MULTIPLE BIOMARKERS FOR THE PREDICTION OF FIRST MAJOR CARDIOVASCULAR EVENTS AND DEATH.

Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, Jacques PF, Rifai N, Selhub J, Robins SJ, Benjamin EJ, D'Agostino RB, Vasan RS
Framingham Heart Study, Framingham, MA, USA.

Background: Few investigations have evaluated the incremental usefulness of multiple biomarkers from distinct biologic pathways for predicting the risk of cardiovascular events. **Methods:** We measured 10 biomarkers in 3209 participants attending a routine examination cycle of the Framingham Heart Study: the levels of C-reactive protein, B-type natriuretic peptide, N-terminal pro-atrial natriuretic peptide, aldosterone, renin, fibrinogen, D-dimer, plasminogen-activator inhibitor type 1, and homocysteine; and the urinary albumin-to-creatinine ratio. **Results:** During follow-up (median, 7.4 years), 207 participants died and 169 had a first major cardiovascular event. In Cox proportional-hazards models adjusting for conventional risk factors, the following biomarkers most strongly predicted the risk of death (each biomarker is followed by the adjusted hazard ratio per 1 SD increment in the log values): B-type natriuretic peptide level (1.40), C-reactive protein level (1.39), the urinary albumin-to-creatinine ratio (1.22), homocysteine level (1.20), and renin level (1.17). The biomarkers that most strongly predicted major cardiovascular events were B-type natriuretic peptide level (adjusted hazard ratio, 1.25 per 1 SD increment in the log values) and the urinary albumin-to-creatinine ratio (1.20). Persons with "multimarker" scores (based on regression coefficients of significant biomarkers) in the highest quintile as compared with those with scores in the lowest two quintiles had elevated risks of death (adjusted hazard ratio, 4.08; P<0.001) and major cardiovascular events (adjusted hazard ratio, 1.84; P=0.02). However, the addition of multimarker scores to conventional risk factors resulted in only small increases in the ability to classify risk, as measured by the C statistic. **Conclusions:** For assessing risk in individual persons, the use of the 10 contemporary biomarkers that we studied adds only moderately to standard risk factors. **(N. Engl. J. Med 2006; 355:2631-2639).**

INFLAMMATORY MARKERS IN A 2-YEAR FOLLOW-UP OF CORONARY ARTERY DISEASE

Mizia-Stec K, Gasior Z, Zahorska-Markiewicz B, Holecki M, Kumor P
Department of Cardiology, Silesian University School of Medicine, Ziolowa Street 45/47, PL-40-635, Katowice, Poland.

Our study was designed in an attempt to determine the dynamics of changes in serum tumor necrosis factor (TNF)-alpha, soluble forms of its receptors (sTNFR 1, sTNFR 2), and adhesion molecules (sE-selectin, sP-selectin, sVCAM-1, sICAM-1) over a 2-year follow-up of patients with coronary artery disease (CAD). The study involved 70 patients with stable CAD

(stable angina class II/III according to the Canadian Cardiovascular Society) and 20 apparently healthy subjects. Over the follow-up period a marked attenuation of angina ($P < 0.001$) was observed. Interventional treatment (percutaneous coronary intervention, coronary artery bypass grafting) was used in 53 CAD patients. Laboratory analysis revealed a significant decrease of serum TNF-alpha and sTNFR1 at 2 years (TNF-alpha: 12.1 ± 0.7 pg/ml; sTNFR 1: 1306 ± 46 pg/ml) as compared to baseline levels (16.5 ± 0.7 pg/ml, $P = 0.030$; 1551 ± 82 pg/ml, $P = 0.048$, respectively). The levels of sP-selectin (159 ± 7 vs 201 ± 14 ng/ml, $P < 0.01$) and sICAM-1 (133 ± 4 vs 153 ± 6 ng/ml, $P < 0.05$) were found to be significantly increased as compared to the baseline. Interventional procedures resulted in suppression of both cytokine (TNF-alpha, sTNFR 2) and adhesion molecule (sE-selectin, sP-selectin) activation in the CAD group. The baseline and post-follow-up TNF-alpha and sTNFR 1 levels showed persistent elevation in CAD patients as compared to the controls (9.0, 956.3 pg/ml, respectively; $P < 0.01$). There were no differences between baseline and final cytokines and adhesion molecules in healthy subjects. The course of CAD as modified by a clinically effective therapy is characterized by changes of immune markers activation. Revascularization seems to be an important factor suppressing both cytokine and adhesion molecule activation in CAD patients. **(Heart Vessels 2006; 21:302-308).**

PREVENTION OF VENOUS THROMBOEMBOLISM.

Pini M, Spyropoulos AC
Medicina Interna II, Ospedale di Fidenza, Fidenza, Parma, Italy.

Patients with clinical conditions such as surgery, trauma, and acute medical illness have a transiently increased risk of venous thromboembolism and merit consideration for adequate thromboprophylaxis. The choice of an appropriate pharmacologic or physical means of prophylaxis should be made taking into account both the thrombotic and bleeding risk associated with patient-related factors and the type of surgery or other disease state involved. A large number of randomized clinical trials, meta-analyses, and guidelines developed by scientific societies worldwide have addressed this issue and have provided information and recommendations that should be considered carefully. The aim of this review is to provide the practicing physician with a brief updated summary of the subject, stratifying those patients at low thrombotic risk who do not require specific thromboprophylaxis apart from early ambulation, from those at moderate or higher thrombotic risk. Patients at moderate thrombotic risk face a 10 to 20% risk of deep vein thrombosis (DVT) and require prophylaxis with low-dose unfractionated heparin or low molecular weight heparins (LMWHs) at a dosage < 3400 U once daily, or with graduated elastic stockings if their bleeding risk is high. Patients with an expected 20 to 40% DVT rate without prophylaxis are considered at high thrombotic risk and should be treated

preferentially with LMWHs at high prophylactic dosage (> 3400 U). Patients undergoing major orthopedic surgery face a DVT rate > 40%, are considered at very high risk of venous thromboembolism, and should be given either LMWHs at high prophylactic dosage, fondaparinux, or vitamin K antagonists-either alone or in association with intermittent pneumatic compression devices. **(Semin Thromb Hemost. 2006; 32:755-766).**

FLUORESCENCE SPECTROSCOPY EVALUATION OF FIBRINOGEN-BETA-ESTRADIOL BINDING

Goncalves S, Santos NC, Martins-Silva J, Saldanha C
Instituto de Biopatologia Quimica and Unidade de Biopatologia Vascular, Instituto de Medicina Molecular, Faculdade de Medicina de Lisboa, 1649-028 Lisboa, Portugal.

Fluorescence spectroscopy experiments were performed in order to study conformational changes induced by the binding of beta-estradiol to fibrinogen at different ligand concentrations. The association constant (K(a)) obtained for the fibrinogen-beta-estradiol binding was 6.47x10(6)M(-1), indicating a high affinity interaction. Fluorescence quenching experiments showed that approximately 30% of the tryptophan residues in the protein quaternary structure are accessible to ionic quenchers. The extent of quenching in the absence and presence of beta-estradiol was maximum for cesium ions and minimum for iodide, suggesting the presence of negatively charged residues in the vicinity of the tryptophan residues. The quenching parameters obtained at different beta-estradiol concentrations show alterations that confirm a conformational change, possibly due to a discrete reorganization of tryptophan residues during fibrinogen-beta-estradiol binding. This binding may be responsible for the effects of beta-estradiol on the decrease of erythrocyte aggregation and on cardiovascular risk reduction. **(J Photochem Photobiol B. 2007; 86:170-176)**.

NO EFFECT OF INCREASED WATER INTAKE ON BLOOD VISCOSITY AND CARDIOVASCULAR RISK FACTORS

Tonstad S, Klemsdal TO, Landaas S, Hoieggen A
Department of Preventive Cardiology, Ulleval University Hospital, N-0407 Oslo, Norway.

Observational data have suggested that increased water intake decreases the risk of CHD. A postulated mechanism is that increased water ingestion reduces blood viscosity. The aim of the present study was to assess the effect of increased fluid intake on blood viscosity. Men (n 67) and postmenopausal women (n 27) with one or more risk factors for CVD who reported intake of < or =0.5 litres water daily were randomised to a control group (n 31), an intervention group (n 32) that increased their daily water intake by 1 litre/d and an intervention group (n 31) that ingested 1 litre blueberry juice/d. All were

encouraged to continue their usual diet and lifestyle. Whole-blood viscosity and blood and urine chemistries were measured by standard techniques after 2 and 4 weeks. Urine volume increased (by a median of 872 and 725 ml in the water and blueberry juice groups, respectively, v. 10 ml in the control group; P< or =0.002), confirming the subjects' adherence to the protocol. Urine osmolality and urinary levels of Na, K and creatinine decreased in the water and blueberry juice groups v. the controls (P<0.05). No change was seen in whole-blood viscosity or in levels of fibrinogen, total protein, lipids, glucose, insulin, C-peptide or other chemistry and haematology variables. In conclusion, a postulated protective effect of increased water or fluid intake is not explained by a change in blood viscosity and increased fluid intake does not influence CVD risk factors in the short term. **(Br J Nutr. 2006; 96:993-996)**

HAEMORHEOLOGICAL, PLATELET AND ENDOTHELIAL INDICES IN RELATION TO GLOBAL MEASURES OF CARDIOVASCULAR RISK IN HYPERTENSIVE PATIENTS: A SUBSTUDY OF THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL

Spencer CG, Felmeden DC, Blann AD, Lip GY
Haemostasis, Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK.

Introduction and Methods: We tested the hypothesis that there was a significant relationship between haemorheological markers [white blood cell count (WCC), plasma viscosity (PV), haematocrit (HCT) and fibrinogen], as well as plasma von Willebrand factor (vWf, an index of endothelial damage/dysfunction) and soluble P-selectin (sP-sel, an index of platelet activation), to five global measures of cardiovascular risk [i.e. Framingham coronary heart disease (CHD), stroke and cardiovascular death score, the Pocock cardiovascular risk score and the sum of individual risk factors]. **Results:** Men with a high (> or = median, n = 156) Framingham 10-year CHD risk score had higher levels of WBC (P = 0.027), fibrinogen (P = 0.012) and vWF (P = 0.002) than 153 men with results < median. Men with a high 10-year stroke risk score had significantly higher levels of fibrinogen (P = 0.01) and vWF (P < 0.0001). In stepwise linear regression analysis in men, vWF and fibrinogen were independent predictors of the number of risk factors (P < 0.0001), whilst WCC, vWF and fibrinogen emerged as independent predictors of Framingham CHD risk (P < 0.0001), and fibrinogen and vWF predicted Framingham stroke risk (R(2) = 0.089, P < 0.0001). vWF, PV and fibrinogen were predictors of Pocock cardiovascular death risk (P < 0.0001) but vWF was the only independent predictor of Framingham cardiovascular death risk (P = 0.001). **Conclusions:** Abnormal haemorheological factors (particularly high plas-

ma fibrinogen levels) and endothelial damage/dysfunction (high vWF), but not platelet activation (sP-sel), are related to established cardiovascular and death risk scores. This relationship was most evident amongst male 'high-risk' hypertensive subjects. **(J Intern Med. 2007; 261:82-90).**

DIETARY FIBRE, NUTS AND CARDIOVASCULAR DISEASES

Salas-Salvado J, Bullo M, Perez-Heras A, Ros E
Unitat de Nutricio Humana, Facultat de Medicina i Ciencies de la Salut de Reus, Universitat Rovira i Virgili, Reus, Spain.

Dietary fibre has a range of metabolic health benefits. Through a variety of mechanisms, dietary fibre, and the viscous variety in particular, slows down gastric emptying and intestinal transit, decreases the rate of intestinal carbohydrate absorption, and increases faecal bile acid excretion. Therefore, consumption of some types of soluble fibre can enhance satiety, which is associated with a lower BMI, and reduce blood cholesterol and the postprandial glucose response. Surprisingly, the consumption of insoluble fibre from whole grains, though metabolically inert, has been associated with a reduction in the risk of developing coronary heart disease and diabetes in epidemiological studies. The likely reason is that whole grains, like nuts, legumes and other edible seeds, contain many bioactive phytochemicals and various antioxidants. After cereals, nuts are the vegetable foods that are richest in fibre, which may partly explain their benefit on the lipid profile and cardiovascular health. **(Br J Nutr. 2006; 96 Suppl 2:S45-S5).**

ARTERIAL ENDOTHELIUM AND ATHEROTHROMBOGENESIS. I – INTACT ENDOTHELIUM IN VASCULAR AND BLOOD HOMEOSTASIS

Martins e Silva J, Saldanha C
Unidade de Biopatologia Vascular do Instituto de Medicina Molecular da Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal.

Normal endothelium constitutes a physical and biological barrier between the blood and the vascular wall, and also acts as a sensor and transducer of various endogenous and exogenous factors that modulate the blood circulation. Endothelial activity in a given individual at any particular moment reflects the balance between cardiovascular risk factors, genetic predisposition and vascular protection mechanisms. The availability and activity of endothelium-derived nitric oxide (NO) is a major factor in these mechanisms. Further, vasoactive substances synthesized by

the vascular wall and/or by blood cells may affect the behavior of the blood-endothelium interface. Vasomotricity is dependent on the balance between vasodilator substances (particularly prostacylin) and vasoconstrictor products (mainly endothelin-1 and angiotensin II). The coagulation-anticoagulation or fibrinolysis balance is also affected by various different proteins. The mechanisms of these factors, on which blood fluidity depends under normal conditions and with intact endothelium, are discussed, along with mention of potential abnormalities, which will be examined in the second part of this review. **(Rev Port Cardiol. 2006; 25:1061-1083).**

ARTERIAL ENDOTHELIUM AND ATHEROTHROMBOGENESIS. II – THE ROLE OF ENDOTHELIAL DYSFUNCTION IN ATHEROTHROMBOTIC LESIONS

Martins e Silva J, Saldanha C
Unidade de Biopatologia Vascular do Instituto de Medicina Molecular, e Instituto de Biopatologia Quimica da Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal.

When cardiovascular risk factors prevail, the endothelial phenotype evolves to a dysfunctional state that is characterized by decreased endothelial-dependent vasodilation and the expression of proinflammatory, procoagulant, pro-oxidant and proliferation signals. Together, these alterations cause perfusion anomalies, promote the development and progression of atherosclerosis, and lead to atherosclerotic cardiovascular events. There is evidence that endothelial dysfunction is a predictor and prognostic risk factor of cardiovascular events, and characterization of the state of endothelial function in all susceptible individuals is strongly recommended as a preventive measure against atherosclerotic disease and to guide and monitor antiatherogenic treatment and atherosclerotic complications. **(Rev Port Cardiol. 2006; 25:1159-1186).**