875-5 Antiinflammatory and Antiangiogenetic Effect of Ramiprilat: Angiotensin Converting Enzyme Inhibition in Monocytes Prevents Their Angiotensin II- and Hypoxia-Induced Cytokine Expression by Downregulation of AT-1 Receptor Expression and NF-kappaB Activation

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Background: There are several controversial reports regarding the effects of ACE-inhibitors on the plaque angiogenesis in atherosclerosis and tumor growth. An antiinflammatory and antiangiogenic effect of ACE-inhibition might be of major relevance in acute coronary syndromes. Because the Angiotensin II (ATII)-AT1-receptor(R) and hypoxia-derived angiogenesis is induced by supporting mononuclear cell (MNC) infiltration and angiogenic cytokine expression we examined the effects of ACE inhibition on the stimulation of Monocytes by ATII and hypoxia.

Methods: Human Mo were stimulated in vitro 1. with 100 and 500 nM ATII and 2. with hypoxia (O2:3%), in 1. Mo were pretreated with 1,5,10microM ramiprilat (Ra), ATII-R inhibitor (I) = enalapril (10microM) or ATII-RI PR1555150 (10microM) and in 2. with 1,5,10microM Ra. Analysis of monocyte ATII-R expression was performed by western blotting, NF-kappaB activation by EMISA, IL6 and MCP-1 by RT-PCR and ELISA, statistics by student's t-test (sign: p<0.05). In 10 samples of advanced human atherosclerotic carotid plaques (AHP) immunohistochemical staining for ACE, IL-8 and MCP-1 was performed.

Results: In 100% of inflammatory shoulder regions of AHP co-localization of MCC-ACE with MCP-1 and IL-8 could be demonstrated. In vitro, hypoxia stimulated Mo IL-8 and MCP-1 expression increased with Ra by 60+13% and 46+11% (P<0.01), respectively. Mo ATII-AT1-R induced IL-6 and MCP-1 expression could also be inhibited by 49+1% and 71+5% with Ra in dose-dependent manner. Ra (10microM) reduced the hypoxia and ATII-induced NF-kappaB activation only slightly (P=0.4). Ra (10microM) reduced the monocyte ATII-R expression by 50+12% and 63+13% after 12 and 24highly significant (P<0.001). The AT1-R activation remained unchanged.

Conclusion: For the first time, it could be demonstrated that antiinflammatory effects of ACE-inhibition could be derived by a marked downregulation of monocyte ATII-R expression, and by an inhibition of the hypoxia-induced proinflammatory and angiogenic MCP-1 and IL-8 production. These effects of Ra might be of major relevance in atherosclerotic plaque vulnerability.

875-6 Effect of Exercise Training in Patients With Coronary Artery Disease on Circulating Endothelial Progenitor Cells

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In patients with coronary artery disease (CAD) exercise training (ET) is regularly associated with a decrease in exercise-induced myocardial ischemia. Recently it has been shown that a symptom-limited exercise test is sufficient to increase circulating endothelial progenitor cells (EPC) in patients with symptomatic CAD. Until now, however less is known about the impact of regular ET on the amount of circulating EPCs. Aim of this study was to investigate the effects of ET on the number of EPCs in patients with symptomatic CAD. To define the role of ischemia during ET we also analyzed the effect of treadmill training in patients with peripheral artery occlusive disease (PAOD) beyond the ischemic threshold. 14 patients with CAD and 14 patients with PAOD were randomly assigned either to (ET) or an inactive control group (C). Ergometer and treadmill training in patients with symptomatic CAD was performed 6 times daily for a period of 4 weeks. The concentration of EPCs was measured 6 times daily.

Results: In the 143 randomized patients, mean age was 63±7 years and 8% were women. Baseline characteristics included total cholesterol 195±31 mg/dl, LDL-C 127±27 mg/dl, HDL-C 34±6 mg/dl, triglycerides 169±82 mg/dl, systolic blood pressure 139±16 mm Hg, and fasting blood sugar 80±14 mg/dl. No difference in baseline characteristics was seen between the 2 groups. Median weight loss during the study was 1% in the placebo group and 4% in the drug group, p<0.001. Total cholesterol increased by 3% in the placebo group but was reduced by 16% in the drug group, p<0.001. LDL-C increased by 21% in the placebo group but dropped by 5% in the drug group, p<0.001. HDL-C increased by 2% in the placebo group and by 37% in the drug group, p<0.001. Triglycerides increased by 3% in the placebo group but were reduced by 45% in the drug group, p<0.001. Fasting blood sugar increased by 8% on placebo group and by 18% on drug therapy, p=0.006. Focal coronary stenoses increased by 1% on placebo but decreased by 1% in the drug group, p=0.043. A combined endpoint of unstable angina, transient ischemic attack and stroke, percutaneous intervention, coronary bypass, or death was reached in 19 placebo patients and 9 drug patients, p=0.039.

Conclusion: A combination of agents aimed at increasing HDL-C dramatically improves cholesterol profiles, arrests angiographic progression, and results in a significant reduction in cardiovascular events.

876-1 Aggressive Treatment Aimed at Raising High-Density Lipoprotein Cholesterol in Stable Patients With Angiographically-Evident Coronary Disease Prevents Stenosis Progression and Reduces Cardiovascular Events


Background: Overwhelming evidence supports that lowering low-density lipoprotein cholesterol (LDL-C), particularly with statins, leads to a reduction in cardiovascular events. High-density lipoprotein cholesterol (HDL-C), despite being a stronger predictor of events in epidemiologic studies, has been mostly neglected as the focus of therapy.

Methods: We performed a randomized double-blind, placebo-controlled trial assessing the effect of gemfibrozil, niacin, and cholestyramine on a baseline of aggressive dietary lifestyle intervention. Patients >7 years of age with angiographically-evident coronary disease in the absence of recent instability were consented and followed over a period of 30 months. Quantitative angiography was performed at baseline and at the completion of the study.

Results: In the 143 randomized patients, mean age was 63±7 years and 8% were women. Baseline characteristics included total cholesterol 195±31 mg/dl, LDL-C 127±27 mg/dl, HDL-C 34±6 mg/dl, triglycerides 169±82 mg/dl, systolic blood pressure 139±16 mm Hg, and fasting blood sugar 80±14 mg/dl. No difference in baseline characteristics was seen between the 2 groups. Median weight loss during the study was 1% in the placebo group and 4% in the drug group, p<0.001. Total cholesterol increased by 3% in the placebo group but was reduced by 16% in the drug group, p<0.001. LDL-C increased by 21% in the placebo group but dropped by 5% in the drug group, p<0.001. HDL-C increased by 2% in the placebo group and by 37% in the drug group, p<0.001. Triglycerides increased by 3% in the placebo group but were reduced by 45% in the drug group, p<0.001. Fasting blood sugar increased by 8% on placebo group and by 18% on drug therapy, p=0.006. Focal coronary stenoses increased by 1% on placebo but decreased by 1% in the drug group, p=0.043. A combined endpoint of unstable angina, transient ischemic attack and stroke, percutaneous intervention, coronary bypass, or death was reached in 19 placebo patients and 9 drug patients, p=0.039.

Conclusion: A combination of agents aimed at increasing HDL-C dramatically improves cholesterol profiles, arrests angiographic progression, and results in a significant reduction in cardiovascular events.

876-2 Statin Therapies for Elevated Lipid Levels Compared Across Dose Ranges to Rosuvastatin: Low-Density Lipoprotein Cholesterol and High-Density Lipoprotein Cholesterol Results

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Background: The primary objective of this large, multicenter trial was to compare the effects of rosvastatin (RVS) versus atorvastatin (ATV), simvastatin (SIM), and pravastatin (PRA) across dose ranges on percent changes in low-density lipoprotein-cholesterol (LDL-C). Treatments included: RVS 10, 20, 40 or 80 mg, ATV 10, 20, 40, or 80 mg, SIM 10, 20, 40, or 80 mg, and PRA 10, 20, or 40 mg. Prospective planned analyses for each lipid included log-dose-response curve analyses and 25 selected pair-wise comparisons of RVS doses with corresponding or higher doses of comparators (with a statistical significance level adjustment to 0.002 to account for multiple comparisons).

Results: The table shows dose-to-dose comparisons. Baseline LDL-C means were 187 to 194 mg/dl. The curves analysis showed that RVS produced a mean 6.2% greater LDL-C reduction (p<0.01) than ATV across the dose ranges. Greater differences in LDL-C reduction were observed between RVS and PRA or SIM.
Least-square mean % changes in LDL-C and high-density lipoprotein-C (HDL-C) from baseline are shown in Table 1. In the fenofibrate group, the mean reduction in LDL-C was significantly reduced compared to the placebo group (p<0.02). The mean reduction in HDL-C was not statistically significant between groups.

Conclusions: The mean reductions in LDL-C and HDL-C were achieved with fenofibrate treatment, with the largest mean reduction in LDL-C and highest increases in HDL-C seen in the highest tertile of baseline LDL-C/HDL-C ratio.