Hotline sessions of the 30th European Congress of Cardiology

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Of the 16 presentations at the three Hotline sessions of the 30th European Congress of Cardiology, held in Munich, Germany, 30 August–3 September 2008, nine are summarized below, since the others have already been published (BEAUTIFUL, Lancet 2008; 372; 807–821; TRANSCEND, Lancet 2008: 372; 1174–1183; GISSI-HF (n-3-PUFA), Lancet 2008 (Epub ahead of print); GISSI-HF (rosuvastatin), Lancet 2008 (Epub ahead of print); LEADERS, Lancet 2008; 372; 1163–1173; IBIS 2, Circulation 2008: 118; 1172–1182; SEAS, N Engl J Med 2008 (Epub ahead of print).

The authors of this summary collected the information given during the presentations of the studies, as well as from press releases prepared by most speakers. This report shows only preliminary results.

During the first Hotline Session, five studies on the medical treatment of heart failure (HF) were presented. Since three of these trials have already been published, only two of them are summarized below.

The first session started with the results of the TIME-HF study (Trial of Intensified BNP-guided vs. Standard symptom-guided Medical therapy in elderly patients with Congestive Heart Failure) presented by Dr Hans Peter Brunner—la Rocca from Basel, Switzerland. Aim of this study was to compare intensified brain natriuretic peptide (BNP)-guided therapy with standard symptom-guided therapy in patients with HF, and to assess if there is a difference in response in the age groups 75 years and younger. Previous smaller studies showed that BNP-guided therapy may improve outcome in chronic HF.

Patients with symptomatic HF, left ventricular ejection fraction (LVEF) $\leq 45\%$, HF hospitalization within the last year, and an NT-BNP level $> 2 \times$ upper limit of normal were included.

Patients were randomized to standard or intensified BNP-guided therapy. The two groups were stratified by age $\geq 75$ years or 65–74 years with follow-up visits at 12 and 18 months. The standard group ($n = 948$) was blinded to BNP levels. The intensified group ($n = 951$) was treated as BNP-guided. All patients were treated according to the current guidelines on treatment of HF. Baseline characteristics showed a mean age of 76 ± 8 years, the younger patients had a significantly lower LVEF (28 ± 7% vs. 31 ± 8%, $P < 0.001$), lower BNP levels (298 vs. 5053 pg/mL, $P < 0.001$) and less kidney disease (45% vs. 63%, $P < 0.001$) when compared with patients $\geq 75$ years.

Intensified BNP-guided therapy did not improve the primary endpoint of survival free of any hospitalization ($P = 0.46$). However, the disease-specific endpoint of survival free of HF hospitalization did improve significantly in the BNP-guided group ($P = 0.008$). Between age groups there was a significant difference in response to therapy in which patients in the age group of 60–74 had reduced mortality and improved survival free of HF hospitalization and patients aged $> 75$ years showed no benefit on survival and showed less improvement in quality of life.

Evidence from trials in younger patients may not simply be applied to older patients according to these results. Specific HF trials in elderly patients are needed.

In the second Hotline session five studies on acute coronary syndromes and interventional cardiology were presented, four of which will be reviewed.

First, the DECREASE III (Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo III) trial was presented by Prof Don Poldermans, Rotterdam, The Netherlands. Decrease III is a single centre, randomized double-blind placebo controlled trial with fluvastatin XL to study cardiac outcomes after major vascular surgery.

Patients undergoing non-cardiac vascular surgery (e.g. abdominal aortic aneurysm, abdominal aortic stenosis, lower limb arterial stenosis, carotid artery stenosis) were included and treated with...
placebo (n = 250) or fluvastatin XL 80 mg (n = 247) in addition to standard beta-blockers. Excluded were patients on current statin therapy, those with contraindications for statins, surgery interfering with continuous ECG registration, emergency surgery, unstable coronary artery disease (CAD), and left main disease. Treatment was started on the day of randomization (median 37 days prior to surgery) and continued until 30 days after surgery. Baseline characteristics were the same for both groups. Perioperative medication and baseline cholesterol levels do not differ in both groups.

The primary endpoint was myocardial ischaemia and occurred in 10.9% in the statin group compared with 18.9% in the placebo group (P = 0.016). Data on the secondary endpoint of cardiac death or MI showed a 52% relative reduction of incidence in the treated group (P = 0.039). No side effects of perioperative fluvastatin were found.

The drug effects were probably due to inflammation reduction rather than lowering cholesterol (hs-CRP reduced by 21 vs. 3%, P < 0.001 and interleukin-6 reduced by 33 vs. 4%, P < 0.001).

Thus, use of perioperative fluvastatin XL is associated with a reduced incidence of myocardial ischaemia and the composite of myocardial infarction and cardiac death and, therefore, fluvastatin XL might be recommended in patients undergoing elective vascular surgery.

The SYNTAX (the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) consisted of two parts presented separately. The first part, the 1-year results from the registry cohort, was presented by Prof Friedrich Mohr from Leipzig, Germany. Syntax is a multicentre randomized all-comers study design with a total inclusion of 3075 patients. Aim of the study is to reassess the values of CABG and PCI in using drug-eluting stents in patients with significant coronary artery disease. Patients with previous intervention, acute MI, or concomitant cardiac surgery were excluded. A local heart team assessed each patient with regard to perioperative risk and coronary lesion complexity. If a patient was judged to be amenable for either CABG or PCI, the patient was enrolled to the randomized arm after stratification to left main disease and diabetes mellitus. If amenable for only one treatment modality, the patient was enrolled to the registry cohort.

Prof Patrick Serruys from Rotterdam presented the results of the randomized trial, in which Taxus was tested for non-inferiority to CABG on the primary endpoint of 12 months major cardiovascular and cerebrovascular event rate (MACCE: all-cause death, stroke, myocardial infarction, repeat revascularization) in 1800 patients (CABG 897, Taxus group 903). There was no statistically significant difference in patient characteristics in CABG when compared with Taxus (mean age 65 years, male 77%, three-vessel disease 66% and left main disease 34%). In Taxus patients, a mean of 3.6 ± 1.6 lesions per patient were treated with 4.6 ± 2.3 stents with an average stent length of 86.1 mm ± 47.9 mm.

About 15% of the CABG procedures was performed off-pump, whereas CABG patients received 2.8 ± 0.7 grafts per patient with 3.2 ± 0.9 distal anastomoses. A total number 18.9% of patients received complete arterial revascularization and 2.6% of patients with complete venous revascularization.

Results showed all-cause death at 12 months of 3.5% in CABG compared with 4.3% in Taxus (P = 0.37). Stroke rate at 12 months differed significantly with 2.2% in CABG vs. 0.6% in Taxus (P = 0.003). MI occurred in 3.2% in CABG vs. 4.8% in Taxus (P = ns). The combined endpoint all-cause death, stroke, MI was 7.7% in CABG and 7.6% in Taxus (P = 0.98). Symptomatic stent occlusion and stent thrombosis at 12 months was 3.4% for CABG and 3.3% for Taxus. There was a statistical significance in repeated revascularizations with 5.9% in CABG and 13.7% in Taxus (P < 0.0001) and a significant difference in MACCE at 12 months [12.1% for CABG and 17.8% in Taxus (P = 0.0005)]. The endpoint of non-inferiority of PCI to CABG was not met. Subgroup analysis revealed a significant advantage for CABG in diabetic patients in 12-month MACCE (DM 26.0% vs. non-DM 14.2%, P = 0.0025) and also in diabetic patients this advantage is merely caused by significantly more repeat revascularizations in Taxus patients (DM 15.1% vs. non-DM 8.3%) when compared with CABG. Interestingly, in non-diabetic patients there was no significant difference in 12-month MACCE between Taxus and CABG (15.1 vs. 11.8%, P = 0.08).

In the registry cohort, two arms of PCI (n = 198, 12 months follow-up completed in 191 patients) and CABG (n = 1077, 12 months follow-up completed in 633 patients) were studied. The PCI arm consists of patients ineligible for CABG due to co-morbidi.ity, no good graft material, poor quality of distal vessel or refusal of CABG. The CABG registry arm consists of patients ineligible for PCI due to complex anatomy, untreated chronic total occlusion, patients not able to take antiplatelet medication, or patients that refused PCI. Treatment schedule and follow-up were identical with the randomized arm.

In comparison with the Taxus randomized control group, the PCI registry patients were older (71.2 ± 10 vs. 65.2 ± 9.7 years), had more diabetes (35.4 vs. 28.2%), more prior MI (40.4 vs. 31.9%), more unstable angina (38.0% vs. 28.9), and a higher Euroscore (5.8 ± 3.1 vs. 3.8 ± 2.6). Also more bifurcation and trifurcation lesions were treated (64.4 vs. 24.8%). In the Taxus randomized trial, more lesions were treated (3.6 ± 1.6 vs. 2.5 ± 1.3), more stents implanted (4.6 ± 2.3 vs. 3.1 ± 1.8), and greater total length of stents implanted (86.1 ± 47.9 vs. 58.5 ± 41.2) than in the registry.

In the CABG registry, more off-pump surgery (18.6 vs. 15.0%), less double LIMA/RIMA (16.1 vs. 27.6%), less complete arterial revascularization (11.2 vs. 18.9%), and more venous grafts only (3.3 vs. 2.6%) were performed than in the randomized trial.

At 12 months, the PCI registry showed 7.3% all-death, 0% stroke, 4.2% MI, combined endpoint death stroke and MI 10.5%, revascularization 12.0%, and total MACCE 20.4%. At 12 months, the CABG registry had 2.5% all-death, 2.2% stroke, 2.5% MI, combined endpoint death CVA and MI 6.6%, 3% revascularization, and total MACCE 8.8%.

In the Syntax-randomized trial, Taxus failed to be non-inferior to CABG in patients with three-vessel disease (3VD) or LM at the primary endpoint of 12-month MACCE and this was, in great part, caused by significantly more repeat revascularizations in the TAXUS group when compared with the CABG group. So, despite of improvement in PCI techniques in patients with LM or 3VD, CABG will continue to be the treatment strategy of choice. In patients unsuitable for PCI (more complex lesions), surgical results are excellent and in patients unsuitable for CABG (more co-morbidi.ity and/or higher EURO score), PCI is a viable
option. In the near future cardiologists are still needed to help patients decide.

Dr Akhil Kapul from London, UK presented the randomized CARDia trial, which challenges the hypothesis that in diabetic patients with multivessel disease, or complex single-vessel disease amenable to both CABG or PCI, optimal PCI is not inferior to up-to-date CABG. A total number of 510 patients were randomized to CABG (n = 254) and PCI (n = 256). One-year follow-up was completed in 97%. The study was terminated prematurely because of slow recruitment (2002–2007) and hereby slightly underpowered. Baseline characteristics were well-balanced between both groups (77% of patients were electively treated). The median number of days from randomization to the index procedure was 64 [interquartile range (IQR) 27–110] in the CABG group and 37 (IQR 13–59) in the PCI group. The median duration of hospitalization was, respectively, 9 (IQR 7–16) vs. 1 (IQR 1–4) days. Of the percutaneously treated patients, 65% had 3VD, the average number of stents was 3.5 (DES 71%) with an average stent length of 71 mm. Fifty-eight percent of patients in the CABG group had 3VD. They received an average of 2.8 grafts of which 89% were LIMA’s and 31% of the procedures were performed off-pump. At 1 year, there was no significant difference in the incidence of the primary endpoint: composite of death (3%), non-fatal myocardial infarction (7%), and non-fatal stroke (1.5%). In consequence of strongly significant more repeat revascularizations in the PCI group [9.9% vs. CABG 2.0%, odds ratio (OR) 5.31, 95% CI 2.0–14.1, P = 0.001], there was a significant difference between groups in reaching the composite endpoint of death, non-fatal myocardial infarction, non-fatal stroke and revascularization at 1 year (PCI 17.5% vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001). In consequence of strongly significant more repeat revascularizations in the PCI group [9.9% vs. CABG 2.0%, odds ratio (OR) 5.31, 95% CI 2.0–14.1, P = 0.001], there was a significant difference between groups in reaching the composite endpoint of death, non-fatal myocardial infarction, non-fatal stroke and revascularization at 1 year (PCI 17.5% vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001). In consequence of strongly significant more repeat revascularizations in the PCI group (17.5%) vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001). In consequence of strongly significant more repeat revascularizations in the PCI group (17.5%) vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001). In consequence of strongly significant more repeat revascularizations in the PCI group (17.5%) vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001). In consequence of strongly significant more repeat revascularizations in the PCI group (17.5%) vs. CABG 11.0%, OR 1.72, 95% CI 1.5–1.94, P = 0.001).

The third Hotline session consisted of six studies handling CAD, out of which four are summarized below.

Michal Tendera, Katowice, Poland presented the results of the REGENT study (Myocardial Regeneration by Intracoronary Infusion of Selected Population of stem cells in myocardial infarction). Primary objective of this multicentre randomized study was to describe the effect of intracoronary infusion of bone marrow-derived selected CD34+ and CXCR4+ cells on LV function in patients with recent STEMI and reduced LVEF. These cells are considered useful for myocardial repair because acute MI induces their mobilization. Circulating CD34+ and CXCR4+ cells are enriched in early cardiac and endothelial markers and can migrate to the infarct area.

In total, 200 patients with acute anterior MI and LVEF ≤40% treated with primary PCI, aged 18–75 years were included of which 117 patients were randomized to three parallel groups: one group with selected CD34+ CXCR4+ bone marrow count infused (n = 51), one with unselected mononuclear bone marrow count (n = 46), and a control group (n = 20). Time from PCI to cell infusion was median 7 (3–12) days and the number of infused CD34+ CXCR4+ cells was median 1.90 × 10⁶ in mononuclear median 1.78 × 10⁸.

Exclusion criteria were previous MI, significant coronary stenosis in non-infarct-related area, pregnancy, malignancy, or contraindications to MRI. Baseline characteristics do not differ between the three groups.

The primary endpoint consisted of change in LVEF and volumes assessed by cardiac MRI and ventriculography. The major secondary endpoint was safety (death, repeat MI, stroke, target vessel revascularization). The LVEF improved within 6 months when compared with baseline by 3% in the treated groups [unselected stem cells LVEF, 37–40%; P = 0.01; selected CD34+ CXCR4+ cells, 35–38%; P = 0.04, control (no cells) 39–39%]. There was no statistical significance between the groups, although there was a trend in favour of cell therapy (P = 0.19). In both treated groups improved LVEF was more pronounced in patients with a baseline EF below median.

Treatment with both selected and unselected bone marrow cells was feasible and safe. Improvement in LVEF in patients with severely depressed LV systolic function treated with both selected and unselected bone marrow cells warrant further studies on their potential clinical application.

Dr John Alexander from Durham, USA, presented the APPRAISE trial: a double-blind, randomized, placebo-controlled, dose-guiding trial assessing the safety of the oral direct and selective factor Xa inhibitor, apixaban in combination with dual-antiplatelet therapy after acute coronary syndromes (64% of patients had undergone PCI). The effect of four different doses of apixaban during 26 weeks on bleeding was evaluated in clinically stable patients with a recent ACS (<7 days) and at least one additive risk factor for recurrent ischaemic events in order to find the optimal dose of apixaban for future investigations. In two different phases of study, a total number of 1715 patients were randomized. In the first phase, 547 patients were randomized to placebo (n = 184), apixaban 2.5 mg b.i.d. (n = 179), and apixaban 10 mg q.i.d. (n = 184). This phase was followed by an interim safety analysis on behalf of the DSMB. In the second phase, 1168 patients were randomized to placebo (n = 427), apixaban 2.5 mg b.i.d. (n = 138), apixaban 10 mg q.i.d. (n = 134), apixaban 10 mg b.i.d. (n = 248), and apixaban 20 mg q.i.d. (n = 221). The therapy in the latter two groups was stopped prematurely because of bleeding excess. Of the other three groups baseline characteristics, index events, and concomitant medication use were equally distributed during both phases of the trial. There was a significant disadvantage on the primary safety outcomes of major bleedings (International Society of Thrombosis and Haemostasis) and clinical relevant non-major bleedings for apixaban 2.5 mg b.i.d. (HR 1.79, 95% CI 0.91–3.49, P = 0.09) and apixaban 10 mg q.i.d. (HR 2.45, 95% CI 1.31–4.91, P = 0.005) when compared with placebo. Both major bleedings and clinically relevant non-major bleedings occurred in patients receiving apixaban 10 mg q.i.d. (1.9 and 7.9%) and apixaban 2.5 mg b.i.d. (1.6 and 5.7%) when compared with placebo (0.3 and 3.4%). There was a trend towards less ischaemic events in patients receiving apixaban 10 mg q.i.d. (6.0%) and apixaban 2.5 mg b.i.d. (7.6%) when compared with placebo (8.7%), but no significant advantage of apixaban on the secondary efficacy outcome (cardiovascular death, MI, severe recurrent ischaemia, and ischaemic stroke) was obtained. APPRAISE puzzles the pattern that adding a new potent anticoagulant drug in the
treatment of patients with ACS does often show a reduction in recurrent ischaemic events, but at the cost of a significant increase in bleeding. In the search for an anticoagulant drug with a favourable safety profile apixaban in a dose between 5 and 10 mg daily seems promising.

Dr Marco Valgimigli from Ferrara, Italy presented the results of the Tailoring Treatment with Tirofiban in patients showing Resistance to aspirin and/or Resistance to clopidogrel (3T/2R) study.

This double-blind randomized trial compared tirofiban (25 μg/kg in 3 min followed by infusion of 0.15 μg/kg/min for 14–24 h) to placebo in combination with aspirin, clopidogrel and UFH/bivalirudin in patients with a poor aspirin and/or clopidogrel response: patients were admitted with silent ischaemia, stable angina, or low-risk non ST-elevation acute coronary syndrome (NSTEACS) (negative cardiac markers) and underwent elective PCI. Poor aspirin response was defined as an aspirin reaction unit (ARU) >550 after an oral dose of aspirin 80 mg for at least five days or an intravenous aspirin dose 15 min before testing. Poor clopidogrel response was defined as <40% platelet inhibition after 600 mg, clopidogrel >2 h before testing, 300 mg clopidogrel, >6 h before testing, or 75 mg clopidogrel >7 days before testing using VerifyNow™ Aspirin and P2Y12 (Accumetrics, USA). A total number of 1277 patients were assessed for eligibility. Screening was performed following two different strategies.

The first strategy consisted of aspirin response (n = 916). In total, 162 patients showed a poor aspirin response and 116 of them were randomized to placebo (n = 52) or tirofiban (n = 64).

The second strategy consisted of screening for clopidogrel response (n = 361) and 121 poor clopidogrel responders were identified. Patients screened by the first strategy were also tested on clopidogrel response (n = 283) and 53 turned out to be poor clopidogrel responders. So, in total a group of 174 poor clopidogrel responders was defined, out of which eventually 147 were randomized to placebo (n = 79) or tirofiban (n = 68). Baseline characteristics were well-balanced between groups and all randomized patients completed a 30-day follow-up.

There was a significant reduction in the primary endpoint of troponin I/T >3 times ULN in >1 blood sample within 48 h after PCI by tirofiban vs. placebo (20.4 vs. 35.1%, RRR 42%, 95% CI 61–12, P = 0.009). Tirofiban also significantly reduced the secondary endpoint of CK-MB mass elevation >1, 3, or 5 times ULN (RRR 62%, P < 0.001, RRR 50%, P = 0.09, and RRR 70%, P = 0.05) and MACE when compared with placebo (21 vs. 37%, P = 0.009). Adverse effects, i.e. minor bleedings and thrombocytopenia, rarely occurred (about 1%) and were equal in both groups (P = 0.99).

The 3T/2R trial suggests a significant advantage of intensified antiplatelet therapy with tirofiban in aspirin/clopidogrel-resistant patients with stable CAD or NSTEACS undergoing PCI. But without a direct comparison to patients with a normal aspirin/clopidogrel response it is hard to identify whether this advantage is merely based on the already described benefits of tirofiban in patients with CAD than really a new treatment strategy for this subgroup. Future studies should be designed to elucidate this question.

Dr Dan Atar from Oslo, Norway presented the FIRE study, a multicenter, double-blind, randomized, placebo-controlled, exploratory ‘proof of concept’ trial to investigate the cardioprotective efficacy of FX06 (the fibrin-derived peptide B1515–45) as an adjunct to primary PCI in patients with STEMI and assess its safety and tolerability. FX06 is a peptide that potently inhibits binding of fibrin E1 fragments to vascular endothelial cadherin, thereby preserving the endothelial barrier function and preventing capillary leak. This inhibits transmigration of inflammatory cells through the endothelium and exhibits an anti-inflammatory effect. Out of 234 STEMI patients, 114 patients received FX06 400 mg and 120 patients received placebo during primary PCI at the moment of passing the guide wire through the occluded vessel and exactly 10 min later. All patients completed 4 months follow-up. Study groups did not differ in baseline characteristics, concomitant medication use, infarct localization (anterior 46%), pre-procedural TIMI flow (TIMI 0, 85%; TIMI 1, 15%), collaterals (20%), and symptom to balloon time (<3 h—48%). The primary endpoint of infarct size was assessed by MRI (microvascular obstruction zone, necrotic core zone, total late-gadolinium enhancement zone) 5 days post-infarction. The secondary endpoint constituted the final infarct size at 4 months, LV-function (5 days and 4 months), troponin I release and combined MACE (cardiovascular death, myocardial infarction, or symptom-driven revascularization, new onset symptomatic HF, NYHA/Killip Class >2, hospitalization for any cardiac cause). Regarding the primary endpoint there was a significant reduction of the necrotic core zone (FX06, 1.77 g vs. placebo, 4.20 g; P = 0.019), whereas microvascular obstruction zone and the total late enhancement zone did not differ 5 days post-PCI. The relevance of the only positive finding of reduction in necrotic zone is doubtful, because the difference was diminished at 4 months follow-up. No statistically significant differences were achieved at the composite secondary endpoint.

In conclusion, FX06 is a safe anti-inflammatory drug, that failed to significantly reduce reperfusion injury parameters in STEMI patients undergoing PCI, although a trend towards a cardioprotective effect was suggested.

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