systemic bioavailability after oral administration of P-06139. These results indicate that the ACAT inhibitor P-06139 not only has potent hypocholesterolemic activity, but could also be effective in the hyperlipemic conditions associated with diabetes.

261 **Withdrawn**

262 **Compliance of long-term lipid-lowering therapy in familial hypercholesterolemia, influence on life quality and progression of coronary heart disease**

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We studied clinical outcome and quality of life in high-risk patients with familial hypercholesterolemia (FH) after 5.5 years of intensive lipid-lowering therapy monitored as outpatients. 60 patients (28 men, 32 women) participated in 1987 in a 1-year study with lovastatin. Mean age was 43 years. 29 patients suffered from coronary heart disease(CHD). 57 of the 60 patients were examined during follow-up in 1993; 1 did not cooperate. In the CHD group 3 had myocardial infarction (MI), 2 fatal and 1 non-fatal. 9 of 14 angina patients had no change or spontaneously improved. 5 patients had worsening. 16 of 28 patients reported regression, 12 no change of xanthomas. All patients were adherent to medication, mainly lovastatin single therapy or combined with resins. 4 patients changed medication due to adverse events. Lipid values are given as mean (mmol/l) with 95% confidence intervals. TC decreased from 9.7 (9.1–10.3) to 6.4 (5.9–6.8)*, LDL-C from 7.2 (6.6–7.8) to 4.6 (4.2–5.0)*, TG from 1.41 (1.21–1.62) to 1.17 (0.98–1.35)*. HDL-C increased from 1.1 (1.1–1.2) to 1.2 (1.1–1.3)**. (*$P < 0.0001$, **$P < 0.05$). In a standard questionnaire the CHD group scored slightly higher than the non-CHD group regarding fear and depression. Both groups scored within normal range.

Conclusion: Intensive cholesterol-lowering therapy may retard the clinical course of FH. Long-term adherence to therapy is possible without loss of life quality.

263 **Influence of angiotensin II receptor antagonists in the ballooned rat carotid artery: differentiating between specific subtype 1 and 2 receptor antagonists**

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The vessel wall contains two subtypes of angiotensin II receptors (AT1 and AT2), of which AT1 is predominantly expressed. Expression of AT2 is increased in intimal thickening following balloon injury. Several studies have previously shown that antagonists to AT1 can effectively inhibit smooth muscle cell (SMC) proliferation and suppress neointimal formation following vascular injury in rats. The function of AT2 is still undefined, however, and this study investigated what effect AT2 antagonists might have on SMC proliferation.

Rats were given the selective receptor antagonists Losartan (AT1; 2× 10 mg/kg/day) p.o. or L159586 (AT2; 2× 10 mg/kg/day) s.c., or both, starting 1 day prior to balloon catheter injury of the carotid artery. The percentage of proliferating SMC in the media (mean ± SD; $n = 7$) 2 days after ballooning was for placebo 24 ± 6, AT1 antagonist 13 ± 4, AT2 antagonist 18 ± 5, and the combination of AT1 + AT2 antagonists 13 ± 3. Biochemically, the AT1 antagonist ($n = 12$) reduced DNA contact by 55% ($P < 0.05$) at 14 days compared to controls, the AT2 antagonist ($n = 7$) only 20% (ns) and the AT1 + AT2 antagonists ($n = 8$) 53%. The neointima/media area (determined histologically) was reduced 24% by the AT1 antagonist $n = 10$ ($P < 0.05$) whereas AT2 antagonist alone ($n = 11$) had no effect. Antagonists to AT1 or AT2 had no significant effect on endothelial migration over the denuded artery, measured 28 days after ballooning.

These results confirm that AT1 antagonists inhibit SMC proliferation and the subsequent neointimal formation following arterial injury. However, the AT2 antagonist had no effect on SMC proliferation or neointima formation, used either alone or in combination with an AT1 antagonist, which suggests that AT2 receptors play no significant role in vascular remodeling in the rat.

264 **Changes in the total content of essential elements in plasma and tissues of rabbits fed a high-cholesterol diet and treated with lovastatin**

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The effects of a high cholesterol diet and of the cholesterol-lowering drug lovastatin on the total content of Fe, Cu, Zn, Mn, Mg and Ca, in plasma, heart, liver, kidney and skeletal muscle were determined in 2-month old male rabbits divided into groups A, B, C and D ($n = 5$). During 4 months, cholesterol (60 mg/day) was administered to groups B and C. Groups C and D were treated with lovastatin (10 mg/day), and group A was used as control. Blood samples were taken weekly the first month, and later every 2 weeks. Then the animals were killed, and tissues were acid-digested and analyzed by atomic absorption spectrometry. Plasma TC was determined enzymatically. Cholesterol induced some changes in mineral distribution: by week 2, group B showed the highest ($P < 0.001$) TC (mg/ml) level (2.87 ± 0.07) and D the lowest (0.79 ± 0.1) in comparison with A (1.32 ± 0.09) and C (1.9 ± 0.06), and plasma Cu (μg/ml) was higher ($P < 0.001$) in lovastatin-treated groups C (1.47 ± 0.17) and D (1.79 ± 0.2) than in B (0.99 ± 0.17) or A (0.75 ± 0.17). Liver Cu (μg/g dry weight) was lower in group C (13.3 ± 1.1) in comparison with A (23.3 ± 4.5); however, heart Cu was lower ($P < 0.01$) in cholesterol-treated group B (17.0 ± 1.6) than in A (21.3 ± 1.7), C and D. Generally, lovastatin opposed the cholesterol effects on mineral content and prevented deleterious Cu changes on heart tissue.

265 **LS3115, a new acyl-CoA:cholesterol acyltransferase inhibitor potentially effective against atherosclerosis**

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LS3115 is a new, potent ACAT inhibitor developed by Lipha. It exhibited a strong inhibitory effect in vitro on microsomal activity of aorta, liver, and intestine of rats, hamsters, and rabbits, with IC_{50} in the range 10–800 nM. In vivo, LS3115 lowered diet-induced hypercholesterolemia in the same species, especially in rabbits where the ED_{25} has been found to be as low as 50 μg/kg when the animals were fed the drug in addition to 0.5% cholesterol for 2 weeks. Furthermore, when fed with a strongly atherogenic diet for 12 weeks (0.5% cholesterol plus 5% lard and 5% peanut oil), LS3115 fully protected the animals against development of atherosclerotic lesions when mixed with the food at a 0.033% level. The plasma level of the drug after a single 50 mg/kg oral dose depends on the species: it is rather low in both rats and rabbits but is significantly higher in dogs. LS3115 is a drug potentially effective against early atherosclerotic lesions in humans (fatty streaks) in addition to having a possible normalizing effect on some dyslipidemias. It is planned to undergo a phase 1 clinical trial.

266 **Marked differences in the response of serum lipoproteins to fenofibrate in women and men with primary hypercholesterolemia**

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