AGLA Update Meeting

Zürich, 31. März 2011
Cardiovascular Medicine
Kardiovaskuläre Medizin / Médecine cardiovasculaire

www.cardiovascmed.ch
Official journal of the Swiss Society of Cardiology, the Swiss Society of Hypertension, the Swiss Society of Angiology and the Swiss Society of Paediatric Cardiology

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Fax +41 (0)61 467 85 86
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Retail price: Fr. 125.–
Single issue; Fr. 20.–
Issues per year: 11
 ISSN 1664-2031

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Supplementum 19 der Zeitschrift «Cardiovascular Medicine»
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Regulation of the 3 lipoxygenases, ALOX12, ALOX15 and ALOX15B, in human macrophages
S. Wüst
Zurich

Atherosclerosis is a chronic disease characterized by two main features, lipid retention and inflammation. Subendothelial retention and modification of low-density lipoproteins initiate the atherosclerotic process leading to an attachment of leukocytes as a first sign of inflammation. The lipoxigenase pathway plays a role in recruitment and adhesion of leukocytes by the generation of two classes of arachidonic acid lipid mediators, the leukotrienes and lipoxins. The leukotrienes occur in the initial phase and have pro-inflammatory effects. The lipoxins have anti-inflammatory effects by counteracting the action of pro-inflammatory factors. 3 different lipoxygenases are essential for the production of the lipoxins, ALOX12, ALOX15 and ALOX15B. To investigate the regulation of the 3 lipoxygenases in human macrophages we measured the expression of ALOX12, ALOX15 and ALOX15B mRNA during differentiation of monocytes to macrophages and stimulated mRNA expression in macrophages. The results showed an increase of ALOX15B during the differentiation of monocytes to macrophages while the expression of ALOX12 and ALOX15 remains on the same low level. Stimulation of macrophages with a set of cytokines and with hypoxia revealed that IL-4, IL-13, and hypoxia further increased the ALOX15B mRNA. IL-4 and IL-13 also enhanced the expression of ALOX15 whereas none of the stimuli had an impact on the ALOX12 expression. These data show that mainly ALOX15B is expressed in differentiated macrophages and that the anti-inflammatory cytokines IL-4 and IL-13, and hypoxia are further activators of its expression. IL-4 and IL-13 increased the expression of ALOX15 whereas only IL-4 stimulation leads to an ALOX15B expression higher than the basal expression of ALOX15B.

Plasma chemerin is associated with markers of inflammation, and coronary artery disease in patients not undergoing aspirin treatment
M. Herová1, M. Schmid1, M. Hersberger1
Zürich

Background: Chemerin is a peptide chemoattractant of macrophages, and dendritic cells and a recently identified adipokine. Active chemerin is found in plasma and was shown to regulate inflammation and adipocyte differentiation. As inflammation, obesity, and metabolic syndrome are pronounced risk factors for coronary artery disease (CAD) we investigated possible association of plasma chemerin levels with inflammatory markers and atherosclerosis in a CAD case-control study.
Research design and method: Total chemerin levels were measured by ELISA in the plasma of angiographically documented CAD patients (n = 249) and healthy controls (n = 221).
Results: Plasma chemerin levels were highly associated with high sensitive C-reactive protein, creatinine, and cholesterol levels as well as with BMI and hypertension, and negatively associated with HDL levels. Plasma chemerin levels were similar in controls and CAD patients. However, chemerin levels were significantly higher in CAD patients not undergoing aspirin treatment than in CAD patients on aspirin treatment and in controls.
Conclusion: Chemerin is strongly associated with markers of inflammation and components of the metabolic syndrome and is associated with CAD in patients not receiving anti-inflammatory treatment. This suggests that high chemerin levels are associated with inflammation accompanying CAD. The association with plasma creatinine levels further suggests a role for the kidney in elimination of chemerin.

Invariant Natural Killer T cells: linking inflammation and neovascularization in human atherosclerosis
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Atherosclerosis is characterized by chronic inflammation that determines the development of atherosclerotic lesions and the progression into vulnerable plaques. Identification of leucocyte populations involved in plaque destabilization is crucial for the effective prevention of cardiovascular events. Invariant Natural Killer T (iNKT) cells are a unique CD1d-restricted T cell subset impacting on both innate and acquired immunity. iNKT cells recognize CD1d-associated lipid antigens, that are still unknown self-molecules or lipids of bacterial origin. Upon antigen encounter, iNKT cells exert a variety of functions, which contribute to atherosclerosis exacerbation. This study investigates iNKT cells and CD1d-expressing cells in human arterial tissue, their correlation with disease and their involvement in plaque formation and/or destabilization.

CD1d-expressing cells were present in advanced plaques of patients who had suffered from cardiovascular events and were most abundant in plaques with ectopic neovascularization. The atherosclerotic lesions of patients with asymptomatic atherosclerosis. iNKT cells were found to enhance endothelial cell migration and sprouting in an IL-8-dependent manner, mechanisms facilitating intraplaque neovascularization. iNKT cells also regulate lipid metabolism, thus directly influencing one of the main atherosclerosis predisposing factors. These findings introduce iNKT cells as novel cellular candidates promoting plaque neovascularization and destabilization in human atherosclerosis. The identification of the lipid antigens stimulating iNKT cells within plaques will disclose new pathogenic mechanisms of atherosclerosis and novel immunotherapeutic targets offering new approaches to therapeutic vaccination.

Identification of iNKT and CD1d-expressing cells in atherosclerotic lesions.
New and old criteria for the diagnosis of diabetes mellitus in patients with coronary artery disease

P. Rein1, C. Saely1, A. Vonbank1, C. Boehnel1, S. Beer1, V. Jankovic1, H. Drexel2
1Feldkirch

Purpose: Recently, a diagnosis of diabetes was recommended with hba1c ≥6.5%. Data on the concordance of new and old criteria for the diagnosis of diabetes are very scarce; no data at all are available for patients with coronary artery disease (CAD).

Design & Methods: We consecutively enrolled 1124 Caucasian patients with angiographically proven CAD who did not have previously known diabetes. An oral glucose tolerance test (OGTT) was performed in all patients.

Results: From the patients with diabetes according to the new diagnostic criterion hba1c ≥6.5% (n = 110), 58 (53%) fulfilled the WHO glucose criteria for diabetes, 13 (12%) had impaired glucose tolerance (IGT), 26 (24%) impaired fasting glucose (IFG), and 13 (12%) normal fasting glucose (NFG). Conversely, the hba1c ≥6.5% criterion was fulfilled in 58 patients (63%) with diabetes according to WHO criteria, in 13 patients (11%) with IGT, in 26 patients (8%) with IFG, and in 13 patients (2%) with NFG. Compared to the standard of WHO criteria, the proposed hba1c ≥6.5% for the diagnosis of diabetes had a sensitivity of 63% and a positive predictive value of 53% for detecting previously undiagnosed diabetes, whereas specificity and negative predictive value were 95% and 97%, respectively.

Conclusions: The recently recommended hba1c criterion for the diagnosis of diabetes among CAD patients is highly specific but not sensitive. This might strongly limit its use as a screening tool.

Population Attributable Coronary Risk is Mainly Driven by LDL-Cholesterol: Similar Observations in Two Distinct Healthy Populations

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1Olten; 2Zurich; 3Basel; 4St. Gallen; 5Lausanne

Aim: To determine population attributable coronary risk for major coronary risk factors and to derive the potential to reduce global coronary risk.

Methods: We compared not randomly selected subjects from self referred CORDICARE (COR) and physician referred KARDIOLAB (KAR) patients for 10 year coronary risk determined by Swiss guidelines (AGLA) and by reclassification (posttest risk derived from total placebo area of carotid arteries). The potential for risk factors to reduce global coronary risk was estimated by substituting measured results by ideal values of risk factors. We calculated the risk reduction attributable to achievement of all AGLA goals, and for single risk factors: smokers became non-smokers (–29% vs –36%), LDL ≤2.0 mmol/l (–51% vs –52%), no smokers (–7% vs –14%), HDL >1.49 mmol/l (–14% vs –27%), blood pressure ≤130 mm Hg (–8% vs –7%), no diabetes (–2% vs –4%).

Conclusions: Achieving LDL ≤2.0 mmol/l would be the single most important intervention to reduce coronary risk (risk reduction by 50%). By achieving all AGLA goals, 10 year risk would fall from 13% to 7% in COR and from 16% to 5% in KAR.

Eccentric endurance exercise significantly lowers liver enzymes in overweight and obese individuals

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1Feldkirch

Purpose: Elevated liver enzymes are highly prevalent in overweight and obese patients, reflect the presence of non-alcoholic fatty liver disease, and are associated with an increased risk of diabetes and cardiovascular events. Liver enzymes can be lowered by physical exercise, but many overweight patients are not willing or not able to engage in strenuous exercise regimens. Eccentric endurance exercise (e.g. hiking downwards) is less strenuous than concentric exercise (e.g. hiking upwards) but its effects on liver enzymes are unknown.

Design & Methods: We allocated 43 overweight and obese sedentary individuals to an exercise intervention program, consisting of hiking downwards a pre-defined route in the Austrian Alps over two months. For the opposite way, a cable car was used where compliance was recorded electronically. The difference in altitude was 540 meters; the distance was covered three to five times a week. Fasting and postprandial metabolic profiles were obtained at baseline and after the two months period.

Results: Compared to baseline, 9 weeks of eccentric endurance exercise significantly lowered serum alanine aminotransferase (ALT; 36 ± 23 vs. 31 ± 18 U/l; p < 0.001), the ALT / aspartate aminotransferase (AST) ratio (1.22 ± 0.41 vs. 1.02 ± 0.33; p < 0.001), and serum gamma-glutamyl transferase (56 ± 98 vs. 44 ± 65 U/l; p = 0.005). Eccentric endurance exercise was well tolerated and there were no serious adverse events.

Conclusion: We conclude that eccentric exercise is a promising new exercise modality which significantly lowers liver enzymes in overweight individuals. Eccentric exercise could be of interest as a therapeutic intervention in non-alcoholic fatty liver disease patients.

Pycnogenol Improves Endothelial Function in Patients with Coronary Artery Disease

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1Zurich

Purpose: Extracts from pine tree bark have been used in traditional medicine. Pycnogenol is a proprietary bark extract of the French maritime pine tree (Pinus pinaster ssp. atlantica). The effects of pycnogenol on surrogates of cardiovascular risk remain still elusive.

Methods: 25 patients with coronary artery disease were included in this randomized, double-blind, placebo-controlled crossover study. Patients received pycnogenol (200 mg/d) for 8 weeks followed by placebo or vice versa on top of standard cardiovascular therapy. Between the 2 treatment periods a 2-week washout period was scheduled. At baseline and after each treatment period, endothelial function, non-invasively assessed by flow-mediated dilation of the brachial artery, platelet adhesion, baroreceptor function and 24-hour blood pressure monitoring were evaluated.

Results: Treatment with pycnogenol increased flow-mediated vasodilation from 5.27 ± 2.59 to 7.03 ± 3.05 (p <0.0001), but remained unchanged after placebo 5.45 ± 2.42 to 4.74 ± 1.97 (p = 0.051). Plasma 8-isoprostanes, an index of oxidative stress, significantly decreased from 0.71 ± 0.09 to 0.68 ± 0.13 (p = 0.049 vs. baseline and p = 0.005 vs placebo). Blood pressure, platelet adhesion and baroreceptor function remained unaltered.

Conclusion: This study provides first evidence that the potent antioxidant pycnogenol improves vascular function in patients with coronary artery disease.

Eccentric endurance exercise is a promising new exercise modality which significantly lowers liver enzymes in overweight and obese patients. Pycnogenol is a proprietary bark extract of the French maritime pine tree. Cardiovascular Medicine 2011;14(3): Suppl 19
Factors Predicting Cardiovascular Events in Statin-Treated Diabetic and Non-Diabetic Coronary Patients: A Prospective Cohort Study

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1Zürich

Purpose: We aimed at identifying which lipid factors drive vascular risk in statin treated patients with coronary artery disease (CAD).

Design & Methods: We recorded vascular events over a mean period of 72 years in 491 consecutive statin-treated patients with angiographically proven stable CAD, covering 3518 patient-years.

Results: In the total population, low HDL cholesterol (standardized adjusted HR 0.80 [0.67–0.94]; p = 0.009), low apolipoprotein A1 (0.84 [0.72–0.98]; p = 0.022), a small LDL particle diameter (0.84 [0.72–0.98]; p = 0.023), and high triglycerides (1.18 [1.04–1.35]; p = 0.013) predicted vascular events, but not total cholesterol, LDL cholesterol, or apolipoprotein B. Factor analysis in the lipid profiles of our patients revealed an HDL-related factor and an LDL-related factor. Concordant with the results for individual lipid parameters, the HDL-related factor (0.76 [0.65–0.90]; p = 0.001) but not the LDL-related factor (p = 0.644) predicted vascular events. Patients with type 2 diabetes (T2DM; n = 116) were at a higher vascular risk than non-diabetic subjects (52.6% vs. 36.8%; p = 0.002), and like in the total population the HDL-related factor (0.63 [0.49–0.81]; p <0.001) but not the LDL-related factor (p = 0.976) predicted vascular risk in diabetic patients.

Conclusions: The pattern of low HDL cholesterol, low apolipoprotein A1, small LDL particles, and high triglycerides drives vascular risk in statin-treated coronary patients, particularly in those with T2DM.

Acute and Chronic Cardiovascular Effects of Flavanol-rich Chocolate in Patients with Heart Failure

I. Sudano1, A. J. Flammer1, M. Wolfurm1, F. Enseleit1, D. Periat1, T. F. Luscher1, F. Ruschitzka1, G. Noll1, R. Corti1, R. Thomas1
1Zürich

Background: Recent studies indicated a beneficial effect of flavanol-rich cocoa on cardiovascular health, especially on vascular and platelet function, on blood pressure and insulin resistance, most likely due to an increase in nitric oxide bioavailability and a decrease in oxidative stress. Patients with congestive heart failure (CHF) are characterized by impaired endothelial as well as increased platelet reactivity and oxidative stress. Therefore, flavanol-rich chocolate might improve cardiovascular health in patients with CHF.

Design, Methods and Results: Twenty patients with CHF were enrolled in a double blind, randomized placebo controlled trial, comparing the effect of flavanol-rich commercially available dark chocolate with cocoa-liquor free control chocolate on endothelial and platelet function, baroreceptor function, blood pressure and heart rate in the short-term (2 hours after ingestion of a chocolate bar) and long-term (4 weeks, two chocolate bars/day). Endothelial function was assessed non-invasively by flow-mediated vasodilatation (FMD) of the brachial artery. FMD significantly improved from 4.98 ± 1.95% to 5.98 ± 2.32% two hours after intake of flavanol-rich chocolate, and to 6.86 ± 1.76% after 4 weeks daily intake (measured after at least 12 hours abstinence). Platelet adhesion significantly decreased from 3.9 ± 1.32% to 2.99 ± 1.31% 2 hours after flavanol-rich chocolate intake, an effect that was not sustained at 2 and 4 weeks. Cocoa-liquor free chocolate had no effect, neither on endothelial nor on platelet function. Baroreceptor function, blood pressure and heart rate did not change in either group.

Conclusion: Flavanol-rich chocolate acutely improves vascular function in patients with CHF. A sustained effect was seen after daily consumption over a 4 weeks period even after 12 hours abstinence. These beneficial effects were paralleled by a inhibition of platelet function in the presence of flavanol-rich chocolate only.

Liquid chromatography-mass spectrometry quantification of bile acids in patients with deficiencies in reverse cholesterol transport

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1Zürich

Introduction: The aim of this study was to investigate bile acid concentrations in patients with mutations in different genes involved in reverse cholesterol transport (RCT). This mechanism serves to transport cholesterol from peripheral tissues back to the liver. Cholesterol, a poorly soluble membrane lipid is eliminated from the human body by conversion into various water-soluble, amphipathic bile acids, which are then secreted into the small intestine. These bile acids are found in the systemic circulation as a consequence of efficient reabsorption from the small intestine. The effects of mutations in RCT genes on cholesterol levels are largely unknown.

Methods: The 15 major human bile acids were quantified using liquid chromatography coupled to mass spectrometry (LC-MS/MS). Samples consisted of 100 µl serum from controls (n = 31) and from patients carrying mutations which affect the following proteins: ATP binding cassette transporter A1 (ABCA1) (n = 9), lecithin-cholesterol acyltransferase (LCAT) (n = 15), cholesteryl ester transfer protein (CETP) (n = 3), apolipoprotein A-I (apoA-I) (n = 3) and scavenger receptor BI (SR-BI) (n = 8).

Results: The most interesting and surprising results of this study showed that serum concentrations of bile acids conjugated with glycine or taurine (in contrast to unconjugated bile acids) were increased in patients carrying mutations in the SR-BI gene. An identical tendency was observed for primary bile acids, which comprise unchanged forms of bile acids synthesized in the liver (in contrast to secondary bile acids which have been modified by intestinal bacteria). In addition, the same bile acids (primary and conjugated) were also increased in patients carrying mutations in the apoA-I gene.

Effect of Folic Acid Supplementation in Patients with Chronic Heart Failure

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1Zürich

Background: Patients with chronic heart failure (CHF) are characterized by endothelial dysfunction, partly due to increased oxidative stress. Since folic acid exerts potential antioxidant activity, the present study was designed to evaluate the impact of folic acid supplementation on endothelial function, as well as on markers of chronic inflammation and oxidative stress.

Design, Methods and Results: 20 patients with CHF were included in this randomized, double blind, placebo-controlled
study to receive folic acid (5 mg/day) or placebo for 1 month, on top of standard optimal therapy. There was a significant increase in plasma folate levels (from 6.9 ± 3.2 to 163.2 ± 147.7 ng/ml, p < 0.01) and a significant reduction in homocysteine plasma concentrations from 14.8 ± 3.5 to 12 ± 2.0 mmol/L (p = 0.01) in the folate-group. However, endothelial function, as assessed non-invasively by flow-mediated vasodilatation, was not significantly affected (from 8 ± 1.7% to 4.1 ± 2.1%, p = 0.64).

Oxidative stress and inflammation parameters did not change significantly after folate substitution. Importantly, 4 weeks of treatment with 5 mg folic acid significantly decreased diastolic blood pressure (DBP) as compared to baseline from 76.1 ± 12 to 69.5 ± 7.2 mm Hg; p = 0.03. A pronounced trend towards lower systolic blood pressure (SBP) levels were also observed (from 115 ± 10.5 to 111 ± 12.8 mm Hg; p = 0.06). There was no change in blood pressure after placebo (SBP from 113.8 ± 8.9 to 116 ± 5.1 mm Hg, p = 0.36 DBP from 66.9 ± 7.2 to 71.0 ± 6.9 mm Hg p = 0.13).

Conclusion: Chronic treatment with folic acid (5 mg/day) over one month did not improve endothelial function and oxidative as well as inflammatory parameters in patients with CHF. However a significant reduction in diastolic blood pressure has been observed.

Generation of recombinant antibodies to nitrotyrosine to facilitate the identification of novel protein biomarkers of atherosclerosis

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Today, several risk factors, like high blood pressure and smoking, help to identify individuals that are at high risk of developing coronary artery disease. However, there is still a high demand for the identification of novel biomarkers to improve the early diagnosis of acute coronary events and to identify pre-symptomatic patients at high risk for coronary events. This project aims at the identification of such biomarkers. Inflammatory processes play a pivotal role in the progression of atherosclerotic plaques, and we hypothesize that proteins in the plaque are modified during plaque rupture and erosion, and are released into the blood stream. Possible posttranslational modifications include proteolytic cleavage and oxidation of amino acids, such as the formation of nitrotyrosine.

Antibodies against nitrotyrosine – in a protein context – are being isolated from large antibody phage display libraries. So far, we have isolated several different antibody specificities, but recognition of the modified amino acids depended on the composition of the surrounding amino acids. Using affinity maturation by error prone PCR of the recombinant antibody gene, followed by novel selections, we have improved the specificities and affinities of these recombinant antibodies. Now, we will use these anti-nitrotyrosine antibodies to detect antigens that contain this modified amino acid and that are specifically present in plasma samples from patients with atherosclerotic cardiovascular disease and acute coronary syndromes. Potential targets will be isolated, using the antibodies as baits, and identified by mass spectrometry.

Effect of inflammatory cytokines on HDL transport and engineered artery equivalent

J. Robert, L. Rohrer, S. Hoerstrup, A. Von Eckardstein* Zurich

Atherosclerosis is a chronic disease characterised by lipid retention and inflammation in the arterial wall. High density lipoproteins (HDL) transports cholesterol from macrophage foam cells to the liver for disposal into the intestine. However it must pass the endothelium to get access to the foam cells, a process which is not well understood. Our previous data show that endothelial cells transport HDL by distinct specific mechanisms involving the scavenger receptor (SR)-BI, the ATP binding cassette transporter (ABC) G1 and endothelial lipase. Furthermore, we are able to engineer functional artificial artery equivalent composed of vascular myofibroblasts and endothelial cells.

Stimulating endothelial cells cultured in regular tissue culture dishes with inflammatory cytokines modulated the expression of the known HDL binding proteins. Upon stimulation with TNFα, IL-1β and IL-6, the expression of ABCG1 was up regulated. Moreover the expression of SR-BI and EL were down regulated by IL-1β. In addition functional experiment demonstrated that HDL cell association was up regulated by IL-6 whereas TNFα and IL-1β did not regulate HDL cell association.

We plan to corroborate the finding of the tissue culture experiments in our artery equivalent model. In addition we will study the molecular consequence of the HDL transport in normal and inflammatory conditions in our artery equivalent.

Electronotic Crosstalk Between Cardiomyocytes and Myofibroblasts: Consequences for Cardiomyocyte Electrophysiology

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Myofibroblasts (MFBS) were shown to induce highly arrhythmic conditions in vitro following establishment of heterocellular gap junctional coupling (GJC) to cardiomyocytes (CMCs). We conducted a characterization of the electrophysiological properties of CMCs, MFBS and hybrid cell pairs including the determinations of gap junctional conductances (gj) in homologous and heterologous cell pairs. Experiments were performed with neonatal rat ventricular CMCs and MFBS of cardiac origin in primary cell culture. Resting potentials, net membrane currents in single cells and gj in hybrid cell pairs were recorded using patch clamp techniques. Presence of functional GJC between CMCs and MFBS was further assayed by destroying MFBS while recording RMFs of coupled CMCs (Data: mean ± S.D.; n = 8 to 23).

Picture 1 lists baseline electrophysiological parameters of cells. Injection of depolarizing current pulses in one cell of CMC-CMC pairs elicited action potentials in the coupled cell without any appreciable delay. In CMC-MFB pairs, eliciting an action potential in CMCs caused similarly shaped voltage deflections in the coupled MFBS. 56% of CMCs coupled to MFBS were active. Experiments performed with ‘Lucifer yellow’ demonstrated extensive dye communication between CMCs and MFBS.

The table below lists baseline electrophysiological parameters of single cells (CMC, MFB), cell pairs (CMC-CMC, CMC-MFB) and CMC-MFB following mechanical destruction of MFBS (CMC-MFB):
These results show that
– the decrease in RMP of CMC coupled to MFBs is due to the depolarizing effect of MFBs on CMCs. The effect is fully reversed after destruction of MFBs which rules out electrical remodeling of CMCs in presence of MFBs.
– inward current densities arising in MFBs are large enough to explain CMC depolarization based on the concept of injury current flow.
These findings not only contribute to the clarification of the mechanisms of arrhythmogenic heterocellular "injury current" flow, but they will form the basis for an in-silico model for investigating arrhythmogenic effects of MFBs on CMCs in models of intact cardiac tissue.

P7
Subclinical hyperthyroidism and the risk of coronary heart disease and mortality: an individual participant data analysis from nine prospective cohorts
1Lausanne; 2Leiden; 3San Francisco; 4Pisa; 5Philadelphia; 6Trondheim; 7Sao Paulo; 8Crawley; 9Milano; 10Pittsburgh

Aims & Purpose: Electrocardiographic (ECG) abnormalities are frequent in older adults, independently of traditional cardiovascular risk factors (CVRFs). Our goal was to determine whether baseline ECG abnormalities or development of new and persistent ECG abnormalities during follow-up are associated with increased incident CHD events in older adults, independently of traditional cardiovascular risk factors (CVRFs).

Design & Methods: We studied 2,191 elderly (age range 65–80 years) without known cardiovascular disease at baseline. During 8 years of follow-up, CHD events were adjudicated by review of medical records. ECG abnormalities were classified as minor and major. After 4 years of follow-up, 1,670 participants had a second ECG to determine the presence of new or persistent ECG abnormalities.

Results: At baseline, 276 participants had minor and 506 had major ECG abnormalities. During 8 years of follow-up, 351 participants had CHD events. Minor and major ECG abnormalities at baseline were associated with an increased risk of CHD (hazard ratios (HR) and 95% confidence interval [CI]: 1.45, CI:1.14–1.65 and 1.51, CI:1.20–1.90 respectively, after adjustment for CVRFs). The presence of any ECG abnormality at baseline accurately reclassified 7.1% overall and 13.6% of intermediate risk participants (both P <0.005). Of the 1,670 adults with a second ECG after 4 years, 208 had a new and 416 had a persistent abnormality. After adjustment for CVRFs, both new and/or persistent ECG abnormalities at 4 years were associated with an increased risk of CHD events (HR = 1.67, CI:1.31–2.96 and HR = 1.52, CI:1.07–2.16, respectively).

Conclusions: Minor and major ECG abnormalities in elderly adults are associated with an increased risk of CHD events and provide additional risk stratification information beyond traditional CVRFs. These data suggest a potential value of performing ECG in the overall assessment of cardiovascular risk in older adults.

P8
Insulin Resistance is Associated with Metabolic Syndrome But Not With Angiographically Determined Coronary Artery Disease
A. Vonbank1, C. Saely1, P. Rein1, S. Beer1, C. Boehnelli, J. Breuss3, H. Drexel1
1Fieldkirch

Aims: Insulin resistance (IR) is the key feature of the metabolic syndrome (MetS) and in prospective studies predicts atherothrombotic events. Its association with directly visualised coronary atherosclerosis is unclear. We hypothesised that IR is associated with both angiographically determined coronary artery disease (CAD) and with the MetS.

Design & Methods: We enrolled 986 consecutive patients undergoing coronary angiography for the evaluation of suspected or established stable CAD; significant CAD was diagnosed in the presence of significant coronary stenoses with lumen narrowing ≥50%. IR was determined by the HOMA index; the MetS was defined according to ATP III criteria.

Results: HOMA IR scores were significantly higher in MetS patients than in subjects without the MetS (6.4 ± 2.1 vs. 2.2 ± 2.0; p <0.001). In contrast HOMA-IR did not differ significantly between patients with significant CAD and those who did not have significant CAD (3.9 ± 14 vs. 3.2 ± 4; p = 0.490). When both, the presence of MetS and of significant CAD were considered, HOMA-IR was significantly higher in patients with the MetS both among those who had significant CAD (7.2 ± 28 vs. 2.3 ± 1; p <0.001) and among those who did not have significant CAD (5.3 ± 5.7 vs. 2.1 ± 1; p <0.001) whereas it did not differ significantly between patients with significant CAD and subjects without significant CAD in patients with the MetS (7.2 ± 28 vs. 5.3 ± 5.7; p = 0.679) nor in those without MetS (2.1 ± 14 vs. 2.3 ± 2; p = 0.411). Similar results were obtained with the IDF definition of the metabolic syndrome.

Conclusion: IR is significantly associated with the MetS but not with angiographically determined coronary atherosclerosis.

P9
Coronary Artery Disease Syndrome But Not With Angiographically Determined Coronary Artery Disease
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Background: Data regarding the cardiovascular risks of subclinical hyperthyroidism are conflicting among large prospective cohort studies. This might reflect differences in participants’ age, gender, thyroid-stimulating hormone (TSH) levels or presence of concomitant cardiovascular disease. We aimed to assess the risks of coronary heart disease (CHD) and total mortality associated with subclinical hyperthyroidism.

Methods: We searched MEDLINE, EMBASE and reference lists of retrieved articles to find prospective cohort studies with baseline thyroid function assessment and follow-up of subsequent total mortality, CHD mortality and CHD events. Individual data on participants with 458686 person-years of follow-up were supplied from 9 prospective cohorts in the US, Europe, Australia and Brazil. We examined the risk of CHD events from 6 cohorts with available data. Euthyroidism was defined as TSH 0.45–4.49 mIU/L and subclinical hyperthyroidism as TSH <0.45 mIU/L with normal thyroid levels.

Results: Among 49030 adults, 1300 had subclinical hyperthyroidism (2.7%). During follow-up, 7988 participants died (1794 of CHD); 3740 had CHD events. Age and gender-adjusted hazard ratios (HRs) were 1.29 (95% confidence interval, CI: 1.09–1.50) for total mortality, 1.32 (CI 1.02–1.72) for CHD mortality and 1.20 (CI 0.99–1.45) for CHD events. Risks of total mortality were increased with lower TSH levels (HR 1.27, CI 1.07–1.50, for TSH 0.10–0.44 mIU/L and HR 1.33, CI 1.00–1.73, for TSH <0.10, P for trend 0.053), and for CHD mortality (HR 1.29, CI 0.96–1.73, for TSH 0.10–0.44 mIU/L and HR 1.89, CI 1.12–3.19, for TSH <0.10, P for trend 0.01). Risks did not significantly differ by age, gender, race, or preexisting cardiovascular disease. Results were similar after further adjustment for cardiovascular risk factors.

Conclusion: Subclinical hyperthyroidism is associated with an increased risk of total and CHD mortality. The risks are higher with lower TSH, particularly in those with TSH below 0.10 mIU/L. Future studies should assess which conditions increase the risk of total and cause-specific mortality associated with subclinical hyperthyroidism.

Should we perform routine ECG in older adults? A prospective evaluation
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1Lausanne; 2San Francisco; 3Atlanta; 4Bethesda; 5Memphis; 6Pittsburgh

Aims & Purpose: Electrocardiographic (ECG) abnormalities are common in older adults, but data on their importance to predict future coronary heart disease (CHD) are conflicting. Our goal was to determine whether baseline ECG abnormalities or
Type 2 diabetes significantly modulates the impact of low left ventricular ejection fraction on the risk of cardiovascular events

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Feldkirch

Purpose: We aimed at prospectively investigating the impact of the left ventricular ejection fraction (LVEF) and of angiographically verified coronary artery disease (CAD) on the risk of cardiovascular events in patients with type 2 diabetes (T2DM) and in non-diabetic subjects.

Design & Methods: Cardiovascular events were recorded over 8 years in 629 consecutive patients undergoing coronary angiography for the evaluation of established or suspected stable CAD. CAD was diagnosed in the presence of significant coronary stenoses with lumen narrowing >=50%, and the baseline LVEF was determined invasively by ventriculography.

Results: The baseline prevalence of significant CAD was higher (68.6% vs. 55.5%; p = 0.006) in patients with T2DM (n = 137) than in non-diabetic subjects (n = 492); the baseline LVEF was similar in these two patient subgroups (65 ± 15% vs. 67 ± 15%; p = 0.253). Prospectively, significant CAD-Personality (150 ± 248) vs. 124 ± 260; p < 0.001) demonstrated a significant impact on LVEF (LVEF>70%: 0.71 ± 0.88 vs. 0.001) after multivariable adjustment both proved significantly predictive of cardiovascular events in a mutually independent manner. The incidence of vascular events was significantly higher in patients with T2DM than in non-diabetic subjects (43.8% vs. 30.1%; p = 0.003). In analyses with respect to the diabetes status, the LVEF strongly and significantly predicted cardiovascular events in non-diabetic subjects (HR = 0.72 [0.62–0.82]; p < 0.001) but not in patients with T2DM (1.00 [0.75–1.22]; p = 0.711). An interaction term LVEF*T2DM was significant (p = 0.047), indicating that the cardiovascular risk conferred by a low LVEF was significantly higher in non-diabetic subjects than in patients with T2DM. The presence of significant CAD proved significantly and independently predictive of vascular events both in non-diabetic subjects and in patients with T2DM (HRs 1.84 [1.26–2.67] vs. 0.001 and 2.45 [1.18–5.06]; p = 0.016, respectively).

Conclusions: From the results of this 8-year prospective cohort study we conclude that T2DM significantly modulates the cardiovascular risk conferred by a low left ventricular ejection fraction.

Development of type-d-personality in coronary patients: a longitudinal study

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²Feldkirch

Purpose: Recently, the association between Type-D-personality, a combination of negative affectivity and social inhibition with cardiovascular events has attracted great interest. No longitudinal data are available on the development of Type-D-personality in patients with established coronary artery disease (CAD). We therefore aimed at prospectively investigating the development of Type-D-personality in CAD patients.

Design & Methods: Over a follow-up period of 6 years we investigated the development of Type-D-personality in 129 patients with angiographically proven stable CAD by means of a validated standardised questionnaire (DS-14).

Results: The initial prevalence of Type-D-Personality was 24.8% in our cohort of coronary patients; during the follow-up of 6 years it increased to 40.3% (p for trend = 0.003). The prevalence rates of the two components of Type-D-Personality, social inhibition and negative affectivity initially were 37.2% and 40.3%, respectively. Whereas the prevalence of social inhibition increased to 72.9% over 6 years (p <0.001), the prevalence of negative affectivity did not change substantially (45.7% after 6 years, p = 0.324).

Conclusions: The prevalence of Type-D-personality in patients with stable CAD increases significantly over time, due to an increase in social inhibition. Given the important role of Type-D-personality for the prognosis for these patients, early preventive psychological interventions in coronary patients appear necessary.

Association Between Bone Mineral Density And Coronary Atherosclerosis in Patients With Type 2 Diabetes

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Feldkirch

Purpose: The association between low bone mass and angiographically determined coronary atherosclerosis in Patients with Type 2 Diabetes is unclear.

Design & Methods: We enrolled 254 consecutive Patients with Type 2 Diabetes undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD). Type 2 Diabetes was diagnosed according to WHO guidelines. BMD was assessed by dual X-ray absorptiometry. CAD was diagnosed in the presence of any coronary artery lumen narrowing at angiography, and coronary stenoses with lumen narrowing >=50% were considered significant.

Results: Of the total study cohort (mean age 67 ± 9 years) 36.2% (n = 92) had osteopenia and 7.1% (n = 29) had osteoporosis. Significant stenoses of coronary arteries were found in 65.4% (n = 166). The prevalence of significant stenoses did not differ between patients with normal bone mass, osteopenia or osteoporosis (70.7%, 59.8% and 58.6%; p = 0.173). This result did not change after multivariable adjustment for LDL cholesterol, HDL cholesterol, systolic and diastolic blood pressure, smoking, BMI, age and gender. Neither osteopenia (OR = 2.03 [95% CI 0.83–4.95]; p = 0.118) nor osteoporosis (OR = 1.23 [0.50–3.00]; p = 0.653) were associated with the presence of significant stenoses.

Conclusions: Low bone mass is not associated with the presence of significant coronary stenoses in patients with Type 2 Diabetes.

Population Attributable Stroke Risk is usually low: Similar Observations in Two Distinct Healthy Populations

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Aim: To determine population attributable stroke risk for major risk factors and to derive the potential to reduce stroke risk.

Methods: We compared rubrics from subjects from self-referred CARDIOCARE (COR) and physician referred KARDIOLAB (KAR) patients for 10 year stroke risk determined by PROCAM (European Journal of Clinical Investigation 2007;37:925–932). The potential for risk factors to reduce stroke risk was estimated by substituting measured results by ideal values of risk factors. We calculated the risk reduction attributable to achievement of two single risk factors: smokers became non-smokers, and systolic blood pressure (BP) was decreased to 130 mm Hg and then 10 year risk was recalculated for every subject.

Results: COR included N = 892 (48% female), mean age 59 ± 9 years, KAR included N = 548 (34% female), mean age 57 ± 9 years. COR vs KAR: less smokers (11% vs 28%), less diabetic patients (3% vs 9%), higher systolic BP (133 ± 15 vs 128 ± 19) and higher HDL (1.6 ± 1.4 vs 1.4 ± 0.4), lower AGLA coronary risk (6.6 ± 6.9 vs 8.3 ± 6.8), lower stroke risk (2.8 ± 3.2 vs 3.2 ± 3.4). Stroke risk for COR and KAR was reduced by achieved goals (non smoking, blood pressure ≤130 mm Hg) to 2.1 ± 2.2 vs 2.1 ± 2.1 (relative risk reduction ~25% and ~35%).

Conclusions: Achieving non smoking status and normal blood pressure in all subjects would reduce stroke risk by about 25% and 35% respectively, but the absolute 10 year risk reduction in an already very low risk population remains modest.

Cardiovascular Medicine 2011;14(3): Suppl 19


**P14**

**Emerging Risk Modifiers Based on Atherosclerosis Imaging: Fancy Radiology or Simple Bedside Ultrasound?**

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*Olten; Zurich; Basel*

**Background:** Atherosclerosis imaging stratifies coronary risk. Total plaque area of carotid arteries (TPA) and coronary artery calcium Agatston scores (CAC) were available in the same subjects. Pretest probability was defined by national guidelines (AGLA: Swiss adopted PROCAM).

**Methods:** In practice based subjects a) gender specific tertiles for TPA (Stroke 2007;38:2873) and CAC (J Am Coll Cardiol 2000;36:1253), b) posttest risk (AGLA-TPA and AGLA-CAC, Cardiovasculare Medizin 2007:10:139) and c) diagnostic performance of TPA and CAC to detect subjects with known vascular disease, measured by the area under the curve (AUC), were compared.

**Results:** 350 asymptomatic practice based subjects aged 59 ± 10 years (women: 31%) had a mean TPA of 57 ± 55 mm² and a mean CAC of 132 ± 346. Kappa agreement was 0.9 (p = 0.0001) for tertiles of TPA and CAC, with 115 (32%) of subjects exhibiting the 3. tertile TPA, but having the 1. tertile CAC (table). In 21 subjects aged 56 ± 10 years (women: 27%), where AGLA was available, posttest risk agreement for low, intermediate and high coronary risk was 0.25 (p < 0.0001). Sensitivity and specificity of AGLA-CAC was 48% and 89% respectively, to detect 10 year risk ≥20% as defined by AGLA-TPA. AUC of TPA and CAC to detect 80 subjects with known vascular disease (76 CAD, 4 TIA or stroke, 18 women) was 63% and 70% respectively (p NS).

**Conclusion:** In our practice based sample with a high prevalence of subclinical atherosclerosis, CAC significantly underestimated cardiovascular risk and has no higher diagnostic ability to detect subjects with known vascular events when compared to TPA.

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**P15**

**High-Density Lipoproteins Protect Pancreatic β-Cells from Apoptosis**

R. Sibler, L. Rohrer, A. Von Eckardstein

*Zurich*

**Aims:** In healthy individuals, an increased metabolic load is compensated by an increased β-cell mass and function. In type 2 diabetes however, this compensation collapses. Pre-diabetic and diabetic patients often exhibit a shift in their lipoprotein profile towards low plasma levels of high density lipoprotein (HDL), a high triglyceride concentration and an elevated fraction of small dense low density lipoprotein. We have described that HDL protects primary β-cells from human and murine pancreatic islets from basal, glucose- and interleukin-1β (IL-1β)-stimulated apoptosis.

In order to study the molecular mechanism of this effect we try to translate the results from primary cells to the INS-1E β-cell line.

**Design and Methods:** HDL was isolated from human plasma of healthy donors by sequential ultracentrifugation. Apolipoprotein (Apo) A-I was purified from HDL by ion exchange chromatography. INS-1E cells, a rat pancreatic tumor β-cell line, were exposed to native HDL, the delipidated protein moiety of HDL, purified apoA-I, sphingosine-1-phosphate (S1P), or reconstituted HDL (i.e. lipidated ApoA-I). Apoptosis was stimulated with IL-1β and analyzed by using the Cell Death Detection ELISA Plus Kit.

**Results:** HDL protects INS-1E cells from IL-1β-induced apoptosis in a robust and dose-dependent manner. Delipidated HDL (i.e. the protein moiety) protects INS-1E cells from IL-1β-induced apoptosis similarly to entire HDL. However the anti-apoptotic effects of purified ApoA-I, reconstituted HDL and S1P were much less pronounced.

**Conclusions:** The anti-apoptotic effects of HDL on β-cells originally observed in primary mouse or human islets can be reproduced in INS-1E cells. This opens avenues to unravel the receptors and signaling cascades mediating these effects. The more pronounced anti-apoptotic effect of the entire HDL protein moiety compared to ApoA-I raises the possibility that HDL contains a yet unknown anti-apoptotic agonist.

**P16**

**Transport of high density lipoproteins through the endothelium**

D. Perisa, P. Ohrsorg, L. Rohrer, A. Von Eckardstein

*Zurich*

Atherosclerosis is an ongoing, progressive accumulation of lipids in the arterial intima leading to plaque formation. Epidemiological studies show an inverse association of high density lipoprotein (HDL) cholesterol with atherosclerotic vascular events. HDL and its main apolipoprotein A-I (ApoA-I) have multiple anti-atherogenic functions: Some of these take place in the vessel wall. To get access to the intima and the lipid-laden macrophages, HDL has to pass the endothelial barrier. Previously, we showed that ApoA-I transcytosis is modulated by ATP binding cassette transporter (ABC) A1, and HDL transcytosis is modulated by ABCG1 and scavenger receptor BI (SR-BI). To elucidate the itinerary of ApoA-I and HDL through endothelial cells (ECs), we investigated localisation and distribution of fluorescently labelled ApoA-I and HDL. ApoA-I and HDL can be detected inside the cells after 5 min incubation. The signal is saturated without further change in intensity and localisation after incubation longer than 30 min. After 10 min, ApoA-I and HDL co-localise perfectly indicating the same route of trafficking. Further experiments show that HDL is not targeted to lysosomes nor the Golgi or the endoplasmic reticulum. However they co-localise with the early endosome marker Rab5 and endosome to trans-golgi network marker Rab9 to some extent, but not at all with the recycling endosome marker Rab11a. Further, we are analyzing the change in HDL distribution in the ECs upon pharmacological inhibition of known trafficking routes through the cells. We are corroborating our findings in the endothelium from aortic tissue. Live microscopy and electron microscopy experiments as well as biochemical data will help us to understand the itinerary of HDL through aortic ECs.

**P17**

**Statins for cardiovascular prevention according to different strategies: a cost analysis**


*Lausanne*

**Background:** several studies have shown that treatment with HMG-CoA reductase inhibitors (statins) can reduce CHD rates. Still, the cost-effectiveness of statin treatment in primary prevention of CHD has not been fully established. Objective: to estimate the costs of CHD prevention using statins in Switzerland according to different guidelines, over a 10-year period.

**Methods:** the overall 10-year costs, costs of one CHD death andverted and of one year without CHD were computed for the European Society of Cardiology (ESC), the International Atherosclerosis Society (IAS) and the US Adult Treatment Panel III (ATP-III) guidelines. Sensitivity analysis was performed by varying number of CHD events prevented and costs of treatment. Still, the cost-effectiveness of statin treatment in primary prevention of CHD has not been fully established.

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represented between 45% and 68% of the overall preventive cost. Changing the cost of statins, inflation rates or number of fatal and non-fatal CHD adverted showed ESC guidelines to be the most cost-effective.

Conclusion: The cost of CHD prevention using statins depends on the guidelines used. The ESC guidelines seem to yield the lowest costs per year of life gained free of CHD.

High sensitivity CRP is not a useful tool to further stratify subjects in primary care for their risk of myocardial infarction

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Background: Coronary risk assessment allows to categorize patients into low (L), intermediate (I) or high (H) risk. Additional risk stratifiers may increase the known low sensitivity of AGLA risk charts.

Methods: In subjects aged ≥45 years AGLA and REYNOLDS risk were calculated on our website (www.scopri.ch/riskalgorithms.htm). Total plaque area of the carotid arteries (TPA) was measured and posttest risk was calculated based on the Bayes formula (Kardiovaskuläre Medizin 2007;10:139) using the results from the TROMSO study (N = 6226, Stroke 2007;38:2873).

Results: A total of 213 subjects aged 59 ± 9 (±1SD) were studied. There were 101 women (47%). Mean 10 year risk was 4.3 ± 5.1% for AGLA, 4.8 ± 5.1 for REY (p = 0.099) and 15.0 ± 7.7 for TROMSO (p <0.0001). REY and TROMSO shifted 13 and 49 subjects into a higher and 8 and 0 into a lower risk category (table 1). The indication for intensified LDL lowering was found with AGLA, REY and TROMSO in 26, 22 (p NS) and 55 cases (p = 0.0007).

Conclusions: In our Swiss German population based middle-aged sample with a low mean global cardiovascular risk as determined by AGLA, the inclusion of hsCRP into risk prediction did not change significantly risk categories or LDL goals when compared to AGLA. However, when atherosclerosis imaging was used, a significantly large proportion of subjects was shifted into higher risk categories with treatment implication for LDL-cholesterol. Therefore, the reliance on hsCRP as clinically important risk modifier in primary care is debatable, whereas TPA posttest risk calculations may increase the sensitivity of AGLA.

Table

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<th>Frequency distribution of risk categories.</th>
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A diet rich in alpha-linolenic acid increases the platelet number by reducing the turnover

S. Stivala1, C. Lohmann1, S. Winnik2, T. F. Lüscher2, C. Matter1, J. H. Beer2
1Zürich; 2Baden

Hypothesis: Our recent studies showed a protective effect of the plant-derived n-3 fatty acid FA alpha-linolenic acid (ALA) by reducing experimental atherosclerosis and thrombosis in mice. Since ALA reduces platelets (P) activatability we hypothesized that this would lead to their prolonged survival.

Methods: 8-week-old male ApoE−/− mice were fed a 0.21 g% cholesterol diet containing either a high ALA (7.3 g%) or low ALA (0.03 g%) content for 23 weeks. The total P-count and the reticulated P fraction were assessed every month. Megakaryocyte-CFU was assessed on collagen-based cultures of bone marrow cells. P turnover was assessed by cleavage of GPibalpha as measured by the plasma glycocalicin (GC) concentration (ELISA), which was normalized by the p count (the GC-Index as parameter of platelets turnover). Plaque VCAM-1 and TNFalpha were analysed by immunohistochemistry and immunofluorescence.

Results: Dietary ALA increased the P-count time-dependently. After 16 weeks the P number differed substantially in the high vs low ALA group (1.893 ± 695x103 vs 1.138 ± 332x103/ul, n = 5, p <0.05), while the tail bleeding times were rather longer in the high ALA group (285 ± 83 vs 221 ± 56 seconds). The reticulated P fraction was not significantly different between the two groups (2.6% vs 3.9%, n = 5), and the number of megakaryocytic colonies was similar (19 ± 7 vs 16 ± 5, n = 2). GC was significantly lower in the high ALA group compared to the low ALA group (18.1 ± 3.2 vs 30.5 ± 5.6 ug/ml), and the GC Index was 6.5 ± 1.14 vs 15.86 ± 2.85, p <0.05. VCAM-1 and TNFalpha expression was significantly lower in the plaques of high ALA mice.

Conclusions: A diet rich in ALA increases the P-count by reducing P clearance. Mechanisms may include the inhibition of the TNF-Tissue Factor pathway and a reduced expression of adhesion molecules (VCAM, PECAM). The phenomenon might be of importance in transfusion medicine.