This year’s Congress of the European Society of Cardiology was held in Stockholm, Sweden from the 3rd to the 7th of September 2005. Summaries of the preliminary results of 12 of the 14 studies presented at the three Hotline Sessions are reported here. The CIBIS-III and BASKET trials have been published in *Circulation* 2005;112:2426–2435 and *Lancet* 2005;366:921–929, respectively. Data reported in this summary have been collected from press releases and presentations of the speakers.

During the first Hotline Session, three trials on heart failure were presented. Prof. Marco Metra from Brescia, Italy presented the ESSENTIAL study. In this randomized placebo-controlled trial, the effect of long-term treatment with low-dose oral enoximone (25–50 mg three times daily), a phosphodiesterase III inhibitor, in patients with advanced heart failure was studied. It was hypothesized that enoximone could reduce the co-primary endpoints time to cardiovascular (CV) hospitalization or all-cause mortality and would improve submaximal exercise tolerance and symptoms. In total, 1854 patients with ‘ischaemic and non-ischaemic’ cardiomyopathy (CMP), heart failure NYHA classes III and IV, and a left ventricular ejection fraction (LVEF) ≤30% were randomized to enoximone (n = 926) or placebo (n = 928). Results were presented for identical studies only differing by geographical location: America and Europe. With respect to baseline characteristics, mean age was 62 years, ischaemic CMP was present in 56%, NYHA class III in 91%, the mean LVEF was 23.6%, and almost 90% of the patients used beta-blockers and ACE-inhibitors. American patients had significantly lower mean LVEF, less exercise tolerance, and a longer duration of heart failure. At the end of the study, non-fatal withdrawal from study drug was 21%. During 16.4 ± 0.2 months follow-up enoximone and placebo did not differ with respect to all-cause mortality and CV hospitalization (49.5 vs. 50.1%, HR 0.98; *P* = 0.71) or all-cause mortality alone (21.7 vs. 22.6%, HR 0.97; *P* = 0.73). The 6 min walking test significantly improved in American patients treated with enoximone with 10 m when compared with placebo, but not in European patients (1.5 m). In the enoximone and placebo groups, a similar improvement in symptoms was found.

Prof. Roberto Ferrari from Ferrara, Italy presented PRE-AMI, a multi-centre, randomized, double-blind, placebo-controlled trial investigating the role of perindopril in elderly patients with acute myocardial infarction (AMI) and preserved left ventricular (LV) function. High-dose perindopril (8 mg once daily) started within 20 days after AMI and continued for 12 months was compared with placebo. Patients older than 65 years, LVEF >40%, and a good apical view on echocardiography were included. The primary composite endpoint was all-cause mortality, hospitalization for heart failure, and LV remodelling defined as ≥8% increase in LV end-diastolic volume (LVEDV) between baseline, 6, and 12 months follow-up echocardiography. In total, 1252 patients were randomized: 631 to perindopril and 621 to placebo. Remodelling was assessed in 455 and 441 patients, respectively. Baseline characteristics were mean age 72 years, mean ejection fraction 59%, NYHA class I in 80%, prior myocardial infarction in 10%, and diabetes in 23%. After enrolment, 70% of patients were treated with beta-blockers and almost 80% used the study drug during complete follow-up. The primary endpoint was significantly reduced with 38% in favour of perindopril-treated patients (*P* ≤ 0.001). This finding was mainly driven by the reduction in incidence of LV remodelling: 27.7 vs. 51.2% (*P* < 0.001). The secondary endpoints CV death, myocardial infarction, unstable angina, and revascularization were not reduced by perindopril. Importantly, adverse events were not noted in patients on perindopril. From this pathophysiologically relevant study, we can conclude that even in the elderly with relatively small infarctions and preserved LV function, perindopril can reduce LV remodelling and is tolerated well. Possibly because of the low-risk population studied, the delayed initiation of ACE-inhibitors after AMI and the relatively short duration of follow-up, reduction in LV remodelling was not translated in improved clinical outcome.
Prof. Veselin Mitrovic from Bad Nauheim, Germany presented the SIRIUS-II study. Ularitide is a natriuretic peptide and counteracts the effects of the renin-angiotensin-aldosterone system. The drug was evaluated in patients with advanced heart failure in a randomized, double-blind, placebo-controlled phase IIb trial. Ularitide may reduce pulmonary capillary wedge pressure (PCWP) and symptoms of dyspnoea as well as may improve haemodynamic parameters without increasing mortality. Three escalating doses of intravenous ularitide (7.5, 15, and 30 ng/kg/min) were compared with placebo. They were administered over 24 h. In total, 221 patients with uncompensated chronic heart failure, dyspnoea at rest or minimal exertion, a PCWP > 18 mmHg, and a cardiac index (CI) ≤ 2.5 L/min/m² were included. Main exclusion criteria were mechanical ventilation or shock. Baseline characteristics did not differ between the four groups: mean age was 61 years and 78% was male, ischaemic CMP was present in 52%, the mean PCWP was 25 mmHg, and the mean CI 1.9 L/min/m², and 94% of patients had an L VEF < 40%. The primary endpoints were PCWP and dyspnoea at 6 h and were significantly reduced in all patient-groups treated with ularitide in comparison with placebo. With respect to the secondary endpoints, treatment with ularitide 15 or 30 ng/kg/min, but not 7.5 ng/kg/min, significantly improved CI and significantly reduced the systemic vascular resistance. Creatinine clearance was not affected. However, ularitide resulted in significantly more hypotension, blood pressure decrease, and dizziness. In this dose-finding study, 30-day mortality was 13.2, 3.3, 3.8, and 1.8% for placebo and 7.5, 15, and 30 ng/kg/min for ularitide, respectively. SIRIUS-II confirms the beneficial effects of treatment with an intravenously administered natriuretic peptide on PCWP and dyspnoea and appears to be safe. However, future studies should address the question whether ularitide improves clinical outcome.

In the second Hotline Session, several issues were addressed. First, Dr Michele Brigalone from Lavagna, Italy presented the results of ISSUE-II. The main objective of this multi-centre, prospective, observational trial, was to assess the effectiveness of a new strategy including the risk stratification and diagnosis of neurally mediated syncope, early application of implantable loop recorders (ILR), and delayed therapy based on the findings with the ILR. Patients older than 30 years were included if neurally mediated syncope was suspected (ESC Guidelines) and the following criteria were met: more than three syncope episodes in the last 2 years, severe presentation of the syncope, and negative carotid sinus massage. Between June 2002 and June 2005, in total, 442 patients were eligible. An ILR was implanted in 417 patients, of which 392 patients were followed until their first documented syncope episode. Baseline characteristics were mean age 66 years, mean number of syncope episodes six, normal ECG in 86%, no structural heart disease in 86%, and 68% suffered from an injury as a result of syncope. A total of 143 (36%) patients suffered from more than one syncope episode during follow-up, of which 106 (27% of the 392 patients with follow-up) were recorded on ILR: asystole (n = 4), tachyarrhythmia (n = 9), and normal sinus rhythm (n = 36). Of the 106 patients with ILR-recordings, three patients had no follow-up, thus 103 patients entered an observational period to determine syncope recurrence. On the basis of the ILR findings, 47 patients received a pacemaker, one an implantable defibrillator, catheter ablation in four and one anti-arrhythmic drugs. The remaining 50 patients did not receive specific therapy. In patients receiving ILR-based therapy, syncope recurrence at 1 year was significantly reduced with 80% (10 vs. 41%, HR 0.20; P = 0.0005). The 1-year syncope recurrence in 47 patients with pacemaker was 5%, significantly lower than in patients without asystole or bradycardia and patients with asystole or bradycardia who did not receive a pacemaker. Severe trauma was seen in 2% of patients and mild trauma in 4%, none of the patients died. Thus, initial evaluation with ILR in selected patients with suspected neurally mediated syncope and therapy delayed until documentation of the syncope is effective and safe. Effort should be made to select patients more carefully for ILR implantation, because only in 27% of the patients, syncope was documented on ILR-recording.

Secondly, Prof. Wiek van Gilst from Groningen, The Netherlands presented the IMAGINE trial. The investigators hypothesized that early initiation of quinapril would improve outcome in post-CABG patients. In this randomized, double-blind, placebo-controlled study, originally 2200 patients were planned. As a result of unexpectedly low event rates, the sample size was increased to 2553 patients, and congestive heart failure and stroke were added to the original primary endpoint: time to first occurrence of CV death, non-fatal myocardial infarction, coronary revascularization, hospitalization for unstable angina, and documented angina not requiring hospitalization. Patients were eligible if they were stable within 7 days after CABG, older than 18 years, and had an L VEF ≥ 40%. Major exclusion criteria were valve replacement, renal impairment, significant peri-operative myocardial infarction (not defined), and an indication for ACE-inhibitors. Of the 2553 patients, 1280 were assigned to quinapril (40 mg once daily) and 1273 to placebo with a median follow-up of 3 years. Baseline characteristics were well balanced in both groups. Mean age was 61 years, prior myocardial infarction occurred in 40%, mean L VEF was 60%, and beta-blockers were used by 80% of patients, aspirin by 98%, and statins by 90%. Neither the 3-year primary endpoint nor the separate components were significantly reduced by treatment with quinapril (CV death in 1.6% in the quinapril group vs. 1.3% in the placebo group and the rate of non-fatal myocardial infarction was 1.3 vs. 1.6%, respectively). However, in the first 3 months, treatment with quinapril resulted in a 52% increase in primary events (P = 0.04) and significantly more adverse events: hypotension (9.2 vs. 3.9% in the first 3 months, P < 0.01; 3.0 vs. 1.7% after 3 months, P = 0.05) and cough (14.0 vs. 7.5% in the first 3 months, P < 0.01; 7.2 vs. 3.5% after 3 months, P < 0.01). In optimally treated low-risk patients, initiation of quinapril within 7 days after CABG does not show a beneficial effect and may even be harmful.

Drs Shamir Mehta and Salim Yusuf from Hamilton, Canada presented the results of the OASIS-5 study: a multi-centre, randomized, double-blind, double-dummy, non-inferiority trial on the efficacy and safety of fondaparinux (2.5 mg once daily) compared with enoxaparin (1 mg/kg twice daily). Fondaparinux is a synthetic pentasaccharide, which specifically inhibits factor Xa through anti-thrombin III. Patients with non-ST-segment elevation acute coronary
syndrome meeting two of three of the criteria, older than 60 years, ST-segment changes, and positive cardiac markers, were eligible. In 20 078 patients, fondaparinux and enoxaparin were given for a mean duration of 5 days. Baseline characteristics were male in 60%, positive troponin in 70%, ST-segment depression in 50%, prior myocardial infarction in 25%, and prior heart failure in 14%. Aspirin, clopidogrel, and beta-blockers were used by 98, 67, and 87% of patients, respectively. The composite primary endpoint death, myocardial infarction, and refractory ischaemia at day 9 was significantly lower in the fondaparinux group (7.0 vs. 3.2%, respectively). The composite secondary endpoint mortality and myocardial infarction were significantly reduced at 6 months by the use of fondaparinux: 5.6 vs. 6.3% (P = 0.036). Excess bleeding seems to be the main cause of the difference in long-term mortality. Administration of fondaparinux once daily, without the need for weight adjusted dosing, in patients with non-ST-segment elevation acute coronary syndromes is as effective as that of enoxaparin in preventing early ischaemic events and improves long-term survival. Bleeding complications occur dramatically less often when using fondaparinux, which may account for decreased mortality.

The NORVIT study was presented by Prof. Kaare Bønaa from Trondheim, Norway. In this multi-centre, randomized, double-blind, placebo-controlled secondary prevention trial, treatment with folic acid alone (0.8 mg once daily with vitamin B12 0.4 mg once daily), folic acid combined with vitamin B6 (40 mg once daily), or vitamin B6 alone is compared with placebo, with a 2 x 2 factorial design. Baseline characteristics were AMI in the last 7 days and age 30–84 years. In total, 3749 patients were enrolled, treated, and followed for 3.5 years (folic acid/vitamin B6, n = 937; folic acid, n = 935; vitamin B6, n = 934; placebo, n = 943). Baseline characteristics for the groups were well balanced: mean age 64 years, males 74%, prior myocardial infarction in 17%, beta-blocker in 90%, and aspirin in 90%. The primary endpoint fatal and non-fatal myocardial infarction and fatal and non-fatal stroke occurred in 19.1% of all patients. Treatment with either folic acid or folic acid and vitamin B6 reduced homocysteine levels from 13.5 to 9 µmol/L. However, the rate of the primary endpoint per 100 person-years did not differ between patients treated with folic acid (6.7%) and vitamin B6 (7.0%) when compared with placebo (6.7%). Strikingly, when comparing the combination folic acid and vitamin B6 with placebo, the relative risk of myocardial infarction and stroke was significantly increased (RR 1.2, P = 0.029). An unexplained finding was the non-significant increased incidence of cancer in patients treated with folic acid or folic acid and vitamin B6. Thus, folic acid or high-dose vitamin B6 is not effective in the secondary prevention of ischaemic events post-myocardial infarction and may even be harmful when administered in combination.

Dr Ingeborg Brouwer from the Centre for Food Sciences from Wageningen, the Netherlands presented a randomized, placebo-controlled trial on the anti-arrhythmic effect of fish-oil in patients with an implantable cardioverter defibrillator (ICD) for secondary prevention: the SOFA trial. Fish-oil contains n-3 fatty acids, which have been proven to reduce total mortality and sudden death after myocardial infarction in the large GISSI-Prevenzione trial. As sudden death is mostly due to ventricular arrhythmias, it was hypothesized that n-3 fatty acids would reduce the 12-month composite primary outcome of pacing and shock delivery by ICD for ventricular tachycardia or ventricular fibrillation (VT/VF) and all-cause mortality. Of the 546 ICD patients with at least one episode of VT/VF in the previous year, 273 patients were randomly assigned to 2 g of fish-oil once daily (containing 900 mg n-3 fatty acids) and 273 to placebo. The baseline characteristics were well balanced: mean age 61 years, patients had in 39% VF and 75% VT. Mean LVEF was 37%, prior myocardial infarction was present in 61%, amiodarone was used by 30% of patients, and beta-blockers in over 70%. The event-free survival at 400 days was 70% in the fish-oil group and 67% in the placebo group (P = 0.24). The events consisted mainly of pacing or shock delivery: 27% in the fish-oil group vs. 28% in the placebo group. Mortality at 400 days was, respectively, 3 vs. 5% (ns), which is very low in comparison with previous studies. However, patients (SOFA) confirms the results of a recently published similar study showing that n-3 fatty acids have no beneficial effect on arrhythmia in patients with an ICD for secondary prevention. The currently conducted placebo-controlled GISSI-HF trial in patients with symptomatic heart failure of any aetiology randomized by 2 x 2 factorial design to fish-oil and rosuvastatin may give the definite answer.

The topics of the third Hotline Session were stenting, revascularization, and thrombosis. The JUPITER-II is a multi-centre, randomized, double-blind study and was presented by Dr Marie-Claude Morice from Massy, France. The objective was to evaluate the safety and effectiveness of the first European drug-eluting stent Janus (a Carbostent with tacrolimus reservoirs instead of coating) when compared with a Tecnic Carbostent. Of the 332 patients, 166 received the Janus and 166 the Tecnic stent. The primary endpoint was in- and peri-stent late lumen loss established with quantitative coronary angiography at 6 months. The secondary endpoints were re-stenosis at 6 months, major adverse cardiac events (MACE), target lesion revascularization (TLR), and stent thrombosis at 1 and 6 months. Major inclusion criteria were angina pectoris (CCS I–IV), silent ischaemia, non-q-wave myocardial infarction, and stenosis ≥50 and ≤100% suitable for direct stenting. Baseline characteristics were mean age 64 years, stable angina in 60%, unstable angina in 16%, and single-vessel disease in 60%. Direct stenting was performed in 76% of the Janus group (100% success) and 86% of the Tecnic group (99% success). In total, 1.18 stents per patient in both groups. Surprisingly, only the secondary endpoints were presented. At 6 months, MACE was non-significantly reduced with a Janus stent: 7.6 vs. 10.6% (P = 0.36). The events in the Janus stent group were target vessel revascularization in 6.4%, cardiac death in 0.6%, and myocardial infarction in 0.6%, whereas in the Tecnic stent group, all events were related to target vessel revascularization (no mortality). As expected in this low-risk population, no benefit of the Janus stent on 6-month clinical outcome was observed. The results of the primary endpoint late lumen loss are eagerly awaited.

Prof. Gilles Montalescot from Paris, France presented the STEEPLE study. This randomized trial tested the safety of
enoxaparin over unfractionated heparin (UFH) in patients undergoing elective percutaneous coronary intervention (PCI) by femoral access. Patients were randomized to enoxaparin bolus 0.5 mg/kg i.v., 0.75 mg/kg bolus i.v., or UFH bolus (70–100 IU/kg without and 50–70 IU/kg with GPIIb/IIIa inhibitor) stratified by the use of GPIIb/IIIa inhibitor. Baseline characteristics were similar in the three groups: mean age 63 years, of whom 70% male, unstable angina or myocardial infarction in the previous 7 days in 14%, prior PCI in 36%, hypertension in 70%, a sheath size less than 7F in 80%, and a closure device was used in 40%. Aspirin was used by 84% of patients, and during the procedure, 40% of patients were treated with GPIIb/IIIa inhibitors. Enrolment of patients randomized to 0.5 mg/kg enoxaparin was prematurely discontinued on DSMB advice because of increased mortality. As a result, 3528 patients underwent PCI, of which 1070 patients received 0.5 mg/kg enoxaparin and 1230 UFH. In 94% of patients, PCI with stenting was performed. The primary endpoint premature mortality was pre-
maturely discontinued because of increased mortality. As a result, 3528 patients underwent PCI, of which 1070 patients received 0.5 mg/kg enoxaparin and 1230 UFH. In 94% of patients, PCI with stenting was performed. The primary endpoint non-CABG related major and minor bleeding at 48 h was lower in patients receiving enoxaparin 0.5 and 0.75 mg/kg in comparison with UFH (6.0%, P = 0.014; 6.6%, P = 0.052 and 8.7%, respectively), mainly driven by a significant 57% reduction in major bleeding (1.2%, P = 0.005; 1.2%, P = 0.007 and 2.8%, respectively). With GPIIIb/IIIa inhibitors, the risk of bleeding increased, but was similar in all groups. With respect to the secondary endpoint (composite of major and minor bleeding, death, myocardial infarction, or urgent target vessel revascularization), no significant differences were found between enoxaparin and UFH (7.2, 7.9, and 8.4%, respectively). When specifically analysing the 0.5 mg/kg enoxaparin group, neither a relationship with increased ischaemic events nor an increase in death or myocardial infarction was found. Thus, enoxaparin reduces the risk of major bleeding in patients undergoing elective PCI and is as effective as aspirin in reducing death, myocardial infarction, and target vessel revascularization.

The first results of the multi-centre open-label ASSENT-4 PCI study were presented by Prof. Frans van de Werf from Leuven, Belgium. Hypothetically, full-dose fibrinolysis prior to PCI (facilitated PCI) would improve clinical outcome when compared with primary PCI in patients with ST-segment elevation myocardial infarction and an expected delay to primary PCI of >60 min. Patients with symptom onset within 6 h and cumulative ST-elevation >6 mm were randomized to fibrinolysis (TNK-t-PA) followed by PCI or to PCI alone. The primary endpoint was death or cardiogenic shock or congestive heart failure at 90 days. The trial was prematurely discontinued because of increased mortality in the facilitated PCI group (TNK + PCI), and only 30-day results were presented. In total, 1667 patients were randomized (46% in a PCI centre), Mortality at 30 days in the 829 patients receiving TNK + PCI was 6.0 vs. 3.8% in the 838 patients undergoing PCI only (P = 0.04). In the TNK + PCI group, recurrent myocardial infarction occurred significantly more often (4.1 vs. 1.9%, P = 0.01), as did abrupt vessel closure (1.9 vs. 0.1%, P < 0.001) and repeat target vessel revascularization (4.4 vs. 1.0%, P < 0.001). The median time between administration of TNK and first balloon inflation was 104 min, and an unexpectedly low TIMI flow grade 3 before PCI was found with TNK (43.5%). Bleeding rates were higher in TNK + PCI (31.3 vs. 23.4%, P < 0.001). In the PCI only group, no single stroke occurred, whereas in the TNK + PCI, 0.97% had intracranial haemorrhage and 0.60% had an ischaemic stroke. The mortality rate of 6% in the TNK + PCI group closely matches with the results of previous fibrinolysis trials, but the mortality and rate of stroke in the PCI group seem low in comparison with the 5% mortality and >1% stroke found in a large meta-analysis of primary PCI vs. fibrinolysis trials. In conclusion, these preliminary data suggest that facilitated PCI with full-dose fibrinolytic pre-treatment cannot be recommended.

The last study, ELISA-2, was presented by Mr Saman Rasoul from Zwolle, The Netherlands. In an open-label, single-centre, randomized trial, dual anti-platelet therapy (clopidogrel in a loading dose of 600 mg and aspirin) was compared with triple anti-platelet therapy (clopidogrel in loading dose of 300 mg, aspirin and tirofiban 10 μg/kg bolus, and 0.15 μg/kg/min maintenance continued >24 h) in patients with non ST-elevation acute coronary syndromes (chest pain <24 h, ST-segment depression, or elevated troponins/CK-MB) and planned for PCI. Enzymatic infarct size was calculated by cumulative LDH release. In total, 166 patients were randomized to dual and 162 patients to triple anti-platelet therapy. Baseline characteristics were mean age 65 years, prior myocardial infarction in 20%, elevated troponins were found in 80%, and ST-segment depression in 60% of patients. Mean time from admission to angiography in the dual group was 26 ± 24 vs. 30 ± 42 h in the triple group and PCI was performed in 62 vs. 56%, respectively. The primary endpoint infarct size was not significantly different between both groups (cumulative LDH 392 vs. 331 U/L and peak CK 470 vs. 423 U/L, respectively). The secondary endpoint TIMI flow grade 3 of the culprit artery was seen more often in triple anti-platelet therapy (67 vs. 47%, P = 0.002). In high-risk patients with ST-segment depression or elevated cardiac markers at admission, triple anti-platelet therapy does not seem to reduce enzymatic infarct size, but was associated with a significantly higher rate of TIMI flow grade 3 of the culprit artery.

Conflict of interest: none declared.

References

