## 3269 A randomized comparison of low-molecular-weight heparin (enoxaparin) and unfractionated heparin adjunctive to t-PA thrombolysis and aspirin (HART-II)

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Low-molecular-weight heparin (LMWH) has been used with equivalent or superior clinical results compared with unfractionated heparin (UFH) in patients with UA and Non-Q-wave MI. However, little data exists regarding the use of such agents as antithrombotic adjuncts during acute myocardial infarction (AMI) managed with thrombolytic agents. We performed a multicenter, multinational, open-label randomized comparison in AMI patients treated within 12 hours of symptom onset, all of whom receive a maximum of 100 mg of human recombinant t-PA (90-min regimen) as well as aspirin. Enoxaparin was given as an initial 30-mg bolus intravenously followed by a subcutaneous administration of 1 mg/kg twice daily for at least 3 days. The UFH group controls received a weight-adjusted initial IV bolus followed by a weight-adjusted infusion (per nomogram) with a target aPTT of 2–2.5 times control for a similar period of antithrombin therapy. The principal endpoint is infarct-related artery (IRA) patency 90 min after starting therapy (grade 2 or 3 according to the Thrombolysis In Myocardial Infarction scale). The frequency of hemorrhage and intracranial events (IC events adjudicated by an independent neurologist) are safety endpoints. Reocclusion rates are also assessed at a 1 week follow-up angiogram. Angiographic data are analyzed by a core laboratory blinded to treatment assignment and clinical events. Enrollment of 400 patients was completed in February 2000. Data prepared for the January 2000 DSMB meeting (study groups combined, unblinding deferred until all endpoint data received) was as follows:

| # of Pts in database | n = 337 |
|---|---|
| # of Pts with angio data in database | n = 299 |
| TIMI 2-3 | 234 (78.3%) |
| 1 wk Reocclusion | 16/191 (8.4%) |
| Intracranial Hemorrhage | 4 (1.0%) |
| Other Stroke | 2 (0.5%) |
| Major Bleed (excluding ICH) | 42 (10.6%) |
| 30 day Mortality | 16/328 (4.9%) |

Preliminary results will have been presented at ACC 2000 and final results will be available for ESC 2000.

## LIPIDS, LIPOPROTEINS AND APOLIPOPROTEINS

## 3270 Increased intimal thickening of human CETP/ApoB100 double transjenic mice

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Human CETP/ApoB100 double transgenic mice express both cholesteryl ester transfer protein and apolipoprotein B100 resulting in an animal model with a human-like serum HDL/LDL distribution. We investigated the effect of hypercholesterolemia and HDL/LDL-cholesterol imbalance on intimal thickening after arterial injury in CETP/ApoB100 double transgenic mice. The arterial injury was induced by placing of a cuff (plastic tube, inner diameter 0.5 mm, 2 mm long) around the right carotid artery. We induced injury in wild-type (25 week old male, n = 7) and in CETP/ApoB100 double transgenic mice (25 week old male, n = 7). All mice had high cholesterol chow. 21 days after cuff placement, the areas of intima were measured in 10 cross sections from one edge to the other edge of the cuffed portion, and in a corresponding 2 mm-long segment of the contralateral artery. Plasma cholesterol was also measured. In the contralateral artery without cuff there was no intima in either CETP/ApoB100 double transgenic mice and wild-type. In the cuff sheathed carotid artery, neointima growth was greater in CETP/ApoB100 double transgenic mice compared with wild-type ($29.3 \times 10^{-3}$ mm$^2$ vs $13.4 \times 10^{-3}$ mm$^2$; $p < 0.05$). There is not significant difference of total-cholesterol between CETP/ApoB100 double transgenic mice and wild-type (315 ± 63 mg/dl vs 283 ± 58 mg/dl). However, in CETP/ApoB100 double transgenic mice, the LDL-cholesterol is increased 1.5 fold (187 ± 63 mg/dl vs 128 ± 45 mg/dl: $p < 0.01$) and the HDL-cholesterol is reduced approximately 20 percent as compared to wild-type (120 ± 22 mg/dl vs 147 ± 22 mg/dl: $p < 0.01$). There is not significant difference of VLDL-cholesterol between CETP/ApoB100 double transgenic mice and wild-type (11 ± 10 mg/dl vs 9 ± 8 mg/dl).

**Conclusion:** arterial injury in CETP/ApoB100 double transgenic mice with high LDL-cholesterol and low LDL-cholesterol induces abundant intimal thickening.

## 3271 Implitapide (BAY 13-9952) inhibits secretion of apoB-associated lipoproteins by inhibition of the microsomal triglyceride transfer protein (MTP)

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The object of the present work was to identify inhibitors of lipoprotein secretion that are suitable as cholesterol and triglyceride lowering drugs. In order to find such inhibitors we used the human hepatoma cell line HepG2, which shows differentiation-associated functions of parenchymal liver cells such as secretion of apoB-containing VLDL-like lipoproteins and of alpha-2-macroglobulin. Implitapide [2-(S)-Cyclopentyl-2- [4[(2,4-dimethyl-carbolin-9-yl) methyl]phenyl]acetic acid-N- [2-hydroxy-1-(R)-1-phenylethyl]amide] was found to block the secretion of apoB-associated particles from HepG2 cells with an IC50 value of 1.1 nM. Cell viability and general inhibition of secretory processes are not affected by Implitapide as indicated by the unchanged levels of alpha-2-macroglobulin secretion. As MTP is required for the assembly and secretion of apoB-containing lipoproteins in hepatocytes and small intestinal enterocytes it was investigated whether Implitapide inhibits the MTP-catalysed transport of lipids between synthetic small unilamellar vesicles. In this in vitro system the compound inhibited triglyceride transport with partially purified MTP from porcine liver with an IC50 = 27 nM and with recombinant human MTP complexed with protein disulphide isomerase with an IC50 = 10 nM. Implitapide is being developed as an enantiomerically pure diastereomer. The other 3 isomers are 10 to 300-fold less active in blocking both VLDL secretion by HepG2-cells and MTP-catalysed transport of triglycerides between membranes. This demonstrates that Implitapide is a highly active and diastereoselective inhibitor of MTP with putative use for the treatment of hypercholesterolemia and hypertriglyceridemia. The mechanism offers a new therapeutic principle for the treatment and long-term prevention of coronary artery disease (CAD).

## 3272 Apolipoprotein A-1, but not traditional lipids, predictive for recurrent cardiovascular events in patients with coronary artery disease and lipids treated to target levels

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**Background:** Elevated levels of total cholesterol (TC), and more specifically elevated low density lipoprotein cholesterol (LDL-C) are major risk factors for coronary heart disease CHD), which can effectively be treated with lipid lowering therapy. However, the predictive value of lipid and apolipoprotein levels during lipid lowering therapy on subsequent cardiovascular events has not sufficiently been investigated.

**Methods:** The impact of lipids, apolipoproteins and clinical variables on subsequent myocardial infarction and all cause mortality was studied in 848 patients (675 men and 173 women) with angiographically proven coronary artery disease (CAD) who received statin therapy. Therefore we performed a Cox regression analysis including smoking, diabetes and the first complete lipid profile [TC, LDL-C, triglycerides (TG), apolipoprotein A-1 (apo A-I) apolipoprotein B (apo B)] that demonstrated a decrease of at least 30% of baseline TC level during statin therapy. The event-rate was evaluated from the time of first reduction of at least 30% reduction of baseline TC levels during statin therapy.

**Results:** Patients were treated to target levels according to the National Cholesterol Education Program guidelines (LDL-C 2.55 ± 0.55 mmol/L and 2.58 ± 0.62 mmol/L for men and women, respectively). The only significant predictor in both men and women was apo A-I (P=0.026 and P=0.002, respectively), whereas HDL-C was only predictive in women (P=0.004). TC, LDL-C, TG, apo B, diabetes and smoking did not predict subsequent events.

**Conclusions:** In a population of CAD patients receiving statin therapy, apo A-I levels proved to be significantly associated with the occurrence of all-cause mortality and myocardial infarction for both men and women. HDL-C level was a significant risk factor exclusively for women. TC, LDL-C and TG values during treatment with statin therapy had no predictive value for cardiovascular events, which underscores the importance of HDL-C and Apo A-1 in predicting cardiovascular events.