Hotline sessions of the 28th European Congress of Cardiology/World Congress of Cardiology 2006

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The 28th Congress of the European Society of Cardiology this year was organized together with the World Heart Federation and was presented as the World Congress of Cardiology. During the congress, held in Barcelona in September 2006, the results of 11 new studies were presented in two Hotline sessions. One of these, the PEP-CHF study has already been published in the European Heart Journal.1 Preliminary summaries of the other 10 studies are reported here.

The EuroAction study was presented by David Wood from London, UK. This cluster randomized study assessed a strategy to improve adherence to evidence-based medicine in primary and secondary prevention of cardiovasculardisease. A nurse-led multi-disciplinary prevention programme (intervention arm) was compared to usual care with respect to achieving preventive treatment goals as formulated in the European preventive cardiology guidelines. The patients’ partners or direct relatives also participated in the study. The primary endpoints were the proportion of patients achieving the preventive treatment goals. Patients could enter from two sources. First, patients with chronic stable angina or acute coronary syndrome were recruited from hospitals. Second, patients at high risk for vascular events were recruited from general practices. Patients from the hospital followed a 16-week programme and those from general practices followed a 1-year programme. At the end of the respective programmes, the effect of the intervention was assessed. The data of 8657 patients and partners, recruited from 24 centres spread over eight European countries, were presented. Smoking cessation by patients from the hospital tended to be more frequent in the intervention arm than in the usual care arm (58% vs. 47%, P = 0.06); a little over 70% of the patients from general practice stopped smoking in both arms. The dietary goals, especially regarding the consumption of fruits and vegetables, were achieved more often in the intervention group. With respect to physical activity, targets were reached twice as frequent in the intervention group: ~50% compared with 20%. Among the partners, physical activity was positively influenced as well. The intervention led to more patients achieving an ideal waist circumference: ~30% compared with 20% in the usual care arm, mainly accounted for by more male subjects achieving this treatment goal. Risk factors also were better managed in the nurse-led programme: blood pressure targets were more often reached, glycaemic control was better, and lipid levels more often improved. Finally, the use of cardio-protective drugs was improved. The hospital group with coronary artery disease (CAD) patients more frequently received antplatelet therapy, statins, and beta-blockers. The high-risk patients from general practices more frequently received diuretics, angiotensin-converting enzyme-inhibitors (ACE-inhibitors), and statins. In conclusion, a nurse-led multi-disciplinary approach to cardiovascular risk intervention is associated with a higher proportion of patients reaching treatment targets, and a more optimized pharmacological treatment of coronary patients, and high-risk primary prevention patients.

In the double-blind international multi-centre ACCLAIM trial, presented by Guillermo Torre-Amione from Houston, USA, the effect of broad-spectrum immune-modulation therapy with the Celacade® system was compared with placebo (sham) in patients with chronic heart failure. Inflammatory cytokines and other mediators of inflammation are thought to contribute to the progression of heart failure. The Celacade system uses a 10 mL sample of autologous blood that is subjected to oxidative stress. Then, after intramuscular re-injection, the white blood cells undergo apoptosis, a process that is associated with anti-inflammatory responses. The main inclusion criteria were an ejection fraction of <30% and heart failure New York Heart Association (NYHA) classes II–IV plus hospitalization for heart failure within the past 12 months (classes III and IV also eligible if ejection fraction of <25% and no recent heart failure hospitalization). Moreover, patients should be on standard heart failure therapy. Patients were randomized to immune modulation therapy (n = 1213) or sham treatment (n = 1213). Subjects received treatment on days 1, 2, 14, 28, and every 28 days thereafter for minimally 22 weeks or until the end of the study. The baseline characteristics were well balanced, with 80% males, two-thirds of the patients in NYHA class III, a mean ejection fraction of 22%, and two-thirds of patients with ischaemic aetiology of heart failure. Baseline therapy was of high standard in both groups, with ACE-inhibitors and beta-blockers being used by ~90% of the subjects. The combined primary endpoint of mortality and cardiovascular hospitalization was not significantly reduced in the immune modulation therapy group, compared with placebo (HR 0.92; 95% CI

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0.80–1.05). All-cause mortality did not differ between immune modulation therapy and placebo, 10.6 and 9.7%, respectively ($P = 0.45$). No increase in serious adverse events was observed. The subgroups of patients with NYHA class II and those without a history of myocardial infarction did benefit of immune modulation therapy. In conclusion, immune modulation therapy did not significantly reduce mortality or cardiovascular hospitalization. Much of the presentation focused on the two subgroups that did benefit of immune modulation therapy. However, randomized trials targeted on these subgroups are necessary to provide a definite answer on the value of immune modulation therapy in these patients.

The Home or Hospital in Heart failure study was presented by Andrea Mortara from Monza, Italy. Home telemonitoring may advance detection of clinical deterioration of heart failure patients leading to earlier adaptation of therapy, reducing mortality, and unplanned hospitalization for heart failure. Patients with chronic heart failure were randomly assigned to usual care, or to one of three groups with different home-based telemonitoring strategies. The first telemonitoring group received periodic telephone calls by dedicated nurses and had a 24 h answering machine at their disposal in case of problems. The second group received the same care as group 1 plus weekly monitoring of vital signs, which could be submitted to the hospital through an interactive voice response system. The third group received the same care as group 2 plus monthly 24 h continuous recordings of ECG, respiration, and activity with a Holter style recorder, applied by the patient self. After recording, the results were transmitted to the hospital by a modem. The control group consisted of 160 patients, and the telemonitoring groups included about 100 patients each. Italy, Poland, and UK participated in the study. Patients should meet the following criteria: heart failure NYHA classes II–IV, ejection fraction of $<40\%$, admission for heart failure within the past 12 months, an abnormal diastolic left ventricular function, and optimal medical therapy. Baseline characteristics were well balanced. Mean age was 60 years, 15% were female, aetiology of heart failure was mainly ischaemic, mean NYHA class was 2.4, and the mean left ventricular ejection fraction was 29%. Transmission of telemonitoring data was feasible: 81% of vital sign transmissions and 78% of the transmissions of the home cardio-respiratory recordings were practicable. The primary endpoint of hospitalization due to heart failure after 1 year was similar in the control group and in the three telemonitoring groups (16.3 vs. 16.9%, respectively), as was the combined endpoint of death and hospitalization (18.8 vs. 20.6%, respectively). In both groups, 6.3% of patients had been hospitalized twice or more. The results for the three individual telemonitoring groups were not shown. Interestingly, in Italy, the primary endpoint was reduced in the telemonitoring arm, whereas in Poland, it was increased, mainly due to increased numbers of patients being hospitalized twice or more. In conclusion, home telemonitoring in heart failure patients is feasible, and patient compliance to monitoring is high. However, the main clinical outcome of the trial is neutral.

The session ended with the presentation of two meta-analyses on the hot topic of late stent thrombosis with drug-eluting stents (DESs). Currently, the majority of stents implanted worldwide is a DES (55%), and its use is still steadily increasing. In some countries, even 90% of stents implanted are DESs. Although DESs spectacularly reduce the rate of the rather benign event of in-stent restenosis, in the past years, concern has been raised with respect to a possibly increased risk of stent thrombosis, a complication associated with high mortality. The following two meta-analyses address this important issue.

The first meta-analysis was presented by Edoardo Camenzind from Geneva, Switzerland and studied the risk of death and non-fatal myocardial infarction in the randomized controlled trials comparing sirolimus- (SESS) or paclitaxel-eluting stents (PESs) with bare-metal stents (BMSs). On the basis of the latest available follow-up data of four studies comparing SES with BMS, a significant increase in death or non-fatal Q-wave myocardial infarction was observed: 6.3 vs. 3.9%, respectively ($P = 0.03$), consistent with a 38% relative increase after a maximum of 4 years of follow-up. For five studies that compared PES with BMS, no increased risk for the combined endpoint of death or infarction was observed after a maximum of 3 years of follow-up: 2.6 vs. 2.3%, respectively ($P = 0.68$).

The second meta-analysis presented by Alain Nordmann from Basel, Switzerland compared SES or PES with BMS to evaluate its effect on total, cardiac, and non-cardiac death during long-term follow-up. Seventeen studies were included in the analysis. Overall mortality with DES during follow-up tended to be increased, compared with BMS. The odds ratios (ORs) after 1, 2, and 3 years were 0.94, 1.11, and 1.25, respectively ($P = \text{ns}$). Cardiac death with the use of DES tended to be less in the first 2 years after implantation when compared with BMS (OR after 1 year 0.84 and after 2 years 0.73), but was identical after 3 years (OR 1.0). Non-cardiac death was increased for DES compared with BMS: OR 1.72 (CI 1.01–2.94) after 2 years and 1.45 (CI 0.93–2.25) after 3 years. The difference was driven by a significantly higher rate of non-cardiac mortality in SES-treated patients at these time points: ORs 2.74 (CI 1.22–6.13) and 2.04 (CI 1.00–4.15), respectively. PES also tended to lead to higher non-cardiac death rates, but less pronounced than SES.

Thus, overall mortality of DES tended to be higher than that of BMS. Death and re-infarction were significantly increased in patients who received an SES and tended to be increased in patients who received a PES. Unexpectedly, non-cardiac mortality was significantly increased in the SES-treated patients, but not in the PES-treated patients. The discussant Salim Yusuf from Hamilton, Canada urged for further research, especially long-term clinical follow-up for the occurrence of late stent thrombosis and non-cardiac mortality. As DESs do not reduce the risk of infarction or mortality, these should be used cautiously at least until these data are available.

The second Hotline session opened with the WAVE trial, presented by Sonia Anand from Hamilton, Canada. The WAVE trial was a randomized open-label study of aspirin alone vs. the combination of aspirin plus moderate intensity oral anticoagulation (INR 2–3) in patients with peripheral artery disease. As combination therapy has been shown to be beneficial in high-risk patients with recent myocardial infarction, the hypothesis was tested whether this would also be the case for peripheral artery disease. In addition, the assessment of bleeding risk was a major endpoint. Follow-up was performed every 3 months for 3 years. The major inclusion criteria were intermittent claudication with objective evidence, previous vascular reconstruction, or asymptomatic peripheral artery disease (ankle/brachial
index <0.9 and/or carotid stenosis >50%). Patients with a high bleeding risk, indication for oral anticoagulation, and recent stroke were excluded. A run-in phase of 2–4 weeks during which patients used combination therapy was started by 2417 patients, of these 256 stopped, and 2161 patients were evenly randomized between the two treatment groups. In the combination therapy group, the mean INR achieved was 2.2, and 319 patients permanently discontinued study medication. In the aspirin group, 45 patients switched to the use of oral anticoagulation. Baseline characteristics were well balanced. Mean age was 64 years, one-quarter of the patients was female, one-third smoked, almost half had CAD, and ~15% had a history of stroke. The qualifying condition was arterial disease of the limbs in over 80% of the patients. Before enrolment, 99% of the subjects already used antiplatelet therapy. The first co-primary composite efficacy endpoint of cardiovascular death, myocardial infarction, and stroke was not reduced by combination therapy, compared with aspirin alone: 12.2 vs. 13.3%, respectively (P = 0.49). The second co-primary endpoint, the first primary plus severe ischaemia, was not affected either: 15.9 vs. 17.4%, respectively (P = 0.38). None of the components of the primary endpoint were reduced. However, life threatening bleedings were significantly increased by combination therapy, compared with aspirin: 4.0 vs. 1.2%, respectively (P < 0.001). Of these bleeds, 0.9 vs. 0.3% were fatal (P = 0.051) and 1.3 vs. 0%, respectively, were intracranial (P = <0.001). In explanation of the lack of benefit of combination therapy, most likely, the thrombotic risk in this population was too low for the antithrombotic benefits to outweigh the increased risk of bleeding complications. In general, combination therapy cannot be recommended for patients with peripheral artery disease.

The RIVIERA study presented by Gilles Montalescot from Paris, France includes a registry of elective and primary percutaneous coronary interventions (PCIs) in patients not pre-treated with anticoagulation. Current practice in PCI was characterized, and predictors of adverse clinical and angiographic outcomes were studied, with special attention for the use of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in the cath lab. In 23 countries, 144 centres participated, including 7962 patients. Prior myocardial infarction was present in 31% prior coronary artery bypass grafting (CABG) in 5%, and prior PCI in 13%. Indications for PCI were stable CAD in 45%, non-ST-elevation acute coronary syndrome in 36%, ST-elevation myocardial infarction (STEMI) ≤12 h of symptom onset in 9%, STEMI >12 h of symptom onset in 11%, and other indications in 7%. In 11%, a radial approach was used. In 95% of patients, one or more stents were placed. Most patients received aspirin and clopidogrel, and 18% also received a glycoprotein (GP) IIb/IIIa inhibitor. Anticoagulation consisted of UFH alone in 36%, of LMWH alone in 58%, and of UFH plus LMWH or other anticoagulation in 6%. In-hospital clinical outcome was excellent: 0.3% mortality and 1.0% myocardial infarction. Major bleeding was seen in 0.3%. The most important independent predictor of increased risk of death or myocardial infarction was PCI for all indications other than stable CAD. Factors associated with lower risk of death or infarction were radial approach, pre-treatment with a thienopyridine, and the use of LMWH compared with UFH. Strong predictors of mortality were PCI of the left main trunk and female gender. Important predictors of bleeding included the use of GP IIb/IIIa inhibitors, the combined use of UFH and LMWH, and PCI of bypass grafts. Radial access reduced the bleeding risk. The most frequent angiographic complications were coronary dissection (3.7%), no reflow (2.0%), and thrombus (1.9%). The strongest risk factors for angiographic complications were STEMI and plain balloon angioplasty. In conclusion, rates of mortality, infarction, and bleeding were strikingly low in this registry. Important predictors of the outcome events were PCI of the left main trunk and of bypass grafts. With respect to bleeding, it appears important to avoid the combined use of UFH and LMWH and to use GP IIb/IIIa blockers only selectively. Radial access seems safer with respect to bleeding complications. However, these results should be interpreted cautiously as they are not based on randomized data.

Patrick Serruys from Rotterdam, the Netherlands, presented the 6-month angiographic, intravascular ultrasound (IVUS) and the clinical results of the SPIRIT-2 trial. In this international, multi-centre randomized, single-blind non-inferiority trial, the new everolimus-eluting stent (EES) was compared with the PES. Everolimus, like sirolimus, interferes in the G1 phase of the cell cycle. Three hundred patients were randomized in a 3:1 fashion to EES or PES, respectively. In all patients angiography was performed at baseline and after 180 days, in half of the patients combined with IVUS. Patients were eligible if they had a de novo target lesion, without thrombus, length ≤28 mm, vessel diameter between 2.5 and 4.25 mm, stenosis severity ≥50 and <100%, and TIMI flow grade ≥1. Baseline characteristics were equally distributed. The mean age was 62 years, ~25% was diabetic, lesions were type III in 13%, and mean lesion length was 13 mm. Dual lesions treated were 17 and 18% in the EES and PES groups, respectively, and procedural success was 99 and 97% respectively. In both arms, diameter stenosis was reduced from ~60% at baseline to 13% post-procedural. Pre-procedural minimal luminal diameter was 1.06 and 1.14 mm in the EES and PES arms, respectively, with a reference vessel diameter of 2.70 and 2.82 mm respectively; post-procedural minimal luminal diameter was 2.49 vs. 2.62 mm, respectively (P < 0.05). The primary endpoint of late loss of luminal diameter at 180 days was significantly reduced by the EES compared with the PES: 0.11 (SD 0.27) vs. 0.39 mm (SD 0.39), P < 0.0001, meeting the criteria for superiority. Nevertheless, binary restenosis rate was similar between EES and PES arms. After 6 months, IVUS analysis showed that in EES, neointimal volume and volume obstruction were 70% lower than that in PES. Both arms had one patient with late stent thrombosis. The composite of cardiac death, myocardial infarction, and target lesion revascularization tended to be lower in the EES arm: 2.7 vs. 6.5%. Thus, angiographic and IVUS outcomes of EES are superior to PES. The risk of major cardiac events was low. However, in the light of the current discussion on the risk of late stent thrombosis associated with DESs, large phase 3 randomized trials with long-term clinical follow-up are awaited.

The randomized VIAMI trial was presented by Gerrit Veen from Amsterdam, the Netherlands. Patients with viable myocardium in an infarction area are at increased risk of ischaemic events when compared with those without viability. VIAMI investigated whether shortly after acute myocardial infarction, patients with viability in the
infarction area would benefit of an invasive strategy compared with a conservative, ischaemia-guided strategy. Patients were eligible if they had a myocardial infarction that could be located on ECG, received either fibrinolysis or no reperfusion therapy, and were uneventful until assessment of viability. Viability was assessed by low-dose dobutamine stress echocardiography (DSE) performed 48–72 h after admission. Randomization took place after the core lab had detected viability. Patients in the invasive group underwent angiography and immediate PCI when feasible. Additionally, a prospective registry was kept of patients without viability. DSE was performed in 291 patients, of which 216 (74%) had viability: 106 were randomized to the invasive strategy and 110 to the conservative strategy. The mean age was 60 years, ~75% were men, few had a previous infarction, and the index event was anterior infarction in one-third. Only about half of the patients had received fibrinolysis; the rest was managed conservatively before stress echocardiography. In the invasive group, 73% had a PCI and 11% had CABG. No revascularization was done in 16%. The 6-month composite primary endpoint of death, myocardial infarction, or unstable angina was significantly reduced in the invasive arm when compared with the conservative arm: 6.6 vs. 15.5% (P = 0.04). This difference was completely accounted for by a reduction in unstable angina in the invasive group when compared with the conservative group: 2.8 vs. 11.8% (P = 0.01). Overall mortality and re-infarction rates were low: 1.4 and 2.3%, respectively. The risk of the primary outcome in the registry of patients without viability was low: 5.3%. It was concluded that patients with viability in an area of recent infarction benefit of a routine invasive strategy, but clinical applicability of the studied strategy seems limited for several reasons. First, DSE is time-consuming with limited availability, especially in smaller centres. Furthermore, it is performed after 48–72 h, a period after infarction in which the majority of recurrent events has already taken place. Despite these practical limitations, the results are highly interesting conceptually and add to the body of evidence in favour of viability testing followed by an invasive management after myocardial infarction.

The JIKEI Heart Study was presented by Seibu Mochizuki from Tokyo, Japan, and Björn Dahlöf from Göteborg, Sweden. This randomized open-label study compared a valsartan-based antihypertensive treatment with an anti-hypertensive treatment without angiotensin receptor blockers (ARBs). In the large studies on ARBs and ACE-inhibitors, the Asian population was largely underrepresented; therefor, the current study was performed solely in Japan. Patients were eligible if they had hypertension, coronary heart disease, and/or heart failure. They were evenly randomized to both strategies. The blood pressure target was 139/81 mmHg in both groups and was modestly reduced to 131/77 mmHg in both treatment arms. After 3 years, the study was halted because of an unequivocal benefit in the valsartan group. The composite primary endpoint of cardiovascular mortality and morbidity occurred in 92 patients in the valsartan group, compared with 149 patients in the non-ARB group, consistent with a highly significant 39% relative risk reduction (RRR) (P < 0.001). The components of the primary endpoint that were particularly reduced were stroke, hospitalization for heart failure, and hospitalization for angina (RRR 40, 46, and 65%, respectively). Mortality and myocardial infarction were unaffected. Thus, in this Japanese population of predominantly hypertensive patients, the strategy that included valsartan had a favourable effect on a broad range of cardiovascular outcomes. Interestingly, despite the comparable level of blood pressure control in both treatment arms, a strategy based on valsartan seems more effective in the prevention of cardiovascular events.

The final presentation of this year’s Hotline sessions was the TROICA trial, presented by Bernd Böttiger from Heidelberg, Germany. TROICA was a randomized, placebo-controlled, double-blind trial of tenecteplase in out-of-hospital cardiac arrest. As most cardiac arrests have a thrombotic aetiology, early treatment with fibrinolysis may be beneficial. Patients were eligible if they had a witnessed out-of-hospital cardiac arrest, and study medication could be administered within 20 min of collapse. Originally, all initial rhythms were allowed for enrolment in the study. However, after protocol amendment, asystolic patients were excluded, as survival among these patients was <1%. Patients with ventricular fibrillation (VF) or ventricular tachycardia (VT) could be randomized after three unsuccessful shocks. Patients with pulseless electrical activity could be randomized immediately. The study was halted after enrolment of 1050 patients instead of the planned 1300 because of futility. Patients with asystole were excluded from the analysis; therefore, these results are based on 827 patients. The patients had a mean age of 65 years, and >80% were men. The initial rhythm was VF in ~70%, VT in 2%, and pulseless electrical activity in the remainder. The aetiology of cardiac arrest was myocardial infarction in 60%, pulmonary embolism in ~4%, primary ventricular arrhythmia in ~20%, the rest was of other causes. The primary endpoint of hospital admission was not different between the treatment groups: 59.0 vs. 59.5% for tenecteplase and placebo, respectively (P = 0.9). The same was seen in 30-day survival: 18.2 vs. 20.2%, respectively (P = 0.5). Safety was acceptable: intracranial haemorrhage 1.0 vs. 0% and major bleeding 8.9 vs. 7.4% for tenecteplase and placebo, respectively. These results demonstrate that fibrinolysis cannot be generally recommended as standard treatment for patients with refractory out-of-hospital cardiac arrest.

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References