The Hotline Sessions of the 23rd European Congress of Cardiology

Of the 18 presentations at the three Hotline Sessions of the 23rd European Congress of Cardiology, held in Stockholm, 1–4 September 2001, 15 are summarized, since three have already been published. The information given was collected by the authors during the presentations and also from press releases prepared by some speakers. This report shows only preliminary results.

During the first Hotline Session, studies on early and long-term treatment of acute coronary syndromes were presented.

Dr Uwe Zeymer from Kassel, Germany, presented the ESCAMI trial. This placebo-controlled randomized trial evaluated eniporide, an intravenous sodium hydrogen exchange inhibitor, in patients undergoing reperfusion therapy for acute myocardial infarction, of whom about 35% received primary PTCA and the others fibrinolytic therapy. The trial, which comprised 959 patients, consisted of both a dose finding and a dose confirmation phase. The primary endpoint of the study was enzymatic infarct size measured using the area under the curve of $\Delta$HBDH.

The two different dosages of eniporide (100 mg and 150 mg compared to placebo) revealed no significant differences in enzymatic infarct size. In addition, clinical outcome was similar in the eniporide and placebo treated patients.

Professor P. Touboul from Lyon, France, presented an important, and so far unique trial, comparing pre-hospital fibrinolytic therapy with primary angioplasty in patients with acute myocardial infarction. Dr Harvey White from Auckland, New Zealand, presented the HERO-2 study. This study addresses the role of a specific thrombin inhibitor (hirulog) compared to heparin in conjunction with streptokinase for acute myocardial infarction. Ever since the GUSTO-2B and TIMI-9 trials, in which hirudin was shown to be slightly, but not significantly superior to heparin in fibrinolytic therapy for acute myocardial infarction to show a non-significant survival benefit for pre-hospital fibrinolysis. Treatment could be initiated one full hour earlier in the pre-hospital setting, which may explain the 30-day mortality differences. Of course, this study is too small to be conclusive on hard end-points, but it emphasizes the feasibility, safety and possible benefits of pre-hospital fibrinolysis in the primary angioplasty era.

The HERO-2 study was presented by Dr Harvey White from Auckland, New Zealand. This study addresses the role of a specific thrombin inhibitor (hirulog) compared to heparin in conjunction with streptokinase for acute myocardial infarction. Ever since the GUSTO-2B and TIMI-9 trials, in which hirudin was shown to be slightly, but not significantly superior to heparin in fibrinolytic therapy for acute myocardial infarction, the search was on for a less expensive direct thrombin inhibitor. The less expensive bivalirudin, or hirulog, was compared to intravenous heparin over 48 h in 17,073 patients treated with lytic therapy, the total ischaemic time in the fibrinolytic group was 220 min and the measured total ischaemic time in the angioplasty group was 215 min. The primary end-point consisting of death, non-fatal reinfarction or non-fatal disabling stroke was 6.2% in the primary angioplasty group and 8.2% in the rt-PA group (RR 0.76, 95% CI 0.46–1.24, $P=0.29$). Death was 4.8 vs 3.8% ($P=0.60$), non-fatal re-myocardial infarction was 1.7 vs 3.7% ($P=0.13$) and disabling stroke was 0 vs 1.0% ($P=0.12$). Intracranial haemorrhage was only seen in the fibrinolytic group (0.5%). However, the occurrence of severe extracranial bleeding was 2.0% in the primary angioplasty group vs 0.5% in the rt-PA group ($P=0.06$). Urgent (re)PTCA was needed in 4% of the angioplasty group vs 33% in the rt-PA group ($P<0.01$).

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Most of the procedures were performed in the first 24 h. This is the first randomized trial comparing two established strategies of reperfusion therapy for acute myocardial infarction to show a non-significant survival benefit for pre-hospital fibrinolysis. Treatment could be initiated one full hour earlier in the pre-hospital setting, which may explain the 30-day mortality differences. Of course, this study is too small to be conclusive on hard end-points, but it emphasizes the feasibility, safety and possible benefits of pre-hospital fibrinolysis in the primary angioplasty era.
were from Eastern Europe. Bivalirudin was given in a dose of 25 mg·kg⁻¹ as a bolus, 0.5 mg·kg⁻¹ per hour in the first 12 h and 0.25 mg·kg⁻¹ for the remaining 36 h. Heparin was given in a dose between 800 and 1000 U·h⁻¹ for 48 h, aiming at an aPTT of 50–75 s. The mean aPTT at 12 h was 108 s in the bivalirudin group vs 77 s in the heparin group. At 24 h these figures were 80 and 57 s (P<0.001). The mortality was the primary endpoint and was 10.8% in the bivalirudin group and 10.9% in the heparin group (RR=0.99, P=0.88). Death and reinfarction were 12.6 and 13.6%, respectively (RR=0.92, P=0.07). Non-fatal reinfarction was 2.8 vs 3.6% (RR=0.77, 95% CI 0.36–0.90, P=0.004). Non-fatal stroke was 1.25 vs 0.96 (P=0.07). Intracranial haemorrhage was seen in 0.55 vs 0.37% (P=0.09). Severe bleeding was increased 0.7 vs 0.5% (RR=1.45, P=0.08), as were blood transfusions 1.4 vs 1.1% (RR=1.25). The addition of the direct thrombin inhibitor bivalirudin, which is less expensive than hirudin, to the inexpensive streptokinase does not lead to better survival than the streptokinase–heparin combination, and thus, should not be replacing heparin as a routine. Bivalirudin seems to be safe and also decreases reinfarction, which, however, does not translate into better survival. Interestingly, in this trial, and also in GUSTO-5 and ASSENT-3, reinfarction does not lead to a worse 30-day outcome. The aggressive approach towards reinfarction apparently does not influence mortality in the short term. Whether this is the case for long-term survival should be revealed by the long-term results of these megatrials.

Dr Harald Arnesen, Oslo, Norway, presented the long awaited results of the WARIS-2 trial. In 20 hospitals in Norway, 3630 patients between the ages of 20 and 75 were randomized at hospital discharge following acute myocardial infarction towards aspirin alone 160 mg daily, a combination of aspirin 75 mg daily with warfarin at a target INR of between 2.0 and 2.5 or full intensity warfarin with a target INR of between 2.8 and 4.2 without aspirin. Mean follow-up was 4 years and the achieved INR in the combination group was 2.2 and the warfarin alone group 2.8. The primary end-point (first event: death, non-fatal reinfarction and thromboembolic stroke) was 20.0% in the aspirin group, 15.0% in the aspirin plus warfarin group and 16.7% in the warfarin alone group. For the primary end-point, combination treatment was superior to aspirin (OR 0.71, 95% CI 0.58–0.86, P=0.0005) alone, but not superior to warfarin alone (OR 0.88, 95% CI 0.72–1.07, P=ns). Warfarin alone was also better than aspirin alone (OR 0.81, 95% CI 0.67–0.98, P=0.028). These differences were also found when all ischaemic events were taken into account. Non-fatal major bleeding was the lowest with aspirin alone, 0.15% per year, with the combination it was 0.52% and with warfarin alone it was 0.58%. Minor bleedings were 0.81, 2.75 and 2.16% per year, respectively. Together with the APRICOT-2 and ASPECT-2 trials presented at the Hotline Sessions at the ESC meeting in 2000, the WARIS-2 data are conclusive in the protective effect of medium intensity warfarin in combination with aspirin compared to aspirin alone in the prevention of death, recurrent myocardial infarction and stroke. Secondly, warfarin alone is also significantly better than aspirin alone. Again it was shown that an INR over 2.0, is necessary to generate significant protection. These trials show acceptable safety both for the combination treatment and for warfarin alone. Although inexpensive, warfarin treatment is a laborious strategy, which is only possible in selected countries. However, this large quantity of data emphasizes the role of prolonged anticoagulation following myocardial infarction, as clearly shown in the trials such as ASSENT-3, HART-2, ASSENTPLUS and AMI-SK, of >48 h treatment with low molecular weight heparin after fibrinolysis.

The second Hotline Session was dedicated to coronary revascularization and to atrial fibrillation.

Professor Christian Hamm from Bad Nauheim, Germany, presented the TRUST study. This multicentre study randomized 485 patients with unstable angina undergoing PTCA to either a silicone carbide coated (Tenax XR) stent or to a conventional stent. All patients received aspirin and ticlopidine or clopidogrel. There was no significant difference in the combined primary end-point of death, myocardial infarction and target lesion revascularization (13% vs 17%). In the Braunwald class IIB subgroup, the risk of death, myocardial infarction and target lesion revascularization was significantly reduced at 6 months in the silicone-coated stent group, mainly caused by less target lesion revascularization. At 12 months, no significant difference was shown between the two groups. Therefore, in patients with unstable angina, the use of silicone-coated stents seems to lack benefit compared to conventional stents.

Professor Matthias Pfisterer from Basel, Switzerland, presented the TIME study. This multicentre prospective study assessed the quality of life in 301 elderly patients with angina pectoris of at least CCS II despite at least two antianginal drugs, randomized to either revascularization or optimized drug therapy. Mean age was 80 years and 50% of the patients had a history of myocardial infarction. In the revascularization group (n=153) 52% of the patients underwent PCI and CABG. In the conservative
group, both the number and the dose of the antiangiial drugs were increased. At 6 months, quality of life was improved in both groups, but more in the revascularized group. The combined end-point of death, myocardial infarction and acute coronary syndromes was 49% in the conservative and 19% in the revascularized group ($P<0.0001$). The mortality rate was more than twice as large in the revascularization group (8·5% vs 4·1%, not significant at this sample size). Hospital admission for acute coronary syndromes followed by revascularization occurred significantly more frequently in the conservative group (37% vs 7%, $P=0.001$). These data suggest that in elderly patients with angina pectoris improvement of medical therapy is beneficial for their well being. Revascularization therapy improves the quality of life even more and reduces the risk of acute coronary syndromes. However, in the individual patient, the benefits of an invasive strategy should be carefully weighed against the potential risks.

Dr P. Wahrborg from Gothenburg, Sweden, presented a substudy of the multicentre randomized Stent or Surgery (SoS) trial. In this substudy, neuropsychological performance and depression were assessed in 83 patients undergoing PCI and 70 patients undergoing CABG (10% off-pump). Before intervention and at 6 weeks, 6 and 12 months, occurrence of aphasia, agnosia, apraxia and other neurological deficits were scored using the WAIS and WMS tests. Depression was scored with the Zung self-rating depression scale. Neither PCI nor CABG resulted in worsening of neurological symptoms and depression scale. There was no difference between CABG and PCI. These results contradict the general idea that neuropsychological performance is often (temporarily) impaired after CABG.

Dr John Camm from London, Great Britain, presented the Atrial Fibrillation Therapy study. This prospective randomized trial investigated the use of conventional DDD pacemaker therapy and novel antiarrhythmic algorithm pacemakers in patients with paroxysmal atrial fibrillation to prevent recurrences. In 372 patients with drug-refractory paroxysmal atrial fibrillation, a DDD pacemaker was implanted. Due to technical problems, only 125 patients entered phase 2 of the trial, in which conventional DDD pacemaker therapy at different paced heart rates (40–70–85/min) was assessed. No significant differences were seen between frequency groups. At phase 3, 42 patients were randomized to the algorithm switched off and 56 patients to the algorithm switched on. At 2 months, the antiarrhythmic fibrillation algorithm group showed a significantly lower median atrial fibrillation burden (0 vs 0.78 hours/day, $P=0.01$). Average duration of sinus rhythm was longer (828 vs 40 min, $P=0.05$) and fewer patients suffered from periods of atrial fibrillation lasting more than 7 min (69·7% vs 84·6%, $P=0.01$). Therefore, the antiatrial fibrillation algorithm proved to increase the duration of sinus rhythm, although in almost 70% of the patients paroxysms of atrial fibrillation still occurred.

Dr T. Fetsch from Munich, Germany, presented the results of the PAFAC study. This double-blind, placebo-controlled, randomized trial investigated the recurrence of atrial fibrillation after successful electrical cardioversion and whether recurrence could be reduced with antiarrhythmic drugs. Of 1182 chronic atrial fibrillation patients, 848 were successfully cardioverted and 88 patients were randomized to placebo, 383 to sotalol and 377 to quinidine and verapamil. Every day, an ECG was recorded using a small ECG-recorder. The primary end-point was recurrence of atrial fibrillation lasting more than 30 s and death at 1-year follow-up. At 1 year, only 12% remained event free in the placebo group, significantly lower compared to 30% in the sotalol group and 27% in the quinidine/verapamil group. Chronic atrial fibrillation occurrence was significantly higher in the placebo group, 70% vs 50% and 38% respectively. In 70% of atrial fibrillation no symptoms were reported. No patient died in the placebo group vs six (1·6%) in the sotalol and five (1·4%) in the quinidine/verapamil group. Torsades de pointes were reported in nine patients on sotalol (2·3%). Thus, antiarrhythmic drugs appear to reduce recurrence of atrial fibrillation after successful cardioversion; however, the risk of adverse events should be taken into account. Despite drug therapy, in only 25% of all patients did atrial fibrillation not recur within the first year.

The third Hotline Session consisted of trial reports on hypertension and heart failure.

The session was opened by Dr Roumen Nakov from Ludwigshafen, Germany, who presented the HEAT-2 study. This double-blind, randomized, placebo-controlled trial studied the blood pressure lowering effects of darusentan, a selective endothelin receptor blocker, in 387 patients with moderate hypertension. They were randomized to placebo or darusentan 10, 30, or 100 mg daily. The primary end-point was blood pressure at 6 weeks. Blood pressure (systolic/diastolic) was significantly reduced in the darusentan groups: 6/4 mmHg ($P<0.05$), 7/5 ($P<0.01$), and 11/8 ($P<0.001$), respectively. Pulse-rate remained unchanged. In the 100 mg group, side effects such as headache (14%), flushing (9%) and peripheral oedema (7%) were reported more frequently.

Dr A. Zanchetti from Milan, Italy, presented the results of the ELSA study. This double-blind randomized trial investigated the effects of 4-years’ treatment with the beta-blocker atenolol and the third generation calcium blocker lacidipine on intima thickness of the carotid artery measured by echography. A 4-year follow-up was completed in 764 and 755 patients, respectively. Blood pressure reduction was 15 mmHg, similar in both groups. The mean maximum intima thickness of the common carotid artery and its lateral bifurcation was 0.03 mm less thick in lacidipine-treated patients (P<0.0001). No significant differences were seen in adverse cardiovascular events and deaths between the groups. The increase/year of intima thickness was significantly lower in the lacidipine group compared to the atenolol group (0.006 vs 0.015 mm, P<0.001). Whether lacidipine can decrease the risk of cardiovascular events in hypertensive patients will have to be investigated in a future study.

Professor John Chalmers from Sydney, Australia, presented the PROGRESS study. This randomized double-blind placebo-controlled study assessed the effect of the ACE-inhibitor perindopril combined with the diuretic indapamide on the recurrence of stroke in patients with prior ischaemic or haemorrhagic stroke. In total 3051 patients were randomized to perindopril/indapamide and 3054 to placebo. The primary end-point was total stroke at 4 years follow-up. Treatment reduced blood pressure by 9/4 mmHg (systolic/diastolic). Treatment with perindopril/indapamide resulted in a significant risk-reduction of 28% in total stroke (95% CI 17%–38%, P=0.0001). The combination of stroke, myocardial infarction and death was reduced by 26% (95% CI 16%–33%, P=0.0001). Patients with a contraindication for diuretic therapy received perindopril only instead of the combination therapy. Interestingly, in this subgroup the risk reduction for stroke was only 5%. These results clearly demonstrate the beneficial vascular effects of the combination of perindopril/indapamide in stroke patients. Whether this is due to blood pressure reduction solely or also to direct vascular effects remains unsolved. Furthermore, it remains unclear what the effects of treatment with perindopril without indapamide would have been in these patients.

Professor Marc Pfeffer from Boston, U.S.A., presented the IDNT study. This double-blind randomized study assessed the effect of the angiotensin II receptor antagonist irbesartan on the progression of nephropathy in patients with diabetes mellitus type II, proteinuria (>900 mg . day−1), and hypertension. The patients were randomized to placebo (n=569), irbesartan (n=579) or amlodipine (n=567). The primary end-point at 2 years of follow-up was doubling of serum creatinine, need for dialysis, or death. Treatment with irbesartan significantly reduced the occurrence of the primary end-point compared to either placebo (risk reduction 20%, P<0.02) or amlodipine (risk reduction 23%, P=0.006). The occurrence of cardiovascular events did not differ significantly between the groups. Irbesartan appears to have a beneficial effect on the progression of nephropathy in these high-risk patients. Since this effect is not seen in amlodipine treatment, the effect of angiotensin II receptor antagonism on renal function seems to be more than blood pressure reduction alone, which was similar with either drug compared to placebo.

Dr James Coman Jr, from Tulsa, U.S.A., presented the CONTAK CD study. This randomized trial prospectively assessed the effect of pacemaker-based cardiac resynchronization therapy on progression of heart failure. The combined primary end-point at 4.5 months follow-up was death, hospitalization, worsening of heart failure and ventricular fibrillation/ventricular tachycardia. Of 581 patients with heart failure, NYHA II–IV, QRS>120 ms, ejection fraction <35%, and indication for AICD therapy, 490 patients were randomized to cardiac resynchronization therapy active or non-active. Cardiac resynchronization therapy resulted in a non-significant reduction (21%) of the primary end-point. VO2 max increased significantly in a subgroup of patients with advanced heart failure, but not in the total study group. In this study, cardiac resynchronization therapy did not improve outcome in patients with heart failure, possibly due to insufficient power, patient selection and short duration of follow-up. Whether cardiac resynchronization therapy might be beneficial in severe heart failure patients has to be assessed in a future study.

The last Hotline trial was the RITZ-1 study, presented by Professor John Teerlink from San Francisco, U.S.A. This double-blind placebo-controlled randomized trial assessed the effects of the non-selective endothelin antagonist tezosentan on the clinical outcome of patients hospitalized for acute heart failure. Patients (n=669) were randomized to intravenous tezosentan (50 mg . h−1) or placebo. Treatment was started 24 h after admission to hospital. The primary end-point was dyspnoea score at 72 h. The dyspnoea score showed no significant difference between the groups. However, significantly more headaches, nausea and vomiting were reported in the tezosentan group. These disappointing results were in sharp contrast to the positive results of the RITZ-2 trial. In RITZ-1, patients were treated 24 h after admission and 75% of them no longer suffered from dyspnoea, while in RITZ-2 treatment was
started immediately after admission. Whether these results can be explained by this, by dose finding problems, or by the fact that endothelin antagonists are simply not beneficial in the treatment of heart failure remains unsolved.