EVIDENCE FOR DIRECT ANTI-INFLAMMATORY ACTIVITY OF STATINS AND FIBRATES FROM STUDIES IN HUMAN C-REACTIVE PROTEIN TRANSGENIC MICE AND IN CULTURED HUMAN HEPATOCYTES

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Besides cholesterol, inflammatory processes play a central role in atherogenesis. Cholesterol-lowering statins reduce atherosclerosis and plasma human C-reactive protein (huCRP) levels. HuCRP signals systemic inflammation and independently predicts future cardiovascular risk. In the present study, evidence is sought for a direct anti-inflammatory statin effect *in vivo*, unrelated to effects on plasma cholesterol and atherogenesis. The effect of atorvastatin on huCRP expression was studied in non-atherosclerotic huCRP transgenic mice and compared to another hypolipidemic drug, fenofibrate. Fibrates, like statins, combine anti-atherosclerotic properties with huCRP-lowering effects. Dietary treatment with atorvastatin or fenofibrate decreased basal and IL-1-induced plasma huCRP levels independent of cholesterol-lowering. These direct anti-inflammatory *in vivo* effects occurred at the transcriptional level and could be confirmed in cultured human liver slices and in human hepatoma cells transiently transfected with a huCRP promoter-driven luciferase reporter. A molecular rationale for the suppression of IL-1-induced huCRP transcription is provided by showing that statins and fibrates upregulate IκB-α protein levels. This results in a reduced nuclear translocation of p50-NFκB and thereby decreased amounts of nuclear p50-NFκB~C/EBPβ complexes, which determine the huCRP transcription rate. These data provide conclusive evidence for a direct suppressive effect of statins and fibrates on huCRP expression unrelated to effects on plasma cholesterol and atherogenesis.

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THE PPAR-α-AGONIST FENOFIBRATE REDUCES DEVELOPMENT OF ATHEROSCLEROSIS BEYOND AND INDEPENDENTLY OF ITS PLASMA CHOLESTEROL-LOWERING EFFECT IN APOE*3-LEIDEN TRANSGENIC MICE.

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Fibrates can exert anti-inflammatory effects, independently of lowering cholesterol. Using APOE*3-Leiden mice we investigated whether the PPAR-α-agonist fenofibrate can decrease atherogenesis beyond the effect achieved by its cholesterol-lowering properties alone. Two groups of 17 female mice received either a high-cholesterol diet (HC) or HC supplemented with 30 mg/kg bodyweight fenofibrate (HC+F). HC alone resulted in a plasma cholesterol (Chol) level of 25.8±2.8 mmol/L. Fenofibrate lowered plasma Chol to 12.4±2.8 mmol/L (-52%). The plasma triglyceride (TG) concentration was reduced from 1.2±0.3 mmol/L in the HC group to 0.4±0.4 mmol/L in the HC+F group (-67%). The decrease in plasma Chol and TG was caused by a reduction of the amount of apoB-containing lipoproteins, whereas HDL increased in the HC+F group. In a separate low-cholesterol (LC) control group, the dietary cholesterol intake was reduced, which did not alter TG levels (1.2±0.4 mmol/L) and which resulted in plasma Chol levels comparable to the HC+F group (12.7± 2.4mmol/L). After 19 weeks of intervention, atherosclerosis in the aortic root was quantified. Compared to the HC group, the LC group displayed a 87% ($P<0.001$) reduced total lesion area and the HC+F group showed a further decrease in total lesion area (92%,$P<0.001$), lesion number (66%,$P<0.05$), and lesion severity (13%,$P<0.05$). Compared to the HC group the LC group showed a significant decrease in monocyte adhesion (44%,$P<0.005$) which was further reduced in the HC+F group and was paralleled by a strong reduction of the macrophage lesion content (83%, $P<0.05$). In conclusion, treatment with fenofibrate strongly reduced atherosclerosis beyond and independently of the reduction achieved by cholesterol-lowering.

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THE EFFECT OF NICOTINIC ACID AND ALCOHOL CO-ADMINISTRATION IN WISTAR RATS

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The administration of nicotinic acid (NA) in combination with alcohol (Alc) consumption is frequently observed in dyslipidaemic patients. We evaluated the safety and efficacy of the co-adminastration of NA and Alc in male Wistar rats.

The rats were randomized into 4 groups, which were tube fed with: 1) Olive oil (Oil) (n=10), 2) Alc+Oil (n=10), 3) NA+Oil (n=8), 4) NA+Alc+Oil (n=9). Another 13 rats were served as controls. After 8 weeks, blood samples were drawn and alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), total cholesterol and triglycerides (TG) levels were measured. Liver histopathology was also assessed.

The Alc+Oil group had higher TG levels compared to all other groups. NA+Oil group had higher levels of AP compared to Alc+Oil and Oil groups. The NA+Oil group had higher ALT levels compared to Oil group. Oil group had lower ALT levels compared to control group. Alc+Oil group had higher AST levels compared to all other groups. Liver histopathology was within the normal range.

A moderate amount of Alc daily together with NA is safe in rats. NA administration in rats protects from the Alc-induced TG and AST rises.

ALLEVIATION OF MTP INHIBITOR-INDUCED HEPATIC STEATOSIS IN HYPERLIPIDEMIC FA/FA RATS BY FENOFIBRATE

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The microsomal triglyceride transfer protein (MTP) is an intracellular lipid carrier protein of liver and intestine that is required for the intracellular production and secretion of apolipoprotein B-containing lipoproteins. Several MTP inhibitors (MTPIs) had entered clinical trials (e.g. BMS-201038) for improving the lipoprotein profile of hyperlipidemic patients, but none has yet been approved. A potential drawback of MTPIs is the mechanism-related accumulation of lipids in the liver. The aim of the present study was to test in an animal model the hypothesis that this adverse effect can be alleviated by co-administration of a fibrate to simultaneously stimulate fat oxidation in the liver.

Here, we studied the pharmacology of an MTPI from the pyrrole carboxamide class (BIBS 2276) that inhibited MTP with an IC50 of 3 nM in rat liver preparations and blocked apoB secretion in HepG2 cells with an IC50 of 1.5 nM. The compound completely inhibited lipoprotein secretion in Wistar rats up to 24 hours after single oral administration of 10 mg/kg. After subchronic treatment of obese hyperlipidemic fa/fa rats for 1 week, plasma triglycerides were reduced by 76% at 3 mg/kg and by 96% at 10 mg/kg. Plasma cholesterol was reduced by 26% at 3 mg/kg and by 31% at 10 mg/kg.

The inhibition of lipoprotein production by BIBS 2276 in the liver resulted in an accumulation of lipids in hepatocytes (hepatic steatosis; > 10fold increase in hepatic triglycerides at 3 mg/kg). Liver cells of fa/fa rats were damaged by this degree of steatosis as indicated by a 5-9fold increase in plasma transaminases. However, co-administration of fenofibrate (an activator of the transcription factor PPARalpha) at 100 mg/kg bid completely normalized liver function tests and reduced hepatic steatosis.

Our results indicate that the mechanism-related liver toxicity of MTPIs can be alleviated by combination with a fibrate, possibly by stimulation of beta-oxidation of fatty acids in the liver.

ROSUVASTATIN ATTENUATES HYPERTENSION-INDUCED CARDIOVASCULAR REMODELLING WITHOUT AFFECTING BLOOD PRESSURE IN DOCA-SALT HYPERTENSIVE RATS

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Pleiotropic effects of statins represent potential novel mechanisms for the treatment of hypertension, cardiovascular remodelling and heart failure. We have investigated cardiac remodelling in DOCA-salt hypertensive rats treated with rosuvastatin (R). Male 8 week old Wistar rats were uninephrectomised and treated with deoxycorticosterone acetate (DOCA, 25 mg every 4th day sc) and 1% NaCl in their drinking water for 4 weeks; uninephrectomised (UNX) rats served as controls. R-treatment groups received 20mg/kg/day R in 10% Tween 20 by oral gavage for 32 days commencing 4 days before uninephrectomy. R did not alter systolic blood pressure, but decreased left ventricular weight relative to body weight compared to DOCA rats (DOCA 3.05±0.10, DOCA+R 2.68±0.10 mg/kg; UNX 1.81±0.04, UNX+R 1.92±0.04 mg/kg). Diastolic stiffness was increased in DOCA rats, but lowered from 24.9±0.4 (DOCA, n=12) to 21.5±0.5 by R (DOCA+R, n=7), whilst UNX rats remained unchanged (UNX 21.4±0.4, UNX+R 21.9±0.4). The left ventricular interstitial collagen content (DOCA 4.39±0.59, DOCA+R 2.61±0.39 %area; UNX 2.58±0.16, UNX+R 2.38±0.31 %area) was reduced to control levels in DOCA-salt rats treated with R. Drug treatment failed to alter aortic media thickening observed in DOCA-salt rats (DOCA: 105.6±2.8 μm UNX: 84.7±1.8 μm). Action potential duration at 90% of repolarisation from microelectrode recordings of isolated papillary muscle preparations was reduced from 114.4±3.3 to 95.2±3.1 msec with R treatment in DOCA-salt rats (UNX 45.99±0.99, UNX+R 51.36±3.91 msec). Rosuvastatin shows a marked beneficial effect by attenuating increases in cardiac stiffness and collagen deposition, and also both cardiac hypertrophy and action potential prolongation in the DOCA-salt model of hypertension in rats without altering systolic blood pressure.

ROSUVASTATIN PREVENTS CARDIOVASCULAR REMODELLING WITHOUT LOWERING BLOOD PRESSURE IN AGEING MALE SPONTANEOUSLY HYPERTENSIVE RATS

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Statins exert direct beneficial effects on cardiovascular remodelling, hypertension and heart failure, which are independent of their intrinsic cholesterol lowering ability. This project investigated cardiac remodelling and heart failure in ageing SHR rats treated with rosuvastatin (R, 20mg/kg/day) by oral gavage for 24 weeks, commencing at 15 months of age. Age-matched Wistar Kyoto (WKY) rats served as controls (n≥6/group)(*p<0.05 vs untreated). R did not alter systolic blood pressure (SHR 200±6, SHR+R 190±8; WKY 148±7, WKY+R 159±2 mmHg), but decreased left ventricular weight/body weight ratio in SHR (SHR 4.09±0.10, SHR+R 3.50±0.13*; WKY 2.29±0.05, WKY+R 2.14±0.05 mg/kg). Thoracic aorta media width was unaltered with treatment (SHR 146.0±4.2, SHR+R 142.6±4.3; WKY 106.1±2.1, WKY+R 99.8±2.1mm). Diastolic stiffness was lowered from 33.1±0.8 (SHR) to 27.5±0.6* (SHR+R), whilst WKY rats were unchanged (WKY 24.6±0.4, WKY+R 22.2±0.4). Rosuvastatin treatment reduced left ventricular interstitial collagen content in SHRs (SHR 19.6±1.0, SHR+R 14.6±1.2*; WKY 7.6±0.5, WKY+R 8.0±0.7 % area), whilst perivascular collagen content remained unchanged (SHR: 33.9±1.4, SHR+R 30.9±1.4; WKY 23.9±1.8, WKY+R 24.7±1.3 % area). Statin treatment significantly lowered mitral E/A flow in 19 and 20 month old SHRs (19mth: SHR 2.27±0.11, SHR+R 1.82±0.08*; 20mth: SHR 2.65±0.36, SHR+R 1.69±0.07*), as imaged by echocardiography. Thus, in the ageing SHR, rosuvastatin prevented increases in cardiac stiffness, interstitial collagen deposition, mitral E/A flow and cardiac hypertrophy without altering systolic blood pressure, aortic media width and perivascular collagen deposition, suggesting a role for rosuvastatin in the attenuation of cardiovascular remodelling during the development of heart failure.

PLEIOTROPIC EFFECT OF CLOFIBRATE IN WISTAR RATS

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Clofibrate is a hypolipidemic agent than can cause peroxisoamal proliferation in rodents. The aim of our study was to determine the pleiotropic effect of clofibrate in a dose of 250 mg/1000 g/24h for 10 days in male Wistar rats.
Material for our study was liver analyzed for morphological changes and peroxisomal fraction analyzed for biochemical changes.
We found morphological changes of peroxisomes in a treated group that result in an increased number of peroxisomes. Biochemical changes in the increase activity of D-amino acid oxidase; urate oxidase and palmytoyl Co oxidase were statistically significant in comparison with the control group. On the other hand the activity of glutathione peroxidase and superoxide dismutase were statistically significantly decreased and the activity of catalase was statistically significant increased in comparison with the control group. There was statistically significant enlargement of the liver in comparison with the control group as well as, in the somatic index.
We may conclude that clofibrate caused pleiotropic effect male Wistar rats.

ATHEROMA STABILIZING EFFECTS OF SIMVASTATIN IS DUE TO DEPRESSION OF MACROPHAGES

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[Background] Both hydrophilic and lipophilic statins reduce coronary events and SMC is important in stabilization of atheromatous plaques although in vitro studies demonstrated that lipophilic statins inhibited proliferation of arterial SMCs. **[Objective]** We examined whether lipophilic simvastatin (Simva) reduces smooth muscle cells in atheromatous plaque and how Simva affects stability of atheroma in vivo. **[Methods]** Simva was administered orally to 10 WHHL rabbits (10 months old) for 52 weeks at a dose of 15 mg/kg. At the end of the drug administration, plasma Simva concentration was measured. The coronary arteries were perfusion-fixed and embedded in paraffin. Each serial section was stained histopathologically or immunohistologically. Degree of coronary plaques was evaluated as cross sectional narrowing. Plaque composition was evaluated by measuring the area of each component. **[Results]** Compared to the placebo group, the plasma cholesterol levels decreased by about 20%. In the Simva group, the lipid component (macrophages + extracellular lipids) was decreased in the coronary and aortic atheroma despite no decrease in the fibromuscular components. Consequently, the frequency of vulnerable plaque decreased. In the coronary plaque of the Simva group, PCNA-positive cells (which appeared to be macrophages) of the plaques decreased but the TUNEL-positive cells did not show significant change. Finally, fully differentiated SMCs increased in the aortic lesions of the Simva group. The average plasma Simva concentration was 0.18 μg/ml. **[Conclusion]** Simva did not depress the fibromuscular components in atheromatous plaques and the plaque-stabilizing effects were due to the reduction of macrophages / lipid deposits in the plaque.

EVALUATION AT CELLULAR, TISSUE AND FUNCTIONAL LEVELS OF THE EFFECTS OF FLUVASTATIN CHRONIC TREATMENT IN RAT SKELETAL MUSCLE

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Statin, cholesterol-lowering drugs, can produce skeletal muscle injury. We demonstrated that the resting chloride channel conductance (gCl), which controls sarcolemma excitability, and the structures involved in Ca^{2+} handling are cellular targets of statin-induced muscle damage (Pierno et al. J Pharmacol Exp Ther 1995;275:1490-6). We currently undertaken a large analysis to understand the mechanism of muscle toxicity by statin chronic treatment. We monitored, in parallel, the above mentioned functional cellular parameters, body and organs weight, blood and urine profile and muscle histopathology. The effects of 2-month oral treatment with fluvastatin (5 and 20 mg/kg/day) are here reported. Five out of five rats treated with 20 mg/kg, showed progressive loss of body weight and proteinuria, while no changes were observed at 5 mg/kg. The plasma creatine kinase was slightly increased in the 5 mg/kg treated rats, while it was paradoxically decreased in the 20 mg/kg group, a finding most likely related with protein urine loss. At both doses, fluvastatin significantly reduced gCl by 20% in extensor digitorum longus (EDL) muscle fibers, leading to a concomitant increase in membrane excitability parameters. FURA-2 cytofluorimetric analysis showed that fluvastatin at 5mg/kg did not affect either the resting intracellular Ca^{2+} concentration, or the sarcolemmal Ca^{2+} permeability, or the caffeine-induced Ca^{2+} release. At 20 mg/kg we observed a 40% increase of cytosolic Ca^{2+} and an altered response to caffeine, suggesting a depletion of intracellular Ca^{2+} stores. We confirmed that the reduction of gCl is an early event in fluvastatin-induced muscle damage, occurring at lower doses than the modification of the cellular system responsible for Ca^{2+} handling. This latter may be responsible for hypercontraction and muscle degeneration. (Supported by FIRB-RBAU015E9T).

EFFECT OF HMG-CoA REDUCTASE INHIBITION ON CRP EXPRESSION IN PRIMARY HUMAN HEPATOCYTES

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The C-reactive protein (CRP) is an acute phase protein, predominantly synthesised in hepatocytes. It is widely used as a systemic marker for inflammation. Moreover, since elevated levels of CRP, even in the absence of overt dyslipidemia, are associated with an increased risk of coronary events, CRP is considered as a novel marker of cardiovascular risk. CRP may also be actively involved in the development of atherosclerosis. Treatment with 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors (HMGRI) has proven the most successful strategy to reduce the concentration of LDL in the circulation. Beyond lipid lowering, statins have been hypothesized to have direct anti-inflammatory effects. We here assessed the hypothesis that HMG-CoA-reductase inhibition reduces CRP expression directly rather than by acting on inflammatory processes in the vessel wall.
Primary human hepatocytes were incubated for 24 hours with IL-6/IL-1 and various concentrations of HMGRI. IL6 [25ng/ml] / IL1 [10ng/ml] increased CRP expression by 39 ± 2 % compared to mock cells. Treatment with HMGRI resulted in a dose dependent reduction of CRP expression with a maximum of -87 % at 1μM HMGRI compared to IL6/IL1 stimulated cells. NF-kappa-B p65/p50 knockdown, performed by Oligo-Decoy-Technique showed no effect on CRP expression. To verify that the reduction of CRP expression by HMGRI is specific mediated via HMG-CoA-Reductase inhibition, cells were co incubated with mevalonate, IL6/IL1 and HMGRI. The inhibitory effect of HMGRI on CRP expression was blunted by co incubation with mevalonate (45±5 %) compared to IL6/IL1 stimulated cells (39±2 %).
Reduction of CRP during statin therapy may be explained by a direct effect on hepatocytes. This, however, may be clinically beneficial as CRP may have an active role in atherogenesis.

ANTITHROMBOTIC AND ANTIINFLAMMATORY PROPERTIES OF ROSUVASTATIN IN CULTURED HUMAN ENDOTHELIAL CELLS.

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Rosuvastatin (R) is a new 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitor with distinct physicochemical, pharmacokinetic and pharmacologic properties. It is relatively hydrophilic, with a plasma half-life of about 20 h and, besides plasma LDL-cholesterol level reduction, it lowers triglycerides and increases HDL-cholesterol in patients with mixed dyslipidemia or hypertriglyceridemia. Statins, independently of their lipid lowering effect, modulate several mechanisms that are involved in the atherothrombotic process. In the present study we evaluated the effect of rosuvastatin on PAI-1 and tissue factor (TF) in cultured human umbilical vein endothelial cells (HUVEC). Moreover, the capacity of the drug to control inflammation was assessed through the evaluation of eNOS and Cox-2 levels. Rosuvastatin, concentration-dependently (10 -100 μM) reduced PAI-1 antigen, either secreted or stored, in resting HUVEC (10 μM R: - 68%, $p< 0.01$). In contrast, TF activity induced by TNFalpha was scarcely affected, even at the highest concentration used (100 μM). eNOS levels, detected by Western blot analysis, were increased by rosuvastatin in a concentration-dependent fashion (25 μM R: +76%, $p<0.05$). In addition, the drug reduced Cox-2 synthesis induced by PMA (10 μM R: - 46 %, $p<0.01$). Mevalonate (100 μM) added concomitantly with rosuvastatin prevented all these effects. None of the treatment condition used resulted in substantial changes in cell morphology. In conclusion, the decrease of PAI-1 antigen levels coupled with eNOS up-regulation in resting endothelial cells is promising for the antithrombotic profile of the drug. Moreover, the inhibition of COX-2 synthesis in stimulated endothelial cells points to a protective effect of rosuvastatin in the development of the inflammatory reaction that takes place in atherothrombosis.

THE ANTIOXIDANT DEFENSE PROTEIN HEME OXYGENASE-1 IS A NOVEL TARGET SITE FOR ROSUVASTATIN IN ENDOTHELIAL CELLS

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Cholesterol-independent, pleiotropic actions of HMG CoA reductase inhibitors (statins) lead to anti-inflammatory and antioxidant actions by mechanisms which are currently not clearly understood. Heme oxygenase-1 (HO-1) has a central role in cellular antioxidant defence and tissue-protective action. This study explores the potential protective role of rosuvastatin on HO-1 as a regulatory target in vascular dysfunction. In cultured endothelial cells derived from human umbilical vein, rosuvastatin (3-100 μM) increased HO-1 mRNA and protein levels in a concentration-dependent fashion. HO-1 induction by rosuvastatin remained unaffected by mevalonate and L-NAME, precluding the involvement of isoprenoid- and NO-dependent pathways. Pretreatment of endothelial cells with rosuvastatin, at concentrations that were also effective at raising HO-1, reduced NADPH-dependent production of oxygen radicals. Antioxidant activity in endothelial cells persisted after rosuvastatin had been removed from the incubation medium. The HO-1 metabolite bilirubin, when added exogenously to the cells at low micromolar concentrations, virtually abolished NADPH-dependent oxidative stress. Rosuvastatin-induced inhibition of free radical formation was rescued in the presence of the HO inhibitor, tin protoporphyrin-IX (SnPP).
Our results demonstrate that HO-1 is a target site and antioxidant mediator of rosuvastatin in endothelial cells. This novel pathway may contribute to and in part, explain the pleiotropic anti-inflammatory and antiatherogenic actions of rosuvastatin.

ROSUVASTATIN REGULATES MIGRATION OF HUMAN VASCULAR SMOOTH MUSCLE CELLS VIA THE RHOA AND uPA/uPAR SYSTEMS

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Migration and proliferation of vascular smooth muscle cells (VSMC) play a pivotal role in vascular remodeling. A growing body of data from animal models and human subjects suggest that the serine protease urokinase (uPA) and its specific receptor (uPAR), are central to VSMC migration and proliferation processes. This study addresses possible non-lipid lowering effects of the HMG-CoA-reductase inhibitor, rosuvastatin, on the uPA/uPAR-related functions of human VSMC.

Treatment of VSMC with rosuvastatin significantly increased expression of uPA and uPAR, as shown by TaqMan analysis. Rosuvastatin stimulated VSMC migration in the modified Boyden chamber at concentration ranges from 25-50 nM and slightly inhibited VSMC migration at micromolar concentrations, whereas cell proliferation remained arrested. However, uPA-stimulated VSMC migration was not affected by rosuvastatin treatment.

We assessed the activation status of Rho proteins required for the uPA-directed cell migration using a pull down assay. Treatment of VSMC with rosuvastatin led to increase of GTP-RhoA content, but had no effect on Rac1 or Cdc42 expression. In agreement with pull down assay data, we observed an increased amount of RhoA associated with the membrane fraction of VSMC following rosuvastatin treatment. Addition of uPA to rosuvastatin failed to activate RhoA further. This supports the data for cell migration, and might be a result of preactivation of VSMC by endogenous uPA expressed in response to rosuvastatin.

To test the effects of rosuvastatin on neointima formation in the intact vessel wall, isolated endothelial-cell denuded porcine coronary arteries were used in an *ex vivo* model of vascular remodeling. The histological studies confirmed an impact of rosuvastatin on VSMC functional behavior, which might explain neointima reduction in response to rosuvastatin.

Our data demonstrate that rosuvastatin may exert its effects on vascular remodeling by regulating the fibrinolytic uPA/uPAR system in VSMC. The underlying molecular mechanism indicates the activation of uPA/uPAR expression in response to rosuvastatin that, in turn, leads to upregulation of GTP-RhoA, its intracellular redistribution to cell membranes and the stimulation of VSMC migration.

LIPID LOWERING RESPONSE OF PATIENTS SWITCHING FROM STATIN MONOTHERAPY TO EZETIMIBE CO-ADMINISTERED WITH SIMVASTATIN

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Patients who entered a 1 year extension study and received ezetimibe (EZE) co-administered with simvastatin (SIM) experienced an additional 23.7% reduction in LDL-C at 12 wks after simvastatin monotherapy. In this post-hoc analysis we explore the changes in lipid parameters for a subgroup of patients who switch from statin monotherapy in the primary study to EZE co-administered with SIM in the extension. Patients who completed a study of statin monotherapy versus EZE co-administered with statin were allowed to continue in a 1 year extension study. At completion of the initial study patients were switched to an approximately equipotent dose of SIM during a 6 wk run-in period. At completion of the run-in period, all patients were randomized (4:1) to receive EZE or placebo. Patients were monitored for lipid changes every 12 weeks for one year. The percent change in LDL-C, total cholesterol (TC), triglycerides (TG), and HDL from completion of the primary study to the 12 wk lipid evaluation in the extension study was estimated for patients who received statin monotherapy during the primary phase. Patients (n=134) who switched from statin monotherapy to EZE co-administered with an approximately equipotent dose of SIM experienced a 27.5%, 18.8%, and 10.1% reduction in LDL-C, TC, and TG respectively. HDL increased by 1.8%. Results were consistent across initial statin and SIM dose. These data provide information to clinicians on changes in lipid parameters for patients switching from statin monotherapy to combination therapy with SIM and EZE.

LIPID ALTERING EFFICACY OF EZETIMIBE COADMINISTERED WITH SIMVASTATIN COMPARED WITH ROSUVASTATIN: A META-ANALYSIS OF POOLED DATA FROM 14 CLINICAL TRIALS

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A meta-analysis of data from 14 randomized clinical trials that compared the effectiveness of two new options for cholesterol lowering was performed. Efficacy results from clinical trials with the coadministration or combination of ezetimibe 10 mg with simvastatin (ezetimibe/simvastatin 10, 20, 40, and 80 mg) were compared with efficacy results from clinical trials of rosuvastatin 5, 10, 20, and 40 mg on patients with primary hypercholesterolemia. This analysis compared pooled data for LDL-C, HDL-C, non-HDL-C, triglycerides, total cholesterol, apolipoprotein (apo) A-I, and apo B between the two drugs at their lowest doses (ezetimibe /simvastatin 10 mg , and rosuvastatin 5 mg) through their highest doses (ezetimibe /simvastatin 80 mg , and rosuvastatin 40 mg), and estimated percent changes in these parameters. LDL-C differences at common dose comparisons ranged from 3.6% to 4.6% lower for ezetimibe/simvastatin, and at the 80 mg dose comparison the difference was 2.3%. At each of the dose comparisons, estimates of reduction in non-HDL-C, total cholesterol, and apo B were generally 1.5 to 4.5 percentage points greater for ezetimibe/simvastatin than for the corresponding dose of rosuvastatin. Decreases in triglycerides and increases in HDL-C were generally comparable between treatments. Increases in apo A-I were generally higher for rosuvastatin than for ezetimibe/simvastatin. In conclusion, the results of this meta-analysis suggest greater LDL-C lowering with ezetimibe/simvastatin compared with rosuvastatin. These results need to be confirmed in a head-to-head comparison of both therapies.

EVALUATION OF THE SAFETY AND EFFICACY OF THE EZETIMIBE/SIMVASTATIN COMBINATION TABLET (E/S) VERSUS ATORVASTATIN (A) IN PATIENTS WITH HYPERCHOLESTEROLEMIA

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Guidelines recommend LDL-C <100 mg/dL in patients at high risk for CHD events, and recent clinical trials suggest that the optimal LDL-C may be well <100 mg/dL. This study was performed to test a hypothesis that E/S would provide superior efficacy to A for LDL-C reduction across dose ranges. This was a multicenter, double-blind, 6-wk parallel group study. 1902 patients with LDL-C exceeding NCEP ATP III CHD guidelines for their CHD risk categories were randomized equally to 8 arms: A10, 20, 40 and 80 (mg), and E/S 10/10, 10/20, 10/40, and 10/80 (mg). Baseline values were comparable across groups. After 6 wk, at each dose comparison, and averaged across dose ranges, patients on E/S showed greater reduction in LDL-C (47 to 59%) compared to A (36 to 53%). At E/S 10/40 vs. A40 and E/S 10/80 vs. A80, E/S provided significantly greater increases in HDL-C (3.8, 1.4% for A; 9.0, 7.6% for E/S). % reductions in TG were similar. There was significantly greater incidence of consecutive elevations in ALT and/or AST ≥3X ULN in the pooled A group (1.2%) compared with the pooled E/S group (0.1%, p=0.006). There were no myopathy-related (CK≥10X ULN and muscle symptoms) or liver-related AEs that lead to study discontinuation. In patients with hypercholesterolemia, E/S is an effective treatment with significantly greater LDL-C reductions at all mg-equivalent dose comparisons, and greater HDL-C increases than A at higher mg-equivalent dose comparisons with an excellent safety profile.

	A10	E/S 10/10	A20	E/S 10/20	A 40	E/S 10/40	A 80	E/S 10/80	All A	All E/S
	N=235	N=230	N=230	N=233	N=232	N=236	N=230	N=224	N=927	N=923
LDL-C										
% ch from base	-36.1	-47.1	-43.7	-50.6	-48.3	-57.4	-52.9	-58.6	-45.3	-53.4
p-Value		<.001		<.001		<.001		<.001		<.001
HDL-C										
% ch from base	6.9	7.7	5.1	7.2	3.8	9.0	1.4	7.6	4.3	7.9
p-Value		0.530		0.090		<.001		<.001		<.001
TG[1]										
% ch from base	-21.3	-25.5	-24.8	-25.4	-23.6	-27.3	-32.1	-30.8	-25.5	-27.4
p-Value		0.372		0.516		0.193		0.894		0.177

All A = A pooled across all doses All E/S = E/S pooled across all doses [1]% change from baseline and between-treatment differences for dose comparisons are LSmeans and differences in LSmeans, respectively.
[1]Triglycerides: Nonparametric results are presented.

SAFETY AND EFFECTIVENESS OF COMBINED TREATMENT WITH SIMVASTATIN AND FENOFIBRATE IN HIGH-RISK PATIENTS WITH MIXED DYSLIPIDEMIA

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PURPOSE: To asses the safety and effectiveness of combined treatment with simvastatin (S) and fenofibrate (F) in patients with mixed dyslipidemia and coronary heart disease (CHD) or multiple cardiovascular risk factors.
METHODS: Medical records from patients with combined therapy were reviewed, according to a profile of clinical and biochemical parameters.
RESULTS: 57 patients (p) (42 men, 53.6±10.4 years) were studied. 31p had diagnosis criteria of familial combined hyperlipidemia. Diabetes was diagnosed in 43 and HTA in 31p. IMC was >25 in 50p. CHD was documented in 21. Criteria to begin combined therapy were: a) CHD documented or cardiovascular risk factor association; b) Monotherapy had failed to control the dyslipidemia. Patients were informed about potential risks of combined therapy. In addition to a hypolipidemic diet, they received S and F. Serum ALT, AST and creatinine kinase (CK) were monitored. Patient-years on combination therapy equaled 138 (average 33.4 months per patient); 33 patients were treated for >1 year, 21 for >3y and 14 for >5 years. During hypolipidemic diet, the pre-treatment mean values (±SD) in mg/dl were: total cholesterol (TC) 325±66, triglycerides (TG) 626±439, HDL-C 39±8, nonHDL-C 280±66, apo B 205±52. At the 8th week modification of values was recorded: TC -26.9%, TG -55.5%, HDL-C +10%, nonHDL-C -31.8%. Changes were maintained at the last visit recorded, when 34p were taking 20 mg and 10p 40mg of S. Two patients left combined therapy because they had secondary effects: 1 gastrointestinal disturbances, 1 because myalgias without rise of CK. Another had transient myalgias that disappeared without leaving treatment. One left after an acute coronary event, 1 because therapy wasn't effective. No patient developed myopathy or liver disfunction. No significant rise of ALT, AST or CK was recorded. 79% patients reached C-HDL >35mg/dl, 15p TG <200, 11p TC <200, 19p nonHDL <190. Only 17% patients with CHD reached LDL-C <100mg/dl; 50% of these reached LDL-C <130, and 25% nonHDL-C <160mg/dl.
CONCLUSIONS: The combined administration of S and F is an effective and safe therapeutic choice for selected high risk patients with mixed dyslipidemia.

EFFICACY AND TOLERABILITY OF ORLISTAT AND SIMVASTATIN FOR THE TREATMENT OF DYSLIPIDEMIA ASSOCIATED WITH TYPE 2 DIABETES

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OBJECTIVE: Control of body weight and lipid parameters appears to be crucial for the prevention and treatment of type 2 diabetes. High triglyceride levels, low HDL cholesterol levels and predominance of atherogenic small, LDL subclasses, characterize diabetic dyslipidemia. In the present study, we investigate the efficacy and tolerability of Orlistat and simvastatin on the fasting lipid profile including LDL and HDL subclasses.
METHODS: During 12 months, double – blind, placebo – controlled trial, 104 patients were randomized to placebo (n = 34) or to 120 mg. Orlistat (n=20) or 20-40 mg simvastatin (n=46) Evaluated parameters were: BMI kg/m, HbA, lipid levels, blood pressure.
RESULTS: Simvastatin reduces concentrations of total cholesterol for 18% with 20 mg daily and34% to patients with 40mg daily. These reductions were significant higher than group of patients with placebo ($p<0,01$). Reductions of LDL particles was (19% to 39% $p<<0,01$) and reduces concentrations of triglycerides (7 % to 12%), HDL cholesterol levels were increased (6 % to 12%) vs. placebo significant. Patients treated with Orlistat had significant decreasing of body weight -9,4% vs. placebo -5,1%. Orlistat had significant effects on reduction of total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio ($p<0,001$). The values of glycosylated hemoglobin levels were reduced for 2% and blood pressure was decreased about 10-15 mmHg.
CONCLUISION: Simvastatin and Orlistad, the both confirmed efficacy and tolerability, no hepatotoxic effects or myopathy were observed. Reducing the risk factors such as hyperlipidemia, obesity, hyperglycemia and hypertension we will help prevent cardiovascular diseases to patients of diabetes.

SHORTENING THE TIME BETWEEN DISCOVERY AND DELIVERY. MODULATION OF MULTIPLE ATHEROGENIC RISK FACTORS WITH COMBINATION THERAPY DELIVERED IN A PRIMARY CARE SETTING IN 'CORONARY VALLEY'

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Brown et al. has shown combination therapy to reduce vascular events by 80 to 95% and death from those events by 90% [1,2,3]. 'Coronary Valley', i.e. Ky. and Tn., has the highest incidence of vascular diseases in the United States. Resistance to adopt combination therapy, as the standard of vascular care, results in less than optimal reduction in myocardial infarctions, strokes, angioplastic procedures, vascular stint placements, coronary artery bypass grafts, and deaths. A substantial time lag exists between the discovery and delivery of beneficial combination therapies to a significant number of patients. This report demonstrates how these benefits are currently being delivered in a primary care setting.

Brown et al.[1,3] values using:		Tapp Medical Clinic
triple- drug therapy	simvastatin + niacin	Study parameters
LDL-C - 106 mg/dL	75 mg/dL	< 60 mg/dL
HDL-C – 53 mg/dL	40 mg/dL	> 60 mg/dL
Trig – 134 mg/dL	126 mg/dL	< 60 mg/dL

Additional parameters include: 50 – 80% of the Total HDL in the large sub-fraction (H4 + H5); Sm. Dense LDL-C = 0 mg/dL; Total-C < 200 mg/dl; Lg. VLDL < 7 mg/dL; IDL = 0 mg/dL; LDL-C Particle No. < 700 nmol/L;LDL-C Particle Size –Pattern A (20.6 - 22.0 nm);LPa - < 10 mg/dL;Total Homocysteine < 9 mMol/L;Hs-CRP < 0.5 mg/L;ALT 10 – 60 IU/L;AST 10 – 42 IU/L.
All patients entered the study as they usually present to a primary care setting; i.e. regardless of medications or diagnoses (unless there was a contraindication). Appropriate blood profiles, including Nuclear Magnetic Resonance studies were performed. Treatments were specifically tailored to each of the patient's multiple risk factors. The various combinations employed to modulate the above listed parameters included: extended release niacin, extended release niacin-lovastatin, rosuvastatin, folacin/cobalamin/pyridoxine combination, eztimibe, and/or fenofibrate. A diet and a daily walk of forty-five minutes were also prescribed.
Conclusions: The time from discovery to delivery of beneficial combination therapies can be shortened and delivered in a primary care setting to optimally reduce vascular disease.

1. Brown BG et al. Circulation. 1998; 98 (suppl. l):1-635.Abstr 3341
2. Brown G et al. N Eng J Med. 1990;323:1289
3. Brown BG et al. N Eng J Med. 2001;345:1583

EFFECTS OF FENOFIBRATE AND EZETIMIBE ON LIPOPROTEIN SUBCLASSES AND LDL SUBCLASSES IN PATIENTS WITH MIXED HYPERLIPIDEMIA

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In a large, 12-wk, placebo-controlled trial, coadministered fenofibrate 160 mg/d and ezetimibe 10 g/d (FENO+EZE) produced complementary, beneficial effects on LDL-C (-20.4%), triglycerides (-44.0%), non-HDL-C (-30.4%), and HDL-C (+19.0%) levels in patients (pts) with mixed hyperlipidemia. This abstract includes effects of FENO and EZE, alone and coadministered, on lipoprotein subclasses. Cholesterol associated with individual lipoprotein subclasses was quantified with the VAP II method and LDL subclass pattern was determined with S_3GGE. Compared to placebo and EZE alone, treatment with FENO+EZE or FENO alone produced a redistribution of the LDL particle profile with a decrease in smaller, denser particles (e.g., LDL-C 4) and an increase in LDL-C 2. FENO+EZE resulted in significant reductions in LDL-C 1 and 3 beyond those obtained with FENO alone consistent with the greater overall LDL-C lowering. FENO+EZE also significantly reduced TG-rich lipoproteins including IDL-C and VLDL-C subclasses (not shown) vs. other treatments. At baseline, >70% of pts exhibited the small, dense LDL pattern B profile. At endpoint, 65% of pts in the FENO+EZE and FENO alone groups were shifted to the larger, more buoyant LDL pattern A. Thus, in addition to improving lipids and lipoproteins, FENO+EZE produced favorable effects on atherogenic lipoprotein subclasses and LDL subclass pattern in pts with mixed hyperlipidemia.

	Placebo (N = 59)	EZE (N = 167)	FENO (N= 171)	FENO + EZE (N = 171)
	(%)[1]	(%)[1]	(%)[1]	(%)[1]
IDL-C	10.0[a]	-23.8[a]	-27.0[a]	-44.0
LDL-C 1	6.3[a]	-14.0[a]	-8.0[a]	-24.9
LDL-C 2	-1.4[a]	-2.2[a]	108	80.8
LDL-C 3	1.8[a]	-6.6	-5.3[a]	-14.3
LDL-C 4	18.1[a]	-12.3[a]	-62.2	-67.3

[1]Change = Median percent change; [a]$p<0.01$ compared FENO + EZE

ELEVATED SERUM CONCENTRATIONS OF PLANT STEROLS DURING TREATMENT WITH ATORVASTATIN DECREASE PROGRESSIVELY DURING 1-YEAR CO-ADMINISTRATION OF EZETIMIBE

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It has been shown that long-term treatment with atorvastatin increases the absolute and relative (ratio to cholesterol) concentrations of serum plant sterols in patients with coronary heart disease (CHD) [1]. The aim of the present study was to investigate the effect of 1-year treatment with ezetimibe (10 mg/d), an inhibitor of intestinal sterol absorption, on the serum plant sterols campesterol and sitosterol in patients on long-term treatment with atorvastatin (40 mg/d).
In 10 patients with hypercholesterolemia baseline levels of serum sterols before treatment with ezetimibe were determined by the mean sterol concentrations of three serum samples taken from each patient within a period of 6-18 months during treatment with atorvastatin. Under monotherapy with atorvastatin campesterol and sitosterol baseline concentrations (mean ± SEM) as well as their ratios to cholesterol were markedly elevated and averaged 1.72 ± 0.29 mg/dl, 0.85 ± 0.13 mg/dl, 7.80 ± 1.41 µg/mg cholesterol, and 3.74 ± 0.52 µg/mg cholesterol, respectively. Co-administration of ezetimibe to the ongoing atorvastatin treatment significantly reduced campesterol and sitosterol in a progressive manner during the 1-year treatment. The mean relative reduction of campesterol and sitosterol levels vs. baseline levels was 54 ± 3% and 54 ± 4% after 1 month, 66 ± 3% and 65 ± 3% after 6 months, and 69 ± 3% and 65 ± 3% after 12 months, respectively (all p <0.001). Their ratios to cholesterol showed a similar decline (46 ± 4% and 46 ± 5% after 1 month, 60 ± 4% and 59 ± 5% after 6 months, and 66 ± 4% and 62 ± 4% after 12 months, respectively, with p <0.001 for all).
Reduction of plant sterol absorption by ezetimibe lowers elevated plant sterol serum concentrations during atorvastatin treatment to normal levels within 1-year treatment. The present results suggest that atorvastatin increases serum plant sterol concentration by enhancing their absorption rates, which are compensatory reduced by the addition of ezetimibe.

[1] Miettinen et al. J Lab Clin Med 2003;141:131-7.

OLMESARTAN AND PRAVASTATIN ADDITIVELY REDUCE DEVELOPMENT OF ATHEROSCLEROSIS

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Angiotensin II receptor (ATIIR) blockers are recognized primarily for their use in hypertension, in heart failure, and after myocardial infarction. Emerging clinical data indicate that ATIIR blockers may possibly modulate atherosclerosis as well. The present study was designed to evaluate the effects of the ATIIR antagonist olmesartan (10 mg/kg body weight (bw)), the cholesterol-lowering drug pravastatin (4 mg/kg bw) and the combination of both on the development of atherosclerosis in APOE*3-Leiden transgenic mice, a well-established mouse model for hyperlipidemia and atherosclerosis, during an intervention period of 25 weeks at an average plasma cholesterol and triglyceride level of 17 and 1.5 mmol/L. Pravastatin and pravastatin + olmesartan decreased plasma cholesterol and triglycerides by ~17% (p<0.05) and ~36% (p<0.001), respectively. Olmesartan and olmesartan + pravastatin reduced systolic blood pressure by 16% (p<0.002) and 12% (p<0.01), respectively. The atherosclerotic lesion area in the aortic root was significantly reduced by pravastatin (39%, p<0.03), by olmesartan (46%, p<0.02), and by combined treatment with olmesartan and pravastatin (91%, p<0.001). The combined treatment also resulted in a strongly reduced lesion number, lesion size, severity of lesions, number of smooth muscle cells and number of macrophages per cross-section as compared to the control group, with the olmesartan and pravastatin groups in between. In all drug treated groups, the general inflammation marker serum amyloid A was reduced to the same extent (~40%, p<0.05). Notably, the number of monocytes adhered to the activated endothelium was markedly (25%, p<0.02) reduced in the olmesartan- and olmesartan/pravastatin-treated groups only. In conclusion, combination treatment with olmesartan and pravastatin showed an additional effect of the two drugs on retarding atherogenesis, reflecting their different anti-atherosclerotic mode of action.

CONCOMITANT THERAPY WITH DILTIAZEM HAS NO EFFECT ON THE LIPID-LOWERING RESPONSE TO SIMVASTATIN IN CHINESE SUBJECTS

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Diltiazem is an inhibitor of cytochrome P450 3A4 that increases the serum concentrations of simvastatin and simvastatin acid after single doses of simvastatin. We performed this study to investigate the impact of the simvastatin-diltiazem pharmacokinetic interaction on the lipid-lowering effects of simvastatin. The study was a randomized, open-label, crossover study conducted in 30 Chinese patients with mild to moderate hypercholesterolaemia. Patients received simvastatin 20 mg once daily alone or together with diltiazem 60 mg thrice daily for 4 weeks with a washout period of 4 weeks. Blood pressure, fasting serum lipid profile, liver function tests and creatine kinase were determined at baseline and after each treatment period. Trough serum concentration of diltiazem was measured at the end of the 4-week combination simvastatin-diltiazem study phase.
The mean reductions in serum LDL cholesterol with simvastatin alone or in combination with diltiazem were almost identical ($P > 0.05$), both being 41%. There were also no significant differences in the changes in total cholesterol, HDL cholesterol and triglycerides between the two treatments. The mean trough serum diltiazem concentration was 85.0 ± 37.1 ng/mL. The differences in reduction of serum LDL cholesterol showed a weak positive correlation with the trough serum diltiazem concentration ($R^2 = 0.165$, $P = .044$) so that higher concentrations tended to be associated with greater reductions in LDL cholesterol. In conclusion, co-administration of diltiazem 60 mg thrice daily with simvastatin 20 mg daily had no significant effect on the changes in lipid parameters in these Chinese subjects.

METABOLIC PROPERTIES OF OPEN ACID FORM AND LACTONE FORM OF STATINS

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To gain a better understanding of the metabolic properties between the open acid and lactone form of HMG-CoA reductase inhibitors (statins), the investigation focused primarily on characterizing the metabolic properties of statins. We compared the metabolism of the acid form and lactone form of several statins, such as atrovastatin, cerivastatin fluvastatin, simvastatin and pitavastatin in regard to metabolic clearance, CYP enzymes involved and drug-drug interactions. The metabolic switching of CYP between acids and lactones was noted in the metabolism of cerivastatin, fluvastatin and pitavastatin. CYP2Cs were critically involved in the metabolism of these acids. In contrast, CYP2Cs were not involved in the metabolism of these lactones and CYP3A4 was closely involved. Also, a remarkable increase of metabolic clearance was noted in all lactones except for pitavastatin lactone. Moreover, quite a difference in the metabolic inhibition of statins was found between acids and lactones. These results reminded us to pay close attention to the metabolic properties of lactones. The present study demonstrates that CYP-mediated metabolism of lactones is also a common metabolic pathway for statins and CYP3A4-mediated metabolic properties of lactone form clearly will need to be taken into account in assessing mechanistic aspects of drug-drug interaction involving statins.

STATINS THAT INHIBIT CYP 450 3A4 MAY INCREASE GAMMA-TOCOPHEROL
WHEN MR HYDE TURNS INTO DR JEKILL

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In oxidative stress, superoxide anion reacts with NO producing peroxynitrite, putatively involved in atherogenesis. Pleiotropic effects of statins include inhibition of free radical production, reduction of lipoprotein oxidation and increased NO synthesis. We hypothesize that statins with inhibitory activity on CYP 450 3A4 may increase plasma levels of the effective peroxynitrate scavenger gamma-tocopherol (g-T), which is itself metabolized by this CYP isoenzyme. Aim of this study was to compare the effect on plasma levels of g-T of a statin (simvastatin:S) possessing CYP450 3A4 inhibitory activity with that of another statin devoid of this activity (pravastatin:P), administered at equipotent LDL-C lowering doses. Patients with high LDL-C levels according to ATP III were randomly allocated to S 20 mg/d (n = 9) or P 40 mg/d (n = 8). Plasma levels of lipids and alfa tocopherol (a-T) and g-T were determined at baseline and after six weeks of treatment.
Results: LDL-C levels in the groups were similar at baseline and both statins induced significant and equipotent LDL-C reductions (45±14 % vs 49±11 %, p NS). S significantly increased g-T (31±14%, p=0.05) and reduced the ratio a-T/g-T (-22±8%, p=0.02), without significant variation of a-T. On the contrary, P was associated with non significant changes in g-T (-23±11%) and the a-T/g-T ratio (22±13%). Intergroup differences were significant for g-T (p= 0.01) and a-T/g-T ratio (p=0.02) but not for a-T. No significant correlations were found between LDL-C reduction and g-T changes. In conclusion: simvastatin but not pravastatin increases g-T, presumably as a result of inhibition of the activity of the CYP 450 3A4. CYP – statin interactions, usually considered for their role in the risk of toxicity by drug associations, may thus theoretically turn into a favourable pharmacodynamic action.

MUSCLE-RELATED ADVERSE EFFECTS ARE COMPARABLE WITH ATORVASTATIN VERSUS PLACEBO IN 1660 PATIENTS

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Serious muscle-related adverse effects of statins are rare; however, concern about the potential for muscle side effects represents a barrier to appropriate treatment of dyslipidemia. While creatine phosphokinase (CPK) elevations and muscle symptoms are perceived to be dose-related, there is limited published information correlating small changes in CPK levels with muscle symptoms. The present analysis describes the incidence of CPK elevations, myalgia, and myopathy in the RESPOND trial, a placebo (PBO)-controlled, double-blind, 8-week trial of fixed doses of atorvastatin (ATV) and amlodipine in 1660 dyslipidemic patients with hypertension. Patients were randomized to combination treatment with amlodipine (PBO, 5 mg, 10 mg) and ATV (PBO, ATV 10 mg, 20 mg, 40 mg, or 80 mg). Data are reported here for patients by ATV dose irrespective of amlodipine dose. Incidences of CPK elevations and myalgia were low, were comparable to the PBO group, and did not increase across the ATV dose range (see table). CPK levels rose to >2x upper limit of normal (ULN) in <3% of the patients in any treatment group. CPK levels >5x ULN were seen in 2 patients in the PBO group; 1 of these patients had a CPK level >10x ULN. Only 2 patients with elevated CPK levels (>2x, but <5x, ULN) developed myalgia, 1 each in the 10-mg and 20-mg ATV treatment groups. No cases of myopathy were seen. In conclusion, contrary to the perception that muscle-related adverse events increase with statin dose, there was no relationship between the development of muscle-related adverse events and ATV dose in this study.

Percentage of Patients Experiencing Muscle-related Adverse Events

	PBO	ATV 10 mg	ATV 20 mg	ATV 40 mg	ATV 80 mg
CPK >2× ULN	2.8	2.9	1.9	1.3	2.2
CPK >5× ULN	0.6	0	0	0	0
Myalgia	1.5	0.9	2.1	1.5	2.1

FENOFIBRATE RESULTS IN FEWER REPORTED CASES OF RHABDOMYOLYSIS THAN GEMFIBROZIL WHEN USED IN COMBINATION WITH ANY STATIN

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The complementary effects of HMG-CoA reductase inhibitors (statins) and fibric acid derivatives (fibrates) have led to increasing use of statin/fibrate combination therapy, particularly for those patients with mixed dyslipidemia. Clinical experience indicates that there may be an increased risk of myotoxicity associated with fibrate/statin combination therapy. However, it is not known whether there are differences in the rate of myotoxicity between the use of fenofibrate and gemfibrozil in combination with statins. To evaluate this, data from the Food and Drug Administration's Adverse Event Reporting System was reviewed to determine how many adverse events were reported for patients treated concomitantly with fibrates and statins. Using these data, the number of reported cases of rhabdomyolysis per million prescriptions dispensed was calculated. Differences were found in the reporting rate of rhabdomyolysis for fenofibrate and gemfibrozil. When used in combination with cerivastatin, the number of cases of rhabdomyolysis reported per million prescriptions dispensed was approximately 33-times lower for fenofibrate than for gemfibrozil. When used in combination with statins other than cerivastatin, the number of cases of rhabdomyolysis reported per million prescriptions dispensed was approximately 15-times lower for fenofibrate than for gemfibrozil. These findings suggest that the use of fenofibrate in combination with statins results in fewer reported cases of rhabdomyolysis per million prescriptions dispensed than the use of gemfibrozil. Therefore, when considering concomitant use of a fibrate and a statin, these data suggest that it may be safer to use fenofibrate rather than gemfibrozil.

ACUTE RHABDOMYOLYSIS: ROLE OF ACUTE SERIOUS ILLNESS OR A DIRECT STATIN SIDE EFFECT? CASE ILLUSTRATION

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Aim: Illustration of an event of a probable acute rhabdomyolysis, which occurred after resuscitation during a hospitalisation for chronic heart failure. Do serious illness and concomitant therapy, causing drug interaction, interfere with statin metabolism? What afterwards: should we continue to treat a highly at risk patient with a statin?
Patient, Methods and Results: A 58 years old Type 2 diabetic woman with a 25 year history of diabetes and the subsequent late complications: peripheral occlusive angiopathy, diabetic neuropathy, diabetic foot and toe amputation due to thermic trauma, ischaemic heart disease and silent non Q myocardial infarction (March 2003), has taken statins (simvastatin) for the last 4 years.
In January 2004, the patient was referred to cardiology department because of a chronic, predominantly right-sided heart failure with an EF of 0.40 and pain in proximal leg muscles. At that time she was taking the subsequent therapy: DIA 6,7 MJ diet, 30/70 insulin mixture in the morning and gliquidon at evening, acarbose 300 mg daily, simvastatin 40 mg, fosinopril 10 mg, carvediol 50 mg, spironolactone 25 mg, furosemide 40 mg. During the hospitalisation, she suffered from a cardiac arrest due to electromechanic dissociation and she was successfully resuscitated. As a consequence, a rise in CK to 350 micro Kat/L, myoglobin to 19700 micro g/L, AST to 18,7, ALT to 17,0, LDH to 31,2 micro Kat/L, cTi to 0,24 micro g/L were detected, renal function tests were normal. After 3 days the lab tests were: AST 10,8, ALT 12,3, CK 126, myoglobin 8600, LDH 17,4. After 6 days: LDH 9,0, CK 0,29, myoglobin 104, cTi 0,04. Muscle biopsy showed no distinctive pathology. Lipid values before the event (on 40 mg simvastatin treatment) were: total cholesterol: 4,01; HDL-C: 1,15; LDL-C: 2,39; TG 1,60 mmol/L and after (no statin): 4,66; 1,26; 3,15; 0,76. Doppler perfusion pressure was measured and ankle/brachial index was calculated on dorsal pedal 0,78; 0,69 and tibial posterior arteries 0; 0,56, on left and right side, respectively.
Conclusions: Type 2 diabetics are at higher risk for micro and macrovascular events, therefore a complex, multi-drug treatment is necessary. Even after an occurrence of rhabdomyolysis, a possible statin treatment side effect, the statin treatment is still supposed to be continued in such patients. The rise of previously mentioned laboratory values could be a consequence to chest/heart trauma because of resuscitation as well as to drug interactions during the course of the therapy. Since the muscle biopsy shows no pathology, there is no strict evidence of rhabdomiolysis because of a statin.

A NOVEL ACAT-1 INHIBITOR, K-10191 REDUCES MACROPHAGES IN HIGH CHOLESTEROL-FED RABBITS WITHOUT AFFECTING PLASMA CHOLESTEROL LEVELS

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Objective: We have developed a new and selective inhibitor for Acyl-CoA: cholesterol acyltransferase (ACAT)-1, K-10191. The aim of this study was to evaluate the effect of K-10191 on the atherosclerotic legions in rabbits.
Methods: K-10191 (0.3, 1, and 3 mg/kg, bid) was orally administered to 1% cholesterol-diet fed NZW rabbits for 8 weeks. After necropsy, plasma lipids were measured and quantitative morphometric analysis of atherosclerotic legions was conducted.
Results: The mean plasma TC level was about 2000 mg/dL in control and K-10191 did not influence the level at every dose. Macrophages in atherosclerotic legions densely distributed at almost all of the lesions in control microscopically. The results of image analyses indicated the percentages of the composition of macrophages in atherosclerotic legions were 67.0, 62.5, 44.0 and 36.1% (in average at control and K-10191 0.3, 1 and 3 mg/kg, respectively), and among them, the values in the case of 1 and 3 mg/kg K-10191 were significant. K-10191 showed a dose-dependent suppression of macrophage accumulation within the lesions. Macrophage size and number were also reduced by K-10191 treatment. Moreover, both 1 and 3mg/kg K-10191 significantly showed the decrease in monocyte chemoattactant protein (MCP)-1 positive area (37% and 61%).
Conclusion: From above results, K-10191 suppressed the accumulation of macrophages in the atherosclerotic legions. The reduction of macrophage area seemed to depend on the reduction of cell size and number. As K-10191 did not influence the levels in plasma lipids, the inhibition of ACAT may directly alter the progression of the atherosclerotic legions by limiting its macrophage enrichment. Our observations on atheroma in rabbits provide important support for a component of lipid-independent mechanism of benefit in K-10191 treatment.

A NOVEL ACAT INHIBITOR, K-10191 DISPLAYS A SELECTIVE INHIBITION FOR ACAT-1 IN VITRO AND AN ANTI-ATHEROSCLEROTIC EFFICACY WITHOUT AFFECTING PLASMA LIPID LEVELS ON HIGH-FAT FED HAMSTERS.

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Acyl-coenzyme A:cholesterol acyltransferase(ACAT) is a key enzyme in reconstructing acylated cholesterols within cells, but causes foamy macrophages to induce atherosclerotic lesions. We designed a novel inhibitor of ACAT, K-10191 and examined the biochemical and pharmacological profiles of the compound in vitro and in vivo. We used two types of CHO cells that independently express human ACAT-1 or 2 from Dr. T.Y.Chang to show the selective inhibition for ACAT-1 in 66.2-fold (IC50 for ACAT-1, 40.9 and for ACAT-2, 2710 nmol/L, respectively). K-10191 also inhibited ACAT activity of human monocytic macrophages (IC50, 95 nmol/L). In mouse J774 and human THP-1 macrophages, the accumulation of cholesteryl ester by acetyl-LDL was dose-dependently suppressed (IC50, 59 and 32 nmol/L, respectively). Moreover, K-10191 dose-dependently increased the efflux of cholesterol to HDL in THP-1 cells as low as 10 nM. In high-fat fed hamsters, K-10191 was mixed with the diet (0.3% cholesterol and 10% coconut oil) to show the suppression of lipid accumulation on aortic wall selectively. The mixed-diet was loaded to BioF1B hamster for 10 weeks to cause fatty streaks. K-10191 suppressed the formation of fatty streaks dose-dependently and significantly at 1-10mg/kg without affecting the levels of plasma lipids. From above results, K-10191 possesses a selective inhibitory activity for ACAT-1 and improved the atherogenecity in vitro as well as in vivo. Therefore, K-10191 is considered to be very promising at showing an anti-atherosclerotic activity without affecting plasma lipid levels.

A NOVEL ACAT-1 INHIBITOR, K-10191, ACCELERATES PLAQUE STABILIZATION IN APOE KNOCKOUT MICE

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Objective: The pharmacological profile of K-10191, a novel and selective inhibitor for acyl-CoA: cholesterol acyltransferase (ACAT)-1 was evaluated in the atherosclerosis model in apoE knockout mice. Our interest was focused on the plaque composition histopathologically by the treatment of K-10191.
Methods: K-10191 or CI-1011 (both 100mg/kg bid, for 12 weeks) was orally administered to apoE knockout mice aged 8 weeks. At the end of the administration, total plasma lipid levels were measured enzymatically, and quantitative morphometric analysis at aortic sinus was conducted.
Results: Both K-10191 and CI-1011 significantly reduced the plasma TC (16.6 and 43.9%, respectively). In the control group, a large number of foamy cells were observed in atherosclerotic lesions, and the extracellular matrix accumulation including collagen was slightly observed at the bottom of plaque. CI-1011 showed the tendency to increase the occupied area of macrophage (32.5%), and decreased those of collagen fibers (27.0%) and smooth muscle cells (28%). K-10191 decreased the occupied area of macrophages (39.8%), and increased those of collagen fibers (55.2%), but did not affect the occupied area of smooth muscle cells. The reduction in macrophage area by K-10191 treatment reflected a change in the cell size and number.
Conclusions: In the present study, K-10191 showed the direct antiatherosclerotic effect to stabilize the plaque in apoE knockout mice, compared with CI-1011. These interesting results imply a similar strategy may have therapeutic promise in patients for coronary heart disease (CHD) events resulting from plaque rupture.

SMP-797, A NEW CLASS OF HYPOLIPIDEMIC DRUGS, INHIBITED ACAT ACTIVITIES AND ENHANCED LDL RECEPTOR ACTIVITY

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SMP-797 is a novel hypolipidemic drug that inhibits acyl coenzyme A: cholesterol acyltransferase (ACAT) activities and increases the activity of low-density lipoprotein receptor (LDL-R). In this study, we investigated the pharmacological profile of SMP-797 in vitro and in vivo.
SMP-797 inhibited the ACAT activities in several human cell lines and the IC_{50} values were 31- 270 nM. In addition, SMP-797 increased the activity of LDL-R in HepG2 cells at 10-1000 nM. The effect of SMP-797 on the LDL-R activity was as potent as that of atorvastatin, an HMG-CoA reductase inhibitor, however, SMP-797 had little effect on *de novo* cholesterol synthesis and mRNA level of LDL-R. The combination of SMP-797 with atorvastatin enhanced the LDL-R activity more potently than either agent alone did. These results suggest that SMP-797 regulates the activity of LDL-R at the post-translational level, different from the mechanism of action of statins. In cholesterol-fed hamsters, 1-week oral administration of SMP-797 lowered the LDL-cholesterol level by 30 - 42 %, dose-dependently (0.3-3 mg/kg) and increased the fractional catabolic rate of LDL 3.2-fold at 3 mg/kg. The data suggest that the increase in plasma LDL clearance contributes to the hypolipidemic action of SMP-797.
In conclusion, SMP-797 is a potent ACAT inhibitor and also potent LDL-R up-regulator, which may be valuable for the treatment of hyperlipidemia and atherosclerosis.

THE ENDOCANNABINOID (ECB) SYSTEM: A NEW PLAYER IN THE REINFORCEMENT AND ENERGY CONTROL FUNCTIONS

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Endocannabinoids (ECBs) and in particular anandamide and 2-arachidonoylglycerol are endogenous lipids capable of binding to, and subsequently activating, the 2 cannabinoid (CB) receptors CB_1 and CB_2. These receptors belong to the G-protein–coupled family receptors and they were discovered in the early 1990s while investigating the molecular mode of action of the principal psychoactive component of *Cannabis*, Δ^9-tetrahydrocannabinol, to which they bind with high affinity. CB_1 is the most widespread CB receptor in mammalian tissues, with the highest concentrations in some brain areas, but also present in many other peripheral organs, including the adipose tissue, gastrointestinal system, the airways, the reproductive organs, and the cardiovascular system. Stimulation of the CB_1-receptor by its agonists, including the ECBs, leads to inhibition of neurotransmitter release in central and peripheral (both autonomic and sensory) neurons. In non-neurons, several functions have been associated with CB_1 stimulation, including the regulation of proliferation, differentiation, motility, and apoptosis, possibly through modulation of the expression of various growth factors. ECBs are biosynthesized subsequent to the Ca^{2+}-dependent remodeling of membrane phospholipids, followed by the enzymatic hydrolysis of specific lipid precursors. This means that ECBs are not stored in neurons prior to their release, but are rather released "on demand" immediately after their *de novo* biosynthesis. In other words, the basal levels of ECBs are barely detectable as they are produced only "when and where needed," to be then rapidly inactivated by hydrolytic enzymes. Regarding their possible biologic function, the general picture emerging from studies carried out during the last 10 years is that ECBs are produced, and CB_1 receptors stimulated, in response to stressful stimuli to help establish the steady state homeostasis of other neurotransmitters, mediators, hormones, and cytokines. Therefore, CB_1-receptor stimulation is short-lasting, limited to those cells or tissues that have been subjected to stress or damage, and normally ends once the organism has recovered from a transient "unbalanced" condition. However, some chronic pathologic states lead to long-lasting overstimulation of ECB synthesis (or hypo-stimulation of their degradation), resulting in permanent overactivation of CB_1 receptors, which may then contribute to the symptoms of these disorders. The ECB system is present in brain and peripheral sites involved in the control of energy balance and body weight, as well as in neurons of the mesolimbic system that participate in reinforcing reward and in "translating motivation into action". At central nervous system level CB_1-receptors are necessary to induce food intake after a short period of food deprivation and when activated they also preferentially stimulate the ingestion of palatable food. Their stimulation leads to modulation of the release and/or expression of some hypothalamic anorexigenic and orexigenic mediators, as well as of dopamine in the nucleus accumbens shell. Importantly, at peripheral level CB1 activation has been shown to stimulate lipogenesis into adipocytes, and CB1blockers are important positive modulators of adiponectin secretion. These physiological properties of ECB and CB1, the pathologic consequences of an altered endocannabinoid tone, and its pharmacological management will be discussed.

A NEW GENERATION OF COMPUNDS ACTIV ON REGULATION OF DYSLIPIDEMIA LOWERING BOTH CHOLESTEROL AND TRIGLYCERIDES - SEQUENCIAL MICRONUTRITION

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Introduction:Current recommendations focus on the decrease of LDL-cholesterol which is considered as a major element in the primary and secondary prevention of cardiovascular diseases. The metabolism of lipids is a complex biological system. Bioresearch and Partners teams chose to approach this syndrome non-medicinally opening up the possibility of effective supplementary therapies. Bioresearch and Partners's objective is to exploit a new and original nutritional approach which preserves and strengthens the homeostasis in order to facilitate the regulation of the whole lipid metabolism which is always a question of balance between food intake, cellular assimilation and combustion: ie. reducing total cholesterol levels to physiological norms. Method:The trial aimed to measure, for patients in monotherapy in open study, the decrease of CT and the LDL-C, as well as the decrease of triglycerides (TG). The studied population presents, despite having been on diet for a month, an excess of CT 6.05 mmol/l, of LDL-C 3.9mmol/l and/or TG 1.69 mmol/l. The nutritional intervention has been runned during 12 weeks; the population treated by lipid-lowering agents or complemented by fish oil or stanols was excluded. The population was divided into 2 groups according to the type of hypercholesterolemia (combined or not).Results:In the population studied: 44 adults (19 male and 25 female), mean age: 61.3, presenting at D0 an average level of cholesterol of 7.23 mmol/l and LDL-C of 4.94 mmol/l, the objective results show an average decrease of 18% of CT and 24% of LDL-C in 77% (34 cases). In the group presenting combined hyperlipidemia (13 cases) with an average level of TG at D0 of 2.95 mmol/l, 77% (10 cases) record an average decrease of 37% of TG. Conclusion:Research is currently turning towards possible associations of lipid-lowering agents(2) in view of the prevailing preventive strategy which is due to an increase of the lipidic metabolic disorders, cardiovascular risks unsatisfactorily taken care of in the daily practice, variations of real efficacy and dose-dependent side-effects in relation to the molecules used. Nutrisequence offers a new generation of product which has its own mode of action, totally compatible with all other therapeutic modes (omega-3, stanols, statins, fibrates), and works on both cholesterol and triglycerides. It can be used in monotherapy, in primary prevention alone, or in association with any other hypolipidemic substances in the secondary prevention of cardiovascular diseases. It is an innovative nutritional option which can be used in tablet or integrated into food, thus faciliting the patient's acceptance and compliance.

EFFECT OF RIMONABANT ON METABOLIC MARKERS AND CHD RISK IN OVERWEIGHT/OBESE DYSLIPIDEMIC SUBJECTS: THE RIO-LIPIDS TRIAL

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Leptin and adiponectin are important markers of energy balance. Patients with visceral obesity and features of the metabolic syndrome have reduced plasma concentration of adiponectin. Rimonabant (R) is the first selective cannabinoid type 1 (CB_1) blocker and has been found to increase adiponectin mRNA expression in white adipose tissue of obese rats. RIO-Lipids, a randomized, double-blind, parallel-group, placebo-controlled, one-year treatment study was designed to assess the effect of rimonabant on weight loss/maintenance and is part of a large clinical development phase III program including 6600 overweight/obese subjects conducted to investigate the drug's effectiveness on body weight and obesity-related metabolic risk factors. Main inclusion criteria were BMI > 27 kg/m², untreated dyslipidemia with TG > 1.69 mmol/L and/or TC/HDL-C > 4.5 (female), > 5 (male) and fasting plasma glucose < 6.99 mmol/L. The primary efficacy outcome was the change in body weight at 1 year. Secondary efficacy endpoints were changes in TG, HDL-C, glucose and insulin levels during an oral glucose tolerance test (OGTT). Plasma leptin and adiponectin (in 150 subjects only) levels were measured at baseline and endpoint. After a 4-week, single-blind run-in period with placebo and hypocaloric diet, 1036 subjects, mean age 47.8 years, mean BMI 34.0 kg/m², mean weight 96.1 kg, mean waist circumference (WC) 107.1 cm, were randomized to receive a fixed once daily dose of rimonabant 5 mg (R5mg), 20 mg (R20mg) or placebo (P) with a mild hypocaloric diet for 52 weeks. R20mg induced a significant reduction in both body weight (-6.9 kg) and WC (-7.1 cm), such reductions being significantly greater than in the P group ($p<0.001$). During the OGTT, R20mg induced significant improvements in the overall plasma glucose and insulin responses as compared to placebo ($p<0.001$). R20mg significantly reduced leptin levels (mean difference -3.8 ng/mL, $p<0.001$ vs. P) and increased adiponectin levels (mean difference +1.6 µg/mL, $p=0.001$ vs. P). Changes in leptin levels produced by R20mg were correlated with weight loss ($r=0.45$, $p<0.0001$) whereas changes in adiponectin concentrations were related with changes in HDL-C levels ($r=0.42$, $p=0.0016$). R5mg results were either similar to those of P or intermediate to those of P and R20mg. Overall rimonabant was well tolerated.
These results suggest that rimonabant therapy could be useful for the management of clustering cardiovascular disease risk factors in high-risk abdominally obese patients through its marked effects on both abdominal adiposity and related metabolic risk factors.

APOPTOSIS OF FOAM CELLS INDUCED BY COPPER ION IN THE PRESENCE OF LDL: EFFECTS OF ANTIOXIDANTS AND ACAT INHIBITORS

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Oxidized LDL (oxLDL) has been reported to induce apoptosis in foam cells, which plays an important role in the progression of atherosclerosis. In the present study, THP-1 cells were differentiated to macrophages by the phorbol ester PMA (200 nM) in the presence of acetylLDL (acLDL) to form foam cells for 3 days, then washed and further incubated with acLDL and/or Cu^{2+} (5 µM). Combined treatment with acLDL and Cu^{2+} (acLDL/Cu^{2+}) but not acLDL or Cu^{2+} alone for 6 hrs caused caspase-dependent apoptotic changes in the foam cells. During treatment for 24 hrs, cells progressed to death with increased LDH leakage and Trypan Blue staining. Ascorbic acid (1 mM) prevented apoptosis and cell death during incubation with acLDL/Cu^{2+}. YM-750, a ACAT inhibitor had little effect on apoptosis but decreased intracellular esterified cholesterol and increased free cholesterol in surviving cells. YM-750 combined with ascorbic acid decreased esterified cholesterol without causing apoptosis. KY-455, an antioxidative ACAT inhibitor exerted the same effect as a combination of ACAT inhibitor and antioxidant: it prevented apoptosis and decreased esterified cholesterol. It is concluded that combination of an antioxidant and ACAT inhibitor or an antioxidative ACAT inhibitor could effectively prevent progression and promote regression of atherosclerosis.

INHIBITION OF LYMPHATIC CHOLESTEROL TRANSPORT IN RAT INTESTINE BY SCH 58053

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Ezetimibe is an inhibitor of cholesterol absorption and has been shown to decrease the cholesterol concentrations of hypercholesterolemic patients. To clarify the pharmacological mechanism of ezetimibe, SCH 58053, an analog of ezetimibe, was intraduodenally administered to lymph-fistula rats, and its effect on lymphatic lipid transport in the intestine was monitored. The main mesenteric lymph duct of rats was cannulated with clear vinyl tubing and silicone tubing was introduced into the duodenum through the fundus of the stomach. On the day after surgery, SCH 58053, 5.0 mg/kg body weight, was administered one hour before a infusion of a lipid emulsion containing 40 μmol/h of triolein and 2.74 μmol/h of cholesterol. SCH 58053 administration significantly inhibited lymphatic cholesterol transport, but not triglyceride transport, in the experimental rats compared to control rats that did not receive SCH 58053. The percentage of free cholesterol to total cholesterol in the lymph of the treated rats was unchanged compared to the control rats. Thus, the results showed that SCH 58053 is a rapid and selective inhibitor of lymphatic cholesterol transport in the intestine, and they supported the hypothesis that ezetimibe acts in the brush border membrane of enterocytes.

EFFECT OF A NON-ABSORBABLE SPECIFIC BILE ACID REABSORPTION INHIBITOR ON BILE ACID AND LIPOPROTEIN METABOLISM IN SYRIAN HAMSTER

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Interruption of the enterohepatic circulation of bile acids by lowering intestinal bile acid reabsorption is one approach to the treatment of hypercholesterolemia. The drugs available at present with this mechanism of action are anion-exchange resins and have to be taken in high doses three times daily. An alternative approach is to specifically target the ileal bile acid transporter (IBAT) with small molecules. HMR1453 is a non-absorbable bile acid reabsorption inhibitor (BARI) currently in development as new cholesterol-lowering drug. We investigated the effect of HMR1453 on bile acid, lipoprotein metabolism cholesterol synthesis and LDL receptor transcription in male Syrian hamster (Mesocricetus auratus, Han:Aura). The hamster is an established model for hyperlipidemia and can be used for prediction of in human active doses. Groups of 6 hamsters received cholesterol-enriched (0.1%) diet and were treated once or twice daily by gavage with 4 different oral doses of HMR1453 for 21 subsequent days. The primary objective of the study was to investigate whether the different doses are effective on bile acid excretion and cholesterol turnover after chronic oral treatment, the secondary objective was to predict the therapeutic dose and dose regime for therapeutic use. Bile acid excretion, liver cholesterol, 7 a-hydroxylase (Cyp 7 a) and liver LDL receptor activity were all dose dependently increased. Plasma LDL cholesterol was dose dependently decreased, up to 50 % below the level of animals on normal chow. Twice daily or administration with each meal is not necessary for therapeutic efficacy. The potency and ED_{50} are nearly the same when HMR1453 was administered twice daily or once daily.
The predicted daily dose for therapeutic use is in a feasible range and will be investigated in subsequent clinical trials.

EFFECTS OF A NOVEL DUAL LIPID REGULATING COMPOUND ON HEPATIC LIPID SYNTHESIS AND SECRETION *IN VITRO*

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ESP55016 is a novel ω-hydroxy-alkanedicarboxylic acid that improves serum lipid levels and enhances ketogenesis *in vivo*. ESP55016 inhibits *de novo* lipogenesis and increases fatty acid oxidation in cultured rat hepatocytes. We studied the changes in cellular and secreted lipids in response to ESP55016 alone or in combination with 500 μM oleic acid. Hepatocytes incubated without oleic acid accumulate triglycerides (TG) and cholesteryl ester (CE) during 24 hours of incubation. The lipid accrual was completely inhibited by 30μM ESP55016. Cellular free cholesterol content was unchanged. The masses of lipids secreted by cells corresponded to the cell lipid changes. ESP55016 reduced secretion of TG and CE by 90.6% and 40%, respectively. Incubations with oleic acid raised cellular masses of CE 3.2-fold and TG 7.8-fold over 24 hr. Addition of 30 μM ESP 55016 with oleic acid, reduced cellular CE content by 58% but did not change cellular TG, compared to incubations with oleic acid alone. Oleic acid addition increased TG secretion 5.1 fold over fatty acid-free incubations whereas CE secretion was unchanged. ESP55016 did not modify lipid secretion in the presence of oleic acid. Intracellular cholesterol levels were relatively unchanged by ESP55016 with or without oleic acid addition. Analyses of lipogenic rates by a 1 hr pulse with [^{14}C]-acetate showed ESP55016 inhibited nonsaponifiable lipid synthesis by 85% to 90% in the absence or presence of exogenous oleic acid. Nonsaponifiable lipid synthesis was not influenced by oleic acid addition under any condition. In contrast, oleic acid reduced label incorporation into saponifiable lipids by more than 60%, relative to tests without oleic acid. ESP55016 reduced saponifiable lipid synthesis by 30-80%, with or without oleic acid addition. In summary, ESP55016 inhibits *de novo* lipogenesis and enhances fatty acid oxidation with the consequence of diminishing the cellular accumulation and secretion of TG and CE. ESP55016 is most effective in reducing cellular CE storage in the absence or presence of exogenous fatty acid.

TREATMENT OF MASSIVE HYPERTRIGLYCERIDEMIA RESISTANT TO PUFA AND FIBRATES: A POSSIBLE ROLE FOR THE COENZYME Q10?

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Objective: to describe the effect of CoQ10 (added to either a fibrate, or PUFA or association of both) in patients affected by massive hypertriglyceridemia (MHTG) resistant to fibrates and PUFA. *Design:* Open, sequential, comparative intervention study. *Setting:* Specialised centres for dyslipidemia management. *Subjects*: 15 subjects (mean age: 45.1±12.5 years) affected by MHTG (TG>1000 mg/dL) and hyporesponsive to either fibrates, or PUFA, or fibrates-PUFA association (defined as TG reduction <20%), and 15 age-matched subjects regularly responders to PUFA and fenofibrate treatment. *Interventions:* Treatment for periods of 6 weeks each with the following consecutive treatments: CoQ10 150mg/day, PUFA 3000mg/day, fenofibrate 200mg/day, PUFA 3000mg/day + fenofibrate 200mg/day, PUFA 3000mg/day + CoQ10 150mg/day, fenofibrate 200mg/day + CoQ10 150mg/day, and finally, fenofibrate 200mg/day + PUFA 3000mg/day + CoQ10 150mg/day. *Results*: CoQ10 supplementation did not improve any monitored parameter in the control group except for systolic and diastolic blood pressure, creatinine and Lp(a) plasma levels, both during fenofibrate and/or PUFA treatment. In MHTG group, CoQ10 supplementation significantly improved TG, TC, Lp(a), uric acid and blood pressure during fenofibrate treatment, but only Lp(a) and blood pressure during PUFA treatment. Fenofibrate appeared to have better effect on hsCRP and -GT plasma levels than PUFA. No significant change was observed in any group and under any treatment in regards to homocysteinemia, PAI-1, or t-PA. *Conclusion*: Even though the mechanism of action through which the effects were obtained is yet to be elucidated, adding CoQ10 to fenofibrate could improve the drug's efficacy in MHTG patients not responding to fenofibrate alone.

SMP-797 A NOVEL LIPID LOWERING COMPOUND: SAFETY, TOLERABILITY AND PHARMACOKINETICS IN HEALTHY VOLUNTEERS

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SMP-797 exhibited novel pharmacology in pre-clinical studies that suggests a highly promising therapeutic profile, in the treatment of hypercholesterolaemia and atherosclerosis. *In vitro* SMP-797 is a potent inhibitor of human Acyl-CoA: cholesterol O-acyltransferase (ACAT) derived from liver, intestine and macrophage. In addition, SMP-797 increased the expression and activity of the LDL-receptor both *in vitro* and *in vivo*. The mechanism for this is believed to be independent of ACAT inhibition and distinct from that of HMG-CoA reductase inhibitors.

In first administration in humans SMP-797 was safe, well tolerated and exhibited slightly non-linear pharmacokinetics and a half life of around 6 hours in healthy male Caucasian volunteers up to the maximum administered oral dose of 5mg. Administration with food resulted in a reduction in both C_{max} and AUC.

In multiple dosing, the safety, tolerability and pharmacokinetics of 1mg and 3mg of SMP-797 administered orally once daily were evaluated over 28 days in healthy male Caucasian volunteers. Two groups of 12 subjects were dosed. In each group 8 subjects received SMP-797 and 4 subjects received placebo, the allocation of which was randomised and blinded. Safety was assessed by means of physical examination, measurement of heart rate and blood pressure, ECG and laboratory parameters. Overall, safety data indicates the drug to be well tolerated at both doses and pharmacokinetic data indicates that once daily dosing should be possible. Detailed safety and pharmacokinetic data from 2 studies will be presented. Progression to the first patient study is now planned.

THE AUDIT STUDY: REGIONAL VARIATIONS IN PHYSICIAN ATTITUDES TO DIABETIC DYSLIPIDAEMIA

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Patients with type 2 diabetes mellitus (T2DM) benefit from lipid-lowering therapy, but lipid treatment and goal attainment rates in clinical practice are poor. The Analysis and Understanding of Diabetes and Dyslipidaemia: Improving Treatment (AUDIT) Study was a confidential, web-based survey comparing worldwide clinical practice patterns in the evaluation and treatment of dyslipidaemia in T2DM. Diabetes specialists (n=2043) in 50 countries from 7 geographic regions participated. Physicians estimated that a mean of 62% of their T2DM patients have dyslipidaemia (range: 75% in N. America to 49% in Asia/Pacific). A lipid profile was obtained in 91% of all patients (range: 99% in N. America to 81% in E. Europe). Stated LDL-C, triglyceride and total cholesterol goals were lower for T2DM patients with CVD than those without CVD and varied among regions. More physicians had an LDL-C goal of 2.6 mmol/L for T2DM patients with CVD (85%) than those without CVD (59%). Physicians reported that only about 50% of patients achieve lipid goals. Estimated goal attainment rates were highest in N. America (range: 56% for triglycerides to 69% for LDL-C) and lowest in E. Europe (range: 43% for LDL-C to 47% for triglycerides). The most common perceived barrier to goal attainment was patient compliance in W. Europe, Scandinavia, N. America, and Asia/Pacific compared with financial constraint to product access in E. Europe, S. America, and Africa/Middle East. Guidelines had the greatest influence on lipid goals; the guidelines followed varied widely, with most physicians following their respective national guidelines. **Conclusion**: The AUDIT Study has revealed a disparity in dyslipidaemia management in T2DM patients with CVD vs those without CVD, suggesting that diabetes is not widely considered a CVD risk equivalent. Regional differences are apparent in lipid goals, barriers to goal attainment, and guidelines followed.

EFFECTS OF ROSIGLITAZONE ALONE AND IN ASSOCIATION WITH SIMVASTATIN ON LIPID AND LIPOPROTEIN PARAMETERS IN PATIENTS WITH METABOLIC SYNDROME

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The aim of our study is to evaluate the differential effects on lipid and lipoprotein parameters of rosiglitazone alone and in association with simvastatin in patients with metabolic syndrome according to ATP III recommendations. We evaluated 98 type 2 diabetic patients with metabolic syndrome, after an 8-week, open-label, run-in treatment phase with rosiglitazone, 8 mg/day and 94 were randomized to a 24-week, double-blind clinical trial (48 males and 50 females; 16 males and 17 females, aged 52±4 with rosiglitazone plus placebo; 15 males and 15 females, aged 53±5 with rosiglitazone plus simvastatin (20 mg/day), and 15 males and 16 females, aged 51±3 with rosiglitazone plus simvastatin (40 mg/day). All were required to have been diagnosed as being diabetic for at least 6 months, and did not have glycemic control only with diet and sulfonylureas. We evaluated lipid profile [total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and triglycerides (Tg)], lipoprotein parameters [apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B)], and LDL phenotype subfractions. With rosiglitazone alone, a modest increase in LDL-C, a shift in LDL phenotype from dense to large buoyant subfractions, and an increase in HDL-C, predominantly in HDL_2, occurred from week 0 to week 8. When simvastatin was added, there was an increase in HDL-C, in HDL_3, and in Apo A-I and expected significant reductions in LDL-C, Apo B, and Tg. We can conclude that the association of simvastatin to rosiglitazone treatment of diabetic subjects with metabolic syndrome is associated to an improvement in lipid and lipoprotein variables.

ARMOLIPID, A NUTRITIONAL SUPPLEMENT, EFFECTIVELY REDUCES PLASMA TOTAL AND LDL CHOLESTEROL IN MODERATE HYPERCHOLESTEROLEMIA.

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Aim of this study was to verify the effect of ARMOLIPID, a nutritional supplement, on plasma lipid and lipoproteins in a group of patients with moderate hypercholesterolemia. ARMOLIPID contains natural components such as policosanol, folic acid, monacolin and astaxantin.
25 subjects were asked to participate in this preliminary study, 12 received a placebo (P) and 13 the dietary supplement (A) after 4 weeks of dietary hypolipidaemic regimen. Plasma lipids were: total cholesterol 232±17 (A) and 227±19 (P), triglycerides 110±37(A) and 122±63(P), LDL cholesterol 160±19 (A) and 152(P), and HDL cholesterol 50±11 (A) and 51±10 (P) mg/dL respectively.
Plasma lipids and lipoproteins were evaluated at 15 (T1) and 30 days (T2) after the beginning of ARMOLIPID supplementation. Total cholesterol decreased by 17 and 15 % at T1 and T2 as compared to T0 and 13 and 12 % vs placebo(both $p<0,01$). LDL cholesterol decreased by by 23 and 22 % at T1 and T2 respectively as compared to T0 and 20 and 21 % vs placebo(both $p<0,01$). No statistically significant changes were observed for HDL cholesterol and plasma triglyceride levels. The biochemical parameter related to safety revealed no changes with the exception of a small and transient increase of AST (+15%) at T1 in the A group. No subject had, however increases > UNL. CPK values showed no changes. During the period of dietary supplementation the subjects reported no adverse effects with the exception of a single case of moderate GI distress that resolved spontaneously in a subject in the A group without stopping the assumption of the dietary supplement.
In summary these preliminary data suggest that ARMOLIPID effectively reduces plasma total and LDL cholesterol levels in subjects with mild-moderate hypercholesterolemia. Further studies are under way to confirm these findings also in different forms of dyslipidemia.

DIFFERENCES IN PATIENTS WITH LATTER ISCHEMIC CEREBROVASCULAR STROKE EPISODES WITH PROGRESS IMPROVEMENT OR DEATH

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Purpose: The aim of this study was to investigate the basic differences between patients with latter acute thrombolic or embolic stroke episode in Greek population, with progress death or improvement during of nursing.
Material and Methods: 589 inpatients with latter acute thrombolic or embolic stroke episodes, 318 females (F) and 271 males (M) aged 76±9,5 years were studied during the last three years. Investigated the lipid profile as Total Cholesterol (TC), Triglycerides (TG), HDL, and LDL, and recorded the sex, presence hypertension (B.P.), diabetes mellitus (D.M.), smoke and consumption alcohol, relative to progress between group death (D) and group improvement (I). All results were analyzed in the same laboratory.
Results: The lipids of groups was TC 216±58 I - 216±80 D mg/dl (p=0,22), TG 132±73 I - 123±71 D mg/dl (p=0,50), HDL 44±12 I - 46±14 D mg/dl (p=0,21), LDL 142±47 I - 138±45 D mg/dl (p=0,87). 77,8% from all patients had B.P. (75% I - 94% D, p=0,016), 43 % had D.M. (42% I-53% D, p=0,06), 24% smoke (22% I - 32% D, p=0,17) and 16% consumption alcohol (17% I - 13% D, p=0,56). The overall mortality was 16,6%.
Conclusion: The study shows that lipids, D.M., smoke and alcohol in group with improvement patients from latter thromboembolic stroke versus death have not difference statistically significant, while the hypertension are increased statistically significant in group of death.

DIFFERENCE BETWEEN MALE AND FEMALE PATIENTS WITH LATTER ISCHEMIC CEREBROVASCULAR EPISODES

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Purpose: The aim of this study was to investigate the difference between male and female patients with latter acute thrombolic or embolic stroke episode in Greek population.
Material and Methods: 775 inpatients with latter acute thrombolic or embolic stroke episodes, 412 females (F) aged 77±9 and 363 males (M) aged 74±9 years were studied during the last three years. Investigated the lipid profile as Total Cholesterol (TC), Triglycerides (TG), HDL, and LDL, relative to sex and recorded the presence hypertension (B.P.), diabetes mellitus (D.M.), smoke and consumption alcohol. All patients belong to our Internal Medicine Clinic and results were analyzed in the same laboratory.
Results: The lipid profile of female and male patients was TC 217±63 F - 212±58 M mg/dl (p=0,50), TG 132±71 F - 126±70 M mg/dl (p=0,60), HDL 46±12 F - 43±12 M mg/dl (p=0,99), LDL 139±47 F - 141±46 M mg/dl (p=0,89). 78 % from all patients had B.P. (76% F - 81% M, p=0,31), 43 % had D.M. (45% F - 42% M, p=0,48), 22,6% smoke (5% F - 46% M, p=0,00) and 16,5% consumption alcohol (3,4% F - 31,5% M, p=0,00)
Conclusion: The study shows that in patients with latter thromboembolic stroke the lipids, the hypertension and mellitus diabetes between female and male have not statistically significant, while the smoke and consumption alcohol are increased statistically significant in males.

FEMALE VS. TO MALE, CAD PATIENTS HAVE A GREATER PREVALENCE OF HYPERFIBRINOGENEMIA AND ELEVATED HS-CRP DESPITE NO DIFFERENCE IN NATIONAL LIPID GOALS.

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Introduction: The incidence of CAD is increasing in women. We hypothesized that in patients with CAD, women, compared to men, would have a higher incidence of metabolic risk factors other than LDL-C. We explored the prevalence of metabolic disorders in 549 consecutive CAD patients.
Methods: ATP lipid goals were defined as TG < 1.69, LDL-C < 2.59, HDL> 1.03 in men and > 1.29 mmol/L in women. Fasting total cholesterol and triglycerides were determined by enzymatic methods, HDL-C by precipitation and LDL-C by calculation. LDL peak particle diameter (PPD) was determined by S_3 polyacrylamide gradient gel electrophoresis. Lp(a), homocysteine (Hcy), fibrinogen, insulin, high sensitivity C-reactive protein (hs-CRP), and apo B by immunoassay.

Results:	Men (435)	Women (114)	p
TG > 1.69 mmol/L	31.0%	38.6%	0.13
HDLC < 1.03 (M), < 1.29 mmol/L (F)	46.9%	48.3%	0.12
LDLC > 2.59 mmol/L	34.3%	36.0%	0.73
Hs-CRP > 0.40 mg/dl	17.0%	32.9%	0.002
Fibrinogen > 400 mg/dl	25.2%	37.0%	0.03
LDL PPD < 257 Angstroms	46.1%	35.1%	0.03
Fasting Insulin > 12 uU/ml	30.8%	21.6%	0.09
Lp(a) > 25 mg/dl	24.4%	28.6%	0.37
THcy > 14 (umol/L)	10.7%	11.5%	0.79
HDL2b<20%M,<30%W	78.9%	85.5%	0.12

Conclusion: There is no difference in the prevalence of men or women who do not meet ATP-III lipid guidelines. The prevalence of the small LDL trait is high in both men and women with CAD. Compared to men, women have significantly more elevated hs-CRP, and fibrinogen, and, significantly less small LDL.

FEMALES RISK LESS BUT OVERESTIMATE THEIR RISK LEVEL.

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The FAO Medical Service, in collaboration with the CNR, has prepared a programme for the prevention of coronary heart disease (CHD) for its multinational staff working in Rome: males (M) 45 years of age and females (F) 50 years of age (<50 if in premature menopause). The programme has been conducted in several phases: collection of data via a questionnaire and screening; calculation of the individual CHD risk profile over the next 10 years using a computerized programme based on data from the Framingham Heart Study; identification of subjects with a high risk profile (risk level >20% in 10 years) or with multiple risk factors and inclusion in a programme of intervention. 30% of eligible staff members took part in the study (267 males and 204 females). The prevalence of risk factors was very high for overweight-obesity (M 65%, F 45%) and hypertension (M 38%, F 25%). Moreover, 16% of M vs 9% of F had 3 risk factor. On the contrary, only the 19% of M vs 60% of F had a high HDL-cholesterol. The calculated risk level was overall low-mild in F and mild-moderate for M. We asked the participating staff to assess their own overall CHD risk in the next 10 years: while M evaluated correctly their risk, F overestimate their risk level. For effective prevention the awareness of the existing risk factors and of the overall level of risk is a basic step. F, in different geographic and socio-cultural context, seems to appear more attentive of their health care.

THE RISK OF CORONARY HEART DISEASE IN HYPERCHOLESTEROLEMIC PATIENTS WITH DIABETES MELLITUS IN JAPANESE POPULATION – SUB-ANALYSIS OF THE J-LIT STUDY, A LARGE-SCALE COHORT STUDY

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[Object] Japan lipid intervention trial (J-LIT) was conducted to clarify the relationship between serum lipid levels and occurrence of coronary events (CE) in Japanese patients with hypercholesterolemia. Diabetes mellitus (DM) is stressed as the most important risk factor of coronary heart disease (CHD). We analyzed the results of J-LIT study, focusing on CHD risk in DM patients. [Methods] All patients were treated with low dose simvastatin (5 mg/day) for 6 years. Hypercholesterolemic patients with DM (n=6,543) and non-DM (n=35,258) in primary prevention cohort, and DM (n=878) and non-DM (n=3,721) in secondary prevention cohort were analyzed. CE as the primary endpoint was acute myocardial infarction or sudden cardiac death. [Results] In the primary and secondary prevention cohort, the average ages were 57.8±7.8 and 60.1±7.0 years old, and proportions of female patients were 68.4% and 57.8%, respectively. In the primary prevention cohort, the adjusted incidence of CE was 4.1/1,000 patient-6years in non-DM and 8.5/1,000 patient-6years in DM patients. In the secondary prevention cohort the incidence of CE was 15.1/1,000 patient-6years in non-DM and 34.3/1,000 patient-6years in DM patients. With each 10 mg/dL increase in LDL-C level during the treatment, the risk of CE for patients without prior CHD was increased by 19% (P<0.001) in non-DM and 18% (P<0.001) in DM groups, for patients with prior CHD that was increased by 10% (P<0.001) in non-DM and 6% (P=0.25) in DM groups. [Conclusion] The risk of CE in DM patients with prior CHD was 8 times higher than in non-DM patients without prior CHD We concluded that serum LDL-C level should be lowered strictly to prevent primary or secondary CE in hypercholesterolemic patients with DM as well as controlling blood glucose level.

POPULATION VALUES OF BLOOD LIPID PROFILE IN ADULT URBAN POPULATION OF SIBERIA (STUDY OF WHO-PROJECT «MONICA»)

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The aim of the study was to evaluate the population values of blood lipid profile in adult urban population of Western Siberia.
Design and methods: According to WHO-project «MONICA», a representative sample of men and women 25-64 years old in the two administrative districts of Novosibirsk was examined with 200 people in each ten-year age-related group. 9836 people on the whole were examined included 4899 men and 4937 women. The blood lipid profile parameters were determined by enzymatic biochemical methods.
Results: The average total cholesterol (CH) level was 5,6 mmol/l (220 mg/dl), LDL-CH – 3,8 mmol/l (146 mg/dl), triglycerides (TG) - 1,2 mmol/l (109 mg/dl), HDL-CH - 1,4 mmol/l (54 mg/dl), LDL-CH/HDL-CH ratio was 2,7 and non-HDL-CH/HDL-CH ratio – 3,0. The total CH and LDL-CH levels in men in the two first ten-year age-related groups were somewhat higher than in women. On the other hand, these indexes in men in the two elders' ten-year age-related groups were somewhat lower than in women (differences consequence, p<0,01). The frequency of hypercholesterolemia (HCH) according to the criterion total CH>5,0 mmol/l was present in 55% of men and 59% of women. The frequency of hypertriglyceridemia (TG>1,7 mmol/l) was present in 19% of men and 16% of women. The HDL-CH level <1,0 mmol/l was present in 22% of men and 11% of women.
Conclusion: In adult urban population of Western Siberia the population values of blood lipid profile were determined; high frequency of hypercholesterolemia was registered.

FREQUENCY OF DIABETES AND CARDIOVASCULAR DISEASE IN ELEVATED RISK GROUPS

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Background and Aims: The prevalence of diabetes was reported to be about 7.3% in Georgia, though this number is thought to be much higher. It is presumed that prevalence of impaired fasting glucose (IFG) and post-prandial glycemia (PPG) that may stay undiagnosed for years and comprise a risk factor for cardio-vascular disease (CVD) is also very high. DM and IFG develop more frequently in smoking, overweight, leading sedentary life people. The aim of the present work was to estimate the incidence and prevalence of diagnosed/undiagnosed type 2 diabetes (T2DM), IFG/PPG and CVD in a randomly selected typical population, of predominantly low physical activity, a large part of participants were smokers. In general, life-style in Georgia today is characterized by low physical activity, unhealthy diet and smoking habits. **Materials and Methods:** In total 96 lecturers/tutors of Tbilisi State University aged 36-75 yrs., (male/female – 63/33, mean BMI – 29kg/m², smokers/non-smokers – 44/52 were studied). Participants were questioned on family history of diabetes and presence of T2DM, CAD and other chronic diseases in anamnesis. Following tests: fasting and post-prandial glycemia (load with continental breakfast), ECG; and consultations: of endocrinologist, cardiologist and angiologist were carried out. Presence of diabetes was defined as a self-reported history of diabetes confirmed by use of insulin or oral hypoglycemic agents. **Results:** Eight persons (prs) had known diabetes, a self-reported diagnosis. Participants without prior diagnoses of diabetes were categorized in following groups: undiagnosed diabetes 2 prs (PPG – 337 and 244mg/dl); FBG >110 mg/dl in 4 cases; PPG >140 mg/dl in 5 cases. In all four groups BMI, fat%, waist circumference, waist-to-hip ratio and smoking status were determined. According to cardiological examinations 20 prs had CHD, 53 prs had hypertension >140/90mmHg; in 2 cases there was myocardial infarction in patients-history. One prs had stroke in anamnesis. Angiologic examination revealed presence of different vascular disorders. All prs with IFG and/or PPG or those having cardiovascular or angiologic problems were sent to specialized centers for further thorough clinical and laboratory investigations. **Conclusion:** According to the data obtained prevalence of diagnosed and undiagnosed T2DM, FBG and/or PPG as well as newly diagnosed T2DM and CVD might be much higher than it was previously reported for adult population of Georgia. This is the indicator of progressive rise of metabolic disorders in Georgia – the rise that was predicted for all developing countries in coming decades. These preliminary data underscore the urgency for continuing screening in randomly selected population and necessity to create a population-based diabetes-screening program. Besides, screening and prevention of mentioned conditions must be placed on top of the Health Care System priority list.

CARDIOVASCULAR RISK FACTORS AND PHYSICAL ACTIVITY IN OBESE URBAN TYPE 2 DIABETICS

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Background and Aims: The aim of this study was to assess the related with type 2 diabetes metabolic disorders and prevalence life-style in Central Asian urban diabetics.
Materials and Methods: We obtained the data from 9 Primary Care Service of the Tashkent city National Health system; information about known type 2 diabetes patients has been registered. In all subjects a personal history of diabetes, obesity, hypertension and macro vascular disease, fasting blood glucose level and physical activity were observed.
Results: 2291 patients with type 2 diabetic patients were registered. Mean age of patients was 63,06±10,25 years; mean time of diabetes evolution was 9± 4,1years, mean fasting blood glucose was 8,43±2,19 mmol/l. Hypertension (BP>135/80mmHg) was found in 65%, cardiac angina 52%, myocardial infarction 7%, cerebral vascular disease 11%, sedentary 41%. BMI>25 was found in 63,25 % diabetic patients, (27% of them with BMI>30), more frequent in women than in men (p<0,05). In patient with BMI>25 mean fasting blood glucose was 9,67±1,9 mmol/l. Most part of examined parameter was founded in obese patients: hypertension 64%, cardiac angina 63%, myocardial infarction 53%, cerebral vascular disease 65%, sedentary –71%.
Conclusions: Results from this study raises serious concerns from a public health perspective in Tashkent underlying needs to increase public awareness and to emphasize on life-style modifications.

PREVALENCE OF OBESITY, INFANT BREAST FEEDING AND PHYSICAL ACTIVITY IN HEALTHY FIRST GRADERS

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Background and aims
The PEP-Project (Prevention Education Program) in Nuremberg means preventing cardiovascular diseases only by lifestyle with healthy first graders and their families in an ongoing prospective study representative for this area including all elementary school districts.

Materials and Methods
287 first graders in the age 6 – 8 years participated in PEP in 2003(structured interview , the physical examination and exercise questionnaire (evaluated with SPSS).

Results
In the first graders were 147 girls and 140 boys. (In the age of 6 y were 74 boys and 87 girls, 7 years were 59 boys and 47 girls and in the age of 8 y we found 7 boys and 13 girls.)The mean BMI in the 6 y- old boys was 16,2 kg/m² (± 2,4), also in the girls. Mean BMI in the 7- y old boys: 16,2 kg/m2 (± 2,6) and in the girls: 16,6 kg/m² (± 3,0). Mean BMI in the boys of 8: 16,7 kg/m² (± 2,6) , in the girls: 17,4 kg/m² (± 2,4).
Normal weight, overweight and obesity was defined by TJ Cole.
In the female first graders we found: normal weight 68%,overweight 18% and obese 14%, in the male ones: 76% normal weight, 12% overweight and 12% obese.The best values we saw in the 7 y-old boys (80% of the them had normal weight).

Breast fed boys: normal weight 91% overweight 76% obese 78%
Breast fed girls: normal weight 83% overweight 97% obese 88%

Regular physical activities in their leisurure time had 50% of the normal weight with 1.5 times a week, 70 minutes per one activity (± 25 min each) vs. 47% and 44%.The normal weight girls'activities were (4 times a week/ a, 60 min (± 20 min each) 40% vs. 40% also and 38%.

CARDIOVASCULAR RISK FACTORS AND LIFESTYLE IN YOUNG HEALTHY ADULTS

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Backgropund and aims
In Nuremberg 1209 subjects/ 100 000 inhabitants died from ischemic heart disease (ICD 10 120-125) in 2000. We wanted to assess the prevalence of cardiovascular risk factors in the healthy parents of the index children (first graders) from PEP Nuremberg.

Materials and Methods
From the 3910 participants in the 9th PEP-Survey 1867 were in the age group 20-50 years and participated in the structured interview and the physical examination. Out of them 1436 came for the fasting blood test. From the 472 subjects (20-50Y) participating in PEP for the first time 224 completed the dietary protocol and exercise questionnaire.

Results
The mean age was 40.1 ± 5.4 y for the 751 men and 37.8± 5.5 y for the 1116 women with 21% active smokers in both sexes. 249 men (33%) had elevated blood pressure (≥130/85 mmHg) compared to only 10% of the women and high LDL-Cholesterol (≥130mg/dl) was two times higher in men then in women (47% vs. 23%). Also fasting triglycerides and blood glucose concentrations were substantially higher in men (23% respectively 22%) than in women (4% vs. 10%). However, HDL-Cholesterol, overweight for men and waist circumference were not significantly different between men and women.
22% of the new participants with the complete data set were overweight. The men daily consumed 11% more energy than those with a BMI <27.8kg/². In addition they reported more sedentary hours per day than the normal weight men.
The overweight men reported more sedentary hours / day (6 vs. 4) and less physical activity than the normal weight (150 min / week vs. 225 min / week). In contrast physical exercise and sedentary hours differed only slightly between the normal and overweight women.

CARDIOVASCULAR RISK FACTORS PREVALENCE IN THE ARGENTINE REPUBLIC. CARDIOVASCULAR MORTALITY AFTER 5 YEARS

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Cardiovascular disease is one of the main death causes in the Western world. Several studies have shown the benefits of coronary risk factors (CRF) control and the relationship between them and cardiovascular disease. Considering this background we recorded population data from a representative region in the Argentine Republic, to analyze the truth regarding CRF incidence and their relationship with mortality after 5 years due to cardiovascular causes. **Material and Methods**: Observational, prospective study. Data were collected through a survey during interviews, medical and laboratory checkups done to spontaneous volunteers in two sanitary control mobile units. Individuals belonged to both sexes, representative of 4 geographical regions from central Argentine Republic, from June 2000 to December 2001. Statistical method used was Cox´s proportional risks model, with a death probability estimation after five years concerning populations without CRF, after the model submitted by Pocock et. al. Results: 17,177 people were registered in Córdoba, Santa Fe, Buenos Aires, and the Federal Capital. There were 7,271 men (42.4%) and 9,880 women (57.6%). 63.1% of individuals were between 50-79 years. 16.2% were smokers, 22.02% had a >240 mg/dl cholesterol value, 3.11% were diabetics and 48.82% had high pressure values. Moreover, 30.16% of surveyed population had a cardiovascular history. Data in our registries were contrasted with official death data from the CNRA 2001. 39% of interviewed individuals had risk factors: cholesterol>240mg/dl and hypertension (stages II & III). **Conclusions**: Death relative risk (RR) for a CRF due to cardiovascular disease after 5 years, in reference to an ideal sample without risk factors, regardless of age, as per Pocock´s index was: 1.01 and 1.02 for diabetics; 1.15 and 1.08: hypercholesterolemia; 1.24 and 1.30: cardiovascular history; 1.32 and 1.26: hypertension and 1.28 and 1.36: smokers, for men and women, respectively. Besides, RR was calculated for 2 and 3 CRF.

DISLIPIDEMIAS AND NON-LIPID RISK FACTORS IN SUBJECTS WITH ISHEMIC HEART DISEASE AND ESSENTIAL HYPERTENTION

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Objective: to investigate the character of risk-factor clusterisation in subjects with ishemic heart disease (IHD) and essential hypertention (EH). **Methods**: it was included 40 patients with IHD (mean 53 yers), 20 patients with EH (mean 55 years), 35 – with combination of EH and IHD. Group of comparison consisted of 30 subjects with functional diseases of cardiovascular system. Serum lipoproteins including lipoprotein (a) (Lp(a)), triglycerides, waist-to-hip ratio, body mass index, family history of CVD were investigated. For smoking subjects index of smoking man (ISM) and pack years were calculated. **Results**: 90% hypertensive subjects had abdominal obesity (AO) that correlted with higher level of serum cholesterol and glucose. Only 43% ishemic subjects had AO. In this group the highest ISM and pack years well as the highest level of Lp(a) (30,2 mg/dl) were found. Ishemic men with AO had significantly higher ISM and pack years as well as hig level of Lp(a) and lower level of high (HDL) density lipoproteins in comparison with ishemic men without AO. Among ishemic men with history of miocardial infarction (IM) smoking and AO were met in 3 times oftener than among ishemic men without hystory of IM while we didn"t fix the differenses in levels of serum lipoproteins. For women family history of IHD correlated with risk of IHD. **Conclusion**: for men combination of smoking and AO in one subject correlated with lowering of HDL and growing of Lp(a) as well as assosiated with risk of IM independ of serum lipoproteins. Among ishemic women no smoking no metabolic and lipid disorders had significance for risk of IHD. Only family history of IHD assosiated with it.

ANALYSIS OF LIPIDOGRAM AT HEALTHY INDIVIDUALS WITH ESTIMATION OF RISK FOR CORONARY ARTERY DISEASE

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The connection between arteriosclerosis and the frequency of the coronary artery disease and the level of cholesterol, TG and HDL cholesterol is already showed in many studies.
The aim of this study was to determine the relation between LDL cholesterol and HDL cholesterol who is defined as index of arteriosclerosis, which is used for estimation of the risk for developing cardiovascular disease.
The group had 59 subjects (41 men and 18 women) from 20 to 60 years old. The subjects were elected with the method of accidental choice. They all belong in the so called "healthy population" (without any heart problems, with normal blood pressure during the examination, normal ECG and basic laboratory find, including the values of glucose in blood, and they didn't receive any kind of therapy). They were all examined the total cholesterol, TG, HDL cholesterol and electrophoresis of lipoproteins, according to what the type of hiperlipoproteinemia was determined. With examing of 59 subjects of both sexes who fulfilled the criteria for somatic healthy population between 20 and 60 years old (the majority of subjects were between 20 and 30 years of age (32%) and 38% aging between 31 and 40 years old), where we found pathological lipidogram at 25 subjects or more than 42%. The majority of hiperlipidemia belongs to type IV – 23% of which 21 subjects had higher TG or 35%, cholesterol 13 (22%), VLDL 25 (42%) and lower HDL cholesterol 19 (32%). These results imply calculating of ERF (Established Risk Factor) which represents a relation between the total cholesterol and HDL cholesterol, with normal value of 4,97. That factor for our examined group was 5,48, which means that received findings are above-average risk for coronary artery disease. It's obvious that with this preliminary examination of lipid components at 59 healthy individuals we received data that require further analysis, but also education of the subjects for changing the life style. Even more, it's about young individuals who have lipid-disturbance what is probably serious risk for creating coronary artery disease.

RELATIONS BETWEEN PLASMA HOMOCYSTEINE LEVELS AND LEFT VENTRICULAR FUNCTION AFTER MYOCARDIAL INFARCTION

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Backgrounds: Elevated plasma homocysteine (Hcy) levels are associated with coronary artery disease (CAD). However, it is unclear whether elevated Hcy levels are a risk for lower cardiac function after myocardial infarction (MI).
Methods: We enrolled consecutive 32 patients (mean age 58 yr.) suffered acute myocardial infarction and age-matched 68 subjects without coronary artery disease (no-CAD) evaluated by coronary angiography. Of MI patients, plasma Hcy levels were measured at subacute phase (mean 14 days after MI) and at chronic phase (mean 180 days after MI), and left ventriculography was also performed. Results: Hcy levels were significantly higher in MI patients at chronic phase (12.4 +/- 3.7 nmol/L) than in MI patients at subacute phase (11.4 +/- 2.9 nmol/L) and in no-CAD (9.7 +/- 2.7 nmol/L). Of no-CAD, coronary stenosis index was associated with Hcy levels ($r=0.43$, $p<0.01$), however, no relationship was found between left ventricular ejection fraction (LVEF) and Hcy levels ($p=0.50$). Of MI patients, LVEF was negatively associated with Hcy levels at chronic phase ($r=-0.60$, $p<0.01$), but not at subacute phase ($p=0.07$). The change of LV enddiastolic volume between at chronic phase and at subacute phase was positively associated with plasma BNP levels ($r=0.42$, $p<0.05$), but not with Hcy levels ($p=0.75$) measured at subacute phase.
Conclusion: After suffered myocardial infarction, elevated plasma Hcy levels are likely associated with lower LV function, but not with cardiac remodeling.

TOTAL/HDL CHOLESTEROL RATIO AND PLASMA LIPOPROTEIN(a) CONCENTRATIONS AS RELATIVE RISK IN PATIENTS WITH CORONARY ARTERY DISEASE

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Elevated levels of lipoprotein(a) (higher than 30mg/dl) in the blood are linked to a greater risk for coronary artery disease (CAD) in both men and women. The risk is even more significant if the Lp(a) elevation is accompanied by high total/HDL cholesterol ratios.
The aim of the study was to analyze the interactive effect for combination of plasma Lp(a) levels and calculated ranks of total/HDL cholesterol ratios. The concentrations of Lp(a), ApoB, and ApoA-1 were determined K3EDTA plasma in 119 patients with verified CAD using nephelometric method on BNA100. The lipid parameters were determined using standard commercial test kits.
The Lp(a) concentration was statistically significant higher in all CAD patients than in the control group ($p<0.01$). More significant statistically higher Lp(a) values were measured in patients with angina pectoris ($p< 0.001$), then in the group of patients treated with PTCA ($p<0.0001$) and especially in patients with coronary bypass ($p=1 \times 10^{-5}$). The 5-fold increase in risk was found in CAD patients with low Lp(a) levels (< 15 mg/dl) and maximum total HDL cholesterol ratio (95%CI 2.72-9.10; $p<0.0001$). The highest increased in risk (14- fold) for development of atherosclerosis was found in the group of CAD patients with highest plasma Lp(a) levels (>30 mg/dl) and maximum calculated total/HDL cholesterol ratio (>5.8) (95%CI 3.25-58.24; $p<1.8 \times 10^{-6}$) compared to the control group.
Because lipid-lowering medications have limited effect in lowering Lp(a) levels it would be more effective in decreasing total but increasing HDL cholesterol levels in-patients with CAD.

THE LEUKOCYTE COUNT IS STRONGLY RELATED TO HEART RATE VARIABILITY – A PREDICTOR OF SUDDEN CARDIAC DEATH

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Slightly elevated inflammatory markers, reflecting low grade inflammation, are predictive of cardiovascular events. Recently, C-reactive protein has also been related to sudden cardiac death (SCD) and an attenuated heart rate variability (HRV), which is a predictor of SCD. A relation between the leukocyte count and HRV has previously been reported in healthy young subjects.
Purpose: To investigate a possible relation between the leukocyte count and HRV in patients with coronary artery disease (CAD).
Methods: Subjects were recruited among patients referred for elective coronary angiography at the Department of Cardiology, Aalborg Hospital, Aarhus University Hospitals, Denmark, due to suspected CAD. Before the angiograms, a 24-hour Holter recording was obtained from each patient and time-domain HRV indices were analysed. The leukocyte count was measured using standard methods.
Results: A total of 269 subjects (171 men and 98 women; mean age 60 ± 8 yrs) were included. Thirty-six % had prior myocardial infarction (MI) and 70 % had a positive angiogram. The mean leukocyte count was 6.5×10^9/l ± 1.9×10^9/l. The subjects were divided into quartiles based on HRV indices. The subjects in the upper quartiles of SDNN, SDNNindex and SDANN had significantly lower leukocyte count than subjects in the lower quartiles (all $P < 0.001$). Looking at subjects with and without a prior MI separately, a statistically significant inverse relation was found in both groups ($P = 0.006$ and $P = 0.001$). The association was stronger for subjects with significant coronary stenoses than for those without stenoses ($P < 0.001$ vs. $P = 0.03$).
Conclusion: We report a strong inverse relation between the leukocyte count and HRV in patients with CAD. While the causal relations remain undetermined, an increased leukocyte count appear to be associated with alterations in cardiac autonomic modulation. The finding supports a link between elevated markers of inflammation and the risk of suffering SCD.

SERUM 7-KETOCHOLESTEROL LEVELS IN PATIENTS WITH LACUNAR INFARCTION

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We reported that 7-ketocholesterol, one of oxysterols accumulated in atherosclerotic lesion, induced apoptosis of human vascular smooth muscle cells[1,2]. This finding might indicate that 7-ketocholesterol makes atherosclerotic plaque unstable. In this study, we measured serum 7-ketocholesterol levels in 152 type 2 diabetes mellitus patients, and studied the effect of serum 7-ketocholesterol levels on lacunar infarction. Serum 7-ketocholesterol was assayed by gas chromatography- mass spectrometry. Serum 7-ketocholesterol levels were significantly high in metabolic syndrome diagnosed by National Cholesterol Education Program compared to subjects with diabetes mellitus only (38.4 μg/ml vs 27.7 μg/ml, respectively $p<0.05$). Serum 7-ketocholesterol levels in subjects with lacunar infarction were significantly high compared to subjects without lacunar infarction (35.3 μg/ml vs 30.6 μg/ml, $p<0.05$). Next, in subjects with carotid artery plaque, the relationship between serum 7-ketocholesterol levels and lacunar infarction was studied. In high 7-ketocholesterol group (≧30 μg/ml), the incidence of lacunar infarction was higher than in low 7-ketocholesterol group (< 30 μg/ml) (70% vs 38%, respectively). In case of subjects without carotid artery plaque, the incidence of lacunar infarction was low (38%), although serum 7-ketocholesterol levels showed high (≧30 μg/ml). These results suggested that serum 7-ketocholesterol levels might increase according to increase of insulin resistance, and 7-ketocholesterol could be concerned to the attack of lacunar infarction by destruction and rupture of carotid artery plaque.

References: 1) Miyashita et al. J Atheroscler Thromb 1997; 4: 73-8
2) Miyashita et al. J Atheroscler Thromb 2001; 9: 65-71

C-REACTIVE PROTEIN AND HOMOCYSTEINE IN PATIENTS WITH AND WITHOUT CORONARY HEART DISEASE

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Epidemiological studies indicate that C-reactive protein (CRP) at the upper end of the healthy reference range is associated with an enhanced risk for cardiovascular disease. CRP has been also recognized by AHA experts as an important risk marker which may be useful in clinical practice. It has been also shown that moderately elevated levels of homocysteine (Hcy) increase the risk of atherosclerosis and it is believed that Hcy measurement may improve risk assessment. For clinical practice the question of which new biochemical markers should be added to conventional markers to better differentiate patients at risk, is of great importance. Therefore, in the present study we compared CRP and Hcy levels in the group of 121 patients with documented CHD and 118 disease free control subjects matched for age, sex, serum lipids and body mass index. The studied subjects had no hypertension and were not obese. Both CRP and Hcy concentrations were significantly higher in CHD patients as compared to controls: 1.7± 1.1mg/l vs 4.3± 2.1 mg/l ($p<0.000$) and 9.9± 3.1μmol/l vs 14.1± 4.4μmol/l ($p<0.001$). However, the power of CRP to differentiate healthy subjects from CHD patients was 3-times greater than that of Hcy. We have also found a significant correlation r-0.61 ($p<0.001$) between CRP and Hcy levels. Higher value of correlation coefficient was observed in the control group ($r=0.57$) than in CHD group ($r=0.46$) and in the subgroup with low serum cholesterol levels (<200 mg/dl) than in the hyperlipidemic subgroup: $r=0.64$ vs $r=0.58$. No significant relationship was observed between cholesterol and Hcy and between CRP and cholesterol. These data suggest that enhanced Hcy levels may stimulate the development of the inflammatory process, and indicate that CRP can be used in clinical practice as a first additional marker to identify individuals who do not have classical risk factors but are at enhanced CHD risk.

LDL-CONTAINING CIRCULATING IMMUNE COMPLEXES AS A MARKER OF EARLY ATHEROSCLEROSIS

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LDL-containing circulating immune complexes (LDL-CIC) may play an important role in atherogenesis. It has been shown that LDL-CIC can induce lipid accumulation in cells cultured from uninvolved human aortic intima and in macrophages. Recently it has been shown that increased level of LDL-CIC is of high diagnostic significance in clinically manifested atherosclerosis, but little is known about its diagnostic and prognostic significance in early atherosclerosis. Two-years prospective study was performed in 98 asymptomatic men aged 40-74 in whom early atherosclerotic lesions of common carotid arteries were revealed under ultrasonographic examination. The rate of atherosclerosis progression was estimated by high-resolution B-mode ultrasonography as the increase in intima-media thickness (IMT) of carotid arteries. Elevated levels of LDL-CIC were concomitant with significantly higher levels of LDL cholesterol and significantly increased carotid IMT. Among all baseline lipid parameters, only LDL-CIC and LDL cholesterol were contingent with the extent of early carotid atherosclerosis ($p=0.042$ and $p=0.049$, respectively) and had the highest levels of relative risk and odds ratio. The increased levels of LDL-CIC, total serum cholesterol and LDL cholesterol had similar prognostic significance with the respect of atherosclerosis progression. The normal level of LDL-CIC (below than 16.0 μg/ml) was the only lipid parameter that predicted the absence of carotid atherosclerosis progression for two following years at prognostic value of 78.3%. The results of the study allow assuming that LDL-CIC level may be employed not only as a marker of early atherosclerosis, but also has a sufficient prognostic value for clinical implications. Although LDL-CIC amounts to no more than 2% of total circulating LDL pool, this LDL fraction seems to be fundamental for primary cholesterol accumulation in vascular cells, the crucial step in early atherogenesis. As intracellular cholesterol accumulation is accompanied by stimulation of other atherosclerotic manifestations at the cellular level, it is possible that the presence of LDL-CIC in the blood promotes the emergence and development of atherosclerotic process in the vessel wall.

ARE ADIPONECTIN AND HS CRP MARKERS OF VASCULAR INFLAMMATORY DISEASE IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA?

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Over the past decade a large body of research has concluded that inflammatory processes are involved in all stages of the pathogenesis of the atherosclerotic lesion. Adiponectin an adipocytokine secreted by the adipocytes has been reported to have antiatherogenic and anti-inflammatory properties. Adiponectin has been found to inhibit crucial steps in the development of atherosclerosis including monocyte adhesion to the endothelium and conversion of macrophages to foam cells. Subjects with familial hypercholesterolaemia (FH) are known to suffer from severe, premature atherosclerosis. If a deficiency of adiponectin is a crucial factor in the pathogenesis of atherosclerosis in these subjects, it would be expected that these patients would have markedly reduced levels of adiponectin. High sensitivity C-reactive protein is a well established marker of the inflammatory process in patients with atherosclerosis. In keeping with increased inflammation resulting from a proposed decrease in adiponectin it would be anticipated that high levels of hs-CRP would occur in this patient group.

Aim: To evaluate the usefulness of adiponectin and hs-CRP levels as inflammatory markers in FH subjects and to determine whether these levels can be used to determine the risk of coronary artery disease in this group of patients. **Methods:** 2 0 Homozygous FH (HoFH) subjects, 20 untreated heterozygous FH (HeFH) subjects and 20 normal control subjects were enrolled in the study. HeFH subjects were treated with 80 mg Rosuvastatin for six weeks following a wash out period. Lipograms, Adiponectin levels and hs-CRP were measured on all patients at the commencement of the study and repeated in the HeFH group post therapy. **Results:** Using the Kruskal Wallis test no significant differences were detected in the concentrations of adiponectin and hs-CRP in the Ho-FH and He-FH groups compared to the control group. Using Spearman correlation no relationship was found between total cholesterol or LDL cholesterol and adiponectin and hs-CRP in both the untreated and treated He-FH group as well as with the Ho-FH group. **Conclusion:** These results suggest that adiponectin does not play a significant role in moderating the inflammatory process and the development of atherosclerosis in patients with FH. Furthermore hs-CRP levels do not reflect the degree of atherosclerosis in this patient group. Both of these results indicate that the pathogenesis of atherosclerosis in patients with FH may differ from that in other patient groups.

ASSOCIATION OF NON HDL CHOLESTEROL WITH EARLY STRUCTURAL CHANGES OF ATHEROSCLEROSIS IN ASIAN INDIAN TYPE 2 DIABETIC SUBJECTS – THE CHENNAI URBAN RURAL EPIDEMIOLOGY STUDY (CURES)

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Aim of the study: To determine the association of non-HDL cholesterol with carotid intimal medial thickness (IMT), a marker of early structural changes of atherosclerosis in Type 2 diabetic subjects.

Methods: Type 2 diabetic subjects (n=1024) were randomly selected from CURES, an ongoing population based study on a representative population (aged ≥ 20 years – 26001 individuals) of Chennai, the largest city in Southern India. IMT was measured using high resolution B-mode ultrasonography. The age specific cut off of IMT for diagnosis of carotid atherosclerosis was determined using a healthy normal cohort [non-smokers, non-diabetic, normotensive, who had no evidence of CAD] from CURES. Serum lipids were measured in an overnight fasting sample along with other biochemical parameters. Hypercholesterolemia, and non-HDL levels were diagnosed based on NCEP ATP III guidelines.

Results: Prevalence of carotid atherosclerosis was significantly higher in subjects with hypercholesterolemia (21.5% *vs* 14.9%, p=0.0001), and high non-HDL cholesterol (20.3% *vs* 10.5%, p=0.0001) levels. IMT showed a strong correlation with age, (p<0.001), systolic blood pressure (p<0.001), serum cholesterol (p=0.001) and non-HDL cholesterol (p=0.002). Mean IMT values increased with increase in quartiles of serum cholesterol (ANOVA p=0.003) and non-HDL cholesterol (ANOVA p=0.008). Regression analysis revealed that IMT had a strong association with cholesterol (p<0.001) and non-HDL cholesterol (p<0.001) even after adjusting for age, sex and HbA1c.

Conclusion: The study results suggest a significant association between non-HDL cholesterol and carotid atherosclerosis.

LEPTIN, LIPIDS AND HYPERTENSION

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The obese gene product, leptin, plays a central role in food intake and energy metabolism. Leptin is an hormon a hormone linking adiposity and central nervous circuits to reduce appetite and enhance energy expenditure. Also there are speculation that leptin of the physiological levels may serve as a physiological regulator of the cardiovascular function, whereas high plasma leptin levels may act as a pathophysiological trigger and/or a marker for cardiovascular diseases due to tissue leptin resistance.

The goal of our study was to evaluate the concentration of leptin, body mass index (BMI), serum total cholesterol, triglycerides and glucose in patients (n=55) under antihypertension therapy and control group of healthy subjects (n=59). The subjects understudy were of both sexes, ranging from 40 to 60 years old, the age considered as the most at risk group to coronary heart diseases. The male patients compared to the male control group had significantly increased blood pressure levels (145/92 vs. 127/84 mmHg) and BMI (27,4 vs. 29), but no difference in leptin levels (3,19±2,6 vs. 3,18±3,96 ng/ml). The female patients compared to the female control group had significantly increased blood pressure levels (145/92 vs. 130/83 mmHg), BMI (27,4 vs. 29,0), leptin (14,12±7,7 vs. 11,9±10,2 ng/ml) and triglycerides (6,22±1,5 vs. 5,66±1,0 mmol/L). The levels of serum total cholesterol, triglycerides and glucose in the patient's group were close to the higher position of the reference range. Our results show that there is positive correlation between the leptin level and the blood pressure of females, but not to that of males. The leptin level's is also in positive correlation with body mass index for both sexes. Therefore in addition to other factors such as high body mass and high serum lipids, hyperleptinemy may be considered as one of the possible risk factors for coronary heart diseases

TRIGLYCERIDE LEVELS PREDICT VASCULAR COMPLICATIONS IN FAMILIAL HYPERCHOLESTEROLEMIA.

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Background and aims: Patients with familial hypercholesterolemia (FH) are at high risk of cardiovascular events.

Aim of our study was to determine which lipid factors (other than total and LDL cholesterol levels) and non-lipid risk factors predict vascular complications in patients with FH.

Patients and Methods: A group of 306 heterozygous FH patients free of cardiovascular disease were compared to 67 FH patients with a cardiovascular event in their history. All patients fulfilled the MedPed criteria for FH.

The logistic regression model used included age, BMI, blood pressure, TC, HDL-c, LDL-c, fasting triglycerides (TG), levels of apolipoprotein B and Lp(a).

Lipid variables were assayed using standard enzymatic methods, LDL-c was calculated, apolipoprotein levels were measured by imunoelectrophoresis. The statistical analysis employed t-test, Wilcoxon's test and the logistic regression model.

Results: Univariate analyses showed statistically significant difference in age, BMI and fasting TG between FH patients without and with a cardiovascular event (age 50.7 vs. 65.0 yrs, BMI 25.11 vs. 27 kg/m^2, TG 1.64 vs.2.21 mmol/l). BMI was adjusted to age. Logistic regression analysis proved age and fasting TG as independent predictors of cardiovascular events. (odds ratios 1.064 and 1.384, respectively)

Conclusion: In patients with familial hypercholesterolemia age and levels of fasting triglycerides independently predict cardiovascular complications. This finding can have important implications for the treatment strategies of FH.

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USING BODY MASS INDEX AND WAIST TO HIP RATIO TO PREDICT CARDIOVASCULAR RISKS IN CHINESE AMERICANS

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The body mass index (BMI) measures overall obesity and waist-to-hip ratio (WHR) measures abdominal obesity. These indices have been used to predict cardiovascular risks in the Western population. We examined the interrelationships between obesity and cardiovascular risks among Chinese Americans in New York City. METHODS: Chinese Americans, aged 18 years or older, who participated in a cardiovascular disease risks survey in 2003 were recruited. Relationship of BMI and WHR was studied with systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high density lipoprotein (HDL), fasting triglycerides (FTG), fasting plasma glucose (FPG), and cluster of risk factors. The cutoff criteria for cardiovascular risks were: SBP ≥140 mmHg, DBP ≥90 mmHg; HDL <40 mg/dL in men and <50 mg/dL in women; FTG ≥150 mg/dL; and FPG ≥110 mg/dL. The International Obesity Task Force classification system for obesity for Asian was used for BMI ≥23 kg/m^2 and WHR ≥ 0.9 in men and ≥0.85 in women. RESULTS: Data of 134 Chinese men and women with a mean age of 50.58 (standard deviation, 17.05) years was analyzed. The mean BMI and WHR were 23.36 kg/m^2 and 0.84, respectively. Correlation studies revealed significant association between each of the obesity indices with SBP, DBP, TC, HDL, FTG, and FPG (all variables, r >0.8, p<0.001). Subjects with more than three cardiovascular risks had higher BMI and WHR levels (all p-values <0.001). Centrally obese subjects had a lower mean of HDL and a higher mean of SBP and DBP (all variables p<0.05) when compared with centrally non-obese individuals. Increased BMI was significantly associated with increased in FPG (p=0.01) and DBP (p=0.034). CONCLUSIONS: Chinese Americans with increased BMI and/or WHR may carry higher cardiovascular risks than those without it.

THE SIGNIFICANCE OF C-REACTIVE PROTEIN AS A CARDIO-VASCULAR RISK FACTOR AMONG JAPANESE

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C-reactive protein (CRP), a marker of inflammation, has been accepted as a useful predictor of cardiovascular events in Caucasians. In order to evaluate the meaning of CRP among Japanese, we investigated the distribution of CRP levels and the relationships between age, sex, alcohol, smoking, obesity, exercise and parameters of metabolic syndrome (blood pressure, serum lipids, serum glucose, etc). Further we investigated the occurrence of acute coronary syndrome and diabetes mellitus (DM) during 3 years, and then we analyzed the relationship with the baseline CRP levels.
The distribution of serum CRP levels in 3,515 subjects without apparent infection inclined toward the low value and the maximum value was 2.0 mg/L without sex difference. In 9,087 random subjects, CRP correlated with age, BMI, smoking number, and negatively correlated with HDLc. Moreover, CRP was lower in the continued exercise group than in the inactive group. When 3,601 men who didn't suffer from DM were pursued for 3 years, 40 subjects have developed DM. The baseline CRP level in DM group was higher than in non-DM group (1.51 *vs.* 0.89 mg/L, $p < 0.05$). The rate of diabetes development in subjects whose baseline CRP level were over 1.0 mg/L is higher than in subjects under 0.5 mg/L (2.9 % *vs.* 0.7%). Further we similarly pursued for 3 years aiming the incidence of cardiovascular disease. The baseline CRP levels of all CVD patients exceeded 1.0 mg/L.
It is concluded that CRP is a useful predicting marker of the future acute coronary syndrome and diabetes mellitus among Japanese.

BILIRUBIN LEVELS PREDICT CHD RISK IN THE LIPID STUDY

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Bilirubin has antioxidant properties and is thought to lower lipoprotein atherogenicity. LIPID, one of the largest cholesterol-lowering coronary-event trials, provided the opportunity to explore the relationship between serum bilirubin and coronary risk and any interaction with pravastatin therapy.

Methods: In LIPID, 9014 patients with coronary heart disease (CHD) were randomised to pravastatin or placebo and followed up for a median of 6 years. Serum bilirubin was measured at baseline, at 1 year, 5 years, and trial end. The relationship between bilirubin at baseline and subsequent CHD events (CHD death or nonfatal myocardial infarction) was assessed by time-to-event analysis, separately for placebo and pravastatin groups.

Results: For each quartile increase in the bilirubin level at baseline, an average 5% decrease in coronary events was observed (HR 0.95, 95% CI 0.91–0.998, P=0.043), with similar associations in the placebo and pravastatin groups (P interaction=0.24).

At randomisation, median bilirubin was 10 μmol/L in both treatment groups. After one year on study, patients randomised to pravastatin had a significantly higher bilirubin level than those randomised to placebo (median 12 vs 11 μmol/L, Wilcoxon test, P=<0.001). This difference was maintained for the rest of the study period. The benefits of pravastatin on CHD risk did not appear to be explained by these small changes in bilirubin level.

Conclusion: There is an inverse association between baseline bilirubin level and coronary events. Similar relative effects of pravastatin therapy on CHD risk were seen irrespective of baseline bilirubin level.

PLASMA LIPIDS AND LIPOPROTEINS IN HEALTHY SUBJECTS ARE CLOSELY RELATED TO INR

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Hypercholesterolemia may be related to an increased tendency to develop thrombosis. However, no data exists regarding the relation between INR (International Normalized Ratio) and lipids and lipoproteins in apparently healthy subjects. We therefore included 100 healthy subjects (without any medication) with INR levels within the reference range (0.9 – 1.2). Also, plasma lipids and lipoproteins in the fasting state were measured in each subject. Two analyses failed leaving 98 subjects for final analysis. The study comprised 46 women and 52 men with the following mean values (SD): Age 40 years (13), t-cholesterol 5.1 mmol/l (1.1), LDL-cholesterol 3.1 mmol/l (1.0), HDL-cholesterol 1.4 mmol/l (0.3), triglycerides 1.2 mmol/l (0.9), and INR 1.04 (0.07). Univariate correlation analysis between INR and the plasma lipids and lipoproteins revealed the following Spearman correlation coefficients: t-cholesterol – 0.5 ($p<0.001$), LDL-cholesterol – 0.4 ($p<0.001$), HDL-cholesterol 0.03 (ns), and triglycerides – 0.4 ($p<0.001$). Accordingly, the t-cholesterol level was 5.5 mmol/l in the lowest INR quartile compared to 4.2 mmol/l in the upper quartile ($p< 0.001$). In conclusion, INR is strongly negatively associated with t-cholesterol, LDL-cholesterol and plasma triglycerides in healthy subjects. This suggests that slightly elevated cholesterol levels in even healthy subjects might have an increased risk of thrombosis.

ASSOCIATION OF APOLIPOPROTEIN E GENOTYPE WITH EARLY ONSET OF CORONARY HEART DISEASE IN GREEK MEN

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Apolipoprotein E (apo E) polymorphism has been associated with coronary heart disease (CHD) though, its relation to age of CHD onset is still not defined. We evaluated whether any of the apo E genotypes are associated with the age of onset of CHD.
Based on the age of CHD onset, 502 Greek men were divided into: earlier (< 50), intermediate (50-61), later (> 61 years) groups. Univariate analysis showed that the apo ε3/3 genotype predominated in the earlier-onset compared to the later-onset group (78% vs. 59%, $p < 0.001$), while the apo ε3/4 genotype was more frequent in the later-onset compared to the earlier-onset group (33% vs. 10%, $p < 0.001$). Multivariate analysis revealed that compared to the ε3/4 the presence of the ε3/3 genotype was associated with 5.7–fold of the risk of early CHD onset (95% CI 1.17 to 28.5, p=0.03), after taking into account several potential cofounders.
There is a relation of apo E polymorphism with the age of clinically evident CHD in Greek men. Carriers of apo ε4 alleles seem to have a later onset of CHD, while individuals with a double apo ε3 allele are at higher risk for premature CHD. The relationship between apo E genotype and CHD may be ethnic-related rather than universal.

APOLIPOPROTEIN E ALLELE FREQUENCY DISTRIBUTION IN THE HUNGARIAN GENERAL POPULATION AND HYPERCHOLESTEROLAEMIC GROUP

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The apolipoprotein E gene is polymorphic with 3 common alleles (ε2, ε3 and ε4). Results of numerous studies regarding the relationship between apoE polymorphism and serum lipid parameters support the hypothesis that the presence of apoE ε2 allele has protective, while that of ε4 allele has permissive effect on the development of hypercholesterolaemia and, consequently, atherosclerosis. Numerous studies were carried out on risk groups but only a few data are available on genetic polymorphism predisposing multifactorial diseases in the general population. The aims of our recent studies were 1.) to determine the apoE allele and isoform frequencies in the Hungarian population, and 2.) to clarify whether the accumulation of the permissive allele can be observed in the Eastern Hungarian hypercholesterolaemic group. ApoE 112/158 polymorphism studies were carried out on DNA samples from 1185 individuals representing the Hungarian general population, and 568 hypercholesterolaemic patients using LightCycler real time PCR technology based on fluorescence resonance energy transfer combined with melting point analysis. The distribution of apoE alleles were ε2: 7.31%; ε3: 77.90%; ε4: 14.79% in the hypercholesterolaemic group, while in the reference group representing the Hungarian general population the allele frequencies were found to be the followings: ε2: 6.1%, ε3: 84.1%, ε4: 9.8%. Our results strongly confirm the hypothesis of the ε4 allele accumulation in the hypercholesterolaemic group: of individuals with ε4 allele (27.8%) had significantly higher proportion compared to those in the general population (18.1%) ($p<0.001$).

CAROTID INTIMA MEDIA THICKNESS (IMT) AND IMT-PROGRESSION AS PREDICTORS OF VASCULAR EVENTS IN A HIGH RISK EUROPEAN POPULATION: *"THE IMPROVE STUDY"*.

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The intima-media thickness (IMT) of extracranial carotid arteries, assessed by ultrasound techniques, has been shown to be associated with most vascular risk factors for atherosclerosis and with the prevalence and extent of cardiovascular disease and coronary atherosclerosis. On this basis, this ultrasonic variable has been proposed as a surrogate index of atherosclerosis of other vascular regions. Studies have supported this hypothesis showing that IMT is a good predictor of new myocardial infarction and stroke. However, limited information has been provided on the relationship between IMT-progression, that is the real end point used in pharmacological studies, and cardiovascular events. Generally, attempts to delay IMT-progression using "anti-atherosclerotic" agents have provided encouraging results. However, no one of the studies so far published has been able to address, on a prospective basis, whether IMT-progression may effectively reflect the efficacy of the treatment in reducing the rate of cardiovascular events. To address these issues we designed *"the IMPROVE study"*, a currently on going prospective multicenter, longitudinal, long-term, observational study funded by the European community. The major objective of *the IMPROVE study* is to evaluate the association between IMT, IMT-progression and the rate of new vascular events in subjects at high risk of atherosclerosis. The effect of gene polymorphisms, lipid peroxidation, socio-economic and psychological variables on the same ultrasonic end points will be also evaluated. In order to achieve the project objectives, 3600 patients will be recruited in 7 European countries and followed ultrasonically and clinically for 30 months. Clinical events will be monitored up to 36 months. Data will be analysed with conventional statistics and with innovative approaches based on artificial neural networks. The study is considered as positive if a difference of at least 3% in the cumulative incidence of acute vascular events between the lowest and the highest quintiles of IMT or IMT-progression is detected. A summary of aims and design of the study will be presented.

DETECTION OF EARLY ATHEROSCLEROSIS USING THE ULTRASOUND PARAMETER OF THE INTIMA-MEDIA THICKNESS OF THE COMMON CAROTID ARTERY IN FAMILIES WITH FAMILIAL COMBINED HYPERLIPIDEMIA

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The aim of the study was to quantify intima-media thickness (IMT) in clinically asymptomatic members of familial combined hyperlipidemia (FCHL) families and to evaluate its association with cardiovascular risk factors. 82 individuals from 29 FCHL families /47 hyperlipidemic (HL) and 35 normolipidemic (NL)/ were compared with age and sex adjusted healthy controls. IMT was measured by ultrasound at a far wall of both common carotid arteries (CCA). Hyperlipidemic subjects had increased IMT compared with healthy controls (0.695±0.118 vs. 0.599±0.074 mm), with an age and sex corrected difference of 86 μm ($p<0.001$). No difference in IMT was recorded in NL FCHL members in comparison with their healthy controls. In HL subjects, significantly positive univariate correlations were observed between IMT and age, sex, total cholesterol, LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B, SBP, DBP, BMI, waist, fasting glycemia, C-peptide and proinsulin, whereas in NL subjects IMT correlated only with age. Backward stepwise regression analysis in FCHL subjects (HL+NL) revealed, that age ($p<0.001$), sex ($p<0.001$), non-HDL cholesterol ($p<0.01$) and BMI ($p<0.05$) were significant and independent predictors of IMT.

Conclusion. The increase of IMT CCA in hyperlipidemic still clinically asymptomatic FCHL subjects corresponds to acceleration of the clinically „silent" atherosclerosis by about 8-14 years and is in agreement with their increased risk of atherosclerosis.

HOW TO AVOID SOME OF THE VAGARIES OF THE IMT WHEN IT IS USED IN A CLINICAL TRIAL

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The use of surrogate endpoints may save sponsor time and money, provided their limitations are kept in mind and they are properly used. Carotid Intima Media Thickness (cIMT) assessed by ultrasound represents the most studied and validated surrogate end-point for atherosclerosis. It seems to be a simple and non invasive routine technique. However many points need to be taken into account when it is used in a clinical trial. The presentation will focus on methodological, technical and practical aspects to consider when cIMT is chosen as an end-point. The following points will be addressed :

- Investigators / Sonographers qualification and training,
- Equipment,
- Imaging procedure,
- Imaging Sites : common carotid versus "12 sites",
- Site of measurement registration,
- ECG gating,
- Use of contrast agent (pro/cons),
- Blinded central reading,
- Manual reading versus semi-automatic,
- Quality Control program.

The experience of a vascular core lab having conducted large IMT trials as investigator as well as central reader, and using various techniques, will be shared.

CAROTYD ARTERY INTIMA-MEDIA THICKNESS - RELATIONSHIP WITH SOME CARDIOVASCULAR RISK FACTORS

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Background and Aim:
Current available noninvasive imaging methods to assess subclinical atherosclerosis are promising for cardiovascular risk (CR) management and therapeutic interventions monitoring.
This study aims to determine the relationship between carotid artery intima-media thickness (CIMT) and some other cardiovascular risk factors - age, previous cardiovascular disease, Diabetes Mellitus, arterial hypertension, tabagism, cardiovascular disease family history and lipids and lipoprotein parameters (total cholesterol, LDL-c, HDL-C, Apo A1 and B, Lp(a) and homocystein).
Methods and Results:
A retrospective study was performed in 63 patients followed in the Endocrinology Department Outpatient Clinic. Twenty six had high CR and 37 were in secondary prevention.
Patients included 44 men and 19 women, with a mean age of 56,97 years. Twenty five patients had arterial hypertension and 10 patients were smokers.
CIMT in common carotid artery and lipids and lipoprotein parameters were measured in all of them.
CIMT was lower in women (0,79vs1,07mm; p=0,003) and higher in patients in secondary prevention (1,08vs0,85mm; p=0,007), with arterial hypertension (1,11vs0,89mm; p=0,009) and with age >55 years (1,06vs0,84; p=0,014). We didn't find any statistic significant correlation with the other cardiovascular risk factors.
Conclusions:
We believe that lack of correlation between CIMT and the other cardiovascular risk factors, namely tabagism, homocystein and LP(a), results from cardiovascular risk homogeneity in the studied group.

IDENTIFYING CARDIOVASCULAR RISK: ASSESSMENT OF ARTERIAL STIFFNESS DURING AN ACUTE ISOMETRIC EXERCISE GRIP TEST

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Introduction: The development of vascular stiffness may be an early indicator for elevated cardiovascular risk in young adults. Measurement of resting pulse wave velocity (PWV) provides a non-invasive index of arterial stiffness or its inverse, reduced compliance. Earlier detection of impaired compliance using exercise may allow for better preventative management of cardiovascular disease (CVD). Acute isometric handgrip exercise (ISOMEX) increases stiffness by amplifying sympathetic discharge. We investigated whether alterations of arterial compliance at rest or during ISOMEX had any relationship with known risk factors for CVD in otherwise healthy subjects.
Methods: PWV (carotid–radial), BP and HR were recorded in the relaxed dominant arm of 51 healthy subjects (29 females, age (mean ± SD) 37.7 ± 15 yrs, BMI 26.1± 3.8 kg/m^2) during 3 minutes of non-dominant arm ISOMEX (30% maximum voluntary contraction).
Results: Age was positively associated with resting PWV ($r = 0.31$, $P < 0.05$). Males ($n = 22$) elicited significantly higher PWV than females at rest (8.16 ± 0.9 v 7.69 ± 0.8 m/s, $P < 0.05$) and during ISOMEX (9.18 ± 1.2 v 8.38 ± 0.8 m/s, $P < 0.01$). BMI was a strong determinant of both resting ($r = 0.49$, $P < 0.01$) and ISOMEX PWV ($r = 0.59$, $P < 0.01$) among non-smokers ($n= 39$). Compared to subjects without a definite family history for CVD ($n = 15$), subjects with a positive family history (FH+, $n =15$) had equivalent PWV at rest (8.0 ± 0.8 v 8.1± 0.9 m/s, P = NS). However, there was a significantly greater PWV increase during ISOMEX in the FH+ subjects (14.4 ± 10.8 v 7.1± 4.8%, $P < 0.05$).
Conclusions: Even within a muscular arterial segment in the resting state, age, gender and BMI exert detrimental effects on the vasculature. ISOMEX induces amplified sympathetic responses and an elevated PWV that is also strongly determined by gender, BMI and family history. Such data suggests that arterial abnormalities may be present early in subjects likely to develop CVD. The results could be valuable for designing a widely applicable vascular stress test for early identification of subjects in need of rigorous lifestyle modification using exercise, diet, weight control or even therapeutics.

PROGNOSTIC VALUE OF FLOW-MEDIATED DILATION IN BRACHIAL ARTERY IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Endothelial dysfunction is thought to represent the initial stage in the development of atherosclerosis. Recently, noninvasive examination of endothelial function has become possible using flow-mediated endothelium-dependent dilation of the brachial artery (FMD) during reactive hyperemia. We prospectively examined whether FMD has prognostic value for the prediction of subsequent cardiovascular events. The study subjects comprised 221 consecutive patients (men 108, mean age 61.4±10.6). All patients enrolled received conventional therapy for their heart disease at the outpatient clinic. Patients were followed prospectively every month until the occurrence of cardiovascular events. The patients were prospectively followed up to 113 months (mean follow-up period 63.5±24.0 months). Twenty-two cardiovascular events and 1 cardiac death occurred during follow-up, and these patients required hospitalization. The mean FMD was 4.77±2.85% and this value was used to divide the patients into the 2 groups (Group 1: FMD 4.7%; Group 2: FMD <4.7%). There were 110 patients in Group 1 (men 36, mean age 60.5±10.9), and 111 patients in Group 2 (men 72, mean age 62.2±10.3). There were more male patients, smokers, patients with hypertension, and diabetes in Group 2 than in Group 1. As compared with Group 1, HDL cholesterol tended to be lower in Group 2. Seven cardiovascular events (angina pectoris 3, congestive heart failure 1, stroke 3) occurred in Group 1 (6.4%, 1.14 events per 100 patients-years), while 16 (angina pectoris 5, acute myocardial infarction 2, congestive heart failure 4, stroke 2, others 3) occurred in Group 2 (2.88 events per 100 patients-years). Kaplan-Meier analysis demonstrated a significantly higher probability of developing cardiovascular events in Group 2 than in Group 1. The present results demonstrated that the magnitude of FMD in the brachial artery was one of the good predictive markers of subsequent cardiovascular events.

PLASMA LIPOPROTEIN(A) CONCENTRATION AND ANGIOGRAPHICALLY ASSESSED CORONARY ATHEROSCLEROSIS

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Background: Findings from previous studies relating lipoprotein(a) [Lp(a)] as an independent risk factor for coronary atherosclerosis and the presence of angiographically detectable coronary atherosclerotic lesions are not consistent. This study was performed to determine whether the plasma concentration of Lp(a) is associated with coronary atherosclerosis asessed by coronary angiography.
Methods: We studied a total of 100 men and women (41 women, 59 men, age 63,7+/-11.0 years) who were referred for coronary angiography. The relation between plasma Lp(a) levels and the severity and extension of coronary lesions was studied. The coronary angiograms were evaluated in a blinded manner according to three scores: vessel score (0 to 3 points for 0 to 3 vessels with CAD), stenosis score (0 to 3 points; number and severity of coronary stenoses or lesions; 0 for no, 1 for coronary lesion with diameter stenosis less than 50%, 2 for 50-75%, and 3 for more than 75% diameter stenosis), and extent score (0 to 3 points; segment-extension of all coronary lesions within the total coronary vessel length).
Results: Estimates of the relative risk of coronary heart disease for the fifth quintile of plasma Lp(a) as compared with the first quintile were 0,87 (95 percent confidence interval, 0,66 to 1,34). Plasma Lp(a) were 22,5 (+/-30,4)mg/dl, 29,08 (+/-28,68) mg/dl and 19,01 (+/- 27,74) mg/dl in groups A, B and C and represented no risk factor for CAD severity assessed by coronary angiography (p=0,81). The presence of angiographic CAD was associated with patient age (p=0.048), male sex (p<0.01), high LDL-cholesterol levels (p=0.02), low HDL-cholesterol levels (p=0,02), high plasma fibrinogen levels (p<0,01) and high fasting total homocysteine levels (p=0,04).
Conclusion: These results suggest that the plasma concentration of Lp(a) is not associated with presence and severity of coronary artery disease in patients referred for coronary angiography.