence from randomized clinical trials is still scarce and inconsistent. In fact, the latest trial even suggested potential harm from late recanalization of the infarct vessel. The DESobstruction CORonary Post Infarctus (DECOPI) trial is a French and Belgian study, presented by P. G. Steg (Paris, France), which randomized 212 patients with TIMI flow grade 0/1 in the infarct artery on angiography performed 2 to 15 days after infarct onset to either angioplasty or standard medical therapy. All patients received optimal medical care, and angiography was repeated at six months. The primary end point of the trial was the combination of cardiovascular death, nonfatal MI, and severe ventricular tachyarrhythmias. After an average of 34 months of follow-up, the comparison between the two strategies shows no difference in the primary end point (8.7% in the medical group; 7.3% in the PCI group, \( p = 0.64 \)). There were also no differences between groups in the rates of death, MI, ventricular arrhythmias, admission for heart failure, admission for cardiac causes, revascularization, or ischemia at six-month stress test. Because of spontaneous recanalization on one hand and reocclusions on the other, at six months, patency of the infarct artery was seen in 39.7% of the patients in the medical arm and 82.7% of patients in the angioplasty arm (\( p < 0.0001 \)). Importantly, there was a 47.1% restenosis rate in the angioplasty arm. At six months, angiographic LV EF was superior by approximately 3.5% in the angioplasty arm (\( p = 0.025 \)). Functional status at the end of the trial (dyspnea and angina) was comparable between groups. Costs were higher in the angioplasty arm (€13,484 vs. €12,468, \( p < 0.0001 \)). This amounts to $17,101 and $15,813 USD, respectively, assuming 1 Euro = $1.2629 USD. Overall, the event rates in this population were low, and there was no obvious clinical benefit to systematic angioplasty of the infarct-related vessel.

Although PCI was associated with a higher LV EF at six months and a higher coronary patency rate, this did not translate into statistically significant differences in outcomes, at the expense of higher costs. Because these results were observed in a small population at relatively low risk, care should be exercised before generalizing these conclusions. Whether a strategy of angioplasty would be beneficial in a higher-risk population is currently being tested in a large-scale international trial, the Open Artery Trial (OAT). The study discussant, E. Braunwald (Boston, Massachusetts), noted that, while this was the largest trial to date, and the first one to use modern therapy including stents, it addressed a low-risk patient population and was underpowered. Therefore, the investigator concluded that the “open artery hypothesis” was still alive and well and that it was necessary to await results of the large-scale OAT trial, performed in high-risk patients, for definitive conclusions.

**Secondary prophylaxis after MI: oral direct thrombin inhibition with ximelagatran—ESTEEM.**

The Efficacy and Safety of the oral direct Thrombin inhibitor ximElagatran in patients with rEcent Myocardial damage (ESTEEM) trial investigated the efficacy and safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage (7). The results were presented by L. Wallentin (Uppsala, Sweden). This was a placebo-controlled, double-blind trial in 1,883 patients who underwent recent ST-elevation or non-ST-elevation MI. Either ximelagatran in different doses or a placebo was given for six months, both on top of acetylsalicylic acid. The primary outcome was the composite of death, nonfatal MI, and severe recurrent ischemia. Ximelagatran significantly reduced the primary end point from 16.3% to 12.7% (\( p = 0.036 \)). The frequency of major bleeds did not differ between the groups. However, the cumulative risk of bleeding, both major and minor, was higher in the ximelagatran group than in the placebo group. Ximelagatran was associated with a rise in liver enzyme concentrations. It was concluded that oral direct thrombin inhibition with ximelagatran and acetylsalicylic acid is more effective than acetylsalicylic acid alone in preventing major cardiovascular events during six months of treatment in patients who have had a recent MI. Further trials are needed, including studies on safety aspects, to define the role of ximelagatran in this patient population.
Treatment of multivessel coronary disease: PCI or CABG—GABI. The German Angioplasty Bypass surgery Investigation (GABI) trial was a German multicenter study comparing PCI and coronary artery bypass graft (CABG) surgery in patients with multivessel coronary disease. The original results were published in 1994, showing that PCI and CABG as initial treatments resulted in equivalent improvement in angina after one year. However, patients treated with PCI were more likely to require further interventions and antianginal drugs, whereas patients treated with CABG were more likely to sustain an acute MI at the time of the procedure. J. Kaehler (Hamburg, Germany) presented the long-term follow-up of that trial. After 10 years of follow-up, no difference was seen in the rate of cardiac deaths between the two arms. Reinterventions were clearly more frequent in the angioplasty arm (p = 0.004); thereafter, it was the reverse (p = 0.004).

NEWS FROM BASIC RESEARCH

Cardiac remodeling: mechanisms. In the area of basic research, a major focus was on cardiac remodeling and approaches to reverse remodeling. “Remodeling” originally described the alterations in LV shape and function that follow MI. The use of the term has since expanded considerably, and remodeling is now commonly used to describe changes in morphology and function at the cellular and molecular level, in particular with cardiac hypertrophy and cardiac failure. Hypertrophy of the cardiac myocyte occurs in response to mechanical and neurohormonal stimuli and is accompanied by functional remodeling resulting from altered expression and regulation of a large number of genes. Although hypertrophy has been linked to reexpression of a fetal gene program, it is clear that the phenotype (e.g., the contractile or electrical function) can vary depending on the stimulus. Both DNA microarrays and proteomic analysis offer a novel approach to explore the underlying mechanisms.

In Vienna, several studies were presented confirming different expression patterns in studies of human biopsies with different etiology of heart failure (8), and in comparison of different animal models for hypertrophy (9). An important complementary approach is functional analysis at the cellular and subcellular levels to evaluate and interpret findings at the protein level. Studies investigating the changes in sarcoplasmic reticulum function in models of cardiac hypertrophy and heart failure reported alterations in phosphorylation status of calcium transporters (10,11) and opposite responses of SERCA expression to volume or pressure overload (12). These studies illustrate that various mechanisms can be involved and that we should not oversimplify our view of the phenotype of the cardiac myocyte in the hypertrophied or failing heart.

A major mechanism underlying this diversity may be the activation of different signaling pathways. The signaling cascades leading to cardiac cell growth or hypertrophy are diverse and complex, with several links to the apoptosis pathways. An interesting pathway currently under investigation is the PI3K/Akt pathway, which is believed to lead to cellular hypertrophy with preserved or even supernormal function. Further evidence was presented that this might also be the pathway for the so-called physiological hypertrophy during exercise (13). Activation of this pathway could theoretically be called upon to improve contractile function, and data were presented on the anti-apoptotic effect of this pathway (14). Novel links to hypertrophy and remodeling currently under investigation are the cell-cycle regulatory proteins that were shown to be activated by hypertrophic stimuli (15). The apoptotic pathways could also be a novel target to influence postinfarction remodeling. It was reported that constitutive block of these pathways in transgenic mice have a positive effect on cardiac morphology and function after induction of MI (16). The p38/MAPK pathways are also activated following MI and could contribute to hypertrophy as well as apoptosis. A novel study (17) has linked this pathway to fibrosis and showed that blocking this pathway could reduce fibrosis following infarction.

Stem cells and enhanced angiogenesis in the treatment of heart disease. Although several clinical trials are currently investigating whether infusion of stem cells, bone-marrow derived or endothelial progenitor cells, in the infarct area improves cardiac function (18), the basic question of whether these cells will eventually form cardiomyocytes in situ and contribute to contraction remains unanswered. Several studies presented in Vienna addressed this issue, looking at differentiation in vitro using different culture techniques (19–21) and/or phenotyping of cells after injection in animal models (22–24). These reports should be viewed with cautious optimism; several markers for cardiomyocytes are present, but a full adult ventricular cell phenotype has not yet been reported. In the in vitro conditions, cells appear to remain in the neonatal stage in terms of electrical characteristics and excitation–contraction coupling. This may be related to the lack of interaction with adult myocytes, the lack of appropriate loading conditions, and/or of humoral factors, and is reminiscent of the phenotype adopted by isolated adult ventricular myocytes in long-term culture. The presentations reminded us that more experimental studies are needed to establish the relationship between cell therapy and specific functional improvement. Although positive results are reported (25), very different regimens are used, and the optimal timing, dose, cell type, and mechanism of action of cell therapy remain undetermined.
As an alternative to cell transplantation, several studies looked for activation of endogenous progenitor cells. Such activation can be demonstrated (22,26–28), but it remains unclear whether this would eventually lead to a significant increase in the number of functional cardiomyocytes.

The increased angiogenesis induced and mediated by the injected stem cells may be an alternative mechanism leading to improved cardiac function (22). Improving perfusion by enhanced angiogenesis was another important theme. A novel function was reported for the adipocytokine leptin, which was shown to stimulate collateral formation in a hindlimb model of ischemia (29). The same group further investigated signaling pathways for arteriogenesis and demonstrated a central role for CD44 as arteriogenesis was significantly reduced in CD44 knockout mice (30). The clinical perspective was illustrated by the association of poor collateralization in patients with low levels of expression of CD44.

Electrophysiology: new insights. In the area of electrophysiology, several studies reported on modulation of normal and abnormal automaticity. The pacemaker current If, normally present in the sinoatrial node cells, is encoded by the HCN gene. In the heart isofoms, HCN1, HCN2, and HCN4 are expressed, with a predominance of HCN4 in the sinoatrial node and no or extremely low levels of expression in the ventricle of the HCN2 isoform. Ectopic expression of HCN2 in the atrium induces pacemaker activity, an approach with potential to treat sinus node dysfunction, as presented by M. Rosen (New York, New York) (31). During cardiac remodeling and hypertrophy the expression of HCN in ventricular cells can increase and potentially contribute to arrhythmias. In Vienna a study was presented that links increased expression of HCN2 to abnormal automaticity in endothelin-induced hypertrophy of adult ventricular myocytes (32).

The relation between calcium handling and pacemaker activity is currently another area under intense research. Spontaneous sarcoplasmic reticulum calcium release events contribute to the normal diastolic depolarization process in the sinoatrial node, even though their relative importance remains a matter of debate, as addressed by D. Di Francesco (Milan, Italy) and D. A. Terrar (Oxford, United Kingdom). Atrial myocytes isolated from patients with atrial dilation showed a higher incidence of spontaneous release events, which could potentially contribute to arrhythmogenes and atrial fibrillation (33). Finally, altered calcium handling was also proposed to be at the basis of an increased propensity for atrial fibrillation in mice with a deficiency of Annexin-7 (34).

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