ESC Congress 2008 in Munich: Hot news from Hot lines!

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At the ESC Congress in Munich from 30 August to 2 September 2008, three important Hot Line sessions were presented, involving many important clinical trials. In this Editorial, a selection has been made of one of the trials from each Hot Line session.

BEAUTIFUL (Hot Line 1, Sunday August 31)

The BEAUTIFUL (Morbidity-Mortality Evaluation of the If inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction) trial was designed to evaluate whether pure heart rate reduction with ivabradine improved cardiovascular outcome in coronary artery disease (CAD) patients with left ventricular (LV) systolic dysfunction. BEAUTIFUL was a randomised, double-blind, placebo-controlled, parallel-group trial which recruited 10,917 CAD patients with LV ejection fraction <40% (87% on β -blockade). Patients received ivabradine 5 mg, with the intention of up-titrating to 7.5 mg twice daily ($n=5479$) or placebo ($n=5438$) on top of the medication recommended in the guidelines.

Ivabradine produced a sustained reduction in heart rate over long-term follow-up. Ivabradine was well-tolerated, with a similar rate of adverse events compared with control. The primary composite endpoint (cardiovascular death, hospitalisation for acute myocardial infarction, or hospitalisation for new onset or worsening heart failure) was not reached, which was true for the entire group of patients with heart rate >60 beats/min and also for the pre-specified subgroup with a heart rate >70 beats/min. Among patients in the pre-specified subgroup with a heart rate >70 beats/min there was no difference in secondary endpoints of 1) mortality (all-cause death, cardiovascular death, CAD and heart failure death), and

2) heart failure endpoints (hospitalisation for heart failure, cardiovascular death or hospitalisation for heart failure). However, it was shown that CAD patients with LV dysfunction and a heart rate >70 beats/min had a significantly higher risk of major cardiovascular events. In patients with a heart rate >70 beats/min, ivabradine further reduced the risk of coronary events such as fatal and non-fatal myocardial infarction and coronary revascularisation by one third, even when these patients were already receiving optimal therapy. Further studies are indicated to determine the potential benefit by which CAD patients with a resting heart rate >70 beats/min improve outcomes if treated by ivabradine therapy in addition to standard guidelines-recommended treatments.

To summarise, although the BEAUTIFUL trial showed that among patients with stable CAD and LV dysfunction, the use of ivabradine did not improve cardiac outcome compared with placebo, ivabradine did reduce the incidence of hospitalisation for myocardial infarction and subsequent coronary revascularisation procedures among patients with a baseline heart frequency of ≥ 70 beats/min. Consequently, the results of the BEAUTIFUL study emphasise the importance of routinely measuring heart rate in CAD patients and to consider treating CAD patients when the heart rate is above 70 beats/min.

SYNTAX (Hot Line II, Monday 1 September)

One of the most debated studies during the Hot Line II session was the SYNTAX study (The SYNERgy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery). The goal of SYNTAX was to compare the relative efficacy of CABG versus drug-eluting-stent PCI in patients with severe three-vessel disease or left main disease who were deemed eligible for either CABG or PCI. All patients in the PCI group received TAXUS (paclitaxel-eluting) stents, whereas all patients in the CABG group underwent on- or off-pump bypass. A total of 1800 patients were randomised, of whom 897 patients to CABG and 903 patients to PCI.

The incidence of the primary endpoint of major adverse cardiac and cerebrovascular events at 12 months

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was lower in the CABG group compared with PCI (12.1 vs. 17.8%, $p=0.0015$). As a result, SYNTAX did not meet the pre-specified non-inferiority threshold for PCI. This was driven predominantly by a significant reduction in the incidence of repeat revascularisation in the CABG group compared with PCI (5.9 vs. 13.7%, $p=0.0001$). Among patients who had PCI, nearly 14% needed another procedure after a year, compared with about 6% of CABG patients. There was no difference in the incidence of death ($p>0.05$) or myocardial infarction between the two groups ($p=0.11$). The incidence of cerebrovascular accidents was significantly higher in the CABG group (2.2 vs. 0.6%, $p=0.003$), whereas the incidence of symptomatic graft occlusion and stent thrombosis was similar between the two groups (3.4 vs. 3.3%, $p=0.89$).

The SYNTAX trial therefore demonstrated that in patients with left main disease and/or severe three-vessel disease, CABG might be superior to PCI with TAXUS drug-eluting stents. This was especially true for reducing 12-month major adverse clinical event rates mainly due to the need for repeat revascularisation in the PCI group. The largest benefit from CABG appeared to be in patients with diabetes mellitus. The strengths of the SYNTAX study were its inclusive 'all comers' design and the high quality of care the patients received after randomisation to either PCI or CABG for left main or three-vessel CAD management.

It has however been commented that the SYNTAX trial might have been underpowered, therefore not providing a definitive result for the primary outcome, which was non-inferiority of PCI. SYNTAX leaves unresolved the appropriateness of use of PCI in patients with left main/three-vessel disease who are willing to accept the risk of a second (or more) PCI to avoid the more invasive CABG. Longer follow-up is needed to define the true difference between these two revascularisation strategies.

SEAS (Hot Line III, Tuesday 2 September)

In Hot Line III the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) trial was presented. SEAS investigated the effects of intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) in patients with aortic stenosis. The SEAS study was the first large-scale randomised trial to assess the effects of lowering LDL cholesterol in patients with aortic stenosis. The study was designed by academic researchers at 173 centres in Northern Europe. SEAS included 1873 patients with mild to moderate aortic stenosis without symptoms who were not considered to have a clear indication for treatment with cholesterol-lowering drugs. Patients were randomly assigned to receive either a combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) or matching placebo.

Compared with placebo, the combination of simvastatin and ezetimibe reduced LDL cholesterol by an average of 61% (2 mmol/l, 76 mg/dl), and this effect was sustained throughout the study. A total of 688 patients had one or more primary endpoint events (composite of cardiovascular death, aortic valve replacement surgery, nonfatal myocardial infarction, congestive heart failure from aortic stenosis progression, CABG, PCI, hospitalised unstable angina, and non-haemorrhagic stroke). There was no significant difference between the treatment groups for the combined primary endpoint (333 patients with an event on LDL-lowering treatment versus 355 on placebo). There was also no significant difference for the secondary endpoint of aortic valve disease events alone. The combination of simvastatin and ezetimibe did, however, produce a statistically significant 22% ($p=0.02$) reduction in the secondary endpoint of atherosclerotic events alone: 148 (15.7%) in the simvastatin plus ezetimibe group versus 187 (20.1%) in the placebo group. In the subsidiary safety analyses, a total of 175 patients were recorded with a serious adverse event attributed to cancer. More of these events were observed among patients assigned the combination of simvastatin and ezetimibe than among patients assigned placebo (105 [11.1%] versus 70 [7.5%]; $p=0.01$). Cancer deaths were also more frequent in the ezetimibe/simvastatin group (4.1 vs. 2.5%, $p=0.05$). These differences did not seem to be related to any particular type of cancer and did not become significantly larger with more prolonged treatment. The observed differences in cancer in the SEAS study are, however, based on small numbers and could have occurred as a result of chance.

In conclusion, the results of the SEAS trial demonstrate that ezetimibe/simvastatin 10/40 mg daily was not associated with a reduction in the progression of aortic stenosis in asymptomatic patients with mild to moderate aortic stenosis. There was, however, a significant reduction in atherosclerotic events in patients who received ezetimibe/simvastatin compared with placebo, driven by a reduction in the need for CABG. Although the higher incidence of cancer and cancer-related deaths in the ezetimibe/simvastatin group may represent a safety concern, combined analysis of other major trials with simvastatin/ezetimibe (IMPROVE-IT, SHARP) does not support this association.

To summarise, the three Hot Line sessions were again a great success at our ESC Congress 2008. Although many Hot Line trials were so-called 'negative', this just means – no more and no less – that different treatment options were at least similar. In some cases this might sound very positive to both physicians and patients. This is our true primary endpoint. ■