LIPID LOWERING THERAPY

1287 Regression of atheroma seen with intravascular ultrasound: a placebo controlled study of the effect of gemfibrozil on peripheral atherosclerosis

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The Killingbeck Regression of Atheroma Study (KRAS) was a double blind placebo controlled study of the effect of gemfibrozil on atheroma in the aortoiliac arteries of patients with coronary artery disease and moderately raised lipids (mean total cholesterol = 6.8 $mmol^{-1}$). Serial cross-sectional images of these vessels were recorded using a 20 MHz intravascular ultrasound (IVUS) catheter during a controlled pull back in 39 patients (male 26, ages 38–70). Patients were given dietary advice and randomized to treatment with gemfibrozil 600 mg bd or placebo. After treatment for a mean of 371 days the 31 patients (17 in gemfibrozil group) who completed the study underwent repeat imaging. Segments of arteries were matched using the position of bifurcations. 1144 segments of arteries were matched and measurements of cross sectional area of atheroma made. Baseline demographics, physical and lipid data were well matched between the groups. In the gemfibrozil group significant reductions compared to the placebo group were seen in total cholesterol (9%, $p = 0.03$), triglycerides (55%, $p = 0.0001$) and LDL/HDL ratio (26%, $p = 0.02$), a significant increase in HDL cholesterol level (27% $p = 0.05$) was seen. No overall significant change in the mean cross-sectional area of atheroma was seen in the placebo group but there was a 10.3% decrease of this measurement in the gemfibrozil group ($p = 0.011$, 95% CI = −5.0 to −0.8 mm^2). Analysis of cross-sectional plaque area changes within individual patients showed significant ($p < 0.05$) regression in 6 gemfibrozil and 4 diet only patients and significant progression in 2 diet only patients. Analysis of the relationship between atheroma change and baseline risk factors baseline lipids and change in lipids in the gemfibrozil group, showed significant correlations of atheroma change with baseline systolic blood pressure, baseline Apolipoprotein B and baseline HDL cholesterol but not with change in any lipid parameter. Analysis of the relation of plaque type with severity of atheroma found that extent of calcification was related to severity of atheroma both between and within patients. Analysis of the pattern of atheroma change within patients showed regression most often occurred at the edge of plaques. By using IVUS we were able to show regression of atheroma in response to treatment with diet and gemfibrozil and provide new insights into the nature of atherosclerosis in vivo.

1288 Simvastatin reduced coronary mortality and subsequent coronary and atherosclerosis-related events in patients who sustained a non-fatal myocardial infarction during the Scandinavian Simvastatin Survival Study (4S)

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Treatment with simvastatin 20–40 mg daily in 4S reduced risk of death by 30% ($p = 0.0003$), due to a 42% reduction in risk for CHD death. Risk of hospital-verified nonfatal myocardial infarction (MI) was reduced by 37%. In the present analysis, the incidence of *subsequent* coronary mortality and coronary events was investigated among the 757 patients who sustained one or more hospital-verified non-fatal MI during the study (n = 300 in the simvastatin group, n = 457 in the placebo group). The numbers (percentages) of patients and events in the two treatment groups for different event categories are listed in the Table below:

	Simvastatin (n = 300)		Placebo (n = 457)	
	# events	# patients	# events	# patients
CHD death	29	29 (10.1)	66	66 (15.0)
Non-fatal MI	95	55 (18.3)	154	105 (23.0)
CABG/PTCA	104	91 (30.3)	184	170 (37.2)
Atherosclerosis-related events	420	155 (51.7)	669	291 (63.7)

Although treatment group comparisons are not strictly valid (since patients were not randomly assigned to the groups analyzed) Cox proportional hazards analyses strongly suggest treatment effects within each of the above event categories. We conclude that cholesterol-lowering with simvastatin is effective in reducing subsequent CHD mortality and risk of CHD/atherosclerotic events in patients who sustain a nonfatal MI during treatment. Therapy should be continued in such patients.

1289 The effect of red wine on experimental atherosclerosis extension: lipid independent protection

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There is epidemiological evidence that red wine (RW) protects against atherosclerosis.

Methods and Results. To objectively test this hypothesis, New Zealand rabbits were given 1% cholesterol diet for 12 weeks. Control animals received only diet; treated animals received 3.2 ml/kg/day of either RW or non-alcoholic products of wine (NAPW), in the drinking water. NAPW were obtained by extracting alcohol from RW at high temperatures. Macroscopic plaque extension was assessed by computerized planimetry after Sudam IV staining of excised aortas. Microscopic evaluation was based on intima/media (I/M) thickness ratio of 5 aortic segments after hematoxilin/eosin staining. Lipids were measured by standard methods. LDL oxidizability was assessed in rabbits treated for 3–4 weeks; lag-phase diene formation was measured by spectrophotometry after $CuSO_4$-LDL incubation. Diet produced a 22% increase in weight of all animals and about 20-fold increase in total cholesterol (TC). Results are shown in the table (Final TC and HDL in mg%. Lag phase in min.

	Plaque (%Ao)	I/M ratio	TC	HDL	Lag phase
Control	69 ± 9	0.6 ± 0.2	879 ± 38	19 ± 4	77 ± 6
RW	38 ± 4*	0.1 ± 0.09*	1102 ± 41	17 ± 7	82 ± 18
NAPW	47 ± 12*	0.4 ± 0.2*	824 ± 50	23 ± 6	84 ± 8

*$p < 0.001$ vs control, ANOVA).

Conclusion. Both RW and NAPW decreased plaque formation in hypercholesterolemic rabbits despite high lipid plasma levels and unaltered LDL susceptibility to oxidation. Blockade of endothelial adhesion molecules expression by flavonoids, which are present in RW, may explain these results.

1290 Evaluation of lipid-lowering therapy by functional assessment. A substudy of the Regression Growth Evaluation Statin Study (REGRESS)

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In symptomatic men with significant coronary atherosclerosis treatment with pravastatin (prav.) in comparison with placebo (plat.) resulted in less progression of coronary atherosclerosis. The purpose of this study was to assess the effect of prav. on regional myocardial blood flow and on exercise parameters.

Methods: In Nijmegen 69 patients were randomised to prav. 40 mg o.d. or plac. according to the REGRESS protocol. Before and after two years of therapy regional myocardial blood flow was assessed by digital subtraction angiography after i.e. papaverine with video-densitometrie calculation of the hyperemic mean transit time (HMTT). Exercise testing was performed before and after two years of therapy in the medical management (M) stratum of the study, evaluating: exercise time (EXT) and Maximal ST-segment depression (MST).

Results: Complete follow-up after 2 years was available in 26 patients in the M, 10 in the PTCA (P) and 14 in the CABG (C) stratum, respectively. Effect analysis of prav. versus plac. was based on 36 patients (M and P strata, PTCA vessels excluded). Regional myocardial perfusion was assessed in 40 regions in the prav. group and 31 regions in the plat. group. HMTT decreased by 0.17 s (−5%) in the prav. group whereas HMTT increased by 0.36 s (+12%) in the plac. group ($p = 0.02$). In the M stratum EXT changed from 649 ± 192 to 632 ± 116 s (−17 s, $p = 0.65$) in the prav. group and from 759 ± 240 to 653 ± 224 s (−106 s, $p = 0.06$) in the plac. group. ST max changed from 1.0 ± 1.0 to 0.7 ± 1.1 mm ($p = 0.13$) in the prav. group and remained stable 0.7 ± 0.7 to 0.7 ± 0.7 mm in the plac. group.

In conclusion: These results indicate that the treatment with pravastatin favorably affects regional myocardial blood flow. There is a trend to reduced exercise induced ischemia and preserved exercise capacity.