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ABSTRACTS

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these techniques have shown that vascular calcification is highly correlated with cardiovascular disease mortality, especially in chronic kidney disease and diabetic patients. In vivo animal modeling and in vitro cell cultures studies are being used to determine inductive and inhibitory pathways that regulate vascular calcification.

Results: We have shown that major inhibitors of vascular calcification include pyrophosphate and osteopontin, and work in part by preventing calcium phosphate nucleation and crystal growth. In addition, phosphate has emerged as a major inducer of vascular calcification via effects on cell signaling as well as alterations in calcium x phosphate product. Small interfering RNA studies indicate that a major mediator of phosphate-induced smooth muscle cell mineralization is the sodium-dependent phosphate cotransporter, Pit-1.

Conclusions: Vascular calcification is an actively regulated process involving both inhibitory and inductive factors. Understanding which of these processes contributes to vascular calcification under different pathological conditions, and the underlying mechanisms regulating them, will aid in development of new therapies aimed at preventing and/or regressing vascular calcification.

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We-W39:5 FLOW-MEDIATED VASODILATION PREDICTS OCCULT CORONARY ARTERY DISEASE DETECTED BY POSITRON EMISSION TOMOGRAPHY

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Introduction: Impaired endothelium-dependent vasodilation predicts subsequent coronary events in patients with coronary artery disease (CAD), but its relationship to CAD in asymptomatic subjects is unclear.

Methods: We examined 198 male twins aged 47 to 57 years, free of symptomatic CAD. Subclinical ischemia was diagnosed by [¹³N] ammonia positron emission tomography (PET) at rest and after adenosine stress. A perfusion defect score quantified defects in 20 regions. Endothelial function was measured by ultrasound evaluation of brachial artery flow-mediated dilation (FMD). Generalized estimating equations (GEE) and fixed models were used for analysis.

Results: Hypertension was present in 32% of the subjects and hyperlipidemia in 39%; 18% were smokers and 40% obese. Myocardial perfusion defects were found in 72 (36%); most (83%) were reversible, indicating subclinical ischemia. There was a strong inverse correlation between FMD and reversible perfusion defect score (Spearman $r = -0.22$, $p = 0.002$) but not fixed defect score ($r = 0.002$, $p = 0.97$). From the lowest to the highest quartile of FMD, the prevalence of reversible defects was 15%, 25%, 36% and 43% respectively ($p < .001$). In multivariable analysis adjusting for CAD risk factors, the probability of reversible defects increased 34% (95% CI, 10%-65%, $p = .004$) for each quartile of decreasing FMD. In 28 twin pairs discordant for reversible defects, twins with defects were 5 times more likely to have abnormal FMD ($< 7\%$ dilation) than their co-twins without defects ($p = .03$).

Conclusions: In middle aged-men, endothelial dysfunction is a strong independent predictor of silent ischemia.

We-W39:6 EFFECT OF SMOKING HABITS ON THE RELATIONSHIPS BETWEEN ATHEROSCLEROSIS RISK FACTORS AND CAROTID IMT

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Objective: To evaluate the existence of an interaction between smoking habit and hypertension (HBP), diabetes (DBT), hypercholesterolemia (HC), hypertriglyceridemia (HTG) and hypoalbuminoproteinemia (Hypo-ALPHA) in determining carotid artery intima-media thickness (IMT) in patients attending a Lipid Clinic.

Methods: Data from 1113 never-smokers (564 HBP, 34 DBT, 961 HC, 226 HTG, 159 Hypo-ALPHA patients), 377 former-smokers (208 HBP, 24 DBT, 301 HC, 110 HTG, 109 Hypo-ALPHA patients), 315 current-smokers (126 HBP, 13 DBT, 272 HC, 115 HTG, 102 Hypo-ALPHA patients) were analysed. Among the 692 former/current smokers, 435 were light-smokers (packyear < 30) and 257 were heavy-smokers (packyear ≥ 30).

Results: Independent to the presence/absence of each vascular risk factor considered, carotid artery IMT was always higher in current-smokers, lower in

former-smokers and lowest in never-smokers. Similarly, IMT was also always higher in heavy-smokers, lower in light-smokers and lowest in never-smokers. A significant interaction with smoking habits was found, however, only when hypertension ($p = 0.03$) or diabetes ($p = 0.04$) were considered.

Conclusions: Smoking habit acts as an additional independent determinant of carotid IMT either in presence or absence of HC, HTG and Hypo-ALPHA. In view of the significant interaction with hypertension and diabetes, smoking cessation is particularly advisable in this kind of patients.

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We-W39:7 CAROTID INTIMA-MEDIA THICKNESS TESTING IDENTIFIES AT RISK PATIENTS MISSED BY FRAMINGHAM 10-YEAR RISK SCORING

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Objective: We compared common carotid intima-media thickness testing (cIMT) and the presence of carotid artery plaque to Framingham global 10-year CHD risk estimates (FRS) in identifying patients in need of aggressive risk modification.

Methods: Patients referred to our prevention clinic between 11/03-1/05 were evaluated using FRS and digital B-mode ultrasound to identify the presence of carotid artery plaque. Plaque was defined as an area of IMT ≥ 1.2 mm. Framingham 10-year risk categories included moderate risk ($< 10\%$), moderately high risk (10-20%) and high risk ($> 20\%$).

Results: We evaluated 209 patients at baseline. Mean age was 56 ± 9 years. Other FRS risk factors included: diabetes 12%, hypertension 68%, and smoking 7%. FRS at baseline: 59% were at moderate risk; 18% were at moderately high risk; and 22% were at high risk (CHD or CHD risk equivalent). Carotid plaque was identified in 67% of patients with moderate FRS risk, 92% of patients at moderately high FRS risk, and 83% at high FRS risk. Thus, plaque was identified in 74% of patients evaluated, including 73% of patients in the moderate and moderately high risk FRS groups. Additionally, there was an average of 1.6 ± 1.5 , 2.7 ± 1.4 and 2.3 ± 1.4 plaques/patient in the moderate FRS risk, moderately high FRS, and high risk FRS, respectively.

Conclusions: A majority of patients in both the moderate and moderately high FRS were actually shown to be high risk as per plaque identified by cIMT. Thus, cIMT is a powerful adjunct clinical tool to FRS in determining appropriate therapeutic management.

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We-W40 ANTITHROMBOTIC THERAPY

We-W40:1 NEW ANTICOAGULANTS FOR ATHEROTHROMBOSIS

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Limitations of existing anticoagulants have prompted the search for new agents that target specific steps in coagulation. In particular, there is a need for oral anticoagulants that are more convenient to administer than the vitamin K antagonists. When considering the targets for new anticoagulants, it is useful to divide the coagulation process into 3 steps; initiation, propagation, and thrombin activity. Thus, clotting is initiated by the factor VIIa/tissue factor complex, which activates factors IX and X, and propagated by factors IXa and Xa, which, in concert with their cofactors, factors VIIIa and Va, respectively, generate thrombin. The final step in coagulation is thrombin-mediated conversion of fibrinogen to fibrin.

Initiation of coagulation can be blocked by tissue factor pathway inhibitor (TFPI), nematode anticoagulant peptide (NAPc2) or active-site-blocked factor VIIa (FVIIai), all of which are parenteral agents. When compared with placebo in a Phase III trial, TFPI failed to reduce mortality in patients with severe sepsis. In a Phase II trial, NAPc2 reduced the risk of venous thromboembolism (VTE) in patients undergoing elective knee arthroplasty. This agent is now being evaluated in patients with acute coronary syndromes. In a Phase II trial, FVIIai, with or without adjunctive heparin, was no more effective than heparin alone in patients undergoing percutaneous coronary interventions. Attention is now focused on orally active inhibitors of inhibitors of factor VIIa.

Propagation of coagulation can be blocked by inhibitors of factors IXa or Xa, or by agents that inactivate the cofactors. TTP880, an orally active