194 Bay 13-9952 (Implitapide), an inhibitor of the microsomal triglyceride transfer protein (MTP), inhibits atherosclerosis and prolongs lifetime in apo-E knockout mice

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Objective: To demonstrate anti-atherosclerotic effects of the MTP-inhibitor Bay 13-9952 and to investigate whether MTP inhibition has a positive effect on life expectancy in apoE knockout mice.

Methods: All animals were fed with a Western-type diet containing 0, 5, 15 or 45 ppm of Bay 13-9952. In an atherosclerosis study animals (n=15/group) were sacrificed after 14 weeks of treatment and cross-sectional plaque areas of the aortic root were determined by a computer-aided morphometric system. In a subsequent study, the animals (n=25/group) were checked daily for survival.

Results: Bay 13-9952 fed in all dosages to a significant reduction of lipid concentrations and atherosclerotic lesions. The average cross-sectional plaque area in the 0 ppm control group was 0.135 mm^2. The corresponding values in the 5, 15 and 45 ppm Bay 13-9952-treated groups were 0.046 mm^2, 0.034 mm^2 and 0.009 mm^2, corresponding to reductions of 66%, 75% and 93%, respectively. Histopathological examinations revealed in portions of the small intestine of treated animals cytoplasmatic vacuoles in the enterocytes which increased dose-dependently. The liver of all animals showed hepato-cellular fat accumulation. In the ongoing survival study all animals have died in the 0 ppm group after 20 months (0% survival). The number of surviving animals dose-dependently increased in the treated groups: 3 animals were still alive in the 5 ppm group, 9 in the 15 ppm group and 23 in the 45 ppm group. This corresponds to survival rates of 12%, 36% and 92%, respectively.

Conclusion: The MTP-inhibitor Bay 13-9952 dose-dependently suppresses atherosclerotic plaque formation in apoE knockout mice and improves survival.

195 A randomised study to evaluate the clinical efficacy of a high-dosed concentrate of n-3 fatty acids introduced early after an acute myocardial infarction

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There is still some controversy regarding the optimal dose of n-3 fatty acids for secondary prophylaxis after myocardial infarction (MI). We performed a prospective randomised, double-blind unicenter study to evaluate clinical outcome on high dosed n-3 fatty acids as compared to corn oil after an acute MI.

Methods: Three hundred patients with an acute MI were randomised to receive a daily dose of 4 grams of highly concentrated n-3 fatty acids or the same amount of corn oil administered double-blindly over a period of 12-24 months. Clinical follow-up was performed at 6 weeks, 6 months, 1 year, 18 months and 2 years after inclusion. The median follow-up time was 1.5 years. Statistical analyses was based on intention-to-treat. Survival curves were compared by means of the Kaplan Meier method, and hazard ratios were calculated in a Cox PH regression model. The main outcome consisted of combined cardiac endpoints; cardiac death, resuscitation, re-MI and unstable angina. Coronary revascularisations were considered in some analyses. Additional analyses ignoring events within the first month, as well as restricting the analyses to complete compliance at six weeks, were also performed. Relative changes in total cholesterol, HDL-cholesterol and triglycerides during the first year of follow-up were examined in the ANCOVA model. Findings: Demographics were similar in both patient groups. A total of 42 (28%) patients in the n-3 group and 36 (24%) patients in the corn oil group (p=0.44) experienced at least one cardiac event. Forty-three patients in the n-3 group and 49 in the corn oil group were revascularised during the observation period, but most of these patients (30 and 33, respectively) had none of the other cardiac events. No significant differences in hazard of clinical outcomes between the groups were observed, neither for single or combined events. A significant overall decrease in total cholesterol levels was observed, but there was no significant difference between groups. HDL-cholesterol increased in both groups, but significantly more pronounced in the n-3 group. The triglyceride level decreased significantly in the n-3 group and was significantly reduced in these patients as compared to controls. Interpretation: This study did not demonstrate any clinical benefit of a high-dosed concentrated ethylester compound of n-3 fatty acids administerd early after an acute MI, despite an improvement in serum lipids. Favourable effects of such concentrates may be related to a dose optimum below the chosen dose in this trial.

196 HMG-CoA reductase inhibition inhibits vascular NADH oxidase activity, prevents uncoupling of nitric oxide synthase and improves endothelial dysfunction in cholesterol fed rabbits

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Background: Hypercholesterolemia has been shown to cause endothelial dysfunction by increasing oxidative stress secondary to an activation of the endothelial NADH-oxidase . In addition in vitro evidence suggests that native LDL may cause an uncoupling of the endothelial nitric oxide synthase (NOS III) leading to increased vascular superoxide levels. With the present studies we sought to determine whether treatment of cholesterol fed animals with the HMG-CoA reductase inhibitor atorvastatin is able to improve endothelial dysfunction and whether this may be related to a reduction in NADH-oxidase and NOS III mediated oxidative stress.

Methods and Results: Vascular responses were determined using isometric tension studies and relative rates of vascular O2- production were determined using lucigenin-enhanced chemiluminescence (5μM). Cholesterol feeding for 6-8 weeks resulted in a marked increase in plasma cholesterol levels. Hypercholesterolemia was associated with impaired endothelium-dependent vasodilation and increased O2- production and increased superoxide production in response to 100μM NADH in intact vessels. Further, incubation of vessels from hypercholesterolemic animals with the NO-synthase inhibitor L-NMMA markedly decreased LDCL, suggesting NOS-mediated superoxide production. Treatment of cholesterol fed animals with the HMG-CoA reductase inhibitor atorvastatin (10mg/kg/die) resulted in a marked reduction in total cholesterol and LDL levels, improved endothelial function and normalized vascular O2-.NADH-oxidase activity and L-NMMA response indicating restoration of basal NO production. In control animals treated with atorvastatin where LDL levels were not detectable anymore endothelial-dependent relaxations improved.

Conclusions: Cholesterol lowering therapy improves endothelial function mainly by reducing oxidative stress due to inhibition of the vascular NADH oxidase and by inhibiting NOS-mediated superoxide production.

197 Atorvastatin, simvastatin and vessel wall permeability: suggestions for an effect independent of LDL-lowering

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Introduction: Our knowledge of the beneficial effects of statins is evolving toward the idea that these drugs do more than simply lower cholesterol. Statins improves endothelial function, plaque stability, thrombosis and inflammation but if these effects could be due entirely to the reduction in LDL remains an unresolved question.

Methods: The Transcapillary Escape Rate of albumin (TERalb, the fraction of the intravascular albumin leaving the vascular bed per hour) a measure of microvessel permeability, has been assessed in two groups of non-diabetic, non-obese normotensive patients with hypercholesterolemia.

Results: The first group (Group 1, n. 18 subjects with atherosclerotic peripheral vascular disease) whose baseline LDL-cholesterol was 173±36 mg/dl took 40 mg simvastatin for 1 month; LDL was reduced by 45% to 102±26 mg/dl. TERalb moved from 10.4±2.0%/h to 8.4± 2.9%/h (p=0.0096). The second group (Group 2, n. 22) has familial hypercholesterolemia and baseline LDL cholesterol was 304±43 mg/dl. After 6-month-40 mg atorvastatin treatment, LDL was reduced by 47% to 157±36 mg/dl. TERalb decreased from 8.9±2.0 %/h to 7.7±2.0%/h (p=0.02). Baseline Group 1 LDL cholesterol was not different from 6-month atorvastatin cholesterol level observed in Group 2 (173±36 vs 157±36 mg/dl, p=0.178). TERalb was 10.4±2.0%/h in Group 1 at baseline and 7.7±2.0 %/h in Group 2 after 6-month atorvastatin treatment (p=0.0001). So, we observed largely different TERalb levels in two groups of patients with superimposable LDL-cholesterol values.

Conclusion: These data might suggest that the effects of statins on microvesset wall permeability may be partially independent of cholesterol lowering.