(C) of ≥207 mg/dl after diet. Treatment with up to 40 mg simvastatin (S) or placebo (P) o.d. included diet and — as a reserve medication: — colestyramine, and was pursued for 2.3 years (S/P: 865/835 days). The two treatment groups (see below) were comparable with respect to *baseline variables*, e.g. average age (49.9/49.1 y), height (175.4/175.2 cm), weight (80.1/80 kg), blood pressure (123.5/79.8 vs. 123.1/78.6 mmHg), diastolic hypertension ≥90 mmHg (9.6/9.1%), fasting serum glucose ≥120 mg/dl (2.9/5.1%), family history (47.1/48.0%), smoking (83.6/85.9), ventricular score (1.0/0.9), coronary score (2.12/1.93 — vessel-disease), and lipid values, with a baseline LDL-C of 163.8/166.7 mg/dl. *Treatment resulted* in significant changes of serum lipids with a decrease of LDL-C by 33% and −1.5% in the S and P group, respectively. *204 (81%;* 104/100) *patients* had a second angiography.

Two *primary end points* were chosen: — the within-patient change in minimum diameter avenged over all assessable coronary segments ("ΔminD", determined by quantitative analysis using the CAAS system), and — the visual Global Change Score ("GCS", Blankenhorn), and calculated according to Bonferroni-Holme on a multiple significance level of 5%. The detailed results will be presented.

Supported by MSD Sharp and Dohme, Munich, Germany

4:45

769-4 Lowering of Cholesterol With Simvastatin may Prevent Development of Heart Failure in Patients With Coronary Heart Disease

John Kjekshus, Terje Pedersen on behalf of the 4S Study Group. *University of Oslo, Oslo, Norway*

While treatment of myocardial overload effectively reduces death from progression of heart failure, it is not known whether the retardation of progressive coronary heart disease obtained with lipid lowering treatment will prevent onset of heart failure. In the 4S trial 4444 patients without evidence of heart failure were randomised to placebo (P), (n = 2221) or simvastatin 20–40 mg (S), (n = 2223) and followed for more than 5 years. In P 189 patients (8.5%) were diagnosed with heart failure during follow up vs. 147 in S (6.2%) $p < 0.003$. Respectively 37 and 24 had occurrence of acute heart failure. Heart failure patients were more likely to have higher triglyceride and lower HDL than patients who did not develop congestive heart failure.

Conclusion: Long term prevention with simvastatin prevents occurrence of heart failure in a cohort of patients with coronary heart disease, without previous evidence of heart failure.

5:00

769-5 Reduction of Silent Myocardial Ischemia by Pravastatin Additional to the Conventional Treatment of Patients with Angina Pectoris

Ad J. van Boven, J. Wouter Jukema, Aeilko H. Zwinderman, Kong I. Lie, Albert V.G. Bruschke, REGRESS study group *Interuniversity Cardiology Institute, Utrecht, The Netherlands*

With conventional treatment, including PTCA and CABG, complete abolishment of Silent Myocardial Ischemia (SMI) is not attained. Cholesterol-lowering therapy restores endothelial function and possibly lowers SMI mediated by disturbed vasomotion. We hypothesized that pravastatin 40 mg (P) in addition of conventional therapy may reduce SMI and studied its 2 year treatment effect in 339 patients from the REGRESS study, using 48 hour ambulatory ECG's. In this placebo controlled study only patients with angina pectoris, documented coronary artery disease and a cholesterol between 4 and 8 mmol/l are included. During Holter anti-ischemic medication was continued.

Results: At baseline (B) 28% of the patients had SMI and at follow up (F) 15%. A pronounced reduction of P was observed in the development of new SMI in the group of patients with beta blockers (N = 141) at both B + F: compared to placebo 7 patients less had new SMI ($p = 0.05$, Chi-Square) In the group of patients (N = 173) taking nitrates 10 patients less had new SMI, ($p = 0.01$). Also patients with triple anti-anginal medication (N = 72) at B + F showed a beneficial effect of P on SMI (5 pts.less, $p = 0.05$). P reduced number of ischemic episodes, duration of ischemia and ischemic burden. Without the adjustment for concomitant medication the effect of P was not significant.

Conclusion: Pravastatin causes an additional reduction of silent myocardial ischemia in angina pectoris patients, who develop ischemia despite beta blockers, nitrates or triple medication. A new anti-ischemic mode of action of pravastatin in this subset is suggested, possibly by improving endothelial function.

5:15

769-6 Inhibitory Effect of Lovastatin on Human Coronary Smooth Muscle Cell Proliferation

Vidya S. Banka, Peter S. Fail, Vasundhra Sharma *Episcopal Heart Institute, Episcopal Hospital, Philadelphia, PA*

Longterm administration of lipid lowering agents has been shown to cause regression of coronary atherosclerosis. To evaluate the mechanism of such regression, we studied the effect of Lovastatin (HMG coenzyme A reductase inhibitor) on the smooth muscle cells cultured from atherosclerotic plaque obtained from 5 human coronary arteries undergoing directional coronary atherectomy for de novo lesions. Arterial smooth muscle cell lines were created by 3–5 passages. These cells were then placed at a density of 3000 cells/ml in M-199 medium with 10% fetal bovine serum. They were exposed to Lovastatin at varying concentrations between 10^{-9} to 10^{-4} M. The coronary arterial smooth muscle cells were inhibited in a dose dependent manner. The table below shows the actual cell counts at various concentrations of Lovastatin in the 5 patients.

Effect of Lovastatin on smooth muscle cell proliferation

PT	Control	Mitogen	10^{-9}	10^{-8}	10^{-7}	10^{-6}	10^{-5}	10^{-4} M
J.B.	2575	5216	4325	3875	3320	2975	2575	1901
M.P.	2879	4390	4125	3979	3629	3098	2095	1971
I.H.	2389	3613	3368	3153	2841	2221	2006	1696
M.L.	2900	5938	4817	3909	3199	2729	2072	1092
W.C.	2830	3729	3210	2710	2093	1773	1292	934
Mean	2715	4581	3969	3525	3016	2559	2008	1519

Conclusion: HMG Coenzyme A reductase inhibitor Lovastatin has a strong antiporliferative effect on human coronary smooth muscle cells. These observations suggest that antiproliferative effect of Lovastatin may be responsible for causing regression of atherosclerotic lesions in addition to its lipid lowering effects.

770 Calcium Regulation of Animal and Human Cardiac Muscle

Tuesday, March 21, 1995, 4:00 p.m.–5:30 p.m.
Ernest N. Morial Convention Center, Room 21

4:00

770-1 Exogenously Administered Growth Hormone and IGF-1 Alter Intracellular Calcium Handling and Enhance Cardiac Performance

Hinrik Strömer, Antonio Cittadini, Pamela S. Douglas, James P. Morgan. *Beth Israel Hospital and Harvard Medical School, Boston, MA*

To further elucidate the mechanisms by which growth hormone (GH) and IGF-1 modulate cardiac function, we studied isolated, isovolumic, buffer-perfused rat hearts after 4 weeks of treatment with high doses of GH, IGF-1 or combination of both (G + I). Flow rate was 10 ml/min/g heart wt., baseline perfusate Ca^{2+} was 1.0 mmol/l. Functional parameters including systolic and diastolic pressure (P_{sys}, P_{dias}, mmHg), maximal +dP/dt/DevP (sec^{-1}) and (calculated) peak systolic circumferential wall stress (σ_{sys}, $kdyn/m^2$) were measured at 50% of the intracardiac balloon volume at which maximal developed pressure (DevP) occurred. EC_{50} (μmol/l) of the force Ca^{2+} relationship and maximum Ca^{2+} activated force (σ_{sysmx}, $kdyn/cm^2$) were assessed by stepwise increase of Ca^{2+} in the perfusate and plotting σ_{sys} vs. intracellular peak systolic Ca^{2+} measured by the aequorin bio-luminescence method. Results at baseline and Ca^{2+} response were as follows:

	P_{sys}	σ_{sys}	+dP/dt/DevP	EC_{50}	σ_{sysmx}
Control	139 ± 5#	68 ± 5	15.4 ± 0.1	0.67 ± 0.01	78 ± 5
IGF-1	169 ± 6#*	68 ± 2	17.7 ± 0.2#*	0.73 ±0.02*	103 ± 4*
GH	162 ± 5#*	67 ± 3	16.5 ± 0.2*	0.74 ± 0.01*	107 ± 4*
G + I	153 ± 4*	69 ± 3	15.6 ± 0.3	0.72 ± 0.02*	106 ± 2*

Data are mean ± SEM; *$p < 0.05$ vs. control, #vs. G + I

P_{dias}, Ca_{sys}, Ca_{dias}, shape and duration of the Ca^{2+} transient were not influenced by the treatments. All treatments caused a similar increase of heart wt. although the heart wt. to body wt. ratio remained unchanged. σ_{sys} was unchanged by the treatments despite increasing P_{sys}, suggesting a concentric growth pattern. In addition to the increased P_{sys} enhanced systolic performance was demonstrated by an increased σ_{sysmx}, although this effect is not seen on σ_{sys} at baseline due to an increased EC_{50}.

These data support the hypothesis, that both IGF-1 and GH have a direct effect on cardiac performance by influencing geometry and maximum Ca^{2+} activated force capacity.