Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis.

Clejan S, Japa S, Clemetson C, Hasabnis SS, David O, Talano JV.

BACKGROUND: Mast cells are prevalent in the shoulder of unstable atheromas; cardiac mast cells secrete proteases capable of activating matrix metalloproteinases. Histamine is essential in the inflammatory cascade of the unstable plaque. Ascorbate depletion has been correlated with histaminemia which has been shown to impair endothelial-dependent vasodilation. This study evaluates whether oxidative stress as measured by isoprostanes (PGF(2alpha)) coupled with an inflammatory state characterized by histaminemia predisposes patients to acute coronary syndrome (ACS). METHODS: Whole blood histamine, serum vitamin C, and serum PGF(2alpha) levels were drawn on 50 patients with ACS as determined by standard diagnostic criteria, 50 patients with stable coronary artery disease (SCAD), and 50 age and sex matched normal controls (C). RESULTS: Data were analyzed by stepwise discriminant and Spearman's rank correlation coefficient. A significant relationship exists between histamine and PGF(2alpha). As PGF(2alpha) rises above 60 pg/mL, an increase in histamine occurs in both the ACS and SCAD groups. A significant inverse relationship exists between ascorbate and histamine in the ACS versus C groups (P < 0.01) and the SCAD versus C groups (P < 0.01). CONCLUSION: Histamine and isoprostane levels increase in SCAD and ACS patients. Mast cell activation and lipid oxidation generated during atherosclerosis manifest this inflammatory response. Accelerated isoprostane formation and depleted ascorbate paired with histaminemia is active in CAD and predispose patients to acute coronary syndrome. Blood histamine alone may be a better risk factor for coronary events, and a better prognostic indicator than CRP even when combined with lipid indexes.
Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals.

Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukov A, Kondos GT.

PURPOSE: Electron beam tomography (EBT) is a noninvasive measure of coronary artery calcium (CAC), a marker for atherosclerosis. In this study we examined the association between conventional risk factors for coronary artery disease (CAD) and CAC. METHODS: EBT CAC screening was performed on 30,908 asymptomatic individuals aged 30 to 90 years. Prior to EBT screening, individuals provided demographic and CAD risk factor information. EBT utilized a C-100 EBT scanner, and the amount of CAC was determined using the Agatston scoring method. RESULTS: The results of this study demonstrate that for both men and women, all conventional risk factors were significantly associated with the presence of any detectable CAC, and the mean CAC score increased in proportion to the number of CAD risk factors. In age-adjusted (multivariable) logistic regression analysis, cigarette use, histories of hypercholesterolemia, diabetes, and hypertension were each significantly associated with mild to extensive CAC scores ($>/=10.0$). CONCLUSION: CAD risk factors are associated with higher atherosclerotic plaque burden in both men and women. The odds ratios associated with each risk factor relative to the extent of CAC are similar to those reported for the development of clinical CAD, suggesting the existence of an association between CAC (subclinical disease) and CAD (clinical disease).
Socioeconomic status variables predict cardiovascular disease risk factors and prospective mortality risk among women with chest pain. The WISE Study.


This study examined the relationship between socioeconomic status (SES), coronary artery disease (CAD) risk factors, and all-cause mortality in a cohort of women with chest pain. A total of 743 women (mean age = 59.6 years) with chest pain who were referred for coronary angiography completed a diagnostic protocol including CAD risk factor assessment, ischemic testing, psychosocial testing, and queries of SES. Patients were followed for about 2 years to track subsequent all-cause mortality. Results indicated that low SES was associated with CAD risk factors, including higher BMI and waist-hip ratios, cigarette smoking, lower reported activity levels, and a greater probability of hypertension. Low income also predicted all-cause mortality (RR = 2.7, 95% CI 1.4, 5.2), including after adjusting for proposed psychosocial and behavioral variables (RR = 5.9, 95% CI 1.2–29.7). Future research will require a thorough a priori focus on potential mechanisms to better understand SES effects on health.
Uncontrolled hypertension as a risk for coronary artery disease: patient characteristics and the role of physician intervention.

Hyman DJ, Pavlik VN.

Hypertension is the most widely treated cardiovascular risk factor, and there is clear evidence of the efficacy of treating systolic and diastolic blood pressure with existing antihypertensive agents in reducing stroke and cardiac disease. However, only about 25% of the US population has blood pressure controlled to at least 140 mm Hg systolic and 90 mm Hg diastolic. Hypertension control is a complex function of patient and physician behavior. Although poor hypertension control has historically been attributed to lack of health insurance or low utilization of available services, recently published analyses of national survey data and local physician and community samples suggest that physicians have a permissive attitude toward isolated mild systolic blood pressure elevations in the range of 140 to 160 mm Hg. The great majority of participants in health surveys report seeing a physician at least two times per year, and several investigators have documented that physicians are unlikely to increase treatment intensity for systolic elevations alone. Physician inaction toward elevated systolic blood pressure may be due to a reluctance to prescribe multiple drugs and/or lack of belief in the benefits of aggressive treatment to lower systolic blood pressure below 140 mm Hg.
Postchallenge hyperglycemia but not hyperinsulinemia is associated with angiographically documented coronary atherosclerosis in Korean subjects.

Kim HK, Lee SK, Suh CJ, Yoon HJ, Lee KY, Park HY, Kang MH.

Although hyperinsulinemia has attracted considerable attention as a possible risk factor for coronary artery disease (CAD), previous studies have not shown consistent results. Hyperglycemia could be an alternative explanation for the association between type 2 diabetes and atherosclerosis. Since previous studies have been mostly lacking coronary angiographic data, we analyzed the relationship between the presence and severity of coronary atherosclerosis based on angiography and hyperinsulinemia or hyperglycemia. Two hundred and thirty subjects underwent coronary angiography and a 75-g oral glucose tolerance test. Age, sex, waist-to-hip ratio, postchallenge 1-h and 2-h glucose levels, plasma triglyceride and HDL-cholesterol levels were different between those with or without CAD. However, there was no significant difference in the plasma insulin levels, area of insulin under the curve, and the ratio of the insulin- and glucose areas between the groups with and without CAD. Multiple logistic regression analysis including fasting-, 1-h, and 2-h glucose values and a variety of atherosclerosis risk factors showed that age, sex and postchallenge 2-h glucose levels were independent determinants of the presence of CAD. These results suggest that coronary atherosclerosis might be associated with postchallenge hyperglycemia, but not with hyperinsulinemia in Korean subjects.
Smoking and relation to other risk factors in postmenopausal women with coronary artery disease, with particular reference to whole blood viscosity and beta-cell function.


OBJECTIVES: To investigate possible associations between smoking habits and other coronary risk factors in postmenopausal women with known coronary heart disease (CHD). SETTING: The study was conducted at a university clinic. SUBJECTS: A total of 118 postmenopausal women with CHD verified with angiography, consecutively recruited. INTERVENTIONS: Conventional treatment for CHD. The women were randomized to hormone replacement therapy (HRT) with transdermal 17-beta oestradiol and medroxyprogesterone acetate, or to a control group. RESULTS: Smokers were younger (P = 0.005), had lower body mass index (P = 0.04) and lipoprotein Lp(a) levels (P = 0.02) compared with nonsmokers. Smokers had reduced beta-cell function (homeostasis model assessment, P = 0.006), whereas whole blood viscosity (WBV) was higher at all shear rates. WBV was not affected by HRT over a 12-month period. Oestrone levels were higher in smokers. CONCLUSIONS: Smoking adversely affects insulin secretion (beta-cell function) and WBV in postmenopausal women with established CHD, which could be of importance as a mechanism for the increased risk of CHD in smokers. The importance of smoking as a risk factor, overrides the effect of Lp(a), which is lower in smokers compared with nonsmokers.
Lack of association between plasma lipoprotein(a) concentrations and the presence or absence of coronary atherosclerosis.


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 assessed 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. Base-line data collection comprised conventional risk factors for coronary artery disease, lipids, fasting total homocysteine, and clinical characteristics. The relation between plasma Lp(a) levels and the presence or absence of coronary lesions was studied. The coronary angiograms were evaluated in a blinded manner. Any coronary stenosis was considered as coronary artery disease (CAD).

RESULTS: From the 100 patients, 40 were found to have no CAD and 60 had CAD assessed by coronary angiography. 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). After adjustment for age, sex, lipoproteins, and homocysteine levels, estimates of the relative risk of coronary heart disease for the fifth quintile of plasma Lp(a) as compared with the first quintile were 1.06 (95 percent confidence interval, 0.81 to 1.39). 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 the presence of coronary artery disease in patients referred for coronary angiography.
Association between the risk of coronary artery disease in South Asians and a deletion polymorphism in glutathione S-transferase M1.

Wilson MH, Grant PJ, Kain K, Warner DP, Wild CP.

South Asians living in Western societies show a greater risk of coronary artery disease (CAD) than the indigenous Caucasian population, probably related to the change to a Westernised lifestyle and an associated genetic susceptibility. Modulation of DNA damage and mutation caused by polymorphisms in detoxification enzymes, including the glutathione S-transferases (GSTs), is a well-established risk factor for tobacco-related carcinogenesis, and a similar change in cellular damage may be involved in the risk of vascular disease associated with tobacco smoking. In this study we examined whether polymorphisms in GST genes influence the risk of CAD in a case-control group of South Asians, following our recent observation of such an association in Caucasians from the same region of the UK. Blood was obtained from 170 patients of South Asian origin admitted for angiographic investigation of chest pain and from 203 controls. Patients were subdivided into those with and without previous acute myocardial infarction (AMI), and DNA was analysed for deletions in the GSTM1 and GSTT1 genes. An association was found between the prevalence of the GSTM1 null genotype and the risk of developing CAD in this study population. The frequency of the null genotype was 52.7% in healthy controls and 41.2% in patients (odds ratio [OR] 0.63, 95% confidence interval [95% CI] 0.42–0.95, p = 0.029). The effect was similar in subjects with or without a prior history of AMI. The association was also independent of smoking history, with both non-smokers and smokers showing a similar pattern of genotype distribution, the frequency of the null genotype being 51.2% in controls versus 37.0% in patients in 'never' smokers (OR 0.56, 95% CI 0.33–0.94, p = 0.037) and 60.0% in controls versus 46.2% in patients in 'ever' smokers (OR 0.57, 95% CI 0.25–1.28, p = 0.223). The association remained after adjusting for age, sex, body mass index and the presence or absence of stenosis. No significant associations were observed between the GSTT1 genotype and cardiovascular disease (chi(2) test, p > 0.1). The results of this study indicate that the GSTM1 null genotype is protective against both CAD and AMI. However, further study is required in order to elucidate the, as yet unexplained, mechanisms underlying this association.
The association of cholesteryl ester transfer protein polymorphism with high-density lipoprotein cholesterol and coronary artery disease in Koreans.

Park KW, Choi JH, Kim HK, Oh S, Chae IH, Kim HS, Oh BH, Lee MM, Park YB, Choi YS.

Cholesteryl ester transfer protein (CETP) is a key protein involved in high-density lipoprotein cholesterol (HDL-C) metabolism. It is known to affect plasma HDL-C levels, and its genetic regulation may be involved in the development of coronary artery disease (CAD). The aim of this study was to determine the frequency of the CETP Taq1B polymorphism in Koreans, and to investigate its relationship with plasma HDL-C levels and CAD. One-hundred and nineteen patients with significant CAD and 106 controls were examined with respect to their genotypes, lipid profiles and other risk factors of CAD. The genotype frequencies of B1B1:B1B2:B2B2 in males and females were 35.5%:50%:14.5% and 34.7%:42.6%:22.7%, respectively, which is comparable to previous reports in other ethnic groups. The B1B1 homozygote was associated with significantly lower HDL-C levels in females (p = 0.049) and non-smoking males (p = 0.037). After controlling for gender, body mass index (BMI) and smoking, the Taq1B polymorphism was still significantly associated with HDL-C levels (p = 0.046) and explained 5.4% of the HDL-C variation in this study. By univariate analysis, the B1B1 homozygote was a significant predictor of CAD (p = 0.043), and this was confirmed by multivariate analysis with traditional risk factors, i.e. the B1B1 homozygote was an independent predictor of CAD (p = 0.026, odds ratio = 1.97, 95% confidence interval: 1.08–3.57). In conclusion, the B1B1 homozygote of the CETP Taq1B polymorphism is associated with low HDL-C levels in females and non-smoking males, and may be an independent genetic risk factor of CAD in the Korean population.
The endothelial nitric oxide synthase (Glu298Asp and -786T>C) gene polymorphisms are associated with coronary in-stent restenosis.

Gomma AH, Elrayess MA, Knight CJ, Hawe E, Fox KM, Humphries SE.

AIMS: Coronary stent deployment is a major advance in percutaneous treatment of ischaemic heart disease, but 10–40% of patients still develop angiographic restenosis by 6 months due to neointimal hyperplasia. Patient-specific factors, including genetic factors, can contribute to this process. We have conducted a prospective study to examine the involvement of genetic risk factors (eNOS, ACE, MMP-3, IL-6, and PECAM-1) in restenosis following coronary stent deployment. METHODS AND RESULTS: A total of 226 patients who underwent elective and successful coronary artery stenting to de novo lesions in native coronary arteries were studied. Two hundred and five (90.7%) patients were restudied by coronary angiogram at 6 months and the stented lesions were assessed using an automated quantitative angiography system. Genotype was determined by polymerase chain reaction (PCR) and restriction enzyme digestion. Restenosis rate, defined as >or=50% diameter stenosis, was 29.3%. The overall genotype frequency distributions were in Hardy–Weinberg equilibrium for all variants. Carriers of the 298Asp allele of the eNOS Glu298Asp polymorphism showed a higher frequency of restenosis with an odds ratio of 1.88 (95%CI: 1.01–3.51, P=0.043) compared to 298Glu homozygotes. Carriers of the -786C allele of the eNOS -786T>C polymorphism also showed a higher frequency of restenosis with odds ratio of 2.06 (95%CI: 1.08–3.94, P=0.028). These effects were essentially additive and were independent of other classical risk factors. Other studied genes did not show significant association with coronary in-stent restenosis. CONCLUSION: In patients with coronary artery disease, the possession of the 298Asp and -786C variants of the eNOS gene are a risk factor for coronary in-stent restenosis, demonstrating the importance of the nitric oxide system in restenosis.
The association of lower testosterone level with coronary artery disease in postmenopausal women.

Kaczmarek A, Reczuch K, Majda J, Banasiak W, Ponikowski P.

OBJECTIVE: Testosterone (T) is assumed to be a risk factor for coronary artery disease (CAD). However, recent studies have demonstrated a beneficial effect of T on myocardial ischaemia in men with CAD. To assess the potential role of T in CAD in postmenopausal women we investigated the association between T level and CAD and relationship between T and other CAD metabolic risk factors. RESULTS: Within the 12-month study period, 108 consecutive, postmenopausal women (age 62+/−7 years) referred for diagnostic coronary angiography were prospectively included in the study. In all patients serum level of T, sex hormone-binding globulin (SHBG), total cholesterol (T-chol), LDL-chol, HDL-chol, triglycerides (TG), apolipoproteins A(1) and B (apo A(1), apo B), lipoprotein a [Lp(a)], and C reactive protein were measured. Testosterone free index (TFI) was calculated as Tx100/SHBG. CAD was documented in 51 (47%) patients (CAD+). Women with CAD had decreased T level and lower TFI (T: 0.99+/−0.4 vs. 1.41+/−0.7 nmol/l, P=0.005; TFI: 3.2+/−1.4 vs. 4.2+/−2.2, P=0.04, CAD+ vs. CAD−, respectively). No difference in SHBG was found between the two groups. In 16 women (six CAD+, 10 CAD−) who were on hormonal replacement therapy (HRT+) we observed significantly elevated T level and TFI (T: 1.62+/−0.5 vs. 1.15+/−0.7 nmol/l; TFI: 5.0+/−2.2 vs. 3.5+/−1.8, HRT+ vs. HRT−, respectively, P<0.05). When these women were excluded from the analysis, T level remained decreased in CAD+ group (0.96+/−0.4 vs. 1.22+/−0.5 nmol/l, CAD+ vs. CAD− respectively, P<0.02). CAD+ group had an unfavourable profile of metabolic CAD risk factors as evidenced by elevated T-chol, LDL-chol, Lp(a), apoB, and decreased apoA(1) (P<0.05 vs. CAD− in all comparisons). Neither T nor TFI correlated with CAD metabolic risk factors (r<0.2, P>0.1 for all correlations), apart from an inverse correlation between T and Lp(a) (r=−0.24, P=0.04). CONCLUSION: In postmenopausal women decreased T level is associated with CAD independently of the other CAD metabolic risk factors. Hormonal replacement therapy tends to increase T level which may further support the beneficial role of HRT in postmenopausal women.
Chlamydia pneumoniae as an emerging risk factor in cardiovascular disease.

Kalayoglu MV, Libby P, Byrne GI.

Recent appreciation of atherosclerosis as a chronic, inflammatory disease has rekindled efforts to examine the role that infectious agents may play in atherogenesis. In particular, much interest has focused on infection with Chlamydia pneumoniae. The possibility that a prokaryote contributes to atherogenesis has high clinical interest, as C pneumoniae infection may be a treatable risk factor. To review the evidence implicating C pneumoniae in the pathogenesis of atherosclerosis, we searched MEDLINE for articles published between January 1966 and October 2002 on the association of C pneumoniae and atherosclerosis. We also used online resources, texts, meeting abstracts, and expert opinion. We included 5 types of studies (epidemiological, pathology based, animal model, cell biology, and human antibiotic treatment trials) and extracted diagnostic, pathophysiologic, and therapeutic information from the selected literature; consensus was reached on interpretation discrepancies. Chlamydia pneumoniae is associated with atherosclerosis by epidemiological and pathology-based studies. Animal model and cell biology studies suggest that the pathogen can modulate atheroma biology, including lipid- and inflammatory-related processes. Although some preliminary antibiotic treatment trials in patients with coronary artery disease indicated a reduction in recurrent coronary events, larger studies have not shown benefits in individuals with stable coronary artery disease. It is unlikely that C pneumoniae infection is necessary to initiate atherosclerosis. Furthermore, conventional antibiotic therapy may not eradicate the organism or reduce mortality in individuals with atherosclerotic vascular disease. Nevertheless, the current body of evidence establishes this pathogen as a plausible, potentially modifiable risk factor in cardiovascular disease.
New coronary risk factors: is there a difference between diabetic patients with microalbuminuria compared to those without microalbuminuria?

Yeo CK, Hapizah MN, Khalid BA, Nazaimoon WM, Khalid Y.

Diabetes mellitus is an important risk factor for the development of coronary artery disease. The presence of microalbuminuria, which indicates renal involvement in diabetic patients, influences the progression of coronary artery disease. New coronary risk factors such as C-reactive protein (CRP), Lipoprotein a [Lp (a)] and fibrinogen are increasingly being recognized as important cardiovascular prognostic factors. These new coronary risk factors could account for the worse cardiovascular prognosis in diabetic patients with microalbuminuria. Our cross sectional study was to compare the prevalence of elevated CRP and the levels of Lp (a) and fibrinogen between diabetic patients with microalbuminuria and those without microalbuminuria. Diabetic patients with overt coronary artery disease were excluded from the study. A total of 108 patients were recruited of which 57 patients had microalbuminuria and 51 were without microalbuminuria. There was no difference in the number of patients with elevated CRP between these two groups. There were also no significant differences in the mean values of Lp (a) and fibrinogen between diabetic patients with and without microalbuminuria. The inflammatory marker CRP and coagulopathy markers i.e. Lp (a) and fibrinogen seem not to be perturbed in diabetic patients with microalbuminuria.
Small LDL and its clinical importance as a new CAD risk factor: a female case study.

Superko HR, Nejedly M, Garrett B.

The underlying metabolic cause of coronary heart disease in many patients is not high blood cholesterol. In fact, the Framingham study has reported that 80% of individuals who go on to have coronary artery disease have the same total blood cholesterol values as those who do not go on to have a cardiovascular event. The most common metabolic contributor to coronary artery disease is the atherogenic lipoprotein profile, characterized by an abundance of highly atherogenic small, dense low-density lipoprotein particles and a deficiency of the high-density lipoprotein (HDL) subtype most associated with coronary artery disease protection (HDL(2b)). This trait is present in 50% of men with coronary artery disease and is not reflected by total or low-density lipoprotein cholesterol values. While fasting triglycerides tend to be higher, and HDL cholesterol lower in patients with the atherogenic lipoprotein profile, the majority have triglyceride and HDL cholesterol values generally accepted to be in the "normal" range. An abundance of basic science and clinical trial evidence convincingly indicates that the presence of an atherogenic lipoprotein profile signifies a three-fold increased risk for a cardiovascular event and rapid arteriographic progression, but it also identifies a group of patients who respond particularly well to specific therapeutic interventions. Often the most effective interventions are the least expensive.
Homocysteine, folate and vitamin B12 as risk factors for acute myocardial infarction in a Southeast Asian population.

Ng KC, Yong QW, Chan SP, Cheng A.

INTRODUCTION: Hyperhomocysteinaemia is an emerging risk factor for coronary artery disease (CAD) and most studies done to date are in Caucasian populations. We aimed to determine whether hyperhomocysteinaemia is a risk factor for acute myocardial infarction (AMI) in a Southeast Asian population comprising different ethnic groups and relate it to the traditional risk factors and plasma vitamin B12 and folate levels. MATERIALS AND METHODS: This was a case-control study comprising 168 AMI patients and 141 controls with a median age of 55 years (range, 27 to 77 years), living in Singapore. Homocysteine was measured by fluorescence polarisation immunoassay and vitamin B12 and folate were measured by electrochemiluminescence immunoassay. Logistic regression analysis was use to test the association of homocysteine, vitamin B12 and folate with the occurrence of AMI. The study was approved by the Tan Tock Seng Ethics Committee. RESULTS: We found that the odds of having AMI was higher for subjects with hypertension, smoking habit, lower plasma folate and vitamin B12 levels and non-Chinese ethnic group. On the other hand, plasma homocysteine level was not significantly associated with AMI. The baseline levels of plasma total homocysteine in both AMI patients and controls were higher than other studies (median values between 12 and 14 umol/L). CONCLUSION: In our population, plasma total homocysteine levels were not associated with AMI but low plasma levels of folate and vitamin B12 were independently associated.
The effect of Mediterranean diet on the risk of the development of acute coronary syndromes in hypercholesterolemic people: a case–control study (CARDIO2000).

Pitsavos C, Panagiotakos DB, Chrysohoou C, Skoumas J, Papaioannou I, Stefanadis C, Toutouzas PK.

BACKGROUND: Hypercholesterolemia has been identified as a major risk factor for the development of coronary artery disease. The aim of this study was to assess the effect of a Mediterranean diet on the development of non–fatal acute coronary syndromes (ACS) in hypercholesterolemic people, with or without statin treatment. METHODS: During 2000–2001, 848 randomly selected patients with a first event of coronary heart disease and 1078 cardiovascular disease–free people, matched to the patients by sex, age and region, were studied. Treatment of hypercholesterolemia with statin and the adoption of a Mediterranean diet were recorded. RESULTS: Hypercholesterolemia with statin and the adoption of a Mediterranean diet were recorded in 534 (63%) out of 848 coronary patients and 399 (37%) out of 1078 control participants. One hundred and seventy-one (32%) of the hypercholesterolemic patients and 168 (42%) of the hypercholesterolemic control participants were treated with statins and also followed a Mediterranean diet. The analysis showed that the combination of a Mediterranean diet and statin medical therapy is associated with an additional reduction of the coronary risk (odds ratio = 0.57, P < 0.01), independently from cholesterol levels and the other cardiovascular factors. CONCLUSION: The adoption of a Mediterranean diet by hypercholesterolemic people seems to reinforce the benefits from statin treatment on lipid levels and reduces the risk of developing ACS. However, it is hard to claim that our findings suggest causal evidence, and in order to explain the potential common mechanism between diet and statin treatment much remains to be learned.
Altered fibrin clot structure in the healthy relatives of patients with premature coronary artery disease.

Mills JD, Ariens RA, Mansfield MW, Grant PJ.

BACKGROUND: A family history of premature coronary artery disease (CAD) is an independent cardiovascular risk factor. Fibrin clots composed of dense fiber networks are found in young CAD patients and may occur in the relatives of such individuals. METHODS AND RESULTS: The ex vivo fibrin structure of 100 healthy male relatives of patients with premature CAD and 100 age-matched control subjects was assessed by measurement of permeability (K(s)), fiber mass–length ratio (micro), and turbidity (lag phase and maximum absorbency [max DeltaAbs]). Scanning electron microscopy was performed on selected samples. Relatives and controls shared similar levels of conventional cardiovascular risk factors. K(s) was lower in relatives than in controls, 12.2 (11.1 to 13.3) versus 15.2 (14.0 to 16.5) x10(-9) cm(2) (P<0.001), associated with a smaller decrease in micro, 8.5 (7.7 to 9.2) versus 9.7 (8.9 to 10.5) x 10(13) Da/cm (P<0.05), respectively. Lag phase was shorter in relatives than in controls, 39 (37 to 41) versus 47 (44 to 50) seconds (P<0.001), and max DeltaAbs was higher in relatives, 0.78 (0.74 to 0.82) versus 0.71 (0.67 to 0.74) in controls (P=0.02), which indicates the presence of thicker fibers in relatives. After adjustment for fibrinogen levels, lag phase and K(s) remained significantly different between relatives and control subjects. Scanning electron microscopy images confirmed increased fiber diameter in relatives, possibly of reduced density. Factor XIII Val34Leu and fibrinogen Aalpha Thr312Ala and Bbeta −455 G/A showed no association with clot structure. CONCLUSIONS: The male relatives of patients with premature CAD form fibrin clots that begin polymerization more quickly, have thicker fibers, and are less permeable than those of control subjects.
Obesity and cardiovascular disease.

Poirier P, Eckel RH.

Obesity is a major contributor to the prevalence of cardiovascular disease in the developed world, and yet has only recently been afforded the same level of attention as other risk factors of coronary artery disease. Obesity is a chronic metabolic disorder associated with cardiovascular disease and increased morbidity and mortality. It is apparent that a variety of adaptations/alterations in cardiac structure and function occur as excessive adipose tissue accumulates, even in the absence of comorbidities. Shifts toward a less physically demanding lifestyle are observed today throughout different populations, and this scourge associated with obesity implicates a corresponding increase in the number of individuals afflicted with the metabolic syndrome, which defines the obese patient as being "at risk." Adipose tissue is not simply a passive storehouse for fat, but an endocrine organ that is capable of synthesizing and releasing into the bloodstream a variety of molecules that may impact unfavorably the risk factor profile of a patient. Indeed, obesity may affect atherosclerosis through unrecognized variables and risk factors for coronary artery disease such as dyslipidemia, hypertension, glucose intolerance, inflammatory markers, and the prothrombotic state. By favorably modifying lipids, decreasing blood pressure, and decreasing levels of glycemia, proinflammatory cytokines, and adhesion molecules, weight loss may prevent the progression of atherosclerosis or the occurrence of acute coronary syndrome events in the obese high-risk population.
Minor thalassemia as a protective factor against cerebrovascular accidents.

Namazi MR.

Hypertension, hypercholesterolemia, and coronary artery disease are among the risk factors of cerebrovascular accidents. After age, hypertension is the most powerful stroke risk factor. Abnormalities of serum lipids are regarded as risk factors for cerebrovascular accidents. A significant reduction in stroke risk among persons treated with cholesterol-reducing medicines known as statins are reported. Stroke risk nearly doubles in those with antecedent coronary artery disease. Moreover, polycythemia and high hematocrit levels are considered to be potential stroke risk factors. Minor thalassemia is associated with decreased prevalence of arterial hypertension and myocardial infarction (the second effect observed only in males.) Total cholesterol and LDL levels are lower in minor thalassemics, as is the blood viscosity. Therefore, it could be hypothesized that minor thalassemia could afford some protection against cerebrovascular accidents.
The roles of stromelysin-1 and the gelatinase B gene polymorphism in stable angina.

Kim JS, Park HY, Kwon JH, Im EK, Choi DH, Jang YS, Cho SY.

Matrix metalloproteinases contribute to vascular remodeling by breaking down extracellular-matrix while new matrix is synthesized. Of the variety of MMPs, stromelysin-1 and gelatinase B may have key roles in coronary artery atherosclerosis. Moreover, The 5A/6A polymorphism in the promoter region of the stromelysin-1 gene may be a pathogenetic risk factor for acute myocardial infarction. Gelatinase B (92-kDa type IV collagenase and MMP-9) is one of the MMPs found to be highly expressed in the disruption-prone regions of atherosclerotic plaques. C- to T substitution at the promoter site (-1562) resulted in the higher promoter activity of the T-allelic promoter. The R279Q polymorphism in exon 6 led to the substitution of adenosine by guanine, and was a common polymorphism in the general population. We evaluated the relation between these polymorphisms and stable angina, the severity of atherosclerosis in coronary artery disease, and in-stent restenosis after percutaneous coronary angioplasty. The study population was composed of 131 patients with stable angina (mean age 61.3 years, 89 males) and 117 control subjects (mean age 59.3 years, 59 males). Coronary angiographies were performed in all cases at Yonsei University Cardiovascular Hospital from February 1998 to June 2000. The genotype for each polymorphism was determined using a SNaPshot™ kit and by restriction fragment length polymorphism (RFLP). The prevalence of 5A containing a polymorphism of the stromelysin-1 gene was higher in the stable angina group than in control patients, but no difference in the two polymorphisms of the gelatinase B gene was found between the two groups. By multiple logistic analysis, the 5A-allele of the stromelysin-1 gene was found to be an independent risk factor of stable angina with an odds ratio of 2.29 (95% CI: 1.19–4.38). However, the severity of atherosclerosis in coronary artery or in stent restenosis was not related to any polymorphism of stromelysin-1 or gelatinase B. Our results show that functional genetic variation of stromelysin-1 could be a significant risk factor for stable angina, and might play an important role in coronary atherosclerosis involving vascular remodeling.
Aortic pulse pressure and extent of coronary artery disease in percutaneous transluminal coronary angioplasty candidates.


BACKGROUND: Pulse pressure and aortic stiffness are both predictors of coronary artery disease. Whether these parameters are directly related to coronary structural alterations has never been studied. METHODS: From September 1999 to September 2000, the following data were collected from 99 eligible patients: invasive intra-aortic systolic and diastolic blood pressures (BP), extent of coronary artery disease, cardiovascular risk factors, and the incidence of angiographically documented restenosis after coronary angioplasty. RESULTS: In the study population, independent determinants of aortic pulse pressure were age, gender, aortic mean BP, heart rate, and extent of coronary artery disease ($r^2 = 0.57$, $P < .0001$). In univariate analysis, invasive aortic, but not noninvasive brachial, mean pressure ($P = .017$) and pulse pressure ($P = .027$) were significantly associated to the extent of coronary artery disease. In a multiple regression analysis, only male gender ($P = .013$) and the level of aortic pulse pressure ($P = .023$) were independently associated with the extent of coronary heart disease. Restenosis was angiographically documented in 11 patients (11%). There was a borderline significant association of restenosis to aortic mean BP ($P = .05$) and to a past history of multiple previous angioplasties ($P = .03$). CONCLUSIONS: In this study, aortic pulse pressure was a significant risk factor for the extent of coronary artery disease. There was only a borderline significant association of restenosis to the steady, but not pulsatile, component of aortic BP in the stent era.
Risk factors for coronary artery disease in women.

Knopp RH.

Because cardiovascular disease (CVD) is the most important cause of death in women in the United States, it is imperative that the main risk factors for CVD in women be identified and modified. The risk factors that have the strongest impact on the incidence of CVD in women are not necessarily the same as those for men. The risk for women increases at menopause, most likely because of the decrease in levels of circulating estrogen. The classic risk factor for CVD is altered lipid levels. In middle-aged women, elevated low-density lipoprotein cholesterol levels are somewhat less important relative to lowered levels of high-density lipoprotein cholesterol and elevated triglyceride levels as independent risk factors. The metabolic syndrome, which encompasses a range of conditions known to be CVD risk factors, also has a greater impact on the incidence of CVD in women than in men. Various emerging risk factors appear to be important indicators for vascular disease in women, including C-reactive protein, homocysteine, and lipoprotein(a) levels. Many of these risk factors are affected by hormone replacement therapy, which may diminish CVD risk in postmenopausal women. Because of the complex origin of CVD, it is important to target the full array of risk factors for modification, rather than focusing on a single factor or treatment to the exclusion of other important markers.
Polymorphism in the 5'-flanking region of human glutamate-cysteine ligase modifier subunit gene is associated with myocardial infarction.

Nakamura S, Kugiyama K, Sugiyama S, Miyamoto S, Koide S, Fukushima H, Honda O, Yoshimura M, Ogawa H.

BACKGROUND: Human glutamate-cysteine ligase (GCL) is a rate-limiting enzyme for the synthesis of glutathione that plays a crucial role in antioxidant defense mechanisms in most mammalian cells, including vascular cells. Oxidants transcriptionally upregulate GCL genes for glutathione synthesis, providing a protective mechanism against oxidative stress-induced cellular dysfunction. This study examined the hypothesis that variation in the GCL genes may be associated with coronary artery disease in which oxidative stress plays a pathogenetic role. METHODS AND RESULTS: We searched for the common variants in the 5'-flanking region of the GCL modifier subunit (GCLM) gene in patients with myocardial infarction (MI). We found a polymorphism (−588C/T) in which the T allele showed lower promoter activity (40% to 50% of C allele) in response to oxidants in the luciferase reporter gene assay. Allele frequencies were determined by polymerase chain reaction–based analysis of restriction fragment length polymorphism in 429 patients with MI and 428 control subjects (as defined by angiography) in Kumamoto Prefecture, Japan. The frequency of the T polymorphism was significantly higher in the MI group than in the control group (CT and TT genotypes: 31.5% in MI group versus 19.2% in control group; P<0.001). In multiple logistic regression analysis, the T polymorphism was a risk factor for MI independent of traditional coronary artery disease risk factors (odds ratio, 1.98; 95% confidence interval, 1.38 to 2.83; P<0.001). CONCLUSIONS: These findings suggest that the −588T polymorphism of the GCLM gene may suppress GCLM gene induction in response to oxidants and that it is a genetic risk factor for MI.
Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease.


After rupture of an arteriosclerotic plaque in a coronary artery, platelets play a crucial role in the subsequent thrombus formation, leading to myocardial infarction. An increased mean platelet volume (MPV), as an indicator of larger, more reactive platelets, may represent a risk factor for myocardial infarction. However, this hypothesis is still controversial and most studies addressing the role of MPV were performed comparing patients suffering from myocardial infarction with healthy controls. We intended to identify patients at high risk of suffering myocardial infarction in a group of patients with known coronary artery disease. One hundred and eighty-five consecutive patients with stable coronary artery disease were compared with 188 individuals who had suffered myocardial infarction. Patients within the highest quintile of MPV (≥ 11.6 fl) had a significantly higher risk of experiencing a myocardial infarction compared with patients within the lowest quintile (OR = 2.6, 95% CI 1.3–5.1) in a multivariate analysis that included sex, age, body mass index, hyperlipidaemia, hypertension, smoking and diabetes mellitus. Our results indicate that patients with pre-existing coronary artery disease and an increased MPV (≥ 11.6 fl) are at higher risk of myocardial infarction. These patients can be easily identified during routine haematological analysis and could possibly benefit from preventive treatment.
Angiotensin II as a cardiovascular risk factor.

Gavras I, Gavras H.

A renin-angiotensin level that is inappropriately high for the systemic blood pressure and the state of sodium balance is now recognized to be one of the modifiable cardiovascular risk factors. Angiotensin acts both as a circulating hormone and as a locally acting paracrine/autocrine/intracrine factor. The adverse effects of angiotensin on the heart include the mechanical results of elevated resistance to the pumping function of the myocardium, as well as the effects of neurohumoral abnormalities on various cardiac structures. In addition, cardiac damage follows acute ischaemic injury or chronic energy starvation due to coronary artery disease, attributable to either mechanical obstruction (atherosclerotic and/or thrombotic) or functional stenosis (vasospasm). Activation of the renin-angiotensin system has several haemodynamic and humoral consequences, all of which may damage the myocardium. These include acute myocardial ischaemia, left-ventricular hypertrophy, arrhythmias, alterations in the coagulation-fibrinolysis equilibrium, increased oxidative stress, and pro-inflammatory activity. A brief review of some of the mechanisms by which activation of the renin-angiotensin system can inflict damage on the heart is presented.
BACKGROUND: Fibrinogen, known to influence the coagulation process, is an independent risk factor for coronary artery disease (CAD). However, its association with myocardial infarction (MI) and its predictive potential for short-term mortality, in an ongoing clinical practice, has not been characterized. OBJECTIVES: In a high-risk outpatient practice we sought to demonstrate whether baseline fibrinogen levels related to MI rather than CAD alone, and whether baseline serum fibrinogen levels predicted mortality over a short-term follow-up. METHODS AND RESULTS: From a total of 2126 patients with baseline fibrinogen measurements (mean age, 56 +/- 12 years, 35% female), 1187 patients with CAD (n = 606 with MI) and 939 patients without CAD were evaluated in an active preventive cardiology unit of a large city hospital. Logistic regression models were used to determine the association of fibrinogen with differing CAD presentations. Fibrinogen quartile showed a significant correlation with CAD both univariately and after adjustment for Framingham risk score (odds ratio [OR] = 1.22, P <.001). Fibrinogen levels were significantly associated with the presence of CAD and history of MI (adjusted OR = 1.25, P =.001). Fibrinogen did not show a significant association to CAD when MI was not considered in the analysis (OR = 1.01, P =.82). In this same clinical cohort, after a mean follow-up of 24 +/- 13 months, 41 patients had died. Consistent with the observed association with MI, fibrinogen quartile showed a graded independent relation to mortality in a cohort of both men and women (hazard ratio = 1.81, P <.001). CONCLUSIONS: In the clinical setting of an outpatient clinic, fibrinogen was directly associated with the presence of MI and was revealed to be an independent short-term predictor of mortality.
Platelet membrane glycoprotein Ibalpha gene –5T/C Kozak sequence polymorphism as an independent risk factor for the occurrence of coronary thrombosis.


OBJECTIVE: To explore the potential of the GPIbalpha gene variable number tandem repeat (VNTR) and –5T/C Kozak polymorphisms to act as independent risk factors for myocardial infarction. METHODS: 256 patients aged 33–80 years (180 caucasian, 76 Indian Asian) were recruited at cardiac catheterisation for any diagnostic indication, and divided into two groups: group A, with confirmed previous myocardial infarction evident on ECG or ventriculogram (88 patients, 79 men, 9 women) and group B, with no evidence of myocardial infarction (168 patients, 101 men, 67 women). RESULTS: There was no significant difference in race, age, hypertension, smoking status, or family history between the infarct and non-infarct groups, though there was a significant difference in sex (89.8% male in group A, 60.1% male in group B, p < 0.001). Genotype analysis showed a strong association between the GPIbalpha Kozak homozygous TT genotype and the occurrence of myocardial infarction (group A: TT 85.2%, TC 12.5%, CC 2.3%; group B: TT 67.3%, TC 32.7%, p = 0.001). No significant association was found between myocardial infarction and the GPIbalpha VNTR, although analysis of the CC VNTR genotype against all other GPIbalpha VNTR genotypes showed a marginal association with myocardial infarction (p = 0.059). There was no association between the Kozak sequence polymorphism (p = 0.797) or GPIbalpha VNTR (p = 0.714) and the degree of vessel disease. CONCLUSIONS: The homozygous TT Kozak genotype may be a significant factor in the outcome of coronary artery disease completed by myocardial infarction. Conversely, the Kozak C allele in the heterozygous state TC may confer some protection against myocardial infarction.
LDL Particles Containing Apolipoprotein CIII Are Independent Risk Factors for Coronary Events in Diabetic Patients.

Lee SJ, Campos H, Moye LA, Sacks FM.

OBJECTIVE: Triglyceride-rich lipoproteins that contain apolipoprotein CIII (apoCIII) are prominent in diabetic dyslipidemia. We hypothesized that these lipoproteins increase coronary disease risk in diabetic patients beyond that caused by standard lipid risk factors. METHODS AND RESULTS: Diabetic patients with previous myocardial infarction were followed for 5 years, and 121 who had a recurrent coronary event were matched to 121 who did not. VLDL and LDL that contained or did not contain apoCIII (CIII+ or CIII−) were prepared by immunoaffinity chromatography and ultracentrifugation. IDL was included in the LDL fraction. LDL CIII+, rich in cholesterol and triglyceride, was the strongest predictor of coronary events (relative risk [RR] 6.6, P<0.0001, for 4th versus 1st quartile). LDL CIII+ comprised 10% of total LDL. The main type of LDL, LDL CIII−, was less strongly predictive (RR 2.2, P=0.07). The increased risk associated with LDL CIII+ was unaffected by adjustment for plasma lipids, apoB, non−HDL cholesterol, or the other VLDL and LDL types. For VLDL CIII+, RR 0.5, P=0.07; for VLDL CIII−, RR 2.3, P=0.046. The presence of apolipoprotein E with CIII on VLDL and LDL did not affect risk. CONCLUSIONS: LDL with apoCIII strongly predicts coronary events in diabetic patients independently of other lipids and may be an atherogenic remnant of triglyceride−rich VLDL metabolism.
A prospective study in primary care in patients without vascular disease comparing levels of coronary risk factors in those recommended for lipid-lowering drugs based on either absolute risk or absolute risk reduction.

Ramachandran S, Croft P, Neary RH.

In the United Kingdom, the current recommendation is that lipid-lowering drugs should be prescribed for primary prevention only to subjects with an absolute coronary risk (AR) greater than 15% in 5 years (i.e., myocardial infarction or angina). However, to achieve greater benefit it may be preferable to direct treatment to those patients showing the greatest absolute risk reduction (ARR). The aim of this study was to compare the characteristics of subjects eligible for lipid-lowering drugs based on the AR criteria or on an ARR of >4.45%. A prospective study was carried out over 29 months in primary care in a part of the United Kingdom with a prevalence of coronary disease nearly 20% above the national average. Risk factors were recorded in men and women aged 30-75 years who were being considered by their primary care physician for lipid-lowering drug therapy. Of the 2351 patients included in the study, 2139 (91%) and 101 (4.3%) were, respectively, below and above the criteria for treatment by both AR and ARR criteria. In 111 (4.7%) subjects, treatment was recommended based on only one of the criteria—82 on AR and 29 on ARR. Comparing these two groups, those treated on AR only were older (mean age 68.1 years [SD, 4.1] vs. 49.1 years [SD, 4.6]; p<0.0001) and had a lower total cholesterol (260 vs. 288 mg/dL; p=0.015), higher high-density lipoprotein cholesterol (50 vs. 43 mg/dL; p=0.003), lower low-density lipoprotein cholesterol (160 vs. 184 mg/dL; p=0.03), a lower total to high-density lipoprotein cholesterol ratio (5.4 vs. 7.1; p<0.0001), and lower triglycerides (258 vs. 435 mg/dL; p=0.007). The AR group also had a higher mean systolic blood pressure (170.9 vs. 158.9 mm Hg; p=0.013), presumably an attribute of their greater age. Although the AR and ARR groups did not show a difference in the proportion of males or diabetics, there was a significantly greater proportion of smokers in the latter group (72% vs. 35%; p=0.001). In conclusion, treatment recommendations based on AR alone would result in nontreatment of young subjects with significant hyperlipidemia and at high relative risk of coronary disease, whereas lipid-lowering drugs would be given preferentially to patients whose main coronary heart disease risk factors are age and hypertension but not hyperlipidemia. By contrast, treatment recommendations based on ARR ensure that lipid-lowering drugs are directed to patients who will derive the most benefit. Furthermore, delaying treatment in younger subjects at high relative risk but not high AR results in their accumulating significant coronary risk in the years before their AR exceeds an arbitrary threshold.
before lipid-lowering drugs are prescribed.
A common variant in the ABCA1 gene is associated with a lower risk for premature coronary heart disease in familial hypercholesterolaemia.


Familial hypercholesterolaemia (FH) is a common autosomal codominant hereditary disease caused by defects in the LDL receptor (LDLR) gene, and one of the most common characteristics of affected subjects is premature coronary heart disease (CHD). In heterozygous FH patients, the clinical expression of FH is highly variable in terms of the severity of hypercholesterolaemia and the age of onset and severity of CHD. Identification of mutations in the ATP binding cassette transporter 1 (ABCA1) gene in patients with Tangier disease, who exhibit reduced HDL cholesterol and apolipoprotein A1 concentrations and premature coronary atherosclerosis, has led us to hypothesise that ABCA1 could play a key role in the onset of premature CHD in FH. In order to know if the presence of the R219K variant in the ABCA1 gene could be a protective factor for premature CHD in FH, we have determined the presence of this genetic variant by amplification by PCR and restriction analysis in a group of 374 FH subjects, with and without premature CHD. The K allele of the R219K variant was significantly more frequent in FH subjects without premature CHD (0.32, 95% CI 0.27 to 0.37) than in FH subjects with premature CHD (0.25, 95% CI 0.21 to 0.29) (p<0.05), suggesting that the genetic variant R219K in ABCA1 could influence the development and progression of atherosclerosis in FH subjects. Moreover, the K allele of the R219K polymorphism seems to modify CHD risk without important modification of plasma HDL-C levels, and it appears to be more protective for smokers than non-smokers.
Importance of identifying the overweight patient who will benefit the most by losing weight.

Reaven GM.

Because being overweight increases the risk for type 2 diabetes, hypertension, and coronary heart disease, the rapid increase in the prevalence of overweight and obesity in the United States represents a major health problem. The relationship between overweight and obesity and these conditions is probably due to insulin resistance and compensatory hyperinsulinemia. However, although it is known that weight loss in insulin-resistant and hyperinsulinemic persons will be of substantial metabolic benefit, it is equally well established that many overweight and obese persons are not insulin resistant. In the absence of insulin resistance and its manifestations, the risk for type 2 diabetes, hypertension, and coronary heart disease is reduced and the metabolic benefit of weight loss in the substantial number of overweight persons who are insulin sensitive is relatively minimal. Consequently, it is important to identify which overweight persons are most likely to be insulin resistant by considering their family history; blood pressure; and plasma glucose, triglyceride, and high-density lipoprotein cholesterol concentrations. Thoughtful use of this information will help identify the subset of persons who will benefit the most from intense therapeutic efforts to lose weight.
Identifying women at risk for coronary artery disease.

Women differ from men in presentation, pathology, and prevention of CAD. After women at risk are identified, primary and secondary prevention measures should be implemented for individual workers and their families. To be effective in managing CAD, risk reduction measures should be employed. However, nurses also need to be able to identify the often atypical symptoms that women present with in CAD to provide appropriate and swift care (Anderson, 2001). The occupational health nurse is in a unique position to assist in improving the health of many within the worksite. The nurse can perform the risk assessment and plan with employees to reduce the identified risks and, thus, improve the quality of their lives. Getting employees engaged in self care by helping to set realistic goals and acting as a support in their endeavors toward this end could be the incentive needed to begin on the path to a healthier lifestyle.
Prospective evaluation of the effect of an angiotensin I converting enzyme gene polymorphism on the long term risk of major adverse cardiac events after percutaneous coronary intervention.

Hamon M, Fradin S, Denizet A, Filippi-Codaccioni E, Grollier G, Morello R.

OBJECTIVE: To evaluate prospectively the influence of an angiotensin I converting enzyme (ACE) gene polymorphism on long term clinical outcome of patients with established coronary artery disease treated by percutaneous coronary intervention. DESIGN AND SETTING: Prospective observational study in a university hospital. PATIENTS: Consecutive series of 1010 patients with symptomatic coronary artery disease who underwent successful coronary stent placement from November 1996 to April 1998. MAIN OUTCOME MEASURES: Long term clinical outcome was obtained and the rates of major adverse cardiac events (death, non-fatal acute myocardial infarction, unstable angina, and revascularisation) were compared according to the insertion/deletion (I/D) polymorphism of the ACE gene. RESULTS: Of the 1010 patients 29% had the DD genotype, 51% had the ID genotype, and 20% had the II genotype. All baseline clinical angiographic and procedural characteristics were identical in the three groups of patients. Event-free survival during the follow up period (median two years) was identical in patients with the II genotype compared to those with one or two D alleles. The predictors of long term survival were age, diabetes, ejection fraction, and extension of coronary artery disease. ACE genotype had no influence on the long term survival. Additional analyses assuming dominant and recessive effects of the D allele also failed to find any association; nor did the examination of low risk subgroups. CONCLUSIONS: The ACE I/D polymorphism does not influence the long term prognosis of patients with coronary disease treated by percutaneous coronary intervention, and screening patients for this gene polymorphism is not useful for secondary prevention strategies.
Screening of family members of patients with premature coronary heart disease: results from the EUROASPIRE II family survey.

De Sutter J, De Bacquer D, Kotseva K, Sans S, Pyorala K, Wood D, De Backer G; EUROpean Action on Secondary Prevention through Intervention to Reduce Events II study group

AIMS: To determine whether the Joint European Societies' recommendations that first degree blood relatives of patients with premature coronary heart disease (CHD) should be screened for coronary risk factors is being followed and, if so, how effectively these relatives are being managed.

METHODS AND RESULTS: Using a postal questionnaire, 3322 relatives (siblings and children ≥18 years of age) of 1289 index patients in the EUROASPIRE II survey who had suffered from premature CHD (men under 55 years and women under 65 years) were asked whether screening for coronary risk factors had occurred and, if so, how they were being managed in terms of lifestyle advice and drug therapies. Overall, screening for coronary risk factors because of CHD in the family was only performed in 11.1% of siblings and 5.6% of children. However, prevalences of different cardiac risk factors were high both in relatives and offspring and a clear familial clustering could be documented. Less than 50% of siblings and 25% of children were given some general lifestyle advice regarding cardiac risk factors. Moreover, active interventions such as starting antihypertensive or lipid lowering drugs were rarely carried out, particularly in children of patients with premature CHD.

CONCLUSIONS: European physicians rarely screen family members of patients with premature CHD for cardiac risk factors. General lifestyle style advice or active treatment for these risk factors are also rarely given. However, since these family members have a high prevalence and familial clustering of cardiac risk factors, they form an ideal target population for primary prevention of CHD in high-risk patients.
Diagnostic value of C-reactive protein in patients with angiographically documented coronary heart disease.

Eren E, Yilmaz N, Pence S, Kocoglu H, Goksu S, Kocabas R, Kadayifci S.

AIM: The aim of this study was to evaluate the diagnostic value of serum C-reactive protein (CRP) level measurement in predicting coronary artery disease (CAD) that can be shown angiographically. METHODS: CRP levels were determined in the blood of 198 patients (patients group, PG) with angiographically documented coronary artery disease and compared with that of 85 patients (control group, CG) who had a clinical indication for coronary angiography but have no angiographically determined coronary artery stenosis, as well as with that of 41 healthy volunteers as a healthy control group (HG) who did not have any complaint and did not have coronary angiography. CRP levels were measured 24 hours prior to angiography in PG and CG patients, and in the morning after not having eaten for same time. Any coronary artery stenosis or plaque formation was defined as CAD. Severity of the disease was assessed by both the number of diseased vessels (0 to 3) and the degree of stenosis (<50% mild, 50-70% moderate and >70% severe). RESULTS: Receiver Operating Characteristics (ROC) curves of CRP in angiographically documented CAD group showed a diagnostic value of 0.659 in female patients, followed by 0.542 in male patients, in predicting CAD. CRP levels were found to be significantly different between groups, higher in PG (6.2 +/- 0.86 mg/L) than those of CG (3.7 +/- 0.92 mg/L) and HG (0.854 +/- 0.2 mg/L) (p<0.05). CRP levels were not associated with the number of diseased vessels, neither with the degree of the occlusion (p>0.05). Multiple logistic regression analysis after adjustment for the established coronary risk factors showed CRP as an independent discriminating risk factor for CAD. CONCLUSION: It is concluded that CRP measurement has a value in predicting the presence of angiographically documented CAD. However, CRP levels were not associated with the degree or severity of CAD.
Negative emotion and coronary heart disease. A review.

Sirois BC, Burg MM.

This article reviews literature regarding the influence of negative emotions, specifically depression, anger/hostility, and anxiety on coronary heart disease (CHD). For each domain, evidence is presented demonstrating the deleterious effects of negative affect on health outcomes in patients with CHD. This is followed by a discussion of the manner in which emotional factors are transduced into cardiac health risk factors. The pathophysiological mechanisms by which negative emotions have been found to exert an influence on CHD are highlighted. Finally, a general overview of the outcomes of interventions designed to ameliorate the effects of these negative emotional states on cardiovascular health are reviewed. Several treatment studies are described in detail for the purpose of elaborating the types of multicomponent interventions that attempt to address negative emotions in populations with CHD.
Socioeconomic status variables predict cardiovascular disease risk factors and prospective mortality risk among women with chest pain. The WISE Study.


This study examined the relationship between socioeconomic status (SES), coronary artery disease (CAD) risk factors, and all-cause mortality in a cohort of women with chest pain. A total of 743 women (mean age = 59.6 years) with chest pain who were referred for coronary angiography completed a diagnostic protocol including CAD risk factor assessment, ischemic testing, psychosocial testing, and queries of SES. Patients were followed for about 2 years to track subsequent all-cause mortality. Results indicated that low SES was associated with CAD risk factors, including higher BMI and waist-hip ratios, cigarette smoking, lower reported activity levels, and a greater probability of hypertension. Low income also predicted all-cause mortality (RR = 2.7, 95% CI 1.4, 5.2), including after adjusting for proposed psychosocial and behavioral variables (RR = 5.9, 95% CI 1.2–29.7). Future research will require a thorough a priori focus on potential mechanisms to better understand SES effects on health.
Lifestyle intervention of hypocaloric dieting and walking reduces abdominal obesity and improves coronary heart disease risk factors in obese, postmenopausal, African-American and Caucasian women.

Nicklas BJ, Dennis KE, Berman DM, Sorkin J, Ryan AS, Goldberg AP.

BACKGROUND: There are few empirical data to support the claim that weight loss improves coronary heart disease (CHD) risk factors in postmenopausal women; nor is it known if there are racial differences in changes of body fat distribution, lipids, glucose tolerance, and blood pressure with weight loss. This study determined the efficacy of a lifestyle weight loss intervention in reducing total and abdominal obesity and improving CHD risk factors in obese Caucasian and African-American postmenopausal women. METHODS: Body composition (dual-energy x-ray absorptiometry), abdominal fat areas (computed tomography scan), lipoprotein lipids, insulin, glucose tolerance, and blood pressure were measured before and after 6 months of hypocaloric diet and low-intensity walking in 76 overweight or obese (body mass index > 25 kg/m(2)), Caucasian (72%) or African-American (28%), postmenopausal (age = 60 +/- 5 years) women who completed the study. RESULTS: Absolute amount of body weight lost was similar in Caucasians (-5.4 +/- 3.6 kg) and African Americans (-3.9 +/- 3.6 kg), but Caucasian women lost relatively more fat mass (p < .05). Both groups decreased their subcutaneous abdominal fat, and Caucasian women decreased their visceral fat area, but there were no racial differences in the magnitude of abdominal fat lost. The intervention decreased triglyceride and increased high-density lipoprotein and high-density lipoprotein 2 cholesterol in both races, and it decreased total and low-density lipoprotein cholesterol in Caucasian women (p < .05–.0001). Fasting glucose and glucose area during the oral glucose tolerance test decreased (p < .0001) in Caucasian women, whereas insulin area decreased in both Caucasian (p < .01) and African-American (p < .05) women. Blood pressure decreased the most in women with higher blood pressures at baseline. Changes in lipids, fasting glucose and insulin, their responses during the oral glucose tolerance test, and blood pressure were not different between racial groups. CONCLUSIONS: Weight loss achieved through a lifestyle intervention of energy restriction and increased physical activity is an equally effective therapy in African-American and Caucasian obese, postmenopausal women for improving glucose and lipid CHD risk factors.
Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes.

de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, McCabe CH, Cannon CP, Braunwald E.

BACKGROUND: Monocyte chemoattractant protein-1 (MCP-1) is a chemokine responsible for the recruitment of monocytes to sites of inflammation. MCP-1 appears to play a critical role at multiple stages in atherosclerosis, including the initiation of the fatty streak, promotion of plaque instability, and remodeling after myocardial infarction. METHODS AND RESULTS: MCP-1 was measured from frozen plasma specimens in 279 healthy volunteers and 2270 patients with acute coronary syndromes enrolled in the Oral Glycoprotein IIb/IIIa Inhibition with Orbifiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI) 16 trial. Median [25th, 75th percentiles] MCP-1 levels were 157 [124, 196] pg/mL in healthy volunteers and 178 [128, 238] pg/mL in the OPUS-TIMI 16 population (P<0.001). In OPUS-TIMI 16, baseline MCP-1 levels were associated with older age, female sex, hypertension, diabetes, prior coronary disease, and renal insufficiency (P<0.01 for each) but not with smoking status, body mass index, ejection fraction, troponin I or C-reactive protein. After adjustment for differences in baseline characteristics, ECG changes, troponin I, and C-reactive protein, an MCP-1 level >75th percentile (corresponding to the 90th percentile in the healthy volunteers) was associated with an increased risk of death or myocardial infarction through 10 months of follow-up (adjusted hazard ratio, 1.53; 95% CI, 1.09 to 2.14; P=0.01). CONCLUSIONS: In a large cohort of patients with acute coronary syndromes, an elevated baseline level of MCP-1 was associated both with traditional risk factors for atherosclerosis as well as an increased risk for death or myocardial infarction, independent of baseline variables. Because it appears to play a crucial role at multiple stages of atherosclerosis, MCP-1 is attractive as a surrogate biomarker and merits further study as a potential therapeutic target.
Area characteristics, individual-level socioeconomic indicators, and smoking in young adults: the coronary artery disease risk development in young adults study.

Diez Roux AV, Merkin SS, Hannan P, Jacobs DR, Kiefe CI.

The 10-year follow-up examination in 1995–1996 to the population-based Coronary Artery Disease Risk Development in Young Adults Study was used to compare the strength with which socioeconomic indicators at the individual and area levels are related to smoking prevalence and to investigate contextual effects of area characteristics. When categories based on similar percentile cutoffs were compared, differences across area categories in the odds of smoking were smaller than differences across categories based on individual-level indicators. In Whites, there was evidence of a significant contextual effect of area characteristics on smoking: Living in the most disadvantaged area quartiles was associated with 50–110% higher odds of smoking, even after controlling for individual-level socioeconomic indicators. Clear contextual effects of area characteristics were not present in Blacks, but there was evidence that contextual effects may emerge at higher levels of individual-level socioeconomic position. Similar results were obtained for census tracts and block groups. Even in the presence of contextual effects, area measures may underestimate associations of individual-level variables with health outcomes. On the other hand, as illustrated by the presence of contextual effects, area- and individual-level measures are likely to tap into different constructs.
Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI–sponsored WISE study.


OBJECTIVES: We sought to evaluate hypoestrogenemia of hypothalamic origin and its association with angiographic coronary artery disease (CAD) in premenopausal women. BACKGROUND: Coronary artery disease in premenopausal women appears to have a particularly poor prognosis. Primate animal data suggest that premenopausal CAD is strongly determined by psychosocial stress–induced central disruption of ovulatory cycling and resulting hypoestrogenemia. METHODS: We assessed reproductive hormone blood levels and angiographic CAD using core laboratories in 95 premenopausal women with coronary risk factors who were enrolled in the National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation and were undergoing coronary angiography for evaluation for suspected ischemia. RESULTS: Premenopausal women with angiographic CAD (n = 13) had significantly lower estradiol, bioavailable estradiol, and follicle-stimulating hormone (FSH) (all p < 0.05) than women without angiographic CAD (n = 82), even after controlling for age. Hypoestrogenemia of hypothalamic origin, defined as estradiol <184 pmol/l (50 pg/ml), FSH <10 IU/l, and luteinizing hormone <10 IU/l, was significantly more prevalent among the women with CAD than those without CAD (9/13 [69%] vs. 24/82 [29%], respectively, p = 0.01). Hypoestrogenemia of hypothalamic origin was the most powerful predictor of angiographic CAD in a multivariate model (odds ratio [OR] 7.4 [confidence interval (CI) 1.7 to 33.3], p = 0.008). Anxiolytic/sedative/hypnotic and antidepressant medication use were independent predictors of hypoestrogenemia of hypothalamic origin in a multivariate model (OR 4.6 [CI 1.3 to 15.7], p = 0.02, OR 0.10 [CI 0.01 to 0.92], p = 0.04, respectively). CONCLUSIONS: Among premenopausal women undergoing coronary angiography for suspected myocardial ischemia, disruption of ovulatory cycling characterized by hypoestrogenemia of hypothalamic origin appears to be associated with angiographic CAD.
Serum fatty acid levels, dietary style and coronary heart disease in three neighbouring areas in Japan: the Kumihama study.

Nakamura T, Azuma A, Kuribayashi T, Sugihara H, Okuda S, Nakagawa M.

CHD mortality is extremely low in Japan, particularly in rural districts, when compared with that in Western countries. This has been partly attributed to the difference in dietary lifestyle. We investigated the factors influencing CHD mortality in a rural coastal district of Japan, comprising mercantile, farming, and fishing areas with distinct dietary habits. We prospectively examined the incidence of CHD from 1994 to 1998, as well as coronary risk factors and serum fatty acid concentrations. The incidence of angina pectoris was significantly (P=0.01) lower in the fishing area than in the mercantile and farming areas. Blood pressure, physical activity, prevalence of diabetes, serum levels of uric acid and HDL-cholesterol were similar between the three areas. Total- and LDL-cholesterol levels were significantly lower but the smoking rate was markedly higher in the fishing area than in the other two areas. Serum levels of saturated fatty acids and n-6 polyunsaturated fatty acids (PUFA) were lowest in the fishing area, but n-3 PUFA did not differ significantly. The n-6:n-3 PUFA ratio was lowest and eicosapentaenoic:arachidonic acid was highest in the fishing area. Although many previous studies have emphasized the beneficial effect of n-3 PUFA in preventing CHD, the present study indicated that a lower intake of n-6 PUFA and saturated fatty acids has an additional preventive effect on CHD even when the serum level of n-3 PUFA is high because of high dietary fish consumption.
Poor sleep increases the prospective risk for recurrent events in middle-aged women with coronary disease. The Stockholm Female Coronary Risk Study.

Leineweber C, Kecklund G, Janszky I, Akerstedt T, Orth-Gomer K.

OBJECTIVE: We investigated the prognostic impact of sleep complaints in women with CHD and also examined whether the association between sleep problems and cardiac events could be explained by depression. METHODS: All women patients, aged 65 or under who were admitted with an acute coronary syndrome between 1991 and 1994 in Stockholm, were followed for 5 years for recurrent coronary events. Sleep complaints and depression were measured at baseline using standardized questionnaires. Quality of sleep, restorative function of sleep, and snoring were assessed by the Karolinska Sleep Questionnaire (KSQ), and depressive symptoms by a questionnaire developed by Pearlin. RESULTS: Poor sleep quality was associated with recurrent cardiac events. After multivariate adjustment for age, and standard risk factors, the hazard ratio (HR) for women with poor as compared with good sleep quality was 2.5 (95% CI: 1.2–5.2). Controlling for depression did not change this result substantial. Not waking up well-rested yielded a similarly increased risk (HR=2.4; 95% CI: 1.2–4.6). Women with both poor sleep quality and depression had a worse prognosis than women free from these complaints (HR=2.6; 95% CI: 1.0–6.4). Heavy snoring was not related to prognosis. CONCLUSIONS: Our results indicate that poor sleep and sleep without a restorative function are associated with poor prognosis in female coronary patients. This association is not explained by depressive symptoms or by standard coronary risk factors.
Large-scale evidence that the cardiotoxicity of smoking is not significantly modified by the apolipoprotein E epsilon2/epsilon3/epsilon4 genotype.


Results from two small studies, involving a total of only 174 cases, have suggested that the increased risk of coronary heart disease conferred by cigarette smoking is substantially affected by genotype at the apolipoprotein E (APOE) epsilon2/epsilon3/epsilon4 polymorphism. We have established APOE genotypes in 4484 patients with acute myocardial infarction diagnosed before the age of 55 years for male and 65 years for female patients, and in 5757 controls with no history of cardiovascular disease. On average, the hazard ratio for myocardial infarction was 1.17 (95% CI 1.09–1.25; p<0.00001) per stepwise change from epsilon3/2 to epsilon3/3 to epsilon3/4 genotype. Among individuals in this study with known cigarette smoking status, the hazard ratio for myocardial infarction in smokers versus non-smokers was 4.6 (4.2–5.1). There was, however, no significant difference between the smoker/non-smoker hazard ratios for those with different APOE genotypes (chi2(2)=0.69; p=0.7). When differences in risk between different genotypes are not extreme (as with this APOE polymorphism), reliable assessment of hypothesised gene-environment interactions will often require the study of many thousands of disease cases.
Aortic valve sclerosis is associated with systemic endothelial dysfunction.

Poggianti E, Venneri L, Chubuchny V, Jambrik Z, Baroncini LA, Picano E.

OBJECTIVES: We sought to examine the association between aortic valve sclerosis (AVS) and systemic endothelial manifestations of the atherosclerotic process. BACKGROUND: Clinical and experimental studies suggest that AVS is a manifestation of the atherosclerotic process. Systemic endothelial dysfunction is an early sign of the atherosclerotic process and can be assessed by ultrasonography of the brachial artery. METHODS: A total of 102 in-hospital patients (76 men; mean age 63.5 +/- 9.7 years) referred to the stress echocardiography laboratory underwent: 1) transthoracic echocardiography, with specific assessment of AVS (thickened valve leaflets with a transaortic flow velocity <2.5 m/s); 2) stress echocardiography; 3) coronary angiography, with evaluation of the Duke score (from 0 [normal] to 100 [most severe disease]); and 4) an endothelial function study, with assessment of endothelium-dependent, post-ischemic, flow-mediated dilation (FMD). RESULTS: Aortic valve sclerosis was present in 35 patients (group I) and absent in 67 (group II). Groups I and II were similar in terms of the frequency of stress-induced wall motion abnormalities (35.3% vs. 19.4%, p = NS) and the angiographic Duke score (33.8 +/- 28.6 vs. 35.2 +/- 29.1, p = NS). Patients with AVS showed a markedly lower FMD than those without AVS (2.2 +/- 3.5% vs. 5.3 +/- 5.3%, p < 0.01). On multivariate analysis, only FMD was highly predictive of AVS, with an odds ratio of 1.18 for each percent decrease in FMD (95% confidence interval 1.05 to 1.32; p = 0.01). CONCLUSIONS: Aortic valve stenosis is associated with systemic endothelial dysfunction. This observation may provide a mechanistic insight into the emerging association between AVS and cardiovascular events.
Randomized clinical trials on the effects of dietary fat and carbohydrate on plasma lipoproteins and cardiovascular disease.

Sacks FM, Katan M.

Several dietary approaches have reduced cardiovascular events in randomized clinical trials. Replacing saturated fat with polyunsaturated fat prevented coronary events in men, and a Mediterranean diet and fatty fish improved survival. None of these trials had much impact on total fat intake but rather increased vegetable oils, n-3 fatty acids, or many other plant foods or nutrients that are linked to coronary prevention. The reductions in cardiovascular disease (CVD) caused by these dietary therapies compare favorably with drug treatments for hyperlipidemia and hypertension. Improvement in blood lipid risk factors is an important mechanism to explain the results of trials of unsaturated fats. When saturated or trans unsaturated fats are replaced with monounsaturated or n-6 polyunsaturated fats from vegetable oils, primarily low-density lipoprotein (LDL) cholesterol decreases. The LDL to high-density lipoprotein (HDL) cholesterol ratio decreases. When carbohydrates are used to replace saturated fats, in a low-fat diet, LDL and HDL decrease similarly, and the ratio is not improved; triglycerides increase as well when carbohydrate increases, except when low glycemic index foods are used. The n-3 polyunsaturated fats in fish oils suppress cardiac arrhythmias and reduce triglycerides, but they have little effect on LDL or HDL cholesterol levels. The theme should be that diet has benefits that come directly from foods, as well as from the reduction in saturated fats, cholesterol, meats, and fatty dairy foods. It is likely that many diets could be designed that could prevent CVD. This potential diversity is crucial for engaging the diverse cultures and tastes of people worldwide in cardiovascular disease prevention.
Epidemiologic studies on dietary fats and coronary heart disease.

Ascherio A.

The results of large prospective epidemiologic investigations support the hypothesis that coronary disease risk depends on the quality rather than quantity of dietary fat. Whereas saturated fat and cholesterol appear to increase the risk of coronary heart disease (CHD) as predicted by their effects on blood lipids, strong evidence has emerged that the deleterious effects of trans unsaturated fatty acids (trans fatty acids) extend beyond those predicted by their well-known adverse influence on the ratio of low-density lipoprotein to high-density lipoprotein cholesterol. On the other hand, increased consumption of the polyunsaturated fats, linoleic acid and linolenic acid, appears to reduce the risk of CHD.
Cardiac risk in men with angiographically normal coronary arteries or minimal coronary arteriosclerosis.

Schulz H, Sinn R, Wolf R.

It is accepted that the assessment of the global cardiac risk for the occurrence of a coronary event is basically for preventive strategies. In a retrospective study, we have estimated the initial 10-year risk in 54 consecutive men (mean age 53.1 years) without clinically coronary artery disease (CAD) by using the PROCAM Score Scheme and the FRAMINGHAM Scoring System. All individuals underwent coronary angiography for diagnostic reasons. Inclusion criteria were angiographically normal coronary arteries or coronary vessels with minimal arteriosclerosis (luminal diameter reduction <35%). The extent of initial coronary arteriosclerosis was estimated semiquantitatively by the number of wall changed vessel segments S (proximal, medial, distal) of the 3 large epicardial coronary arteries. Individuals were devided into 3 risk categories with a 10-year risk/PROCAM <5% (gr. I), 5-20% (gr. II) and >20% (gr. III). The mean 10-year risk/PROCAM and FRAMINGHAM of the entire group was 14.0 and 14.1%, respectively. The number of vessel segments with minimal arteriosclerosis averaged S=2.6. There was a significant linear relation between the number of arteriosclerotic segments, grouped by S=0, 1-2, 3-4, >4 and the mean corresponding 10-year risk/PROCAM (r=0.97; p<0.025). The mean 10-year risk/PROCAM and FRAMINGHAM in gr. I was 2.1+/−1.1 and 5.1+/−3.5%, in gr. II 11.1+/−4.4 and 14.5+/−7.1% and in gr. III 25.4+/−3.3 and 20.4+/−6.2%, respectively (gr. I vs II vs III: p<0.005). In gr. I an average of S=0.8+/−1.4 segments, in gr. II of S=2.4+/−1.8 and in gr. III of S 4.1+/−1.8 vessel segments revealed initial coronary arteriosclerosis (gr. I vs II vs III: p<0.01 <0.0025, respectively). In 42 of the 54 men (78%) there were 10-year follow-up data regarding sudden cardiac death, fatal and non-fatal myocardial infarction available. Thirty-two men of the follow-up group (78%) showed no cardiac event (gr. A, mean age 53.3+/−8.3 years). In 10men (23.8%, 95% CI 19.7−32.5%) a fatal or non-fatal event occurred (gr. B, mean age 55.6+/−7.5 years). At the beginning of the study, the 10-year risk/PROCAM and FRAMINGHAM in gr. A was 12.0+/−9.3 and 14.1+/−8.0%, respectively. In gr. B the estimated 10-year risk was 18.7+/−8.0% (gr. A vs B: p<0.025) and 17.6+/−7.6%, respectively (gr. A vs B: p=ns). No cardiac event occurred in the low risk group <5% (mean 2.4+/−1.2%). In 23.8% (95% CI 19.2−36.8%) of the group with mild or moderate risk (5−20%, mean 10.4+/−4.1%) and in 38.5% (95% CI 29.5−53.1%) of the high risk group (>20%, mean 25.6+/−3.3%) a fatal or non-fatal event occurred. The total cardiac mortality was 7.1% (95% CI 6.6−15.1%). Our study indicates that men mean aged 53 years without clinical CAD and with a high 10-year risk (>20%),
judged by the PROCAM Score Scheme, have a high probability of subclinical coronary arteriosclerosis and for the occurrence of a cardiac event. Thus, a strict distinction between primary and secondary prevention does not seem to be justified any more.
Glutathione peroxidase 1 genotype is associated with an increased risk of coronary artery disease.

Winter JP, Gong Y, Grant PJ, Wild CP.

OBJECTIVE Oxidative stress is implicated in the pathogenesis of many human diseases including atherosclerosis. Human glutathione peroxidase 1 (hgpx1) participates in limiting cellular damage caused by oxidation. A characteristic polyalanine sequence polymorphism in exon 1 of hgpx1 produces three alleles with five, six or seven alanine (ALA) repeats in this sequence. The objective of this study was to determine whether hgpx1 genotype is associated with an altered risk of coronary artery disease (CAD). METHOD The frequency of the ALA6 allele was determined in 207 men with angiographic evidence of significant CAD compared to a control group (n = 146), by analysing the lengths of polymerase chain reaction fragments containing the ALA repeat polymorphism. Additional information was collected on severity of CAD, presence or absence of a prior acute myocardial infarction (AMI), smoking status, body mass index (BMI) and other clinical data. RESULTS There was a significant association between individuals with at least one ALA6 allele and an increased risk of CAD after adjustment for age, BMI and smoking status (odds ratio, 2.07, 95% confidence interval, 1.08–3.99, P = 0.029). However, there was no association between hgpx1 genotype and a previous history of AMI or hgpx1 genotype and severity of CAD. CONCLUSION We conclude that individuals possessing one or two ALA6 alleles appear to be at a modest increased risk of CAD. This observation merits further investigation in other patient populations.
Plasma oxidized LDL: a predictor for acute myocardial infarction?

Nordin Fredrikson G, Hedblad B, Berglund G, Nilsson J.

Nordin Fredrikson G, Hedblad B, Berglund G, Nilsson J (Malmo University Hospital, Lund University; and Biomedical Laboratory Science, Malmo University, Sweden). Plasma oxidized LDL: a predictor for acute myocardial infarction? J Intern Med 2003; 253: 425-429. OBJECTIVES: Oxidized LDL has been attributed a key role in the development of atherosclerosis. Previous studies have demonstrated increased plasma levels of oxidized LDL in patients with established coronary artery disease. The aim of the present study was to investigate if plasma oxidized LDL also predicts risk for development of coronary heart disease (CHD). DESIGN: We used a nested case-control design to study the association between plasma levels of oxidized LDL and risk for development of acute myocardial infarction (AMI) and/or death by CHD. SUBJECTS: Oxidized LDL was analysed by ELISA in cases (n = 26), controls (n = 26) and controls with LDL cholesterol >5.0 mmol L⁻¹ (n = 26). RESULTS: Oxidized LDL correlated with total plasma and LDL cholesterol in both cases (r = 0.72, P < 0.01, r = 0.69, P < 0.01, respectively) and controls (r = 0.71, P < 0.01, r = 0.77, P < 0.01, respectively). The oxidized LDL/plasma cholesterol ratio was higher amongst cases (13.5, range 10.7–19.8) than in controls (12.6, range 9.5–15.8, P < 0.05) and hypercholesterolaemic controls (12.2, range 8.0–16.0, P < 0.01). CONCLUSIONS: These findings identify high plasma oxidized LDL/total cholesterol ratio as a possible indicator of increased risk for AMI.
L-homocysteine sulfinic Acid and other acidic homocysteine derivatives are potent and selective metabotropic glutamate receptor agonists.

Shi Q, Savage JE, Hufeisen SJ, Rauser L, Grajkowska E, Ernsberger P, Wroblewski JT, Nadeau JH, Roth BL.

Moderate hyperhomocysteinemia is associated with several diseases, including coronary artery disease, stroke, Alzheimer’s disease, schizophrenia, and spina bifida. However, the mechanisms for their pathogenesis are unknown but could involve the interaction of homocysteine or its metabolites with molecular targets such as neurotransmitter receptors, channels, or transporters. We discovered that L-homocysteine sulfinic acid (L-HCSA), L-homocysteic acid, L-cysteine sulfinic acid, and L-cysteic acid are potent and effective agonists at several rat metabotropic glutamate receptors (mGluRs). These acidic homocysteine derivatives 1) stimulated phosphoinositide hydrolysis in the cells stably expressing the mGluR1, mGluR5, or mGluR8 (plus Galpha(q19)) and 2) inhibited the forskolin-induced cAMP accumulation in the cells stably expressing mGluR2, mGluR4, or mGluR6, with different potencies and efficacies depending on receptor subtypes. Of the four compounds, L-HCSA is the most potent agonist at mGluR1, mGluR2, mGluR4, mGluR5, mGluR6, and mGluR8. The effects of the four agonists were selective for mGluRs because activity was not discovered when L-HCSA and several other homocysteine derivatives were screened against a large panel of cloned neurotransmitter receptors, channels, and transporters. These findings imply that mGluRs are candidate G-protein-coupled receptors for mediating the intracellular signaling events induced by acidic homocysteine derivatives. The relevance of these findings for the role of mGluRs in the pathogenesis of homocysteine-mediated phenomena is discussed.
Lipid and apolipoprotein ratios: association with coronary artery disease and effects of rosuvastatin compared with atorvastatin, pravastatin, and simvastatin.

Rader DJ, Davidson MH, Caplan RJ, Pears JS.

Plasma lipid and apolipoprotein ratios that include both an atherogenic and an antiatherogenic lipid component (eg, total cholesterol/high-density lipoprotein [HDL] cholesterol ratio, low-density lipoprotein [LDL] cholesterol/HDL cholesterol ratio, non-HDL cholesterol/HDL cholesterol ratio, and apolipoprotein [apo] B/apo A-I ratio) have been found to be strong predictors of coronary artery disease (CAD) risk. Three trials that compared the effects of rosuvastatin 10 mg versus atorvastatin 10 mg and 2 trials that compared the effects of rosuvastatin 10 mg versus simvastatin 20 mg and pravastatin 20 mg on lipid ratios in patients with hypercholesterolemia were prospectively designed for pooled analysis. At 12 weeks, in the 3-trial pooled analysis, rosuvastatin 10 mg (n = 389) showed significantly greater reductions in all 4 lipid ratios compared with atorvastatin 10 mg (n = 393) (p <0.001). The mean percent reduction from baseline in the LDL cholesterol/HDL cholesterol ratio was 51% in patients treated with rosuvastatin 10 mg versus 39% in patients treated with atorvastatin 10 mg. In the 2-trial pooled analysis, treatment with rosuvastatin 10 mg (n = 226) also resulted in significantly greater reductions in all 4 lipid ratios compared with both simvastatin 20 mg (n = 249) and pravastatin 20 mg (n = 252) (p <0.001). Mean percent reductions from baseline in the LDL cholesterol/HDL cholesterol ratio were 52%, 39%, and 30% for rosuvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg, respectively, in these 2 trials.
Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals.

Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG.

Both the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the Second Joint Task Force of European Societies guidelines have established low-density lipoprotein (LDL) cholesterol goals for lipid-lowering treatment to reduce the risk of coronary artery disease. Data from 3 trials that compared rosuvastatin 10 mg (n = 389) with atorvastatin 10 mg (n = 393) and 2 trials that compared rosuvastatin 10 mg (n = 226) with pravastatin 20 mg (n = 252) and simvastatin 20 mg (n = 249) were pooled separately to compare the achievement of LDL cholesterol goals over 12 weeks of treatment in hypercholesterolemic patients. Noncomparative pooling of rosuvastatin 10 mg results from all 5 trials (n = 615) showed that 80% achieved NCEP ATP III goals and 81% achieved the European goal of <3.0 mmol/L. Compared with atorvastatin 10 mg, significantly more patients treated with rosuvastatin 10 mg achieved their ATP III (76% vs 53%) and European (82% vs 51%) goals (p <0.001). Also, in comparisons with simvastatin 20 mg and pravastatin 20 mg, 86% of patients treated with rosuvastatin 10 mg achieved ATP III goals, compared with 64% of simvastatin-treated patients and 49% of pravastatin-treated patients (p <0.001). The proportions of patients who achieved the European goal were 80%, 48%, and 16% for rosuvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg, respectively, in this comparison (all p <0.001). A total of 71% of patients treated with rosuvastatin 10 mg who had triglyceride levels >/=200 mg/dL met both their LDL cholesterol and their non-high-density lipoprotein cholesterol goals.
Oxidized LDL receptor gene (OLR1) is associated with the risk of myocardial infarction.


Lectin-like oxidized low-density lipoprotein receptor (LOX-1/OLR1) has been suggested to play a role in the progression of atherogenesis. We analyzed the OLR1 gene and found a single nucleotide polymorphism (SNP), G501C, in patients with ischemic heart disease from a single family, which resulted in the missense mutation of K167N in LOX-1 protein. We compared the group of patients with myocardial infarction (MI) (n=102) with a group of clinically healthy subjects (n=102), and found that the MI group had a significantly high frequency of 501G/C+501C/C (38.2%) compared with the healthy group (17.6%; p<0.002). The odds ratio for the risk of MI associated with the 501G/C+501C/C genotype was 2.89 (95% CI, 1.51–5.53). These findings suggest that OLR1 or a neighboring gene linked with G501C SNP is important for the incidence of MI. Manipulating LOX-1 activity might be a useful therapeutic and preventative approach for coronary artery disease, especially for individuals with the G501C genotype of OLR1.
Food restriction and fish oil suppress atherogenic risk factors in lupus-prone (NZB x NZW) F1 mice.

Muthukumar A, Zaman K, Lawrence R, Barnes JL, Fernandes G.

Atherosclerosis-mediated coronary artery disease is a significant cause of mortality in lupus patients. Both an activated immune system and hyperlipidemia are implicated in the pathogenesis of the atherosclerotic lesions of lupus. In this study, the increases in anticardiolipin antibodies, total cholesterol, and LDL cholesterol with age were significantly lowered by fish oil and food restriction, either alone or in combination. Food restriction also significantly decreased the elevation in anti-dsDNA antibody production seen with age in ad libitum groups. Interestingly, effects of food restriction and fish oil on both lipid profile and autoantibody production were seen from a young age. Accumulation of leukocytes in the blood vessels and deposition of IgG in the glomerular mesangium also were suppressed by food restriction. Thus, beneficial effects of fish oil and food restriction on lupus nephritis and survival could be, at least in part, due to their selective effect on atherogenic risk factors.
Oxidative stress: new approaches to diagnosis and prognosis in atherosclerosis.

Heinecke JW.

Oxidative modifications of low-density lipoprotein (LDL) have been proposed to play a critical role in atherogenesis. To test the role of proposed antioxidants in inhibiting LDL oxidation and vascular disease, it is important to identify the biologically relevant sources of oxidative stress in the human arterial wall. Mass spectrometric (MS) quantification of oxidized amino acids in proteins was used as a "molecular fingerprint" to identify the pathways that inflict oxidative damage in vivo. For example, myeloperoxidase is expressed in macrophages in human atherosclerotic lesions, and immunohistochemical studies suggest that it might be a pathway for LDL oxidation. We found that hypochlorous acid, tyrosyl radical, and reactive nitrogen species generated by myeloperoxidase each yielded a unique pattern of protein oxidation products in vitro. MS analysis of human atherosclerotic tissue revealed a similar pattern of oxidation products. This strategy has pinpointed myeloperoxidase as a pathway that promotes LDL oxidation in the human artery wall. It is noteworthy that vitamin E fails to inhibit LDL oxidation by myeloperoxidase in vitro. Because the utility of an antioxidant depends critically on the nature of the oxidant that inflicts tissue damage, interventions that specifically inhibit physiologically relevant pathways would be logical candidates for clinical trials of antioxidants. Such a rational approach to therapy is likely to accelerate progress against oxidative stress and coronary artery disease.
Role of oxidative stress in atherosclerosis.

Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H.

The common risk factors for atherosclerosis increase production of reactive oxygen species (ROS) by endothelial, vascular smooth muscle, and adventitial cells. These ROS initiate processes involved in atherogenesis through several important enzyme systems, including xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, and nitric oxide synthase. Physical forces also regulate vascular production of ROS. Oscillatory shear, which is present at sites where atherosclerosis develops, seems a particularly potent stimulus of superoxide production. The signaling cascade for activation of the NAD(P)H oxidase by angiotensin II has recently been elucidated and seems to involve a feed-forward mechanism that permits ongoing production of ROS for prolonged periods. Oxidative stress in humans with coronary artery disease is also exacerbated by a reduction of vascular extracellular superoxide dismutase, normally an important protective enzyme against the superoxide anion.
The relation of obesity to cardiovascular risk factors among children: the CARDIAC project.

Muratova VN, Demerath EW, Spangler E, Ogershok P, Elliott E, Minor VE, Neal WA.

West Virginia’s prevalence of obesity is among the highest in the nation, contributing to an excess mortality rate from heart disease. Individuals who are overweight and obese have a greater risk for coronary artery disease. To gain insight into the impact of obesity on other modifiable cardiovascular disease (CVD) risk factors among children, 5,887 students from 27 rural West Virginia counties participated in the school-based Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project during the 1999–2002 school years. Results confirmed a very high prevalence of overweight and obese children in this rural, pre-adolescent population. Almost 43 percent of the children screened were considered to be overweight (BMI \( \geq \) 85th percentile), and over one-fourth of them were obese (BMI \( \geq \) 95th percentile). This high rate of obesity among schoolchildren in West Virginia is associated with increased prevalence of other CVD risk factors such as hypertension, dyslipidemia, and insulin resistance. Interventions for prevention of excess weight and obesity should be implemented through schools and community-based programs.
C-reactive protein and other inflammatory risk markers in acute coronary syndromes.

Blake GJ, Ridker PM.

Markers of myocyte necrosis such as cardiac troponin or creatine kinase–myocardial band are invaluable tools for risk stratification among patients presenting with acute coronary syndromes (ACS). Nonetheless, many patients without any evidence of myocyte necrosis may be at high risk for recurrent ischemic events. In consideration of the important role that inflammatory processes play in determining plaque stability, recent work has focused on whether plasma markers of inflammation may help improve risk stratification. Of these markers, C-reactive protein (CRP) has been the most widely studied, and there is now robust evidence that CRP is a strong predictor of cardiovascular risk among apparently healthy individuals, patients undergoing elective revascularization procedures, and patients presenting with ACS. Moreover, even among patients with troponin-negative ACS, elevated levels of CRP are predictive of future risk. Other, more upstream markers of the inflammatory cascade, such as interleukin (IL)–6, have also been found to be predictive of recurrent vascular instability. A recent report from the second FRagmin during InStability in Coronary artery disease trial investigators suggests that elevated levels of an inflammatory marker such as IL–6 may indicate which patients may benefit most from an early invasive strategy. Other inflammatory markers currently under investigation include lipoprotein–associated phospholipase A(2), myeloperoxidase, and pregnancy–associated plasma protein A. Of all these novel markers, CRP appears to meet most of the criteria required for potential clinical application. Furthermore, the benefits of lifestyle modification and drug therapy with aspirin or statins may be most marked among those with elevated CRP levels.
The role of non-LDL:non-HDL particles in atherosclerosis.

Segrest JP.

Elevated concentrations of circulating apolipoprotein B (apoB)-containing lipoproteins, other than low-density lipoprotein (LDL), have been implicated as causative agents for the development of atherosclerosis. A form of dyslipidemia, the atherogenic lipoprotein profile, that consists of elevated intermediate-density lipoprotein (IDL), triglycerides (TGs), dense LDL and dense very low density lipoprotein (VLDL), and low high density lipoprotein-2, occurs in 40% to 50% of patients with coronary artery disease (CAD). The recently released Adult Treatment Panel III guidelines suggest that because elevated TGs are an independent CAD risk factor, some TG-rich lipoproteins, commonly called remnant lipoproteins, must be atherogenic. Relevant to this series on diabetes, a number of studies have shown that in type 2 diabetes, the severity of CAD is positively related to the numbers of TG-rich particles in the plasma. Although less clear, other studies in type 2 diabetes suggest that elevated levels of lipoprotein (a) [Lp(a)] may also be independently associated with CAD. In this article, we summarize evidence for the role of apoB-containing lipoprotein particles other than LDL in the development of atherosclerosis and discuss methods of quantification and possible pharmacologic interventions for lowering their plasma concentrations. The particles reviewed include the TG-rich lipoproteins: VLDL and its remnants, chylomicron remnants and IDL, and the C-rich lipoprotein: Lp(a).
Diagnosis of CAD in patients with diabetes: who to evaluate.

Young LH, Jose P, Chyun D.

Effective diagnosis and treatment of coronary artery disease (CAD) are key to the management of patients with diabetes. Although the use of specialized cardiac testing for CAD screening in asymptomatic patients varies widely and is the source of current controversy, evidence is emerging on the prevalence and predictors of asymptomatic ischemia in diabetic patients. Accurate diagnosis and risk stratification are essential in symptomatic patients with known or suspected CAD. Noninvasive cardiac testing has an important role in these patients, although evaluation for revascularization with cardiac catheterization is warranted in high-risk circumstances. This article reviews recent information that may help guide the clinician in the appropriate use of cardiac testing in diabetic patients.
Apolipoprotein A-II: beyond genetic associations with lipid disorders and insulin resistance.

Kalopissis AD, Pastier D, Chambaz J.

PURPOSE OF REVIEW Apolipoprotein A-II, the second major HDL apolipoprotein, was often considered of minor importance relatively to apolipoprotein A-I and its role was controversial. This picture is now rapidly changing, due to novel polymorphisms and mutations, to the outcome of clinical trials, and to studies with transgenic mice.

RECENT FINDINGS The -265 T/C polymorphism supports a role for apolipoprotein A-II in postprandial very-low-density lipoprotein metabolism. Fibrates, which increase apolipoprotein A-II synthesis, significantly decrease the incidence of major coronary artery disease events, particularly in subjects with low HDL cholesterol, high plasma triglyceride, and high body weight. The comparison of transgenic mice overexpressing human or murine apolipoprotein A-II has highlighted major structural differences between the two proteins: they have opposite effects on HDL size, apolipoprotein A-I content, plasma concentration, and protection from oxidation. Human apolipoprotein A-II is more hydrophobic, displaces apolipoprotein A-I from HDL, accelerates apolipoprotein A-I catabolism, and its plasma concentration is decreased by fasting. Apolipoprotein A-II stimulates ATP binding cassette transporter 1-mediated cholesterol efflux. Human and murine apolipoprotein A-II differently affect glucose metabolism and insulin resistance. A novel beneficial role for apolipoprotein A-II in the pathogenesis of hepatitis C virus has been shown.

SUMMARY The hydrophobicity of human apolipoprotein A-II is a key regulatory factor of HDL metabolism. Due to the lower plasma apolipoprotein A-II concentration during fasting, measurements of apolipoprotein A-II in fed subjects are more relevant. More clinical studies are necessary to clarify the role of apolipoprotein A-II in well-characterized subsets of patients and in the insulin resistance syndrome.
Novel LPL mutation (L303F) found in a patient associated with coronary artery disease and severe systemic atherosclerosis.


BACKGROUND: Patients with lipoprotein lipase (LPL) deficiency had been generally thought to be spared accelerated atherosclerosis in spite of a marked elevation of plasma triglyceride levels. However, it has been recently reported that some heterozygous and homozygous LPL-deficient patients are associated with premature atherosclerosis. In this paper, we report a 55-year-old type I hyperlipidaemic patient with a novel missense mutation in the LPL gene. PATIENT AND RESULTS: The patient had suffered from coronary artery disease, abdominal aortic aneurysm, and stenoses of the bilateral renal arteries and superficial femoral arteries. Sequencing of the genomic DNA revealed that the patient was a homozygote for the mutation, a G to C transition at nucleotide position 1069 in the exon 6, resulting in an amino acid substitution of Phe for Leu303 (L303F). Approximately 6% and approximately 40% of normal LPL activity and LPL mass, respectively, were detected in the patient's postheparin plasma. An in vitro expression study demonstrated that COS7 cells transfected with L303F mutant cDNA produced a 40% amount of LPL protein in cell lysates compared with normal cDNA, but no protein was detected in the media. Lipoprotein lipase activity was completely absent in both lysates and media of the cells transfected with the mutant cDNA, suggesting that this mutation in the LPL gene results in the production of a functionally inactive protein. CONCLUSION: This case suggests that the LPL missense mutation (L303F), which impairs lipolysis but preserves the LPL mass, is proatherogenic.
Antiphospholipid antibodies: are they pro-atherogenic or an epiphenomenon of atherosclerosis?

Sherer Y, Shoenfeld Y.

Antiphospholipid antibodies are the hallmark of the antiphospholipid syndrome which is characterized by thrombosis. There are currently data supporting an association between these autoantibodies and atherosclerosis as well. Human studies suggest that anti-cardiolipin and anti-beta2-glycoprotein-I antibodies are elevated in patients having coronary artery disease compared with controls. Anti-cardiolipin antibodies are also associated with typical chest pain, significant coronary artery stenosis on angiography and prediction of myocardial infarction. Laboratory studies and murine models support the pro-atherogenic role of these autoantibodies, as they are involved in uptake of oxidized LDL into macrophages, and immunization of mice with them results in enhanced atherosclerosis. There is some evidence that high anti-beta2-glycoprotein-I antibodies can present a risk factor for atherosclerosis, but more epidemiological data are required in order to confirm whether the pro-atherogenic properties of anti-phospholipid antibodies signifies an independent risk factor for atherosclerosis and its complications.
Chlamydia pneumoniae and coronary artery disease: the antibiotic trials.

Higgins JP.

Parallel with the mounting evidence that atherosclerosis has a major inflammatory component, provoking agents that may initiate and drive this process have been sought. Infectious agents such as Chlamydia pneumoniae have been alleged to be activators of inflammation that may contribute to atherosclerosis and thus coronary artery disease (CAD) and its associated complications. A logical pneumoniae extension of this theory whether treating C pneumoniae infection with antibiotics and/or modulating inflammatory processes can affect CAD and its sequelae. This article discusses the potential role of C pneumoniae in atherosclerosis, its detection, and the rationale for antibiotics. Additionally, it summarizes the current randomized clinical trials of antichlamydial antibiotics in patients with CAD and draws conclusions based on the results.
Increased osteoprotegerin serum levels in men with coronary artery disease.

Schoppet M, Sattler AM, Schaefer JR, Herzum M, Maisch B, Hofbauer LC.

Osteoprotegerin (OPG) regulates osteoclast and immune functions and appears to represent a protective factor for the vascular system. However, the role of OPG in human atherosclerosis has not been evaluated. In this study, we assessed OPG serum levels in 522 age-matched men who, on the basis of coronary angiography, had either absence of coronary artery disease (CAD) or presence of single-vessel disease, double-vessel disease, or severe triple-vessel disease. OPG serum levels were positively correlated with age (r = 0.28; P < 0.001) and were higher in men with diabetes mellitus (P < 0.01). OPG serum levels in men without CAD were 5.4 +/- 2.0 pmol/liter, compared with 6.1 +/- 2.1 pmol/liter in single-vessel disease (P < 0.005), 5.9 +/- 2.4 in double-vessel disease (P < 0.05), and 6.3 +/- 2.3 pmol/liter in triple-vessel disease (P < 0.001). Moreover, OPG serum levels were positively correlated with the severity of CAD as determined by a CAD scoring system (r = 0.17; P < 0.01). In conclusion, our data underline that OPG serum levels are associated with the severity of CAD and are increased in elderly men and patients with diabetes mellitus. We conclude that increased OPG serum levels may reflect advanced cardiovascular disease in men.
The association of plasma homocysteine, coronary risk factors and serum nitrite in patients with coronary artery disease, vascular syndrome x and healthy subjects.

Soysal D, Savas S, Susam I, Cevik C, Goldeli E, Sozmen E, Guneri S.

OBJECTIVE: We evaluated the association of plasma total homocysteine (tHcy), cardiac risk factors and total nitrite in coronary artery disease (CAD) patients, cardiac syndrome X patients and in healthy subjects. METHODS: Forty two CAD, 22 cardiac syndrome X patients and 30 healthy subjects, aged 30 to 75 years were included into the study. Blood samples of tHcy, serum total nitrite and cardiac risk factors were studied appropriately. The results were compared between the groups. The independent contributions of tHcy and total nitrite to CAD and cardiac syndrome X and their interactions with cardiac risk factors were evaluated. RESULTS: After adjusting for age, median values of tHcy and total nitrite were evaluated for their skewness. Coronary artery disease patients had higher median plasma tHcy levels than cardiac syndrome X patients (p<0.001) and healthy subjects (p<0.001) and lower serum total nitrite levels than patients in the two other groups (p<0.05), respectively. Using a univariate linear regression analysis tHcy had a moderately significant positive correlation with age (b=0.34, p=0.002) and a weakly significant inverse correlation with female gender (b=-0.24, p=0.032). Using a partial correlation analysis by controlling for age, gender and clinical situations tHcy had a positive but moderately significant correlation with LDL cholesterol (r=0.23, p=0.01) and triglycerides (r=0.27, p=0.016). Total nitrite had a positive but weakly significant correlation with HDL cholesterol (r=0.23, p=0.04) and fibrinogen (r=0.24, p=0.03) and an inverse but moderately significant correlation with LDL cholesterol (r=-0.37, p=0.001). Using a multivariate stepwise regression analysis total nitrite was inversely and significantly associated with tHcy (b=-0.45) in the control group. The contribution of HDL cholesterol to the association was b=-0.45, p=0.044, R²=36.2%, HDL cholesterol with fibrinogen - b=-0.45, p=0.05, R²=36.6% and HDL cholesterol with LDL cholesterol - b=-0.45, p=0.05, R²=36.3%. In a forward stepwise logistic regression analysis the age adjusted odds ratio (OR) for coronary artery disease per standard deviation change in log- transformed tHcy concentration was - 0.82, p=0.013 and in total nitrite concentration was - 1.08, p=0.02. Using the same model neither tHcy nor total nitrite was associated with cardiac syndrome X (p=0.221 and p=0.112), respectively. CONCLUSION: The low nitrite levels can be a marker of endothelial dysfunction in the presence of hyperhomocysteinemia and other cardiac risk factors. Our results might support endothelial dysfunction in CAD but not in cardiac syndrome X patients.
C-reactive protein and rapidly progressive coronary artery disease—-is there any relation?

Zairis MN, Manousakis SJ, Stefanidis AS, Vitalis DP, Tsanis EM, Hadjigeorgiou SM, Fakiolas CN, Pissimissis EG, Olympios CD, Foussas SG.

BACKGROUND: High plasma C-reactive protein (CRP) levels have been associated with an unfavorable outcome in patients with coronary artery disease (CAD), and a direct participation of CRP in the atherosclerotic process has been postulated. HYPOTHESIS: The aim of this study was to evaluate the possible relationship of high plasma CRP levels with the rapid progression of coronary atherosclerosis (RPCAD). METHODS: In all, 194 patients who were readmitted and underwent repeat coronary angiography because of recurrence of symptoms following successful percutaneous coronary intervention were studied. Median angiographic follow-up time was 6 months. Rapid progression CAD was defined as the presence of a new lesion, > 25% in luminal diameter stenosis, in a previously nondiseased vessel, or deterioration of a known, nontreated lesion by at least 25%. RESULTS: By multivariate analysis, patients with high plasma CRP levels upon first admission were at higher risk of RPCAD. In particular, odds ratio (OR) = 1.8; 95% confidence interval (CI) = 1.3–3.6; p value = 0.02 in patients with CRP = 0.5–2 mg/dl versus patients with CRP < 0.5 mg/dl, and OR = 7.1; 95% CI = 3.8–9.5; p value < 0.001 in patients with CRP > 2 mg/dl versus patients with CRP < 0.5 mg/dl. CONCLUSION: Increased plasma CRP levels could possibly identify patients at high risk for the development of RPCAD.
Hyperlipidaemias and serum cytokines in patients with coronary artery disease.


OBJECTIVE: The inflammatory processes as well as the lipid disturbances play an important role in the pathogenesis of atherosclerosis. The aim of the study was to evaluate the influence of the hyperlipidaemias on serum levels of tumour necrosis factor (TNF) alpha, the soluble form of TNF receptor (sTNFR) 1 and 2, Interleukin (IL)-10 in patients with stable coronary artery disease (CAD).

METHODS AND RESULTS: The study group comprised 94 consecutive admissions with stable CAD: 39 patients with hypercholesterolaemia (group HC), 22 patients with mixed hyperlipidaemia (group HL) and 33 patients with normal lipids (group NL). Twenty healthy volunteers were the controls (group C). Serum TNFalpha levels were higher in all CAD groups (p < 0.001) than in healthy subjects. Mean serum concentrations of sTNFR 1 were significantly higher in group NL (p < 0.05) in comparison both to group HC and controls. IL-10 levels were higher in group HC than in controls (p < 0.5). In all CAD patients TNFalpha showed a negative correlation with HDL-cholesterol (p < 0.001) and a positive correlation with triglycerides (p < 0.001). Moreover, sTNFR 1 and IL-10 showed a negative (p < 0.05) and sTNFR 2 a positive correlation with LDL-cholesterol (p < 0.001). CONCLUSIONS: CAD patients are characterized by increased serum concentrations of TNFalpha. It seems likely that immune activation (TNFalpha, sTNFR 1, sTNFR 2, and IL-10) in CAD patients is related to serum lipids levels.
The stromelysin-1 5A/6A promoter polymorphism is a disease marker for the extent of coronary heart disease.

Schwarz A, Haberbosch W, Tillmanns H, Gardemann A.

Background. Matrix metalloproteinases, such as stromelysin-1, are implicated in the pathogenesis of coronary artery disease (CAD) and acute myocardial infarction (MI). A 5A/6A promoter polymorphism can regulate the transcription of the stromelysin-1 gene in an allele-specific manner. Evidence has been presented that the 6A allele is associated with the progression of coronary heart disease (CHD). In contrast, the 5A allele may be linked to the risk of MI. Results. To analyse the relation of the 5A/6A polymorphism with the risk and severity of CHD and the risk of MI, a case-control study of 515 healthy controls and 1848 participants who underwent coronary angiography for diagnostic purposes was conducted. In the total sample, the mean CHD scores – according to Gensini – were different between 5A/6A genotypes: 5A5A homozygotes had the lowest, 6A6A genotypes the highest and 5A6A heterozygotes intermediate scores. These differences were even more pronounced when the participants were restricted to individuals with a high coronary risk profile (high apoB levels, high Lp(a) levels, high glucose levels, combinations of either high apoB and Lp(a) levels or high apoB, Lp(a) and glucose plasma levels). Mean values were used as cut points for high-risk populations, respectively. In contrast, the 5A allele was not associated with the risk of CHD or MI. Even when angiographically controlled individuals without MI were compared with MI patients in subpopulations of participants with no, single, double and triple vessel disease, the frequencies of the 5A/6A and/or the 5A5A genotypes were not higher in each subgroup, respectively. Conclusions. The present results do not confirm an association of the 5A allele with the risk of MI, observed in another investigation, but strengthen the hypothesis of earlier studies that the 6A allele is a disease marker for progression of coronary heart disease. Further investigations should evaluate whether 6A allele carriers and especially 6A homozygotes might benefit from a more aggressive therapy against CHD progression.
Association of Coronary Artery Disease With Glucocorticoid Receptor N363S Variant.

Lin RC, Wang XL, Morris BJ.

Overweight is associated with the N363S variant in the glucocorticoid receptor (encoded by nuclear receptor subfamily 3, group C, member 1 gene: NR3C1). The present study examined whether the N363S polymorphism might also be associated with coronary artery disease (CAD). This involved 556 patients with CAD, of which 437 were analyzed, and 302 control subjects, all being of Anglo-Celtic descent residing in Sydney. An extensive range of phenotypic parameters was collected from the patients, and leukocyte DNA from all subjects was genotyped by polymerase chain reaction–restriction fragment length polymorphism analysis for the A1218G (N363S) variant. Frequency of the S363 allele was 0.04 in healthy normal–weight control subjects but was 0.15 in patients with CAD (P=2.0x10⁻⁵) and was also elevated in subjects with CAD who were not overweight (0.14) (P=2.6x10⁻⁵), supporting a primary association with CAD. Frequency of S363 allele carriers in subjects with CAD who had angina was particularly high: unstable angina (0.45), stable angina (0.29), and no angina (0.26) (P for trend=0.016). Elevated cholesterol (P=0.027), triglycerides (P=0.005), and total cholesterol/HDL ratio (P=0.011), after Bonferroni, tracked with the S363 allele, consistent with accentuation of mechanisms that predispose to atheroma formation in coronary vessels. The data suggest a role for glucocorticoid receptor variation in the underlying cause of CAD.
Insulin sensitivity and the diffuseness of coronary artery disease in humans.

Hong T, Zhao G, Gao W, Huo Y, Zhu G.

OBJECTIVE: To study the relationship between insulin sensitivity and diffuse coronary artery disease. METHODS: Ninety-two consecutive patients underwent coronary angiography were enrolled in the study. Relationships between the results of angiograms and both glucose tolerance and blood lipids were analyzed. RESULTS: The mean age of the 92 patients (70 males, 22 females) was 65.4 +/- 6.3 y. In the 78 patients diagnosed by angiography as coronary artery disease, diffuse lesion was more common in diabetic patients than in those without a diabetes history (12/13 vs 24/65, P = 0.00026). Fasting glucose [(6.06 +/- 2.43) x 10(-3) mol/L vs (4.80 +/- 1.47) x 10(-3) mol/L, P = 0.009], glucose levels at one hour [(12.37 +/- 4.38) x 10(-3) mol/L vs (9.10 +/- 3.97) x 10(-3) mol/L, P = 0.003] and three hours [(8.11 +/- 5.51) x 10(-3) mol/L vs (5.56 +/- 3.46) x 10(-3) mol/L, P = 0.020] after food were higher in patients with diffuse coronary disease than in those with non-diffuse coronary disease. Differences in the insulin sensitivity index (ISI) between the two groups was statistically significant (-4.36 +/- 0.52 vs -3.89 +/- 0.69, P = 0.003). The incidence of multiple-vessel disease in diabetic patients was higher than that in non-diabetic patients (12/13 vs 33/65, P = 0.00565). Glucose levels at two hours [(10.22 +/- 5.57) x 10(-3) mol/L vs (7.67 +/- 4.43) x 10(-3) mol/L, P = 0.031] and three hours [(7.90 +/- 5.47) x 10(-3) mol/L vs (5.22 +/- 2.79) x 10(-3) mol/L, P = 0.007] after food were higher in patients with multiple-vessel disease than in those with single-vessel disease. Impaired insulin sensitivity without a history of diabetes mellitus was commonly seen in patients with coronary artery disease. CONCLUSIONS: The diffuseness of coronary artery disease is associated with insulin sensitivity and blood glucose levels. Insulin resistance is a common phenomenon in non-diabetic patients.
G protein beta 3 subunit 825T allele carriage and risk of coronary artery disease.


C825T polymorphism in the G protein beta3 subunit gene (GNB3) is associated with increased transmembrane signal transduction via adenylyl cyclase inhibiting G (G(i)) proteins. We tested whether GNB3 C825T is associated with an increased risk of coronary artery disease (CAD). Genotypes were determined with polymerase chain reaction and allele-specific fluorogenic probes. Angiographically examined, consecutive patients (n=998) with CAD and angiographically examined, sex- and age-matched controls (n=340) with no evidence of CAD were studied. The proportion of T allele carriers was significantly higher in the group with CAD compared with the control group (55.6 vs. 48.5; P=0.02). T allele carriage was associated with a 33% increase in the unadjusted risk (OR 1.33 [95% confidence interval, 1.04–1.70]) and a 37% increase in the adjusted risk (OR from the multivariate model 1.37 [95% CI, 1.06–1.76]) for CAD. Moreover, an increase in T allele carriage was associated with an increase in disease severity (P=0.006; test for trend). The strongest association was observed between T allele carriage and three-vessel disease (unadjusted OR 1.47 [95% CI, 1.10–1.96]). Thus, carrying this allele is associated with the presence as well as the severity of CAD.
Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors.

Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H.

Variations of circulating C-reactive protein (CRP) levels are supposed to reflect chronic inflammatory process of the cardiovascular system. In particular, it has been reported that high-sensitivity CRP (hsCRP) is a promising marker of coronary heart disease. In the present study, we assessed the relationship between hsCRP and classic cardiovascular risk factors, such as age, blood pressure, smoking habit and serum lipids. Plasma hsCRP was measured by ELISA in 908 subjects, aged 30–79 years, who entered our health-check program. Plasma hsCRP level was 0.54 +/- 0.02 mg/l in 566 subjects without any disease currently treated. The level was significantly higher in patients treated for hypertension (0.74 +/- 0.06 mg/l, P=0.002), diabetes mellitus (0.77 +/- 0.09 mg/l, P=0.016) or coronary artery disease (0.99 +/- 0.16 mg/l, P=0.008) than in subjects without diseases. In a simple regression analyses of the 566 subjects without diseases, plasma hsCRP positively correlated with male gender, smoking, body mass index, systolic blood pressure, white blood cell count, blood hemoglobin, fasting blood glucose, serum gamma-GTP, uric acid and triglycerides, and inversely correlated with serum albumin and HDL-cholesterol. In multiple regression analysis, white blood cell count (r=0.276, P<0.001), body mass index (r=0.246, P<0.001), age (r=0.122, P=0.001) and smoking (r=0.112, P=0.009) showed independent correlations with plasma hsCRP. It is suggested that variation of circulating hsCRP, even within normal range, is involved in the interrelation of cardiovascular risk factors, such as age, smoking, obesity, high blood pressure and dyslipidemia, which are supposed to promote atherosclerosis and ultimately provoke cardiovascular diseases, such as coronary artery disease.
The association between inflammation markers, coronary artery disease and smoking.

de Maat MP, Kluft C.

Inflammation and smoking are associated with risk of cardiovascular disease, but not much is known yet about their relationship. We studied in 15 smoking and 15 nonsmoking patients with coronary artery disease (CAD) and in 15 smoking and 15 nonsmoking healthy subjects the relationships with the inflammatory markers C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 beta (IL-1 beta) and tumour necrosis factor-alpha (TNF-alpha). IL-6 and TNF-alpha were significantly higher in patients than in controls, both in smokers and in nonsmokers. Smoking only had a significant effect on IL-6, and mainly in the controls. In conclusion, inflammation is affected by both smoking and cardiovascular disease.
Body iron stores and coronary atherosclerosis assessed by coronary angiography.


BACKGROUND AND AIM: Epidemiological studies have suggested an association between higher body iron stores and coronary artery disease (CAD), but recent trials have reported conflicting data on the role of ferritin in CAD. To assess these findings, we examined the association between serum ferritin and the angiographic extent of coronary atherosclerosis in consecutive patients referred for coronary angiography. METHODS AND RESULTS: We studied 100 consecutive white subjects (41 women and 59 men; mean age 63.7 +/- 11.0 years) who underwent coronary angiography. The data collected at baseline included conventional risk factors for coronary artery disease (CAD), lipid and fasting total homocysteine levels, serum ferritin levels and transferrin saturation, and clinical characteristics. Serum ferritin levels and transferrin saturation (serum iron concentration divided by total iron-binding capacity) were used as measures of the amount of circulating iron available to tissues. Two experienced cardiologists blinded to the clinical and laboratory data reviewed the angiographic cinefilms, and defined the angiographic severity of CAD on the basis of the sum of three vessel scoring systems. The risk of CAD assessed by coronary angiography was not related to ferritin concentrations or transferrin saturation levels. The estimated relative risk of CAD for the fifth vs the first quintile of serum ferritin was 0.83 (95% CI: 0.63-1.24). Forty of the 100 patients had no or minimal CAD (group A; score 0-3), 33 moderate CAD (group B; score 4-8) and 27 severe CAD (group C; score > 8): the serum ferritin levels in the three groups were respectively 165 +/- 126, 167 +/- 121 and 164 +/- 110 ng/ml, and did not represent an independent risk factor for CAD (p = 0.98). Transferrin saturation in the three groups was 22.9 +/- 10%, 21 +/- 9% and 19.9 +/- 10%, with no significant relationship to the severity of CAD (p = 0.23). The presence of angiographic CAD was associated with patient age (p = 0.048), male gender (p < 0.01), high lowdensity lipoprotein cholesterol levels (p = 0.02), low high-density lipoprotein cholesterol levels (p = 0.02), high plasma fibrinogen levels (p < 0.01) and high fasting total homocysteine levels (p = 0.04). CONCLUSION: In patients referred for coronary angiography, higher ferritin concentrations and transferrin saturation levels were not associated with an increased extent of coronary atherosclerosis.
Relationship of visceral fat distribution to angiographically assessed coronary artery disease: results in subjects with or without diabetes or impaired glucose tolerance.

Morricone L, Donati C, Hassan T, Cioffi P, Caviezel F.

BACKGROUND AND AIM: To evaluate the relationship between the degree of coronary artery disease (CAD) and the amount of visceral fat deposition in a mixed population of CAD patients with or without diabetes or impaired glucose tolerance (IGT), and with different body weights. METHODS AND RESULTS: A total of 55 patients undergoing coronary angiography (43 men and 12 women with a mean age of 58.9 +/- 1.1 years, range 37-70, and a mean body mass index [BMI] of 27.9 +/- 0.4, range 21.3-38.7) were studied in order to establish whether the coronary damage exclusively depends on intra-abdominal adipose tissue per se, or may be influenced by the coexistence of diabetes or IGT. Twenty-one subjects were non-diabetic, 13 had type 2 diabetes, and 21 IGT. Hypertension was found in 47% and dyslipidemia in 55%; 69% were smokers. The angiographic evaluation of CAD was made using the method of Gensini, and computed tomography (CT) was used to estimate the amount of visceral adipose tissue (VAT) based on a single scan at L4 level. Clinical, anthropometric, biochemical and hormonal variables, as well as smoking and alcohol consumption were determined. In the study population as a whole, the coronary score did not correlate with VAT, but only with smoking. However, both univariate and multivariate regression analysis showed that CAD significantly correlated with VAT in the non-diabetic patients, particularly in those with VAT of > 130 cm². This correlation did not appear in the diabetic or IGT patients, nor when the group of patients with VAT > 130 cm² was extended to include diabetic or IGT patients. No relationship was found between CAD and BMI or the other considered variables. CONCLUSIONS: In a mixed population of CAD patients with or without diabetes, CAD correlates with VAT only in the absence of diabetes or IGT, and especially when VAT exceeds 130 cm² at an L4 CT scan, regardless of weight or obesity. Diabetes or IGT therefore seem to contribute towards the development of CAD regardless of the amount of VAT.
Blood histamine is associated with coronary artery disease, cardiac events and severity of inflammation and atherosclerosis.

Clejan S, Japa S, Clemetson C, Hasabnis SS, David O, Talano JV.

BACKGROUND: Mast cells are prevalent in the shoulder of unstable atheromas; cardiac mast cells secrete proteases capable of activating matrix metalloproteinases. Histamine is essential in the inflammatory cascade of the unstable plaque. Ascorbate depletion has been correlated with histaminemia which has been shown to impair endothelial-dependent vasodilation. This study evaluates whether oxidative stress as measured by isoprostanes (PGF(2alpha)) coupled with an inflammatory state characterized by histaminemia predisposes patients to acute coronary syndrome (ACS). METHODS: Whole blood histamine, serum vitamin C, and serum PGF(2alpha) levels were drawn on 50 patients with ACS as determined by standard diagnostic criteria, 50 patients with stable coronary artery disease (SCAD), and 50 age and sex matched normal controls (C). RESULTS: Data were analyzed by stepwise discriminant and Spearman's rank correlation coefficient. A significant relationship exists between histamine and PGF(2alpha). As PGF(2alpha) rises above 60 pg/mL, an increase in histamine occurs in both the ACS and SCAD groups. A significant inverse relationship exists between ascorbate and histamine in the ACS versus C groups (P < 0.01) and the SCAD versus C groups (P < 0.01). CONCLUSION: Histamine and isoprostane levels increase in SCAD and ACS patients. Mast cell activation and lipid oxidation generated during atherosclerosis manifest this inflammatory response. Accelerated isoprostane formation and depleted ascorbate paired with histaminemia is active in CAD and predispose patients to acute coronary syndrome. Blood histamine alone may be a better risk factor for coronary events, and a better prognostic indicator than CRP even when combined with lipid indexes.
Conventional coronary artery disease risk factors and coronary artery calcium detected by electron beam tomography in 30,908 healthy individuals.

Hoff JA, Daviglus ML, Chomka EV, Krainik AJ, Sevrukov A, Kondos GT.

PURPOSE: Electron beam tomography (EBT) is a noninvasive measure of coronary artery calcium (CAC), a marker for atherosclerosis. In this study we examined the association between conventional risk factors for coronary artery disease (CAD) and CAC.

METHODS: EBT CAC screening was performed on 30,908 asymptomatic individuals aged 30 to 90 years. Prior to EBT screening, individuals provided demographic and CAD risk factor information. EBT utilized a C-100 EBT scanner, and the amount of CAC was determined using the Agatston scoring method.

RESULTS: The results of this study demonstrate that for both men and women, all conventional risk factors were significantly associated with the presence of any detectable CAC, and the mean CAC score increased in proportion to the number of CAD risk factors. In age-adjusted (multivariable) logistic regression analysis, cigarette use, histories of hypercholesterolemia, diabetes, and hypertension were each significantly associated with mild to extensive CAC scores (≥10.0).

CONCLUSION: CAD risk factors are associated with higher atherosclerotic plaque burden in both men and women. The odds ratios associated with each risk factor relative to the extent of CAC are similar to those reported for the development of clinical CAD, suggesting the existence of an association between CAC (subclinical disease) and CAD (clinical disease).
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Endothelial nitric oxide synthase gene polymorphisms and risk of coronary artery disease.

Colombo MG, Paradossi U, Andreassi MG, Botto N, Manfredi S, Masetti S, Biagini A, Clerico A.

BACKGROUND: Endothelial nitric oxide synthase (eNOS) could be a candidate gene for coronary artery disease (CAD). This study investigated the relationship of the eNOS Glu(298)--->Asp and T(786)--->C polymorphisms with the presence and severity of CAD in the Italian population.

METHODS: We enrolled 415 unrelated individuals who underwent coronary angiography. The severity of CAD was expressed by means of the Duke score. The eNOS Glu(298)--->Asp and T(786)--->C variants were analyzed by PCR.

RESULTS: There was significant linkage disequilibrium between the two eNOS polymorphisms (P <0.0001). Both variants were significantly associated with the occurrence and severity of CAD (P = 0.01 and 0.004 for Glu(298)--->Asp and T(786)--->C, respectively). The risk of CAD was increased among individuals homozygous for the C allele of the T(786)--->C polymorphism compared with individuals homozygous for the T allele (odds ratio = 2.5; P <0.01) and was independent of the other common risk factors (P = 0.04). Moreover, individuals with both the Asp/Asp genotype of the Glu(298)--->Asp polymorphism and at least one C allele of the T(786)--->C variant in the promoter region of the eNOS gene had an increased risk of CAD (odds ratio = 4.0; P <0.001) and a significantly higher mean Duke score (26.2 +/- 2.9 vs 45.2 +/- 3.7; P = 0.002) compared with individuals with the TT genotype and the Glu allele.

CONCLUSIONS: The present study provides evidence that the Glu(298)--->Asp and T(786)--->C polymorphisms of the eNOS gene are associated with the presence and severity of angiographically defined CAD in the Italian population and that those individuals carrying both eNOS variants simultaneously might have a higher risk of developing CAD.
Identifying women at risk for coronary artery disease.

Birchfield PC.

Women differ from men in presentation, pathology, and prevention of CAD. After women at risk are identified, primary and secondary prevention measures should be implemented for individual workers and their families. To be effective in managing CAD, risk reduction measures should be employed. However, nurses also need to be able to identify the often atypical symptoms that women present with in CAD to provide appropriate and swift care (Anderson, 2001). The occupational health nurse is in a unique position to assist in improving the health of many within the worksite. The nurse can perform the risk assessment and plan with employees to reduce the identified risks and, thus, improve the quality of their lives. Getting employees engaged in self care by helping to set realistic goals and acting as a support in their endeavors toward this end could be the incentive needed to begin on the path to a healthier lifestyle.
Increased C-reactive protein level after coronary stent implantation in patients with stable coronary artery disease.

Almagor M, Keren A, Banai S.

BACKGROUND: Elevation of C-reactive protein (CRP), among other markers of inflammation, is associated with an increased risk for cardiac events in patients with known coronary diseases and in apparently healthy individuals. Moreover, in patients with acute coronary syndromes, elevated serum levels of CRP are strongly predictive of the risk for death from cardiac causes. The purpose of this study was to investigate whether mechanical rupture of an atherosclerotic coronary plaque during elective stent implantation in patients with stable coronary artery disease (CAD) at low risk will cause a significant increase in serum levels of CRP. METHODS AND RESULTS: We measured serum CRP levels in 40 patients. Group 1 consisted of 12 consecutive patients with stable coronary disease who were at low risk, before and after elective coronary stent implantation. We compared the results in these patients to those of patients in 2 control groups: group 2 consisted of 12 consecutive patients with non-ST-segment elevation acute coronary syndrome (NSTSE ACS) who were undergoing coronary stent implantation, and group 3 included 16 consecutive patients with stable or unstable CAD who were undergoing diagnostic coronary angiography only without PCI. Peripheral blood samples for CRP level testing were withdrawn before percutaneous coronary intervention or angiography at the completion of the procedure, and 6, 20, and 48 hours thereafter. All patients with stable CAD (group 1) had a significant and uniform increase in serum CRP levels after elective stent implantation. The low mean baseline serum CRP levels increased 4.9 +/- 4.1-fold 20 hours after coronary intervention (2.1 +/- 1.2 before, 7.9 +/- 3.4 after, P < .002). The baseline CRP level was much higher in the patients with unstable coronary syndromes (group 2). In this group, only a 2.1-fold increase in mean CRP level was observed after stent implantation (7.4 +/- 5.5 before, 14.1 +/- 9.6 after, P < .004). Also, the response in this group was less uniform when compared with that in the stable CAD group. By contrast, in patients undergoing diagnostic coronary angiography, the mean baseline CRP level was higher than in the patients in the group with stable CAD; however, the mean CRP after the procedure was not significantly elevated in this group (4.5 +/- 3.6 before, 5.5 +/- 3.7 20 hours after, P = not significant). CONCLUSIONS: Mechanical disruption of an atherosclerotic coronary plaque during elective coronary stent implantation in patients with stable CAD who are at low risk causes a systemic inflammatory response expressed by marked elevation in CRP concentration.
Increased secretion of insulin during oral glucose tolerance test can be a predictor of stent restenosis in nondiabetic patients.

Babalik E, Gurmen T, Orhan L, Bulur H, Gulbaran M, Ersanli M, Ozturk S.

Insulin is known to stimulate proliferation and migration of vascular smooth muscle cells. As the predominant mechanism of restenosis after stent implantation is neointimal tissue proliferation, one can expect a relationship between hyperinsulinemia and restenosis in these patients. The aim of this study was to determine whether hyperinsulinemia during oral glucose tolerance test is a predictor of the development of restenosis after stent implantation in nondiabetic patients. We prospectively studied 52 nondiabetic patients with effort angina who underwent elective stent implantation for single-vessel coronary artery disease. In order to increase the statistical power of the study, numerous exclusion criteria were applied. All patients were subjected to a 75 g oral glucose tolerance test a day before the stent implantation and underwent follow-up angiography 6 months later. Plasma insulin levels in fasting (6.77 +/- 1.57 vs. 5.36 +/- 1.35 micro U/ml; P = 0.005), at 30 min (102.48 +/- 10.6 vs. 47.74 +/- 12.75 micro U/ml; P = 0.001), 1 hr after (120.23 +/- 14.1 vs. 63.08 +/- 12.62 micro /ml; P = 0.001), 2 hr after (63.58 +/- 8.64 vs. 34.88 +/- 6.82 micro /ml; P = 0.001), and 3 hr after (25.71 +/- 5.65 vs. 23.02 +/- 4.61 micro /ml; P = 0.04) loading were significantly higher in patients with stent restenosis than in patients without stent restenosis. Insulin area and insulin area/glucose area were also significantly higher in patients with stent restenosis than in patients without (219.5 +/- 23.8 vs. 118.9 +/- 21.8, P = 0.001, and 0.62 +/- 0.09 vs. 0.33 +/- 0.06, P = 0.001, respectively). By multiple logistic regression analysis, insulin area during oral glucose tolerance test was found to be an independent predictor of stent restenosis (OR = 1.12; 95% CI = 1.01-1.25; P = 0.031). In conclusion, nondiabetic patients with hyperinsulinemia during oral glucose tolerance test have a high risk for restenosis after stent implantation, and performing this simple test before intervention may be useful for the prediction of stent restenosis.
Smallest LDL particles are most strongly related to coronary disease progression in men.

Williams PT, Superko HR, Haskell WL, Alderman EL, Blanche PJ, Holl LG, Krauss RM.

OBJECTIVE: LDLs include particle subclasses that have different mobilities on polyacrylamide gradient gels: LDL-I (27.2 to 28.5 nm), LDL-IIa (26.5 to 27.2 nm), LDL-IIb (25.6 to 26.5 nm), LDL-IIIa (24.7 to 25.6 nm), LDL-IIIb (24.2 to 24.7 nm), LDL-IVa (23.3 to 24.2 nm), and LDL-IVb (22.0 to 23.3 nm in diameter). We hypothesized that the association between smaller LDL particles and coronary artery disease (CAD) risk might involve specific LDL subclasses. METHODS AND RESULTS: Average 4-year onstudy lipoprotein measurements were compared with annualized rates of stenosis change from baseline to 4 years in 117 men with CAD. The percentages of total LDL and HDL occurring within individual subclasses were measured by gradient gel electrophoresis. Annual rate of stenosis change was related concordantly to onstudy averages of total cholesterol (P=0.04), triglycerides (P=0.05), VLDL mass (P=0.03), total/HDL cholesterol ratio (P=0.04), LDL-IVb (P=0.01), and HDL(3a) (P=0.02) and inversely to HDL(2)-mass (P=0.02) and HDL(2b) (P=0.03). The average annual rate in stenosis change was 6-fold more rapid in the fourth quartile of LDL-IVb (>or=5.2%) than in the first quartile (<2.5%, P=0.03). Stepwise multiple regression analysis showed that LDL-IVb was the single best predictor of stenosis change. CONCLUSIONS: LDL-IVb was the single best lipoprotein predictor of increased stenosis, an unexpected result, given that LDL-IVb represents only a minor fraction of total LDL.
Short-term triglyceride lowering with fenofibrate improves vasodilator function in subjects with hypertriglyceridemia.


OBJECTIVE: The objective of this study was to investigate the effects of lowering plasma triglycerides (TGs) on endothelial function and gain insight into the role played by free fatty acids (FFAs) in hypertriglyceridemia–associated vascular dysfunction. METHODS AND RESULTS: Eleven hypertriglyceridemic subjects without coronary artery disease, diabetes, elevated low-density lipoprotein cholesterol, tobacco use, or hypertension were studied using a randomized, double-blinded, crossover design (fenofibrate and placebo, 14 days). After each regimen, forearm blood flow was assessed by plethysmography in response to arterial acetylcholine, nitroprusside, and verapamil infusion. Hourly plasma TGs, FFA, glucose, and insulin were measured during a 24-hour feeding cycle to characterize the metabolic environment. Changes in plasma FFA after intravenous heparin were used to estimate typical FFA accumulation in the luminal endothelial microenvironment. Fenofibrate lowered plasma TG (P<0.001), total cholesterol (P<0.01), and apolipoprotein B (P<0.01) without altering high-density lipoprotein or low-density lipoprotein cholesterol concentrations. Forearm blood flow in response to acetylcholine (P<0.0001), nitroprusside (P<0.001), and verapamil (P<0.0001) improved after fenofibrate. Fenofibrate lowered 24-hour (P<0.0001) and post-heparin (P<0.001) TG and tended to lower 24-hour (P=0.054) and post-heparin (P=0.028) FFA. CONCLUSIONS: Vascular smooth muscle function significantly improves after lowering plasma TG without changes in confounding lipoproteins or insulin resistance. The data raise additional questions regarding the role of FFA in hypertriglyceridemia–associated vascular dysfunction.
Low-density-lipoprotein peak particle size in a Mediterranean population.


BACKGROUND: The predominance of small, dense low-density lipoprotein (LDL) particles ('LDL phenotype B') has been associated with a three-fold increased risk of myocardial infarction, but the feasibility of the identification of small, dense LDL as independent predictors of coronary artery disease risk in population studies remains questioned. Design We evaluated the LDL peak particle size and its relation with other established risk factors for coronary heart disease in a group of 156 randomized subjects living on the Mediterranean island of Ustica (71 males and 85 women, range of age 20–69 years), representing approximately 30% of the total population. RESULTS: The prevalence of LDL phenotype B subjects was low (approximately 15% in both men and women) and there was a clear trend for both genders in reducing the LDL peak particle size with age. Moreover, LDL phenotype B subjects had higher BMI values, prevalence of diabetes and plasma triglyceride (TG) levels and lower plasma HDL-C concentrations in comparison with LDL phenotype A individuals; in a multivariate analysis, plasma TG levels were the only variable independently associated with LDL peak particle size. CONCLUSIONS: In this population, which appears to be somewhat protected by premature coronary artery disease, a low prevalence of the LDL pattern B was found in both men and women, and plasma TG could have a key role in regulating the LDL peak particle size. The follow up, still ongoing, will provide useful information on the predictive role of LDL peak particle size on cardiovascular risk, at least in a low-risk population.
Detecting occult coronary disease in a high-risk asymptomatic population.

Blumenthal RS, Becker DM, Yanek LR, Aversano TR, Moy TF, Kral BG, Becker LC.

BACKGROUND: Exercise stress testing alone or with perfusion imaging is the standard screening method to determine the presence of obstructive coronary artery disease (CAD) in people with chest pain. In asymptomatic individuals with a family history of premature CAD, it is unclear whether abnormalities on these functional exercise tests represent significant coronary disease. METHODS AND RESULTS: An abnormal exercise test, thallium scan, or both occurred in 153 (21%) of 734 asymptomatic siblings of persons with documented CAD, of whom 105 underwent coronary angiography with quantitative analysis of stenosis severity. Overall, 95% had coronary atherosclerosis, but only 39% had 1 or more stenoses with \(\geq 50\%\) narrowing. Of 30 siblings in whom the exercise test and perfusion scan were both abnormal, 70% had \(\geq 50\%\) stenoses. The mean stenosis in arteries that fed perfusion defects was only 43+/−31%, and 68% of such stenoses were <50%. However, in 71% of all defects, the location matched arteries with the most severe stenoses. CONCLUSIONS: In asymptomatic persons with a family history of CAD, abnormal exercise scintigraphy identifies predominantly mild coronary atherosclerosis. Perfusion defects may be caused by coronary vasomotor dysfunction in addition to atherosclerotic plaque.
Temporal increases in plasma markers of oxidized low-density lipoprotein strongly reflect the presence of acute coronary syndromes.


OBJECTIVES: This study was conducted to test the hypothesis that plasma markers of oxidized low-density lipoprotein (OxLDL) reflect acute coronary syndromes (ACS). BACKGROUND: Oxidized LDL contributes to the pathogenesis of atherosclerosis, but its role in ACS is not established. METHODS: Serial plasma samples were prospectively obtained from patients with an acute myocardial infarction (MI) (n = 8), unstable angina (UA) (n = 15), stable coronary artery disease (CAD) (n = 17), angiographically normal coronary arteries (n = 8), and from healthy subjects (n = 18), at entry into the study, hospital discharge (MI group only), and at 30, 120, and 210 days. Chemiluminescent enzyme-linked immunosorbent assay was used to quantitate plasma levels of: 1) immunoglobulin (Ig)M and IgG OxLDL autoantibody titers (presented as a mean OxLDL autoantibody titer by averaging the results of four distinct epitopes); 2) LDL-autoantibody immune complexes (LDL-IC); and 3) minimally OxLDL measured by antibody E06 (OxLDL-E06), as determined by the content of oxidized phospholipids (OxPL) per apolipoprotein B-100. RESULTS: Baseline OxLDL IgG autoantibody levels were higher in the MI group (p < 0.0001). At 30-day follow-up, the mean IgM OxLDL titers increased by 48% (p < 0.001) and 20% (p < 0.001), and IgM LDL-IC increased by 60% (p < 0.01) and 26% (p < 0.01) in the MI and UA groups, respectively. The OxLDL-E06 levels increased by 54% (p < 0.01) in the MI group at hospital discharge and by 36% at 30 days. No significant changes in any OxLDL markers were noted in the other groups. The OxLDL-E06 levels strongly paralleled the acute rise in lipoprotein(a), or Lp(a), in the MI group, suggesting that toxic OxPL are preferentially bound to Lp(a). Oxidized LDL–E06 also correlated extremely well with Lp(a) in the entire cohort of patients (r = 0.91, p < 0.0001). CONCLUSIONS: Circulating OxLDL-specific markers strongly reflect the presence of ACS, implying immune awareness to newly exposed oxidation-specific epitopes and possible release of OxLDL in the circulation. The OxLDL-E06 measurements provide novel insights into plaque rupture and the potential atherogenicity of Lp(a).
**Inflammation, bioactive lipids and atherosclerosis: potential roles of a lipoprotein-associated phospholipase A2, platelet activating factor-acetylhydrolase.**

Tselepis AD, John Chapman M.

It is well established that inflammation is an integral feature of atherosclerosis and of the cardiovascular diseases which it underlies. Oxidative stress is also recognized as a key actor in atherogenesis, in which it is closely associated with the inflammatory response and bioactive lipid formation. Several bioactive lipids have been identified in the atherosclerotic plaque, including the potent inflammatory mediator platelet activating factor (PAF), PAF-like lipids, oxidised phospholipids (oxPL) and lysophosphatidylcholine (lyso-PC). Recent evidence has established a central role of two phospholipases (PL) in atherogenesis, the non-pancreatic Type II secretory phospholipase A2 (sPLA2) and the lipoprotein-associated PLA2—alternatively termed as PAF-acetylhydrolase (PAF-AH). sPLA2 is calcium-dependent and hydrolysates the sn-2 acyl group of glycerophospholipids of lipoproteins and cell membranes to produce lyso-PC and free fatty acids. It is also implicated in isoprostane production from oxPL. sPLA2 is an acute phase reactant, which is upregulated by inflammatory cytokines and may represent a new independent risk factor for coronary heart disease. In contrast to sPLA2, PAF-AH is calcium-independent and is specific for short acyl groups at the sn-2 position of the phospholipid substrate and with the exception of PAF, can equally hydrolyze oxPL to generate lyso-PC and oxidized fatty acids. Thus PAF-AH plays a key role in the degradation of proinflammatory oxPL and in the generation of lyso-PC and oxidized fatty acids. PAF-AH equally can also hydrolyze short-chain diacylglycerols, triacylglycerols, and acetylated alkanols, and displays a PLA1 activity. Whereas sPLA2 may represent a new independent risk factor for coronary artery disease, the potential relevance of PAF-AH to atherosclerosis remains the subject of debate, and recent results suggest that the potential role of the LDL-associated PAF-AH in atherogenesis may be distinct to that of the HDL-associated enzyme. This review is focused on the main structural and catalytic features of plasma PAF-AH, on the association of the enzyme with distinct lipoprotein particle subspecies, on its cellular sources, and finally on the potential significance of this lipoprotein-associated PLA2 in cardiovascular disease.
Cardiovascular risk factors in the elderly: the Tehran Lipid and Glucose Study.


BACKGROUND Coronary artery disease is becoming more prevalent in developing countries, particularly in urban areas. Because the proportion of elderly individuals in the population is on the rise, this study was conducted to determine the prevalence of cardiovascular risk factors among the Tehran urban elderly population.

DESIGN AND METHODS Among 15 005 urban individuals of 3 years old and over who had been chosen in a cross-sectional phase of a longitudinal study in Tehran, there were 1799 people aged 60 years and over. The prevalence and distribution of high blood pressure, cigarette smoking, dyslipoproteinemia, diabetes mellitus and obesity were determined in this population. Dietary intake was assessed in a subsidiary of 54 people by means of two 24 h dietary recalls.

RESULTS The percentage of women with two or more cardiovascular disease risk factors was significantly greater than in men (74% compared with 53%, < 0.001). One fourth of men and 55% of women had high serum cholesterol levels (>/=240 mg/dl). The prevalence of diabetes mellitus and impaired glucose tolerance was 24% and 21% in men and 29% and 20% in women, respectively. The prevalence of obesity (body mass index >/=30 kg/m ) was 15% for men and 36% for women. Fifty-five per cent of men and 94% of women had high waist-to-hip ratios (>0.95 in men and >0.8 in women). The mean percentage values of energy intake derived from carbohydrate, protein and fat were 60.5 +/- 8.0, 11.5 +/- 2.0 and 27.8 +/- 8.9, respectively.

CONCLUSIONS The prevalence of cardiovascular risk factors among the Tehran urban elderly population is high. Some efforts should be made to reverse the recent trend towards increasing age-related mortality and morbidity rates of coronary heart disease.
Plasma homocysteine concentration and coronary artery disease in Asian Indians.

Snehalatha C, Ramachandran A, Satyavani K, Sivasankari S, Sathyamurthy I, Viswanathan V.

OBJECTIVE: This study was done (a) to evaluate the relationship between the plasma total homocysteine (tHcy) levels and coronary artery disease (CAD) in Asian Indians and (b) to see the relationship between tHcy and glucose intolerance. METHODS: Fasting concentrations of plasma tHcy was measured in 137 men, aged ≥ 25 years who underwent coronary angiography while investigating for chest pain. Among them 71 had no CAD and 66 had CAD. Fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA1c) were estimated. Total Hcy was measured using the Elisa method (Axis Biochemicals ASA-Oslo, Norway) in fasting EDTA plasma. RESULTS: The subjects with CAD were significantly older but had similar body mass index (BMI), waist–hip ratio (WHR), FPG and HbA1c values compared with the non-CAD subjects (P < 0.001). The median tHcy and the percentages of abnormal values were similar in non-CAD and CAD groups. No significant differences were seen in the four subgroups with respect to the mean tHcy or the percentage of abnormal values. The highest tHcy values were seen in the non-diabetic, non-CAD group (group 1--control). CONCLUSION: This preliminary data indicates that tHcy concentrations are not elevated in subjects with CAD and probably there is no association between total homocysteine and CAD in Indians. Homocysteine values were not influenced by the glucose tolerance status. Measurement of homocysteine concentrations may be more appropriate when the blood levels of vitamin B12 and folate are also measured.
Plasma kinetics of a cholesterol-rich emulsion in subjects with or without coronary artery disease.

Santos RD, Hueb W, Oliveira AA, Ramires JA, Maranhao RC.

A cholesterol-rich emulsion (LDE) that resembles the LDL lipidic structure is taken-up by LDL receptors after intravenous injection by means of apolipoprotein E it acquires in the circulation and can be used to probe LDL metabolism. In this study, LDE was labeled with [14C]cholesteryl oleate and [3H]cholesterol and injected into 19 patients with coronary artery disease (CAD) and into 14 subjects without CAD to verify whether the kinetic behavior of the radioactive lipids is different in CAD. Blood was sampled over 24 h for radioactivity measurement after lipid extraction and separation by thin-layer chromatography. Fractional clearance rate (FCR, in h⁻¹) of [14C]cholesteryl ester was not different in CAD and nonCAD expressed as median (25%; 75%): 0.08 (0.062; 0.134) h⁻¹ versus 0.06 (0.04; 0.083) h⁻¹, P = 0.167. However, [3H]cholesterol FCR was greater in CAD than in nonCAD (mean +/- SEM): 0.163 +/- 0.016 h⁻¹ versus 0.077 +/- 0.014 h⁻¹, P < 0.001. Esterification of the LDE [3H]cholesterol was also greater in CAD subjects than nonCAD at 10 h and 24 h after emulsion injection (P = 0.029 and 0.024 respectively). In conclusion, both removal from the plasma and esterification of the LDE-cholesterol were increased in CAD. These findings may contribute for unraveling pro-atherogenic mechanisms and the establishment of novel CAD markers.
Impact of simvastatin and niacin with and without antioxidants on plasma cholesterol absorption and synthesis markers in coronary artery disease patients with low HDL.

Matthan NR, Giovanni A, Schaefer EJ, Brown BG, Lichtenstein AH.

The HDL Atherosclerosis Treatment Study demonstrated clinical benefit in coronary artery disease patients with low HDL cholesterol levels treated with simvastatin and niacin (S-N), or S-N plus antioxidants (S-N+A), compared to antioxidants alone or placebo. Angiographically documented stenosis regressed in the S-N group but progressed in all other groups. To assess mechanism(s) responsible for these observations, surrogate markers of cholesterol absorption and synthesis were measured. Treatment with S-N reduced desmosterol and lathosterol levels (cholesterol synthesis indicators) 46% and 36% (p<0.05), and elevated campesterol and -sitosterol levels (cholesterol absorption indicators) 70% and 59% (p<0.05), relative to placebo and antioxidant but not S-N+A. Treatment with antioxidants alone had no significant effect. Combining S-N with antioxidants reduced desmosterol and lathosterol by 37% and 31%, and elevated campesterol and -sitosterol levels by 54% and 46%, but differences did not attain significance. Percent change in stenosis was not associated with total and LDL cholesterol levels, but was positively associated with lathosterol (r=0.26, p<0.05), and negatively associated with -sitosterol (r=-0.21, p<0.01). These data suggest that changes in stenosis were attributable in part, to changes in cholesterol metabolism. Measurement of cholesterol absorption and synthesis markers may help better predict changes in stenosis than plasma cholesterol levels alone.
Inflammation and immune system response against unstable angina and its relationship with coronary angiographic findings.

Gokce M, Erdol C, Orem C, Tekelioglu Y, Durmus I, Kasap H.

The aim of this study was to assess the relations between inflammation, immune response, and coronary angiographic findings in patients with unstable angina pectoris (UAP). Recent studies suggest a role for inflammation in the pathophysiology of UAP. Although activation of neutrophils, monocytes and lymphocytes has been shown in UAP, no studies have correlated the activation findings with clinical and angiographic features of patients with UAP. Seventy-three patients undergoing coronary angiography were classified according to their ischaemic syndrome, stable angina pectoris (SAP) \((n=25)\) and UAP \((n=48)\). Patients with UAP were classified using the Braunwald classification: UAP class I \((n=15)\), UAP class II \((n=15)\), and UAP class III \((n=18)\). Patients with UAP were also classified into a progression to myocardial infarction (MI (+)) group \((n=15)\) and a non-progression to myocardial infarction (MI(-)) group \((n=33)\). Venous blood samples were taken from all patients. Cell surface receptors (CD4, CD8, CD3, CD14, CD45, CD56+16, and HLA-DR) were detected by flow cytometry using monoclonal antibodies tagged with fluorescent markers and serum levels of C-reactive protein (CRP) were measured. The serum levels of CRP and the percentages of HLA-DR, CD14, and CD16+56 were higher in UAP than SAP. The serum levels of CRP and percentages of HLA-DR, CD14, and CD16+56 were higher in UAP class II than UAP class I. The serum levels of CRP and percentages of HLA-DR, CD14, and CD16+56 were higher in UAP class III than UAP class II and UAP class I. The serum levels of CRP and percentages of CD16+56 were higher in the MI(+) group than the MI(-) group. The CRP levels in serum and the percentages of cell surface antigens had no correlation with extent of coronary artery disease (no differences among one, two or three vessels) but Type C lesion had significantly higher percentages of HLA-DR, CD14, CD16+56 and the serum levels of CRP than Type A and Type B lesions. This investigation shows that inflammatory and immunological components may be detectable in UAP and were correlated with the clinical severity, progression to myocardial infarction, and lesion morphology, but were not correlated with the extent of coronary artery disease.
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Am J Cardiol, 2001 Apr 1;87(7):827-31
Effect of orlistat-assisted weight loss in decreasing coronary heart disease risk in patients with syndrome X.

Reaven G, Segal K, Hauptman J, Boldrin M, Lucas C.

This study describes the changes in risk factors for coronary heart disease in obese persons with syndrome X after orlistat-assisted weight loss. Data were available for 1,700 patients who completed 52 weeks of weight loss; 128 were defined as having syndrome X by being in the quintile with the highest plasma triglyceride levels (>2.2 mM/L) and the lowest high-density lipoprotein cholesterol (HDL, <1.0 mM/L) concentrations. Initial characteristics of those with syndrome X were similar to the 119 subjects (non-syndrome X) in the lowest quintile of plasma triglyceride (<0.975 mM/L) and highest quintile of HDL cholesterol (>1.5 mM/L). Subjects were placed on a calorie-restricted diet, and randomized to receive orlistat or placebo. Initial values were higher in those with syndrome X for diastolic blood pressure (p = 0.03), plasma insulin (p = 0.0001), triglyceride (p = 0.0001) concentrations, and ratio of low-density lipoprotein cholesterol to HDL cholesterol (p = 0.0001), and were lower for HDL cholesterol (p = 0.001) concentrations. Weight loss was greater in both groups of orlistat-treated patients (p = 0.026); in those with syndrome X, it was associated with a significant reduction in plasma insulin (p = 0.019) and triglyceride (p = 0.0001) concentrations, an increase in HDL cholesterol concentration, and a decrease in low-density lipoprotein/HDL cholesterol ratio (p = 0.0001). There were no significant changes in plasma insulin, triglycerides, or HDL cholesterol concentration in the non-syndrome X group. In conclusion, weight loss attenuates coronary heart disease risk factors in obese persons with syndrome X, and the risk factor reduction is enhanced with administration of orlistat.

Am Heart J, 2001;141(4):599-602

Effect of smoking status and abciximab use on outcome after percutaneous coronary revascularization: Pooled analysis from EPIC, EPILOG, and EPISTENT.

Cho L, Bhatt DL, Wolski K, Lincoff M, Topol EJ, Moliterno DJ.

BACKGROUND: Tobacco use has been studied in relation to the development of atherosclerotic heart disease and outcome after acute coronary syndromes, though outcome data after percutaneous coronary intervention (PCI) are limited. Tobacco use has been associated with increased fibrinogen levels, thrombin generation, and
increased platelet aggregation, and these factors may cause ischemic events after PCI. METHODS: We assessed whether smokers undergoing PCI have more ischemic events and if glycoprotein IIb/IIIa receptor blockade is particularly beneficial in preventing ischemic events in this cohort. We examined clinical outcomes for smokers and nonsmokers by using pooled analysis from 3 large, placebo-controlled trials of the glycoprotein IIb/IIIa antagonist abciximab during PCI. RESULTS: Among 6519 patients, 34% were smokers. The primary end point of death, myocardial infarction, or urgent revascularization within 30 days was reduced by abciximab from 12.3% to 6.4% (relative risk reduction, 48%; P <.001) in smokers and from 11.3% to 5.9% (relative risk reduction, 48%; P <.001) in nonsmokers treated with abciximab. At 6 months, death, myocardial infarction, or urgent revascularization was reduced from 14.4% to 8.5% (relative risk reduction, 41%; P <.001) in smokers and from 14.6% to 8.8% (relative risk reduction, 40%; P <.001) in nonsmokers. Adjusting for baseline differences, smoking was an independent predictor of poor outcome at 30 days (odds ratio, 1.22; 95% confidence interval, 1.02, 1.47; P =.03). CONCLUSIONS: This pooled analysis demonstrates that after PCI, smokers had worse 30-day outcomes than did nonsmokers. However, both groups had a comparable degree of benefit with platelet inhibition through the use of abciximab.

Am J Cardiol, 2001;87(8):947-50; A3

Difference in the mortality of the CABRI diabetic and nondiabetic populations and its relation to coronary artery disease and the revascularization mode.

Kurbaan AS, Bowker TJ, Ilsley CD, Sigwart U, Rickards AF; On behalf of the CABRI Investigators (Coronary Angioplasty versus Bypass Revascularization Investigation).

In diabetics with coronary artery disease (CAD), there remains uncertainty as to whether revascularization by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass surgery (CABG) is preferable. To address this, 4-year mortality and level of pre- and postrevascularization angiographic CAD (measured by a series of coronary scores) were compared between both diabetics and nondiabetics and between revascularization modes in the Coronary Angioplasty versus Bypass Revascularization Investigation population as a whole, and then substratified by diabetic status and then by procedure to which they were randomized. The 1,054 randomized subjects contained 125 diabetics (11.9%) who had significantly greater mortality than nondiabetics (RR 2.19, p = 0.001). Among diabetics or nondiabetics, there was no significant mortality difference between those randomized to PTCA versus those to CABG. Diabetics randomized to PTCA
and those to CABG had higher mortalities than respective nondiabetics; the association reached significance only in the former (RR 2.41, p = 0.002). All subgroups had similar prerevascularization CAD. Postrevascularization residual CAD was consistently significantly greater in PTCA than in respective CABG subgroups. Most measurements of CAD were greater in diabetic than in nondiabetic subgroups, but none was significant. In the Coronary Angioplasty versus Bypass Revascularization Investigation, diabetics had double the mortality of nondiabetics; this difference was statistically significant both for the entire population and for those randomized to PTCA, but not for those randomized to CABG. Among diabetics or nondiabetics, there was no significant mortality difference between PTCA and CABG. The higher diabetic mortality was more likely related to more rapid disease progression than to greater postrevascularization disease.

Diabetes Care, 2001;24(4):683-9

Cardiovascular morbidity and mortality associated with the metabolic syndrome.


OBJECTIVE: To estimate the prevalence of and the cardiovascular risk associated with the metabolic syndrome using the new definition proposed by the World Health Organization. RESEARCH DESIGN AND METHODS: A total of 4,483 subjects aged 35-70 years participating in a large family study of type 2 diabetes in Finland and Sweden (the Botnia study) were included in the analysis of cardiovascular risk associated with the metabolic syndrome. In subjects who had type 2 diabetes (n = 1,697), impaired fasting glucose (IFG)/impaired glucose tolerance (IGT) (n = 798) or insulin-resistant with normal glucose tolerance (NGT) (n = 1,988), the metabolic syndrome was defined as presence of at least two of the following risk factors: obesity, hypertension, dyslipidemia, or microalbuminuria. Cardiovascular mortality was assessed in 3,606 subjects with a median follow-up of 6.9 years. RESULTS: In women and men, respectively, the metabolic syndrome was seen in 10 and 15% of subjects with NGT, 42 and 64% of those with IFG/IGT, and 78 and 84% of those with type 2 diabetes. The risk for coronary heart disease and stroke was increased threefold in subjects with the syndrome (P < 0.001). Cardiovascular mortality was markedly increased in subjects with the metabolic syndrome (12.0 vs. 2.2%, P < 0.001). Of the individual components of the metabolic syndrome, microalbuminuria conferred the strongest risk of cardiovascular death (RR 2.80; P = 0.002). CONCLUSIONS: The WHO definition of the metabolic syndrome identifies subjects with increased cardiovascular morbidity and mortality and offers a tool for comparison of results from different studies.
Early growth and coronary heart disease in later life: longitudinal study.

Eriksson JG, Forsen T, Tuomilehto J, Osmond C, Barker DJ.

OBJECTIVE: To determine how growth during infancy and childhood modifies the increased risk of coronary heart disease associated with small body size at birth. DESIGN: Longitudinal study. SETTING: Helsinki, Finland. SUBJECTS: 4630 men who were born in the Helsinki University Hospital during 1934-44 and who attended child welfare clinics in the city. Each man had on average 18.0 (SD 9.5) measurements of height and weight between birth and age 12 years. MAIN OUTCOME MEASURES: Hospital admission or death from coronary heart disease. RESULTS: Low birth weight and low ponderal index (birth weight/length(3)) were associated with increased risk of coronary heart disease. Low height, weight, and body mass index (weight/height(2)) at age 1 year also increased the risk. Hazard ratios fell progressively from 1.83 (95% confidence interval 1.28 to 2.60) in men whose body mass index at age 1 year was below 16 kg/m(2) to 1.00 in those whose body mass index was >19 (P for trend=0.0004). After age 1 year, rapid gain in weight and body mass index increased the risk of coronary heart disease. This effect was confined, however, to men with a ponderal index <26 at birth. In these men the hazard ratio associated with a one unit increase in standard deviation score for body mass index between ages 1 and 12 years was 1.27 (1.10 to 1.47; P=0.001). CONCLUSION: Irrespective of size at birth, low weight gain during infancy is associated with increased risk of coronary heart disease. After age 1 year, rapid weight gain is associated with further increase in risk, but only among boys who were thin at birth. In these boys the adverse effects of rapid weight gain on later coronary heart disease are already apparent at age 3 years. Improvements in fetal, infant, and child growth could lead to substantial reductions in the incidence of coronary heart disease.

Circulation 2001 Apr 17;103(15):1955-60

Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes.

BACKGROUND: There is accumulating data that acute coronary syndromes relate to recent onset activation of inflammation affecting atherosclerotic plaques. Increased blood levels of oxidized low density lipoprotein (ox-LDL) could play a role in these circumstances. METHODS AND RESULTS: Ox-LDL levels were measured in 135 patients with acute myocardial infarction (AMI; n=45), unstable angina pectoris (UAP; n=45), and stable angina pectoris (SAP; n=45) and in 46 control subjects using a sandwich ELISA method. In addition, 33 atherectomy specimens obtained from a different cohort of patients with SAP (n=10) and UAP (n=23) were studied immunohistochemically for ox-LDL. In AMI patients, ox-LDL levels were significantly higher than in patients with UAP (P<0.0005) or SAP (P<0.0001) or in controls (P<0.0001) (AMI, 1.95+/-1.42 ng/5 microgram LDL protein; UAP , 1.19+/-0.74 ng/5 microgram LDL protein; SAP , 0.89+/-0.48 ng/5 microgram LDL protein; control, 0.58+/-0.23 ng/5 microgram LDL protein). Serum levels of total, HDL, and LDL cholesterol did not differ among these patient groups. In the atherectomy specimens, the surface area containing ox-LDL-positive macrophages was significantly higher in patients with UAP than in those with SAP (P<0.0001). CONCLUSIONS: This study demonstrates that ox-LDL levels show a significant positive correlation with the severity of acute coronary syndromes and that the more severe lesions also contain a significantly higher percentage of ox-LDL-positive macrophages. These observations suggest that increased levels of ox-LDL relate to plaque instability in human coronary atherosclerotic lesions.

Circulation, 2001;103(15):1936-41

Impaired coronary tissue plasminogen activator release is associated with coronary atherosclerosis and cigarette smoking: direct link between endothelial dysfunction and atherothrombosis.

Newby DE, McLeod AL, Uren NG, Flint L, Ludlam CA, Webb DJ, Fox KA, Boon NA.

BACKGROUND: The aim of the study was to establish the influence of proximal coronary artery atheroma and smoking habit on the stimulated release of tissue plasminogen activator (tPA) from the heart. METHODS AND
RESULTS: After diagnostic coronary angiography in 25 patients, the left anterior descending coronary artery (LAD) was instrumented, and the proximal LAD plaque volume was determined by use of intravascular ultrasound (IVUS). Blood flow and fibrinolytic responses to selective LAD infusion of saline, substance P (10 to 40 pmol/min; endothelium-dependent), and sodium nitroprusside (5 to 20 microgram/min; endothelium-independent) were measured by intracoronary IVUS and Doppler, combined with arterial and coronary sinus blood sampling. Mean plaque burden was 5.5±0.8 mm³/mm vessel (range 0.6 to 13.7 mm³/mm vessel). LAD blood flow increased with both substance P and sodium nitroprusside (P<0.001), although coronary sinus plasma tPA antigen and activity concentrations increased only during substance P infusion (P<0.006 for both). There was a strong inverse correlation between the LAD plaque burden and release of active tPA (r=-0.61, P=0.003). Cigarette smoking was associated with impaired coronary release of active tPA (current smokers, 31+/−23 IU/min; ex-smokers, 50+/−33 IU/min; nonsmokers 202+/−73 IU/min; P<0.05). CONCLUSIONS: We found that both the coronary atheromatous plaque burden and smoking habit are associated with a reduced acute local fibrinolytic capacity of the heart. These important findings provide evidence of a direct link between endogenous fibrinolysis, endothelial dysfunction, and atherothrombosis in the coronary circulation and may explain the greater efficacy of thrombolytic therapy for myocardial infarction in cigarette smokers.

Eur Heart J, 2001 22(7):554-72

Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries; principal results from EUROASPIRE II Euro Heart Survey Programme.

AIMS: The principal aim of the second EUROASPIRE survey was to determine in patients with established coronary heart disease whether the Joint European Societies?recommendations on coronary prevention are being followed in clinical practice. METHODS: This survey was undertaken in 1999-2000 in 15 European countries: Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Slovenia, Sweden, Spain and the U.K., in selected geographical areas and 47 centres. Consecutive patients, men and women < or =70 years were identified retroactively with the following diagnoses: coronary artery bypass graft, percutaneous transluminal coronary angioplasty, acute myocardial infarction and myocardial ischaemia. Data collection was based on a review of medical records and interview and risk assessment at least 6 months after hospital admission. RESULTS: 8181 medical records (25% women) were reviewed and 5556 patients (adjusted participation rate 76%) interviewed. Recording of risk factor history and risk factor measurement in hospital notes was incomplete, particularly for discharge documents. At interview
(median time 1.4 years after hospital discharge), 21% of patients smoked cigarettes, 31% were obese, 50% had raised blood pressure (systolic blood pressure \( \geq 140 \) mmHg and/or diastolic blood pressure \( \geq 90 \) mmHg), 58% had elevated serum total cholesterol (total cholesterol \( \geq 5 \) mmol x l\(^{-1}\)) and 20% reported a medical history of diabetes. Glucose control in these diabetic patients was poor with 87% having plasma glucose \( \geq 6.0 \) mmol x l\(^{-1}\) and 72% \( \geq 7.0 \) mmol x l\(^{-1}\). Among the patients interviewed the use of prophylactic drug therapies on admission, at discharge and at interview was as follows: aspirin or other antiplatelets drugs 47%, 90% and 86%; beta-blockers 44%, 66% and 63%; ACE inhibitors 24%, 38% and 38%; and lipid-lowering drugs 26%, 43% and 61%, respectively. With the exception of antiplatelets drugs, wide variations in the use of prophylactic drug therapies exist between countries. CONCLUSIONS: This European survey of coronary patients shows a high prevalence of unhealthy lifestyles, modifiable risk factors and inadequate use of drug therapies to achieve blood pressure and lipid goals. There is considerable potential throughout Europe to raise the standard of preventive cardiology through more effective lifestyle intervention, control of other risk factors and optimal use of prophylactic drug therapies in order to reduce coronary morbidity and mortality.

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J Am Coll Cardiol, 2001 ;37(6):1516-22

An insertion/deletion polymorphism in the alpha2B-adrenergic receptor gene is a novel genetic risk factor for acute coronary events.


OBJECTIVES: Our aim was to study whether an insertion/deletion (I/D) polymorphism in the alpha2B-adrenoceptor gene is associated with the risk for cardiovascular diseases. BACKGROUND: alpha2-adrenoceptors mediate contraction of vascular smooth muscle and induce coronary vasoconstriction in humans. The alpha2-adrenoceptor subtype B mediates vasoconstriction in mice. A variant of the human alpha2B-adrenoceptor gene that encodes a D of three residues in an intracellular acidic motif has been shown to confer decreased receptor desensitization. This receptor variant could, therefore, be involved in diseases associated with enhanced vasoconstriction. METHODS: This study was part of a prospective population-based study investigating risk factors for cardiovascular diseases in a cohort of middle-aged men from eastern Finland. Nine hundred twelve men aged 46 to 64 years were followed for an average time of 4.5 years. RESULTS: In this
study population, 192 men (21%) had the D/D genotype; 256 (28%) had the I/I genotype, and 464 (51%) had a heterozygous genotype. In a Cox model adjusting for other coronary risk factors, men with the D/D genotype had 2.2 times (95% confidence interval: 1.1 to 4.4, p = 0.02) the risk to experience an acute coronary event (n = 15 for D/D, 10 for I/I and 12 for I/D) compared with men carrying either of the other two genotypes. The alpha2B-adrenoceptor genotype was not associated with hypertension in this study population. CONCLUSIONS: The D/D genotype of the alpha2B-adrenoceptor is a novel genetic risk factor for acute coronary events, but not for hypertension.

J Am Coll Cardiol, 2001;37(6):1536-42


OBJECTIVES: We examined the relationship between the angiotensinogen (AGT) gene M235T polymorphism, the variant promoter of the AGT gene A(-6)G and the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism and coronary heart disease (CHD) in native Gran Canaria Island inhabitants, who have the highest rates of CHD in Spain. BACKGROUND: Some studies subject that the ACE (I/D) polymorphism could be associated with CHD, while AGT (M235T) has been related to essential hypertension. METHODS: We studied 304 subjects with angiographic evidence of coronary artery disease and a clinical diagnosis of myocardial infarction or unstable angina and 315 age- and gender-matched controls. Blood was drawn and DNA extracted. Angiotensin-converting enzyme (I/D) gene polymorphism was analyzed by polymerase chain reaction (PCR) and AGT gene polymorphisms by restriction fragment length polymorphism-PCR and mutagenically-separated PCR. RESULTS: The ACE (I/D) polymorphism showed no association with CHD, whereas the frequency distribution of AGT (M235T) genotypes among patients and controls (235T: 29.1% and 19.0%; M235T: 48.5% and 50.2%; M235: 22.4% and 30.8%, respectively) was statistically different (p = 0.005) and not related to the presence of essential hypertension. Similar results were observed with the AGT A(-6)G polymorphism. In multiple logistic regression analysis, CHD odds ratio associated with 235T and M235 homozygotes were 1.7 (1.1 to 2.6) and 0.54 (0.36 to 0.82), respectively. CONCLUSIONS: This study shows that genetic variation of the AGT (M235T), but not the ACE (I/D),
genotypes contributes to the presence of CHD independently of blood pressure profile in a subset of the Spanish population with a high prevalence of cardiovascular disease.

Circulation, 2001;103(20):2436-40

G20210A prothrombin gene polymorphism and prothrombin activity in subjects with or without angiographically documented coronary artery disease.


BACKGROUND: G20210A prothrombin mutation has been associated with high prothrombin levels and an increased risk of venous thrombosis. The role of this common polymorphism, as well as that of prothrombin levels, in determining the risk of arterial disease is still somewhat controversial. METHODS AND RESULTS: We determined the prevalence of the G20210A mutation and prothrombin activity in 660 individuals, of whom 436 had angiographically documented severe coronary artery disease (CAD patients) and 224 had normal coronary angiography (CAD-free control subjects). Heterozygosity for the 20210A allele was found in 5.3% of the CAD patients versus 3.1% of the CAD-free subjects (P=0.21). Similarly, no statistically significant difference was found between CAD patients with or without previous myocardial infarction (4.5% versus 5.3%, respectively; P=0.73). The genotype-phenotype correlation study showed a significant influence of the 20210A allele on prothrombin activity, with higher levels in carriers compared with noncarriers (153.2% versus 122.2%, respectively; P<0.001). Prothrombin activity was significantly higher in CAD patients than in CAD-free subjects (132.8% versus 123.3%, respectively; P<0.005). By multiple logistic regression, prothrombin activity in the upper tertile of the control distribution was significantly associated with CAD compared with prothrombin activity in the lower tertile (adjusted odds ratio 1.86, 95% CI 1.01 to 3.4). CONCLUSIONS: In a population with a clear-cut definition of the phenotype, the G20210A prothrombin mutation was not significantly associated, per se, with either angiographically documented CAD or myocardial infarction, whereas it significantly influenced prothrombin activity. In our population, high prothrombin activity itself was independently associated with CAD but not with the presence or absence of previous myocardial infarction.

Am J Cardiol, 2001;87(9):1074-9
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS): additional perspectives on tolerability of long-term treatment with lovastatin.


This study presents the long-term safety data from AFCAPS/TexCAPS, the first primary prevention trial to demonstrate that men and women with average levels of low-density lipoprotein cholesterol (LDL-C) and below average levels of high-density lipoprotein cholesterol (HDL-C) can significantly benefit from long-term treatment to lower LDL-C; lovastatin 20 to 40 mg/day reduced the risk of a first acute major coronary event (fatal or nonfatal myocardial infarction, unstable angina, or sudden death) by 37% (p = 0.00008). This double-blind randomized, placebo-controlled trial, in 6,605 generally healthy middle-aged and older men and women, had prespecified end point and cancer analyses. All analyses were intention-to-treat. Safety monitoring included history, physical examination, and laboratory studies (including hepatic transaminases and creatine phosphokinase [CPK]). All participants, even those who discontinued treatment, were contacted annually for vital status, cardiovascular events, and cancer history. After an average of 5.2 years of follow-up, there were 157 deaths (80 receiving lovastatin and 77 receiving placebo; relative risk [RR] 1.04; 95% confidence interval [CI] 0.76 to 1.42; p = 0.82); of which 115 were noncardiovascular (RR 1.21; CI 0.84 to 1.74; p = 0.31), and of these, 82 were due to cancer (RR 1.41; CI 0.91 to 2.19; p = 0.13). There were no significant differences between treatment groups in overall cancer rates, discontinuations for noncardiovascular adverse experiences, or clinically important elevations of hepatic transaminases or CPK. Among those who used cytochrome P450 isoform (CYP3A4) inhibitors, there were no treatment group differences in the frequency of clinically important muscle-related adverse events. Treatment with lovastatin 20 to 40 mg daily for primary prevention of coronary heart disease was well tolerated and reduced the risk of first acute coronary events without increasing the risk of either noncardiovascular mortality or cancer.

Am J Cardiol, 2001;87(9):1051-7

M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study).
Previous studies have identified a number of echocardiographic variables that predict cardiovascular disease (CVD) events and mortality, but have not focused on a large elderly cohort. The purpose of this study was to determine whether M-mode echocardiographic variables predicted all-cause mortality, incident coronary heart disease (CHD), congestive heart failure (CHF), and stroke in a large prospective, multicenter, population-based study. In the Cardiovascular Health Study, a biracial cohort of 5,888 men and women (mean age 73 years) underwent 2-dimensional M-mode echocardiographic measurements of left ventricular (LV) internal dimensions, wall thickness, mass and geometry, as well as measurement of left atrial dimension and assessment for mitral annular calcium. Participants were followed for 6 to 7 years for incident events; analyses excluded subjects with prevalent disease. One or more echocardiographic measurements were independent predictors of all-cause mortality and incident CHD, CHF, and stroke. After adjustment for anthropometric and traditional CVD risk factors, LV mass was significantly related to incident CHD, CHF, and stroke. The highest quartile of LV mass conferred a hazards ratio of 3.36, compared with the lowest quartile, for incident CHF. Furthermore, incident CHF-free survival was significantly lower for participants with LV mass in the highest versus the 2 lowest quartiles (86% vs 97%, respectively, at 2,500 days). Eccentric and concentric LV hypertrophy, respectively, conferred adjusted hazards ratios, compared with normal LV geometry, of 2.05 and 1.61 for incident CHD, and 2.95 and 3.32 for incident CHF. Thus, in an elderly biracial population, selected 2-dimensional M-mode echocardiographic measurements were important markers of subclinical disease and conferred independent prognostic information for incident CVD events, especially CHF and CHD.

J Am Coll Cardiol, 2001;37(6):1558-64

Independent contribution of myocardial perfusion defects to exercise capacity and heart rate recovery for prediction of all-cause mortality in patients with known or suspected coronary heart disease.

Diaz LA, Brunken RC, Blackstone EH, Snader CE, Lauer MS.

OBJECTIVES: The goal of this study was to determine the value of thallium201 single photon emission
computed tomography (SPECT) imaging for prediction of all-cause mortality when considered along with functional capacity and heart rate recovery. **BACKGROUND:** Myocardial perfusion defects identified by thallium201 SPECT imaging are predictive of cardiac events. Functional capacity and heart rate recovery are exercise measures that also have prognostic implications. **METHODS:** We followed 7,163 consecutive adults referred for symptom-limited exercise thallium SPECT (mean age 60 +/− 10, 25% women) for 6.7 years. Using information theory, we identified a probable best model relating nuclear findings to outcome to calculate a prognostic nuclear score. **RESULTS:** There were 855 deaths. Intermediate- and high-risk prognostic nuclear scores were noted in 28% and 10% of patients. Compared with those with low-risk scans, patients with an intermediate-risk score were at increased risk for death (14% vs. 9%, hazard ratio: 1.67, 95% confidence interval [CI]: 1.44 to 1.95, p <0.0001), while those with high-risk scores were at greater risk (24%, hazard ratio: 2.98, 95% CI: 2.49 to 3.56, p < 0.0001). In multivariable analyses that adjusted for clinical characteristics, functional capacity and heart rate recovery, an intermediate-risk nuclear score remained predictive of death (adjusted hazard ratio: 1.50, 95% CI: 1.28 to 1.76, p < 0.0001), as did a high-risk score (adjusted hazard ratio: 2.76, 95% CI: 2.13 to 2.56, p < 0.0001). Impaired functional capacity and decreased heart rate recovery provided additional prognostic information. **CONCLUSIONS:** Myocardial perfusion defects detected by thallium SPECT imaging are independently predictive of long-term all-cause death, even after accounting for exercise capacity, heart rate recovery and other potential confounders.

J Am Coll Cardiol, 2001;37(6):1543-50

New diagnostic criteria for diabetes and coronary artery disease: insights from an angiographic study.

Ledru F, Ducimetiere P, Battaglia S, Courbon D, Beverelli F, Guize L, Guermonprez JL, Diebold B.

**OBJECTIVES:** The goal of this research was to study coronary atherosclerosis in patients with type 2 diabetes compared with patients without diabetes according to the new definition of diabetes advocated by the American Diabetes Association in 1997. **BACKGROUND:** Patients with diabetes (fasting plasma glucose above 7.0 mM/L) have a higher risk of cardiovascular death. The correlation with the pattern and severity of their coronary atherosclerosis, especially in the new patients with diabetes (7.0 mM/L < or = fasting plasma glucose < 7.8 mM/L), remains unclear. **METHODS:** A cohort of 466 patients undergoing coronary angiography but free of any previous infarction, coronary intervention and insulin therapy were prospectively recruited. Ninety-three had diabetes (fasting plasma glucose > 7.0 mM/L or hypoglycemic oral treatment). Five
angiographic indexes were calculated to describe severity and extent of coronary atherosclerosis. RESULTS: Overall, patients with diabetes had more diffuse coronary atherosclerosis, a greater prevalence of mild, moderate and severe stenoses and a two-fold higher occlusion rate than patients without diabetes, even after adjustment for age, gender, body mass index, hypertension, lipid parameters, smoking, family history of cardiovascular events and ischemic symptoms. Patients with ?ild diabetes? had a coronary atherosclerosis pattern more similar to patients with normal fasting plasma glucose than to patients formerly defined as diabetic according to the World Health Organization criteria, except that they had a higher prevalence of <50% stenoses. CONCLUSIONS: In patients with type 2 diabetes, those with 7.0 mM.L < or = fasting plasma glucose < 7.7 mM.L have a slightly greater prevalence of mildly severe lesions that may partly explain their higher cardiovascular event rate.

Am Coll Cardiol, 2001;37(6):1523-8

Obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries.

Al Suwaidi J, Higano ST, Holmes DR Jr, Lennon R, Lerman A.

OBJECTIVES: This study evaluates the impact of obesity on coronary endothelial function in patients with normal or mild coronary artery disease. BACKGROUND: The American Heart Association (AHA) has recently classified obesity as a modifiable risk factor for coronary heart disease. METHODS: A total of 397 consecutive patients with normal or mildly diseased coronary arteries at angiography underwent coronary vascular reactivity evaluation using intracoronary adenosine, acetylcholine and nitroglycerin. Patients were divided into three groups based on the body mass index (BMI): Group 1, patients with a BMI <25 (n = 117, normal weight); Group 2, patients with a BMI 25-30 (n = 149, overweight) and Group 3, patients with a BMI >30 (n = 131, obese). RESULTS: There were no significant differences among the groups in regard to other cardiovascular risk factors, except that overweight but not obese patients were significantly older than normal-weight patients (47 +/- 1 years in Group 1, 53 +/- 1 years in Group 2 and 50 +/- 1 years in Group 3, p < 0.001). The percent change of coronary blood flow to acetylcholine (%delta CBF Ach) was significantly lower in the obese patients than in the normal-weight group (85.2 +/- 12.0% in Group 1, 63.7 +/- 10.0% in Group 2 and 38.1 +/- 9.6% in Group 3, p = 0.009). By multivariate analysis, overweight (odds ratio, 1.55; 95% confidence interval, 1.2-2.0) and obesity (odds ratio, 2.41; 95% confidence interval, 1.5-4.0) status were independently associated with impaired
coronary endothelial function. CONCLUSIONS: The study demonstrates that obesity is independently associated with coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries.

Eur Heart J, 2001;22(9):762-8

Gender differences in recurrent coronary events; the FINMONICA MI register.


BACKGROUND: Male gender is an established risk factor for first myocardial infarction, but some studies have suggested that among myocardial infarction survivors, women fare worse than men. Therefore, we examined the long-term prognosis of incident myocardial infarction survivors in a large, population-based MI register, addressing gender differences in mortality as well as the number of events and time intervals between recurrent events. METHODS AND RESULTS: Study subjects included 4900 men and women, aged 25-64 years, with definite or probable first myocardial infarctions who were alive 28 days after the onset of symptoms. At first myocardial infarction, women were older and more likely to be hypertensive or diabetic than men, and had a greater proportion of probable vs definite events. After adjustment for age and geographic region, men had 1.74 times the risk of fatal coronary heart disease relative to women (hazard ratio=1.63 and 1.55 for cardiovascular disease and all-cause mortality, respectively) over an average of 5.9 years of follow-up. Number and time intervals between any recurrent event?fatal and non-fatal?did not differ by gender. CONCLUSION: These data suggest that men are far more likely to have a fatal recurrent event than women despite comparable numbers of events.

Circulation, 2001 ;103(19):2323-7

Fibrin D-dimer and coronary heart disease: prospective study and meta-analysis.

BACKGROUND: It is unknown whether modest increases of fibrin D-dimer, a circulating marker of fibrin turnover, are relevant to coronary heart disease (CHD) in the general population. Methods and RESULTS: We measured serum concentrations of D-dimer antigen in the stored baseline blood samples of 630 CHD cases and 1269 controls tested in a prospective cohort of 5661 men who were monitored for 16 years, and we conducted a meta-analysis of previous relevant studies to place our findings in context. In a comparison of men in the top third compared with those in the bottom third of baseline fibrin D-dimer values (tertile cutoffs, >94 versus <49 ng/mL), the odds ratio for CHD was 1.67 (95% CI, 1.31 to 2.13; P<0.0001) after adjustments for age and town. The odds ratio increased slightly after further adjustment for smoking, other classic risk factors, and indicators of socioeconomic status (1.79; 95% CI, 1.36 to 2.36). Strong correlations were observed of fibrin D-dimer values with circulating concentrations of C-reactive protein and serum amyloid A protein but not with smoking, blood lipids, blood pressure, and other risk factors. CONCLUSION: Although there may be an association between circulating D-dimer values and CHD, further studies are needed to determine the extent to which this is causal.

Circulation, 2001;103(21):2579-84

Different prognostic impact of 24-hour mean blood pressure and pulse pressure on stroke and coronary artery disease in essential hypertension.


BACKGROUND: We tested the hypothesis that the steady and pulsatile components of blood pressure (BP) exert a different influence on coronary artery disease and stroke in subjects with hypertension. METHODS AND RESULTS: We analyzed data on 2311 subjects with essential hypertension. All subjects (mean age 51 years, 47% women) underwent off-therapy 24-hour ambulatory BP monitoring. Over a follow-up period of up to 14 years (mean 4.7 years), there were 132 major cardiac events (1.20 per 100 person-years) and 105 cerebrovascular events (0.90 per 100 person-years). After adjustment for age, sex, diabetes, serum cholesterol, and cigarette smoking (all P<0.01), for each 10 mm Hg increase in 24-hour pulse pressure (PP), there was an independent 35% increase in the risk of cardiac events (95% CI 17% to 55%). Twenty-four-hour mean BP was not a significant predictor of cardiac events after controlling for PP. After adjustment for age, sex, and diabetes (all P<0.05), for every 10 mm Hg increase in 24-hour mean BP, the risk of cerebrovascular events increased by 42% (95% CI 19%
to 69%), and 24-hour PP did not yield significance after controlling for 24-hour mean BP. Twenty-four-hour PP was also an independent predictor of fatal cardiac events, and 24-hour mean BP was an independent predictor of fatal cerebrovascular events. CONCLUSIONS: In subjects with predominantly systolic and diastolic hypertension, ambulatory mean BP and PP exert a different predictive effect on the cardiac and cerebrovascular complications. Although PP is the dominant predictor of cardiac events, mean BP is the major independent predictor of cerebrovascular events.

Circulation, 2001;103(21):2544-9

Plasma total cysteine as a risk factor for vascular disease: The European Concerted Action Project.

El-Khairy L, Ueland PM, Refsum H, Graham IM, Vollset SE; European Concerted Action Project.

BACKGROUND: Elevated plasma total homocysteine (tHcy) is a risk factor for cardiovascular disease. Although cysteine is structurally similar and metabolically linked to tHcy, its relation to the risk of cardiovascular disease has received little attention. We studied the relation between plasma total cysteine (tCys) levels and the risk of vascular disease in the coronary, cerebral, and peripheral vessels. METHODS AND RESULTS: This case-control study included 750 patients with vascular disease and 800 age- and sex-matched control subjects recruited from 19 centers in 9 European countries. Conventional risk factors for cardiovascular disease were recorded. In addition, plasma levels of tCys, tHcy, folate, B(6), B(12), and creatinine were measured. Overall, a U-shaped relationship was observed between tCys and risk of vascular disease. With the middle range of 250 to 275 micromol/L tCys used as the reference category, the adjusted risk of vascular disease at low (</=225 micromol/L) tCys levels was 2.1 (95% CI 1.2 to 3.6), and the risk at high (>300 micromol/L) tCys levels was 1.6 (95% CI 1.1 to 2.3). Different shapes of the dose-response relationship were seen for the 3 vascular disease categories. The relation with peripheral vascular and cerebrovascular disease was U-shaped, whereas a weak positive relation was observed with coronary heart disease. CONCLUSIONS: Our data show a significant U-shaped relationship between tCys and cardiovascular disease after adjustment for tHcy, creatinine, and other cardiovascular disease risk factors.

Circulation, 2001;103(22):2674-80
Low dietary folate intake is associated with an excess incidence of acute coronary events: The Kuopio Ischemic Heart Disease Risk Factor Study.

Voutilainen S, Rissanen TH, Virtanen J, Lakka TA, Salonen JT; Kuopio Ischemic Heart Disease Risk Factor Study.

BACKGROUND: Although several prospective studies have shown that low folate intake and low circulating folate are associated with increased risk of coronary heart disease (CHD), the findings are inconsistent. METHODS AND RESULTS: We studied the associations of dietary intake of folate, vitamin B(6), and vitamin B(12) with the risk of acute coronary events in a prospective cohort study of 1980 Finnish men 42 to 60 years old examined in 1984 to 1989 in the Kuopio Ischemic Heart Disease Risk Factor Study. Nutrient intakes were assessed by 4-day food record. During an average follow-up time of 10 years, 199 acute coronary events occurred. In a Cox proportional hazards model adjusted for 21 conventional and nutritional CHD risk factors, men in the highest fifth of folate intake had a relative risk of acute coronary events of 0.45 (95% CI 0.25 to 0.81, P=0.008) compared with men in the lowest fifth. This association was stronger in nonsmokers and light alcohol users than in smokers and alcohol users. A high dietary intake of vitamin B(6) had no significant association and that of vitamin B(12) a weak association with a reduced risk of acute coronary events. CONCLUSIONS: The present work in CHD-free middle-aged men is the first prospective cohort study to observe a significant inverse association between quantitatively assessed moderate-to-high folate intakes and incidence of acute coronary events in men. Our findings provide further support in favor of a role of folate in the promotion of good cardiovascular health.

Am J Cardiol, 2001;87(12):1361-6

Correlation of polymorphisms to coagulation and biochemical risk factors for cardiovascular diseases.

Wu AH, Tsongalis GJ.

Currently, the established risk factors for cardiovascular disease (CVD) are largely environmental in nature. Conflicting studies have suggested that mutations in specific coagulation genes may also provide a genetic
basis for CVD risk. We reviewed clinical studies that examined the role of single nucleotide polymorphisms in coagulation and platelet factors, and a biochemical factor to determine if specific genotypes are correlated with patients with a history of arterial thrombotic diseases (acute coronary syndromes or stroke). A meta-analysis was performed on studies for factors II (G20210A variant), V Leiden (G1691A), VII (R353Q), glycoprotein (GP) IIIa receptor (PI(A1/A2)), and methylenetetrahydrofolate reductase (MTHFR, C677T). There was no correlation for factor II or factor V polymorphisms to coronary artery disease (CAD) in 5,607 and 5,431 patients studied, respectively. There was also no correlation for factor II variants and stroke in 3,451 patients studied. For factor V, statistical significance was achieved for the G1691A variant on 3,399 patients with stroke (odds ratio [OR] 1.43, 95% confidence intervals [CI] 1.03 to 1.97). The GP IIIa PI(A1/A2) genotype was associated with increased risk for CAD in 7,920 patients (OR 1.12, 95% CI 1.01 to 1.24), but not for 1,855 patients who had a stroke (OR 0.80, 95% CI 0.62 to 1.04). The combined RQ and RR genotypes of factor VII R353Q were correlated to a reduced risk for CVD in 2,574 patients (OR 0.78, 95% CI 0.65 to 0.93), whereas the QQ genotype had offered more protection (OR 0.53, 95% CI 0.27 to 1.03). The TT homozygous variant of MTHFR was associated with CAD risk in 5,644 patients studied (OR 1.30, 95% CI 1.11 to 1.52) but not for 3,075 patients with stroke. This study shows that for some genes, further studies are unnecessary, whereas for others, no more enrollments are needed. The impact of certain genotypes must be examined in relation to other established risk factors and potentially new therapeutic strategies.

Circulation, 2001;103(24):2915-21

Cytomegalovirus infection with interleukin-6 response predicts cardiac mortality in patients with coronary artery disease.


BACKGROUND: Prospective data relating previous exposure to cytomegalovirus (CMV) to the risk of cardiac mortality are controversial. We investigated the effect of previous exposure to CMV infection on the risk of future cardiac disease-related death in relation to an underlying inflammatory response. METHODS AND RESULTS: coronary angiography was performed in 1134 subjects, and 989 patients with documented coronary artery disease were studied prospectively. CMV-IgG titers and interleukin (IL)-6 levels were measured before angiography. Increasing titers of CMV correlated with the elevation of IL-6 levels (P<0.001) after adjustment for
possible confounders. All patients were followed up for a median of 3.1 years (maximum 4.3 years). During follow-up, 96 patients died, 70 of cardiac disease. Overall, CMV seropositivity was not related to cardiac mortality after adjustment for confounding variables (P=0.19). In contrast, in patients with elevated IL-6 levels (>=11.9 pg/mL, median level), CMV seropositivity was independently associated with a 3.2-fold (95% CI 1.4 to 7.3, P=0.007) increase in risk of future cardiac death, whereas in individuals without IL-6 elevation, previous CMV infection had no effect on cardiac mortality. CONCLUSIONS: MV seropositivity in patients with an inflammatory response is independently associated with future cardiac mortality, whereas this association is lost in patients who do not demonstrate an inflammatory response. These data support the hypothesis that the atherosclerotic effects of CMV are mediated through an underlying inflammatory response.


Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events.

Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr; Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators.

BACKGROUND: Elevated levels of C-reactive protein, even in the absence of hyperlipidemia, are associated with an increased risk of coronary events. Statin therapy reduces the level of C-reactive protein independently of its effect on lipid levels. We hypothesized that statins might prevent coronary events in persons with elevated C-reactive protein levels who did not have overt hyperlipidemia. METHODS: The level of C-reactive protein was measured at base line and after one year in 5742 participants in a five-year randomized trial of lovastatin for the primary prevention of acute coronary events. RESULTS: The rates of coronary events increased significantly with increases in the base-line levels of C-reactive protein. Lovastatin therapy reduced the C-reactive protein level by 14.8 percent (P<0.001), an effect not explained by lovastatin-induced changes in the lipid profile. As expected, lovastatin was effective in preventing coronary events in participants whose base-line ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol was higher than the median ratio, regardless of the level of C-reactive protein (number needed to treat for five years to prevent 1 event, 47; P=0.005). However, lovastatin was also effective among those with a ratio of total to HDL cholesterol that was lower than the median and a C-reactive protein level higher than the median (number needed to treat, 43; P=0.02). In contrast, lovastatin was ineffective among participants with a ratio of total to HDL cholesterol and a
C-reactive protein level that were both lower than the median (number needed to treat, 983; P=0.80).

CONCLUSIONS: Statin therapy may be effective in the primary prevention of coronary events among subjects with relatively low lipid levels but with elevated levels of C-reactive protein.

Eur Heart J, 2001;22(13):1119-27


Wilhelmsen L, Pyorala K, Wedel H, Cook T, Pedersen T, Kjekshus J.

AIMS: To analyse (1) the prognostic importance of clinical findings and lipids in patients with a previous myocardial infarction and (2) the relative and absolute benefit of simvastatin in patients at low, medium and high predicted risk. METHODS: The 4S was a double-blind, randomized, clinical trial of long-term treatment with simvastatin or matching placebo in patients with myocardial infarction or angina pectoris, serum total cholesterol 5.5-8.0 mmol x l(-1), and serum triglycerides <or=2.5 mmol x l(-1). The present study only deals with those 3525 patients who had a previous myocardial infarction. End-points comprised coronary death, definite and probable hospital verified myocardial infarction, and resuscitated cardiac arrest. Because there were few women the primary analyses were performed among men. RESULTS: A Cox model analysis in the placebo group identified the following independent predictors of coronary events: a history of hypertension (P=0.023), diabetes (P=0.0001), smoking after the myocardial infarction (P=0.010), total cholesterol (P=0.020), and HDL cholesterol (P=0.062). The relative reduction of risk by simvastatin treatment in patients at low, medium and high predicted risk was 38%, 39% and 42%, respectively, but the corresponding absolute benefit per 100 patients treated for 6 years increased from 7.9 to 16.2. CONCLUSION: In addition to serum lipids, clinical variables contributed significantly to prediction. The relative benefit from simvastatin treatment was independent of predicted risk, but the absolute benefit increased from low to high risk.

Eur Heart J, 2001;22(11):934-41

Long-term clinical outcome after coronary balloon angioplasty: identification of a population at low risk of
recurrent events during 17 years of follow-up.

van Domburg RT, Foley DP, de Feyter PJ, van der Giessen W, van den Brand MJ, Serruys PW.

AIMS: This study reports the clinical outcome, up to 17 years, of the first 856 consecutive patients treated by coronary angioplasty at a single centre and attempts to identify a subgroup of patients at low risk of adverse events. METHODS AND RESULTS: Follow-up status was established via hospital and general practitioner records and the civil registry. Median follow-up was 16 years. The overall 5-, 10-, 15- and 17-year survival was 90%, 78%, 64% and 58%, respectively and corresponding event-free survival was 53%, 33%, 22% and 19%. After 32% of patients had experienced a major adverse cardiac event in the first year, the annual coronary re-intervention incidence thereafter and, even beyond year 10, remained at 2%-7%. Using multivariable Cox regression, significant independent predictors of mortality were advanced age, diabetes, multivessel disease and impaired left ventricular function at the time of PTCA. A subgroup of 26% of the patients with none of these risk factors had a survival rate similar to the general Dutch population matched for age and gender (at 5 years: 96%, at 10 years: 89% and at 15 years: 83%). CONCLUSION: Although the majority of patients (>80%) experienced a further cardiac event during the 17 years after their first angioplasty procedure, in those non-diabetics under 60 years with single-vessel disease and good left ventricular function, prognosis was similar to the general population.

Circulation, 2001;104(2):191-6

Prognostic significance of endothelial dysfunction in hypertensive patients.


BACKGROUND: Forearm endothelial dysfunction, characterized by an impaired vasodilating response to acetylcholine (ACh), may be associated with several cardiovascular risk factors, including essential hypertension. Although the prognostic value of coronary endothelial dysfunction has been demonstrated, that of forearm endothelial dysfunction is still unknown. Methods and Results: Endothelium-dependent and -
independent vasodilation was investigated in 225 never-treated hypertensive patients (age, 35 to 54 years) by intra-arterial infusion of increasing doses of ACh and sodium nitroprusside. Patients were divided into tertiles on the basis of their increase in ACh-stimulated forearm blood flow (FBF) from basal: group 1, from 30% to 184%; group 2, from 185% to 333%; and group 3, from 339% to 760% increase from basal. During a mean follow-up of 31.5 of months (range, 4 to 84 months), there were 29 major adverse events at the cardiac (n=19), cerebrovascular (n=9), or peripheral vascular (n=1) level. Events included myocardial infarction, angina, coronary revascularization procedures, stroke, transient cerebral ischemic attack, and aortoiliac occlusive disease. Event rate per 100 patient-years was 8.17, 4.34, and 2.02 in the first, second, and third tertiles of peak percent increase in FBF during ACh infusion. The excess risk associated with an FBF increase in the first tertile was significant (relative risk, 2.084; 95% CI, 1.25 to 3.48; P=0.0049) after controlling for individual risk markers, including 24-hour ambulatory blood pressure. CONCLUSIONS: Our data suggest that forearm endothelial dysfunction is a marker of future cardiovascular events in patients with essential hypertension.

Circulation, 2001;104(2):145-50

C-reactive protein, insulin resistance, central obesity, and coronary heart disease risk in Indian Asians from the United Kingdom compared with European whites.


BACKGROUND: Indian Asians in the United Kingdom have increased coronary heart disease (CHD) mortality compared with European whites, but the causes are not well understood. Increased circulating concentrations of C-reactive protein (CRP) are an independent risk factor for CHD. Therefore, we investigated this marker of inflammation in healthy UK Indian Asian and European white men. Methods and Results?We measured serum CRP concentrations and conventional CHD risk factors in 1025 healthy male subjects (518 Indian Asians and 507 European whites) aged 35 to 60 years who were recruited at random from general practitioner lists. The geometric mean CRP concentration was 17% higher (95% confidence interval, 3% to 33%) in Indian Asians compared with European whites. CRP values were strongly associated with conventional CHD risk factors, measures of obesity, and metabolic disturbances associated with insulin resistance in both racial groups. The difference in CRP concentrations between Indian Asians and European whites remained after adjustment for conventional CHD risk factors but was eliminated by an adjustment for central obesity and insulin resistance score in Asians. On the basis of these results, we estimate that the processes underlying elevated CRP and,or
increased CRP production itself are associated with an approximately 14% increase in population CHD risk among Indian Asians compared with European whites. CONCLUSIONS: CRP concentrations are higher in healthy Indian Asians than in European whites and are accounted for by greater central obesity and insulin resistance in Indian Asians. Our results suggest that inflammation or other mechanisms underlying elevated CRP values may contribute to the increased CHD risk among Indian Asians.

JAMA, 2001;286(4):436-41
Acute effects of passive smoking on the coronary circulation in healthy young adults.


CONTEXT: Recent studies have shown that passive smoking is a risk factor for ischemic heart disease and may be associated with vascular endothelial dysfunction. The acute effects of passive smoking on coronary circulation in nonsmokers are not known. OBJECTIVE: To determine the acute effects of passive smoking on coronary circulation using coronary flow velocity reserve (CFVR), assessed by noninvasive transthoracic Doppler echocardiography. DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional study conducted from September 2000 to November 2000 among 30 Japanese men (mean age, 27 years; 15 healthy nonsmokers and 15 asymptomatic active smokers) without history of hypertension, diabetes mellitus, or hyperlipidemia. MAIN OUTCOME MEASURES: Coronary flow velocity reserve, calculated as the ratio of hyperemic to basal coronary flow velocity induced by intravenous infusion of adenosine triphosphate and measured in each participant before and after a 30-minute exposure to environmental tobacco smoke. RESULTS: Heart rate and blood pressure responses to adenosine triphosphate infusion were not affected by passive smoking exposure in either group. Passive smoking exposure had no effect on basal coronary flow velocity in either group. Mean (SD) CFVR in nonsmokers was significantly higher than that in active smokers before passive smoking exposure (4.4 [0.91] vs 3.6 [0.88], respectively; P=.02), while CFVR after passive smoking exposure did not differ between groups (P=.83). Passive smoking exposure significantly reduced mean (SD) CFVR in nonsmokers (4.4 [0.91] vs 3.4 [0.73], respectively; P<.001). CONCLUSIONS: Passive smoking substantially reduced CFVR in healthy nonsmokers. This finding provides direct evidence that passive smoking may cause endothelial dysfunction of the coronary circulation in nonsmokers.
Am Coll Cardiol, 2001;38(1):111-6

Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine.


OBJECTIVES: The aim of this study was to investigate endothelial function and common carotid intima-media thickness (IMT) in healthy young men with mild-to-moderate hypertriglyceridemia. Plasma asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, was measured to further elucidate the mechanisms involved. BACKGROUND: Hypertriglyceridemia is a risk factor for coronary heart disease although the mechanisms behind the increased risk remain to be defined. Acute elevation of plasma triglycerides induced by an intravenous fat load is associated with impaired endothelial function. The results of studies examining acute effects induced by a high-fat meal or effects of chronic hypertriglyceridemia on endothelial function are more inconsistent. METHODS: Flow-mediated vasodilation and nitroglycerin-induced vasodilation of the brachial artery and common carotid IMT were measured noninvasively by ultrasound technique in 15 hypertriglyceridemic (HTG) subjects and 15 matched controls, mean age 34 years. Plasma concentrations of ADMA were measured by high-performance liquid chromatography. RESULTS: Flow-mediated vasodilation was decreased in the HTG group (p < 0.0001), whereas nitroglycerin-induced vasodilation and carotid IMT did not differ significantly. Asymmetric dimethylarginine concentrations were higher in the HTG group (p < 0.05). CONCLUSIONS: Hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentration of ADMA but not with increased IMT of the common carotid artery. The corollary is that chronic hypertriglyceridemia results in endothelial dysfunction, possibly due to increased ADMA concentration, and that endothelial dysfunction might precede increased IMT among the early manifestations of atherosclerosis.


Exercise-induced silent myocardial ischemia and coronary morbidity and mortality in middle-aged men.

OBJECTIVES: We investigated the prognostic significance of exercise-induced silent myocardial ischemia in both high and low risk men with no prior coronary heart disease (CHD). BACKGROUND: Silent ischemia predicts future coronary events in patients with CHD, but there is little evidence of its prognostic significance in subjects free of CHD. METHODS: We investigated the association of silent ischemia, as defined by ST depression during and after maximal symptom-limited exercise test, with coronary risk in a population-based sample of men with no prior CHD followed for 10 years on average. RESULTS: Silent ischemia during exercise was associated with a 5.9-fold (95% CI 2.3 to 11.8) CHD mortality in smokers, 3.8-fold (95% CI 1.9 to 7.9) in hypercholesterolemic men and 4.7-fold (95% CI 2.4 to 9.1) in hypertensive men adjusting for other risk factors. The respective relative risks (RRs) of any acute coronary event were 3.0 (95% CI 1.7 to 5.1), 1.9 (95% CI 1.2 to 3.1) and 2.2 (95% CI 1.4 to 3.5). These associations were weaker in men without these risk factors. Furthermore, silent ischemia after exercise was a stronger predictor for the risk of acute coronary events and CHD death in smokers and in hypercholesterolemic and hypertensive men than in men without risk factors. CONCLUSIONS: Exercise-induced silent myocardial ischemia was a strong predictor of CHD in men with any conventional risk factor, emphasizing the importance of exercise testing to identify asymptomatic high risk men who could benefit from risk reduction and preventive measures.

J Am Coll Cardiol, 2001;38(1):56-63

Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. LIPID Study Investigators.


OBJECTIVES: We developed a prognostic strategy for quantifying the long-term risk of coronary heart disease (CHD) events in survivors of acute coronary syndromes (ACS). BACKGROUND: Strategies for quantifying long-term risk of CHD events have generally been confined to primary prevention settings. The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, which demonstrated that pravastatin reduces CHD events in ACS survivors with a broad range of cholesterol levels, enabled assessment of long-term prognosis in a secondary prevention setting. METHODS: Based on outcomes in 8,557 patients in the LIPID study, a multivariate risk factor model was developed for prediction of CHD death or nonfatal myocardial infarction. Prognostic indexes were developed based on the model, and low-, medium-, high- and very high-
risk groups were defined by categorizing the prognostic indexes. RESULTS: In addition to pravastatin treatment, the independently significant risk factors included: total and high density lipoprotein cholesterol, age, gender, smoking status, qualifying ACS, prior coronary revascularization, diabetes mellitus, hypertension and prior stroke. Pravastatin reduced coronary event rates in each risk level, and the relative risk reduction did not vary significantly between risk levels. The predicted five-year coronary event rates ranged from 5% to 19% for those assigned pravastatin and from 6.4% to 23.6% for those assigned placebo. CONCLUSIONS: Long-term prognosis of ACS survivors varied substantially according to conventional risk factor profile. Pravastatin reduced coronary risk within all risk levels; however, absolute risk remained high in treated patients with unfavorable profiles. Our risk stratification strategy enables identification of ACS survivors who remain at very high risk despite statin therapy.

J Am Coll Cardiol, 2001 ;38(1):111-6

Mild-to-moderate hypertriglyceridemia in young men is associated with endothelial dysfunction and increased plasma concentrations of asymmetric dimethylarginine.


OBJECTIVES: The aim of this study was to investigate endothelial function and common carotid intima-media thickness (IMT) in healthy young men with mild-to-moderate hypertriglyceridemia. Plasma asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, was measured to further elucidate the mechanisms involved. BACKGROUND: Hypertriglyceridemia is a risk factor for coronary heart disease although the mechanisms behind the increased risk remain to be defined. Acute elevation of plasma triglycerides induced by an intravenous fat load is associated with impaired endothelial function. The results of studies examining acute effects induced by a high-fat meal or effects of chronic hypertriglyceridemia on endothelial function are more inconsistent. METHODS: Flow-mediated vasodilation and nitroglycerin-induced vasodilation of the brachial artery and common carotid IMT were measured noninvasively by ultrasound technique in 15 hypertriglyceridemic (HTG) subjects and 15 matched controls, mean age 34 years. Plasma concentrations of ADMA were measured by high-performance liquid chromatography. RESULTS: Flow-mediated vasodilation was decreased in the HTG group (p < 0.0001), whereas nitroglycerin-induced vasodilation and carotid IMT did not differ significantly. Asymmetric dimethylarginine concentrations were higher in the HTG group (p < 0.05). CONCLUSIONS: Hypertriglyceridemia in young men is associated with
endothelial dysfunction and increased plasma concentration of ADMA but not with increased IMT of the common carotid artery. The corollary is that chronic hypertriglyceridemia results in endothelial dysfunction, possibly due to increased ADMA concentration, and that endothelial dysfunction might precede increased IMT among the early manifestations of atherosclerosis.

Neighborhood of residence and incidence of coronary heart disease.


BACKGROUND: Where a person lives is not usually thought of as an independent predictor of his or her health, although physical and social features of places of residence may affect health and health-related behavior. METHODS: Using data from the Atherosclerosis Risk in Communities Study, we examined the relation between characteristics of neighborhoods and the incidence of coronary heart disease. Participants were 45 to 64 years of age at base line and were sampled from four study sites in the United States: Forsyth County, North Carolina; Jackson, Mississippi; the northwestern suburbs of Minneapolis; and Washington County, Maryland. As proxies for neighborhoods, we used block groups containing an average of 1000 people, as defined by the U.S. Census. We constructed a summary score for the socioeconomic environment of each neighborhood that included information about wealth and income, education, and occupation. RESULTS: During a median of 9.1 years of follow-up, 615 coronary events occurred in 13,009 participants. Residents of disadvantaged neighborhoods (those with lower summary scores) had a higher risk of disease than residents of advantaged neighborhoods, even after we controlled for personal income, education, and occupation. Hazard ratios for coronary events in the most disadvantaged group of neighborhoods as compared with the most advantaged group were 1.7 among whites (95 percent confidence interval, 1.3 to 2.3) and 1.4 among blacks (95 percent confidence interval, 0.9 to 2.0). Neighborhood and personal socioeconomic indicators contributed independently to the risk of disease. Hazard ratios for coronary heart disease among low-income persons living in the most disadvantaged neighborhoods, as compared with high-income persons in the most advantaged neighborhoods were 3.1 among whites (95 percent confidence interval, 2.1 to 4.8) and 2.5 among blacks (95 percent confidence interval, 1.4 to 4.5). These associations remained unchanged after adjustment for established risk factors for coronary heart disease. CONCLUSIONS: Even after controlling for personal income, education, and occupation, we found that living
in a disadvantaged neighborhood is associated with an increased incidence of coronary heart disease.

JAMA, 2001;286(2):180-7

Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation.


CONTEXT: The Framingham Heart Study produced sex-specific coronary heart disease (CHD) prediction functions for assessing risk of developing incident CHD in a white middle-class population. Concern exists regarding whether these functions can be generalized to other populations. OBJECTIVE: To test the validity and transportability of the Framingham CHD prediction functions per a National Heart, Lung, and Blood Institute workshop organized for this purpose. DESIGN, SETTING, AND SUBJECTS: Sex-specific CHD functions were derived from Framingham data for prediction of coronary death and myocardial infarction. These functions were applied to 6 prospectively studied, ethnically diverse cohorts (n = 23 424), including whites, blacks, Native Americans, Japanese American men, and Hispanic men: the Atherosclerosis Risk in Communities Study (1987-1988), Physicians’Health Study (1982), Honolulu Heart Program (1980-1982), Puerto Rico Heart Health Program (1965-1968), Strong Heart Study (1989-1991), and Cardiovascular Health Study (1989-1990). MAIN OUTCOME MEASURES: The performance, or ability to accurately predict CHD risk, of the Framingham functions compared with the performance of risk functions developed specifically from the individual cohorts’ data. Comparisons included evaluation of the equality of relative risks for standard CHD risk factors, discrimination, and calibration. RESULTS: For white men and women and for black men and women the Framingham functions performed reasonably well for prediction of CHD events within 5 years of follow-up. Among Japanese American and Hispanic men and Native American women, the Framingham functions systematically overestimated the risk of 5-year CHD events. After recalibration, taking into account different prevalences of risk factors and underlying rates of developing CHD, the Framingham functions worked well in these populations. CONCLUSIONS: The sex-specific Framingham CHD prediction functions perform well among whites and blacks in different settings, and can be applied to other ethnic groups after recalibration for differing prevalences of risk factors and underlying rates of CHD events.
Simple bedside additive tool for prediction of in-hospital mortality after percutaneous coronary interventions.


BACKGROUND: Risk-adjustment models for percutaneous coronary intervention (PCI) mortality have been recently reported, but application in bedside prediction of prognosis for individual patients remains untested. METHODS AND RESULTS: Between July 1, 1997 and September 30, 1999, 10 796 consecutive procedures were performed in a consortium of 8 hospitals. Predictors of in-hospital mortality were identified by use of multivariate logistic regression analysis. The final model was validated by use of the bootstrap technique. Additional validation was performed on an independent data set of 5863 consecutive procedures performed between October 1, 1999, and August 30, 2000. An additive risk-prediction score was developed by rounding coefficients of the logistic regression model to the closest half-integer, and a visual bedside tool for the prediction of individual patient prognosis was developed. In this patient population, the in-hospital mortality rate was 1.6%. Multivariate regression analysis identified acute myocardial infarction, cardiogenic shock, history of cardiac arrest, renal insufficiency, low ejection fraction, peripheral vascular disease, lesion characteristics, female sex, and advanced age as independent predictors of death. The model had excellent discrimination (area under the receiver operating characteristic curve, 0.90) and was accurate for prediction of mortality among different subgroups. Near-perfect correlation existed between calculated scores and observed mortality, with higher scores associated with higher mortality. CONCLUSIONS: Accurate predictions of individual patient risk of mortality associated with PCI can be achieved with a simple bedside tool. These predictions could be used during discussions of prognosis before and after PCI.
OBJECTIVE: The objective of this study was to evaluate the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for exercise testing (EXT) after successful coronary revascularization (CR) using the Bypass Angioplasty Revascularization Investigation experience. BACKGROUND: The ACC/AHA guidelines state that EXT within three years of successful CR is not useful. METHODS: The 1,678 patients randomized to CR by either angioplasty or bypass surgery were required to take symptom-limited treadmill tests one, three and five years after revascularization. RESULTS: Patients who took the test at each specified time had a much lower subsequent two-year mortality than those who did not (1.9% vs. 9.4%, 3.5% vs. 12.6% and 3.3% vs. 11.0% at one, three and five years, respectively, after CR [p < 0.0001 for each]). Exercise parameters at the one- and three-year test did not improve a multivariable model of survival after including clinical parameters. Exercising to Bruce stage 3 or generating a Duke score >-6 were independently predictive of two-year survival after the five-year test. ST depression on the one-year test was associated with more revascularizations (relative risk = 1.6; p < 0.001). CONCLUSIONS: Patients with stable multivessel coronary disease who took a protocol-mandated exercise test at one, three and five years after revascularization were at low risk for mortality in the two years subsequent to each test. Exercise parameters did not improve prediction of mortality in the two years after the one- and three-year tests. The ACC/AHA guidelines on exercise testing after CR (no value for routine testing in stable patients for three years after revascularization) are supported by these results.

Lancet, 2001 ;358(9276):115-9

Apolipoprotein E4 and coronary heart disease in middle-aged men who smoke: a prospective study.

Humphries SE, Talmud PJ, Hawe E, Bolla M, Day IN, Miller GJ.

BACKGROUND: The common isoforms of apolipoprotein E (apoE), E2, E3, and E4, are important determinants of plasma lipid concentrations, and the epsilon4 allele is associated with raised risk of coronary heart disease. We investigated whether the effect of smoking on coronary heart disease risk is affected by APOE genotype. METHODS: We enrolled 3052 middle-aged men who were free of coronary heart disease for prospective cardiovascular surveillance in the second Northwick Park Heart Study (NPHSII). Smoking habit was ascertained at baseline and yearly by questionnaire. APOE genotype was identified by PCR and restriction
enzyme digestion. Endpoints were fatal coronary heart disease, non-fatal myocardial infarction, and coronary artery surgery and silent myocardial infarction at follow-up. FINDINGS: During 18836 person years of surveillance, 96 men had an acute myocardial infarction, 26 needed coronary artery surgery, and 14 had silent myocardial infarctions. Compared with never-smokers, risk of coronary heart disease in ex-smokers was 1.34 (95% CI 0.86-2.08) and in smokers it was 1.94 (1.25-3.01). This risk was independent of other classic risk factors. In never-smokers, risk was closely similar in men with different genotypes. Risk in men homozygous for the epsilon3 allele was 1.74 (1.10-2.77) in ex-smokers and 1.68 (1.01-2.83) in smokers, whereas in men carrying the epsilon4 allele risk was 0.84 (0.40-1.75) and 3.17 (1.82-5.50), respectively, with no significant differences in risk in the epsilon2 carriers. For the epsilon3 group, the genotype effect on risk was no longer significant after adjustment for classic risk factors (including plasma lipids). However, even after adjustment, smokers who were carriers of the epsilon4 allele, showed significantly raised risk of coronary heart disease compared with the non-smoking group (2.79, 1.59-4.91, epsilon4-smoking interaction p=0.007). INTERPRETATION: Smoking increases the risk of coronary heart disease in men of all genotypes but particularly in men carrying the epsilon4 allele.

Circulation, 2001;104(4):412-7

Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography.

Keelan PC, Bielak LF, Ashai K, Jamjoum LS, Denktas AE, Rumberger JA, Sheedy II PF, Peyser PA, Schwartz RS.

BACKGROUND: Electron-beam CT (EBCT) quantification of coronary artery calcification (CAC) allows noninvasive assessment of coronary atherosclerosis. We undertook a follow-up study to determine whether CAC extent, measured at the time of angiography by EBCT, predicted future hard cardiac events, comprising cardiac death and nonfatal myocardial infarction (MI). We also assessed the potential of selected coronary artery disease (CAD) risk factors, prior CAD event history (MI or revascularization), and angiographic findings (number of diseased vessels and overall disease burden) to predict subsequent hard events. METHODS AND RESULTS: Two hundred eighty-eight patients who underwent contemporaneous coronary angiography and EBCT scanning were contacted after a mean of 6.9 years. Vital status and history of MI during follow-up were determined. Cox proportional hazards models were used to compare the predictive ability of CAC extent with selected CAD risk factors, CAD event history, and angiographic findings. Median CAC score was 160 (range 0 to 7633). The 22 patients who experienced hard events during follow-up were older and had more extensive
CAC and angiographic disease (P<0.05). Only 1 of 87 patients with CAC score <20 experienced a subsequent hard event during follow-up. Event-free survival was significantly higher for patients with CAC scores <100 than for those with scores >/=100 (relative risk 3.20; 95% CI 1.17 to 8.71). When a stepwise multivariable model was used, only age and CAC extent predicted hard events (risk ratios 1.72 and 1.88, respectively; P<0.05).

CONCLUSIONS: In patients undergoing angiography, CAC extent on EBCT is highly predictive of future hard cardiac events and adds valuable prognostic information.

Circulation, 2001;104(5):527-32

Abnormal longitudinal, base-to-apex myocardial perfusion gradient by quantitative blood flow measurements in patients with coronary risk factors.

Hernandez-Pampaloni M, Keng FY, Kudo T, Sayre JS, Schelbert HR.

BACKGROUND: A longitudinal, base-to-apex myocardial perfusion gradient has been described in patients with coronary artery disease (CAD) and was attributed to diffuse coronary luminal narrowing. We asked whether an abnormal perfusion gradient also existed in patients without CAD but with coronary risk factors. We measured myocardial blood flow (MBF) with (13)N-ammonia and PET at rest and during hyperemia in patients with coronary risk factors but without CAD. METHODS AND RESULTS: Regional MBF was measured in absolute units with (13)N-ammonia and PET at rest and during dipyridamole hyperemia in 36 patients with coronary risk factors (age, 55+/−10 years) and in 36 age-matched (age, 53+/−10 years) and in 28 young (age, 25+/− 5 years) normal subjects. MBF was determined globally, for each of the 3 coronary territories, and in the mid and mid-to-apical sections of the left ventricle (LV). Myocardial perfusion on qualitative analysis was normal at rest and during hyperemia, and no flow defects were present. MBF in absolute units was similar in the 3 coronary territories. However, hyperemic MBFs in the mid-to-apical LV section were lower than in the mid LV section in the ?t-risk?group (2.04+/−0.61 versus 1.71+/−0.40 mL·min⁻¹·g⁻¹; P<0.004) but not in the age-matched or in the young normal subjects. CONCLUSIONS: The abnormal longitudinal, base-to-apex perfusion gradient observed during dipyridamole MBF suggests the presence of a functional and/or structural alteration of the coronary circulation associated with coronary risk factors, possibly reflecting developing coronary atherosclerosis or preclinical CAD.
Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study.

Dagenais GR, Yusuf S, Bourassa MG, Yi Q, Bosch J, Lonn EM, Kouz S, Grover J; HOPE Investigators.

BACKGROUND: In trials of patients with left ventricular dysfunction or heart failure, ACE inhibitor use was unexpectedly associated with reduced myocardial infarction (MI). Using the Heart Outcomes Prevention Evaluation (HOPE) trial data, we tested prospectively whether ramipril, an ACE inhibitor, could reduce coronary events and revascularization procedures among patients with normal left ventricular function.

METHODS AND RESULTS: In the HOPE trial, 9297 high-risk men and women, >/=55 years of age with previous cardiovascular disease or diabetes plus 1 risk factor, were randomly assigned to ramipril (up to 10 mg/d), vitamin E (400 IU/d), their combination, or matching placebos. During the mean follow-up of 4.5 years, there were 482 (10.4%) patients with clinical MI and unexpected cardiovascular death in the ramipril group compared with 604 (12.9%) in the placebo group [relative risk reduction (RRR), 21% (95% CI) (11,30); P<0.0003]. Ramipril was associated with a trend toward less fatal MI and unexpected death [4.0% versus 4.7%; RRR, 16% (-3, 31)] and with a significant reduction in nonfatal MI [5.6% versus 7.2%; RRR, 23% (9,34)]. Risk reductions in MI were documented in participants taking or not taking beta-blockers, lipid lowering, and/or antiplatelet agents. Although ramipril had no impact on hospitalizations for unstable angina [11.9% versus 12.2%; RRR, 3% (-9,14)], it reduced the risk of worsening and new angina [27.2% versus 30.0%; RRR, 12% (5,18); P<0.0014] and coronary revascularizations [12.5% versus 14.8%; RRR, 18%; (8,26) P<0.0005]. CONCLUSIONS: In this high-risk cohort, ramipril reduced the risk of MI, worsening and new angina, and the occurrence of coronary revascularizations.

JAMA, 2001;286(4):436-41

Acute effects of passive smoking on the coronary circulation in healthy young adults.

CONTEXT: Recent studies have shown that passive smoking is a risk factor for ischemic heart disease and may be associated with vascular endothelial dysfunction. The acute effects of passive smoking on coronary circulation in nonsmokers are not known. OBJECTIVE: To determine the acute effects of passive smoking on coronary circulation using coronary flow velocity reserve (CFVR), assessed by noninvasive transthoracic Doppler echocardiography. DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional study conducted from September 2000 to November 2000 among 30 Japanese men (mean age, 27 years; 15 healthy nonsmokers and 15 asymptomatic active smokers) without history of hypertension, diabetes mellitus, or hyperlipidemia. MAIN OUTCOME MEASURES: Coronary flow velocity reserve, calculated as the ratio of hyperemic to basal coronary flow velocity induced by intravenous infusion of adenosine triphosphate and measured in each participant before and after a 30-minute exposure to environmental tobacco smoke. RESULTS: Heart rate and blood pressure responses to adenosine triphosphate infusion were not affected by passive smoking exposure in either group. Passive smoking exposure had no effect on basal coronary flow velocity in either group. Mean (SD) CFVR in nonsmokers was significantly higher than that in active smokers before passive smoking exposure (4.4 [0.91] vs 3.6 [0.88], respectively; P =.02), while CFVR after passive smoking exposure did not differ between groups (P =.83). Passive smoking exposure significantly reduced mean (SD) CFVR in nonsmokers (4.4 [0.91] vs 3.4 [0.73], respectively; P<.001). CONCLUSIONS: Passive smoking substantially reduced CFVR in healthy nonsmokers. This finding provides direct evidence that passive smoking may cause endothelial dysfunction of the coronary circulation in nonsmokers.

J Am Coll Cardiol, 2001;38(1):41-8

Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators.


BACKGROUND: The Fragmin and fast Revascularization during InStability in Coronary artery disease (FRISC II) trial compared the effectiveness of an early invasive versus a noninvasive strategy in terms of the incidence of death and myocardial infarction (MI) in patients with unstable coronary artery disease (CAD). OBJECTIVES: In this subanalysis, we sought to evaluate gender differences in the effect of these different strategies.
METHODS: The patients (749 women and 1,708 men) were randomized to early invasive or noninvasive strategies. Coronary angiography was performed within the first 7 days in 96% and 10% of the invasive and noninvasive groups, respectively, and revascularization was performed within the first 10 days in 71% and 9% of the invasive and noninvasive groups, respectively. RESULTS: Women presenting with unstable CAD were older, but fewer had previous infarctions, left ventricular dysfunction and elevated troponin T levels. Women had fewer angiographic changes. There was no difference in MI or death at 12 months among women in the invasive and noninvasive groups (12.4% vs. 10.5%, respectively), in contrast to the favorable effect in the invasively treated group of men (9.6% vs. 15.8%, p < 0.001). In an interaction analysis, there was a different effect of the early invasive strategy for the two genders (p = 0.008). CONCLUSIONS: Women with symptoms and/or signs of unstable CAD are older, but still have less severe CAD and a better prognosis compared with men. In contrast to its beneficial effect in men, an early invasive strategy did not reduce the risk of future events among women. Further research is warranted to identify the most appropriate treatment strategy in women with unstable CAD.

Circulation, 2001;104(8):876-80

Platelet glycoprotein Ibalpha HPA-2 Met/VNTR B haplotype as a genetic predictor of myocardial infarction and sudden cardiac death.

Mikkelsson J, Perola M, Penttila A, Karhunen PJ.

BACKGROUND: Sudden cardiac death (SCD) is one of the leading manifestations of coronary heart disease in early middle age. Platelet glycoprotein (GP) Ib-IX-V receptor complexes play a key role in the initial adhesion of platelets to collagen during the formation of a coronary thrombus. The HPA-2 (Thr145 Met) and VNTR polymorphisms of the gene for GP Ibalpha have been studied previously in hospitalized patients with acute coronary syndromes. The significance of these polymorphisms in victims of sudden cardiac death is not known. METHODS AND RESULTS: The association of these 2 polymorphisms with coronary atherosclerosis, coronary artery stenosis, coronary thrombosis, myocardial infarction (MI), and SCD was studied in the Helsinki Sudden Death Study, which comprised 2 large autopsy series, collected 10 years apart during 1981 to 1982 and 1991 to 1992, of 700 middle-aged white Finnish men who suffered sudden or violent out-of-hospital death. The 2 polymorphisms showed an almost complete linkage disequilibrium. Men with acute MI (n=80) and coronary thrombosis (n=65) were more likely to be carriers of the HPA-2 Met allele (OR 2.0 and 2.6, respectively, P<0.005
for both) than were control subjects who died of noncardiac causes (n=367). In men <55 years old, the Met allele was overrepresented (OR 2.2) among victims of SCD (n=98) compared with control subjects (n=249). In men <55 years old, 17 of 29 men with acute MI (58.6%) and 16 of 23 men with coronary thrombosis (69.6%) were carriers of the HPA-2 Met allele compared with the 49 of 249 (19.7%) who had died of noncardiac causes (ORs 5.6 and 9.2, respectively). Similar associations were observed in the separate analyses of both autopsy series. CONCLUSIONS: Our results suggest that the HPA-2 Met/VNTR B haplotype of the platelet von Willebrand factor and thrombin receptor protein GP Ib-V-IX may be considered to be a major risk factor of coronary thrombosis, fatal MI, and SCD in early middle age.

Heart, 2001;86(2):133-8

Impact of diabetes mellitus on long term survival after acute myocardial infarction in patients with single vessel disease.


OBJECTIVE: To assess the influence of diabetes on long term prognosis after reperfusion treatment and its interaction with multivessel disease. DESIGN: A retrospective observational study. SETTING: Hiroshima City Hospital. PATIENTS: 1660 consecutive patients with acute myocardial infarction who underwent coronary angiography within 24 hours after the onset of chest pain. MAIN OUTCOME MEASURES: Influence of diabetes on 10 year survival after infarction was assessed using the generalised Wilcoxon test and Cox proportional hazards regression. Follow up was completed in 1622 patients (98%). RESULTS: Diabetic patients had more multivessel disease than non-diabetic patients (53% v 34%, p < 0.001). When only patients with single vessel disease were compared, diabetes was associated with a reduced 10 year survival after infarction (p = 0.002). On the other hand, in patients with multivessel disease there was no significant difference in survival between diabetic and non-diabetic patients (p = 0.70). Multivariate analysis also showed that diabetes was an independent risk factor related to 10 year mortality after infarction in patients with single vessel disease (odds ratio (OR) 1.81, 95% confidence interval (CI) 1.27 to 2.54; p = 0.001) and not in patients with multivessel disease (OR 1.17, 95% CI 0.85 to 1.60; p = 0.34). CONCLUSIONS: Diabetes is an independent predictor of long term mortality after infarction in patients with single vessel disease. However, in the presence of multivessel disease, prognosis after infarction is impaired regardless of diabetes, and the influence of diabetes is less obvious.
Microalbuminuria during acute myocardial infarction; a strong predictor for 1-year mortality.


AIMS: Urinary albumin excretion increases during acute myocardial infarction but little is known on the prognostic significance and the pathophysiological mechanisms of microalbuminuria in this clinical setting. The primary aim of the study was to examine whether urinary albumin excretion has predictive power for 1-year mortality after acute myocardial infarction. A secondary objective was to gain insight into the pathophysiological mechanisms of increased urinary albumin in myocardial infarction. METHODS AND RESULTS: This is a prospective cohort study conducted in three coronary care units (Northeast Italy). Four hundred and thirty-two unselected, consecutively enrolled patients with acute myocardial infarction (66.3+/−12.3 years of age) were studied. The incidence of mortality was related to the baseline urinary albumin:creatinine ratio. The best cut-off for total mortality approximated to 50 mg x g(-1) on the first day after myocardial infarction, 30 mg x g(-1) on the third day, and to 20 mg x g(-1) on the seventh day. At multivariable Cox analysis, the albumin:creatinine ratio was the strongest among several independent predictors of mortality (adjusted relative risks: 3.6 (95% CI, 2.1?2.2) on the first day, 4.9 (95% CI, 2.9?2.2) on the third day and 4.0 (95% CI, 2.3?8) on the seventh day). Independent determinants of urinary albumin were plasma aldosterone on the first day, and inflammatory markers on the third and seventh days. CONCLUSION: Urinary albumin assessed in the first week after acute myocardial infarction is a strong prognostic marker for 1-year mortality. Copyright 2001 The European Society of Cardiology.

Serum levels of the antiinflammatory cytokine interleukin-10 are decreased in patients with unstable angina.

Smith DA, Irving SD, Sheldon J, Cole D, Kaski JC.
BACKGROUND: Proinflammatory cytokines play a role in acute coronary events. However, the potential role of antiinflammatory cytokines in the modulation of the atherosclerotic process remains unknown. Interleukin (IL)-10, which is expressed in human atherosclerotic plaques, has potent deactivating properties in macrophages and T cells. The aim of this study was to assess whether serum concentrations of IL-10 differed between patients with unstable and stable angina pectoris. METHODS AND RESULTS: A total of 95 patients with angina pectoris and angiographically documented coronary artery disease were studied. Of these, 50 patients had chronic stable angina (with stable symptoms over 3 months), and 45 patients had Braunwald class IIIB unstable angina with ST-segment changes. Serum IL-10 and IL-6 concentrations were measured on admission using commercially available immunoassays. Serum IL-10 concentrations were lower in unstable angina patients compared with those who had chronic stable angina (28.4 versus 14.0 pg/mL; 95% CI, 9.8 to 19.0; P<0.0001), even after adjustment for variables that were significantly different on univariate analysis. IL-6 concentrations were higher in the unstable angina group (20.9 versus 11.4 pg/mL; 95% CI, 1.0 to 12.6; P=0.04). CONCLUSIONS: Patients with unstable angina had significantly lower serum IL-10 concentrations than did patients with chronic stable angina. This important finding is in keeping with previous data from animal model studies that suggest that IL-10 has a protective role in atherosclerosis.

Circulation, 2001;104(8):876-80

Platelet glycoprotein Ibalpha HPA-2 Met/VNTR B haplotype as a genetic predictor of myocardial infarction and sudden cardiac death.

Mikkelsson J, Perola M, Penttila A, Karhunen PJ.

BACKGROUND: Sudden cardiac death (SCD) is one of the leading manifestations of coronary heart disease in early middle age. Platelet glycoprotein (GP) Ib-IX-V receptor complexes play a key role in the initial adhesion of platelets to collagen during the formation of a coronary thrombus. The HPA-2 (Thr145 Met) and VNTR polymorphisms of the gene for GP Ibalpha have been studied previously in hospitalized patients with acute coronary syndromes. The significance of these polymorphisms in victims of sudden cardiac death is not known. METHODS AND RESULTS: The association of these 2 polymorphisms with coronary atherosclerosis, coronary artery stenosis, coronary thrombosis, myocardial infarction (MI), and SCD was studied in the Helsinki Sudden Death Study, which comprised 2 large autopsy series, collected 10 years apart during 1981 to 1982 and 1991 to
1992, of 700 middle-aged white Finnish men who suffered sudden or violent out-of-hospital death. The 2 polymorphisms showed an almost complete linkage disequilibrium. Men with acute MI (n=80) and coronary thrombosis (n=65) were more likely to be carriers of the HPA-2 Met allele (OR 2.0 and 2.6, respectively, P<0.005 for both) than were control subjects who died of noncardiac causes (n=367). In men <55 years old, the Met allele was overrepresented (OR 2.2) among victims of SCD (n=98) compared with control subjects (n=249). In men <55 years old, 17 of 29 men with acute MI (58.6%) and 16 of 23 men with coronary thrombosis (69.6%) were carriers of the HPA-2 Met allele compared with the 49 of 249 (19.7%) who had died of noncardiac causes (ORs 5.6 and 9.2, respectively). Similar associations were observed in the separate analyses of both autopsy series.

CONCLUSIONS: Our results suggest that the HPA-2 Met/VNTR B haplotype of the platelet von Willebrand factor and thrombin receptor protein GP Ib-V-IX may be considered to be a major risk factor of coronary thrombosis, fatal MI, and SCD in early middle age.

Am J Cardiol, 2001;88(4):359-64

Effect of gender on the outcomes of contemporary percutaneous coronary intervention.


Limited information exists regarding the outcomes of newer percutaneous coronary intervention (PCI) technologies in women. This study sought to determine whether female gender is an independent risk factor for PCI mortality and/or complications in contemporary practice. Using information from the National Cardiovascular Network (NCN) Database on 109,708 (33% women) PCI cases from 22 hospitals between January 1994 and January 1998, we examined the association of gender with unadjusted and risk-adjusted procedural outcomes. Women undergoing PCI were older, smaller, and had more comorbid illness than men, but less extensive coronary disease. Temporal trends in PCI device selection were similar in men and women. Compared with men, women had higher unadjusted procedural mortality rates (1.8% vs 1.0%, p <0.001), more strokes (0.4% vs 0.2%, p <0.001), and higher vascular complication rates (5.4% vs 2.7%, p <0.001). However, after adjusting for baseline clinical risk factors, and importantly, body surface area, women and men had similar PCI mortality risks (adjusted odds ratio 1.07, 95% confidence interval 0.92 to 1.24). Gender was not an independent risk factor for mortality among subgroups receiving coronary stent or atherectomy devices after risk adjustment. However, women undergoing PCI remained at higher risk for stroke, vascular complications, and
repeat in-hospital revascularization than men, even after risk adjustment. We conclude that in contemporary practice, a patient's body size rather than gender, conveys independent risk for mortality after PCI.

Am J Cardiol, 2001;88(4):347-52

The platelet Pl(A2) and angiotensin-converting enzyme (ACE) D allele polymorphisms and the risk of recurrent events after acute myocardial infarction.

Bray PF, Cannon CP, Goldschmidt-Clermont P, Moye LA, Pfeffer MA, Sacks FM, Braunwald E.

Chromosome 17q21-23 harbors genes for platelet glycoprotein IIIa and angiotensin-converting enzyme (ACE), which are polymorphic for alleles Pl(A2) and ACE D. These alleles have been independently and often associated with ischemic coronary artery disease (CAD). We sought to determine if the Pl(A2) and ACE D polymorphisms were risk factors for recurrent coronary events. In the Cholesterol And Recurrent Events (CARE) trial, 4,159 men and women with documented myocardial infarction (MI) were randomized to receive either placebo or pravastatin, and were followed prospectively for 5 years. Pl(A) and ACE genotypes were determined in 767 patients: 385 cases who had experienced a recurrent primary event (death due to coronary disease or nonfatal MI), and 382 age- and gender-matched controls. In patients receiving placebo, the Pl(A1,A2) genotype conferred a relative risk (RR) of 1.38 (confidence intervals [CI] 1.04 to 1.83; p = 0.028; adjusted RR = 1.32, CI = 0.99 to 1.76; p = 0.058]) for the primary end point. Compared with the placebo group, pravastatin reduced the excess RR of coronary disease death and recurrent MI in the Pl(A1,A2) patient population by 31% (p = 0.06). The ACE D allele appeared to have modestly additive effects on the Pl(A1,A2) risk. Among the Pl(A1,A2) patients, pravastatin had little effect on the risk of recurrent events with the ACE II genotype, but reduced the adjusted RR from 1.42 (placebo) to 0.58 for ACE ID patients, and from 1.56 (placebo) to 0.83 for ACE DD. The Pl(A1,A2) genotype was associated with an excess of recurrent coronary events in patients after MI who did not receive pravastatin, and the ACE D allele added to this risk. These data suggest that it would be important to perform a larger study to address the potential role of these genotypes in therapeutic decision making.

JAMA, 2001-29;286(8):936-43
Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond.

Tice JA, Ross E, Coxson PG, Rosenberg I, Weinstein MC, Hunink MG, Goldman PA, Williams L, Goldman L.

CONTEXT: A high homocysteine level has been identified as an independent modifiable risk factor for coronary heart disease (CHD) events and death. Since January 1998, the US Food and Drug Administration has required that all enriched grain products contain 140 microg of folic acid per 100 g, a level considered to decrease homocysteine levels. OBJECTIVES: To examine the potential effect of grain fortification with folic acid on CHD events and to estimate the cost-effectiveness of additional vitamin supplementation (folic acid and cyanocobalamin) for CHD prevention. DESIGN AND SETTING: Cost-effectiveness analysis using the Coronary Heart Disease Policy Model, a validated, state-transition model of CHD events in adults aged 35 through 84 years. Data from the third National Health and Nutrition Examination Survey (NHANES III) were used to estimate age- and sex-specific differences in homocysteine levels. INTERVENTION: Hypothetical comparison between a diet that includes enriched grain products projected to increase folic acid intake by 100 microg/d with the same diet without folic acid fortification; and a comparison between vitamin therapy that consists of 1 mg of folic acid and 0.5 mg of cyanocobalamin and the diet that includes grains fortified with folic acid. MAIN OUTCOME MEASURES: Incidence of myocardial infarction and death from CHD, quality-adjusted life-years (QALYs) saved, and medical costs. RESULTS: Grain fortification with folic acid was predicted to decrease CHD events by 8% in women and 13% in men, with comparable reductions in CHD mortality. The model projected that, compared with grain fortification alone, treating all patients with known CHD with folic acid and cyanocobalamin over a 10-year period would result in 310 000 fewer deaths and lower costs. Over the same 10-year period, providing vitamin supplementation in addition to grain fortification to all men aged 45 years or older without known CHD was projected to save more than 300 000 QALYs, to save more than US $2 billion, and to be the preferred strategy. For women without CHD, the preferred vitamin supplementation strategy would be to treat all women older than 55 years, a strategy projected to save more than 140 000 QALYs over 10 years. CONCLUSIONS: Folic acid and cyanocobalamin supplementation may be cost-effective among many population subgroups and could have a major epidemiologic benefit for primary and secondary prevention of CHD if ongoing clinical trials confirm that homocysteine-lowering therapy decreases CHD event rates.

Am J Cardiol, 2001;88(5):509-15
Usefulness of the Framingham risk score and body mass index to predict early coronary artery calcium in young adults (Muscatine Study).

Mahoney LT, Burns TL, Stanford W, Thompson BH, Witt JD, Rost CA, Lauer RM.

The value of a coronary artery disease prediction algorithm, the Framingham risk score (score), for detecting coronary artery calcium (CAC) was examined in 385 men and 472 women, aged 29 to 43 years. Scores were compared in subjects with and without CAC and were also used to predict presence of CAC. Receiver-operating characteristic curves were computed to compare different prediction models. The score model was compared with age only, natural logarithm of body mass index (lnBMI) only, and score plus lnBMI models. CAC was detected in 30% of men and 16% of women. The mean score was significantly higher in men and women with CAC. For every 2-point increase in the score, the odds of CAC increased by 30% in women and 20% in men. Significant associations between CAC status and risk factors were observed for age in women, and high-density lipoprotein cholesterol and blood pressure in men and women. The area under the receiver-operating characteristic curve for the score was 0.67 and 0.57 for women and men, respectively. When lnBMI was added to the score model, the area increased to 0.76 in women (lnBMI p <0.0001, score p <0.005). For men, the area increased from 0.57 to 0.67, and the score was no longer significant (p >0.60) in the model with lnBMI (p <0.0001). Score predicts CAC in asymptomatic young adults. Inclusion of lnBMI in the score model adds significantly to the prediction of CAC in women and men. The lnBMI model has a greater predictive value than the score in this young population.

Am J Cardiol, 2001;88(5):473-7

Reasons for higher in-hospital mortality >24 hours after percutaneous transluminal coronary angioplasty in women compared with men.

Welty FK, Lewis SM, Kowalker W, Shubrooks SJ Jr.

Women have a higher in-hospital mortality rate than men after percutaneous transluminal coronary angioplasty (PTCA). To determine reasons for this, we analyzed the outcome of PTCA at our institution from
1989 to 1995 for 5,989 patients (2,101 women). Women were older than men (66.8 +/− 10.9 vs 61.0 +/− 11.2 years, respectively; p <0.0001) and more likely to have diabetes mellitus, hypertension, or a history of congestive heart failure than men. In-laboratory complications at the time of PTCA were similar for women and men. During the first 24 hours after PTCA, women were more likely than men to become hypotensive (0.33% vs 0.08%, p = 0.04) and had a higher rate of vascular injury than men (1.6% vs 0.6%, p <0.001). More than 24 hours after the procedure, women had a significantly higher mortality rate (1.2% vs 0.52%, p = 0.017), which was no longer significantly different after adjustment for age (odds ratio 0.72, 95% confidence interval 0.39 to 1.32). Multivariate correlates of death >24 hours after PTCA were age, a prior history of congestive heart failure, vascular injury, and use of thrombolytic agents. Of those dying >24 hours after the procedure, 67% of women suffered a noncardiac-related death compared with only 10% of men (p <0.001). The noncardiac death rate was 0.8% for women and 0.05% for men. These deaths were related to renal failure, vascular complications, bleeding, hypotension, and stroke, especially hemorrhagic stroke. In conclusion, immediate procedural complications at PTCA were similar for women and men; however, mortality was higher for women >24 hours after PTCA and before discharge due to a higher rate of noncardiac death.

Am J Cardiol, 2001;88(5):467-72

Body mass index and the risk of recurrent coronary events following acute myocardial infarction.

Rea TD, Heckbert SR, Kaplan RC, Psaty BM, Smith NL, Lemaitre RN, Lin D.

Although excess adiposity appears to increase the risk of coronary heart disease in the general population, its importance in patients with established coronary disease is less defined. We evaluated a population-based inception cohort of survivors to hospital discharge following first acute myocardial infarction (AMI) (n = 2,541) to assess the association between body mass index (BMI) and the risk of recurrent coronary events and to explore the mechanisms for this relation. Using Cox proportional-hazards regression, we assessed the risk of recurrent coronary events associated with levels of adiposity as defined by BMI and then investigated potential mechanisms through which adiposity conferred risk by examining how adjustment for diabetes mellitus, systemic hypertension, and dyslipidemia affected the association. Forty-one percent of the cohort were overweight (BMI 25 to 29.9), and 27.8% were obese (BMI ≥30). After adjustment for other risk factors, the risk of recurrent coronary events (n = 418) increased as BMI increased, especially among those who were obese. Using a BMI of 16 to 24.9 as the reference group, for mildly overweight patients (BMI 25 to 27.4), the relative
risk (RR) was 0.93 (95% confidence interval [CI] 0.70 to 1.24); it was 1.16 for more severe overweight patients (BMI 27.5 to 29.9; 95% CI 0.87 to 1.55). For patients with class I obesity (BMI 30 to 34.9), the RR was 1.49 (95% CI 1.12 to 1.98), and for class II to III obesity (BMI ≥ 35), the RR was 1.80 (95% CI 1.30 to 2.48). We estimated that clinical measurements of diabetes, hypertension, and dyslipidemia explained approximately 43% of this risk. Thus, excess adiposity as measured by BMI was associated with an increased risk of recurrent coronary events following AMI, particularly among those who were obese.

BMJ, 2001;323(7312):541-5

Sex matters: secular and geographical trends in sex differences in coronary heart disease mortality.

Lawlor DA, Ebrahim S, Davey Smith G.

OBJECTIVE: To examine secular trends and geographical variations in sex differences in mortality from coronary heart disease and investigate how these relate to distributions in risk factors. DESIGN: National and international data were used to examine secular trends and geographical variations in sex differences in mortality from coronary heart disease and risk factors. SETTING: England and Wales, 1921-98; Australia, France, Japan, Sweden, and the United States, 1947-97; 50 countries, 1992-6. DATA SOURCES: Office for National Statistics, World Health Organization, and Food and Agriculture Organization of the United Nations. RESULTS: The 20th century epidemic of coronary heart disease affected only men in most industrialised countries and had a very rapid onset in England and Wales, which has been examined in detail. If this male only epidemic had not occurred there would have been 1.2 million fewer deaths from coronary heart disease in men in England and Wales over the past 50 years. Secular trends in mean per capita fat consumption show a similar pattern to secular trends in coronary heart disease mortality in men. Fat consumption is positively correlated with coronary heart disease mortality in men (r(s)=0.79; 95% confidence interval 0.70 to 0.86) and inversely associated with coronary heart disease mortality in women (-0.30; -0.49 to -0.08) over this time. Although sex ratios for mortality from coronary heart disease show a clear period effect, those for lung cancer show a cohort effect. Sex ratios for stroke mortality were constant and close to unity for the entire period. Geographical variations in the sex ratio for coronary heart disease were associated with mean per capita fat consumption (0.64; 0.44 to 0.78) but were not associated with the sex ratio for smoking. CONCLUSION: Sex differences are largely the result of environmental factors and hence not inevitable. Understanding the factors that determine sex differences has important implications for public health, particularly for countries and parts
OBJECTIVES: This study examined gender differences and temporal changes in the clinical characteristics of patients referred for nuclear stress imaging, their imaging results and subsequent utilization of coronary angiography and revascularization. BACKGROUND: Gender bias may influence resource utilization in patients with coronary artery disease (CAD). No study has analyzed gender differences and time trends in patients referred for noninvasive testing and subsequent use of invasive procedures. METHODS: Between January 1986 and December 1995, 14,499 patients (5,910 women and 8,589 men) without established CAD underwent stress myocardial perfusion imaging. The clinical characteristics, imaging results, coronary angiograms and revascularization outcomes were compared in women and men over time. RESULTS: The mean pretest probability of CAD was lower in women (45%) than in men (70%) (p < 0.001). More women (69%) than men (42%) had normal nuclear images (p < 0.001). Men (17%) were more likely than women (8%) to undergo coronary angiography (p < 0.001). Male gender was independently associated with referral for coronary angiography (multivariate model: chi-square = 16, p < 0.001) but was considerably weaker than the imaging variables (summed reversibility score: chi-square = 273, p < 0.001). Revascularization was performed in more men (46% of the population undergoing angiography) than women (39%) (p = 0.01), but gender was not independently associated with referral to revascularization. There were no significant differences in clinical, imaging or invasive variables between the genders over time. CONCLUSIONS: There was little evidence for a bias against women in this study. Women were somewhat less likely to undergo coronary angiography but were referred for stress perfusion imaging more liberally. Practice patterns remained constant over this 10-year period.

Circulation 2001 Sep 4;104(10):1135-9

Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive procedures in patients undergoing evaluation for coronary artery disease.

Miller TD, Roger VL, Hodge DO, Hopfenspirger MR, Bailey KR, Gibbons RJ.
Previous cytomegalovirus infection and restenosis after coronary stent placement.


BACKGROUND: Reactivated cytomegalovirus may promote neointima formation after percutaneous coronary interventions by facilitating cell cycle progression through inhibition of the eukariotic tumor suppressor protein p53. This prospective study sought to investigate the effect of previous cytomegalovirus infection on restenosis after coronary stenting. METHODS AND RESULTS: In 551 consecutive patients with successful stent placement, we determined cytomegalovirus IgG titers. Primary and secondary end points were the rate of angiographic restenosis at 6 months and the rate of target vessel reintervention at 1 year, respectively. Three hundred forty patients (62%) had a positive cytomegalovirus IgG titer. We obtained angiographic follow-up in 82% of all patients. Angiographic restenosis rate was 28.7% in patients with positive cytomegalovirus titers and 34.6% in patients with negative titers (P=0.18). Between the groups with and without positive cytomegalovirus titers, there were no significant differences in late lumen loss (1.16±/0.90 mm and 1.23+/0.86 mm, respectively, P=0.44). Target vessel reintervention was performed in 16.8% of the patients with positive cytomegalovirus titers and in 17.5% of those without (P=0.82). Even after correction for potential confounding variables by multivariate analysis, positive cytomegalovirus titers did not manifest as a predictor of angiographic restenosis (adjusted odds ratio [95% confidence interval], 0.78 [0.52 to 1.19]). CONCLUSIONS: Previous cytomegalovirus infection does not carry an increased risk of restenosis after stenting.

Circulation, 2001;104(10):1108-13

Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study.

Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W; Atherosclerosis Risk in Communities Study Group.

BACKGROUND: Despite consensus on the need for blood cholesterol reductions to prevent coronary heart
disease (CHD), available evidence on optimal cholesterol levels or the added predictive value of additional lipids is sparse. METHODS AND RESULTS: After 10 years follow-up of 12 339 middle-aged participants free of CHD in the Atherosclerosis Risk in Communities Study (ARIC), 725 CHD events occurred. The lowest incidence was observed in those at the lowest LDL cholesterol (LDL-C) quintile, with medians of 88 mg/dL in women and 95 mg/dL in men, and risk accelerated at higher levels, with relative risks (RRs) for the highest quintile of 2.7 in women and 2.5 in men. LDL-C, HDL-C, lipoprotein(a) [Lp(a)], and in women but not men, triglycerides (TG) were all independent CHD predictors, providing an RR, together with blood pressure, smoking, and diabetes, of 13.5 in women and 4.9 in men. Lp(a) was less significant in blacks than whites. Prediction was not enhanced by HDL-C density subfractions or apolipoproteins (apo) A-I or B. Despite strong univariate associations, apoB did not contribute to risk prediction in subgroups with elevated TG, with lower LDL-C, or with high apoB relative to LDL-C. CONCLUSIONS: Optimal LDL-C values are <100 mg/dL in both women and men. LDL-C, HDL-C, TG, and Lp(a), without additional apolipoproteins or lipid subfractions, provide substantial CHD prediction, with much higher RR in women than men.

Circulation, 2001;104(12):1336-42

Circulating cell adhesion molecules and death in patients with coronary artery disease.


BACKGROUND: Vascular cell adhesion molecule (VCAM)-1, intercellular adhesion molecule (ICAM)-1, and E-selectin mediate adhesion and transmigration of leukocytes to the vascular endothelial wall and may promote plaque growth and instability. In a prospective study, we evaluated the effect of soluble adhesion molecules on the risk of future cardiovascular events among patients with angiographically documented coronary artery disease (CAD). Methods and Results- -We obtained baseline samples from a prospective cohort of 1246 patients with CAD. Besides various markers of inflammation, soluble VCAM-1 (sVCAM-1), sICAM-1, and sE-selectin were determined. Follow-up information on cardiovascular events was obtained (mean, 2.7; maximum, 4.1 years). Independently higher levels of sVCAM-1 (1932 versus 1128 ng/mL; P<0.0001), sICAM-1 (353 versus 287 ng/mL; P=0.015), and sE-selectin (81 versus 63 ng/mL; P=0.003) were observed in patients with future death from cardiovascular causes. In a multivariate model, fatal risk was 2.1-fold (1.1 to 4.0) higher in patients within the top quartile of baseline sVCAM-1 concentrations compared with lower quartiles. This association was present independent of general inflammatory response as reflected by low or high C-reactive protein (hs-CRP)
levels. In a model that simultaneously controlled for all inflammatory and soluble adhesion markers determined, only sVCAM-1 remained independently significant for future fatal cardiovascular events, with a 2.8-fold increase in risk (P=0.003). CONCLUSIONS: Soluble adhesion molecules sVCAM-1, sICAM-1, and sE-selectin were significantly related to future death from cardiovascular causes among patients with documented CAD. Especially sVCAM-1 added to the predictive value of classic risk factors and hs-CRP in determining the risk of future cardiovascular death.

JAMA, 2001;286(12):1468-74

Low-density lipoprotein size, pravastatin treatment, and coronary events.

Campos H, Moye LA, Glasser SP, Stampfer MJ, Sacks FM.

CONTEXT: Small low-density lipoprotein (LDL) particle size has been hypothesized to be a risk factor for coronary heart disease (CHD). Animal models link large LDL to atherosclerosis. However, the strong association between small LDL and other risk factors, particularly triglyceride levels, impedes determining whether LDL size independently predicts CHD in humans. OBJECTIVE: To examine whether LDL size is an independent predictor of recurrent coronary events in patients with known CHD, as opposed to a marker for other lipid abnormalities. DESIGN AND SETTING: Prospective, nested case-control study in the Cholesterol and Recurrent Events (CARE) trial, a randomized placebo-controlled trial of pravastatin conducted in 1989-1996. PARTICIPANTS: Survivors of myocardial infarction with typical LDL concentrations (416 cases and 421 controls). MAIN OUTCOME MEASURE: Subsequent myocardial infarction or coronary death during the 5-year follow-up, analyzed by quintile of LDL particle size and by treatment group. RESULTS: Overall, the mean LDL size was identical in cases and controls (25.6 nm). In patients in the placebo group, large LDL predicted coronary events in models adjusted only for age (relative risk [RR], 1.79; 95% confidence interval [CI], 1.01-3.17) and for age and lipid and nonlipid risk factors (RR, 4.00; 95% CI, 1.81-8.82), comparing those in the highest (mean, 26.6 nm) and lowest (mean, 24.5 nm) quintiles of LDL size. This increased risk was not present in those taking pravastatin (age-adjusted analysis: RR, 0.98; 95% CI, 0.47-2.04; P =.046 for interaction for a difference in the effect of LDL size on coronary events between the placebo and treatment groups; multivariable analysis: RR, 1.33; 95% CI, 0.52-3.38; P =.11 for interaction). CONCLUSIONS: Large LDL size was an independent predictor of coronary events in a typical population with myocardial infarction, but the adverse effect was not present among patients who were treated with pravastatin. Identifying patients on the basis of LDL size may not be
useful clinically, since effective treatment for elevated LDL cholesterol concentrations also effectively treats risk associated with large LDL.

JAMA, 2001;286(11):1356-9

Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3.

Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, McCabe CH, Barron HV, Braunwald E.

CONTEXT: The Thrombolysis in Myocardial Infarction (TIMI) risk score for ST-elevation myocardial infarction (STEMI) is a simple integer score for bedside risk assessment of patients with STEMI. Developed and validated in multiple clinical trials of fibrinolysis, the risk score has not been validated in a community-based population. OBJECTIVE: To validate the TIMI risk score in a population of STEMI patients reflective of contemporary practice. DESIGN, SETTING, AND PARTICIPANTS: The risk score was evaluated among 84 029 patients with STEMI from the National Registry of Myocardial Infarction 3 (NRMI 3), which collected data on consecutive patients with myocardial infarction (MI) from 1529 US hospitals between April 1998 and June 2000. MAIN OUTCOME MEASURES: Ability of the TIMI risk score to correctly predict risk of death in terms of model discrimination (c statistic) and calibration (agreement of predicted and observed death rates). RESULTS: Patients in NRMI 3 tended to be older, to be more often female, and to have a history of coronary disease more often than those in the derivation set. Forty-eight percent received reperfusion therapy. The TIMI risk score revealed a significant graded increase in mortality with rising score (range, 1.1%-30.0%; P<.001 for trend). The risk score showed strong prognostic capacity overall (c = 0.74 vs 0.78 in derivation set) and among patients receiving acute reperfusion therapy (c = 0.79). Predictive behavior of the risk score was similar between fibrinolytic-treated patients (n = 23 960; c = 0.79) and primary percutaneous coronary intervention patients (n = 15 348; c = 0.80). In contrast, among patients not receiving reperfusion therapy, the risk score underestimated death rates and offered lower discriminatory capacity (c =0.65).

CONCLUSIONS: Sufficiently simple to be practical at the bedside and effective for risk assessment across a spectrum of patients, the TIMI risk score may be useful in triage and treatment of patients with STEMI who are treated with reperfusion therapy.
The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes.

de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E.

BACKGROUND: Brain (B-type) natriuretic peptide is a neurohormone synthesized predominantly in ventricular myocardium. Although the circulating level of this neurohormone has been shown to provide independent prognostic information in patients with transmural myocardial infarction, few data are available for patients with acute coronary syndromes in the absence of ST-segment elevation. METHODS: We measured B-type natriuretic peptide in plasma specimens obtained a mean (+/-SD) of 40+/20 hours after the onset of ischemic symptoms in 2525 patients from the Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infarction 16 study. RESULTS: The base-line level of B-type natriuretic peptide was correlated with the risk of death, heart failure, and myocardial infarction at 30 days and 10 months. The unadjusted rate of death increased in a stepwise fashion among patients in increasing quartiles of base-line B-type natriuretic peptide levels (P<0.001). This association remained significant in subgroups of patients who had myocardial infarction with ST-segment elevation (P=0.02), patients who had myocardial infarction without ST-segment elevation (P<0.001), and patients who had unstable angina (P<0.001). After adjustment for independent predictors of the long-term risk of death, the odds ratios for death at 10 months in the second, third, and fourth quartiles of B-type natriuretic peptide were 3.8 (95 percent confidence interval, 1.1 to 13.3), 4.0 (95 percent confidence interval, 1.2 to 13.7), and 5.8 (95 percent confidence interval, 1.7 to 19.7). The level of B-type natriuretic peptide was also associated with the risk of new or recurrent myocardial infarction (P=0.01) and new or worsening heart failure (P<0.001) at 10 months. CONCLUSIONS: A single measurement of B-type natriuretic peptide, obtained in the first few days after the onset of ischemic symptoms, provides powerful information for use in risk stratification across the spectrum of acute coronary syndromes. This finding suggests that cardiac neurohormonal activation may be a unifying feature among patients at high risk for death after acute coronary syndromes.

High-density lipoproteins and endothelial function.
Elevated plasma levels of HDL cholesterol or apolipoprotein A-I, the major protein moiety of HDL particles, are protective against coronary artery disease. HDL particles remove cholesterol from peripheral cells and transfer it to the liver for bile acid synthesis. The interaction between lipoproteins is not mediated through simple contact between 2 phospholipid membranes but involves specific protein-receptor interactions, charged phospholipid-phospholipid contact, and activation of cellular signaling pathways. These lead to regulation of genes or the modification of proteins involved in vasomotor function, platelet activation, thrombosis and thrombolysis, cell adhesion, apoptosis and cell proliferation, and cellular cholesterol homeostasis.

Am Heart J, 2001;142(4):657-63

Hematocrit and the risk of coronary heart disease mortality.

Brown DW, Giles WH, Croft JB.

BACKGROUND: An association between hematocrit (Hct) and coronary heart disease (CHD) mortality has been previously observed. However, the relationship of Hct and CHD independent of other cardiovascular disease (CVD) risk factors and differences between men and women remain unclear. METHODS: We examined the association between Hct and CHD mortality with Cox regression analyses of data from 8896 adults, aged 30-75 years, in the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study (1976-1992). Covariates included age, sex, race, education, smoking status, hypertensive status, total serum cholesterol, body mass index, white blood cell count, and history of CVD and diabetes. Hct was categorized by use of sex-specific tertiles, and all analyses were stratified by sex. RESULTS: During 16.8 years of follow-up, there were 545 (men 343, women 202) deaths from CHD (International Classification of Diseases, 9th revision [ICD-9] 410-414), 778 (men 426, women 279) deaths from diseases of the heart (ICD-9 390-398, 402, 404, 410-414, 415-417, 420-429), and 2046 (men 1216, women 830) all-cause deaths. Among men, the crude CHD mortality rate per 10,000 population was 42.6, 31.9, and 46.3 among those with Hct in the lower, middle, and upper
tertiles, respectively. The corresponding crude CHD mortality rates among women were 12.6, 18.6, and 27.7.

After adjustment for age and other CVD risk factors, there was no association between Hct in the upper tertile compared with the lower tertile and mortality from either CHD, diseases of the heart, or all causes among men. Women with Hct in the upper tertile were 1.3 times (95% CI 0.9-1.9) more likely to die from CHD than were women with Hct in the lowest tertile, after multivariate adjustment. The effect of high Hct on CHD mortality among women younger than 65 years of age was slightly stronger (relative risk 2.2, 95% CI 1.0-4.6).

CONCLUSIONS: These results suggest that the association between Hct and mortality from CHD and all causes is complex, differing both by sex and age. Further research is needed to gain a better understanding of these age and sex differences.

Am Heart J, 2001;142(4):633-40

Chlamydia pneumoniae and cytomegalovirus seropositivity, inflammatory markers, and the risk of myocardial infarction at a young age.


BACKGROUND: Pathogens causing chronic infections may promote atherosclerosis. The aim of our study was to evaluate the association of Chlamydia pneumoniae (Cp) and cytomegalovirus (CMV) infection and of inflammatory activation with premature myocardial infarction (MI). METHODS: Specific anti-Cp and anti-CMV immunoglobulin G (IgG), fibrinogen, white blood cells (WBC), and C-reactive protein (CRP) were measured in 120 post-MI patients ≤50 years old and in 120 age-matched controls. RESULTS: Seropositivity to Cp and elevated concentrations of anti-Cp and anti-CMV IgGs were more frequent (P =.01) in patients than in control subjects, and fibrinogen, CRP, and WBC levels (P =.02) were more elevated. After adjustment for coronary risk factors and socioeconomic status, the odds ratios (95% confidence intervals) for premature MI were 2.4 (1.3-4.6) for Cp infection and 2.9 (1.5-5.8) for CMV. The risk of Cp infection was greater in smokers (3.7, 1.8-7.6). When both infections were present (35% of patients vs 8% of controls, P =.001), CRP was higher (P =.01) and the risk increased by 12 times (12.5, 4-38.9) compared with that in subjects without any infection and by 5 times (4.9, 2.2-10.9) if only one was present. CONCLUSIONS: After adjustment for confounders, seropositivity to both Cp and CMV infections is associated with the diagnosis of premature MI. The combination of both infections is associated with an enhanced inflammatory response and a markedly increased risk of premature
Role of Kozak sequence polymorphism of platelet glycoprotein Ibalpha as a risk factor for coronary artery disease and catheter interventions.


OBJECTIVES: We sought to determine the role of the -5T>C polymorphism of the platelet glycoprotein (GP) Ibalpha as a potential risk factor for coronary artery disease (CAD) and adverse events complicating a coronary catheter intervention. BACKGROUND: The platelet GP Ib-IX-V receptor complex plays a crucial role in arterial thrombus formation. The -5T>C polymorphism of GP Ibalpha is associated with increased receptor density. METHODS: We genotyped 1,000 patients with angiographically confirmed CAD, as well as 1,000 age- and gender-matched control subjects, for this polymorphism by polymerase chain reaction/restriction fragment length polymorphism. Among the patients with CAD, 269 underwent percutaneous transluminal coronary angioplasty (PTCA), 103 underwent directional coronary atherectomy and 278 underwent stenting. This intervention group was followed for a 30-day composite end point of target vessel revascularization, myocardial infarction or death. RESULTS: Carriers of the -5C allele were significantly over-represented in the group of patients developing acute coronary syndromes (relative risk [RR] 1.43, 95% confidence interval [CI] 1.05 to 1.95, p = 0.02). The -5C allele furthermore predicted an increased risk for developing complications after PTCA (RR 3.75, 95% CI 1.15 to 12.27, p = 0.029). CONCLUSIONS: The -5C allele of the GP Ibalpha Kozak polymorphism may represent a risk factor in clinical conditions in which thrombosis plays an important role, such as in acute coronary syndromes and in complications after PTCA.
OBJECTIVES: This study was designed to determine whether patient characteristics collected at presentation can identify which patients benefit from immediate coronary angiography and revascularization.

BACKGROUND: Risk stratification may offer a method for identifying which patients with unstable angina or non-Q-wave myocardial infarction (NQMI) are likeliest to benefit from invasive management strategies.

METHODS: The analysis was based on data from a randomized controlled trial that enrolled 1,473 patients presenting with unstable angina or NQMI who were randomly assigned to an early invasive or early conservative (medical) management strategy. We constructed a risk-stratification score for each patient based on adjusted odds ratios for clinical variables likely to predict adverse outcomes. We stratified all trial subjects by their risk scores and studied the rates of death or myocardial infarction (MI) of the early invasive management strategy in each stratum.

RESULTS: The final multivariate model included older age, ST segment depression on presentation, history of complicated angina before presentation, and elevation in baseline creatine kinase-MB fraction. Although patients with a higher risk score had an increased rate of death or MI within 42 days and 365 days (p < 0.001) in both management strategies, early invasive management for patients in the high and very high risk categories was associated with a lower rate of death or MI within 42 days compared with conservative management. No such benefit was seen in patients in the larger group of patients in the very low, low or moderate risk categories (p = 0.03 for the interaction between risk category and management assignment).

CONCLUSIONS: Risk stratification may be an effective method for identifying those patients with unstable angina or NQMI most likely to benefit from early invasive management. Selective use of early invasive management can have a substantial impact in reducing morbidity and mortality in higher risk patients, but may not be warranted in lower risk patients.

J Am Coll Cardiol, 2001;38(4):1023-7

Role of Kozak sequence polymorphism of platelet glycoprotein Ibalpha as a risk factor for coronary artery disease and catheter interventions.

OBJECTIVES: We sought to determine the role of the -5T/C polymorphism of the platelet glycoprotein (GP) Ibalpha as a potential risk factor for coronary artery disease (CAD) and adverse events complicating a coronary catheter intervention. BACKGROUND: The platelet GP Ib-IX-V receptor complex plays a crucial role in arterial thrombus formation. The -5T/C polymorphism of GP Ibalpha is associated with increased receptor density. METHODS: We genotyped 1,000 patients with angiographically confirmed CAD, as well as 1,000 age- and gender-matched control subjects, for this polymorphism by polymerase chain reaction/restriction fragment length polymorphism. Among the patients with CAD, 269 underwent percutaneous transluminal coronary angioplasty (PTCA), 103 underwent directional coronary atherectomy and 278 underwent stenting. This intervention group was followed for a 30-day composite end point of target vessel revascularization, myocardial infarction or death. RESULTS: Carriers of the -5C allele were significantly over-represented in the group of patients developing acute coronary syndromes (relative risk [RR] 1.43, 95% confidence interval [CI] 1.05 to 1.95, p = 0.02). The -5C allele furthermore predicted an increased risk for developing complications after PTCA (RR 3.75, 95% CI 1.15 to 12.27, p = 0.029). CONCLUSIONS: The -5C allele of the GP Ibalpha Kozak polymorphism may represent a risk factor in clinical conditions in which thrombosis plays an important role, such as in acute coronary syndromes and in complications after PTCA.

J Am Coll Cardiol, 2001;38(4):1012-7


Goldman L, Phillips KA, Coxson P, Goldman PA, Williams L, Hunink MG, Weinstein MC.

OBJECTIVES: We sought to estimate the impact and cost-effectiveness of risk factor reductions between 1981 and 1990. BACKGROUND: Coronary heart disease (CHD) mortality rates have declined dramatically, partly as a result of reductions in CHD risk factors. METHODS: We used the CHD Policy Model, a validated computer-simulation model, to estimate the effects of actual investments made to change coronary risk factors between 1981 and 1990, as well as the impact of these changes on the incidence, prevalence, mortality and costs of CHD during this period and projected to 2015. RESULTS: Observed changes in risk factors between 1981 and 1990 resulted in a reduction of CHD deaths by approximately 430,000 and overall deaths by approximately 740,000, with an estimated cost-effectiveness of about $44,000 per year of life saved during this period, based on the estimated actual costs of the interventions used. However, because much of the benefit of risk factor reductions
is delayed, the estimated reductions for the 35-year period of 1981 to 2015 were 3.6 million CHD deaths and 1.2 million non-CHD deaths, at a cost of only about $5,400 per year of life saved. CONCLUSIONS: Aggregate efforts to reduce risk factors between 1981 and 1990 have led to substantial reductions in CHD and should be well worth the cost, largely because of population-wide changes in life-style and habits. Some interventions are much better investments than others, and attention to such issues could lead to better use of resources and better outcomes in the future.

Lancet, 2001 ;358(9286):971-6

Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis.


BACKGROUND: Previous studies have suggested that circulating concentrations of soluble adhesion molecules are useful predictors of risk of coronary heart disease (CHD). Larger studies are needed, however, to test this hypothesis. METHODS: We measured serum concentrations of four soluble cell adhesion molecules (intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion molecule-1 [VCAM-1], E-selectin, and P-selectin) in the stored baseline serum samples of 643 men with coronary heart disease and 1278 controls nested in a prospective study of 5661 men who were monitored for 16 years. We also did a meta-analysis of previous relevant studies to place our findings in context. RESULTS: Concentrations of soluble adhesion molecules were significantly associated with one another, with other markers of inflammation, and with some classic coronary risk factors. For ICAM-1, the odds ratio for CHD was 1.68 (95% CI 1.32-2.14) in a comparison of men in the top third with those in the bottom third of baseline measurements after adjustments for age and town. This decreased to 1.11 (0.75-1.64) after adjustment for some classic coronary risk factors and indicators of socioeconomic status. For the three other cell adhesion molecules, the odds ratios for CHD, first adjusted for age and town only, and then additionally adjusted for other risk factors, were: VCAM-1: 1.26 (0.99-1.61) and 0.96 (0.66-1.40); E-selectin: 1.27 (1.00-1.61) and 1.13 (0.78-1.62); and P-selectin: 1.23 (0.96-1.56) and 1.20 (0.81-1.76). INTERPRETATION: The measurement of these adhesion molecules is unlikely to add much predictive information to that provided by more established risk factors.

Circulation, 2001 ;104(14):1682-7
Unstable coronary plaque and its relation to coronary calcium.

Schmermund A, Erbel R.

Coronary calcium is intimately associated with coronary atherosclerotic plaque development. The use of electron-beam computed tomography (EBCT) for accurate quantitative measurements has led to an increased interest in understanding the clinical importance of coronary calcium, particularly in terms of the ability to identify unstable coronary plaques that underlie the clinical acute coronary syndromes. Histopathologic studies have demonstrated that calcium is a frequent feature of ruptured plaques, but the presence or absence of calcium does not allow for reliable distinction between unstable versus stable plaques. This issue is complicated by the lack of a prospective definition for unstable. Plaque rupture is sometimes found in apparently healthy subjects and in patients with clinically stable disease. Coronary atherosclerosis is a coronary systemic disease process. Imaging of coronary calcium, although unable to identify a localized unstable plaque, potentially can identify the more clinically pertinent unstable patient. Almost all patients with a recent acute coronary syndrome have measurable coronary calcium because moderate-to-advanced coronary plaque disease is already present, although obstructive disease frequently is not. Prospective studies have demonstrated that extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death. The incremental prognostic value of coronary calcium compared with that of risk factor assessment remains to be fully defined. The occurrence of an acute coronary syndrome is determined by many factors apart from the extent of atherosclerotic plaque disease. Large prospective trials in the general population are needed to define the subgroups that will benefit most from quantitative assessment of coronary calcium.

Circulation, 2001;104(16):1927-32


Pohle K, Maffert R, Ropers D, Moshage W, Stilianakis N, Daniel WG, Achenbach S.
BACKGROUND: Recent studies demonstrated an influence of atherosclerotic risk factors on the progression of aortic valve stenosis. The extent of aortic valve calcification (AVC) was also found to be a strong predictor of stenosis progression. We investigated the influence of the LDL cholesterol level (LDL), other standard cardiovascular risk factors, and the extent of coronary calcification (CC) on the progression of AVC quantified by electron beam tomography (EBT). METHODS AND RESULTS: In 104 patients (64.7+/−8 years, 89 male) with an EBT scan positive for AVC, CC and AVC were quantified using a volumetric score. EBT was repeated at a mean interval of 15 months (10 to 36 months), and the progression of AVC and CC was determined. Patients were divided into 2 groups according to LDL: group 1, LDL</=3.36 mmol/L (130 mg/dL), 57 patients; group 2, LDL>3.36 mmol/L (130 mg/dL), 47 patients. Mean values for CC were 546+/−932 mm(3) in scan 1 and 665+/−1085 mm(3) in scan 2 for AVC 324+/−796 mm(3) and 404+/−1076 mm(3), respectively. The mean progression of CC was 27+/−37% (group 1, 16+/−22%; group 2, 39+/−46%, P</=0.001) and of AVC was 25+/−38% (group 1, 9+/−22%; group 2, 43+/−44%, P</=0.001). CONCLUSIONS: Quantification of AVC by EBT permits new insights into the progression of aortic valve sclerosis. We observed a strong influence of LDL cholesterol level on the progression of AVC and CC, suggesting that lipid-lowering therapy may decrease the progression of aortic valve calcification.

Circulation, 2001 ;104(16):1894-8

Selective serotonin reuptake inhibitors and myocardial infarction.

Sauer WH, Berlin JA, Kimmel SE.

BACKGROUND: Depression is an independent risk factor for myocardial infarction (MI). Selective serotonin reuptake inhibitors (SSRIs) may reduce this risk through attenuation of serotonin-mediated platelet activation in addition to treatment of depression itself. METHODS AND RESULTS: case-control study of first MI in smokers 30 to 65 years of age was conducted among all 68 hospitals in an 8-county area during a 28-month period. Cases were patients hospitalized with a first MI. Approximately 4 community control subjects per case were randomly selected from the same geographic area using random digit dialing. Detailed information regarding use of antidepressant medication as well as other clinical and demographic data were obtained by telephone interview. A total of 653 cases of first MI and 2990 control subjects participated. After adjustment, using multivariable logistic regression, for age, sex, race, education, exercise, quantity smoked per day, body
mass index, aspirin use, family history of MI, number of physician encounters, and history of coronary disease, diabetes, hypertension, or hypercholesterolemia, the odds ratio for MI among current SSRI users compared with nonusers was 0.35 (95% CI 0.18, 0.68; \( P<0.01 \)). Non-SSRI antidepressant users had a nonsignificant reduction in MI risk with wide confidence intervals (adjusted odds ratio 0.48, CI 0.17, 1.32; \( P=0.15 \)). However, analysis of this group was limited by the small number of exposed subjects. CONCLUSIONS: The use of SSRIs may confer a protective effect against MI. This could be attributable to the inhibitory effect SSRIs have on serotonin-mediated platelet activation or possibly amelioration of other factors associated with increased risk for MI in depression.

BMJ, 2001;323(7319):957-62

Randomised trials of secondary prevention programmes in coronary heart disease: systematic review.

McAlister FA, Lawson FM, Teo KK, Armstrong PW.

OBJECTIVE: To determine whether multidisciplinary disease management programmes for patients with coronary heart disease improve processes of care and reduce morbidity and mortality. DATA SOURCES: Randomised clinical trials of disease management programmes in patients with coronary heart disease were identified by searching Medline 1966-2000, Embase 1980-99, CINAHL 1982-99, SIGLE 1980-99, the Cochrane controlled trial register, the Cochrane effective practice and organisation of care study register, and bibliographies of published studies. DATA EXTRACTION: Studies were selected and data were extracted independently by two investigators, and summary risk ratios were calculated by using both the random effects model and the fixed effects model. DATA SYNTHESIS: A total of 12 trials (9803 patients with coronary heart disease) were identified. Disease management programmes had positive impacts on processes of care. Patients randomised to these programmes were more likely to be prescribed efficacious drugs (risk ratio 2.14 (95% confidence interval 1.92 to 2.38) for lipid lowering drugs, 1.19 (1.07 to 1.32) for beta blockers, and 1.07 (1.03 to 1.11) for antiplatelet agents). Five out of seven trials evaluating risk factor profiles showed significantly greater improvements with these programmes in comparison with usual care (with effect sizes in the moderate range). Summary risk ratios were 0.91 (0.79 to 1.04) for all cause mortality, 0.94 (0.80 to 1.10) for recurrent myocardial infarction, and 0.84 (0.76 to 0.94) for admission to hospital. Five of the eight trials evaluating quality of life or functional status reported better outcomes in the intervention arms. Only three of these trials reported the costs of the intervention-the interventions were cost saving in two cases. CONCLUSIONS: Disease management
programmes improve processes of care, reduce admissions to hospital, and enhance quality of life or functional status in patients with coronary heart disease. The programmes’ impact on survival and recurrent infarctions, their cost effectiveness, and the optimal mix of components remain uncertain.

Am Heart J, 2001; 142(5):857-63

Treatment of cardiac risk factors in diabetic patients: How well do we follow the guidelines?

George PB, Tobin KJ, Corpus RA, Devlin WH, O’eill WW.

BACKGROUND: Diabetic patients are at increased risk for both macrovascular and microvascular disease compared with nondiabetic patients. METHODS: We conducted a prospective observational study to assess the control of multiple predetermined cardiovascular risk factors in 235 treated diabetic patients undergoing elective cardiac catheterization at our institution between December 20, 1997, and February 15, 2000. The following parameters were used to define optimal treatment in these patients: hemoglobin (Hgb) A1c <7%, low-density lipoprotein cholesterol (LDL-c) <100 mg/dL, high-density lipoprotein cholesterol (HDL-c) >/=45 mg/dL for men and >/=55 mg/dL for women, triglyceride (TG) level <200 mg/dL, blood pressure (BP) <130/85 mm Hg, body mass index (BMI) <25, daily aspirin therapy, and current nonsmoking status. The use of b-blockers and angiotensin-converting enzyme inhibitors was also evaluated. RESULTS: The average patient age was 64 +/- 11 years; 155 (65%) were male. One hundred ninety-one (81%) patients had documented coronary artery disease at cardiac catheterization. The mean Hgb A1c level for all diabetic patients was 8.2% +/- 1.6%. Overall, 49 (21%) had an Hgb A1c level <7%. The fasting cholesterol panel for all patients revealed a mean LDL-c level of 103 +/- 41 mg/dL, a mean HDL level of 39 +/- 11 mg/dL, and a mean TG level of 164 +/- 128 mg/dL. Only 23 of 233 (10%) diabetics were controlled to a BP of <130/85 mm Hg, and 25 (11%) achieved a BMI <25. CONCLUSIONS: These data demonstrate the poor control of numerous cardiovascular risk factors in treated diabetics undergoing elective cardiac catheterization.
Absence of gender differences in clinical outcomes in patients with cardiogenic shock complicating acute myocardial infarction. A report from the SHOCK Trial Registry.


OBJECTIVES: The aim of this study was to assess the impact of gender on clinical course and in-hospital mortality in patients with cardiogenic shock (CS) complicating acute myocardial infarction (AMI).

BACKGROUND: Previous studies have demonstrated higher mortality for women compared with men with ST elevation myocardial infarctions and higher rates of CS after AMI. The influence of gender and its interaction with various treatment strategies on clinical outcomes once CS develops is unclear.

METHODS: Using the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK? (SHOCK) Registry database of 1,190 patients with suspected CS in the setting of AMI, we examined shock etiologies by gender. Among the 884 patients with predominant left ventricular (LV) failure, we compared the patient demographics, angiographic and hemodynamic findings, treatment approaches as well as the clinical outcomes of women versus men. This study had a 97% power to detect a 10% absolute difference in mortality by gender.

RESULTS: Left ventricular failure was the most frequent cause of CS for both gender groups. Women in the SHOCK Registry had a significantly higher incidence of mechanical complications including ventricular septal rupture and acute severe mitral regurgitation. Among patients with predominant LV failure, women were, on average, 4.6 years older, had a higher incidence of hypertension, diabetes and a lower cardiac index. The overall mortality rate for the entire cohort was high (61%). After adjustment for differences in patient demographics and treatment approaches, there was no significant difference in in-hospital mortality between the two gender groups (odds ratio = 1.03, 95% confidence interval of 0.73 to 1.43, p = 0.88). Mortality was also similar for women and men who were selected for revascularization (44% vs. 38%, p = 0.244).

CONCLUSIONS: Women with CS complicating AMI had more frequent adverse clinical characteristics and mechanical complications. Women derived the same benefit as men from revascularization, and gender was not independently associated with in-hospital mortality in the SHOCK Registry.
Decrease in coronary blood flow reserve during hyperlipidemia is secondary to an increase in blood viscosity.

Rim SJ, Leong-Poi H, Lindner JR, Wei K, Fisher NG, Kaul S.

BACKGROUND: During maximal hyperemia, capillaries provide the greatest resistance to flow. A major determinant of capillary resistance is viscosity. We, therefore, hypothesized that abnormal coronary blood flow (CBF) reserve observed during hyperlipidemia is secondary to increased blood viscosity and not abnormal coronary vasomotion. METHODS AND RESULTS: Maximal hyperemia was induced in 9 dogs using adenosine. Serum triglyceride levels were increased by incremental doses of Intralipid. A good correlation was noted between serum triglyceride levels and blood viscosity (r=0.82). Neither total coronary blood volume nor myocardial blood volume changed with increasing serum triglyceride levels, indicating lack of vasomotion. Myocardial vascular resistance (MVR) increased with increasing triglyceride levels (r=0.84), while hyperemic myocardial blood flow (MBF) decreased (r=0.64). The decrease in hyperemic MBF was associated with a decrease in blood velocity (r=0.56). These findings were confirmed with direct intravital microscopic observations in the mice cremaster muscle. CONCLUSIONS: Increasing lipid levels in a fully dilated normal coronary bed causes no change in large or small vessel dimensions. Instead, the increase in blood viscosity causes capillary resistance to rise, which attenuates hyperemic CBF. Therefore, the abnormal CBF reserve associated with hyperlipidemia is due to increase blood viscosity and not abnormal vascular function.

J Am Coll Cardiol, 2001;38(5):1511-7


Calnon DA, McGrath PD, Doss AL, Harrell FE Jr, Watson DD, Beller GA.

OBJECTIVES: This work was undertaken to define the intrinsic cardiac risk of the patient population referred for dobutamine stress perfusion imaging and to determine whether dobutamine technetium-99m ((99m)Tc)-sestamibi single-photon emission computed tomography (SPECT) imaging is capable of risk stratification in this population. BACKGROUND: In animal models, dobutamine attenuates the myocardial uptake of (99m)Tc-
sestamibi resulting in underestimation of coronary stenoses. Therefore, we hypothesized that the prognostic value of dobutamine stress (99m)Tc-sestamibi SPECT myocardial perfusion imaging might be impaired, owing to reduced detection of coronary stenoses. METHODS: We reviewed the clinical outcome of 308 patients (166 women, 142 men) who underwent dobutamine stress SPECT (99m)Tc-sestamibi imaging at our institution from September 1992 through December 1996. RESULTS: During an average follow-up of 1.9 +/- 1.1 years, there were 33 hard cardiac events (18 myocardial infarctions [MI] and 15 cardiac deaths) corresponding to an annual cardiac event rate of 5.8%/year, which is significantly higher than the event rate for patients referred for exercise SPECT imaging at our institution (2.2%/year). Event rates were higher after an abnormal dobutamine (99m)Tc-sestamibi SPECT study (10.0%/year) than after a normal study (2.3%/year) (p < 0.01), even after adjusting for clinical variables. In the subgroup (n = 29) with dobutamine-induced ST-segment depression and abnormal SPECT imaging, the prognosis was poor, with annual cardiac death and nonfatal MI rates of 7.9% and 13.2%, respectively. CONCLUSIONS: Patients referred for dobutamine perfusion imaging are a high-risk population, and dobutamine stress (99m)Tc-sestamibi SPECT imaging is capable of risk stratification in these patients.

J Am Coll Cardiol, 2001;38(5):1302-6

A prospective evaluation of lipoprotein-associated phospholipase A(2) levels and the risk of future cardiovascular events in women.

Blake GJ, Dada N, Fox JC, Manson JE, Ridker PM.

OBJECTIVES: We sought to determine prospectively whether lipoprotein-associated phospholipase A(2) (Lp-PLA(2)) was a predictor of future cardiovascular risk in women. BACKGROUND: Inflammatory markers may help predict cardiovascular risk. Lp-PLA(2) levels have recently been hypothesized to be an independent predictor of cardiovascular risk in hypercholesterolemic men. METHODS: We conducted a prospective, nested case-control study among 28,263 apparently healthy middle-aged women to assess the risk of death from coronary heart disease, non-fatal myocardial infarction, and stroke associated with baseline levels of Lp-PLA(2) over a mean follow-up of three years. RESULTS: In univariate analysis, mean levels of Lp-PLA(2) correlated strongly with low-density lipoprotein cholesterol (r = 0.51; p = 0.0001), were lower among women currently using hormone replacement therapy (mean 0.98 mg/l vs. 1.23 mg/l; p = 0.0001) and were significantly higher at baseline among cases (n = 123) than controls (n = 123) (mean 1.20 mg/l vs. 1.05 mg/l; p = 0.016). However, the predictive value of Lp-PLA(2) was markedly attenuated after adjustment for these and other cardiovascular
risk factors. Specifically, the multivariate relative risks of future cardiovascular events for women in the lowest (referent) to highest quartiles of Lp-PLA(2) were 1.00, 0.75, 0.64 and 1.17, respectively (all p values non-significant). In contrast, the adjusted relative risks of future cardiovascular events for each increasing quartile of C-reactive protein (another marker of low-grade inflammation) were 1.00, 1.78, 2.02 and 4.66, respectively (p-value for trend = 0.002). Inclusion of Lp-PLA(2) levels did not significantly attenuate this latter observation.

CONCLUSIONS: In contrast to prior data among hyperlipidemic men, the current data suggest that Lp-PLA(2) is not a strong predictor of future cardiovascular risk among unselected women.


The association between white blood cell count and acute myocardial infarction mortality in patients ≥65 years of age: findings from the cooperative cardiovascular project.

Barron HV, Harr SD, Radford MJ, Wang Y, Krumholz HM.

OBJECTIVES: The purpose of the study was to examine the association between white blood cell (WBC) count on admission and 30-day mortality in patients with acute myocardial infarction (AMI). BACKGROUND: Elevations in WBC count have been associated with the development of AMI and with long-term mortality in patients with coronary artery disease. However, the relationship between WBC count and prognosis following AMI is less clear. METHODS: Using the Cooperative Cardiovascular Project database, we evaluated 153,213 patients ≥65 years of age admitted with AMI. RESULTS: An increasing WBC count is associated with a significantly higher risk of in-hospital events, in-hospital mortality and 30-day mortality. Relative to those patients in the lowest quintile, patients in the highest quintile were three times more likely to die at 30 days (10.3% vs. 32.3%; p < 0.001). After adjustment for confounding factors, WBC count was found to be a strong independent predictor of 30-day mortality (odds ratio = 2.37; 95% confidence interval 2.25 to 2.49, p = 0.0001 for the highest quintile of WBC count). CONCLUSIONS: White blood cell count within 24 h of admission for an AMI is a strong and independent predictor of in-hospital and 30-day mortality as well as in-hospital clinical events. Although the mechanism of the association remains speculative, the results of this study have important clinical implications for risk-stratifying patients with AMI.
Multifactorial cardiovascular disease prevention in patients aged 75 years and older: A randomized controlled trial: Drugs and Evidence Based Medicine in the Elderly (DEBATE) Study.

Strandberg TE, Pitkala K, Berglind S, Nieminen MS, Tilvis RS.

BACKGROUND: The number of patients aged 75+ years with cardiovascular diseases (CVD) is increasing, but few studies of secondary prevention in this age group exist. The aim of the Drug and Evidence Based Medicine in the Elderly (DEBATE) study is to test the applicability and effectiveness of established CVD treatments in elderly patients. METHODS: From 1998 to 2000, population-based postal surveys were performed in Helsinki, Finland, including the age groups 75, 80, 85, 90, and 95 years (n = 4821). Of the 812 individuals reporting any atherosclerotic disease, 400 patients (66% of those eligible) were included in a randomized trial. In the intervention group, CVD treatments will be individualized according to current guidelines. A control group will receive the usual care. The trial period will last 2 years with a 3-year extension. The primary end point will be a composite of major CVD. In addition, a number of secondary end points will be recorded, including permanent institutionalization, decline in cognitive and physical function, and quality of life. RESULTS: During 2000, 400 home-dwelling patients were randomized to the intervention (n = 199) and control (n = 201) groups. The mean age is 80.2 years and 65.3% are women. Of the participants, 82% have coronary heart disease (41% with history of myocardial infarction), 37% history of stroke, 19% non-insulin-dependent diabetes mellitus, and 45% hypertension, and 6% are current smokers. Before randomization, 67% used aspirin, 40% b-blockers, 14% angiotensin-converting enzyme inhibitors, 36% nitrates, and 20% lipid-lowering drugs. The groups were well balanced at baseline. CONCLUSION: We have successfully randomized elderly patients with a high degree of comorbidity into a multifactorial CVD prevention trial.

Association between myeloperoxidase levels and risk of coronary artery disease.

Zhang R, Brennan ML, Fu X, Aviles RJ, Pearce GL, Penn MS, Topol EJ, Sprecher DL, Hazen SL.
Myeloperoxidase (MPO), a leukocyte enzyme that promotes oxidation of lipoproteins in atheroma, has been proposed as a possible mediator of atherosclerosis. OBJECTIVE: To determine the association between MPO levels and prevalence of coronary artery disease (CAD). DESIGN, SETTING, AND PATIENTS: Case-control study conducted from July to September 2000 in a US tertiary care referral center, including 158 patients with established CAD (cases) and 175 patients without angiographically significant CAD (controls). MAIN OUTCOME MEASURES: Association of MPO levels per milligram of neutrophil protein (leukocyte-MPO) and MPO levels per milliliter of blood (blood-MPO) with CAD risk. RESULTS: Leukocyte- and blood-MPO levels were both significantly greater in patients with CAD than in controls (P<001). In multivariable models adjusting for traditional cardiovascular risk factors, Framingham risk score, and white blood cell counts, MPO levels were significantly associated with presence of CAD, with an OR of 11.9 (95% CI, 5.5-25.5) for the highest vs lowest quartiles of leukocyte-MPO and an OR of 20.4 (95% CI, 8.9-47.2) for the highest vs lowest quartiles of blood-MPO. CONCLUSIONS: Elevated levels of leukocyte- and blood-MPO are associated with the presence of CAD. These findings support a potential role for MPO as an inflammatory marker in CAD and may have implications for atherosclerosis diagnosis and risk assessment.

Am J Cardiol, 2001;88(11):1221-4

Relation of the leukocyte count to recurrent cardiac events in stable patients after acute myocardial infarction.


Increasing evidence implicates inflammation as a risk factor for coronary artery disease. We determined whether an elevated leukocyte count is associated with an increased risk of death or reinfarction in stable patients with a past acute myocardial infarction (AMI). The current analysis is a substudy of the Multicenter Diltiazem Postinfarction Trial, which investigated the effect of diltiazem on mortality and reinfarction in 2,466 patients hospitalized for AMI. We included 1,294 patients in whom a leukocyte count was obtained 6 months after the index AMI. The composite end point of reinfarction or death was used as the primary end point of the study and reinfarction or cardiac death was used as a secondary end point. The study population was divided into 4 quartiles (Q1, Q2, Q3, and Q4) based on the leukocyte count. During a mean follow-up period of 25 months, 163 patients reached the primary end point: 8.7%, 10.9%, 14.0%, and 16.7%, in Q1, Q2, Q3, and, Q4 respectively (p = 0.01). After adjusting for potential covariates, Cox proportional-hazards analysis revealed that an increased leukocyte count was associated with an increased risk of both the primary end point (hazard ratio/1 quartile increase in leukocyte count, 1.26; p = 0.003; 95% confidence interval 1.08 to 1.47) and secondary
end point (hazard ratio, 1.18/1-quartile increase; \( p = 0.05; \) 95% confidence interval 1.00 to 1.40). In conclusion, an increased leukocyte count measured in the stable post-AMI period is associated with an increased risk of cardiac events. These findings indicate that the leukocyte count may be another marker of an atherosclerotic inflammatory process that contributes to cardiac events in postinfarction patients.

**Eur Heart J, 2001;22(24):2262-6**

Mutation in the promoter region of the beta-fibrinogen gene and the risk of future myocardial infarction, stroke and venous thrombosis.

Blake GJ, Schmitz C, Lindpaintner K, Ridker PM.

AIM: Polymorphisms in the promoter region of the beta-fibrinogen gene are associated with increased plasma fibrinogen levels. We investigated whether the distribution of the C148T polymorphism is associated with an increase in cardiovascular risk. METHODS AND RESULTS: In a nested case-control design, the distribution of the C148T polymorphism was investigated among 751 participants in the Physicians?Health Study who subsequently developed myocardial infarction, stroke or venous thromboembolism (cases) and among 751 age- and smoking-matched controls over follow-up of 8.6 years. Frequency of the T allele was similar among men who had myocardial infarction (22.7%, \( P=0.5 \)), stroke (18.4%, \( P=0.2 \)) or venous thromboembolism (17.0%, \( P=0.1 \)) compared with those with no cardiovascular events (21.5%). The relative risk for any vascular event among men homozygous or heterozygous for the T allele compared with men homozygous for the C allele was 0.94 (95% CI 0.76-1.16). We found no evidence of an association between the T allele and myocardial infarction (relative risk 1.06; 95% CI 0.82-1.36), stroke (0.87, 0.63-1.21) or venous thromboembolism (0.75; 0.51-1.08). Analysis adjusted for aspirin use and traditional cardiovascular risk factors had no significant effect on these findings. CONCLUSION: In a large prospective cohort, carriage of the T allele for the C148T mutation in the beta-fibrinogen promoter gene was not associated with an increased subsequent risk of cardiovascular events.

**Eur Heart J, 2001;22(24):2243-52**

The interleukin-6 -174 G/C promoter polymorphism is associated with risk of coronary heart disease and
systolic blood pressure in healthy men.

Humphries SE, Luong LA, Ogg MS, Hawe E, Miller GJ.

AIMS: Inflammation is a key component of coronary heart disease, and genes coding for cytokines are candidates for predisposing to coronary heart disease risk. We have examined the effect of two polymorphisms (-174G>C and -572G>C) in the promoter of the interleukin-6 (IL-6) gene on risk of coronary heart disease, and on intermediate risk traits including fibrinogen and systolic blood pressure, in 2751 middle-aged healthy U.K. men. RESULTS: The -174C allele (frequency 0.43, 95% CI 0.42-0.44) was not associated with significant effects on fibrinogen levels, but was associated with a significantly (P=0.007) higher systolic blood pressure (mean mmHg (95% CI): GG=135.5 (134.3-136.7); GC=137.9 (136.9-138.9); CC= 138.0 (136.3-139.8)). This effect was of similar magnitude in smokers and non-smokers, and was greater in men in the top two tertiles of body mass index (>24.86 kg x m(-2)) than in those in the bottom tertile. Compared to those with the genotype GG, men carrying the -174C allele had a relative risk of coronary heart disease of 1.54 (95% CI 1.0-2.23, P=0.048) and this effect was greatest in smokers (compared to GG non-smokers, RR 2.66, CI 1.64-4.32). These effects remained statistically significant after adjusting for classical risk factors including blood pressure (P=0.04). The -572C allele (frequency 0.05, 0.04-0.06) was not associated with a significant effect on blood pressure, fibrinogen or relative risk of coronary heart disease. In a subset of the genotyped men (n=494), carriers of the -174C allele had higher levels of C-reactive protein than non-carriers. CONCLUSIONS: These data confirm the importance of the inflammatory system in the development of coronary heart disease. They suggest that, at least in part, the effect of the IL-6 -174G>C polymorphism on blood pressure is likely to be operating through inflammatory mechanisms, but the genotype effect on coronary heart disease risk is largely unexplained by its effect on blood pressure. The molecular mechanisms whereby genetically determined differences in plasma levels of IL-6 are having these effects remain to be determined.

Circulation ,2001 ;104(22):2679-84

Coronary artery calcification in older adults to age 99: prevalence and risk factors.

BACKGROUND: Coronary artery calcification has been proposed as a noninvasive method to assess cardiovascular disease (CVD) risk. However, the prevalence and risk factors for coronary artery calcification in populations ≥65 years have not been well studied. METHODS AND RESULTS: Electron beam tomography was performed to assess coronary artery calcium (CAC) in 614 older adults aged, on average, 80 years (range, 67 to 99 years); 367 (60%) were women, and 143 (23%) were black. Calcium scores ranged from 0 to 5459. Median scores were 622 for men and 205 for women. Scores increased by age and were lower in blacks than in whites. Nine percent of subjects (n=57) had no CAC, and 31% (n=190) had a score lower than 100. A history of CVD was associated with calcium score. Age, male sex, white race, CVD, triglyceride level, pack-years of smoking, and asthma, emphysema, or bronchitis (chronic obstructive pulmonary disease) were independently associated with CAC score in the fourth quartile. CONCLUSIONS: A wide range of CAC scores was observed, suggesting adaptation with aging. CAC may have potential to predict CVD in older adults, but this remains to be determined.

Circulation, 2001;104(23):2815-9

Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study.

Davis PH, Dawson JD, Riley WA, Lauer RM.

BACKGROUND: Higher carotid intimal-medial thickness (IMT) is associated with cardiovascular risk factors and is predictive of coronary artery disease and stroke in older adults. Carotid IMT was measured in young and middle-aged adults to determine its relationship with risk factors measured (1) in childhood, (2) currently, and (3) as a "load" from childhood to adulthood. METHODS AND RESULTS: Carotid ultrasound studies were performed in 346 men and 379 women aged 33 to 42 years who were representative of a cohort followed since childhood and who live in Muscatine, Iowa. The mean of the measurements of maximal carotid IMT at 12 locations was determined for each subject. A medical questionnaire was completed, and measurements of anthropometric characteristics and risk factors were obtained. The mean maximum carotid IMT was 0.79+/−0.12 mm for men and 0.72+/−0.10 mm for women. On the basis of multivariable analysis, the significant current predictors of IMT were age and LDL cholesterol in both sexes and diastolic blood pressure in women. Total cholesterol was a significant childhood predictor in both sexes, while childhood body mass index was
significant only in women. For men, LDL cholesterol, HDL cholesterol, and diastolic blood pressure were predictive of carotid IMT in a risk factor load model, whereas in women, LDL cholesterol, body mass index, and triglycerides were predictive. CONCLUSIONS: Higher carotid IMT in young and middle-aged adults is associated with childhood and current cardiovascular risk factors, as well as risk factor load.

Am J Cardiol, 2001;88(12):1370-3

Comparison of remnant-like lipoprotein particles in postmenopausal women with and without coronary artery disease and in men with coronary artery disease.


It is known that hypertriglyceridemia is a risk factor of coronary artery disease (CAD) in postmenopausal women. This study prospectively examined whether remnant lipoprotein, an atherogenic triglyceride-rich lipoprotein, may have a significant risk and prognostic values in postmenopausal women with angiographically verified CAD. Remnant-like lipoprotein particles cholesterol (RLP cholesterol) levels in fasting serum were measured in 134 consecutive postmenopausal women with (n = 56) or without (n = 78) CAD by an immunoseparation method. The women with CAD were followed for < or =24 months until occurrence of the following clinical coronary events: readmission or coronary revascularization due to recurrent or refractory angina pectoris, nonfatal myocardial infarction, and cardiac death. Multivariate logistic regression analysis showed that high RLP cholesterol levels (>5.7 mg/dl cholesterol; 90th percentile of the distribution of RLP cholesterol levels in controls) were a significant risk factor for the presence of CAD independent of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and other traditional risk factors. Kaplan-Meier analysis demonstrated that women with CAD and higher RLP cholesterol levels had a significantly higher probability of developing coronary events (p <0.001). In multivariate Cox hazard analysis, high RLP cholesterol levels as well as diabetes and hypercholesterolemia were a significant predictor of future coronary events independent of other risk factors in women with CAD (odds ratio 9.7, 95% confidence intervals 1.3 to 20.3, p = 0.02). In conclusion, increased levels of RLP cholesterol are a significant and independent risk factor of CAD and predict future coronary events in postmenopausal women with CAD.
Circulation, 2001;104(24):2892-7

Blood lipids and first-ever ischemic stroke/transient ischemic attack in the Bezafibrate Infarction Prevention (BIP) Registry: high triglycerides constitute an independent risk factor.

Tanne D, Koren-Morag N, Graff E, Goldbourt U.

BACKGROUND: Despite unclear associations between blood lipids, including fractionated cholesterol and triglycerides, and stroke, recent evidence demonstrates that lipid-modifying agents decrease the risk of stroke in patients with coronary heart disease (CHD).

METHODS AND RESULTS: Patients with documented CHD who were screened for but not included in the Bezafibrate Infarction Prevention study and had no history of stroke or transient ischemic attack (TIA) (n=11 177) were followed up. At baseline, medical histories were obtained and blood lipids assessed at a central study laboratory. During a 6- to 8-year follow-up period, 941 patients were identified as having nonhemorrhagic cerebrovascular disease, of whom 487 had verified ischemic stroke (per clinical findings and brain CT) or TIA. Patients experiencing an ischemic stroke/TIA had higher mean levels of triglycerides, lower levels of HDL cholesterol, and lower percentages of cholesterol contained in the HDL cholesterol moiety (%HDL; P<0.01 for all). In a logistic regression model, the adjusted ORs for developing an ischemic stroke/TIA were 1.27 (95% CI 1.01 to 1.60) associated with triglycerides >200 mg/dL and 0.87 (95% CI 0.78 to 0.97) associated with a 5% decrease in %HDL. The increased risk associated with high triglycerides was found across subgroups of age, sex, patient characteristics, and cholesterol fractions.

CONCLUSIONS: High triglycerides constitute an independent risk factor for ischemic stroke/TIA across subgroups of age, sex, patient characteristics, and cholesterol fractions, whereas high %HDL was an independent protective factor among patients with CHD. These findings support the role of blood lipids, including triglycerides, as important modifiable stroke risk factors.

J Am Coll Cardiol, 2001 ;38(7):1843-9

Peripheral vascular endothelial function testing as a noninvasive indicator of coronary artery disease.

Kuvin JT, Patel AR, Sliney KA, Pandian NG, Rand WM, Udelson JE, Karas RH.
OBJECTIVES: We studied whether assessment of endothelium-dependent vasomotion (EDV) with brachial artery ultrasound (BAUS) imaging predicts the presence or absence of coronary artery disease (CAD) as defined by exercise myocardial perfusion imaging (ExMPI). BACKGROUND: Abnormalities in EDV can be detected in arteries before the development of overt atherosclerosis, and its presence may predict poor long-term prognosis. Brachial artery ultrasound during reactive hyperemia is a noninvasive method of assessing peripheral EDV. METHODS: Clinically-indicated ExMPI along with BAUS were performed in 94 subjects (43 women, 51 men). Coronary artery disease was defined by myocardial ischemia or infarction on single photon emission computed tomography images. Flow-mediated dilation (FMD) after upper arm occlusion was defined as the percent change in arterial diameter during reactive hyperemia relative to the baseline. RESULTS: Subjects with CAD by ExMPI (n = 23) had a lower FMD (6.3 +/- 0.7%) than those without CAD by ExMPI (n = 71) (10.5 +/- 0.6%; p = 0.0004). Flow-mediated dilation was highly predictive for CAD with an odds ratio of 1.32 for each percent decrease in FMD (p = 0.001). Based on a receiver-operator analysis, an FMD of 10% was used as a cut-point for further analysis. Twenty-one of 23 subjects who were positive for ExMPI had an FMD < 10% (sensitivity 91%), whereas only two of 40 subjects with an FMD > or =10% were ExMPI-positive (negative predictive value: 95%). There was a correlation between the number of cardiac risk factors and FMD. Individuals with an FMD < 10% exercised for a shorter duration than those with an FMD > or =10% (456 +/- 24 vs. 544 +/- 31 s, respectively; p = 0.02). CONCLUSIONS: Assessment of EDV with BAUS has a high sensitivity and an excellent negative predictive value for CAD and, thus, has the potential for use as a screening tool to exclude CAD in low-risk subjects. Further standardization of BAUS is required, however, before specific cut-points for excluding CAD can be established.

J Am Coll Cardiol, 2001;38(7):1821-8

Coronary endothelial dysfunction in the insulin-resistant state is linked to abnormal pteridine metabolism and vascular oxidative stress.


OBJECTIVES: We investigated whether abnormal pteridine metabolism is related to coronary endothelial
dysfunction in insulin-resistant subjects. BACKGROUND: Depletion of tetrahydrobiopterin (BH(4)) and elevation of the 7,8-dihydrobiopterin (BH(2)) (activating and inactivating cofactors of nitric oxide synthase [NOS], respectively) contribute to impairment of NO-dependent vasodilation through reduction of NOS activity as well as increased superoxide anion generation in insulin-resistant rats. METHODS: Thirty-six consecutive nondiabetic, normotensive and nonobese subjects with angiographically normal coronary vessels were studied. Traditional coronary risk factors, plasma pteridine levels, activities of erythrocyte dihydropteridine reductase (DHPR), the recycling enzyme that converts BH(2) to BH(4) and lipid peroxide (LPO) levels were measured and coronary endothelial function was assessed with graded infusions of acetylcholine (ACh). RESULTS: When we divided patients into tertiles based on insulin sensitivity, we observed stepwise decreases in the maximal ACh-induced vasodilation and plasma BH(4)/7,8-BH(2) ratio, and increases in coronary LPO production as insulin sensitivity decreased. The ACh-induced vasodilation was positively correlated with insulin sensitivity, BH(4)/7,8-BH(2) ratio and DHPR activity. Furthermore, BH(4)/7,8-BH(2) was inversely correlated with DHPR activity and insulin sensitivity. In multiple stepwise regression analysis, BH(4)/BH(2) was independently related to ACh-induced vasodilation and accounted for 39% of the variance. However, no significant correlation existed between other traditional risk factors and BH(4)/7,8-BH(2). CONCLUSIONS: These results indicate that both abnormal pteridine metabolism and vascular oxidative stress are linked to coronary endothelial dysfunction in the insulin-resistant subjects.

J Am Coll Cardiol, 2001;38(7):1814-20

Cardiovascular risk factors as determinants of endothelium-dependent and endothelium-independent vascular reactivity in the general population.

Chan NN, Colhoun HM, Vallance P.

OBJECTIVES: We examined to what extent the variation in risk factors for coronary heart disease (CHD) and the Framingham risk score (FRS) explain the variation in vascular reactivity in adults aged 30 to 53 years. BACKGROUND: The role of risk factors in determining vascular reactivity in the general population has not been quantified. METHODS: Risk factors for CHD were measured, and the FRS was calculated in 69 healthy volunteers. Lipoprotein particle size was measured using proton-nuclear magnetic resonance spectroscopy. Forearm plethysmography was used to assess blood flow responses to acetylcholine (ACh), bradykinin (BK), glycercyl trinitrate (GTN), noradrenaline and N(G)-monomethyl-L-arginine (L-NMMA). RESULTS: Lower ACh
and BK responses were associated with a higher body mass index (BMI), a higher total cholesterol to high-density lipoprotein (HDL) cholesterol ratio, lower HDL cholesterol and a cigarette smoking habit (all p < 0.05). Higher low-density lipoprotein (LDL) cholesterol was also associated with a lower BK response (p = 0.001). A decreased GTN response was associated with a higher BMI and total cholesterol to HDL cholesterol ratio (both p < 0.05). A decreased L-NMMA response was associated with a smoking habit (p < 0.001). Lipoprotein particle sizes did not independently predict any vascular response. A high FRS was associated with a reduced response to ACh (p = 0.07), BK (p = 0.003) and L-NMMA (p = 0.003), and the relationship was stronger in women than in men. Altogether, risk factors explained 13%, 9%, 8% and 15% of the response to ACh, BK, GTN and L-NMMA, respectively. CONCLUSIONS: Lipids, BMI and smoking are important determinants of vascular reactivity. The FRS is predictive of agonist-stimulated, endothelium-dependent vasodilation and basal NO release. However, much of the variation in the vascular responses to these drugs, at this age, remains unexplained.

Circulation, 2001;104(25):3052-6

Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS).

Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N.

BACKGROUND: Leptin plays a role in fat metabolism and correlates with insulin resistance and other markers of the metabolic syndrome, independent of total adiposity. Therefore, we hypothesized that raised leptin levels may identify men at increased risk of a coronary event in the West of Scotland Coronary Prevention Study (WOSCOPS). Methods and Results- Plasma leptin levels were measured at baseline in 377 men (cases) who subsequently experienced a coronary event and in 783 men (controls) who remained free of an event during the 5-year follow-up period of the study. Controls were matched to cases on the basis of age and smoking history and were representative of the entire WOSCOPS cohort. Leptin levels were significantly higher in cases than controls (5.87+/−2.04 ng/mL versus 5.04+/−2.09 ng/mL, P<0.001). In univariate analysis, for each 1 SD increase in leptin, the relative risk (RR) of an event increased by 1.25 (95% confidence interval [CI], 1.10 to 1.43; P<0.001). There was minimal change in this RR with correction for body mass index (RR, 1.24; 95% CI, 1.06 to 1.45; P=0.006) or with further correction for classic risk factors, including age, lipids, and systolic blood pressure (RR, 1.20; 95% CI, 1.02 to 1.42; P=0.03). Leptin correlated with C-reactive protein (r=0.24, P<0.001) and, even with this variable added to the model, leptin retained significance as a predictor of coronary events (RR, 1.18; 95% CI, 1.00 to 1.39; P=0.05) at the expense of C-reactive protein. CONCLUSIONS: We show, for the first time, in a large prospective study that leptin is a novel, independent risk factor for coronary heart disease.
Low hepatic lipase activity is a novel risk factor for coronary artery disease.

Dugi KA, Brandauer K, Schmidt N, Nau B, Schneider JG, Mentz S, Keiper T, Schaefer JR, Meissner C, Kather H, Bahner ML, Fiehn W, Kreuzer J.

BACKGROUND: The crucial function of hepatic lipase (HL) in lipid metabolism has been well established, but the relationship between HL activity and coronary artery disease (CAD) is disputed. METHODS AND RESULTS: We measured HL activity in the postheparin plasma of 200 consecutive men undergoing elective coronary angiography and determined the degree of CAD with the extent score, which has been shown to be better correlated with known risk factors than other measures of CAD extent. We found a significant inverse correlation between HL activity and the extent of CAD (r=-0.19, P<0.01). This association was mainly due to patients with HDL levels >0.96 mmol/L (n=94, r=-0.30, P<0.005). HL activity was lower in 173 patients with CAD than in 40 controls with normal angiograms (286+/−106 versus 338+/−108 nmol. mL(−1). min(−1), P<0.01). To correct for potential confounding factors, we performed multivariate analyses that confirmed the independent association of HL activity with CAD extent. In addition, the presence of the T allele at position -514 in the HL promoter, which leads to a reduced HL promoter activity, was associated with lower HL activity (r=0.30, P<0.001) and higher CAD extent (42.2+/−20.8 versus 35.3+/−23.6 [extent score], P<0.05). In patients with heterozygous familial hypercholesterolemia, calcified lesions in ECG-gated spiral computed tomography were higher in patients with low HL activity (6.3+/−6.8 versus 1.5+/−3.1, P=0.01). CONCLUSIONS: Our data show that low HL activity is associated with CAD. Therefore, HL might be useful for CAD risk estimation and might be a target for pharmacological intervention.

Risk of acute coronary events and serum concentration of asymmetrical dimethylarginine.

Valkonen VP, Paiva H, Salonen JT, Lakka TA, Lehtimaki T, Laakso J, Laaksonen R.
Asymmetrical dimethylarginine (ADMA) is an endogenous nitric oxide synthase inhibitor, which has been suggested to be a novel independent risk factor for endothelial dysfunction and coronary heart disease. We investigated the association of ADMA concentration in serum with risk of acute coronary events. We did a prospective, nested, case-control study in middle-aged men from eastern Finland. In an analysis of men who did not smoke, those who were in the highest quartile for ADMA (>0.62 micromol/L) had a 3.9-fold (95% CI 1.25-12.3, p=0.02) increase in risk of acute coronary events compared with the other quartiles. Our findings suggest that ADMA is a predictor of acute coronary events.

J Am Coll Cardiol, 2002;39(1):49-56

A prospective study of dietary fiber intake and risk of cardiovascular disease among women.

Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE.

OBJECTIVES: This study was designed to examine the hypothesis that higher intake of dietary fiber is inversely related to the risk of cardiovascular disease (CVD) and myocardial infarction (MI) in a large prospective cohort of women. BACKGROUND: Although dietary fiber has been suggested to reduce the risk of coronary disease, few prospective studies have examined the association between the types and amounts of dietary fiber and CVD risk, particularly among women. METHODS: In 1993, we used a semi-quantitative food frequency questionnaire to assess dietary fiber intake among 39,876 female health professionals with no previous history of CVD or cancer. Women were subsequently followed for an average of six years for incidence of nonfatal MI, stroke, percutaneous transluminal coronary angioplasty, coronary artery bypass graft or death due to CVD confirmed by medical records or death certificates. RESULTS: During 230,006 person-years of follow-up, 570 incident cases of CVD were documented, including 177 MIs. After adjustment for age and randomized treatment status, a significant inverse association was observed between dietary fiber intake and CVD risk. Comparing the highest quintile of fiber intake (median: 26.3 g/day) with the lowest quintile (median: 12.5 g/day), the relative risks (RR) were 0.65 (95% confidence interval [CI]: 0.51, 0.84) for total CVD and 0.46 (95% CI: 0.30, 0.72) for MI. Additional adjustment for CVD risk factors reduced the RRs to 0.79 (95% CI: 0.58, 1.09) for total CVD and 0.68 (95% CI: 0.36, 1.22) for MI. The inverse trends across categories generally remained,
although they were no longer statistically significant. Inverse relations were observed between both soluble and insoluble fiber and risk of CVD and MI, and among those who had never smoked and those with body mass index <25. CONCLUSIONS: A higher intake of dietary fiber was associated with a lower risk of CVD and MI, although the association was not statistically significant after further adjusting for multiple confounding factors. Nevertheless, these prospective data generally support current dietary recommendations to increase the consumption of fiber-rich whole grains and fruits and vegetables as a primary preventive measure against CVD.

J Am Coll Cardiol 2002 Jan 2;39(1):49-56

A prospective study of dietary fiber intake and risk of cardiovascular disease among women.

Liu S, Buring JE, Sesso HD, Rimm EB, Willett WC, Manson JE.

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MI, although the association was not statistically significant after further adjusting for multiple confounding factors. Nevertheless, these prospective data generally support current dietary recommendations to increase the consumption of fiber-rich whole grains and fruits and vegetables as a primary preventive measure against CVD.

**Am J Cardiol 2002 Jan 1;89(1):12-7**

Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease.


It is a matter of controversy as to whether uric acid is an independent predictor of mortality in patients with coronary artery disease (CAD) or whether it represents only an indirect marker of adverse outcome by reflecting the association between uric acid and other cardiovascular risk factors. Therefore, we studied the influence of uric acid levels on mortality in patients with CAD. In 1,017 patients with angiographically proven CAD, classic risk factors and uric acid levels were determined at enrollment. A follow-up over a median of 2.2 years (maximum 3.1) was performed. Death from all causes was defined as an end point of the study. In CAD patients with uric acid levels <303 micromol/L (5.1 mg/dl) (lowest quartile) compared with those with uric acid levels >433 micromol/L (7.1 mg/dl) (highest quartile), the mortality rate increased from 3.4% to 17.1% (fivefold increase). After adjustment for age, both sexes demonstrated an increased risk for death with increasing uric acid levels (female patients: hazard ratio [HR] 1.30, 95% confidence intervals [CI] 1.14 to 1.49, p < or = 0.001; male patients: HR 1.39 [95% CI 1.21 to 1.59], p < or = 0.001). In multivariate Cox regression analysis performed with 12 variables that influence overall mortality-including diuretic use-elevated levels of uric acid demonstrated an independent, significant positive relation to overall mortality (HR 1.23 [95% CI 1.11 to 1.36], p <0.001) in patients with CAD. Thus, uric acid is an independent predictor of mortality in patients with CAD.

**Am J Cardiol 2002 Jan 15;89(2):159-63**

Utility and limitation of treadmill exercise echocardiography for detecting significant coronary stenosis in
infarct-related arteries in patients with healed myocardial infarction.


This clinical study examines the diagnostic accuracy of exercise echocardiography for detecting significant coronary stenoses in infarct-related arteries in patients with healed myocardial infarction. Quantitative coronary angiography and exercise echocardiography using treadmill testing were performed within 2 weeks of each other in 123 patients with a prior myocardial infarction. Coronary lumen diameter stenosis $\geq 50\%$ by quantitative coronary angiography and the lack of a hyperdynamic response on exercise echocardiography was considered significant. For detection of infarct-related coronary lesions, treadmill exercise echocardiography was highly sensitive (91\%) but less specific (59\%) than for detection of non-infarct-related artery lesions. The 2 groups of patients with large and small infarct sites had similar sensitivity for detection of residual stenosis of the infarct-related artery (88\% vs 96\%, $p = NS$); however, the specificity of the small infarct sites for this purpose was significantly higher than that of the large infarct sites (86\% vs 33\%, $p < 0.01$). When remote ischemia was detected on exercise echocardiography, the specificity of exercise echocardiography was significantly lower (33\% vs 70\%, $p < 0.05$) than when remote ischemia was not present. Thus, although there is high sensitivity, the specificity of treadmill exercise echocardiography for detecting infarct-related artery lesions is limited. However, high specificity is maintained when the infarct size is small and/or remote ischemia is not present.

J Am Coll Cardiol, 2002;39(2):241-6

Prognostic significance of peripheral monocytosis after reperfused acute myocardial infarction: a possible role for left ventricular remodeling.

Maekawa Y, Anzai T, Yoshikawa T, Asakura Y, Takahashi T, Ishikawa S, Mitamura H, Ogawa S.

OBJECTIVES: The aim of this study was to determine the significance of peripheral monocytosis in clinical outcome after reperfused acute myocardial infarction (AMI), especially relating to post-infarct left ventricular (LV) remodeling. BACKGROUND: Peripheral monocytosis occurs two to three days after AMI, reflecting
infiltration of monocytes and macrophages into the necrotic myocardium. However, the prognostic significance of peripheral monocytosis after AMI remains to be determined. METHODS: A total of 149 patients with first Q-wave AMI were studied. White blood cell (WBC) count, percentage of monocytes and serum C-reactive protein level were measured every 24 h for four days after the onset of AMI. We assessed association between peripheral monocytosis and prognosis including pump failure, LV aneurysm and long-term outcome after AMI. RESULTS: Patients with pump failure (p < 0.0001) or LV aneurysm (p = 0.005) had higher peak monocyte counts than those without these complications. Predischarge left ventriculography revealed that peak monocyte count was positively correlated with LV end-diastolic volume (p = 0.024) and negatively correlated with ejection fraction (p = 0.023). Multivariate analyses showed that peak monocyte count > 900/mm(3) was an independent determinant of pump failure (relative risk [RR] 9.83, p < 0.0001), LV aneurysm (RR 4.78, p = 0.046) and cardiac events (RR 6.30, p < 0.0001), including readmission for heart failure, recurrent myocardial infarction and cardiac deaths, including sudden deaths. CONCLUSIONS: Peripheral monocytosis is associated with LV dysfunction and LV aneurysm, suggesting a possible role of monocytes in the development of LV remodeling after reperfused AMI.

JAMA, 2002;287(2):210-5

Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention.


CONTEXT: A higher mortality risk for women with acute myocardial infarction (AMI) is a common finding in studies that compare the postinfarction outcome of women vs men. It is not clear, however, whether sex is an independent predictor of death among patients systematically treated with aggressive reperfusion and medical strategies. OBJECTIVE: To assess the impact of patient sex on outcome in a consecutive series of patients with AMI treated with a reperfusion strategy largely based on percutaneous coronary interventions. DESIGN, SETTING, AND PATIENTS: Inception cohort of 1937 patients (502 women and 1435 men) who were admitted with a diagnosis of AMI to a tertiary referral institution between January 1995 and December 2000. MAIN OUTCOME MEASURES: Mortality at 1 year after AMI. RESULTS: Compared with men, women were older (70 vs 61 years; P<.001) and had known diabetes or hypertension more often. Both men and women received essentially identical therapy with the majority of patients (86%) receiving reperfusion therapy via percutaneous
coronary interventions. There were no significant differences in 1-year Kaplan-Meier death rates with 13.8% (68 cases) among women and 12.9% (184 cases) among men (unadjusted hazard ratio, 1.06; 95% confidence interval, 0.80-1.39; P =0.70). After age adjustment, women had a lower risk of death (hazard ratio, 0.65; 95% confidence interval, 0.49-0.87; P =.004). CONCLUSION: Despite their more advanced age and greater prevalence of diabetes or hypertension, women with AMI who were treated with a reperfusion strategy largely based on percutaneous coronary interventions show a similar outcome as men

Circulation, 2002;105(2):152-6

New National Cholesterol Education Program III guidelines for primary prevention lipid-lowering drug therapy: projected impact on the size, sex, and age distribution of the treatment-eligible population.

Fedder DO, Koro CE, Lal?tien GJ.

BACKGROUND: The guidelines in the Third Report of the National Cholesterol Education Program (NCEP III) include absolute risk and lower LDL cholesterol (LDL-C) levels to assess eligibility for lipid-lowering drug therapy. We studied the impact of these changes on the size, sex, and age distribution of the target US population using data from the Third Annual National Health and Nutrition Survey (NHANES III) (1988 to 1994). METHODS AND RESULTS: A subsample of NHANES III participants aged 20 to 79 years with known cardiovascular risk factors and LDL-C levels was identified (n=13 589). We assessed their eligibility for drug therapy first using NCEP II guidelines and then using the new NCEP III criteria. We also calculated the number eligible for LDL-C lowering to <100 mg/dL. An estimated 15 million individuals aged 20 to 79 years are eligible for drug therapy under NCEP II; 51% are males, 49% are females, 26% are <45 years old, and 28% are > or =65 years old. Under NCEP III, 36 million would be eligible for treatment; 55% are males, 45% are females, 32% are <45 years old, and 27% are > or =65 years old. This represents a 140% increase in eligibility overall, a 157% increase among males, a 122% increase among females, a 131% increase among those > or =65 years old, and a 201% increase among those <45 years old. Of treatment-eligible individuals, 26% of males, 24% of females, 39% of elderly, and 14% of those <45 years old are targeted for LDL-C lowering to <100 mg/dL. CONCLUSIONS: The NCEP III guidelines will alter the age and sex distributions of the treatment-eligible population, targeting many more younger (<45 years old) and greater numbers of elderly (> or =65 years) individuals, particularly for aggressive intervention.
Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study.

Assmann G, Cullen P, Schulte H.

BACKGROUND: The absolute risk of an acute coronary event depends on the totality of risk factors exhibited by an individual, the so-called global risk profile. Although several scoring schemes have been suggested to calculate this profile, many omit information on important variables such as family history of coronary heart disease or LDL cholesterol. METHODS AND RESULTS: Based on 325 acute coronary events occurring within 10 years of follow-up among 5389 men 35 to 65 years of age at recruitment into the Prospective Cardiovascular Munster (PROCAM) study, we developed a Cox proportional hazards model using the following 8 independent risk variables, ranked in order of importance: age, LDL cholesterol, smoking, HDL cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides. We then derived a simple point scoring system based on the beta-coefficients of this model. The accuracy of this point scoring scheme was comparable to coronary event prediction when the continuous variables themselves were used. The scoring system accurately predicted observed coronary events with an area under the receiver-operating characteristics curve of 82.4% compared with 82.9% for the Cox model with continuous variables. CONCLUSIONS: Our scoring system is a simple and accurate way of predicting global risk of myocardial infarction in clinical practice and will therefore allow more accurate targeting of preventive therapy.
This study examined the effects of exercise and stress management training on clinical outcomes and medical expenditures over a 5-year follow-up period in 94 male patients with established coronary artery disease (CAD) and evidence of ambulatory or mental stress-induced myocardial ischemia. Patients were randomly assigned to 4 months of aerobic exercise 3 times per week or to a 1.5-hour weekly class on stress management; patients who lived too far from Duke to participate in the weekly treatments formed the usual care control group. Follow-up was performed at the end of treatment and annually thereafter for 5 years. Stress management was associated with a significant reduction in clinical CAD events relative to usual care over each of the first 2 years of follow-up and after 5 years. Economic analyses revealed that stress management was associated with lower medical costs than usual care and exercise in the first 2 years, and that the cumulative cost over 5 years was also lower for stress management relative to usual care. These results suggest that there may be clinical and economic benefit to offering the type of preventive stress management and exercise interventions provided to patients with myocardial ischemia. Moreover, these findings suggest that the financial benefits that accrue from an appropriately targeted intervention may be substantial and immediate.

Lancet, 2002;359(9301):118-23

Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study.

Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR.

BACKGROUND: Non-aspirin, non-steroidal anti-inflammatory drugs (NANSAIDs) have complex effects that could either prevent or promote coronary heart disease. Comparison of the NANSAID rofexocib with naproxen showed a substantial difference in acute myocardial infarction risk, which has been interpreted as a protective effect of naproxen. We did an observational study to measure the effects of NANSAIDs, including naproxen, on risk of serious coronary heart disease. METHODS: We used data from the Tennessee Medicaid programme obtained between Jan 1, 1987, and Dec 31, 1998, to identify a cohort of new NANSAID users (n=181 441) and an equal number of non-users, matched for age, sex, and date NANSAID use began. Both groups were 50-84 years of age, were not resident in a nursing home, and did not have life-threatening illness. The study endpoint was hospital admission for acute myocardial infarction or death from coronary heart disease. FINDINGS: During 532634 person-years of follow-up, 6362 cases of serious coronary heart disease occurred, or 11.9 per 1000 person-years. Multivariate-adjusted rate ratios for current and former use of NANSAIDs were 1.05 (95% CI
0.97-1.14) and 1.02 (0.97-1.08), respectively. Rate ratios for naproxen, ibuprofen, and other NANSAIDs were 0.95 (0.82-1.09), 1.15 (1.02-1.28), and 1.03 (0.92-1.16), respectively. There was no protection among long-term NANSAID users with uninterrupted use; the rate ratio among current users with more than 60 days of continuous use was 1.05 (0.91-1.21). When naproxen was directly compared with ibuprofen, the current-use rate ratio was 0.83 (0.69-0.98). INTERPRETATION: Absence of a protective effect of naproxen or other NANSAIDs on risk of coronary heart disease suggests that these drugs should not be used for cardioprotection.


Randomized trial of a medical food for the dietary management of chronic, stable angina.


OBJECTIVES: We determined the electrocardiographic, vascular and clinical effects of a medical food bar enriched with L-arginine and a combination of other nutrients known to enhance endothelium-derived nitric oxide (NO) in patients with stable angina. BACKGROUND: Enhancement of vascular NO by supplementation with L-arginine and other nutrients has been shown to have clinical benefits in patients with angina secondary to atherosclerotic coronary artery disease (CAD). However, the amounts and combinations of these nutrients required to achieve a clinical effect make traditional delivery by capsules and pills less suitable than alternative delivery methods such as a specially formulated nutrition bar. METHODS: Thirty-six stable outpatients with CAD and class II or III angina participated in a randomized, double-blind, placebo-controlled, crossover trial with two treatment periods each of two weeks?duration (two active bars or two placebo bars per day). Flow-mediated brachial artery dilation was measured by ultrasound. Electrocardiographic measures of ischemia, exercise capacity and angina onset time were measured by treadmill exercise testing and by Holter monitor during routine daily activities. Quality of life was assessed by SF-36 and Seattle Angina Questionnaires and by diary. RESULTS: The medical food improved flow-mediated vasodilation (from 5.5 +/- 4.5 to 8.0 +/- 4.9, p = 0.004), treadmill exercise time (by 20% over placebo, p = 0.05) and quality-of-life scores (SF-36 summary score; 68 +/- 13 vs. 63 +/- 21 after placebo, p = 0.04, Seattle Angina Questionnaire summary score; 67 +/- 10 vs. 62 +/- 18, p = 0.04) without affecting electrocardiographic manifestations of ischemia or angina onset time. CONCLUSIONS: These findings reveal that this arginine-rich medical food, when used as an adjunct to traditional therapy, improves vascular function, exercise capacity and aspects of quality of life in patients with stable angina.
New tools for coronary risk assessment: what are their advantages and limitations?

Pearson TA.

The concept of risk assessment and reduction, introduced initially by the Framingham Heart Study and refined in other models, forms the cornerstone of preventive cardiology. Risk factor assessment determines the therapeutic strategy, because the intensity of preventive intervention is tailored to the patient's risk of coronary heart disease. The conventional risk factors for coronary heart disease include elevated serum total cholesterol and LDL cholesterol, low HDL cholesterol, elevated blood pressure, cigarette smoking, diabetes, vascular disease, menopausal status (women only), and age. Aggressive risk factor reduction, formerly used exclusively in secondary prevention, may be pivotal to optimal patient management in high-risk primary prevention. A number of noninvasive imaging modalities have the potential to measure and to monitor atherosclerosis in asymptomatic individuals and include exercise ECG testing, electron beam computed tomography, magnetic resonance coronary angiography, positron emission tomography, ankle-brachial index, and B-mode ultrasound. Novel serum markers, including C-reactive protein and homocysteine, have the ability to gauge risk in the individual patient. Systemic therapy for risk reduction in primary prevention may be preferable to local therapy (eg, angioplasty and bypass) and may more effectively prevent acute coronary events than these more invasive approaches.

Type II diabetes does not prevent the recruitment of collateral vessels and the normal reduction of myocardial ischaemia on repeated balloon inflations during angioplasty.

Kyriakides ZS, Psychari S, Chrysomallis N, Georgiadis M, Sbarouni E, Kremastinos DT.

OBJECTIVE: To test whether type II diabetes prevents the recruitment of collaterals and the normal reduction of myocardial ischaemia on repeated balloon inflations during coronary angioplasty. METHODS: Two groups
of patients were studied. A collateral circulation group consisted of 56 patients, 18 diabetic and 38 non-diabetic. All underwent a minimum of three balloon inflations. A pressure guide wire was used for the measurement of coronary wedge pressure (mm Hg). The angioplasty protocol was repeated in another group of 57 patients (myocardial ischaemia group) using both surface and intracoronary ECGs to assess myocardial ischaemia.

RESULTS: In diabetic patients, mean (SD) coronary wedge pressure was 35 (12) mm Hg during the first balloon inflation, 39 (15) mm Hg during the second (p < 0.05 v first inflation), and 42 (17) mm Hg during the third (p < 0.05 v first inflation); in non-diabetic patients the respective values were 36 (16), 37 (16), and 37 (16) mm Hg (F = 4.73, p = 0.01). The ratio of coronary wedge pressure to mean arterial pressure in diabetic patients in the three balloon inflations was 0.33 (0.11), 0.36 (0.13), and 0.39 (0.15), respectively (p < 0.05 v the first inflation); and in non-diabetic patients it was 0.33 (0.15), 0.34 (0.15), and 0.35 (0.15) (F = 1.92, p = 0.15). In the diabetic group the response was independent of the type of treatment. No difference between diabetic and non-diabetic patients was observed in the normal reduction of myocardial ischaemia on repeated balloon inflations.

CONCLUSIONS: Type II diabetes does not prevent the recruitment of collateral vessels and the normal reduction of myocardial ischaemia on repeated balloon inflations during coronary angioplasty in single vessel disease, regardless of the type of antidiabetic treatment.

Am J Cardiol, 2002 ;89(3):262-7

Relation of coronary artery disease and cerebrovascular disease with atherosclerosis of the thoracic aorta in the general population.


The association between clinical coronary artery disease, cerebrovascular disease, and aortic atherosclerosis has not been examined in the general population. Transesophageal echocardiography was performed in 581 subjects, a random sample of the Olmsted County (Minnesota) population aged >/=45 years, participating in the Stroke Prevention: Assessment of Risk in a Community (SPARC) study. The frequency and severity of atherosclerosis of the thoracic aorta were determined in the population and the association between clinical coronary artery disease, cerebrovascular disease, and aortic atherosclerosis was examined. Previous myocardial infarction, angina pectoris, and coronary artery bypass surgery were significantly associated with aortic atherosclerosis, adjusting for age and gender (p </=0.01). Among subjects with atherosclerosis, these
manifestations were associated with complex atherosclerosis (plaques >4-mm thick, ulcerated plaques, or mobile debris), adjusting for age and gender (p <0.05). Age, smoking, pulse pressure, previous myocardial infarction (odds ratio [OR] 4.67; 95% confidence interval [CI] 1.42 to 15.40), and coronary artery bypass surgery (OR 5.12; 95% CI 1.01 to 26.01) were independently associated with aortic atherosclerosis. Among subjects with atherosclerosis, age, smoking, pulse pressure, hypertension treatment, and coronary artery disease (OR 2.50; 95% CI 1.18 to 5.30) were independently associated with complex atherosclerosis. Weak associations were observed between previous ischemic stroke, transient ischemic attack, and aortic atherosclerosis, associations that were not significant after age- and gender-adjustment (p >0.2). Thus, coronary artery disease is strongly associated with aortic atherosclerosis and complex atherosclerosis in the general population. Cerebrovascular disease is weakly associated with aortic atherosclerosis, thereby questioning the overall importance of aortic atherosclerosis in the pathogenesis of cerebrovascular events in the general population.

Circulation, 2002;105(7):810-5

Fibrillin-1 genotype is associated with aortic stiffness and disease severity in patients with coronary artery disease.

Medley TL, Cole TJ, Gatzka CD, Wang WY, Dart AM, Kingwell BA.

BACKGROUND: Elevated pulse pressure is associated strongly with adverse cardiovascular outcome; however, the genetic basis of this condition is unknown. This study examined whether genotypic variation in the extracellular matrix protein fibrillin-1, the Marfan gene, was associated with aortic stiffening and therefore could contribute to cardiovascular risk associated with pulse pressure elevation in coronary disease. METHODS AND RESULTS: Patients (n=145; 113 men), 62+/-9 years of age (mean+/SD), with angiographically confirmed coronary disease, were studied. Carotid applanation tonometry was used to assess central blood pressures, and in conjunction with Doppler velocimetry, to assess aortic input and characteristic impedance. Fibrillin-1 genotype was characterized by a variable nucleotide tandem repeat and 2 single-nucleotide polymorphisms. The variable nucleotide tandem repeat was a good predictor of underlying haplotypes with 3 genotypes (2-2, 2-4, and 2-3) accounting for 86% of the population. The 2-3 genotype had higher input impedance (P=0.002), characteristic impedance (P=0.005), and carotid pulse pressure (P=0.002) compared with the 2-2 and 2-4 genotypes. Disease severity assessed by previous angioplasties and the number of patients with a stenosis >90% was also greater in the 2-3 genotype. Furthermore, in a multivariate analysis, fibrillin-1
genotype and central pulse pressure were independent of conventional risk factors in determining coronary disease severity. There was no difference in age, sex ratio, body mass index, smoking status, cholesterol level, or medication among the 3 genotypes. CONCLUSIONS: Although a causative link has not been shown, these data are consistent with an important role for fibrillin-1 genotype in cardiovascular risk associated with large-artery stiffening and pulse pressure elevation in individuals with coronary disease.

Circulation, 2002;105(7):800-3

Risk of myocardial infarction and angina in patients with severe peripheral vascular disease: predictive role of C-reactive protein.


BACKGROUND: Patients undergoing revascularization procedures for peripheral vascular disease (PVD) have a greatly increased risk for coronary artery disease (CAD) that is predicted only partly by clinical data and cardiovascular risk factors. We investigated whether the prognostic assessment in PVD patients could be improved by preoperative measurements of C-reactive protein (CRP). METHODS AND RESULTS: We assessed clinical and risk factors profiles, Eagle clinical scores, and preoperative CRP serum levels in 51 patients with PVD at Fontaine-Leriche stages II to IV without severe rest ventricular dysfunction or ischemia. During 24 months of follow-up, 17 patients (34%) had fatal (11) or nonfatal (6) myocardial infarction (MI). With univariate logistic regression analysis, only previous history of CAD, Eagle score, and CRP were independently related to MI. At multivariate logistic regression analysis, only CRP values in the upper tertile (<9 mg/L) were significantly associated with MI (P<0.05) and identified 65% of cases. CONCLUSIONS: The high incidence of MI in patients with PVD severe enough to require revascularization is strongly predicted by preprocedural measurements of serum CRP, independent of previous CAD, Eagle score index, and traditional cardiovascular risk factors. These patients may benefit from therapy modulating the inflammatory response.

Am Heart J, 2002;143(2):277-82

Fibrinogen: associations with cardiovascular events in an outpatient clinic.
Acevedo M, Foody JM, Pearce GL, Sprecher DL.

BACKGROUND: Fibrinogen, known to influence the coagulation process, is an independent risk factor for coronary artery disease (CAD). However, its association with myocardial infarction (MI) and its predictive potential for short-term mortality, in an ongoing clinical practice, has not been characterized. OBJECTIVES: In a high-risk outpatient practice we sought to demonstrate whether baseline fibrinogen levels related to MI rather than CAD alone, and whether baseline serum fibrinogen levels predicted mortality over a short-term follow-up. METHODS AND RESULTS: From a total of 2126 patients with baseline fibrinogen measurements (mean age, 56 +/- 12 years, 35% female), 1187 patients with CAD (n = 606 with MI) and 939 patients without CAD were evaluated in an active preventive cardiology unit of a large city hospital. Logistic regression models were used to determine the association of fibrinogen with differing CAD presentations. Fibrinogen quartile showed a significant correlation with CAD both univariately and after adjustment for Framingham risk score (odds ratio [OR] = 1.22, P <.001). Fibrinogen levels were significantly associated with the presence of CAD and history of MI (adjusted OR = 1.25, P =.001). Fibrinogen did not show a significant association to CAD when MI was not considered in the analysis (OR = 1.01, P =.82). In this same clinical cohort, after a mean follow-up of 24 +/- 13 months, 41 patients had died. Consistent with the observed association with MI, fibrinogen quartile showed a graded independent relation to mortality in a cohort of both men and women (hazard ratio = 1.81, P <.001). CONCLUSIONS: In the clinical setting of an outpatient clinic, fibrinogen was directly associated with the presence of MI and was revealed to be an independent short-term predictor of mortality.

Am Coll Cardiol, 2002 ;39(5):834-40

The impact of body mass index on short- and long-term outcomes inpatients undergoing coronary revascularization. insights from the bypass angioplasty revascularization investigation (BARI).

Gurm HS, Whitlow PL, Kip KE.

We sought to investigate the impact of body mass index (BMI) on short- and long-term outcomes after initial revascularization with percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG).Equivocal results exist on the impact of BMI on the risk of in-hospital complications after
PTCA or CABG, and no long-term mortality data exist from a large series of revascularized patients. From the randomized series and observational registry of the Bypass Angioplasty Revascularization Investigation (BARI), 2,108 patients who had PTCA and 1,526 patients who had CABG were evaluated by taking their BMI at study entry. They were classified as follows: low (<20 kg/m²), normal (20 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class I obese (30 to 34.9 kg/m²) and class II/III obese (greater-than-or-equal35 kg/m²). In-hospital complications and short- and long-term mortalities were compared between levels of BMI within each mode of initial revascularization. Among patients who had PTCA, each unit increase in BMI was associated with a 5.5% lower adjusted risk of a major in-hospital event (death, myocardial infarction, stroke, coma); among patients who had CABG, no difference in the in-hospital outcome was observed according to BMI. In contrast, BMI was not associated with five-year mortality in the PTCA group; among the CABG group, adjusted relative risks of five-year cardiac mortality according to levels of BMI were 0.0 (low), 1.0 (normal), 2.02 (overweight), 3.16 (class I obese) and 4.85 (class II/III obese) (linear p < 0.001). Body mass index appears to have a differential impact on short- and long-term outcomes after coronary revascularization. These results underscore the need for further research to identify factors responsible for the apparent short-term protective effect of a higher BMI in patients undergoing PTCA and to study the impact of weight reduction on the long-term survival of obese patients undergoing CABG.

Am J Cardiol, 2002;89(5):511-7

Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry).


There is conflicting information about gender differences in presentation, treatment, and outcome after acute ST elevation myocardial infarction (STEMI) in the era of thrombolytic therapy and primary percutaneous coronary intervention. From June 1994 to January 1997, we enrolled 6,067 consecutive patients with STEMI admitted to 54 hospitals in southwest Germany in the Maximal Individual TheRapy of Acute myocardial infarction (MITRA), a community-based registry. Women were 9 years older than men, more often had hypertension, diabetes mellitus, and congestive heart failure, and had a history of previous myocardial infarction less often. Women had a longer prehospital delay (45 minutes), had anterior wall infarction more often (odds ratio [OR] 1.21; 95% confidence interval [CI] 1.08 to 1.36), and received reperfusion therapy less
often (OR 0.83; 95% CI 0.74 to 0.94). The percentage of patients who were eligible for thrombolysis and received no reperfusion was higher in women (OR 1.7; 95% CI 1.56 to 1.89). Women had recurrent angina (OR 1.45; 95% CI 1.23 to 1.71) and congestive heart failure (OR 1.26; 95% CI 1.01 to 1.56) more often. There was a trend toward a higher hospital mortality in women (age-adjusted OR 1.16, 95% CI 0.99 to 1.35; multivariate OR 1.21, 95% CI 0.96 to 1.51), but there was no gender difference in long-term mortality after multivariate analysis (age-adjusted OR 0.95, 95% CI 0.78 to 1.15; multivariate OR 0.93, 95% CI 0.72 to 1.19). Thus, women with STEMI receive reperfusion therapy less often than men. They experience recurrent angina and congestive heart failure more often during their hospital stay. The age-adjusted long-term mortality is not different between men and women, but there is a trend for a higher short-term mortality in women.

Circulation, 1996;94:1818-1825

 Coronary Angioplasty in Diabetic Patients
The National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry

Kevin E. Kip, MSPH; David P. Faxon, MD; Katherine M. Detre, MD, DrPH; Wanlin Yeh, MS; Sheryl F. Kelsey, PhD; Jesse W. Currier, MD; for the Investigators of the NHLBI PTCA Registry

Background. Patients with diabetes mellitus are at increased risk of cardiovascular disease. To date, the baseline status and subsequent outcomes of diabetic coronary angioplasty (percutaneous transluminal coronary angioplasty, or PTCA) patients with advanced atherosclerotic disease and with procedures performed across North America have not been well characterized.

Methods and Results. Data on baseline clinical and angiographic characteristics and short- and long-term outcomes of 281 diabetic and 1833 nondiabetic PTCA patients in the multicenter National Heart, Lung, and Blood Institute 1985-1986 PTCA Registry were analyzed. Diabetic patients were older, were more likely to be female, and had more comorbid baseline conditions, triple-vessel disease, and atherosclerotic lesions. Angiographic success and completeness of revascularization did not differ significantly, yet diabetic patients experienced more in-hospital death (women) and nonfatal myocardial infarction. Nine-year mortality was twice as high in diabetic patients (35.9% versus 17.9%). Similarly, 9-year rates of nonfatal myocardial infarction (29.0% versus 18.5%), bypass surgery (36.7% versus 27.4%), and repeat PTCA (43.7% versus 36.5%) were higher in diabetics than in nondiabetics. In multivariate analysis, diabetes remained a significant predictor of decreased 9-year survival and other untoward events.
Conclusions. Compared with nondiabetic PTCA patients, diabetic patients have more extensive and diffuse atherosclerotic disease. Despite similar probability of angiographic success, diabetic patients are more likely to suffer in-hospital death (women) and nonfatal myocardial infarction. Long-term survival and freedom from myocardial infarction and coronary revascularization is also reduced in diabetic PTCA patients. Whether PTCA or coronary bypass surgery is more suitable for these patients is currently under investigation.

Summary


A Comparison of Continuous Infusion of Alteplase with Double-Bolus Administration for Acute Myocardial Infarction

The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators

Background. Accelerated infusion of alteplase (tissue plasminogen activator) over a period of 90 minutes induces more rapid lysis of coronary-artery thrombi than a 3-hour infusion. With two bolus doses of alteplase, further shortening the duration of administration, complete reperfusion was achieved in more than 85 percent of the patients in initial angiographic studies. We tested the hypothesis that double-bolus alteplase is at least as effective as accelerated infusion.

Methods. In 398 hospitals, 7169 patients with acute myocardial infarction were randomly assigned to weight-adjusted, accelerated infusion of 100 mg of alteplase or to a bolus of 50 mg of alteplase over a period of 1 to 3 minutes followed 30 minutes later by a second bolus of 50 mg (or 40 mg for patients who weighed less than 60 kg). The primary end point was death from any cause at 30 days. The trial was stopped prematurely because of concern about the safety of the double-bolus injection. Results. Thirty-day mortality was higher in the double-bolus alteplase group than in the accelerated-infusion group: 7.98 percent as compared with 7.53 percent. The absolute difference was 0.44 percent, with a one-sided 95 percent upper boundary of 1.49 percent, which exceeded the prespecified upper limit of 0.40 percent to indicate equivalence in 30-day mortality between the two regimens. The respective rates of any stroke and of hemorrhagic stroke were 1.92 and 1.12 percent after double-bolus alteplase, as compared with 1.53 and 0.81 percent after an accelerated infusion of alteplase (P = 0.24 and P = 0.23,
respectively). Conclusions. Double-bolus alteplase was not shown to be equivalent, according to the prespecified criteria, to accelerated infusion with regard to 30-day mortality. There was also a slightly higher rate of intracranial hemorrhage with the double-bolus method. Therefore, accelerated infusion of alteplase over a period of 90 minutes remains the preferred regimen.

Circulation 1997 96: 2551-2556

Relationship Between Diabetes Mellitus and Long-term Survival After Coronary Bypass and Angioplasty


Background Recent subgroup analyses of randomized trials have suggested that percutaneous intervention in diabetic patients with multivessel disease results in higher mortality than coronary artery bypass graft surgery (CABG). We studied the relationship between diabetes and survival after revascularization in a large prospective cohort of patients with multivessel coronary artery disease.

Methods and Results By analyzing data for 3220 patients (24% diabetic) with symptomatic two- or three-vessel coronary disease who were undergoing percutaneous transluminal coronary angioplasty (PTCA) or CABG at Duke University Medical Center between 1984 and 1990, we found that at 5 years, unadjusted survival in the group of patients undergoing CABG was 74% in diabetics and 86% in nondiabetics. Similarly, 5-year survival among PTCA patients was 76% in diabetics and 88% in patients without diabetes. After adjustment for baseline characteristics, diabetic patients receiving either PTCA or CABG had significantly poorer survival than nondiabetics (X²=43.56, P<0.001). Unlike previous studies, however, there was no significant differential effect of diabetes on outcome between patients treated with PTCA and those treated with CABG (X²=0.01, P=0.91).

Conclusions Although diabetes was associated with a worse long-term outcome after both PTCA and CABG in patients with multivessel coronary artery disease, the effect of diabetes on prognosis was similar in both treatment groups. Thus, our findings support the concept that the choice of initial revascularization strategy should not be based exclusively on a history of diabetes but rather should rely on other factors, such as angiographic suitability and clinical status.
Objectives. We assessed the safety and efficacy of stent placement in patients with poorly controlled hypertension and renal artery stenoses, which are difficult to treat with balloon angioplasty alone.

Background. Preliminary experience with stent placement suggests improved results over balloon angioplasty alone in patients with atherosclerotic renal artery stenosis.

Methods. Balloon-expandable stents were placed in 100 consecutive patients (133 renal arteries) with hypertension and renal artery stenosis. Sixty-seven of the patients had unilateral renal artery stenosis treated and 33 had bilateral renal artery stenoses treated with stents placed in both renal arteries.

Results. Angiographic success, as determined by quantitative angiography, was obtained in 132 (99%) of 133 lesions. Early clinical success was achieved in 76% of the patients. Six months after stent placement, the systolic blood pressure was reduced from 173 ± 25 to 147 ± 23 mm Hg (p < 0.001); the diastolic pressure from 88 ± 17 to 76 ± 12 mm Hg (p < 0.001); and the mean number of antihypertensive medications per patient from 2.6 ± 1 to 2.0 ± 0.9 (p < 0.001). Angiographic follow-up at a mean of 8.7 ± 5.0 months in 67 patients revealed restenosis (>50% diameter narrowing) in 15 (19%) of 80 stented vessels.

Conclusions. Renal artery stenting is an effective treatment for renovascular hypertension, with a low angiographic restenosis rate. Stent placement appears to be a very attractive therapy in patients with lesions difficult to treat with balloon angioplasty such as renal aorto-ostial lesions and restenotic lesions, as well as after a suboptimal balloon angioplasty result.
Objectives. We assessed the acute effect of intracoronary injection of verapamil on microvascular function after primary percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction (AMI) with myocardial contrast echocardiography (MCE) in relation to functional outcomes.

Background. Recent clinical studies have documented the potential of verapamil for possible increase in coronary blood flow after primary PTCA.

Methods. Forty patients with a first AMI were randomly assigned to the verapamil group (n = 20) or the control group (n = 20). In the verapamil group, verapamil (0.5 mg) was injected into the infarct-related artery shortly after PTCA, followed by the oral administration. We performed MCE with an intracoronary injection of sonicated microbubbles before and after verapamil. To assess microvascular integrity, we determined the baseline-subtracted peak intensity in the risk area and the ratio of the no reflow zone plus the low reflow zone to the risk area (low reflow ratio). We determined the average wall motion score (dyskinesia/akinesia = 3; normal = 0) in the risk area on the day of AMI and a mean of 24 days later.

Results. The low reflow zone was observed shortly after PTCA in 14 verapamil group patients, and the low reflow ratio decreased after verapamil (0.39 ± 0.23 vs. 0.29 ± 0.17 [mean ± SD], p < 0.05). Peak intensity significantly (p < 0.05) increased from 6 ± 5 to 12 ± 6 after verapamil. The reduction in wall motion score from the acute (day -1) to the late stage (day -24) was significantly greater in the verapamil group than in the control group (0.7 ± 0.8 vs. 0.2 ± 1.3, respectively, p <0.05).

Conclusions. Intracoronary administration of verapamil after primary PTCA can attenuate microvascular dysfunction and thereby augment myocardial blood flow in patients with AMI, leading to better functional outcome than with PTCA alone.

Effect of Pravastatin on Angiographic Restenosis After Coronary Balloon Angioplasty

Michel E. Bertrand, MD, FACC, Eugene P. McFadden, MRCP, FACC, Jean-Charles Fruchart, PhD, Eric Van Belle, MD, Philippe Commeau, MD, Gilles Grollier, MD, Jean-Pierre Bassand, MD, Jacques Machecourt, MD, Jean Cassagnes, MD, Jean-Marie Mossard, MD, Andre Vacheron, MD, Alain Castaigne, MD, Nicolas Danchin, MD, FACC, Jean-Marc Lablanche, MD, FACC for the PREDICT Trial Investigators
Objectives. This study sought to determine whether pravastatin affects clinical or angiographic restenosis after coronary balloon angioplasty.

Background. Experimental data and preliminary clinical studies suggest that lipid-lowering drugs might have a beneficial effect on restenosis after coronary angioplasty.

Methods. In a multicenter, randomized, double-blind trial, 695 patients were randomized to receive pravastatin (40 mg/day) or placebo for 6 months after successful balloon angioplasty. All patients received aspirin (100 mg/day). The primary angiographic end point was minimal lumen diameter (MLD) at follow-up, assessed by quantitative coronary angiography. A sample size of 313 patients per group was required to demonstrate a difference of 0.13 mm in MLD between groups (allowing for a two-tailed alpha error of 0.05 and a beta error of 0.20). To allow for incomplete angiographic follow-up (estimated lost to follow-up rate of 10%), 690 randomized patients were required. Secondary end points were angiographic restenosis rate (restenosis assessed as a categorical variable, >50% stenosis) and clinical events (death, myocardial infarction, target vessel revascularization).

Results. At baseline, clinical, demographic, angiographic and lipid variables did not differ significantly between groups. In patients treated with pravastatin, there was a significant reduction in total and low density lipoprotein cholesterol and triglyceride levels and a significant increase in high density lipoprotein cholesterol levels. At follow-up the MLD (mean ± SD) was 1.47 ± 0.62 mm in the placebo group and 1.54 ± 0.66 mm in the pravastatin group (p = 0.21). Similarly, late loss and net gain did not differ significantly between groups. The restenosis rate (recurrence >50% stenosis) was 45.8% in the placebo group and 39.2% in the pravastatin group (p = 0.26). Clinical restenosis did not differ significantly between groups.

Conclusions. Although pravastatin has documented efficacy in reducing clinical events and angiographic disease progression in patients with coronary atherosclerosis, this study shows that it has no effect on angiographic outcome at the target site 6 months after coronary angioplasty.

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B-Mode Ultrasound Assessment of Pravastatin Treatment Effect on Carotid and Femoral Artery Walls and Its Correlations With Coronary Arteriographic Findings: A Report of the Regression Growth Evaluation Statin Study (REGRESS)

Objectives. In this B-mode ultrasound study we assessed pravastatin treatment effects on carotid and femoral artery walls and investigated the correlations between the state and evolution of peripheral and coronary atherosclerosis.

Background. The Regression Growth Evaluation Statin Study (REGRESS) was an 11-center, 2-year, double-blind, placebo-controlled, prospective study of 885 men with coronary artery disease (CAD) (total cholesterol 4 to 8 mmol/liter). The study primarily investigated pravastatin treatment effects on the coronary lumen. This report focuses on the 255 patients who participated in the REGRESS ultrasound study.

Methods. Carotid and femoral artery walls were imaged at baseline and at 6, 12, 18 and 24 months. Pravastatin treatment effect was defined as the difference in progression of the combined intima-media thicknesses (IMT) between treatment groups.

Results. Pravastatin treatment effects were highly significant (combined IMT: p = 0.0085; combined far wall IMT: p < 0.0001; common femoral artery far wall IMT: p = 0.004). Correlations between the IMTs of the arterial wall segments ranged from -0.17 to 0.81. Baseline correlations between IMT and percent coronary lumen stenoses ranged from 0.23 to 0.36. Baseline IMT correlated with the mean coronary segment diameter (r = -0.32, p = 0.001) and minimal coronary obstruction diameter (r = -0.27, p = 0.005). There were no individual correlations between IMT and coronary lumen variables (p > 0.30).

Conclusions. Pravastatin treatment effects on carotid and femoral artery walls were observed. B-mode ultrasound imaging studies of peripheral arterial walls could not describe the state and evolution of the coronary lumen in the individual patient, but proved to be a highly suitable tool for the assessment of antiatherosclerotic properties of agents.

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The effect of hormone replacement therapy alone and in combination with simvastatin on plasma lipids of hypercholesterolemic postmenopausal women with coronary artery disease

Eftihia Sbarouni, Zenon S. Kyriakides, Dimitrios Th Kremastinos

Objectives. This study sought to compare hormone replacement therapy (HRT), simvastatin and their
combination in the management of hypercholesterolemia in postmenopausal women with coronary artery disease (CAD).

Background. Lipid-lowering therapy reduces mortality in hypercholesterolemic women with CAD. In postmenopausal women HRT seems to increase survival, particularly those with ischemic heart disease, and this is partly due to changes in lipid levels.

Methods. We studied 16 postmenopausal women with CAD and fasting total cholesterol <200 mg/dl and low-density lipoprotein (LDL) cholesterol <130 mg/dl. We compared HRT (0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate daily) with simvastatin (20 mg daily) and their combination in a randomized, crossover, placebo-controlled study. Each treatment period was 8 weeks long with a 4-week washout interval between treatments.

Results. Simvastatin, HRT and their combination significantly reduced total and LDL cholesterol by 35%, 13%, and 33% and 45%, 20%, and 46%, respectively, compared to placebo (p < 0.001). However, simvastatin and the combination was superior to HRT (p < 0.001), and none of our patients had total cholesterol <180 mg/dl and LDL cholesterol <100 mg/dl on HRT alone. High-density lipoprotein cholesterol was not significantly affected by any of the active treatments, and triglycerides were lower during simvastatin therapy compared to placebo (p < 0.01). Apolipoprotein B was significantly reduced by simvastatin, alone and combined with HRT, by 39% and 35%, respectively, compared to placebo (p < 0.001). Alone and in combination with simvastatin, HRT significantly increased apolipoprotein A-I by 11% and 12%, respectively, compared to placebo (p < 0.05) and decreased lipoprotein (a) by 23% and 33%, respectively, compared to placebo (p < 0.05), whereas simvastatin had no significant effect on either of these parameters.

Conclusions. In hypercholesterolemic postmenopausal women with CAD, HRT exerts beneficial effects on plasma lipids but the levels currently recommended for secondary prevention are not achieved. Hormone replacement therapy combined with simvastatin is well tolerated and extremely effective, as the two therapies seem to be additive.


Trends in the Incidence of Myocardial Infarction and in Mortality Due to Coronary Heart Disease, 1987 to 1994

Wayne D. Rosamond, Lloyd E. Chambless, Aaron R. Folsom, Lawton S. Cooper, David E. Conwill, Limin Clegg, Chin-Hua Wang, Gerardo Heiss
Background and Methods. To clarify the determinants of contemporary trends in mortality from coronary heart disease (CHD), we conducted surveillance of hospital admissions for myocardial infarction and of in-hospital and out-of-hospital deaths due to CHD among 35- to 74-year-old residents of four communities of varying size in the United States (a total of 352,481 persons in 1994). Between 1987 and 1994, we estimate that there were 11,869 hospitalizations for myocardial infarction (on the basis of 8572 hospitalizations sampled) and 3407 fatal coronary events (3023 sampled).

Results. The largest average annual decrease in mortality due to CHD occurred among white men (change in mortality, -4.7 percent; 95 percent confidence interval, -2.2 to -7.1 percent), followed by white women (-4.5 percent; 95 percent confidence interval, -0.7 to -8.2 percent), black women (-4.1 percent; 95 percent confidence interval, -10.3 to +2.5 percent), and black men (-2.5 percent; 95 percent confidence interval, -6.9 to +2.2 percent). Overall, in-hospital mortality from CHD fell by 5.1 percent per year, whereas out-of-hospital mortality declined by 3.6 percent per year. There was no evidence of a decline in the incidence of hospitalization for a first myocardial infarction among either men or women; in fact, such hospital admissions increased by 7.4 percent per year (95 percent confidence interval, 0.5 to 14.8 percent) among black women and 2.9 percent per year (95 percent confidence interval, -3.6 to +9.9 percent) among black men. Rates of recurrent myocardial infarction decreased, and survival after myocardial infarction improved.

Conclusions. From 1987 to 1994, we observed a stable or slightly increasing incidence of hospitalization for myocardial infarction. Nevertheless, there were significant annual decreases in mortality from CHD. The decline in mortality in the four communities we studied may be due largely to improvements in the treatment and secondary prevention of myocardial infarction.


Value of Serial Troponin T Measures for Early and Late Risk Stratification in Patients With Acute Coronary Syndromes


Background-The baseline cardiac troponin T (cTnT) level strongly predicts short-term mortality in acute coronary syndromes, but the added value of later measures to predict short- and long-term outcome and in the
context of baseline clinical characteristics is unclear.

Methods and Results-Relations between baseline, peak, and 8- and 16-hour (late) cTnT results and outcomes were assessed in 734 patients in a GUSTO-IIa substudy. Proportional-hazards models assessed the prognostic information gained from late cTnT when added to a mortality model containing the baseline cTnT result and clinical factors. At baseline, 260 patients were cTnT-positive (>0.1 ng/mL), 323 became positive later, and 151 remained negative (0.1 ng/mL). Mortality at 30 days was 10% in the baseline-positive group, 5% in late-positive patients, and 0% in negative patients. After adjustment for baseline characteristics, any positive cTnT result predicted 30-day mortality (baseline, 2=8.96, P=0.0113; 8-hour, 2=6.51, P=0.0107; 16-hour, 2=8.40, P=0.0038). Both the 8- and the 16-hour results added to the strength of the baseline result (baselinehour, 2=12.04, P=0.0072; baselinehour, 2=13.52, P=0.0036). Only age and ST-segment elevation were stronger predictors of 30-day mortality than baseline cTnT; results were similar for prediction of 1-year mortality. Most of the mortality difference between cTnT-positive and -negative patients occurred within the first 30 days. Conclusions-The cTnT level is a strong, independent predictor of short-term outcome in acute coronary syndromes. The addition of later samples to a baseline level is useful to evaluate the risk of serious cardiac events.

The American Journal of Cardiology, 82:7:845-850

Comparison of the prognostic value of C-Reactive protein and troponin I in patients with unstable angina pectoris

Hakim Benamer, Philippe Gabriel Steg, Joelle Benessiano, Eric Vicaut, Cedric J. Gaultier, Albert Boccara, Pierre Aubry, Pascale Nicaise, Eric Brochet, Jean-Michel Julliard, Dominique Himbert, Patrick Assayag

This study assessed the prognostic value of cardiac troponin I (cTnI) and C-reactive protein (CRP) in unstable angina, and specifically in patients with angiographically proven coronary artery disease. These biochemical parameters, which are related to myocardial injury or to systemic inflammation, may help in short-term risk stratification of unstable angina. We prospectively studied 195 patients with unstable angina, 100 of whom had angiographically proven coronary artery disease (with normal creatine kinase [CK] and CK-MB mass). Serum concentrations of cTnI (N <0.4 ng/ml) and CRP (N <3 mg/L) were measured at admission, 12, and 24 hours later. The rate of in-hospital major adverse cardiac events (death, myocardial infarction, or emergency revascularization) was higher in patients with increased cTnI within the first 24 hours, regardless of the results of coronary angiography (23% vs 7%; p <0.001). Conversely, events occurred at similar rates in patients with or
without increased CRP. In patients with angiographic evidence of coronary artery disease, multivariate analysis showed that increased cTnI within 24 hours of admission (35 patients) was an independent predictor of major adverse cardiac events (odds ratio 6.7, range 1.7 to 27.3), but not cTnI levels at admission and CRP at 0, 12, and 24 hours. Thus, both in unselected patients with unstable angina and in patients with angiographically proven coronary artery disease, increased cTnI within 24 hours of admission, but not CRP, is a predictor of in-hospital clinical outcome. We also found a temporal link between cTnI increase and late elevation of CRP, suggesting that systemic inflammation may partially be a consequence of myocardial injury.

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Treating patients with documented atherosclerosis to national cholesterol education program-recommended low-density-lipoprotein cholesterol goals with atorvastatin, fluvastatin, lovastatin and simvastatin

Alan S. Brown, Rebecca G. Bakker-Arkema, Laurence Yellen, Robert W. Henley, Jr., Richard Guthrie, Cam F. Campbell, Michael Koren, William Woo, Richard McLain, Donald M. Black

Objectives. This study compared the efficacy and safety of atorvastatin, fluvastatin, lovastatin, and simvastatin in patients with documented atherosclerosis treated to U.S. National Cholesterol Education Program (NCEP) recommended low-density-lipoprotein (LDL) cholesterol concentration (100 mg/dl [2.59 mmol/liter]).

Background. For patients with advanced atherosclerosis, NCEP recommends lipid-lowering drug therapy if LDL cholesterol remains $\geq$130 mg/dl (3.36 mmol/liter).

Methods. A total of 318 men or women with documented atherosclerosis and LDL cholesterol $\geq$130 mg/dl (3.36 mmol/liter) and $\leq$250 mg/dl (6.5 mmol/liter), and triglycerides 400 mg/dl (4.5 mmol/liter) participated in this 54-week, multicenter, open-label, randomized, parallel-group, active-controlled, treat-to-target study. Patients were titrated at 12-week intervals until the LDL cholesterol goal was reached. Number of patients reaching target LDL cholesterol levels and dose to reach target were evaluated.

Results. At the starting doses, atorvastatin 10 mg produced significantly greater decreases ($p < 0.05$) in plasma LDL cholesterol than the other treatments. Subsequently, the percentage of patients reaching goal at the starting dose was 32% for atorvastatin, 1% for fluvastatin, 10% for lovastatin and 22% for simvastatin. Atorvastatin-treated patients required a lower median dose than other treatments. Median doses at week 54 with the last available visit carried forward were atorvastatin 20 mg/day, fluvastatin 40 mg/day + colestipol 20 g/day, lovastatin 80 mg/day, simvastatin 40 mg/day.
Conclusions. A significantly greater number (p < 0.05) of patients with confirmed atherosclerosis treated with atorvastatin reached the target LDL cholesterol concentration at the starting dose than patients treated with fluvastatin or lovastatin, and significantly fewer (p < 0.05) patients treated with atorvastatin required combination therapy with colestipol to achieve target LDL cholesterol concentrations than all other statins tested.

The American Journal of Cardiology, 82:10B:18-21

Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China Study

T. Colin Campbell, Banoo Parpia, Junshi Chen

Investigators collected and analyzed mortality data for >50 diseases, including 7 different cancers, from 65 counties and 130 villages in rural mainland China. Blood, urine, food samples, and detailed dietary data were collected from 50 adults in each village and analyzed for a variety of nutritional, viral, hormonal, and toxic chemical factors. In rural China, fat intake was less than half that in the United States, and fiber intake was 3 times higher. Animal protein intake was very low, only about 10% of the US intake. Mean serum total cholesterol was 127 mg/dL in rural China versus 203 mg/dL for adults aged 20-74 years in the United States. Coronary artery disease mortality was 16.7-fold greater for US men and 5.6-fold greater for US women than for their Chinese counterparts. The combined coronary artery disease mortality rates for both genders in rural China were inversely associated with the frequency of intake of green vegetables and plasma erythrocyte monounsaturated fatty acids, but positively associated with a combined index of salt intake plus urinary sodium and plasma apolipoprotein B. These apolipoproteins, in turn, are positively associated with animal protein intake and the frequency of meat intake and inversely associated with plant protein, legume, and light-colored vegetable intake. Rates of other diseases were also correlated with dietary factors. There was no evidence of a threshold beyond which further benefits did not accrue with increasing proportions of plant-based foods in the diet.

Circulation, 1998; 98: 851-855
Physician Noncompliance With the 1993 National Cholesterol Education Program (NCEP-ATPII) Guidelines

Joseph P. Frolkis, Stephen J. Zyzanski, Jonathan M. Schwartz, and Pamela S. Suhan

Background-We sought to determine the frequency with which physicians follow National Cholesterol Education Program (NCEP-ATPII) guidelines in screening for cardiovascular risk factors and treating hyperlipidemia.

Methods and Results-We conducted a retrospective chart review on randomly sampled charts of 225 patients admitted to the coronary care unit between January and June 1996. The main outcome measures were rates of physician screening for coronary heart disease risk factors; rates of counseling for cigarette cessation, diet, and exercise; and extent of use of NCEP algorithms for obtaining LDL cholesterol values and treating hypercholesterolemia. Screening rates for interns (who performed best) were: cigarette use (89%), known coronary heart disease (74%), hypertension (68%), hyperlipidemia (59%), family history (56%), diabetes (37%), postmenopausal hormone therapy (11%), and premature menopause (1%). Four percent of smokers were counseled to quit, 14% of patients were referred to dietitians, and 1% were encouraged to exercise. A full lipid panel was obtained in 50% of patients in whom it was indicated on the basis of NCEP criteria. Patients were more likely to receive lipid-lowering treatment if NCEP criteria indicated that they should, but 36% of hospitalized patients and 46% of patients who should have been treated on discharge were not.

Conclusions-Physicians are poorly compliant with NCEP guidelines for risk factor assessment and counseling, even in patients at high risk for coronary heart disease. Physicians follow NCEP-ATPII algorithms for obtaining an LDL value, a key step in evaluating the need for treatment, only 50% of the time. NCEP criteria seem to influence the decision to initiate lipid-lowering therapy, but significant numbers of eligible patients remain untreated.


Very Early Risk Stratification Using Combined ECG and Biochemical Assessment in Patients With Unstable Coronary Artery Disease (A Thrombin Inhibition in Myocardial Ischemia [TRIM] Substudy)

Lene Holmvang, Michael S. Luscher, Peter Clemmensen, Kristian Thygesen, and Peer Grande
Background-The diagnostic capability of troponin T (TnT), troponin I (TnI), myoglobin, and creatine kinase (CK)-MB mass for detection of myocardial injury seems evident. Newer studies have found these sensitive markers to carry independent prognostic information in patients with unstable coronary artery disease as well. ST-segment depression in the admission ECG is known to be an important indicator of poor outcome in these patients. The present study investigates the prognostic capacities of the ECG in combination with biochemical admission measurements in 516 patients admitted to hospital with unstable coronary artery disease.

Methods and Results-Baseline ECG recordings and blood samples were collected for central analysis. The patients were followed up for 30 days, and predefined end points, ie, death, myocardial infarction, and refractory angina, were registered as end points. By univariate analysis, ST-segment depression, inverted T waves in ≥5 leads, TnT ≥0.1 μg/L, TnI ≥0.5 μg/L, myoglobin 40 μg/L, female sex, and age ≥65 years were predictors of death and myocardial infarction at 30 days. By multivariate analysis, female sex, ST-segment depression at randomization, or inverted T-waves in ≥5 leads were the only independent predictors of death or myocardial infarction. On the basis of baseline ECG ST-T changes and CK-MB mass/TnT/TnI/myoglobin levels, the patients were divided into 3 subgroups at high (14% event rate), intermediate (6%), and low (3%) risk of early death/myocardial infarction.

Conclusions-The present study found the combination of baseline values of TnT, TnI, CK-MB mass, and ST-T changes in the ECG to be effective for early risk stratification in patients with unstable coronary artery disease.

JAMA, 1998;280:605-613

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley; Deborah Grady; Trudy Bush; Curt Furberg; David Herrington; Betty Riggs; Eric Vittinghoff; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context. Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective. To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal...
women with established coronary disease.

Design. Randomized, blinded, placebo-controlled secondary prevention trial.

Setting. Outpatient and community settings at 20 US clinical centers.

Participants. A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention. Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n=1380) or a placebo of identical appearance (n=1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.

Main Outcome Measures. The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results. Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each P<.001). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).

Conclusions. During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gallbladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this treatment for the purpose of secondary prevention of CHD. However, given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue.

Journal of the American College of Cardiology, 32:2035-2042

Lipoprotein(a) and inflammation in human coronary atheroma: association with the severity of clinical
Objectives. The purpose of this study was the investigation of the in vivo role of lipoprotein(a) [Lp(a)] and inflammatory infiltrates in the human coronary atherosclerotic plaque and their correlation with the clinical syndrome of presentation.

Background. Lipoprotein(a) is an atherogenic and thrombogenic lipoprotein, and has been implicated in the pathogenesis of acute coronary syndromes. Lipoprotein(a) induces monocyte chemoattraction and smooth muscle cell activation in vitro. Macrophage infiltration is considered one of the mechanisms of plaque rupture.

Methods. This study of atherectomy specimens investigated the in vivo role of Lp(a) at different stages of the atherogenic process, and its relationship with macrophage infiltration. We examined coronary atheroma removed from 72 patients with stable or unstable angina. Specimens were stained with antibodies specific for Lp(a), macrophages (KP-1), and smooth muscle cells (alpha-actin). Morphometric analysis was used to quantify the plaque areas occupied by each of the three antigens, and their colocalization.

Results. All specimens had localized Lp(a) staining; the mean fractional area was 58.2%. Ninety percent of the macrophage areas colocalized with Lp(a) positive areas, whereas 31.3% of the smooth muscle cell areas colocalized with Lp(a) positive areas. Patients with unstable angina (n = 46) had specimens with larger mean plaque Lp(a) areas than specimens from stable angina patients (n = 26): 64.4% versus 47.7% (p = 0.004). Unstable angina patients with rest pain (n = 28) had greater mean plaque Lp(a) area than unstable angina patients with crescendo exertional pain (n = 18): 71.1% versus 52.4% (p < 0.001). Mean KP-1 area was 31.2% in unstable rest angina versus 18.3% in stable angina (p = 0.05); alpha-actin area was greater in stable (48.5%) and crescendo exertional angina (48.8%) than in rest angina (30.4%). The strongest correlation between plaque KP-1 and Lp(a) area was in unstable rest angina (r = 0.88, p < 0.001), and between alpha-actin and Lp(a) areas in the crescendo exertional angina (r = 0.62, p < 0.01).

Conclusions. Lipoprotein(a) is ubiquitous in human coronary atheroma. It is detected in larger amounts in tissue from culprit lesions in patients with unstable compared to stable syndromes, and has significant colocalization with plaque macrophages. A correlation of plaque alpha-actin and Lp(a) area suggests a role of Lp(a) in plaque growth.

The American Journal of Cardiology, 82:1489-1495
Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia

Hiroshi Mabuchi, Junji Koizumi, Masami Shimizu, Kouji Kajinami, Susumu Miyamoto, Kousei Ueda, Tadayoshi Takegoshi for the Hokuriku-FH-LDL-Apheresis Study Group

Familial hypercholesterolemia (FH) is characterized by severe hypercholesterolemia and premature coronary heart disease (CHD). The lower the plasma cholesterol level, the more likely it is that CHD can be prevented or retarded; aggressive cholesterol-lowering therapies may be indicated for FH patients with CHD. This study describes the long-term (6 years) safety and efficacy of intensive cholesterol-lowering therapies with low-density lipoprotein (LDL) apheresis in heterozygous FH patients with CHD. One hundred thirty heterozygous FH patients with CHD documented by coronary angiography had been treated by cholesterol-lowering drug therapy alone (n = 87) or LDL apheresis combined with cholesterol-lowering drugs (n = 43). Serum lipid levels and outcomes in each treatment group were compared after approximately 6 years. Both treatment groups had significant reductions in serum cholesterol, LDL cholesterol, and high density lipoprotein cholesterol levels. LDL apheresis significantly reduced LDL cholesterol levels from 7.42 ± 1.73 to 3.13 ± 0.80 mmol/L (58%) compared with group taking drug therapy, from 6.03 ± 1.32 to 4.32 ± 1.53 mmol/L (28%). With Kaplan-Meier analyses of the coronary events including nonfatal myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and death from CHD, the rate of total coronary events was 72% lower in the LDL-apheresis group (10%) than in drug therapy group (36%) (p = 0.0088). It is concluded that LDL-apheresis is effective as treatment of CHD in FH heterozygotes, and may become the therapy of choice in severe types of FH.

The American Journal of Cardiology, 1998;82:6:737-743

Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia

John R. Guyton, Anne C. Goldberg, Robert A. Kreisberg, Dennis L. Sprecher, H. Robert Superko, Christopher M. O’Connor
We performed a multicenter, open-label study to determine the long-term safety and efficacy of a new extended-release once-a-night niacin preparation, Niaspan, in the treatment of hypercholesterolemia. Niaspan, 0.5 to 3.0 g once a night at bedtime, was used alone or in combination with a statin (inhibitor of hydroxymethylglutaryl coenzyme A reductase), a bile acid sequestrant, or both. Patients included 269 hypercholesterolemic male and female adults enrolled in a 96-week study, and 230 additional adults for whom short-term safety data were available. The dosages of Niaspan attained by 269 patients were 1,000 mg (95% of patients), 1,500 mg (86%), and 2,000 mg (65%). After 48 weeks of treatment, Niaspan alone (median dose 2,000 mg) reduced low-density lipoprotein (LDL) cholesterol (18%), apolipoprotein B (15%), total cholesterol (11%), triglycerides (24%), and lipoprotein(a) (36%), and increased high-density lipoprotein (HDL) cholesterol (29%). Niaspan plus a statin lowered LDL cholesterol (32%), apolipoprotein B (26%), total cholesterol (23%), triglycerides (30%), and lipoprotein(a) (19%), and increased HDL cholesterol (26%). Reversible elevations of aspartate aminotransferase or alanine aminotransferase more than twice the normal range occurred in 2.6% of patients. One patient discontinued Niaspan because of transaminase elevations. Intolerance to flushing, leading to discontinuation of Niaspan, occurred in 4.8% of patients. The overall rate of discontinuance due to flushing in this study combined with 2 previous randomized trials was 7.3%. In the long-term treatment of hypercholesterolemia, Niaspan produced favorable changes in LDL and HDL cholesterol, triglycerides, and lipoprotein(a). Adverse hepatic effects were minor and occurred at rates similar to those reported for statin therapy.

Journal of the American College of Cardiology, 1998;32:110-116

Early endothelial dysfunction in adults at risk from atherosclerosis: different responses to L-arginine

Sara Thorne, Michael J. Mullen, Peter Clarkson, Ann E. Donald, John E. Deanfield

Objectives. We sought to examine endothelial responses to L-arginine in three groups with isolated risk factors: hypercholesterolemia, smoking and insulin-dependent diabetes mellitus (IDDM).

Background. Endothelial dysfunction occurs early in atherosclerosis, predating clinical disease. We hypothesized that the nature of endothelial injury associated with individual cardiovascular risk factors might be different and that this might affect the response to L-arginine, the substrate for endothelial nitric oxide synthase.

Methods. We studied the effects of intravenous L-arginine on brachial artery flow-mediated dilation (FMD) and glyceryl trinitrate (GTN)-mediated dilation in 36 young subjects (18 to 40 years old) without clinical
atherosclerosis: 9 each of normal control subjects, hypercholesterolemic subjects, cigarette smokers and subjects with IDDM.

Results. Baseline FMD was significantly impaired in hypercholesterolemic subjects (mean ± SD 1.7 ± 2.3%), smokers (1.6 ± 1.8%) and diabetic subjects (1.8 ± 1.5%) compared with that in control subjects (6.9 ± 3.3%, p = 0.001). The response to GTN was not significantly different between the subjects with risk factors and control subjects, apart from those with IDDM, in whom it was significantly impaired (p = 0.026). After infusion of L-arginine, there was no change in FMD in control or diabetic subjects. In hypercholesterolemic subjects and smokers, FMD improved from 1.9 ± 1.9% to 4.1 ± 2.1% (p = 0.01) and from 2.0 ± 1.71% to 3.1 ± 2.5% (p = 0.02), respectively.

Conclusions. FMD was impaired in all three risk factor groups; however, they responded differently to L-arginine, FMD being improved in hypercholesterolemic subjects and smokers but unchanged in diabetic subjects. These results indicate differing underlying pathophysiologies that may facilitate the design of treatment strategies for subjects with different risk factors.


Associations Between Lipoproteins and the Progression of Coronary and Vein-Graft Atherosclerosis in a Controlled Trial With Gemfibrozil in Men With Low Baseline Levels of HDL Cholesterol


Background-Lipid-lowering secondary-prevention trials of coronary artery disease (CAD) have implicated triglyceride-rich lipoproteins as the main determinants of angiographic progression after elevated LDL cholesterol levels have been lowered with therapy. The present study focuses on the lipoprotein determinants of angiographic CAD progression in men with low HDL cholesterol concentration as their main baseline lipid abnormality who underwent 32 months of randomized therapy with gemfibrozil or placebo.

Methods and Results-Men who had undergone coronary bypass surgery (n=372) completed a randomized, placebo-controlled study with gemfibrozil 1200 mg/d. They were selected primarily for HDL cholesterol levels that corresponded to the lowest third for middle-aged men. Average baseline lipid and lipoprotein levels were serum triglyceride, 1.60; serum cholesterol, 5.17; ultracentrifugally separated LDL cholesterol, 3.43; HDL2 cholesterol, 0.41; and HDL3 cholesterol, 0.61 mmol/L. In the gemfibrozil group, these levels were reduced on
average by 40%, 9%, and 6% or increased by 5% and 9%, respectively. On-trial IDL and LDL triglyceride and cholesterol levels significantly predicted global angiographic progression, taking into account changes in native segments and in bypass grafts. HDL3 but not HDL2 cholesterol concentration was associated with protection against progression, especially focal disease in native coronary lesions. VLDL was the lipoprotein most predictive of new lesions in vein grafts; IDL was also significantly related. Conclusions–This study expands the previous evidence of the triglyceride-rich lipoproteins, especially IDL, as predictors of angiographic progression of CAD but does not negate the significance of mildly elevated LDL levels. Of the HDL subfractions, only HDL3 was protective in this group of men selected for their low initial HDL levels.

The American Journal of Cardiology, 1998;82:409-413

Estrogen replacement therapy and outcome of coronary balloon angioplasty in postmenopausal women


Estrogen replacement therapy (ERT) in women after menopause is associated with prevention of clinical coronary artery disease. However, few studies have investigated possible benefits from ERT in postmenopausal women undergoing treatment for established coronary disease. We therefore retrospectively reviewed the clinical outcomes of 428 postmenopausal women undergoing percutaneous transluminal coronary balloon angioplasty (PTCA) to test the hypothesis that ERT has a beneficial effect in this setting. The women were divided into 2 groups based on ERT status at the time of the procedure. Estrogen users were younger (60 ± 10 vs 68 ± 9 years, p < 0.001), more commonly had family histories of coronary heart disease (54% vs 41%, p = 0.04), had less incidence of hypertension (63% vs 76%, p = 0.02), and had slightly fewer diseased vessels per patient (1.3 ± 0.5 vs 1.5 ± 0.7, p = 0.03) compared with nonusers. No in-hospital deaths occurred in estrogen users compared with 5% hospital mortality in nonusers (p = 0.01). The combined outcome of death or myocardial infarction (MI) also was lower in estrogen users (4% vs 12%, p = 0.04). Of 348 women discharged after successful PTCA, 336 (97%) were able to be contacted at an average follow-up interval of 22 ± 17 months (range 5 to 82). Estrogen users had superior event-free survival both for death as well as for death or nonfatal MI. Repeat revascularizations were similar in both groups (32% vs 24%, p = 0.15). In a Cox proportional-hazards model, nonusers had 4 times the likelihood of death after angioplasty compared with estrogen users
We conclude that estrogen replacement may offer protection against clinical coronary events in postmenopausal women who already have established coronary disease and are undergoing balloon angioplasty. The benefit was independent of age, smoking, presence of diabetes mellitus, or the number of diseased coronary vessels. However, it did not include a reduction in repeat revascularization procedures, suggesting no reduction in restenosis.

JAMA, 1998;280:356-362

Ethnic and Socioeconomic Differences in Cardiovascular Disease Risk Factors
Findings for Women From the Third National Health and Nutrition Examination Survey, 1988-1994

Marilyn A. Winkleby; Helena C. Kraemer; David K. Ahn; Ann N. Varady

Context. - Cardiovascular disease (CVD) risk factors are higher among ethnic minority women than among white women. After adjusting for years of education, highly significant differences in blood pressure, BMI, physical inactivity, and diabetes remained for both black and Mexican American women compared with white women (P<0.001). In addition, women of lower SES from each of the 3 ethnic groups had significantly higher prevalences of smoking and physical inactivity and higher levels of BMI and non-HDL-C than women of higher SES (P<0.001).

Conclusions. - These findings provide the greatest evidence to date of higher CVD risk factors among black and Mexican American women than among white women of comparable SES. The striking differences by both ethnicity and SES underscore the critical need to improve screening, early detection, and treatment of CVD-related conditions for black and Mexican American women, as well as for women of lower SES in all ethnic
Clinical characteristics determining the mode of presentation in patients with acute coronary syndromes

Simon Kennon, Abdul Suliman, Peter K. MacCallum, Kulasegaram Ranjadayalan, Paul Wilkinson, Adam D. Timmis

Objectives. The purpose of this study was to examine clinical characteristics of patients with acute coronary syndromes to identify factors that influence the mode of presentation.

Background. In acute coronary syndromes, presentation with myocardial infarction or unstable angina has major prognostic implications, yet clinical factors affecting the mode of presentation are not well defined.

Methods. A prospective cohort study was made of 1,111 patients with acute coronary syndromes. Baseline demographic, clinical and biochemical data were compared in groups with myocardial infarction (n = 633) and unstable angina (n = 478).

Results. The risk of myocardial infarction relative to unstable angina was increased by age >70 years (odds ratio [OR] 2.21; 95% confidence interval [CI] 1.33 to 3.66), male gender (OR 1.56; CI 1.13 to 2.16) and cigarette smoking (OR 1.49; CI 1.09 to 2.03). A rise in admission creatinine from the 10th to the 90th centile of the distribution also increased the odds of myocardial infarction (OR 1.30; CI 1.05 to 1.94). Conversely, the risk of myocardial infarction relative to unstable angina was reduced by previous treatment with aspirin (OR 0.37; CI 0.27 to 0.52), hypertension (OR 0.64; CI 0.47 to 0.86) and previous acute coronary syndromes (OR 0.36; CI 0.26 to 0.51) and revascularization procedures (OR 0.36; CI 0.21 to 0.62).

Conclusions. The clinical presentation of acute coronary syndromes may be influenced by various factors that have the potential to influence the coagulability of the blood, the collateralization of the coronary circulation and myocardial mass. Myocardial infarction is favored by cigarette smoking, advanced age and renal impairment, while unstable angina is favored by treatment with aspirin, hypertension, previous revascularization and previous coronary syndromes.
Prospective Study of Atherosclerotic Disease Progression in the Renal Artery


Background-The aim of this study was to determine the incidence of and the risk factors associated with progression of renal artery disease in individuals with atherosclerotic renal artery stenosis (ARAS).

Methods and Results-Subjects with ≥1 ARAS were monitored with serial renal artery duplex scans. A total of 295 kidneys in 170 patients were monitored for a mean of 33 months. Overall, the cumulative incidence of ARAS progression was 35% at 3 years and 51% at 5 years. The 3-year cumulative incidence of renal artery disease progression stratified by baseline disease classification was 18%, 28%, and 49% for renal arteries initially classified as normal, <60% stenosis, and ≥60% stenosis, respectively (P=0.03, log-rank test). There were only 9 renal artery occlusions during the study, all of which occurred in renal arteries having ≥60% stenosis at the examination before the detection of occlusion. A stepwise Cox proportional hazards model included 4 baseline factors that were significantly associated with the risk of renal artery disease progression during follow-up: systolic blood pressure ≥160 mm Hg (relative risk [RR]=2.1; 95% CI, 1.2 to 3.5), diabetes mellitus (RR=2.0; 95% CI, 1.2 to 3.3), and high-grade (≥60% stenosis or occlusion) disease in either the ipsilateral (RR=1.9; 95% CI, 1.2 to 3.0) or contralateral (RR=1.7; 95% CI, 1.0 to 2.8) renal artery.

Conclusions-Although renal artery disease progression is a frequent occurrence, progression to total renal artery occlusion is not. The risk of renal artery disease progression is highest among individuals with preexisting high-grade stenosis in either renal artery, elevated systolic blood pressure, and diabetes mellitus.

Low Circulating Folate and Vitamin B6 Concentrations
Risk Factors for Stroke, Peripheral Vascular Disease, and Coronary Artery Disease

Killian Robinson, MD; Kristopher Arheart, EdD; Helga Refsum, PhD; Lars Brattstrom, MD, PhD; Godfried Boers, MD; Per Ueland, PhD; Paolo Rubba, MD; Roberto Palma-Reis, MD; Raymond Meleady, MRCPI; Leslie Daly, PhD; Jacqueline Witteman, MD; Ian Graham, FRCPI; for the European COMAC Group

Background-A high plasma homocysteine concentration is a risk factor for atherosclerosis, and circulating
concentrations of homocysteine are related to levels of folate and vitamin B6. This study was performed to explore the interrelationships between homocysteine, B vitamins, and vascular diseases and to evaluate the role of these vitamins as risk factors for atherosclerosis.

Methods-In a multicenter case-control study in Europe, 750 patients with documented vascular disease and 800 control subjects frequency-matched for age and sex were compared. Plasma levels of total homocysteine (before and after methionine loading) were determined, as were those of red cell folate, vitamin B12, and vitamin B6.

Results-In a conditional logistic regression model, homocysteine concentrations greater than the 80th percentile for control subjects either fasting (12.1 μmol/L) or after a methionine load (38.0 μmol/L) were associated with an elevated risk of vascular disease independent of all traditional risk factors. In addition, concentrations of red cell folate below the lowest 10th percentile (<513 nmol/L) and concentrations of vitamin B6 below the lowest 20th percentile (<23.3 nmol/L) for control subjects were also associated with increased risk. This risk was independent of conventional risk factors and for folate was explained in part by increased homocysteine levels. In contrast, the relationship between vitamin B6 and atherosclerosis was independent of homocysteine levels both before and after methionine loading.

Conclusions-Lower levels of folate and vitamin B6 confer an increased risk of atherosclerosis. Clinical trials are now required to evaluate the effect of treatment with these vitamins in the primary and secondary prevention of vascular diseases.

Summary
1. Homocysteine concentrations greater than the 80th percentile for control subjects either fasting (12.1 μmol/L) or after a methionine load (38.0 μmol/L) - associated with an elevated risk of vascular disease independent of all traditional risk factors.
2. Concentrations of red cell folate below the lowest 10th percentile (<513 nmol/L) and concentrations of vitamin B6 below the lowest 20th percentile (<23.3 nmol/L) for control subjects - associated with increased risk.

Reduction of Stroke Incidence After Myocardial Infarction With Pravastatin: The Cholesterol and Recurrent Events (CARE) Study


Background-The role of lipid modification in stroke prevention is controversial, although increasing evidence
suggests that HMG-CoA reductase inhibition may reduce cerebrovascular events in patients with prevalent coronary artery disease.

Methods and Results-To test the hypothesis that cholesterol reduction with pravastatin may reduce stroke incidence after myocardial infarction, we followed 4159 subjects with average total and LDL serum cholesterol levels (mean, 209 and 139 mg/dL, respectively) who had sustained an infarction an average of 10 months before study entry and who were randomized to pravastatin 40 mg/d or placebo in the Cholesterol and Recurrent Events (CARE) trial. Using prospectively defined criteria, we assessed the incidence of stroke, a prespecified secondary end point, and transient ischemic attack (TIA) over a median 5-year follow-up period. Patients were well matched for stroke risk factors and the use of antiplatelet agents (85% of subjects in each group). Compared with placebo, pravastatin lowered total serum cholesterol by 20%, LDL cholesterol by 32%, and triglycerides by 14% and raised HDL cholesterol by 5% over the course of the trial. A total of 128 strokes (52 on pravastatin, 76 on placebo) and 216 strokes or TIAs (92 on pravastatin, 124 on placebo) were observed, representing a 32% reduction (95% CI, 4% to 52%, P=0.03) in all-cause stroke and 27% reduction in stroke or TIA (95% CI, 4% to 44%, P=0.02). All categories of strokes were reduced, and treatment effect was similar when adjusted for age, sex, history of hypertension, cigarette smoking, diabetes, left ventricular ejection fraction, and baseline total, HDL, and LDL cholesterol and triglyceride levels. There was no increase in hemorrhagic stroke in patients on pravastatin compared with placebo (2 versus 6, respectively).

Conclusions-Pravastatin significantly reduced stroke and stroke or TIA incidence after myocardial infarction in patients with average serum cholesterol levels despite the high concurrent use of antiplatelet therapy.

Circulation, 1999;99: 2986-2992

Comparing AMI Mortality Among Hospitals in Patients 65 Years of Age and Older: Evaluating Methods of Risk Adjustment

Harlan M. Krumholz, Jersey Chen, Yongfei Wang, Martha J. Radford, Ya-Ting Chen, and Thomas A. Marcinak

Background-Interest in the reporting of risk-adjusted outcomes for patients with acute myocardial infarction is growing. A useful risk-adjustment model must balance parsimony and ease of data collection with predictive ability.

Methods and Results-From our analysis of 82 359 patients 65 years of age admitted with acute myocardial infarction to 2401 hospitals, we derived a parsimonious model that predicts 30-day mortality. The model was
validated on a similar group of 78,699 patients from 2386 hospitals. Of the 73 candidate predictor variables examined, 7 variables describing patient characteristics on arrival were selected for inclusion in the final model: age, cardiac arrest, anterior or lateral location of myocardial infarction, systolic blood pressure, white blood cell count, serum creatinine, and congestive heart failure. The area under the receiver-operating characteristic curve for the final model was 0.77 in the derivation cohort and 0.77 in the validation cohort. The rankings of hospitals by performance (in deciles) with this model were most similar to a comprehensive 27-variable model based on medical chart review and least similar to models based on administrative billing codes.

Conclusions-A simple 7-variable risk model performs as well as more complex models in comparing hospital outcomes for acute myocardial infarction. Although there is a continuing need to improve methods of risk adjustment, our results provide a basis for hospitals to develop a simple approach to compare outcomes.

Glycometabolic State at Admission: Important Risk Marker of Mortality in Conventionally Treated Patients With Diabetes Mellitus and Acute Myocardial Infarction: Long-Term Results From the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study

Klas Malmberg, Anna Norhammar, Hans Wedel, and Lars Ryden

Background-The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study addressed prognostic factors and the effects of concomitant treatment and glycometabolic control in diabetic patients with myocardial infarction (AMI).

Methods and Results-Of 620 diabetic patients with AMI, 306 were randomly assigned to a ≥24-hour insulin-glucose infusion followed by multidose subcutaneous insulin. Three hundred fourteen patients were randomized as controls, receiving routine antidiabetic therapy. Thrombolysis and β-blockers were administered when possible. Univariate and multivariate statistical analyses were applied to study predictors of long-term mortality. During an average follow-up of 3.4 years (range, 1.6 to 5.6 years), 102 patients (33%) in the intensive insulin group and 138 (44%) in the control group died (P=0.011). Old age, previous heart failure, diabetes duration, admission blood glucose, and admission Hb Alc were independent predictors of mortality in the total cohort, whereas previous AMI, hypertension, smoking, or female sex did not add independent predictive value. Metabolic control, mirrored by blood glucose and Hb Alc, improved significantly more in patients on intensive insulin treatment than in the control group. β-Blockers improved survival in control subjects, whereas thrombolysis was most efficient in the intensive insulin group.
Conclusions-Mortality in diabetic patients with AMI is predicted by age, previous heart failure, and severity of the glycometabolic state at admission but not by conventional risk factors or sex. Intensive insulin treatment reduced long-term mortality despite high admission blood glucose and Hb A1c.

Circulation, 1999;99: 3241-3247

Aggressive Cholesterol Lowering Delays Saphenous Vein Graft Atherosclerosis in Women, the Elderly, and Patients With Associated Risk Factors: NHLBI Post Coronary Artery Bypass Graft Clinical Trial

Lucien Campeau, Donald B. Hunninghake, Genell L. Knatterud, Carl W. White, Michael Domanski, Sandra A. Forman, James S. Forrester, Nancy L. Geller, Fredarick L. Gobel, J. Alan Herd, Byron J. Hoogwerf, and Yves Rosenberg

Background-The NHLBI Post Coronary Artery Bypass Graft trial (Post CABG) showed that aggressive compared with moderate lowering of low-density lipoprotein-cholesterol (LDL-C) decreased obstructive changes in saphenous vein grafts (SVGs) by 31%. Using lovastatin and cholestyramine when necessary, the annually determined mean LDL-C level ranged from 93 to 97 mg/dL in aggressively treated patients and from 132 to 136 mg/dL in the others (P<0.001).

Methods and Results-The present study evaluated the treatment effect in subgroups defined by age, gender, and selected coronary heart disease (CHD) risk factors, ie, smoking, hypertension, diabetes mellitus, high-density lipoprotein cholesterol (HDL-C) <35 mg/dL, and triglyceride serum levels ≥200 mg/dL at baseline. As evidenced by similar odds ratio estimates of progression (lumen diameter decrease ≥0.6 mm) and lack of interactions with treatment, a similar beneficial effect of aggressive lowering was observed in elderly and young patients, in women and men, in patients with and without smoking, hypertension, or diabetes mellitus, and those with and without borderline high-risk triglyceride serum levels. The change in minimum lumen diameter was in the same direction for all subgroup categories, without significant interactions with treatment. Conclusions-Aggressive LDL-C lowering delays progression of atherosclerosis in SVGs irrespective of gender, age, and certain risk factors for CHD.

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Geographic Variation in the Treatment of Acute Myocardial Infarction
The Cooperative Cardiovascular Project

Gerald T. O’Connor; Hebe B. Quinton; Neal D. Traven; Lawrence D. Ramunno; T. Andrew Dodds; Thomas A. Marciniak; John E. Wennberg

Context  Quality indicators for the treatment of acute myocardial infarction include pharmacologic therapy, reperfusion, and smoking cessation advice, but these therapies may not be administered to all patients who could benefit from them.
Objective To assess geographic variation in adherence to quality indicators for treatment of acute myocardial infarction.
Design Inception cohort using data from the Health Care Financing Administration Cooperative Cardiovascular Project.
Setting Acute care hospitals in the United States.
Main Outcome Measures Adherence to quality indicators for pharmacologic therapy, reperfusion, and smoking cessation advice for patients judged to be ideal candidates for these therapies. The mean rates of adherence to these quality indicators for the entire United States were determined, and the 20th and 80th percentiles of the age- and sex-adjusted rates for each of 306 hospital referral regions were contrasted (mean rate [20th-80th percentiles]).
Results Aspirin was used frequently both during hospitalization (86.2% [82.6%-90.1%]) and at discharge (77.8% [72.5%-83.9%]). Calcium channel blockers were withheld from most patients with impaired left ventricular function (81.9% [73.6%-90.8%]). Lower rates were seen in the use of angiotensin-converting enzyme inhibitors at discharge (59.3% [49.2%-69.2%]); reperfusion, using thrombolytic therapy or coronary angioplasty (67.2% [59.8%-75.1%]); prescription of β-blockers at discharge (49.5% [35.8%-61.5%]); and for smoking cessation advice (41.9% [32.8%-51.3%]).
Conclusions Substantial geographic variation exists in the treatment of patients with acute myocardial infarction, and these gaps between knowledge and practice have important consequences. Therapies with proven benefit for AMI are underused despite strong evidence that their use will result in better patient outcomes.
Incremental prognostic value of serum levels of troponin T and C-reactive protein on admission in patients with unstable angina pectoris

Antonio G. Rebuzzi, Gaetano Quaranta, Giovanna Liuzzo, Giuseppina Caligiuri, Gaetano A. Lanza, J. Ruth Gallimore, Rita L. Grillo, Domenico Cianflone, Luigi M. Biasucci, Attilio Maseri

Management of unstable angina is largely determined by symptoms, yet some symptomatic patients stabilize, whereas others develop myocardial infarction after waning of symptoms. Therefore, markers of short-term risk, available on admission, are needed. The value of 4 prognostic indicators available on admission (pain in the last 24 hours, electrocardiogram [ECG], troponin T, and C-reactive protein [CRP]), and of Holter monitoring available during the subsequent 24 hours was analyzed in 102 patients with Braunwald class IIIB unstable angina hospitalized in 4 centers. The patients were divided into 3 groups: group 1, 27 with pain during the last 24 hours and ischemic electrocardiographic changes; group 2, 45 with pain or electrocardiographic changes; group 3, 30 with neither pain nor electrocardiographic changes. Troponin T, CRP, ECG on admission, and Holter monitoring were analyzed blindly in the core laboratory. Fifteen patients developed myocardial infarction: 22% in group 1, 13% in group 2, and 10% in group 3. Twenty-eight patients underwent revascularization: 37% in group 1, 35% in group 2, and 7% in group 2 (p < 0.01 between groups 1 or 2 vs group 3). Myocardial infarction was more frequent in patients with elevated troponin T (50% vs 9%, p = 0.001) and elevated CRP (24% vs 4%, p = 0.01). Positive troponin T or CRP identified all myocardial infarctions in group 3. Only 1 of 46 patients with negative troponin T and CRP developed myocardial infarction. Among the indicators available on admission, multivariate analysis showed that troponin T (p = 0.02) and CRP (p = 0.04) were independently associated with myocardial infarction. Troponin T had the highest specificity (92%), and CRP the highest sensitivity (87%). Positive results on Holter monitoring were also associated with myocardial infarction (p = 0.003), but when added to troponin T and CRP, increased specificity and positive predictive value by only 3%. Thus, in patients with class IIIB unstable angina, among data potentially available on admission, serum levels of troponin T and CRP have a significantly greater prognostic accuracy than symptoms and ECGs. Holter monitoring, available 24 hours later, adds no significant information.
Background-Cholesterol lowering reduces coronary events. One mechanism could be improvement of endothelial function. In line with this hypothesis, this study investigates whether cholesterol reduction can result in rapid improvement of endothelial function after acute coronary syndromes.

Methods and Results-Patients with acute myocardial infarction or unstable angina and total cholesterol levels at admission $\geq 5.2$ mmol/L or LDL $\geq 3.4$ mmol/L were randomized to placebo (n=30) or pravastatin 40 mg daily (n=30) for 6 weeks. Brachial ultrasound was used to measure endothelium-dependent flow-mediated dilatation (FMD) and response to endothelium-independent nitroglycerin. Changes in the levels of markers of platelet activation, coagulation factors, and plasma endothelin levels were also assessed. Total and LDL cholesterol levels were similar at admission and before randomization in both groups. With pravastatin, but not with placebo, they decreased by 23% ($P<0.05$) and 33% ($P<0.01$), respectively. FMD was unchanged with placebo, 5.43±0.74% (mean±SEM) to 5.84±0.81%, but increased with pravastatin, 4.93±0.81% to 7.0±0.79% ($P=0.02$), representing a 42% relative increase. Responses to nitroglycerin were similar during the time course of the study in the 2 groups. Markers of platelet activity, coagulation factors, and endothelin levels were not affected by pravastatin.

Conclusions-Cholesterol reduction with pravastatin initiated early after acute coronary syndromes rapidly improves endothelial function after 6 weeks of therapy.

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This study was undertaken to project the population-wide effect of full implementation of the Adult Treatment Panel (ATP) II guidelines of the National Cholesterol Education Program (NCEP).

BACKGROUND
The ATP II has proposed guidelines for cholesterol reduction, but the long-term epidemiologic influence of its components has not been fully examined.

METHODS
We used a calibrated, validated simulation of the U.S. population, aged 35 to 84 years to estimate the potential for the NCEP guidelines, under varying assumptions, to reduce coronary heart disease morbidity and mortality and overall mortality from the years 2000 to 2020.

RESULTS
Primary prevention would yield only about half of the benefits of secondary prevention despite requiring nearly twice as many person-years of treatment. The projected increase in quality-adjusted years of life per year of treatment for secondary prevention was 3- to 12-fold higher than for primary prevention. To yield population-wide epidemiologic benefits equivalent to NCEP recommendations for secondary prevention, primary prevention would require a nearly sixfold increase in the number of persons treated compared with NCEP recommendations. All benefits of universal success of the NCEP primary prevention “screen and treat” guidelines could be achieved by a 11 mg/dl (8%) population-wide reduction in low-density lipoprotein cholesterol levels among persons without preexisting coronary heart disease.

CONCLUSIONS
The NCEP guidelines for targeted primary prevention can be a useful component of a rational public health strategy, but only as a complement to the more appealing strategies of secondary prevention and “cross-the-board” programs to lower all cholesterol levels.

Circulation, 1999;100:1154-1160

Role of Lipoprotein(a) and Apolipoprotein(a) Phenotype in Atherogenesis: Prospective Results From the Bruneck Study

Florian Kronenberg, Martina F. Kronenberg, Stefan Kiechl, Evi Trenkwalder, Peter Santer, Friedrich Oberhollenzer, Georg Egger, Gerd Utermann, and Johann Willeit

Background-Experimental studies have suggested both atherogenic and thrombogenic properties of
lipoprotein(a) [Lp(a)], depending on Lp(a) plasma concentrations and varying antifibrinolytic capacity of apolipoprotein(a) [apo(a)] isoforms. Epidemiological studies may contribute to assessment of the relevance of these findings in the general population.

Methods and Results—This study prospectively investigated the association between Lp(a) plasma concentrations, apo(a) phenotypes, and the 5-year progression of carotid atherosclerosis assessed by high-resolution duplex ultrasound in a random sample population of 826 individuals. We differentiated early atherogenesis (incident nonstenotic atherosclerosis) from advanced (stenotic) stages in atherosclerosis that originate mainly from atherothrombotic mechanisms. Lp(a) plasma concentrations predicted the risk of early atherogenesis in a dose-dependent fashion, with this association being confined to subjects with LDL cholesterol levels above the population median (3.3 mmol/L). Apo(a) phenotypes were distributed similarly in subjects with and without early carotid atherosclerosis. In contrast, apo(a) phenotypes of low molecular weight emerged as one of the strongest risk predictors of advanced stenotic atherosclerosis, especially when associated with high Lp(a) plasma concentrations (odds ratio, 6.4; 95% CI, 2.8 to 14.9).

Conclusions—Lp(a) is one of the few risk factors capable of promoting both early and advanced stages of atherogenesis. Lp(a) plasma concentrations predicted the risk of early atherogenesis synergistically with high LDL cholesterol. Low-molecular-weight apo(a) phenotypes with a putatively high antifibrinolytic capacity in turn emerged as one of the leading risk conditions of advanced stenotic stages of atherosclerosis.

Circulation, 1999;100:1161-1168

Role of Oxidant Stress in Endothelial Dysfunction Produced by Experimental Hyperhomocyst(e)inemia in Humans

Prapti M. Kanani, Christine A. Sinkey, Roger L. Browning, Margaret Allaman, Howard R. Knapp, and William G. Haynes

Background—Moderate elevations in plasma homocyst(e)ine concentrations are associated with atherosclerosis and hypertension. We tested the hypothesis that experimental perturbation of homocysteine levels produces resistance and conduit vessel endothelial dysfunction and that this occurs through increased oxidant stress.

Methods and Results—Oral administration of L-methionine (100 mg/kg) was used to induce moderate hyperhomocyst(e)inemia (25 μmol/L) in healthy human subjects. Endothelial function of forearm resistance vessels was assessed by use of forearm vasodilatation to brachial artery administration of the endothelium-dependent dilator acetylcholine. Conduit vessel endothelial function was assessed with flow-mediated dilatation of the brachial artery. Forearm resistance vessel dilatation to acetylcholine was significantly impaired
7 hours after methionine (methionine, 477±82%; placebo, 673±110%; P=0.016). Methionine did not alter vasodilatation to nitroprusside and verapamil. Flow-mediated dilatation was significantly impaired 8 hours after methionine loading (0.3±2.7%) compared with placebo (8.2±1.6%, P=0.01). Oral administration of the antioxidant ascorbic acid (2 g) prevented methionine-induced endothelial dysfunction in both conduit and resistance vessels (P=0.03).

Conclusions-Experimentally increasing plasma homocyst(e)ine concentrations by methionine loading rapidly impairs both conduit and resistance vessel endothelial function in healthy humans. Endothelial dysfunction in conduit and resistance vessels may underlie the reported associations between homocysteine and atherosclerosis and hypertension. Increased oxidant stress appears to play a pathophysiological role in the deleterious endothelial effects of homocysteine.

Circulation, 1999;100: 1945-1950

Physiologically Assessed Coronary Collateral Flow and Intracoronary Growth Factor Concentrations in Patients With 1- to 3-Vessel Coronary Artery Disease

Martin Fleisch, Michael Billinger, Franz R. Eberli, Ali R. Garachemani, Bernhard Meier, and Christian Seiler

Background-The purpose of this study was to test the hypothesis that there is a relation between collateral flow and intracoronary concentrations of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) and that the combined concentrations of both growth factors and the extent of coronary artery disease (CAD) play a role as covariables in such an association.

Methods and Results-In 76 patients undergoing balloon angioplasty, a collateral flow index (CFI, no units) was determined with sensor-tipped guidewires. Simultaneously, serum concentrations of bFGF and VEGF, obtained at the aortic root from the ostium of the collateralized coronary artery (n=76) and from the distal position of the occluded coronary artery (n=34), were determined. There was a direct correlation between CFI and distal VEGF (r=0.33, P=0.05) but not bFGF concentrations. Focusing on the proximal sampling site, there was a direct correlation between CFI and both bFGF (r=0.29, P=0.01) and VEGF concentrations (r=0.44, P<0.0001). The sum of the concentrations of both growth factors was directly associated with CFI irrespective of the proximal (r=0.51, P<0.0001) or distal sampling site (r=0.34, P=0.048). There was a trend toward higher proximal VEGF concentrations in patients with higher numbers of coronary stenotic lesions (r=0.25, P=0.03).

Conclusions-In patients with CAD, there is an association between a directly measured index of collateral flow
and intracoronary concentrations of bFGF and VEGF. This direct relation is dependent on the site of blood sampling within the coronary artery tree. The association is closest when the combined bFGF and VEGF concentrations are taken into account. In the case of VEGF, it is influenced by the degree of coronary atherosclerosis.

Circulation, 1999;99: 2517-2522

Thrombogenic Factors and Recurrent Coronary Events


Background-Thrombosis is a pivotal event in the pathogenesis of coronary disease. We hypothesized that the presence of blood factors that reflect enhanced thrombogenic activity would be associated with an increased risk of recurrent coronary events during long-term follow-up of patients who have recovered from myocardial infarction.

Methods and Results-We prospectively enrolled 1045 patients 2 months after an index myocardial infarction. Baseline thrombogenic blood tests included 6 hemostatic variables (D-dimer, fibrinogen, factor VII, factor VIIa, von Willebrand factor, and plasminogen activator inhibitor-1), 7 lipid factors [cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, lipoprotein(a), apolipoprotein (apo)A-I, and apoB], and insulin. Patients were followed up for an average of 26 months, with the primary end point being coronary death or nonfatal myocardial infarction, whichever occurred first. The hemostatic, lipid, and insulin parameters were dichotomized into their top and the lower 3 risk quartiles and evaluated for entry into a Cox survivorship model. High levels of D-dimer (hazard ratio, 2.43; 95% CI, 1.49, 3.97) and apoB (hazard ratio, 1.82; 95% CI, 1.10, 3.00) and low levels of apoA-I (hazard ratio, 1.84; 95% CI, 1.10, 3.08) were independently associated with recurrent coronary events in the Cox model after adjustment for 6 relevant clinical covariates.

Conclusions-Our findings indicate that a procoagulant state, as reflected in elevated levels of D-dimer, and disordered lipid transport, as indicated by low apoA-1 and high apoB levels, contribute independently to recurrent coronary events in postinfarction patients.
OBJECTIVES
We compared the predictive properties of P-selectin to creatine kinase, MB fraction (CK-MB) for detecting acute myocardial infarction (AMI), acute coronary syndromes (ACS) and serious cardiac events upon emergency department (ED) arrival.

BACKGROUND
Practitioners detecting early diagnosis of ACS have focused on cardiac markers of myocardial injury. Plaque rupture/platelet aggregation precedes myocardial ischemia. Therefore, markers of platelet aggregation may detect ACS earlier than cardiac markers.

METHODS
Consecutive patients with potential ACS presenting to an urban university ED were identified by research assistants who screened all ED patients between November 12, 1997 and January 31, 1998. Whole blood was drawn at presentation and 1 h later and rapidly stained and fixed for membrane P-selectin assay and plasma was separated for soluble P-selectin assay. Creatine kinase, MB fraction values were determined using standard immunoassay techniques. Clinical history and hospital course were followed daily. Outcomes were AMI, ACS (AMI and unstable angina) and serious cardiac events. Receiver operator characteristic curves were derived for CK-MB, and soluble and membrane-bound P-selectin to determine the optimal cutoff values. Predictive properties were calculated with 95% confidence intervals.

RESULTS
A total of 263 patients were enrolled. They had a mean age of 56.5 ± 14 years; 52% were male. There were 22 patients with AMI; 87 patients with ACS and 54 patients with serious cardiac events. Creatine kinase, MB fraction had a higher specificity for detection of AMI, ACS and serious cardiac events than both soluble and membrane-bound P-selectin. At the time of ED presentation, the specificity of CK-MB, and soluble and membrane-bound P-selectin for AMI was 91% versus 76% versus 71%; for ACS, 95% versus 79% versus 71%, and for serious cardiac events, 91% versus 76% versus 72% (p < 0.05). The sensitivities for AMI were 50% versus 45% versus 32%; for ACS, 26% versus 35% versus 30%, and for serious cardiac events, 29% versus 35% versus 36%.
CONCLUSIONS

Although theoretically attractive, the use of soluble and membrane-bound P-selectin for risk stratification of chest pain patients at the time of ED presentation does not appear to have any advantages over the use of CK-MB.

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Temporal Trends in Event Rates After Q-Wave Myocardial Infarction : The Framingham Heart Study

Ursula C. Guidry, Jane C. Evans, Martin G. Larson, Peter W. F. Wilson, Joanne M. Murabito, and Daniel Levy

Background-Short-term (<30 day) mortality after Q-wave myocardial infarction (MI) has declined over the decades, but it is unclear if rates of long-term sequelae after Q-wave MI have improved.

Methods and Results-In 546 Framingham Heart Study subjects (388 men with a mean age of 60 years; 158 women with a mean age of 69 years) with an initial recognized Q-wave MI from 1950 through 1989, we investigated time trends in risk for coronary heart disease (CHD) death (n=199), all-cause mortality (n=287), reinfarction (n=108), and congestive heart failure (CHF; n=121). With 1950 through 1969 as the reference period, hazards ratios (HRs) for these outcomes were determined for the 1970s and 1980s. Trend analyses across the 3 time periods were performed for each outcome. Compared with the 1950 through 1969 reference period, the HRs for CHD death were lower in subsequent decades (1970 through 1979: HR, 0.69; 95% CI, 0.49 to 0.98; 1980 through 1989: HR, 0.48; 95% CI, 0.33 to 0.72). All-cause mortality also declined (1970 through 1979: HR, 0.70; 95% CI, 0.52 to 0.94; 1980 through 1989: HR, 0.59; 95% CI, 0.43 to 0.81). There were no significant temporal changes in the risks for recurrent MI or CHF.

Conclusions-Substantial reductions in risk of CHD death and all-cause mortality occurred over these 4 decades, coincident with improvements in post-MI therapies. The absence of a decline in CHF incidence may be due to improved post-MI survival of individuals with depressed left ventricular systolic function who are at high risk for CHF.

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Elevated Levels of C-Reactive Protein at Discharge in Patients With Unstable Angina Predict Recurrent Instability

Luigi M. Biasucci, Giovanna Liuzzo, Rita L. Grillo, Giuseppina Caligiuri, Antonio G. Rebuzzi, Antonino Buffon, Francesco Summara, Francesca Ginnetti, Giovanni Fadda, and Attilio Maseri

Background-In a group of patients admitted for unstable angina, we investigated whether C-reactive protein (CRP) plasma levels remain elevated at discharge and whether persistent elevation is associated with recurrence of instability.

Methods and Results-We measured plasma levels of CRP, serum amyloid A protein (SAA), fibrinogen, total cholesterol, and Helicobacter pylori and Chlamydia pneumoniae antibody titers in 53 patients admitted to our coronary care unit for Braunwald class IIIB unstable angina. Blood samples were taken on admission, at discharge, and after 3 months. Patients were followed for 1 year. At discharge, CRP was elevated (>3 mg/L) in 49% of patients; of these, 42% had elevated levels on admission and at 3 months. Only 15% of patients with discharge levels of CRP <3 mg/L but 69% of those with elevated CRP (P<0.001) were readmitted because of recurrence of instability or new myocardial infarction. New phases of instability occurred in 13% of patients in the lower tertile of CRP (≤2.5 mg/L), in 42% of those in the intermediate tertile (2.6 to 8.6 mg/L), and in 67% of those in the upper tertile (≥8.7 mg/L, P<0.001). The prognostic value of SAA was similar to that of CRP; that of fibrinogen was not significant. Chlamydia pneumoniae but not Helicobacter pylori antibody titers significantly correlated with CRP plasma levels.

Conclusions-In unstable angina, CRP may remain elevated for at ≥3 months after the waning of symptoms and is associated with recurrent instability. Elevation of acute-phase reactants in unstable angina could represent a hallmark of subclinical persistent instability or of susceptibility to recurrent instability and, at least in some patients, could be related to chronic Chlamydia pneumoniae infection.

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Suppression of Atherosclerotic Development in Watanabe Heritable Hyperlipidemic Rabbits Treated With an Oral Antiallergic Drug, Tranilast

Toshiyuki Matsumura, Kiyotaka Kugiyama, Seigo Sugiyama, Yasutaka Ota, Hideki Doi, Nobuhiko Ogata, Hideki Oka, and Hirofumi Yasue
Background-Inflammatory and immunological responses of vascular cells have been shown to play a significant role in the progression of atheromatous formation. Tranilast [N-(3,4-dimethoxycinnamoyl)anthranilic acid] inhibits release of cytokines and chemical mediators from various cells, including macrophages, leading to suppression of inflammatory and immunological responses. This study tested whether tranilast may suppress atheromatous formation in Watanabe heritable hyperlipidemic (WHHL) rabbits.

Methods and Results-WHHL rabbits (2 months old) were given either 300 mg · kg⁻¹ · d⁻¹ of tranilast (Tranilast, n=12) or vehicle (Control, n=13) PO for 6 months. Tranilast treatment was found to suppress the aortic area covered with plaque. Immunohistochemical analysis showed that there was no difference in the percentage of the RAM11-positive macrophage area and the frequency of CD5-positive cells (T cells) in intimal plaques between Tranilast and Control. Major histocompatibility complex (MHC) class II expression in macrophages and interleukin-2 (IL-2) receptor expression in T cells, as markers of the immunological activation in these cells, was suppressed in atheromatous plaque by tranilast treatment. Flow cytometry analysis of isolated human and rabbit peripheral blood mononuclear cells showed that an increase in expression both of MHC class II antigen on monocytes by incubation with interferon- and of IL-2 receptor on T cells by IL-2 was suppressed by the combined incubation with tranilast.

Conclusions-The results indicate that tranilast suppresses atherosclerotic development partly through direct inhibition of immunological activation of monocytes/macrophages and T cells in the atheromatous plaque.

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Improvement of Impaired Myocardial Vasodilatation Due to Diffuse Coronary Atherosclerosis in Hypercholesteroleemics After Lipid-Lowering Therapy

Ikuo Yokoyama, Shin-ichi Momomura, Tohru Ohtake, Katsunori Yonekura, Weidong Yang, Naoshi Kobayakawa, Teruhiko Aoyagi, Seiryo Sugiura, Nobuhiro Yamada, Kuni Ohtomo, Yasuhito Sasaki, Masao Omata, and Yoshio Yazaki

Background-Diminished myocardial vasodilatation (MVD) in hypercholesteroleemics without overt coronary stenosis has been reported. However, whether the diminished MVD of angiographically normal coronary
arteries in hypercholesterolemics can be reversed after lipid-lowering therapy is not known.

Methods and Results—A total of 27 hypercholesterolemics and 16 age-matched controls were studied. All patients had >1 normal coronary artery, and those segments that were perfused by anatomically normal coronary arteries were studied. Myocardial blood flow (MBF) was measured during dipyridamole loading and at baseline using positron emission tomography and 13N-ammonia, after which MVD was calculated before and after lipid-lowering therapy. Total cholesterol was significantly higher in hypercholesterolemics (263±33.8) than in controls (195±16.6), and it normalized after lipid-lowering therapy (197±19.9). Baseline MBF (ml · min⁻¹ · 100 g⁻¹) was comparable among hypercholesterolemics (both before and after therapy) and controls. MBF during dipyridamole loading was significantly lower in hypercholesterolemics before therapy (189±75.4) than in controls (299±162, P<0.01). However, MBF during dipyridamole loading significantly increased after therapy (226±84.7; P<0.01). MVD significantly improved after therapy in hypercholesterolemics (2.77±1.35 after treatment [P<0.05] versus 2.02±0.68 before treatment [P<0.01]), but it remained significantly higher in controls (3.69±1.13, P<0.01). There was a significant relationship between the percent change of total cholesterol and the percent change of MVD before and after lipid-lowering therapy (r=−0.61, P<0.05).

Conclusions—Diminished MVD of anatomically normal coronary arteries in hypercholesterolemics can be reversed after lipid-lowering therapy.

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Influence of baseline lipids on effectiveness of pravastatin in the CARE trial

Marc A. Pfeffer, Frank M. Sacks, Lemuel A. Moye, Cara East, Steven Goldman, David T. Nash, Jacques R. Rouleau, Jean Lucien Rouleau, Bruce A. Sussex, Pierre Theroux, Ron J. Vanden Belt, Eugene Braunwald

Objectives. We sought to assess the influence of baseline lipid levels on coronary event rates and the effectiveness of pravastatin therapy in the Cholesterol And Recurrent Events (CARE) study.

Background. The CARE study cohort provided a relatively unique opportunity to examine the relation between lipid levels and clinical events in a post-myocardial infarction (MI) population with relatively low cholesterol and low density lipoprotein (LDL) cholesterol values.

Methods. There were 4,159 patients with a previous infarct and a total cholesterol level <240 mg/dl, LDL cholesterol level 115 to 174 mg/dl and triglyceride level <350 mg/dl randomly allocated to placebo (n = 2,078) or
pravastatin 40 mg/day (n = 2,081). Time to either coronary death or nonfatal MI (primary end point) or to the secondary end point, which included undergoing a coronary revascularization procedure, was determined as a function of baseline lipids (total, LDL, high density lipoprotein [HDL] cholesterol and triglyceride levels).

Results. Quartile analysis indicated important effects for LDL cholesterol, in which a higher LDL was associated with greater cardiac event rates (in the placebo group, every 25-mg/dl increment in LDL was associated with a 28% increased risk [5% to 56%, p = 0.015]) in the primary event. The differential event rates with respect to baseline LDL cholesterol for placebo and pravastatin groups reduced the difference in clinical outcomes at lower LDL cholesterol levels. In both the placebo and pravastatin groups, an inverse relation between baseline HDL cholesterol and cardiac events was observed (10 mg/dl lower baseline HDL cholesterol level was associated with a 10% [0% to 19%, p = 0.046] increase in coronary death or nonfatal MI).

Conclusions. Within the LDL cholesterol levels in CARE (115 to 174 mg/dl), baseline values influenced both the risk of events in the placebo group as well as the clinical effectiveness of pravastatin therapy.

Is the development of myocardial tolerance to repeated ischemia in humans due to preconditioning or to collateral recruitment?

Michael Billinger, Martin Fleisch, Franz R. Eberli, Ali Garachemani, Bernhard Meier, Christian Seiler

OBJECTIVES  The purpose of this study in patients with quantitatively determined, poorly developed coronary collaterals was to assess the contribution of ischemic as well as adenosine-induced preconditioning and of collateral recruitment to the development of tolerance against repetitive myocardial ischemia.

BACKGROUND  The development of myocardial tolerance to repeated ischemia is nowadays interpreted to be due to biochemical adaptation (i.e., ischemic preconditioning).

METHODS   In 30 patients undergoing percutaneous transluminal coronary angioplasty, myocardial adaptation to ischemia was measured using intracoronary (i.c.) electrocardiographic (ECG) ST segment elevation changes obtained from a 0.014-in. (0.036 cm) pressure guidewire positioned distal to the stenosis during three subsequent 2-min balloon occlusions. Simultaneously, an i.c. pressure-derived collateral flow index (CFI, no unit) was determined as the ratio between distal occlusive minus central venous pressure divided by the mean aortic minus central venous pressure. The study patients were divided into two groups according to the pretreatment with i.c. adenosine (2.4 mg/min for 10 min starting 20 min before the first
occlusion, n = 15) or with normal saline (control group, n = 15).

RESULTS  Collateral flow index at the first occlusion was not different between the groups (0.15 ± 0.10 in the adenosine group and 0.13 ± 0.11 in the control group, p = NS), and it increased significantly and similarly to 0.20 ± 0.14 and to 0.19 ± 0.10, respectively (p < 0.01) during the third occlusion. The i.c. ECG ST elevation (normalized for the QRS amplitude) was not different between the two groups at the first occlusion (0.25 ± 0.13 in the adenosine group, 0.25 ± 0.19 in the control group). It decreased significantly during subsequent coronary occlusions to 0.20 ± 0.15 and to 0.17 ± 0.13, respectively. There was a correlation between the change in CFI (first to third occlusion; ΔCFI) and the respective ST elevation shift (ΔST): ΔST=0.02 to 0.78×ΔCFI;r=0.54,p=0.02.

CONCLUSIONS  Even in patients with few coronary collaterals, the myocardial adaptation to repetitive ischemia is closely related to collateral recruitment. Pharmacologic preconditioning using a treatment with i.c. adenosine before angioplasty does not occur. The variable responses of ECG signs of ischemic adaptation to collateral channel opening suggest that ischemic preconditioning is a relevant factor in the development of ischemic tolerance.

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Myoglobin, creatine-kinase-MB and cardiac troponin-I 60-minute ratios predict infarct-related artery patency after thrombolysis for acute myocardial infarction: Results from the thrombolysis in myocardial infarction study (TIMI) 10B

Milenko J. Tanasijevic, Christopher P. Cannon, Elliott M. Antman, Donald R. Wybenga, George A. Fischer, Christine Grudzien, C. Michael Gibson, James W. Winkelman, Eugene Braunwald for the TIMI 10B Investigators

OBJECTIVES
We examined the diagnostic performance of serum myoglobin, creatine-kinase-MB (CK-MB) and cardiac Troponin-I (cTnI) for predicting the infarct-related artery (IRA) patency in patients receiving TNK-tissue plasminogen activator (TNK-tPA) therapy for acute myocardial infarction (AMI) in the Thrombolysis in Myocardial Infarction (TIMI) 10B trial.

BACKGROUND
A reliable noninvasive serum marker of IRA patency is desired to permit early identification of patients with a
patent IRA after thrombolysis.

METHODS
We measured myoglobin, CK-MB and cTnI concentrations in sera obtained just before thrombolysis (T0) and 60 min later (T60) in 442 patients given TNK-tPA and who underwent coronary angiography at 60 min.

RESULTS
Angiography at 60 min showed a patent IRA (TIMI flow grade 2, 3) in 344 and occluded IRA (TIMI flow grade 0, 1) in 98 patients. The median serum T60 concentration, the ratio of the T60 and T0 serum concentration (60-min ratio) and the slope of increase over 60 min for each serum marker were significantly higher in patients with patent arteries compared with patients with occluded arteries. The area under the receiver-operating characteristic (ROC) curve for diagnosis of occlusion was 0.71, 0.70 and 0.71 for the 60-min ratio of myoglobin, cTnI and CKMB, respectively. The 60-min ratios of ≥4.0 for myoglobin, ≥3.3 for CK-MB and ≥2.0 for cTnI yielded a probability of patency of 90%, 88% and 87%, respectively.

CONCLUSIONS
The diagnostic performance of serum myoglobin, CK-MB and cardiac Tropinin-I (cTnI) 60-min ratios was similar. The probability of a patent IRA was very high (90%) in patients with 60-min myoglobin ratio ≥4.0, and early invasive interventions to establish IRA patency may not be necessary in this group. Serum marker determinations at baseline and 60-min after thrombolysis may permit rapid triage of patients receiving thrombolytic therapy by ruling out IRA occlusion.

Circulation, 1999;100: 230-235

Long-Term Effects of Pravastatin on Plasma Concentration of C-reactive Protein

Paul M. Ridker, Nader Rifai, Marc A. Pfeffer, Frank Sacks, and Eugene Braunwald

Background-Elevated plasma concentrations of C-reactive protein (CRP) are associated with increased cardiovascular risk. We evaluated whether long-term therapy with pravastatin, an agent that reduces cardiovascular risk, might alter levels of this inflammatory parameter.

Methods and Results-CRP levels were measured at baseline and at 5 years in 472 randomly selected participants in the Cholesterol and Recurrent Events (CARE) trial who remained free of recurrent coronary events during follow-up. Overall, CRP levels at baseline and at 5 years were highly correlated (r=0.60, P<0.001). However, among those allocated to placebo, median CRP levels and the mean change in CRP tended to
increase over time (median change, +4.2%; P=0.2 and mean change, +0.07 mg/dL; P=0.04). By contrast, median CRP levels and the mean change in CRP decreased over time among those allocated to pravastatin (median change, -17.4%; P=0.004 and mean change, -0.07 mg/dL; P=0.002). Thus, statistically significant differences were observed at 5 years between the pravastatin and placebo groups in terms of median CRP levels (difference, -21.6%; P=0.007), mean CRP levels (difference, -37.8%; P=0.002), and absolute mean change in CRP (difference, -0.137 mg/dL; P=0.003). These effects persisted in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline lipid levels. Attempts to relate the magnitude of change in CRP to the magnitude of change in lipids in both the pravastatin and placebo groups did not reveal any obvious relationships.

Conclusions-Among survivors of myocardial infarction on standard therapy plus placebo, CRP levels tended to increase over 5 years of follow-up. In contrast, randomization to pravastatin resulted in significant reductions in this inflammatory marker that were not related to the magnitude of lipid alterations observed. Thus, these data further support the potential for nonlipid effects of this agent.

Circulation, 1999; 99: 1165-1172

Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease : A Prospective Follow-Up Study of 14 786 Middle-Aged Men and Women in Finland

Pekka Jousilahti, Erkki Vartiainen, Jaakko Tuomilehto, and Pekka Puska.
explained about one-third of the age-related increase in CHD risk among men and 50% to 60% among women. Conclusions-Differences in major cardiovascular risk factors explained a substantial part of the sex difference in CHD risk. An increase in risk factor levels was associated with the age-related increase in CHD incidence and mortality in both sexes but to a larger extent in women.


Passive Smoking and the Risk of Coronary Heart Disease -- A Meta-Analysis of Epidemiologic Studies
Jiang He, Suma Vupputuri, Krista Allen, Monica R. Prerost, Janet Hughes, Paul K. Whelton

Background. The effect of passive smoking on the risk of coronary heart disease is controversial. We conducted a meta-analysis of the risk of coronary heart disease associated with passive smoking among nonsmokers.

Methods. We searched the Medline and Dissertation Abstracts Online data bases and reviewed citations in relevant articles to identify 18 epidemiologic (10 cohort and 8 case-control) studies that met prestated inclusion criteria. Information on the designs of the studies, the characteristics of the study subjects, exposure and outcome measures, control for potential confounding factors, and risk estimates was abstracted independently by three investigators using a standardized protocol.

Results. Overall, nonsmokers exposed to environmental smoke had a relative risk of coronary heart disease of 1.25 (95 percent confidence interval, 1.17 to 1.32) as compared with nonsmokers not exposed to smoke. Passive smoking was consistently associated with an increased relative risk of coronary heart disease in cohort studies (relative risk, 1.21; 95 percent confidence interval, 1.14 to 1.30), in case-control studies (relative risk, 1.51; 95 percent confidence interval, 1.26 to 1.81), in men (relative risk, 1.22; 95 percent confidence interval, 1.10 to 1.35), in women (relative risk, 1.24; 95 percent confidence interval, 1.15 to 1.34), and in those exposed to smoking at home (relative risk, 1.17; 95 percent confidence interval, 1.11 to 1.24) or in the workplace (relative risk, 1.11; 95 percent confidence interval, 1.00 to 1.23). A significant dose-response relation was identified, with respective relative risks of 1.23 and 1.31 for nonsmokers who were exposed to the smoke of 1 to 19 cigarettes per day and those who were exposed to the smoke of 20 or more cigarettes per day, as compared with nonsmokers not exposed to smoke (P=0.006 for linear trend).

Conclusions. Passive smoking is associated with a small increase in the risk of coronary heart disease. Given the high prevalence of cigarette smoking, the public health consequences of passive smoking with regard to coronary heart disease may be important.
Clinical outcomes after detection of elevated cardiac enzymes in patients undergoing percutaneous intervention


Objectives. We examined the relations of elevated creatine kinase (CK) and its myocardial band isoenzyme (CK-MB) to clinical outcomes after percutaneous coronary intervention (PCI) in patients enrolled in Integrilin (eptifibatide) to Minimize Platelet Aggregation and Coronary Thrombosis-II (trial) (IMPACT-II), a trial of the platelet glycoprotein IIb/IIIa inhibitor eptifibatide.

Background. Elevation of cardiac enzymes often occurs after PCI, but its clinical implications are uncertain.

Methods. Patients undergoing elective, scheduled PCI for any indication were analyzed. Parallel analyses investigated CK (n = 3,535) and CK-MB (n = 2,341) levels after PCI (within 4 to 20 h). Clinical outcomes at 30 days and 6 months were stratified by postprocedure CK and CK-MB (multiple of the site’s upper normal limit).

Results. Overall, 1,779 patients (76%) had no CK-MB elevation; CK-MB levels were elevated to 1 to 3 times the upper normal limit in 323 patients (13.8%), to 3 to 5 times normal in 84 (3.6%), to 5 to 10 times normal in 86 (3.7%), and to >10 times normal in 69 patients (2.9%). Elevated CK-MB was associated with an increased risk of death, reinfarction, or emergency revascularization at 30 days, and of death, reinfarction, or surgical revascularization at 6 months. Elevated total CK to above three times normal was less frequent, but its prognostic significance paralleled that seen for CK-MB. The degree of risk correlated with the rise in CK or CK-MB, even for patients with successful procedures not complicated by abrupt closure.

Conclusions. Elevations in cardiac enzymes, including small increases (between one and three times normal) often not considered an infarction, are associated with an increased risk for short-term adverse clinical outcomes after successful or unsuccessful PCI.

Circulation, 1999; 99: 121-126
Mobilization of Antioxidant Vitamin Pools and Hemodynamic Function After Myocardial Infarction

Vince P. Palace, Mike F. Hill, Firoozeh Farahmand, and Pawan K. Singal

Background-Although most previous studies have attempted to correlate plasma concentrations of vitamins with specific cardiovascular end points, metabolic considerations suggest that changes in myocardial tissue and storage organs may be better indicators of myocardial oxidative stress.

Methods and Results-Rats fed commercial chow or a diet enriched with vitamin E for 2 weeks were subjected to either a surgical myocardial infarction (MI) or a sham procedure. Rats were hemodynamically assessed 16 weeks after surgery, and their heart, liver, kidney, and plasma were analyzed for antioxidant vitamins E (tocopherol) and A (retinol and total retinyl esters). At 16 weeks, MI rats on a control diet showed depressed peak systolic and elevated diastolic pressures in both right and left ventricles compared with their sham controls. Plasma concentrations of vitamins E and A in MI rats were not different from sham controls fed the same diet. However, concentrations of vitamin E in left ventricle and liver and of vitamin A in liver (retinol) and kidney (retinyl esters) were decreased in rats with MI compared with the sham controls. Vitamin E supplementation improved hemodynamic function in rats with MI and increased plasma, myocardial, liver, and kidney concentrations of vitamin E. The vitamin E diet also prevented the loss of total retinyl esters from the kidney but not of retinol from the liver in MI rats.

Conclusions-Dietary supplements of vitamin E can sustain better cardiac function subsequent to MI. Antioxidant vitamin levels in the myocardium or in storage organs and not in plasma may be better indicators of myocardial oxidative stress.

JAMA, 1999;281:1291-1297

Diabetes and Decline in Heart Disease Mortality in US Adults

Ken Gu; Catherine C. Cowie; Maureen I. Harris

Context Mortality from coronary heart disease has declined substantially in the United States during the past 30 years. However, it is unknown whether patients with diabetes have also experienced a decline in heart
Objective To compare adults with diabetes with those without diabetes for time trends in mortality from all causes, heart disease, and ischemic heart disease.

Design, Setting, and Participants Representative cohorts of subjects with and without diabetes were derived from the First National Health and Nutrition Examination Survey (NHANES I) conducted between 1971 and 1975 (n=9639) and the NHANES I Epidemiologic Follow-up Survey conducted between 1982 and 1984 (n=8463). The cohorts were followed up prospectively for mortality for an average of 8 to 9 years.

Main Outcome Measure Changes in mortality rates per 1000 person-years for all causes, heart disease, and ischemic heart disease for the 1982-1984 cohort compared with the 1971-1975 cohort.

Results For the 2 periods, nondiabetic men experienced a 36.4% decline in age-adjusted heart disease mortality compared with a 13.1% decline for diabetic men. Age-adjusted heart disease mortality declined 27% in nondiabetic women but increased 23% in diabetic women. These patterns were also found for all-cause mortality and ischemic heart disease mortality.

Conclusions The decline in heart disease mortality in the general US population has been attributed to reduction in cardiovascular risk factors and improvement in treatment of heart disease. The smaller declines in mortality for diabetic subjects in the present study indicate that these changes may have been less effective for people with diabetes, particularly women.

Circulation, 1999;99: 779-785

Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction : Final Report of the Lyon Diet Heart Study

Michel de Lorgeril, Patricia Salen, Jean-Louis Martin, Isabelle Monjaud, Jacques Delaye, and Nicole Mamelle

Background-The Lyon Diet Heart Study is a randomized secondary prevention trial aimed at testing whether a Mediterranean-type diet may reduce the rate of recurrence after a first myocardial infarction. An intermediate analysis showed a striking protective effect after 27 months of follow-up. This report presents results of an extended follow-up (with a mean of 46 months per patient) and deals with the relationships of dietary patterns and traditional risk factors with recurrence.

Methods and Results-Three composite outcomes (COs) combining either cardiac death and nonfatal myocardial infarction (CO 1), or the preceding plus major secondary end points (unstable angina, stroke, heart failure, pulmonary or peripheral embolism) (CO 2), or the preceding plus minor events requiring hospital admission (CO 3) were studied. In the Mediterranean diet group, CO 1 was reduced (14 events versus 44 in the prudent Western-type diet group, P=0.0001), as were CO 2 (27 events versus 90, P=0.0001) and CO 3 (95 events...
versus 180, \( P = 0.0002 \)). Adjusted risk ratios ranged from 0.28 to 0.53. Among the traditional risk factors, total cholesterol (1 mmol/L being associated with an increased risk of 18% to 28%), systolic blood pressure (1 mm Hg being associated with an increased risk of 1% to 2%), leukocyte count (adjusted risk ratios ranging from 1.64 to 2.86 with count \( > 9 \times 10^9/L \)), female sex (adjusted risk ratios, 0.27 to 0.46), and aspirin use (adjusted risk ratios, 0.59 to 0.82) were each significantly and independently associated with recurrence.

Conclusions-The protective effect of the Mediterranean dietary pattern was maintained up to 4 years after the first infarction, confirming previous intermediate analyses. Major traditional risk factors, such as high blood cholesterol and blood pressure, were shown to be independent and joint predictors of recurrence, indicating that the Mediterranean dietary pattern did not alter, at least qualitatively, the usual relationships between major risk factors and recurrence. Thus, a comprehensive strategy to decrease cardiovascular morbidity and mortality should include primarily a cardioprotective diet. It should be associated with other (pharmacological?) means aimed at reducing modifiable risk factors. Further trials combining the 2 approaches are warranted.

JAMA, 1999;281:1718-1721

Malondialdehyde-Modified LDL as a Marker of Acute Coronary Syndromes

Paul Holvoet; Desire Collen; Frans Van de Werf

Context  Release of circulating malondialdehyde (MDA)-modified low-density lipoprotein (LDL) may reflect endothelial injury or plaque instability.

Objective. To determine the usefulness of MDA-modified LDL for identifying patients with unstable angina and acute myocardial infarction (AMI). Design  Blinded comparison of MDA-modified LDL, C-reactive protein, and troponin I followed by multiple receiver operating curve analysis. Setting University hospital. Participants  A total of 104 consecutive patients with acute coronary syndromes (42 with unstable angina and 62 with AMI), and 64 patients with stable coronary artery disease (CAD) without evidence of ischemia. Main Outcome Measures. Ability of MDA-modified LDL, C-reactive protein, and troponin I to discriminate patients with stable CAD, unstable angina, or AMI. Results. Malondialdehyde-modified LDL (\( X^2 = 10.2; P = 0.001 \)), but not troponin I or C-reactive protein, discriminated between stable CAD and unstable angina. Troponin I (\( X^2 = 14.5; P < 0.001 \)), but not MDA-modified LDL or C-reactive protein, discriminated between unstable angina and AMI. Both MDA-modified LDL and troponin I (\( X^2 = 14.5; P < 0.001 \) and \( X^2 = 5.3; P < 0.02, \))
respectively) but not C-reactive protein discriminated between stable CAD and AMI. The sensitivity of MDA-modified LDL was 95% for unstable angina and 95% for AMI, with a specificity of 95%. Values for troponin I were 38% and 90%, respectively, with a specificity of 95%. The combination of MDA-modified LDL and troponin I had a sensitivity of 98% for unstable angina and 100% for AMI, with a specificity of 99%.

Conclusion The combination of MDA-modified LDL, which may reflect endothelial injury or plaque instability, and troponin I, which reflects myocardial cell injury, allows better discrimination between stable CAD and acute coronary syndromes than troponin I alone.

JAMA, 1999;281:707-713

Prognostic Value of the Admission Electrocardiogram in Acute Coronary Syndromes

Stefano Savonitto; Diego Ardissino; Christopher B. Granger; Giorgio Morando; Maria D. Prando; Antonio Mafrci; Claudio Cavallini; Giovanni Melandri; Trevor D. Thompson; Alec Vahanian; E. Magnus Ohman; Robert M. Califf; Frans Van de Werf; Eric J. Topol

Context The presence of ischemic changes on electrocardiogram (ECG) correlates with poorer outcomes in patients with acute chest pain. Objective To determine the prognostic value of various ECG presentations of acute myocardial ischemia.

Design Retrospective analysis of the presenting ECGs of patients enrolled in Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb).

Setting Three hundred seventy-three hospitals in 13 countries in North America, Europe, Australia, and New Zealand.

Patients A total of 12,142 patients who reported symptoms of cardiac ischemia at rest within 12 hours of admission and had signs of myocardial ischemia confirmed by ECG. On presenting ECG, 22% of patients had T-wave inversion, 28% had ST-segment elevation, 35% had ST-segment depression, and 15% had a combination of ST-segment elevation and depression.

Main Outcome Measure Ability of presenting ECG to predict death or myocardial reinfarction during the first 30 days of follow-up.

Results The 30-day incidence of death or myocardial reinfarction was 5.5% in patients with T-wave inversion, 9.4% in those with ST-segment elevation, 10.5% in those with ST-segment depression, and 12.4% in those with ST-segment elevation and depression (P<.001). After adjusting for factors associated with an increased risk of 30-day death or reinfarction, compared with those who had T-wave inversion only, the odds of 30-day death or reinfarction were 1.68 (95% confidence interval [CI], 1.36-2.08) in those with ST-segment elevation, 1.62 (95% CI,
1.32-1.98) for those with ST-segment depression, and 2.27 (95% CI, 1.80-2.86) for those with combined elevation and depression. An elevated creatine kinase level at admission correlated with a higher risk of death (odds ratio [OR], 2.36; 95% CI, 1.92-2.91) and death or reinfarction (OR, 1.56; 95% CI, 1.32-1.85). The ECG category and creatine kinase level at admission remained highly predictive of death and myocardial infarction after multivariate adjustment for the significant baseline predictors of events.

Conclusions The ECG at presentation allows immediate risk stratification across the spectrum of acute coronary syndromes. An elevated creatine kinase level at admission is associated with worse outcomes.

Circulation, 1998 98: 839-844

Inflammation, Pravastatin, and the Risk of Coronary Events After Myocardial Infarction in Patients With Average Cholesterol Levels

Paul M. Ridker, Nader Rifai, Marc A. Pfeffer, Frank M. Sacks, Lemuel A. Moye, Steven Goldman, Greg C. Flaker, and Eugene Braunwald

Background-We studied whether inflammation after myocardial infarction (MI) is a risk factor for recurrent coronary events and whether randomized treatment with pravastatin reduces that risk.

Methods and Results-A nested case-control design was used to compare C-reactive protein (CRP) and serum amyloid A (SAA) levels in prerandomization blood samples from 391 participants in the Cholesterol and Recurrent Events (CARE) trial who subsequently developed recurrent nonfatal MI or a fatal coronary event (cases) and from an equal number of age- and sex-matched participants who remained free of these events during follow-up (control subjects). Overall, CRP and SAA were higher among cases than control subjects (for CRP P=0.05; for SAA P=0.006) such that those with levels in the highest quintile had a relative risk (RR) of recurrent events 75% higher than those with levels in the lowest quintile (for CRP RR=1.77, P=0.02; for SAA RR=1.74, P=0.02). The study group with the highest risk was that with consistent evidence of inflammation (elevation of both CRP and SAA) who were randomly assigned to placebo (RR=2.81, P=0.007); this risk estimate was greater than the product of the individual risks associated with inflammation or placebo assignment alone. In stratified analyses, the association between inflammation and risk was significant among those randomized to placebo (RR=2.11, P=0.048) but was attenuated and nonsignificant among those randomized to pravastatin (RR=1.29, P=0.5).

Conclusions-Evidence of inflammation after MI is associated with increased risk of recurrent coronary events.
Therapy with pravastatin may decrease this risk, an observation consistent with a nonlipid effect of this agent.

Circulation, 1999; 100: 1639-1645

Estrogen Inhibits Vascular Smooth Muscle Cell-Dependent Adventitial Fibroblast Migration In Vitro

Guohong Li, Yiu-Fai Chen, Geoffrey L. Greene, Suzanne Oparil, and John A. Thompson

Background-Mounting experimental evidence suggests that estrogen treatment protects against neointima formation in response to vascular injury in vivo. Previous studies have suggested that this process includes the activation and migration of adventitial fibroblasts. The present in vitro study was designed to establish a mechanism whereby estrogen attenuates migration of adventitial fibroblasts.

Methods and Results-Primary cultures of vascular smooth muscle cells (VSMCs) and adventitial fibroblasts were derived from female Sprague-Dawley rats. Reverse transcriptase-polymerase chain reaction and Western blotting were used to determine that expression of the estrogen receptor (ER) was restricted to early-passage VSMCs. Migration of transduced (retrovirally mediated) fibroblasts was determined by counting the number of blue lacZ-expressing cells attached to Boyden-type chambers preconditioned under defined experimental conditions. Compared with growth medium alone, chambers treated with medium conditioned by VSMCs demonstrated a 2-fold increase in fibroblast migration, suggesting that VSMCs release soluble factor(s) competent to bind the Transwell membrane and promote fibroblast migration. In contrast, treatment of VSMCs with 17ß-estradiol (10-9 to 10-7 mol/L) before preconditioning of the chamber induced a dose-dependent inhibition of fibroblast migration. Cotreatment of VSMCs with 17ß-estradiol and the ER antagonist ICI-182780 (10-7 mol/L) blocked the inhibitory effect of estrogen on fibroblast migration.

Conclusions-These observations suggest a novel mechanism of hormonal vasoprotection by which estrogen directly modulates VSMC expression of factor(s) controlling migration of adventitial fibroblasts via an ER-dependent mechanism.

Journal of the American College of Cardiology, 1999; 33:1347-1352

A prospective study of fibrinogen and risk of myocardial infarction in the physicians’ health study
OBJECTIVES
We examined the association of baseline plasma fibrinogen with future risk of myocardial infarction (MI) in the Physicians’ Health Study.

BACKGROUND
Elevated plasma fibrinogen increases and low dose aspirin decreases risk of MI. However, prospective data are limited about their interrelationships.

METHODS
Blood samples were prospectively collected at baseline from 14,916 men in the Physicians’ Health Study, aged 40 to 84 years, who were randomly assigned to take aspirin (325 mg every other day) or placebo for 5 years. We measured baseline plasma fibrinogen among 199 incident cases of MI and 199 age- and smoking-matched control subjects free of cardiovascular disease at the time of the case’s diagnosis.

RESULTS
Cases had significantly higher baseline fibrinogen levels (geometric mean: 262 mg/dl) than did control subjects (245 mg/dl, p = 0.02). Those with high fibrinogen levels (≥343 mg/dl, the 90th percentile distribution of the control subjects) had a twofold increase in MI risk (age- and smoking-adjusted relative risk = 2.09, 95% confidence interval = 1.15 to 3.78) compared with those with fibrinogen below 343 mg/dl. Adjustment for lipids and other coronary risk factors as well as randomized aspirin assignment did not materially change the result. Furthermore, we observed no interaction between fibrinogen level and aspirin treatment.

CONCLUSIONS
Among these apparently healthy U.S. male physicians, fibrinogen is associated with increased risk of future MI independent of other coronary risk factors, atherogenic factors such as lipids and antithrombotics such as aspirin.

Journal of the American College of Cardiology, 33:1005-1012

Lipoprotein(a) and coronary thrombosis and restenosis after stent placement

Anne Wehinger, Adnan Kastrati, Shpend Elezi, Hannsjorg Baum, Siegmund Braun, Franz-Josef Neumann, Albert Schomig
OBJECTIVES
The objective of this prospective study was to evaluate the relation between high lipoprotein(a) levels and thrombotic and restenotic events after coronary stent implantation.

BACKGROUND
Lipoprotein(a) may promote atherogenesis, coronary thrombosis and restenosis after balloon angioplasty, but the clinical significance remains unclear.

METHODS
The study included 2,223 consecutive patients with successful coronary stent placement. According to the serum level of lipoprotein(a), patients were divided in two groups: 457 patients of the highest quintile formed the high lipoprotein(a) group, and 1,766 patients of the lower four quintiles formed the low lipoprotein(a) group. Primary end points were the incidence of angiographic restenosis at six months and the event-free survival at one year. Secondary end point was the incidence of angiographic stent occlusion.

RESULTS
Early stent occlusion occurred in four of the 457 patients (0.9%) with high and 37 of the 1,766 patients (2.1%) with low lipoprotein(a) levels, odds ratio of 0.41 (95% confidence interval, 0.15 to 1.16). Angiographic restenosis occurred in 173 of the 523 lesions (33.2%) in the high lipoprotein(a) group and 636 of the 1,943 lesions (32.7%) in the low lipoprotein(a) group, odds ratio of 1.02 (0.83 to 1.25). The probability of event-free survival was 73.0% in the high lipoprotein(a) group and 74.8% in the low lipoprotein(a) group (p = 0.45). On the basis of the findings in the low lipoprotein(a) group, the power of this study to detect a 25% increase in the incidence of restenosis and adverse events in the group with elevated lipoprotein(a) was 90% and 75%, respectively.

CONCLUSIONS
Elevated lipoprotein(a) levels did not influence the one-year clinical and angiographic outcome after stent placement. Thrombotic events and measures of restenosis were not adversely affected by the presence of high lipoprotein(a) levels.

Circulation, 1999 ;99: 237-242

C-Reactive Protein, a Sensitive Marker of Inflammation, Predicts Future Risk of Coronary Heart Disease in Initially Healthy Middle-Aged Men : Results From the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992

Wolfgang Koenig, Malte Sund, Margit Frohlich, Hans-Gunther Fischer, Hannelore Lowel, Angela Doring,
Background-Inflammatory reactions in coronary plaques play an important role in the pathogenesis of acute atherothrombotic events; inflammation elsewhere is also associated with both atherogenesis generally and its thrombotic complications. Recent studies indicate that systemic markers of inflammation can identify subjects at high risk of coronary events.

Methods and Results-We used a sensitive immunoradiometric assay to examine the association of serum C-reactive protein (CRP) with the incidence of first major coronary heart disease (CHD) event in 936 men 45 to 64 years of age. The subjects, who were sampled at random from the general population, participated in the first MONICA Augsburg survey (1984 to 1985) and were followed for 8 years. There was a positive and statistically significant unadjusted relationship, which was linear on the log-hazards scale, between CRP values and the incidence of CHD events (n=53). The hazard rate ratio (HRR) of CHD events associated with a 1-SD increase in log-CRP level was 1.67 (95% CI, 1.29 to 2.17). After adjustment for age, the HRR was 1.60 (95% CI, 1.23 to 2.08). Adjusting further for smoking behavior, the only variable selected from a variety of potential confounders by a forward stepping process with a 5% change in the relative risk of CRP as the selection criterion, yielded an HRR of 1.50 (95% CI, 1.14 to 1.97).

Conclusions-These results confirm the prognostic relevance of CRP, a sensitive systemic marker of inflammation, to the risk of CHD in a large, randomly selected cohort of initially healthy middle-aged men. They suggest that low-grade inflammation is involved in pathogenesis of atherosclerosis, especially its thrombo-occlusive complications.

Circulation, 1999;99: 2733-2736

Relation Between Direct Detection of Chlamydia pneumoniae DNA in Human Coronary Arteries at Postmortem Examination and Histological Severity (Stary Grading) of Associated Atherosclerotic Plaque

M. Thomas, Y. Wong, D. Thomas, M. Ajaz, V. Tsang, P. J. Gallagher, and M. E. Ward

Background-Numerous studies have suggested a link between Chlamydia pneumoniae infection, atherosclerosis, and coronary artery disease. However, it is still unclear whether C pneumoniae plays a causal
role in the pathogenesis of these conditions. Accordingly, we have performed a systematic dissection of the coronary arteries on postmortem subjects and studied the relationship in individual artery segments between the presence of C pneumoniae DNA and the severity of associated atherosclerosis.

Methods and Results-The prevalence of C pneumoniae DNA in arterial segments was determined by polymerase chain reaction (PCR) after controlling for the presence of PCR inhibitors. Atherosclerosis in each arterial segment was graded histologically with the Stary classification. C pneumoniae was detected by PCR in 78.8% of subjects, but there was no association between the presence of this DNA and cause of death or grade of atherosclerosis. When paired mild and severe atherosclerotic lesions within subjects were compared, mild lesions were as likely to be positive for C pneumoniae as severe lesions.

Conclusions-This study demonstrates that C pneumoniae can frequently be detected in atheromatous plaques in coronary arteries. However, its distribution did not correlate with severity or extent of disease.

Circulation, 1999;100: 1268-1273

Heterozygosity for a Hereditary Hemochromatosis Gene Is Associated With Cardiovascular Death in Women

Mark Roest, Yvonne T. van der Schouw, Bart de Valk, Jo J. M. Marx, Marielle J. Tempelman, Philip G. de Groot, Jan J. Sixma, and Jan Dirk Banga

Background-The genetic background of hereditary hemochromatosis (HH) is homozygosity for a cysteine-to-tyrosine transition at position 282 in the HFE gene. Heterozygosity for HH is associated with moderately increased iron levels and could be a risk factor for cardiovascular death.

Methods and Results-We studied the relation between HH heterozygosity and cardiovascular death in a cohort study among 12 239 women 51 to 69 years of age residing in Utrecht, the Netherlands. Women were followed for 16 to 18 years (182 976 follow-up years). The allele prevalence of the HH gene in the reference group was 4.0 (95% CI 2.9 to 5.4). The mortality rate ratios for HH heterozygotes compared with wild types was 1.5 (95% CI 0.9 to 2.5) for myocardial infarction (n=242), 2.4 (95% CI 1.3 to 3.5) for cerebrovascular disease (n=118), and 1.6 (95% CI 1.1 to 2.4) for total cardiovascular disease (n=530). The population-attributable risks of HH heterozygosity for myocardial infarction and cerebrovascular and total cardiovascular death were 3.3%, 8.8%, and 4.0%, respectively. In addition, we found evidence for effect modification by hypertension and smoking.

Conclusions-We found important evidence that inherited variation in iron metabolism is involved in cardiovascular death in postmenopausal women, especially in women already carrying classic risk factors.
Endothelial Dysfunction, Impaired Endogenous Fibrinolysis, and Cigarette Smoking: A Mechanism for Arterial Thrombosis and Myocardial Infarction

David E. Newby, Robert A. Wright, Catherine Labinjoh, Christopher A. Ludlam, Keith A. A. Fox, Nicholas A. Boon, and David J. Webb

Background—Effective endogenous fibrinolysis requires rapid release of tissue plasminogen activator (tPA) from the vascular endothelium. Smoking is a known risk factor for arterial thrombosis and myocardial infarction, and it causes endothelial dysfunction. We therefore examined the effects of cigarette smoking on substance P-induced tPA release in vivo in humans.

Methods and Results—Blood flow and plasma fibrinolytic factors were measured in both forearms of 12 smokers and 12 age- and sex-matched nonsmokers who received unilateral brachial artery infusions of substance P (2 to 8 pmol/min). In both smokers and nonsmokers, substance P caused dose-dependent increases in blood flow and local release of plasma tPA antigen and activity (P<0.001 for all) but had no effect on the local release of plasminogen activator inhibitor type 1. Compared with nonsmokers, increases in forearm blood flow (P=0.03) and release of tPA antigen (P=0.04) and activity (P<0.001) caused by substance P were reduced in smokers. The area under the curve for release of tPA antigen and activity decreased by 51% and 53%, respectively.

Conclusions—Cigarette smoking causes marked inhibition of substance P-induced tPA release in vivo in humans. This provides an important mechanism whereby endothelial dysfunction may increase the risk of atherothrombosis through a reduction in the acute fibrinolytic capacity.

Homozygosity for 807 T Polymorphism in α2 Subunit of Platelet α2ß1 Is Associated With Increased Risk of Cardiovascular Mortality in High-Risk Women

Mark Roest, Jan Dirk Banga, Diederick E. Grobbee, Philip G. de Groot, Jan J. Sixma, Marielle J. Tempelman, and Yvonne T. van der Schouw
Background-Platelet adhesion to collagen is the initial step in both hemostasis and thrombosis; this adhesion is mediated by α2β1 on the surface of platelet membranes. An 807 C to T single nucleotide exchange polymorphism close to the gene coding for the α2 subunit of α2β1 is associated with the density of α2β1 on the platelet membrane.

Methods and Results-We studied the relation of the α2β1 807 C/T genotype to cardiovascular mortality in a prospective cohort study of 12 239 women who were invited for the breast cancer screening program of Utrecht, the Netherlands. The initial age was between 52 and 67 years. Women were followed on vital status between 1976 and 1995 (168 513 women-years). Data were analyzed by using a nested case-control design. The α2β1 807 C/T genotype was not associated with cardiovascular mortality in the total population: the rate ratio for cardiovascular mortality in 807 TT homozygotes compared with 807 CC wild types was 1.2 (95% CI 0.8 to 1.7). However, the α2β1 807 T polymorphism was associated with an increased risk of cardiovascular mortality in women who smoked or in women who had indications of compromised endothelium, such as diabetes and microalbuminuria. In those who were exposed to ≥2 of these factors, the risk ratio (95% CI) between α2β1 807 TT homozygotes and 807 CC wild types was 14.1 (5.0 to 39.9).

Conclusions- α2β1 807 TT homozygosity, coding for increased α2β1 density on the platelet membrane, is associated with an increased risk of cardiovascular mortality in those women with indications of compromised endothelium.

Circulation, 1999; 99: 1161-1164

Prospective Study of Chlamydia pneumoniae IgG Seropositivity and Risks of Future Myocardial Infarction

Paul M. Ridker, Ruth B. Kundsin, Meir J. Stampfer, Sharon Poulin, and Charles H. Hennekens

Background-Chlamydia pneumoniae has been hypothesized to play a role in atherothrombosis. However, prospective data relating exposure to Chlamydia pneumoniae and risks of future myocardial infarction (MI) are sparse.

Methods and Results-In a prospective cohort of nearly 15 000 healthy men, we measured IgG antibodies directed against Chlamydia pneumoniae in blood samples collected at baseline from 343 study participants who subsequently reported a first MI and from an equal number of age- and smoking-matched control subjects who did not report vascular disease during a 12-year follow-up period. The proportion of study subjects with IgG antibodies directed against Chlamydia increased with age and cigarette consumption. However, prevalence rates of Chlamydia IgG seropositivity were virtually identical at baseline among men who
subsequently reported first MI compared with age- and smoking-matched control subjects. Specifically, the relative risks of future MI associated with Chlamydia pneumoniae IgG titers \( \geq 1:16, 1:32, 1:64, 1:128, \) and \( 1:256 \) were 1.1, 1.0, 1.1, 1.0, and 0.8, respectively (all probability values not significant). There was no association in analyses adjusted for other risk factors, evaluating early as compared with late events, or among nonsmokers. Further, there was no association between seropositivity and concentration of C-reactive protein, a marker of inflammation that predicts MI risk in this cohort.

Conclusions-In a large-scale study of socioeconomiclly homogeneous men that controlled for age, smoking, and other cardiovascular risk factors, we found no evidence of association between Chlamydia pneumoniae IgG seropositivity and risks of future MI.

Circulation, 1998 ;98: 1279-1285

Better Outcome for Women Compared With Men Undergoing Coronary Revascularization : A Report From the Bypass Angioplasty Revascularization Investigation (BARI)

Alice K. Jacobs, Sheryl F. Kelsey, Maria Mori Brooks, David P. Faxon, Bernard R. Chaitman, Vera Bittner, Michael B. Mock, Bonnie H. Weiner, Larry Dean, Carla Winston, Laura Drew, and George Sopko

Background-Numerous studies have shown that women undergoing coronary revascularization procedures do so at a higher risk for an adverse outcome compared with men. However, the impact of advances in technology and improvements in techniques on in-hospital and long-term outcome after revascularization in women is unclear.

Methods and Results-We evaluated 1829 patients with symptomatic multivessel coronary disease randomized to CABG or PTCA in the Bypass Angioplasty Revascularization Investigation (BARI), of whom 27% were women. As expected, women were older (64.0 versus 60.5 years), with more congestive heart failure (14% versus 7%), hypertension (68% versus 42%), treated diabetes mellitus (31% versus 15%), and unstable angina (67% versus 61%) than men but had similar preservation of left ventricular function and extent of multivessel disease. Women assigned to surgery received the same number of total grafts but fewer internal mammary artery grafts (72% versus 85%, \( P<0.01 \)), and those assigned to angioplasty had more intended lesions (76% versus 71%, \( P<0.01 \)) successfully dilated than men. At an average of 5.4 years’ follow-up, crude mortality rates were similar in women (12.8%) and men (12.0%). The Cox regression model adjusting for baseline differences revealed that women had a significantly lower risk of death (relative risk, 0.60; 95% CI, 0.43 to 0.84; \( P=0.003 \)) but
not a significantly lower risk of death plus myocardial infarction (relative risk, 0.84; 95% CI, 0.66 to 1.07; P=0.16) than men.

Conclusions—Although the unadjusted mortality rate suggests that women and men undergoing CABG and PTCA have a similar 5-year mortality, women have higher risk profiles; consequently, contrary to previous reports, female sex is an independent predictor of improved 5-year survival after we control for multiple risk factors.

Circulation, 1999; 99: 1540-1547

Randomized Secondary Prevention Trial of Azithromycin in Patients With Coronary Artery Disease and Serological Evidence for Chlamydia pneumoniae Infection: The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) Study


Background—Chlamydia pneumoniae commonly causes respiratory infection, is vasotropic, causes atherosclerosis in animal models, and has been found in human atheromas. Whether it plays a causal role in clinical coronary artery disease (CAD) and is amenable to antibiotic therapy is uncertain.

Methods and Results—CAD patients (n=302) who had a seropositive reaction to C pneumoniae (IgG titers ≥ 1:16) were randomized to receive placebo or azithromycin, 500 mg, daily for 3 days, then 500 mg, weekly for 3 months. Circulating markers of inflammation (C-reactive protein [CRP], interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]-α), C pneumoniae antibody titers, and cardiovascular events were assessed at 3 and 6 months. Treatment groups were balanced, with age averaging 64 (SD=10) years; 89% of the patients were male. Azithromycin reduced a global rank sum score of the 4 inflammatory markers at 6 (but not 3) months (P=0.011) as well as the mean global rank sum change score: 531 (SD=201) for active drug and 587 (SD=190) for placebo (P=0.027). Specifically, change-score ranks were significantly lower for CRP (P=0.011) and IL-6 (P=0.043). Antibody titers were unchanged, and number of clinical cardiovascular events at 6 months did not differ by therapy (9 for active drug, 7 for placebo). Azithromycin decreased infections requiring antibiotics (1 versus 12 at 3 months, P=0.002) but caused more mild, primarily gastrointestinal, adverse effects (36 versus 17, P=0.003).

Conclusions—In CAD patients positive for C pneumoniae antibodies, global tests of 4 markers of inflammation improved at 6 months with azithromycin. However, unlike another smaller study, no differences in antibody
titers and clinical events were observed. Longer-term and larger studies of antichlamydial therapy are indicated.

Circulation, 1999; 99: 2633-2638

Coronary Calcium Does Not Accurately Predict Near-Term Future Coronary Events in High-Risk Adults


Background—Prognostic risk models have had limited success in predicting coronary events in subjects with multiple risk factors. We and others have proposed an alternative approach using radiographically detectable coronary calcium. We evaluated and compared the predictive value of these 2 approaches for determining coronary event risk in asymptomatic adults with multiple coronary risk factors. In addition, we assessed the predictive value of a risk model that included calcium score and cardiac risk-factor data.

Methods and Results—We recruited 1196 asymptomatic high-coronary-risk subjects who then underwent risk-factor assessment and cardiac electron-beam CT (EBCT) scanning and were followed up for 41 months with a 99% success rate. We applied the Framingham model and our data-derived risk model to determine the 3-year likelihood of a coronary event. The mean age of our cohort was 66 years, and mean 3-year Framingham risk was 3.3±3.6%. Sixty-eight percent (818 subjects) had detectable coronary calcium. There were 17 coronary deaths (1.4%) and 29 nonfatal infarctions (2.4%). The receiver operating characteristic (ROC) curve areas calculated from the Framingham model, our data-derived risk model, and the calcium score were 0.69±0.05, 0.68±0.05, and 0.64±0.05, respectively (P=NS). When calcium score was included as a variable in the data-derived model, the ROC area did not change significantly (0.68±0.05 to 0.71±0.04; P=NS).

Conclusions—Neither risk-factor assessment nor EBCT calcium is an accurate event predictor in high-risk asymptomatic adults. EBCT calcium score does not add significant incremental information to risk factors, and its use in clinical screening is not justified at this time.

Circulation, 1999; 99: 879-882
Detection of Chlamydia pneumoniae But Not Cytomegalovirus in Occluded Saphenous Vein Coronary Artery Bypass Grafts

Claus Bartels, Matthias Maass, Gregor Bein, Rainer Malisius, Nicole Brill, J. F. Matthias Bechtel, Friedhelm Sayk, Alfred C. Feller, and Hans-Hinrich Sievers

Background-A causal relation between atherosclerosis and chronic infection with Chlamydia pneumoniae and/or cytomegalovirus (CMV) has been suggested. Whether the unresolved problem of venous coronary artery bypass graft occlusion is related to infection with C pneumoniae and/or CMV has not been addressed.

Methods and Results-Thirty-eight occluded coronary artery vein grafts and 20 native saphenous veins were examined. Detection of C pneumoniae DNA was performed by use of nested polymerase chain reaction (PCR). Homogenisates from the specimen were cultured for identification of viable C pneumoniae. Both conventional PCR and quantitative PCR for detection of CMV DNA were applied. Differential pathological changes (degree of inflammation, smooth muscle cell proliferation [MIB-1]) were determined and correlated to the detection of both microorganisms. C pneumoniae DNA could be detected in 25% of occluded vein grafts. Viable C pneumoniae was recovered from 16% of occluded vein grafts. Except for 1 native saphenous vein, all control vessels were negative for both C pneumoniae detection and culture. All pathological and control specimens were negative for CMV DNA detection. Pathological changes did not correlate with C pneumoniae detection.

Conclusions-Occluded aorto-coronary venous grafts harbor C pneumoniae but not CMV. The detection of C pneumoniae in occluded vein grafts warrants further investigation.

Circulation, 1999;99:111-120

Age-Dependent Impairment of Angiogenesis

Alain Rivard, MD; Jean-Etienne Fabre, MD; Marcy Silver, BS; Dongfen Chen, MD; Toyoaki Murohara, MD; Marianne Kearney, BS; Meredith Magner, BS; Takayuki Asahara, MD; Jeffrey M. Isner, MD

Background
The effect of aging on angiogenesis in ischemic vascular disease has not been studied. Accordingly, we
investigated the hypothesis that angiogenesis is impaired as a function of age.

Methods and Results

Forty days after the resection of 1 femoral artery, collateral vessel development was significantly impaired in old (aged 4 to 5 years; n=7) versus young (aged 6 to 8 months; n=6) New Zealand White (NZW) rabbits on the basis of reduced hindlimb perfusion (ischemic: normal blood pressure ratio=0.58±0.05 versus 0.77±0.06; P<0.005), reduced number of angiographically visible vessels (angiographic score=0.48±0.05 versus 0.70±0.06; P<0.01), and lower capillary density in the ischemic limb (130.3±5.8/mm2 versus 171.4±9.5/mm2; P<0.001). Angiogenesis was also impaired in old (aged 2 years) versus young (aged 12 weeks) mice as shown by reduced hindlimb perfusion (measured by laser Doppler imaging) and lower capillary density (353.0±14.3/mm2 versus 713.3±63.4/mm2; P<0.01). Impaired angiogenesis in old animals was the result of impaired endothelial function (lower basal NO release and decreased vasodilation in response to acetylcholine) and a lower expression of vascular endothelial growth factor (VEGF) in ischemic tissues (by Northern blot, Western blot, and immunohistochemistry). When recombinant VEGF protein was administered to young and old rabbits, both groups exhibited a significant and similar increase in blood pressure ratio, angiographic score, and capillary density.

Conclusions

Angiogenesis responsible for collateral development in limb ischemia is impaired with aging; responsible mechanisms include age-related endothelial dysfunction and reduced VEGF expression. Advanced age, however, does not preclude augmentation of collateral vessel development in response to exogenous angiogenic cytokines.

Journal of the American College of Cardiology, 1999;33:1:152-156

The prevalence of Chlamydia pneumoniae in atherosclerotic and nonatherosclerotic blood vessels of patients attending for redo and first time coronary artery bypass graft surgery

Yuk-ki Wong, Martine Thomas, Victor Tsang, Patrick J. Gallagher, Michael E. Ward

Objectives. To determine if Chlamydia pneumoniae (C. pneumoniae) is more prevalent in atherosclerotic compared with normal blood vessels of patients requiring redo and first time coronary artery bypass graft surgery (CABG).

Background. Serological and pathological studies have associated atherosclerosis with C. pneumoniae infection.
As atherosclerosis is one of the causes of graft failure following CABG, then it may be expected that the prevalence of the organism in failed grafts and diseased native vessels should be greater than in the new grafts.

Methods. Endarterectomy specimens and failed and new grafts were collected from 49 patients with late graft failure. Endarterectomy specimens and new grafts were also collected from nine patients having first time CABG. The presence of C. pneumoniae DNA was then checked for using a nested polymerase chain reaction.

Results. The prevalence of C. pneumoniae DNA in failed venous grafts (38.2%) was similar to that in endarterectomy specimens from native coronary arteries (38.5%) and greater than that in new saphenous vein grafts (11.8%). However, it was similar to that in new internal mammary artery grafts (30.0%). Also, the interval between surgery in redo patients was the same regardless of whether C. pneumoniae was present or not.

Conclusions. Cross sectional studies cannot determine whether C. pneumoniae is a cause of atherosclerosis since they do not show whether infection precedes or follows its development. However, our results suggest that the organism is not an important factor in graft failure or atherosclerosis.

Circulation, 1999;99:1141-1146

Endogenous Nitric Oxide Synthase Inhibitor: A Novel Marker of Atherosclerosis

Hiroshi Miyazaki, Hidehiro Matsuoka, John P. Cooke, Michiaki Usui, Seiji Ueda, Seiya Okuda, and Tsutomu Imaizumi

Background-Exposure to risk factors such as hypertension or hypercholesterolemia decreases the bioavailability of endothelium-derived nitric oxide (NO) and impairs endothelium-dependent vasodilation. Recently, a circulating endogenous NO synthase inhibitor, asymmetric dimethylarginine (ADMA), has been detected in human plasma. The purpose of this study was to examine the relationship between plasma ADMA and atherosclerosis in humans.

Methods and Results-Subjects (n=116; age, 52±1 years; male:female ratio, 100:16) underwent a complete history and physical examination, determination of serum chemistries and ADMA levels, and duplex scanning of the carotid arteries. These individuals had no symptoms of coronary or peripheral artery disease and were taking no medications. Univariate and multivariate analyses revealed that plasma levels of ADMA were positively correlated with age (P<0.0001), mean arterial pressure (P<0.0001), and glucose (an index of glucose tolerance) (P=0.0006). Most intriguingly, stepwise regression analysis revealed that plasma ADMA levels were significantly correlated to the intima-media thickness of the carotid artery (as measured by high-resolution
Conclusions-This study reveals that plasma ADMA levels are positively correlated with risk factors for atherosclerosis. Furthermore, plasma ADMA level is significantly correlated with carotid intima-media thickness. Our results suggest that this endogenous antagonist of NO synthase may be a marker of atherosclerosis.

Journal of the American College of Cardiology, 2000;35:76-82

Cholesterol reduction improves myocardial perfusion abnormalities in patients with coronary artery disease and average cholesterol levels

Jose M. Mostaza, Maria V. Gomez, Felix Gallardo, Maria L. Salazar, Raquel Martin-Jadraque, Leandro Plaza-Celemin, Isidoro Gonzalez-Maqueda, Luis Martin-Jadraque

OBJECTIVES
We sought to evaluate whether pravastatin treatment increases myocardial perfusion, as assessed by thallium-201 single-photon emission computed tomographic (SPECT) dipyridamole testing, in patients with coronary artery disease (CAD) and average cholesterol levels.

BACKGROUND
Previous studies in hypercholesterolemic patients have demonstrated that cholesterol reduction restores peripheral and coronary endothelium-dependent vasodilation and increases myocardial perfusion.

METHODS
This was a randomized, placebo-controlled study with a cross-over design. Twenty patients with CAD were randomly assigned to receive 20 mg of pravastatin or placebo for 16 weeks and then were crossed over to the opposite medication for a further 16 weeks. Lipid and lipoprotein analysis and dipyridamole thallium-201 SPECT were performed at the end of each period. The SPECT images were visually analyzed in eight myocardial segments using a 4-point scoring system by two independent observers. A summed stress score and a summed rest score were obtained for each patient. Quantitative evaluation was performed by the Cedars-Sinai method. The magnitude of the defect was expressed as a percentage of global myocardial perfusion.

RESULTS
Total and low density lipoprotein cholesterol levels during placebo were $214 \pm 29$ mg/dl and $148 \pm 25$ mg/dl, respectively. These levels with pravastatin were $170 \pm 23$ mg/dl and $103 \pm 23$ mg/dl, respectively. The
summed stress score and summed rest score were lower with pravastatin than with placebo (7.2 ± 2.3 vs. 5.9 ± 2.3, p = 0.012 and 3.2 ± 1.6 vs. 2.4 ± 2.2, p = 0.043, respectively). Quantitative analysis showed a smaller perfusion defect with pravastatin (29.2%) as compared with placebo (33.8%) (p = 0.021) during dipyridamole stress. No differences were found at rest.

CONCLUSIONS
Reducing cholesterol levels with pravastatin in patients with CAD improves myocardial perfusion during dipyridamole stress thallium-201 SPECT.


Effect of Cigar Smoking on the Risk of Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, and Cancer in Men

Carlos Iribarren, Irene S. Tekawa, Stephen Sidney, Gary D. Friedman

Background. The sale of cigars in the United States has been increasing since 1993. Cigar smoking is a known risk factor for certain cancers and for chronic obstructive pulmonary disease (COPD). However, unlike the relation between cigarette smoking and cardiovascular disease, the association between cigar smoking and cardiovascular disease has not been clearly established.

Methods. We performed a cohort study among 17,774 men 30 to 85 years of age at base line (from 1964 through 1973) who were enrolled in the Kaiser Permanente health plan and who reported that they had never smoked cigarettes and did not currently smoke a pipe. Those who smoked cigars (1546 men) and those who did not (16,228) were followed from 1971 through the end of 1995 for a first hospitalization for or death from a major cardiovascular disease or COPD, and through the end of 1996 for a diagnosis of cancer.

Results. In multivariate analyses, cigar smokers, as compared with nonsmokers, were at higher risk for coronary heart disease (relative risk, 1.27; 95 percent confidence interval, 1.12 to 1.45), COPD (relative risk, 1.45; 95 percent confidence interval, 1.10 to 1.91), and cancers of the upper aerodigestive tract (relative risk, 2.02; 95 percent confidence interval, 1.01 to 4.06) and lung (relative risk, 2.14; 95 percent confidence interval, 1.12 to 4.11), with evidence of dose-response effects. There appeared to be a synergistic relation between cigar smoking and alcohol consumption with respect to the risk of oropharyngeal cancers and cancers of the upper aerodigestive tract.

Conclusions. Independently of other risk factors, regular cigar smoking can increase the risk of coronary heart
disease, COPD, and cancers of the upper aerodigestive tract and lung.

Circulation, 1999;99:855-60

Elevated Levels of C-Reactive Protein at Discharge in Patients With Unstable Angina Predict Recurrent Instability

Luigi M. Biasucci, Giovanna Liuzzo, Rita L. Grillo, Giuseppina Caligiuri, Antonio G. Rebuzzi, Antonino Buffon, Francesco Summaria, Francesca Ginnetti, Giovanni Fadda, and Attilio Maseri

Background-In a group of patients admitted for unstable angina, we investigated whether C-reactive protein (CRP) plasma levels remain elevated at discharge and whether persistent elevation is associated with recurrence of instability.

Methods and Results-We measured plasma levels of CRP, serum amyloid A protein (SAA), fibrinogen, total cholesterol, and Helicobacter pylori and Chlamydia pneumoniae antibody titers in 53 patients admitted to our coronary care unit for Braunwald class IIIB unstable angina. Blood samples were taken on admission, at discharge, and after 3 months. Patients were followed for 1 year. At discharge, CRP was elevated (>3 mg/L) in 49% of patients; of these, 42% had elevated levels on admission and at 3 months. Only 15% of patients with discharge levels of CRP <3 mg/L but 69% of those with elevated CRP (P<0.001) were readmitted because of recurrence of instability or new myocardial infarction. New phases of instability occurred in 13% of patients in the lower tertile of CRP (<2.5 mg/L), in 42% of those in the intermediate tertile (2.6 to 8.6 mg/L), and in 67% of those in the upper tertile (>8.7 mg/L, P<0.001). The prognostic value of SAA was similar to that of CRP; that of fibrinogen was not significant. Chlamydia pneumoniae but not Helicobacter pylori antibody titers significantly correlated with CRP plasma levels.

Conclusions-In unstable angina, CRP may remain elevated for at 3 months after the waning of symptoms and is associated with recurrent instability. Elevation of acute-phase reactants in unstable angina could represent a hallmark of subclinical persistent instability or of susceptibility to recurrent instability and, at least in some patients, could be related to chronic Chlamydia pneumoniae infection.

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Association of Serum Antibodies to Heat-Shock Protein 65 With Carotid Atherosclerosis: Clinical Significance
Determined in a Follow-Up Study

Qingbo Xu, Stefan Kiechl, Manuel Mayr, Bernhard Metzler, Georg Egger, Friedrich Oberhollenzer, Johann Willeit, and Georg Wick

Background-Previous work has proved that increased titers of antibodies against heat-shock protein (hsp) 65 are associated with atherosclerotic lesions independently of other established risk factors. The present follow-up study was designed to further scrutinize the association of hsp antibodies and atherosclerosis and evaluate the possible predictive value of these antibodies for the development and progression of lesions in the same population.

Methods and Results-A total of 750 subjects 45 to 74 years old were recruited, and the rate of participation was 93.6%; 58 subjects died between 1990 and 1995. All participants were subjected to determination of serum antibodies against hsp65 and sonography to assess carotid atherosclerotic lesions and evaluate other risk factors, ie, age, sex, body mass index, blood cholesterol, apolipoprotein B, apolipoprotein A, triglycerides, lipoprotein(a), fibrinogen, leukocyte number, antithrombin III, ESR, ferritin, hypertension, smoking, and diabetes mellitus. Our data show that hsp65 antibody titers in the population emerged as highly consistent over a 5-year observation period (r=0.78, P<0.0001). Titers were significantly elevated in subjects with progressive carotid atherosclerosis and correlated with intima-media thickness. Multiple linear regression analysis documented these associations to be independent of age, sex, and other risk factors. Subanalyses revealed a preferential association of hsp65 antibody titers with advanced lesions (odds ratio, 1.42; 95% CI, 1.02 to 1.98; P=0.039). Other risk factors neither confounded nor modified this association. Finally, hsp65 antibody titers significantly predicted the 5-year mortality (hazard ratio, 1.52; 95% CI, 1.14 to 2.03; P<0.001).

Conclusions-These findings indicate a sustained existence of anti-hsp65 antibodies in subjects with severe atherosclerosis, which is predictive for mortality.

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Ability of troponins to predict adverse outcomes in patients with renal insufficiency and suspected acute coronary syndromes: a case-matched study

Frederick Van Lente, Ellen S. McErlean, Sue A. DeLuca, W. Franklin Peacock, J. Sunil Rao, Steven E. Nissen
Objectives
The purpose of this study was to investigate the utility of cardiac troponin T and troponin I for predicting outcomes in patients presenting with suspected acute coronary syndromes and renal insufficiency relative to that observed in similar patients without renal disease.

Background
Cardiac troponin T and troponin I have shown promise as tools for risk stratification of patients with acute coronary syndromes. However, there is uncertainty regarding their cardiac specificity and utility in patients with renal disease.

Methods
We measured troponin T, troponin I and creatine kinase MB in 51 patients presenting with suspected acute coronary syndromes and renal insufficiency and in 102 patients without evidence of renal disease matched for the same peak troponin T or I value, selected from a larger patient cohort. Blood samples were obtained at presentation to an emergency room 4 hours, 8 hours and 16 hours later. The ability of biochemical markers to predict adverse outcomes in both groups including infarction, recurrent ischemia, bypass surgery, heart failure, stroke, death or positive angiography/angioplasty during hospitalization and at six months was assessed by receiver-operator curve analysis. The performance of both troponins was compared between groups.

Results
Thirty-five percent of patients in the renal group and 45% of patients in the nonrenal group experienced an adverse initial outcome; over 50% of patients in all groups had experienced an adverse outcome by 6 months, but these differences were not significant. The area under the curve (AUC) for the ROC curve for troponin T as predictor of initial outcomes was significantly lower in the renal group than in the nonrenal group: 0.56 ± 0.07 and 0.75 ± 0.07, respectively. The area under the curve was also significantly lower in the renal group compared with the nonrenal group for troponin T as predictor of six month outcomes: 0.59 ± 0.07 and 0.74 ± 0.07, respectively. The area under the curve was also significantly lower in the renal group compared to the nonrenal group for troponin I as predictor of both initial and six month outcomes: 0.54 ± 0.06 vs. 0.71 ± 0.07 and 0.53 ± 0.06 vs. 0.65 ± 0.07, respectively. The sensitivity of troponin T for both initial and six month adverse outcomes was significantly lower in the renal group than in the nonrenal group at a similar level of specificity (0.87): 0.29 vs. 0.60 and 0.45 vs. 0.56, respectively. Troponin I also exhibited similar differences in sensitivity in the renal group (0.29 vs. 0.50 and 0.33 vs. 0.40, respectively).

Conclusions
The ability of cardiac troponin T and troponin I to predict risk for subsequent adverse outcomes in patients presenting with suspected acute coronary syndromes is reduced in the presence of renal insufficiency.
Effects of Oral Folic Acid Supplementation on Endothelial Function in Familial Hypercholesterolemia: A Randomized Placebo-Controlled Trial

Marianne C. Verhaar, Robert M. F. Wever, John J. P. Kastelein, Douwe van Loon, Sheldon Milstien, Hein A. Koomans, and Ton J. Rabelink

Background—Folates have been suggested to be of benefit in reducing cardiovascular risk. The present study was designed to examine whether oral folic acid supplementation could improve endothelial function as an intermediate end point for cardiovascular risk in patients with increased risk of atherosclerosis due to familial hypercholesterolemia (FH).

Methods and Results—In a prospective, randomized, double-blind, placebo-controlled study with crossover design, we evaluated the effects of 4 weeks of treatment with oral folic acid (5 mg PO) on endothelial function in FH. In 20 FH patients, forearm vascular function was assessed at baseline, after 4 weeks of folic acid treatment, and after 4 weeks of placebo treatment by venous occlusion plethysmography, with serotonin and sodium nitroprusside used as endothelium-dependent and -independent vasodilators. In addition, we examined the vasoconstrictor response to the NO synthase inhibitor NG-monomethyl-L-arginine to assess basal NO activity. In FH patients, folic acid supplementation restored the impaired endothelium-dependent vasodilation, whereas it did not significantly influence endothelium-independent vasodilation or basal forearm vasomotion. There was a trend toward improvement in basal NO activity.

Conclusions—These data demonstrate that oral supplementation of folic acid can improve endothelial function in patients with increased risk of atherosclerotic disease due to hypercholesterolemia, without changes in plasma lipids.
OBJECTIVES
We sought to examine the individual and combined effects of estrogen/progestin therapy versus lovastatin on lipids and flow-mediated vasodilation in postmenopausal women with heart disease.

BACKGROUND
Little information is available regarding the relative benefits of estrogen replacement therapy versus reductase inhibitors and the potential utility of their combination as lipid-lowering therapy for postmenopausal women.

METHODS
We conducted a randomized, double-blind, crossover trial in 24 postmenopausal women, each of whom received the following drug regimens during three consecutive six-week treatment periods: 1) hormone replacement (oral dose of 0.625 mg/day conjugated equine estrogens and 2.5 mg/day medroxyprogesterone acetate); 2) 20 mg lovastatin/day and 3) hormone replacement pluslovastatin.

RESULTS
Total and low density lipoprotein (LDL) cholesterol were significantly lowered and high density lipoprotein (HDL) cholesterol was significantly increased by all three regimens compared with baseline (p < 0.05). Lovastatin was more effective than estrogen/progestin in reducing LDL (p < 0.001), but estrogen/progestin was slightly more effective in increasing HDL. The hormone replacement and lovastatin regimen blocked the estrogen-associated increase in triglycerides. Hormone replacement (alone and with lovastatin) resulted in increases in brachial artery flow-mediated vasodilator capacity (p = 0.01 for both regimens) and the area under the curve (p = 0.016 and p = 0.005, respectively) compared with baseline. Percent dilation was greatest after the hormone replacement regimen, whereas the area under the curve was greatest after hormone replacement plus lovastatin (69% improvement vs. baseline).

CONCLUSIONS
In postmenopausal women with coronary disease and hyperlipidemia, conjugated equine estrogen produced significant improvements in lipids and vasodilator responses despite the concurrent administration of low dose medroxyprogesterone acetate. Low dose lovastatin produced greater reductions in LDL, but less dramatic improvements in vasodilator responses. Estrogen/progestin pluslovastatin may provide additional benefits via a greater reduction in the LDL/HDL ratio and attenuation of estrogen-associated hypertriglyceridemia. More information is needed about the safety and efficacy of such combinations of hormone replacement and reductase inhibitor therapy.

Circulation, 1999; 99: 475-481
Delayed Response of Myocardial Flow Reserve to Lipid-Lowering Therapy With Fluvastatin

Martin Guethlin, Albert Markus Kasel, Klaus Coppenrath, Sibylle Ziegler, Wolfram Delius, and Markus Schwaiger

Background-Lipid-lowering therapy can improve endothelial function in patients with coronary artery disease (CAD) and hypercholesterolemia. Little is known about induced changes in myocardial microcirculation. This study prospectively investigated the temporal effects of lipid-lowering therapy with fluvastatin on coronary flow and flow reserve (CFR) in patients with CAD assessed by PET.

Methods and Results-In an open clinical trial, CFR was studied in 15 patients with angiographically documented multivessel CAD and hypercholesterolemia (LDL >160 mg.dL). Dynamic 13N-labeled ammonia PET imaging in conjunction with adenosine was used to assess regional and global CFR at baseline as well as at 2 and 6 months during treatment with fluvastatin (60 to 80 mg.dL). Despite a rapid decrease in total cholesterol (29±6%) and LDL (37±9%), myocardial blood flow at rest and during stress was unchanged after 2 months of treatment (2.7±0.9 versus 2.5±0.6 mL · g-1 · min-1). At 6 months, stress blood flow as well as CFR increased significantly (3.4±1.0 mL · g-1 · min-1). No change in hemodynamic parameters was noted during the entire study. Nine of 15 patients increased CFR by >20%. All responders demonstrated improvement in anginal symptoms, whereas nonresponders stated no change (n=4) or worsening of symptoms (n=2). The improvement in CFR was not related to the amount of lipid lowering and was independent of the severity of stenoses.

Conclusions-Improvement in stress blood flow and CFR is delayed compared with the lipid-lowering effect of fluvastatin, suggesting a slow recovery of the vasodilatory response to adenosine.

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Effect of pravastatin on cardiovascular events in women after myocardial infarction: the Cholesterol and Recurrent Events (CARE) trial

Sandra J. Lewis, Frank M. Sacks, Jayne S. Mitchell, Cara East, Stephen Glasser, Sheren Kell, Rebecca Letterer, Marian Limacher, Lemuel A. Moye, Jean L. Rouleau, Marc A. Pfeffer, Eugene Braunwald for the CARE Investigators
Objectives. We sought to determine the effect of pravastatin on recurrent cardiovascular events in women with 
average cholesterol levels after myocardial infarction (MI).

Background. Little information is available on the effectiveness of lipid lowering in secondary prevention of 
coronary heart disease (CHD) in women; in particular, those with CHD and average cholesterol levels.

Methods. In the Cholesterol and Recurrent Events (CARE) trial, 576 postmenopausal women, between 3 and 20 
months after MI, with a total cholesterol level <240 mg/dl and a low density lipoprotein cholesterol level 115 to 
174 mg/dl, were randomized to receive pravastatin 40 mg/day or matching placebo for a median follow-up 
period of 5 years. The main outcome measures were combined coronary events (coronary death, nonfatal MI, 
percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass graft surgery [CABG]), the 
primary trial end point (coronary death or nonfatal MI) and stroke.

Results. Women treated with pravastatin had a risk reduction of 43% for the primary end point (p = 0.035), 46% 
for combined coronary events (p = 0.001), 48% for PTCA (p = 0.025), 40% for CABG (p = 0.14) and 56% for stroke 
(p = 0.07). The 3,583 men in the CARE trial also showed a reduction in risk, but the magnitude tended to be less. 
Pravastatin improved plasma lipids similarly in men and women. There were no differences in risk of coronary 
events in the placebo group between men and women. Minor differences between men and women were 
present in baseline characteristics and treatment for MI, in general, conferring a higher risk status and a lower 
incidence of CABG in the women.

Conclusions. Pravastatin led to significant early reduction of a wide range of cardiovascular events in post-MI 
women with average cholesterol levels.

Circulation, 1999;100:1515-20

A Common Variant of the Endothelial Nitric Oxide Synthase (Glu298→Asp) Is a Major Risk Factor for 
Coronary Artery Disease in the UK

Aroon D. Hingorani, PhD, MRCP; Chia Fan Liang, BA; Jenny Fatibene; Amelia Lyon; Sue Monteith, MSc; Ann 
Parsons, RGN; Stephen Haydock, PhD, MRCP; Ruth V. Hopper, RGN, BSc; Nigel G. Stephens, PhD, MRCP; 
Kevin M. O’Shaughnessy, DPhil, MRCP; Morris J. Brown, MD, FRCP
Background

Endothelium-derived nitric oxide (NO) is synthesised from L-arginine by endothelial nitric oxide synthase (eNOS) encoded by the NOS 3 gene on chromosome 7. Because reduced NO synthesis has been implicated in the development of coronary atherosclerosis, which has a heritable component, we hypothesised that polymorphisms of NOS 3 might be associated with increased susceptibility to this disorder.

Methods and Results

Single-strand conformation polymorphism analysis of NOS 3 identified a GT polymorphism in exon 7 of the gene which encodes a Glu→Asp amino acid substitution at residue 298 of eNOS. We investigated the relationship between this Glu298→Asp variant and atherosclerotic coronary artery disease (CAD) using 2 independent case-controlled studies. In the first study (CHAOS), cases consisted of 298 unrelated patients with positive coronary angiograms and controls were 138 unrelated healthy individuals ascertained through a population health screen. In the second study (CHAOS II), the cases were 249 patients with recent myocardial infarction (MI), and a further 183 unrelated controls. There was an excess of homozygotes for the Asp298 variant among patients with angiographic CAD, and among patients with recent MI when compared with their respective controls (35.9% versus 10.2%, P<0.0001 in CHAOS, and 18.1% versus 8.7%, P<0.02 in CHAOS II). In comparison to Glu298 homozygotes, homozygosity for Asp298 was associated with an odds ratio of 4.2 (95% CI, 2.3 to 7.9) for angiographic CAD and 2.5 (95% CI, 1.3 to 4.2) for MI.

Conclusions

Homozygosity for a common NOS 3 polymorphism (894 G→T) which encodes a Glu298→Asp amino acid substitution in eNOS is a risk factor for angiographic CAD and recent MI in this population.

Circulation, 1999;99: 2523-2529

Calcium Antagonists Ameliorate Ischemia-Induced Endothelial Cell Permeability by Inhibiting Protein Kinase C

Albrecht Hempel, Carsten Lindschau, Christian Maasch, Matthias Mahn, Rostislav Bychkov, Thomas Noll, Friedrich C. Luft, and Hermann Haller

Background-Dihydropyridines block calcium channels; however, they also influence endothelial cells, which do not express calcium channels. We tested the hypothesis that nifedipine can prevent ischemia-induced endothelial permeability increases by inhibiting protein kinase C (PKC) in cultured porcine endothelial cells.
Methods and Results-Ischemia was induced by potassium cyanide/deoxyglucose, and permeability was measured by albumin flux. Ion channels were characterized by patch clamp. [Ca2+]i was measured by fura 2. PKC activity was measured by substrate phosphorylation after cell fractionation. PKC isoforms were assessed by Western blot and confocal microscopy. Nifedipine prevented the ischemia-induced increase in permeability in a dose-dependent manner. Ischemia increased [Ca2+]i, which was not affected by nifedipine. Instead, ischemia-induced PKC translocation was prevented by nifedipine. Phorbol ester also increased endothelial cell permeability, which was dose dependently inhibited by nifedipine. The effects of non-calcium-channel-binding dihydropyridine derivatives were similar. Analysis of the PKC isoforms showed that nifedipine prevented ischemia-induced translocation of PKC-α and PKC-β. Specific inhibition of PKC isoforms with antisense oligodeoxynucleotides demonstrated a major role for PKC-α.

Conclusions-Nifedipine exerts a direct effect on endothelial cell permeability that is independent of calcium channels. The inhibition of ischemia-induced permeability by nifedipine seems to be mediated primarily by PKC-α inhibition. Anti-ischemic effects of dihydropyridine calcium antagonists could be due in part to their effects on endothelial cell permeability.

Circulation, 1999;99: 2239-2242

Effect of Diabetes Mellitus on Formation of Coronary Collateral Vessels

Adnan Abaci, Sinan Kahraman, Namik Kemal Eryol, Huseyin Arinc, and Ali Ergin

Background-Although myocardial ischemia is known to be significantly related to the development of coronary collateral vessels (CCVs), there is considerable variation between patients with ischemic heart disease in the presence of collateral development. The nature of this variability is not well known. Likewise, it remains unclear whether diabetes mellitus (DM) has any effect on CCVs. The aim of this study was to evaluate the effect of DM on CCVs.

Methods and Results-Of the patients who underwent coronary angiography during the interval between March 1, 1993, and June 20, 1998, in our institution, 306 were diabetic. Those patients in whom coronary angiography is normal or severity of coronary artery stenosis is thought not to be sufficient for the development of CCVs (<75%) were excluded from the study. A total of 205 patients (mean age, 59±8 years) met the criteria for the DM group. For case-control matching, 205 consecutive nondiabetic patients (mean age, 58±9 years) who had ≥1 diseased vessel with >75% stenosis were included in the control group. The CCVs were graded according to the
Rentrop scoring system, and the collateral score was calculated by summing the Rentrop numbers of every patient. There was no statistical difference between patients with and without DM in clinical baseline characteristics. The mean number of diseased vessels in the DM group (1.58±0.68) was higher than that in the nondiabetic group (1.42±0.65, P=0.005). The mean collateral score was 2.41±2.20 in the DM group and 2.60±2.39 in the control group. After confounding variables were controlled for, the collateral score in the diabetic group was significantly different from that in the nondiabetic group (P=0.034).

Conclusions-Our findings suggest that CCV development is poorer in patients with than in patients without DM. Thus, we can speculate that DM is an important factor affecting CCV development.

Circulation, 1999 ;100: 1958-1963

Independent Prognostic Value of Elevated C-Reactive Protein in Unstable Angina

Ernesto R. Ferreiros, Carlos P. Boissonnet, Rodolfo Pizarro, Pablo F. Garcia Merletti, Gianni Corrado, Arturo Cagide, and Oscar O. Bazzino

Background-There is growing evidence of the prognostic importance of C-reactive protein (CRP) in unstable angina. However, the independent value of CRP relative to other conventional markers at different stages of treatment has not been established. Therefore, we assessed the in-hospital and 90-day prognostic values of serum CRP in unstable angina. We also compared the relation of CRP at admission and discharge with 90-day outcome.

Methods and Results-One hundred ninety-four consecutive patients were included in a derivation (n=105) and a validation set (n=89). Serum CRP was measured at admission, at 48 hours, and at hospital discharge. A cutoff point of 1.5 mg/dL for CRP provided optimum sensitivity and specificity for adverse outcome, based on the receiver operator curves. No association was found between CRP on admission and in-hospital outcome. CRP at admission, adjusted for age, ECG findings on admission, silent ischemia, left ventricular wall motion score, and high-risk clinical presentation, was related to the combined end point of refractory angina, myocardial infarction, or death at 90 days (hazard ratio [HR] 1.9, 95% CI 1.2 to 8.3, P=0.002). CRP at hospital discharge was the strongest independent marker of an adverse outcome (HR 3.16, 95% CI 2.0 to 5.2, P=0.0001). These results were confirmed in the validation set (CRP at discharge: HR 3.3, 95% CI 2.0 to 7.69, P=0.0001).

Conclusions-In unstable angina, CRP is a strong independent marker of increased 90-day risk. Compared with CRP at admission, CRP at discharge is better related to later outcome and could be of great utility for risk stratification.
Gender differences in myocardial blood flow dynamics: Lipid profile and hemodynamic effects

Claire S. Duvernoy, Christian Meyer, Vanadin Seifert-Klauss, Fırat Dayanıklı, Ichiro Matsunari, Judith Rattenhuber, Cornelia Hoss, Henner Graeff, Markus Schwaiger

Objectives
The purpose of the study was to compare myocardial blood flow (MBF) in hyperlipidemic postmenopausal women and age-matched hyperlipidemic men, and to analyze the relationship between cholesterol subfractions and myocardial blood flow in men and women.

Background
Women are protected from coronary artery disease (CAD) events until well after menopause, in part due to gender-specific differences in lipid profiles.

Methods
To examine the effect of these influences on coronary microcirculation, MBF was quantitated with N-13 ammonia/PET (positron emission tomography) at rest and during adenosine hyperemia in 15 women and 15 men, all nondiabetic, who were matched for age and total cholesterol levels (53 ± 4 vs. 50 ± 8 years, p = NS, 6.44 ± 1.1 vs. 6.31 ± 0.85 mmol/liter, or 249 ± 41 vs. 244 ± 33 mg/dl, p = NS).

Results
Women had significantly higher high density lipoprotein (HDL) and lower triglyceride (Tg) levels than did men, and they showed significantly higher resting MBF and stress MBF levels. Significant correlations were found between resting and hyperemic MBF and HDL and Tg levels (r = 0.44, p < 0.02 for stress MBF vs. HDL; r = 0.48, p < 0.007 for stress MBF vs. Tg). Gender was the strongest predictor of hyperemic MBF in multivariate analysis. Women responded to adenosine hyperemia with a significantly higher heart rate than did men, and hemodynamic factors correlated significantly with blood flow both at rest and during stress.

Conclusions
These data suggest that the favorable lipid profile seen in women may be associated with preserved maximal blood flow in the myocardium.
Tissue Expression and Immunolocalization of Tumor Necrosis Factor-α in Postinfarction Dysfunctional Myocardium

Min W. Irwin, Susanna Mak, Douglas L. Mann, Rong Qu, Josef M. Penninger, Andrew Yan, Fayez Dawood, Wen-Hu Wen, Zhiping Shou, and Peter Liu

Background-Tumor necrosis factor-α (TNF-α) is markedly elevated in advanced heart failure. It is not known whether tissue TNF-α is elevated in the common setting of myocardial infarction leading to heart failure and what the source of TNF-α is. To determine this, we studied the expression and protein localization of TNF-α and its 2 main receptors (TNF-R1/R2) in a rat model of large infarction.

Methods and Results-Male rats were randomized to proximal left anterior descending ligation. The animals were killed on days 1, 3, 10, and 35 after ligation to examine gene expression and protein production of TNF-α and TNF-R1/R2 from the infarct, peri-infarct, and contralateral zones of infarcted heart. There was increased TNF-α mRNA production throughout the myocardium at day 1, and detectable expression persisted to day 35 after myocardial infarction. The expression of this cytokine is not confined strictly to the infarct or peri-infarct zones but is expressed by cardiac myocytes within the myocardium in the contralateral normal zone. Changes in gene expression are mirrored initially by augmented protein production within the myocytes. Levels of TNF-α protein in the infarct and peri-infarct zones rose early to 8- to 10-fold above normal levels and rose to 4- to 5-fold in the contralateral zone. Finally, expression of the TNF-R1 mRNA transcripts was upregulated at days 3 and 10 after ligation in the infarct and peri-infarct zones, suggesting that the signal transduction pathways necessary for TNF-α in the heart remain intact as TNF-α biosynthesis increases.

Conclusions-TNF-α is present early in a model of large myocardial infarction and is sustained into the later stage within the myocardium. Expression of this cytokine is not only confined strictly to the infarct or peri-infarct zone but is expressed by cardiac myocytes within the myocardium contralateral to the infarct. Therefore TNF-α production forms a part of an important intrinsic myocardial stress response system to injury.

Circulation, 1999;100(25):2477-84

Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of platelet IIb/IIIa inhibitor for stenting trial) diabetic substudy
BACKGROUND: Stenting likely decreases the need for target-vessel revascularization procedures in diabetic patients compared with balloon angioplasty. However, the efficacy of stenting with platelet glycoprotein IIb/IIIa blockade has not yet been assessed in diabetics. METHODS AND RESULTS: We analyzed the outcomes of 491 diabetic patients within the multicenter Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT). Diabetic patients were a prospectively defined subset: 173 were randomized to stent-placebo, 162 to stent-abciximab, and 156 to balloon angioplasty-abciximab. The main end point for this analysis was combined 6-month death, myocardial infarction (MI), or target-vessel revascularization (TVR). The composite end point occurred in 25.2% of stent-placebo, 23.4% of balloon-abciximab, and 13.0% of stent-abciximab patients (P=0.005). Abciximab therapy, irrespective of revascularization strategy (stent or balloon angioplasty), resulted in a significant reduction in the 6-month death or MI rate: 12.7% for stent-placebo, 7.8% for balloon angioplasty-abciximab, and 6.2% for the stent-abciximab group (P=0.029). The 6-month TVR rate was 16.6% for stent-placebo, 18.4% for balloon-abciximab, and 8.1% for stent-abciximab (P=0.021). Compared with stent-placebo, stent-abciximab therapy was associated with a significant increase in angiographic net gain (0.88 versus 0.55 mm; P=0.011) and a decrease in the late loss index (0.40 versus 0.60 mm; P=0.061). The 1-year mortality rate for diabetics was 4.1% for stent-placebo and 1.2% for stent-abciximab patients (P=0.11). CONCLUSIONS: The combination of stenting and abciximab therapy among diabetics resulted in a significant reduction in 6-month rates of death, MI, and TVR compared with stent-placebo or balloon-abciximab therapy.

Summary

* vs. stent placebo

Am J Cardiol, 1999;84(9):987-91

Polymorphism of platelet glycoprotein IIb and risk of thrombosis and restenosis after coronary stent placement.


Both glycoprotein (GP) IIb and IIIa of platelet fibrinogen receptor are polymorphic proteins. Unlike GPIIIa,
there is little information about the clinical significance of the GPIIb polymorphism. We designed this prospective study to assess whether patients with the human platelet antigen (HPA)-3 polymorphism of GPIIb are more susceptible to developing thrombosis and restenosis after coronary stent placement. We included 2,178 consecutive patients with coronary artery disease who underwent intracoronary stent implantation, 789 (36.2%) with HPA-3a,a, 1,023 (47.0%) with HPA-3a,b, and 366 (16.8%) with HPA-3b,b genotype. The incidence of stent thrombosis was 1.7% in HPA-3a,a, 1.7% in HPA-3a,b, and 1.6% in HPA-3b,b patients (p = 0.999). The incidence of stent restenosis was 37.3% in HPA-3a,a, 36.2% in HPA-3a,b, and 34.6% in HPA-3b,b patients (p = 0.724). Event-free survival 1 year after stent placement was 76.1% for HPA-3a,a, 76.5% for HPA-3a,b, and 76.4% for HPA-3b,b patients (p = 0.968). We conclude that the HPA-3 polymorphism of platelet GPIIb is not associated with an increase in the risk of thrombosis and restenosis over 1 year after coronary stent placement. These data indicate that unlike the HPA-1 polymorphism of GPIIIa, the HPA-3 polymorphism of GPIIb may not serve as a useful genetic marker for the risk assessment of patients treated with intracoronary stenting.

Summary
Circulation, 1999 ;100(19):1977-82

Attainment and maintenance of platelet inhibition through standard dosing of abciximab in diabetic and nondiabetic patients undergoing percutaneous coronary intervention.

Steinhubl SR, Kottke-Marchant K, Moliterno DJ, Rosenthal ML, Godfrey NK, Coller BS, Topol EJ, Lincoff AM

BACKGROUND: Although the effectiveness of abciximab (c7E3 Fab; ReoPro) in large populations of patients undergoing a percutaneous coronary intervention has been consistently proved in clinical trials, it is unknown whether all patients achieve and maintain target inhibition during treatment. Diabetic patients in particular are a subgroup of patients with known underlying platelet abnormalities whose long-term response to abciximab has been shown to vary from that of nondiabetic patients. METHODS AND RESULTS: Forty-nine diabetic and 51 nondiabetic patients who received adjunctive abciximab therapy during percutaneous coronary interventions were evaluated prospectively. The degree of platelet function inhibition was determined immediately after the abciximab bolus, 8 hours after the bolus (during the 12-hour abciximab infusion), and the next morning (13 to 26 hours after the bolus) with the use of a rapid platelet function assay (Accumetrics). After the abciximab bolus, platelet function was inhibited by 95±4% (mean±SD). By 8 hours, the average percent inhibition had decreased to 88±9%, with 13% of patients with <80% inhibition. The next morning (mean 19 hours after the bolus), mean inhibition was 71±14%. A difference was not found between diabetics and nondiabetics, nor was any physiological parameter found to be predictive of the response to abciximab.
CONCLUSIONS: Although the majority of patients achieve and maintain ≥80% platelet inhibition during the 12-hour infusion with standard-dose abciximab, there is substantial variability among patients. Diabetic status does not appear to influence this variability.

Summary
1. Inhibition of platelet function: after the abciximab bolus - 95+/−4%, by 8 hours - 88+/−9%(13% of patients with <80% inhibition), next morning - 71+/−14%.
2. No difference between diabetics and nondiabetics

Circulation, 1999;100(19):1971-6

Relation between lesion characteristics and risk with percutaneous intervention in the stent and glycoprotein IIb/IIIa era: An analysis of results from 10,907 lesions and proposal for new classification scheme.

Ellis SG, Guetta V, Miller D, Whitlow PL, Topol EJ

BACKGROUND: The currently used American College of Cardiology/American Heart Association lesion classification scheme dates from an era when balloon angioplasty was the only percutaneous treatment available and major complications occurred in approximately 7% of patients. Major advances in treatment options would suggest that this scheme may be outmoded, but the schemes that have been suggested to update lesion classification have not been widely accepted. METHODS AND RESULTS: Four thousand one hundred eighty-one consecutive patients (6,676 lesions) formed a training set and 2,146 patients (4,231 lesions) formed a validation set treated from 1995 to 1997 at a single center used by 3 hospital groups. Twenty-seven pretreatment candidate variables were analyzed with the use of stepwise proportional logistic regression, and 9 (nonchronic total occlusion with TIMI flow 0, degenerated vein graft, vein graft age >10 years, lesion length >= 10 mm, severe calcium, lesion irregularity, large filling defect, angulated >= 45 degrees plus calcium, and eccentricity) were independently correlated (P<0.05) with ranked adverse outcome (death, Q-wave or creatine kinase >= 3x normal myocardial infarction, or emergency coronary artery bypass grafting>> creatine kinase 2 to 3x myocardial infarction>> possibly related to non-Q-wave myocardial infarction>> no complication). A scheme based on these findings and the old American College of Cardiology/American Heart Association scheme were found to have c-statistics in the validation set of 0.672 and 0.620 (P = 0.010 vs old scheme), respectively. CONCLUSIONS: Appreciation of these contemporary risk factors for complications of coronary intervention
may assist in patient selection and in risk adjustment for comparison of outcomes between providers.

Predictors of adverse outcome: nonchronic total occlusion with TIMI flow 0, degenerated vein graft, vein graft age >10 years, lesion length >= 10 mm, severe calcium, lesion irregularity, large filling defect, angulated >= 45 degrees plus calcium, and eccentricity.

J Am Coll Cardiol, 1999;34(4):1045-9

Tissue characteristics of restenosis after percutaneous transluminal coronary angioplasty in diabetic patients.

Moreno PR, Fallon JT, Murcia AM, Leon MN, Simosa H, Fuster V, Palacios IF

OBJECTIVES: The purposes of this study were to analyze coronary specimens from patients with diabetes mellitus (DM) and to compare them with specimens from patients without DM. BACKGROUND: Diabetes mellitus is associated with an increased incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA). Increased hypercellular smooth muscle cell proliferation with exaggerated intimal hyperplasia formation may be responsible for this predisposition. METHODS: Eighteen coronary atherectomy specimens with restenosis after PTCA from patients with DM were compared with 18 coronary atherectomy specimens with restenosis after PTCA from patients without DM. Total and segmental areas were quantified on trichrome-stained tissue of hypercellular tissue, collagen-rich sclerotic tissue, atheroma and thrombus. Demographic and angiographic data were similar in both groups. RESULTS: The percentage of total plaque area composed of hypercellular tissue was lower in restenotic specimens from patients with DM than in restenotic specimens from patients without DM (19 +/- 6% vs. 44 +/- 5%; p = 0.003). The percentage of collagen-rich sclerotic tissue area was larger in restenotic specimens from patients with DM than in restenotic specimens from patients without DM (77 +/- 9% vs. 53 +/- 4%; p = 0.004). The percentages of atheroma and thrombus were similar in both groups. CONCLUSIONS: Intimal hypercellular tissue content is reduced in restenotic tissue from patients with DM. Collagen-rich sclerotic content is increased in restenotic lesions from patients with DM. These results suggest an accelerated fibrotic rather than a proliferative response in diabetic lesions from patients with restenosis after PTCA.

Summary
Plasma urokinase antigen and plasminogen activator inhibitor-1 antigen levels predict angiographic coronary restenosis.

Strauss BH, Lau HK, Bowman KA, Sparkes J, Chisholm RJ, Garvey MB, Fenkell LL, Natarajan MK, Singh I, Teitel JM

BACKGROUND: The fibrinolytic system is intimately involved in several processes that contribute to restenosis, including clot dissolution, cell migration, and tissue remodeling. However, the role of the individual activators (urokinase [uPA] and tissue plasminogen [tPA] activators) and inhibitors (plasminogen activator inhibitor [PAI-1]) of the fibrinolytic system in maintaining patency after coronary artery angioplasty and stenting is unclear. METHODS AND RESULTS: We prospectively studied 159 patients with stable angina who underwent successful elective angioplasty (n=110) or stenting (n=49) of de novo native coronary artery lesions. Plasma samples were drawn at baseline (before angioplasty) and serially after angioplasty (immediately afterward and 6 hours, 24 hours, 3 days, 7 days, 1 month, 3 months, and 6 months afterward). Antigen and activity assays were performed for uPA, tPA, and PAI-1. Follow-up quantitative coronary angiography was performed in 92% of eligible patients. The overall angiographic restenosis rate (diameter stenosis >50%) was 31% (37% in PTCA patients, 17% in stented patients). At all time periods, including baseline, uPA antigen levels were significantly higher and PAI-1 antigen levels were significantly lower in patients with restenosis. Restenosis rates for patients in the upper tertile of baseline uPA antigen levels were 2-fold higher than for those in the lower 2 tertiles (46% versus 24% and 22%, respectively; P<0.004). In a stepwise regression multivariate analysis, obstruction diameter after the procedure and uPA antigen were significant predictors of follow-up diameter stenosis. CONCLUSIONS: Plasma uPA antigen levels and PAI-1 antigen levels identify patients at increased risk for restenosis after percutaneous coronary revascularization.

Summary

Am J Cardiol, 1999;84(3):245-51
Influence of age on outcome after percutaneous transluminal coronary angioplasty.

Taddei CF, Weintraub WS, Douglas JS Jr, Ghazzal Z, Mahoney E, Thompson T, King S 3rd

This study estimates the influence of age on outcomes (mainly survival) of 21,516 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) between 1980 and 1996. We prospectively analyzed the patients in 5 age groups: <50, 50 to 59, 60 to 69, 70 to 79, and > or =80 years old. During the in-hospital period after PTCA, mortality increased from 0.28% in patients aged <50 to 3.45% in patients aged > or =80; Q-wave myocardial infarction was not significantly associated with age, and the 2 older groups were referred less often to coronary artery bypass graft surgery. During follow-up, lasting up to 10 years, the hazard of death was significantly influenced by age; Q-wave myocardial infarction was influenced by age, although the magnitude of the effect was relatively small and of questionable clinical significance; and coronary artery bypass graft surgery was performed less often in the 2 older age groups. Additional PTCA was similarly performed among the age groups. Age, diabetes mellitus, systemic hypertension, heart failure class, angioplasty in graft vessel, number of coronary vessels narrowed, and previous myocardial infarction were predictors of death over the 10-year follow-up. Age was the most important correlate of death after PTCA, with a 65% increase in the hazard of death for each 10-year increase in age. Age has an independent effect on early and late survival after PTCA.

Summary
1. In hospital complication: mortality increased from 0.28% in patients aged <50 to 3.45% in patients aged > or =80; Q-wave myocardial infarction was not significantly associated with age
2. During follow-up up to 10 years: the hazard of death was significantly influenced by age; Q-wave myocardial infarction was influenced by age; CABG was performed less often in the 2 older age groups. Additional PTCA was similarly performed among the age groups.
3. Predictors of death: age, diabetes mellitus, systemic hypertension, heart failure class, angioplasty in graft vessel, number of coronary vessels narrowed, and previous myocardial infarction

J Am Coll Cardiol, 1999;34(3):663-71

Creatine kinase-MB elevation after coronary intervention correlates with diffuse atherosclerosis, and low-to-medium level elevation has a benign clinical course: implications for early discharge after coronary
OBJECTIVES: The study evaluated the incidence and predictors of creatine kinase-MB isoenzyme (CK-MB) elevation after successful coronary intervention using current devices, and assessed the influence on in-hospital course and midterm survival. BACKGROUND: The CK-MB elevation after coronary intervention predominantly using balloon angioplasty correlates with late cardiac events of myocardial infarction (MI) and death. Whether CK-MB elevation after nonballoon devices is associated with an adverse short and midterm prognosis is unknown. METHODS: The incidence and predictors of CK-MB elevation after coronary intervention were prospectively studied in 1,675 consecutive patients and were followed for in-hospital events and survival. RESULTS: CK-MB elevation was detected in 313 patients (18.7%), with 1-3x in 12.8%, 3-5x in 3.5% and ≥5x normal in 2.4% of patients. Procedural complications or electrocardiogram changes occurred in only 49% of the CK-MB-elevation cases; CK-MB elevation was more common after nonballoon devices (19.5% vs. 11.5% after percutaneous transluminal coronary angioplasty; p < 0.01). Predictors of CK-MB elevation on multivariate analysis were diffuse coronary disease (p = 0.02), systemic atherosclerosis (p = 0.002), stent use (p = 0.04) and absence of beta-blocker therapy (p = 0.001). Adverse in-hospital cardiac events were more frequent in patients with ≥5x CK-MB elevation, with no significant difference between 1-5x CK-MB elevation versus normal CK-MB group. During a mean follow-up of 13 +/- 3 months, the incidence of death in the CK-MB-elevation group was 1.6% versus 1.3% in the normal CK-MB group (p = NS). CONCLUSIONS: The CK-MB elevation after coronary intervention was observed even in the absence of discernible procedural complications and was more common in patients with diffuse atherosclerosis. In-hospital clinical events requiring prolonged monitoring were higher in ≥5x CK-MB-elevation patients only. Midterm survival of CK-MB-elevation patients was similar to those with normal CK-MB. Our prospective analysis shows a lack of adverse in-hospital cardiac events and suggests that early discharge of stable 1-5x normal CK-MB-elevation patients after successful coronary intervention is safe.

Summary

Heart, 1999; 138(3 Pt 1):446-55

Primary stenting in acute myocardial infarction: influence of diabetes mellitus in angiographic results and
BACKGROUND: The outcome of patients with diabetes after myocardial infarction (MI) has traditionally been worse than in their nondiabetic counterparts before and during the thrombolytic therapy era. Whether the fate of patients with diabetes might improve with mechanical intervention, particularly with primary stenting, has not previously been studied. METHODS: We compared the angiographic and clinical outcome of 76 nondiabetic patients (aged 61 +/- 14 years; 66% male) and 28 patients with diabetes (aged 65 +/- 12 years; 64% male) consecutively treated with primary stenting for acute MI. Coronary Thrombolysis In Myocardial Infarction grade 3 flow was restored in 96% of diabetic and 97% of nondiabetic patients. RESULTS: Angiographic results after stent deployment were similar in the 2 groups. At 1-month follow-up, all patients in both groups were alive. Patients with diabetes had a much higher incidence of stent thrombosis (18% vs 1%; P =.003), which accounted for the majority of the major cardiac events at 1 month (21% vs 4%; P =.009). At a mean follow-up of 315 +/- 13 days, 99% of nondiabetic and 89% of patients with diabetes were alive (P =.04). Overall freedom from a major cardiac event (death, MI, target vessel revascularization) at 315 +/- 13 day follow-up was 88% for nondiabetics and 54% for patients with diabetes (P =.0003). By multivariate analysis, diabetes mellitus was the most important predictor for development of 1-month (RR 9.89; 95% confidence interval, 1.6-30) and late major cardiovascular events (RR 8.39; 95% confidence interval, 2.93-24). CONCLUSIONS: Primary stenting in acute MI is highly effective in restoring immediate TIMI 3 coronary flow in nondiabetic patients and patients with diabetes. This procedure may improve benefit in terms of mortality rate to both groups, particularly in patients with diabetes, compared with previous reports with thrombolytic therapy. Nevertheless, stent thrombosis and major cardiovascular events at 1 month and late follow-up are more frequent in patients with diabetes.

Summary

J Am Coll Cardiol, 1999;34(2):476-85

Restenosis, late vessel occlusion and left ventricular function six months after balloon angioplasty in diabetic patients.
OBJECTIVES: We studied angiographic outcome and its predictors after traditional coronary balloon angioplasty in diabetics. We further examined whether changes in ejection fraction were influenced by the status of the dilated site(s) at follow-up. BACKGROUND: Recent studies have suggested that diabetics have a particularly poor outcome after balloon angioplasty. The reasons for this observation are not known.

METHODS: We investigated procedural and six-month angiographic outcome, analyzed by quantitative coronary angiography, and left ventricular function in 485 consecutive diabetics (627 lesions) treated by balloon angioplasty without stent implantation. RESULTS: The procedure was successful in 455 (94%) patients; angiographic follow-up was available in 377 patients (83%). At follow-up, the rates of restenosis and total occlusion were 62% and 13%, respectively. Five independent predictors of restenosis were identified: the presence of organ damage, a saphenous vein graft (SVG) angioplasty, a bifurcation lesion, a Thrombolysis in Myocardial Infarction (TIMI) flow <3 preprocedure and the degree of residual stenosis. Four independent predictors of vessel occlusion were identified: treatment with insulin, a SVG angioplasty, a TIMI flow <3 preprocedure and the degree of residual stenosis after angioplasty. Late vessel occlusion at angioplasty site(s) was observed in 15% of patients, ranging from 11% for a one-site procedure to 37% for a three-site procedure. This complication was associated with a decrease in ejection fraction at follow-up (-6.2 +/- 9.9%, p = 0.0001), whereas no significant change was observed in patients without occlusion. CONCLUSIONS: This study shows that late vessel occlusion is a frequent mode of restenosis in diabetic patients and is associated with a significant decrease in ejection fraction. This could partly explain the poor long-term clinical outcome reported in such patients after traditional balloon angioplasty.

Summary
1. Procedural success: 94%
2. Restenosis rate: 62%, total occlusion rate 13%
3. Independent predictors of restenosis: the presence of organ damage, SVG angioplasty, a bifurcation lesion, TIMI flow <3 preprocedure and the degree of residual stenosis.
4. Independent predictors of vessel occlusion: treatment with insulin, a SVG angioplasty, a TIMI flow <3 preprocedure and the degree of residual stenosis after angioplasty.
5. Late vessel occlusion at angioplasty site(s) was associated with a decrease in ejection fraction at follow-up.
Pravastatin prevents clinical events in revascularized patients with average cholesterol concentrations. Cholesterol and Recurrent Events CARE Investigators.

Flaker GC, Warnica JW, Sacks FM, Moye LA, Davis BR, Rouleau JL, Webel RR, Pfeffer MA, Braunwald E

OBJECTIVES: This analysis was carried out to determine if revascularized patients derive benefit from the 3-hydroxy-3 methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor pravastatin. BACKGROUND: The HMG-CoA reductase inhibitors result in substantial reductions in serum cholesterol and stabilization of atherosclerotic plaques in patients with coronary artery disease. METHODS: Pravastatin was found to reduce clinical cardiovascular events in the Cholesterol and Recurrent Events (CARE) trial consisting of 4,159 patients with a documented myocardial infarction and an average cholesterol level (mean 209 mg/dl and all <240 mg/dl). A total of 2,245 patients underwent coronary revascularization before randomization including 1,154 patients with percutaneous transluminal coronary angioplasty (PTCA) alone, 876 patients with coronary artery bypass graft (CABG) alone, and 215 patients with both procedures. Clinical events in revascularized patients were compared between patients on placebo and on pravastatin. RESULTS: In the 2,245 patients who had undergone revascularization, the primary endpoint of coronary heart disease death or nonfatal myocardial infarction (MI) was reduced by 4.1% with pravastatin (relative risk [RR] reduction 36%, 95% confidence interval [CI] 17 to 51, p = 0.001). Fatal or nonfatal MI was reduced by 3.3% (RR reduction 39%, 95% CI 16 to 55, p = 0.002), postrandomization repeat revascularization was reduced by 2.6% (RR reduction 18%, 95% CI 1 to 33, p = 0.068) and stroke was reduced by 1.5% (RR reduction 39%, 95% CI 3 to 62, p = 0.037) with pravastatin. Pravastatin was beneficial in both the 1,154 PTCA patients and in the 1,091 CABG patients who had undergone revascularization before randomization. CONCLUSIONS: Pravastatin reduced clinical events in revascularized postinfarction patients with average cholesterol levels. This therapy was well tolerated and its use should be considered in most patients following coronary revascularization.

Summary
1. The primary endpoint of coronary heart disease death or nonfatal myocardial infarction (MI) was reduced by 4.1% with pravastatin (relative risk [RR] reduction 36%, 95% confidence interval [CI] 17 to 51, p = 0.001).
2. Fatal or nonfatal MI was reduced by 3.3% (RR reduction 39%, 95% CI 16 to 55, p = 0.002),
3. Postrandomization repeat revascularization was reduced by 2.6% (RR reduction 18%, 95% CI 1 to 33, p = 0.068) and stroke was reduced by 1.5% (RR reduction 39%, 95% CI 3 to 62, p = 0.037) with pravastatin.
Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators.


BACKGROUND: Percutaneous coronary revascularization is widely used in improving symptoms and exercise performance in patients with ischemic heart disease and stable angina pectoris. In this study, we compared percutaneous coronary revascularization with lipid-lowering treatment for reducing the incidence of ischemic events. METHODS: We studied 341 patients with stable coronary artery disease, relatively normal left ventricular function, asymptomatic or mild-to-moderate angina, and a serum level of low-density lipoprotein (LDL) cholesterol of at least 115 mg per deciliter (3.0 mmol per liter) who were referred for percutaneous revascularization. We randomly assigned the patients either to receive medical treatment with atorvastatin, at 80 mg per day (164 patients), or to undergo the recommended percutaneous revascularization procedure (angioplasty) followed by usual care, which could include lipid-lowering treatment (177 patients). The follow-up period was 18 months. RESULTS: Twenty-two (13 percent) of the patients who received aggressive lipid-lowering treatment with atorvastatin (resulting in a 46 percent reduction in the mean serum LDL cholesterol level, to 77 mg per deciliter [2.0 mmol per liter]) had ischemic events, as compared with 37 (21 percent) of the patients who underwent angioplasty (who had an 18 percent reduction in the mean serum LDL cholesterol level, to 119 mg per deciliter [3.0 mmol per liter]). The incidence of ischemic events was thus 36 percent lower in the atorvastatin group over an 18-month period (P=0.048, which was not statistically significant after adjustment for interim analyses). This reduction in events was due to a smaller number of angioplasty procedures, coronary-artery bypass operations, and hospitalizations for worsening angina. As compared with the patients who were treated with angioplasty and usual care, the patients who received atorvastatin had a significantly longer time to the first ischemic event (P=0.03). CONCLUSIONS: In low-risk patients with stable coronary artery disease, aggressive lipid-lowering therapy is at least as effective as angioplasty and usual care in reducing the incidence of ischemic events.

Summary
1. Ischemic events in 18-months: atorvastatin - 13 percent, angioplasty - 21%(P=0.048)
2. Atorvastatin group had a significantly longer time to the first ischemic event (P=0.03).
The importance of proteinuria as a determinant of mortality following percutaneous coronary revascularization in diabetics.

Marso SP, Ellis SG, Tuzcu M, Whitlow PL, Franco I, Raymond RE, Topol EJ

OBJECTIVES: The aims of this study were to compare mortality and clinical events following percutaneous coronary intervention (PCI) between nondiabetics and diabetics with and without proteinuria. BACKGROUND: Diabetics have increased rates of late myocardial infarction, repeat revascularization and mortality when compared with nondiabetics following PCI. Proteinuria is a marker for diabetic nephropathy and potentially a surrogate marker for advanced atherosclerosis. It is unknown if proteinuria is a predictor of outcome in diabetics following PCI. METHODS: We performed an observational study of 2,784 patients who underwent PCI at the Cleveland Clinic between January 1993 and December 1995. There were 2,247 nondiabetics and 537 diabetics with urinalysis and follow-up data available (proteinuria n = 217, nonproteinuria n = 320). The diabetic proteinuria group was further prospectively stratified into low concentration (n = 182) and high concentration (n = 35). The end points were all-cause mortality and the composite end point of death, nonfatal myocardial infarction (MI) and need for revascularization. RESULTS: The mean follow-up time was 20.2 months. The two-year mortality rate was 7.3% and 13.5% for nondiabetics and diabetics, respectively (p < 0.001). The two-year mortality rate was 9.1% and 20.3% for the nonproteinuria and proteinuria groups, respectively (p < 0.001). There was a graded increase in mortality comparing the diabetic group. The two-year mortality rate was 9.1%, 16.2% and 43.1% for the nonproteinuria, low concentration and high concentration groups, respectively (p < 0.001). The difference in survival between the nondiabetic and nonproteinuric diabetics was not significant (p = 0.8). CONCLUSIONS: The presence of proteinuria is the key determinant of risk following PCI for diabetics. Diabetics without evidence of proteinuria have similar survival compared with nondiabetics.
Lipoprotein(a) and coronary thrombosis and restenosis after stent placement.

Wehinger A, Kastrati A, Elezi S, Baum H, Braun S, Neumann FJ, Schomig A

OBJECTIVES: The objective of this prospective study was to evaluate the relation between high lipoprotein(a) levels and thrombotic and restenotic events after coronary stent implantation. BACKGROUND: Lipoprotein(a) may promote atherogenesis, coronary thrombosis and restenosis after balloon angioplasty, but the clinical significance remains unclear. METHODS: The study included 2,223 consecutive patients with successful coronary stent placement. According to the serum level of lipoprotein(a), patients were divided in two groups: 457 patients of the highest quintile formed the high lipoprotein(a) group, and 1,766 patients of the lower four quintiles formed the low lipoprotein(a) group. Primary end points were the incidence of angiographic restenosis at six months and the event-free survival at one year. Secondary end point was the incidence of angiographic stent occlusion. RESULTS: Early stent occlusion occurred in four of the 457 patients (0.9%) with high and 37 of the 1,766 patients (2.1%) with low lipoprotein(a) levels, odds ratio of 0.41 (95% confidence interval, 0.15 to 1.16). Angiographic restenosis occurred in 173 of the 523 lesions (33.2%) in the high lipoprotein(a) group and 636 of the 1,943 lesions (32.7%) in the low lipoprotein(a) group, odds ratio of 1.02 (0.83 to 1.25). The probability of event-free survival was 73.0% in the high lipoprotein(a) group and 74.8% in the low lipoprotein(a) group (p = 0.45). On the basis of the findings in the low lipoprotein(a) group, the power of this study to detect a 25% increase in the incidence of restenosis and adverse events in the group with elevated lipoprotein(a) was 90% and 75%, respectively. CONCLUSIONS: Elevated lipoprotein(a) levels did not influence the one-year clinical and angiographic outcome after stent placement. Thrombotic events and measures of restenosis were not adversely affected by the presence of high lipoprotein(a) levels.

Summary

Circulation, 1999;99(10):1290-4

Prior cytomegalovirus infection and the risk of restenosis after percutaneous transluminal coronary balloon angioplasty.

BACKGROUND: Restenosis is a common problem after all revascularization procedures in atherosclerotic coronary arteries. Reactivated human cytomegalovirus (CMV) has been detected in tissues of restenotic vascular lesions and was hypothesized to be a contributing pathogenic factor. Recent data suggest an association of restenosis after optimal coronary atherectomy with CMV serostatus, and a possible role of antiviral therapy was discussed. We therefore tested the hypothesis that prior CMV infection might be a risk factor for restenosis after conventional coronary balloon angioplasty (PTCA). METHODS AND RESULTS: We analyzed 92 consecutive patients who had been admitted for control angiography after previous PTCA within a mean interval of 6 months. Anti-CMV antibodies were measured as an indicator of prior CMV infection and latency. The coronary angiograms before PTCA, directly after, and 6 months later were analyzed quantitatively. Sixty-five percent of the patients were CMV-positive. Before PTCA, the degree (mean ± SD) of stenosis was 69±10% in CMV-positive and 68±8.3% in CMV-negative subjects. PTCA resulted in a residual stenosis of 39% in both groups. After 6 months, the late losses of luminal diameter in the CMV-positive and -negative groups were 11±13% and 12±15%, respectively (P=0.658). In an ANCOVA with 25 potential risk factors for restenosis, CMV serostatus was not significantly associated with restenosis development. CONCLUSIONS: Our data indicate that prior CMV infection, in contrast to optimal atherectomy, is not associated with chronic restenosis after conventional coronary balloon angioplasty.

Summary

Lancet, 1999;353(9154):708-12

A1/A2 polymorphism of glycoprotein IIIa and association with excess procedural risk for coronary catheter interventions: a case-controlled study.

Laule M, Cascorbi I, Stangl V, Bielecke C, Wernecke KD, Mrozikiewicz PM, Felix SB, Roots I, Baumann G, Stangl K

BACKGROUND: A five-fold increase in risk of stent thrombosis in carriers of A1/A2 (Leu33Pro) polymorphism
of glycoprotein Illa has been described. Whether this increased procedural risk applies to other coronary interventions is unknown. We investigated the role of A1/A2 polymorphism as a putative risk factor.

METHODS: We genotyped 1000 consecutive patients with angiographically confirmed coronary-artery disease and 1000 controls matched for age and sex. 653 of the 1000 patients received interventions (271 coronary angioplasty, 102 directional coronary atherectomy, and 280 stenting) and were assessed for a 30-day composite endpoint of need for target-vessel revascularisation, myocardial infarction, and death. FINDINGS: The composite endpoint occurred in 41 (6.3%) patients. There was no evidence that the A2 allele was associated with excess procedural risk (relative risk 1.36 [95% CI 0.70-2.70], p=0.37). Nor, in subgroup analyses, did A2 predict events that complicated coronary angioplasty (1.17 [0.40-2.70]), directional coronary atherectomy (1.50 [0.30-8.70]), or stenting (1.45 [0.60-3.50]). Neither heterozygotes (A1/A2) nor homozygotes (A2/A2) were over-represented in any subgroup, including those with acute coronary syndromes, early disease manifestation (age <40 years), and histories of myocardial infarction. INTERPRETATION: A1/A2 polymorphism is not a major risk factor for 30-day adverse events that complicate coronary angioplasty, directional coronary atherectomy, or stenting. Furthermore, A1/A2 polymorphism has no apparent impact on more chronic processes such as atherogenesis of the coronary arteries.

Summary
1. A2 allele - not associated with excess procedural risk (relative risk 1.36 [95% CI 0.70-2.70], p=0.37).
2. In subgroup analyses: A2 allele - not associated with complicated coronary angioplasty (1.17 [0.40-2.70]), directional coronary atherectomy (1.50 [0.30-8.70]), or stenting (1.45 [0.60-3.50]).

Circulation, 1999; 99(6):736-43

Influence of low HDL on progression of coronary artery disease and response to fluvastatin therapy.

Ballantyne CM, Herd JA, Ferlic LL, Dunn JK, Farmer JA, Jones PH, Schein JR, Gotto AM Jr

BACKGROUND--Patients with coronary artery disease (CAD) commonly have low HDL cholesterol (HDL-C) and mildly elevated LDL cholesterol (LDL-C), leading to uncertainty as to whether the appropriate goal of therapy should be lowering LDL-C or raising HDL-C. METHODS AND RESULTS--Patients in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) had mildly to moderately elevated LDL-C; many also had low HDL-C, providing an opportunity to compare angiographic progression and the benefits of the HMG-CoA
reductase inhibitor fluvastatin in patients with low versus patients with higher HDL-C. Of the 339 patients with biochemical and angiographic data, 68 had baseline HDL-C <0.91 mmol/L (35 mg/dL), mean 0.82+/-.06 mmol/L (31.7+/-.22 mg/dL), versus 1.23+/-.029 mmol/L (47.4+/-.11.2 mg/dL) in patients with baseline HDL-C \geq 0.91 mmol/L. Among patients on placebo, those with low HDL-C had significantly more angiographic progression than those with higher HDL-C. Fluvastatin significantly reduced progression among low-HDL-C patients: 0.065+/-.036 mm versus 0.274+/-.045 mm in placebo patients (P=0.0004); respective minimum lumen diameter decreases among higher-HDL-C patients were 0.036+/-.021 mm and 0.083+/-.019 mm (P=0.09). The treatment effect of fluvastatin on minimum lumen diameter change was significantly greater among low-HDL-C patients than among higher-HDL-C patients (P=0.01); among low-HDL-C patients, fluvastatin patients had improved event-free survival compared with placebo patients. CONCLUSIONS--Although the predominant lipid-modifying effect of fluvastatin is to decrease LDL-C, patients with low HDL-C received the greatest angiographic and clinical benefit.

Summary
1. Fluvastatin significantly reduced progression among low-HDL-C patients: 0.065+/-.036 mm versus 0.274+/-.045 mm in placebo patients (P=0.0004)
2. The treatment effect of fluvastatin on minimum lumen diameter change was significantly greater among low-HDL-C patients than among higher-HDL-C patients (P=0.01)
3. Among low-HDL-C patients, fluvastatin patients had improved event-free survival compared with placebo patients.

J Am Coll Cardiol, 1999;33(2):412-9

Effect of age on outcome with primary angioplasty versus thrombolysis.

Holmes DR Jr, White HD, Pieper KS, Ellis SG, Califf RM, Topol EJ

OBJECTIVES: The purpose of this study was to determine how risks associated with increasing age differed in patients treated with percutaneous transluminal coronary angioplasty versus thrombolysis. BACKGROUND: Advancing age is a risk factor for adverse outcome in patients with acute myocardial infarction. Primary angioplasty has been thought to be particularly beneficial in higher risk patients including the elderly. There is, however, limited data on any differential incremental benefit of angioplasty compared with thrombolysis in
candidates for either treatment. METHODS: In the GUSTO-IIb angioplasty substudy, 1,138 patients were randomized to receive primary angioplasty or accelerated tissue-type plasminogen activator (t-PA). The effect of age on outcome was assessed as a discrete and continuous variable for each treatment group. Models using age as a linear factor as well as cubic spline transformations were used for the major end points of 30-day death or disabling stroke; death or reinfarction; and death, reinfarction or disabling stroke. RESULTS: For each 10-year patient group, outcome was improved with angioplasty (n = 565) compared with t-PA (n = 573). Irrespective of treatment, however, risk increased with age. After adjusting for baseline characteristics, each increment of 10 years of age increased the risk of death or myocardial infarction by 1.32 (95% confidence interval 1.04 to 1.76, p = 0.022). For all adverse outcomes, this incremental effect of increasing age was constant. CONCLUSIONS: Advancing age is associated with worse outcomes, and the risks increase in proportion to age. Although primary angioplasty improves outcomes over thrombolysis, it does not appear to be more beneficial in older than in younger patient groups. The incremental adverse effect of age does not vary by treatment strategy.
Figure. Thirty-day mortality or disabling stroke (A) and 30-day mortality, disabling stroke or reinfarction (B), by treatment group and by age decile.

Circulation, 1999;99(5):633-40

Coronary revascularization in diabetic patients: a comparison of the randomized and observational components of the Bypass Angioplasty Revascularization Investigation (BARI).


BACKGROUND: Patients with treated diabetes in the randomized-trial segment of the Bypass Angioplasty Revascularization Investigation (BARI) who were randomized to initial revascularization with PTCA had significantly worse 5-year survival than patients assigned to CABG. This treatment difference was not seen among diabetic patients eligible for BARI who opted to select their mode of revascularization. We hypothesized that differences in patient characteristics, assessed and unmeasured, together with the treatment selection in the registry, at least partially account for this discrepancy. METHODS AND RESULTS: Among diabetics taking insulin or oral hypoglycemic drugs at entry, angiographic and clinical presentations were comparable between randomized and registry patients. However, more registry patients were white, and registry diabetics tended to be more educated and more physically active and to report better quality of life. Procedural characteristics and in-hospital complications were comparable. The 5-year all-cause mortality rate was 34.5% in randomized diabetic patients assigned to PTCA versus 19.4% in CABG patients (P=0.0024; relative risk [RR]=1.87); corresponding cardiac mortality rates were 23.4% and 8.2%, respectively (P=0.0002; RR=3.10). The CABG benefit was more apparent among patients requiring insulin. In the registry, all-cause mortality was 14.4% for PTCA versus 14.9% for CABG (P=0.86, RR=1.10), with corresponding cardiac mortality rates of 7.5% and 6.0%, respectively (P=0.73; RR=1.07). These RRs in the registry increased to 1.29 and 1.41, respectively, after adjustment for all known differences between treatment groups. CONCLUSIONS: BARI registry results are not inconsistent with the finding in the randomized trial that initial CABG is associated with better long-term survival than PTCA in treated diabetic patients with multivessel coronary disease suitable for either surgical or catheter-based revascularization.

Summary

Sulfonylurea drugs increase early mortality in patients with diabetes mellitus after direct angioplasty for acute myocardial infarction.

Garratt KN, Brady PA, Hassinger NL, Grill DE, Terzic A, Holmes DR Jr

OBJECTIVES: The purpose of this study was to examine the impact of sulfonylurea drug use on outcome in diabetic patients undergoing direct coronary angioplasty for acute myocardial infarction. background: Sulfonylurea drugs impair ischemic preconditioning. Whether sulfonylurea drugs affect outcome adversely in diabetic patients undergoing direct angioplasty for acute myocardial infarction is unknown. METHODS: Clinical outcomes after direct balloon angioplasty for acute myocardial infarction were evaluated in 67 diabetic patients taking oral sulfonylurea drugs and 118 diabetic patients not taking these drugs. RESULTS: Hospital mortality was significantly higher among diabetics treated with sulfonylurea drugs at the time of myocardial infarction (24% vs. 11%). Univariate analysis identified sulfonylurea drug, age, ventricular function, ejection fraction less than 40%, prior bypass surgery and congestive heart failure as correlates of increased in-hospital mortality. Logistic regression found sulfonylurea drug use (odds ratio 2.77, p=0.017) to be independently associated with early mortality. Congestive heart failure, but not sulfonylurea drug use, was associated with an increased incidence of in-hospital ventricular arrhythmias. Congestive heart failure, prior bypass surgery and female gender, but not sulfonylurea drug use, were associated with late adverse events. CONCLUSIONS: Sulfonylurea drug use is associated with an increased risk of in-hospital mortality among diabetic patients undergoing coronary angioplasty for acute myocardial infarction. This early risk is not explained by an increase in ventricular arrhythmias, but may reflect deleterious effects of sulfonylurea drugs on myocardial tolerance for ischemia and reperfusion. For surviving patients sulfonylurea drug use is not associated with an increased risk of serious late adverse events.

Summary
1. Hospital mortality: sulfonylurea group 24%, no sulfonylurea group 11% (p=0.02)
2. Logistic regression found sulfonylurea drug use (odds ratio 2.77, p=0.017) to be independently associated with early mortality.
4. Sulfonylurea drug use - not associated with late adverse events.

J Am Coll Cardiol, 1999;34(1):55-61

Factors correlating with risk of mortality after transmyocardial revascularization.

Burkhoff D, Wesley MN, Resar JR, Lansing AM

OBJECTIVES: The purpose of this study was to determine factors correlating with the risk of postoperative mortality after transmyocardial laser revascularization (TMR). BACKGROUND: Clinical studies have indicated that TMR reduces angina by an average of two classes in patients with medically refractory symptoms not treatable by coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty. Factors which correlate with mortality after TMR, however, have not been extensively investigated. METHODS: One hundred thirty-two patients with severe angina underwent TMR as sole therapy with a CO2 laser. Age, gender, ejection fraction, prior CABG, unstable angina and the severity of coronary artery disease (graded on the basis of a newly proposed Anatomic Myocardial Perfusion index, AMP) were each determined. Each vascular territory (left anterior descending artery [LAD], left circumflex artery and posterior descending artery [PDA]) was graded as either having (AMP = 1) or not having (AMP = 0) blood flow through an unobstructed major vessel in the territory. Univariate and multivariate analysis determined which factors correlated with mortality. RESULTS: Patients with at least one AMP = 1 vascular territory (overall AMP = 1) had a 5% (4/82) postoperative mortality rate (POM), compared with 25% (12/49) with overall AMP 0 (p = 0.002). Left anterior descending artery AMP (p = 0.03) and previous CABG (p = 0.04) each correlated with the risk of POM. However, multivariate analysis indicated that no factor improved the correlation obtained with overall AMP by itself. With regard to overall mortality (Kaplan-Meier curves), univariate analysis also revealed correlations with overall AMP (p < 0.001), LAD AMP (p = 0.005), previous CABG (p = 0.003) and PDA AMP (p = 0.05) each individually correlated with mortality. Multivariate analysis indicated that overall AMP = 1, female gender and previous CABG together correlated best with lower postoperative mortality. CONCLUSIONS: Patients with good blood flow to at least one region of the heart through a native artery or a patent vascular graft have a markedly reduced risk of perioperative and longer term mortality.

Summary
1. Patients with at least one AMP = 1 vascular territory (overall AMP = 1) had a 5% (4/82) postoperative
mortality rate (POM), compared with 25% (12/49) with overall AMP 0 (p = 0.002).
2. LAD AMP (p = 0.03) and previous CABG (p = 0.04) each correlated with the risk of POM.
3. Multivariate analysis indicated that overall AMP = 1, female gender and previous CABG together correlated best with lower postoperative mortality.

Am Heart J., 2000;139:1032-8

Prediction of death after percutaneous coronary interventional procedures

Charanjit S. Rihal, MD, Diane E. Grill, MS, Malcolm R. Bell, MD, Peter B. Berger, MD, Kirk N. Garratt, MD, David R. Holmes, Jr, MD Rochester, Minn

Background The prediction and comparison of procedural death after percutaneous coronary interventional procedures is inherently difficult because of variations in case mix and practice patterns. The impact of modern, expanded patient selection criteria, and newer technologic approaches is unknown. Our objective was to determine whether a risk equation based on patient-related variables and derived from an independent data set can accurately predict procedural death after percutaneous coronary intervention in the current era.

Methods and Results An analysis was made of the Mayo Clinic Coronary Interventional Database January 1, 1995, to October 31, 1997. Expected mortality rate was calculated with the use of the New York State multivariate risk score. In 3387 patients, 3830 procedures (55.1% stents) were performed, with an expected mortality rate of 2.32% and observed mortality rate of 2.38% (P = not significant). The risk score derived from the New York multivariate model was highly predictive of death (chi-square = 213.8; P < .0001). The presence of a high-risk lesion characteristic such as calcium, thrombus, or type C lesion was modestly associated with death.

Conclusions The New York State multivariate model accurately predicted procedural death in our database

Circulation, 2000 ;101: 962-968

Prediction of Restenosis After Coronary Angioplasty by Use of a New Index : TIMI Frame Count/Minimal Luminal Diameter Ratio
Background—It has been shown recently that postangioplasty coronary flow reserve and the degree of residual stenosis have a modest predictive value for short- and long-term clinical outcomes after coronary angioplasty. Corrected TIMI frame count (CTFC) is a simple quantitative index of coronary blood flow. Its relationship with Doppler coronary flow velocity and clinical outcome after coronary angioplasty has not been fully clarified. The aim of this study was to identify clinical, angiographic, and functional predictors of clinical and angiographic restenosis after conventional coronary angioplasty.

Methods and Results—We studied 70 consecutive patients in whom intracoronary Doppler flow-velocity measurements were performed before and after angioplasty. Patients were evaluated for restenosis by clinical follow-up, exercise stress test/201Tl scintigraphy, and follow-up angiography, which was performed at 10.5±10.3 months in 63 patients. According to the results of univariate analysis, a new index, postangioplasty CTFC/minimal luminal diameter (MLD) ratio, was created. Multivariate analysis revealed that CTFC/MLD ratio was the only independent predictor of angiographic (OR 2.02; 95% CI 1.37 to 2.97; P<0.0004) and clinical (OR 1.60; 95% CI 1.15 to 2.21; P<0.005) restenosis. The receiver operating characteristic curve area of this index was 79% for angiographic and 73% for clinical restenosis. The optimal CTFC/MLD ratio cutoff values were 7.88 for angiographic and 7.94 for clinical restenosis, respectively.

Conclusions—Our data indicate that postangioplasty CTFC/MLD ratio, which incorporates both the angiographic and functional features of coronary lesions, is a reliable, objective, and inexpensive index for prediction of angiographic and clinical restenosis after conventional coronary angioplasty.

Journal of the American College of Cardiology, 35:6:1535-1542

Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis

Christopher Heeschen, Christian W. Hamm, Jens Bruemmer, Maarten L. Simoons for the CAPTURE Investigators

OBJECTIVES We evaluated C-reactive protein (CRP) and troponin T (TnT) for predicting six-month cardiac risk in patients with unstable angina.
BACKGROUND Troponin T is predictive of cardiac risk in patients with unstable angina. The clinical implications of elevated CRP in such patients remains controversial.

METHODS Baseline TnT and CRP values were determined in 447 patients with unstable angina enrolled in the placebo group of the Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial (CAPTURE) trial. All patients underwent a coronary intervention and were followed for a six month period in which 13 deaths and 47 myocardial infarctions were documented (MIs).

RESULTS Troponin T was >0.1 g/liter in 30% and CRP was >10 mg/L in 41% of the patients. For the initial 72-h period (including coronary intervention), TnT (17.4% vs. 4.2%; p < 0.001) but not CRP (10.3% vs. 8%; p = 0.41) was predictive of mortality and MI. The TnT-positive patients displayed more frequent recurrent instability before the planned intervention (44.8% vs. 16.9%; p < 0.001), but in the CRP-positive patients, no such increase was observed (25.9% vs. 24.8%; p = 0.92). In contrast, for the six month follow-up period, CRP was predictive of cardiac risk (mortality, MI) (18.9% vs. 9.5%; p = 0.003). Using multivariate analysis, both CRP and TnT emerged as independent predictors of mortality and MI at six-month follow-up. Furthermore, the incidence of coronary restenosis during six-month follow-up was not related to TnT status (3% vs. 4.5%; p = 0.49); however, it was significantly related to CRP status (7% vs. 2.3%; p = 0.03).

CONCLUSIONS Troponin T, but not CRP, was predictive of cardiac risk during the initial 72-h period, whereas CRP was an independent predictor of both cardiac risk and repeated coronary revascularization (coronary artery bypass graft surgery and percutaneous transluminal coronary angioplasty) during six month follow-up.


The Effect of Previous Coronary-Artery Bypass Surgery on the Prognosis of Patients with Diabetes who Have Acute Myocardial Infarction

Katherine M. Detre, Manuel S. Lombardero, Maria Mori Brooks, Regina M. Hardison, Richard Holubkov, George Sopko, Robert L. Frye, Bernard R. Chaitman, for the Bypass Angioplasty Revascularization Investigation Investigators

Background. Acute myocardial infarction in patients with diabetes is associated with high mortality. We studied whether previous revascularization by coronary-artery bypass grafting (CABG), as compared with percutaneous transluminal coronary angioplasty (PTCA), influences the prognosis in such patients.

Methods. We classified all patients eligible for the Bypass Angioplasty Revascularization Investigation who
underwent coronary revascularization within three months after entry into the study according to whether they had diabetes and whether they had undergone CABG, either initially or after PTCA. The protective effect of CABG with regard to mortality in the presence and in the absence of subsequent spontaneous Q-wave myocardial infarction was estimated with the use of Cox regression models.

Results. Among the 641 patients with diabetes and the 2962 without diabetes, the cumulative five-year rates of death were 20 percent and 8 percent, respectively (P<0.001), and the five-year rates of spontaneous Q-wave myocardial infarction were 8 percent and 4 percent (P<0.001). CABG greatly reduced the risk of death after spontaneous Q-wave myocardial infarction in the patients with diabetes (relative risk, 0.09; 95 percent confidence interval, 0.03 to 0.29). Among patients with diabetes who had undergone CABG but did not have spontaneous Q-wave myocardial infarction, the corresponding relative risk of death was 0.65 (95 percent confidence interval, 0.45 to 0.94). Among the patients without diabetes, no protective effect of CABG was evident.

Conclusions. Among patients with diabetes, previous coronary bypass surgery, as compared with coronary angioplasty, has a highly favorable influence on prognosis after acute myocardial infarction and a smaller beneficial effect among patients who do not have infarction. These findings should influence the type of coronary revascularization procedure selected for patients with diabetes who have multivessel coronary artery disease.

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The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification

Helen M. Colhoun, Michael B. Rubens, S. Richard Underwood, John H. Fuller

OBJECTIVES To examine whether the gender difference in coronary artery calcification, a measure of atherosclerotic plaque burden, is lost in type 1 diabetic patients, and whether abnormalities in established coronary heart disease risk factors explain this.

BACKGROUND Type 1 diabetes abolishes the gender difference in coronary heart disease mortality because it is associated with a greater elevation of coronary disease risk in women than men. The pathophysiological basis of this is not understood.

METHODS Coronary artery calcification and coronary risk factors were compared in 199 type 1 diabetic patients and 201 nondiabetic participants of similar age (30 to 55 years) and gender (50% female) distribution.
Only one subject had a history of coronary disease. Calcification was measured with electron beam computed tomography.

RESULTS In nondiabetic participants there was a large gender difference in calcification prevalence (men 54%, women 21%, odds ratio 4.5, p < 0.001), half of which was explained by established risk factors (odds ratio after ADJUSTMENT = 2.2). Diabetes was associated with a greatly increased prevalence of calcification in women (47%), but not men (52%), so that the gender difference in calcification was lost (p = 0.002 for the greater effect of diabetes on calcification in women than men). On adjustment for risk factors, diabetes remained associated with a threefold higher odds ratio of calcification in women than men (p = 0.02).

CONCLUSIONS In type 1 diabetes coronary artery calcification is greatly increased in women and the gender difference in calcification is lost. Little of this is explained by known coronary risk factors.

N Engl J Med 2000;343:530-7

Trends in the Incidence of Coronary Heart Disease and Changes in Diet and Lifestyle in Women

Frank B. Hu, Meir J. Stampfer, JoAnn E. Manson, Francine Grodstein, Graham A. Colditz, Frank E. Speizer, Walter C. Willett

Background. Previous studies have found concurrent declines in blood pressure, serum cholesterol levels, and the incidence of and mortality from coronary disease. However, the effects of changes in diet and lifestyle on trends in coronary disease are largely unknown.

Methods. We followed 85,941 women who were 34 to 59 years old and had no previously diagnosed cardiovascular disease or cancer from 1980 to 1994 in the Nurses’ Health Study. Diet and lifestyle variables were assessed at base line and updated during follow-up.

Results. After adjustment for the effect of age, the incidence of coronary disease declined by 31 percent from the two-year period 1980-1982 to the two-year period 1992-1994. From 1980 to 1992, the proportion of participants currently smoking declined by 41 percent, the proportion of postmenopausal women using hormone therapy increased by 175 percent, and the prevalence of overweight, defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or more, increased by 38 percent. During the study period, diet improved substantially. Statistically, changes in these variables -- when considered simultaneously -- explained a 21 percent decline in the incidence of coronary disease, representing 68 percent of the overall decline from 1980-1982 to 1992-1994. Taken individually, the reduction in smoking explained a 13
percent decline in the incidence of coronary disease; improvement in diet explained a 16 percent decline; and increase in postmenopausal hormone use explained a 9 percent decline. On the other hand, the increase in body-mass index explained an 8 percent increase in the incidence of coronary disease.

Conclusions. Reduction in smoking, improvement in diet, and an increase in postmenopausal hormone use accounted for much of the decline in the incidence of coronary disease in this group of women. An increasing prevalence of obesity, however, appears to have slowed the decline in the incidence of coronary disease.

Circulation, 2000;102:1886-1892

VLDL, Apolipoproteins B, CIII, and E, and Risk of Recurrent Coronary Events in the Cholesterol and Recurrent Events (CARE) Trial

Frank M. Sacks, Petar Alaupovic, Lemuel A. Moye, Thomas G. Cole, Bruce Sussex, Meir J. Stampfer, Marc A. Pfeffer, and Eugene Braunwald

Background-Plasma triglyceride concentration has been an inconsistent independent risk factor for coronary heart disease, perhaps because of the metabolic heterogeneity among VLDL particles, the main carriers of triglycerides in plasma.

Methods and Results-We conducted a prospective, nested case-control study in the Cholesterol and Recurrent Events (CARE) trial, a randomized placebo-controlled trial of pravastatin in 4159 patients with myocardial infarction and average LDL concentrations at baseline (115 to 174 mg/dL, mean 139 mg/dL). Baseline concentrations of VLDL-apolipoprotein (apo) B (the VLDL particle concentration), VLDL lipids, and apoCIII and apoE in VLDL+LDL and in HDL were compared in patients who had either a myocardial infarction or coronary death (cases, n=418) with those in patients who did not have a cardiovascular event (control subjects, n=370) in 5 years of follow-up. VLDL-cholesterol, VLDL-triglyceride, VLDL-apoB, apoCIII and apoE in VLDL+LDL and apoE in HDL were all interrelated, and each was a univariate predictor of subsequent coronary events. The significant independent predictors were VLDL-apoB (relative risk [RR] 3.2 for highest to lowest quintiles, P=0.04), apoCIII in VLDL+LDL (RR 2.3, P=0.04), and apoE in HDL (RR 1.8, P=0.02). Plasma triglycerides, a univariate predictor of coronary events (RR 1.6, P=0.03), was not related to coronary events (RR 1.3, P=0.6) when apoCIII in VLDL+LDL was included in the model, whereas apoCIII remained significant. Adjustment for LDL- and HDL-cholesterol did not affect these results.

Conclusions-The plasma concentrations of VLDL particles and apoCIII in VLDL and LDL are more specific
measures of coronary heart disease risk than plasma triglycerides perhaps because their known metabolic properties link them more closely to atherosclerosis.

JAMA, 2000;284:1256-1262

Relationship of Hospital Teaching Status With Quality of Care and Mortality for Medicare Patients With Acute MI

Jeroan J. Allison; Catarina I. Kiefe; Norman W. Weissman; Sharina D. Person; Matthew Rousculp; John G. Canto; Sejong Bae; O. Dale Williams; Robert Farmer; Robert M. Centor

Context. Issues of cost and quality are gaining importance in the delivery of medical care, and whether quality of care is better in teaching vs nonteaching hospitals is an essential question in this current national debate.

Objective. To examine the association of hospital teaching status with quality of care and mortality for fee-for-service Medicare patients with acute myocardial infarction (AMI).

Design, Setting, and Patients. Analysis of Cooperative Cardiovascular Project data for 114,411 Medicare patients from 4361 hospitals (22,354 patients from 439 major teaching hospitals, 22,493 patients from 455 minor teaching hospitals, and 69,564 patients from 3467 nonteaching hospitals) who had AMI between February 1994 and July 1995.

Main Outcome Measures. Administration of reperfusion therapy on admission, aspirin during hospitalization, and β-blockers and angiotensin-converting enzyme inhibitors at discharge for patients meeting strict inclusion criteria; mortality at 30, 60, and 90 days and 2 years after admission.

Results. Among major teaching, minor teaching, and nonteaching hospitals, respectively, administration rates for aspirin were 91.2%, 86.4%, and 81.4% (P<.001); for angiotensin-converting enzyme inhibitors, 63.7%, 60.0%, and 58.0% (P<.001); for β-blockers, 48.8%, 40.3%, and 36.4% (P<.001); and for reperfusion therapy, 55.5%, 58.9%, and 55.2% (P = .29). Differences in unadjusted 30-day, 60-day, 90-day, and 2-year mortality among hospitals were significant at P<.001 for all time periods, with a gradient of increasing mortality from major teaching to minor teaching to nonteaching hospitals. Mortality differences were attenuated by adjustment for patient characteristics and were almost eliminated by additional adjustment for receipt of therapy.

Conclusions. In this study of elderly patients with AMI, admission to a teaching hospital was associated with better quality of care based on 3 of 4 quality indicators and lower mortality.
Plaque inflammation in restenotic coronary lesions of patients with stable or unstable angina

Jan J. Piek, Allard C. Van Der Wal, Martijn Meuwissen, Karel T. Koch, Steven A.J. Chamuleau, Peter Teeling, Chris M. Van Der Loos, Anton E. Becker

OBJECTIVES
To evaluate immunohistochemically various parameters of inflammation in coronary atherectomy specimens obtained from restenotic culprit lesions of patients presenting with either stable or unstable angina (UA)

BACKGROUND
There is no information regarding the relationship between atherosclerotic plaque inflammation and the severity of the coronary syndromes in patients with restenotic coronary lesions.

METHODS
A total of 37 patients with either stable angina or UA underwent directional coronary atherectomy for restenotic coronary lesions. Cryostat sections of atherectomy specimen were immunohistochemically stained with monoclonal antibodies CD68 (macrophages [MACs]), CD3 (T-lymphocytes) and alpha-actin (smooth muscle cells [SMCs]). Smooth muscle cell contents and MAC contents were planimetrically quantified as the percentage immunopositive tissue area of the total tissue area. T-lymphocytes were counted at 100-× magnification throughout the entire section and expressed as number of cells per mm2.

RESULTS
Restenotic coronary lesions of patients with UA or stable angina showed no significant difference in SMC areas (31.9% ± 16.3% vs. 38.5% ± 18.8%, respectively; p = NS). However, restenotic coronary lesions of patients presenting with unstable angina contained significantly more MACs (24.4% ± 15.1% vs. 10.5% ± 5.8%, p = 0.001) and T-lymphocytes (18.8 cells/mm² ± 15.1 cells/mm² vs. 8.6 cells/mm² ± 9.8 cells/mm²; p = 0.034) than patients with stable angina.

CONCLUSIONS
These results suggested that inflammation appears to affect plaque instability in restenotic coronary lesions resulting in unstable coronary syndromes.
Regular Aerobic Exercise Prevents and Restores Age-Related Declines in Endothelium-Dependent Vasodilation in Healthy Men

Christopher A. DeSouza, Linda F. Shapiro, Christopher M. Clevenger, Frank A. Dinenna, Kevin D. Monahan, Hirofumi Tanaka, and Douglas R. Seals

Background—In sedentary humans endothelium-dependent vasodilation is impaired with advancing age contributing to their increased cardiovascular risk, whereas endurance-trained adults demonstrate lower age-related risk. We determined the influence of regular aerobic exercise on the age-related decline in endothelium-dependent vasodilation.

Methods and Results—In a cross-sectional study, 68 healthy men 22 to 35 or 50 to 76 years of age who were either sedentary or endurance exercise-trained were studied. Forearm blood flow (FBF) responses to intra-arterial infusions of acetylcholine and sodium nitroprusside were measured by strain-gauge plethysmography. Among the sedentary men, the maximum FBF response to acetylcholine was 25% lower in the middle aged and older compared with the young group (P<0.01). In contrast, there was no age-related difference in the vasodilatory response to acetylcholine among the endurance-trained men. FBF at the highest acetylcholine dose was almost identical in the middle aged and older (17.3±1.3 mL/100 mL tissue per minute) and young (17.7±1.4 mL/100 mL tissue per minute) endurance-trained groups. There were no differences in the FBF responses to sodium nitroprusside among the sedentary and endurance-trained groups. In an exercise intervention study, 13 previously sedentary middle aged and older healthy men completed a 3-month, home-based aerobic exercise intervention (primarily walking). After the exercise intervention, acetylcholine-mediated vasodilation increased 30% (P<0.01) to levels similar to those in young adults and middle aged and older endurance-trained men.

Conclusions—Our results indicate that regular aerobic exercise can prevent the age-associated loss in endothelium-dependent vasodilation and restore levels in previously sedentary middle aged and older healthy men. This may represent an important mechanism by which regular aerobic exercise lowers the risk of cardiovascular disease in this population.

Smoking cessation reduces mortality after coronary artery bypass surgery: a 20-year follow-up study
OBJECTIVES
The goal of this study was to determine the influence of smoking cessation on mortality after coronary artery bypass graft surgery (CABG), which has still not been established clearly.

BACKGROUND
Cigarette smoking is one of the known major risk factors of coronary artery disease.

METHODS
One thousand and forty-one patients underwent CABG between 1971 and 1980. The preoperative and postoperative smoking habits of 985 patients (95%) could be retrieved and were analyzed in a multivariate Cox analysis.

RESULTS
The median follow-up was 20 years (range 13 to 26 years). Smoking status before surgery did not entail an increased risk of mortality: patients who had smoked before surgery and those who had not smoked in the year before surgery had a similar probability of survival. However, smoking cessation after surgery was an important independent predictor of a lower risk of death and coronary reintervention during the 20-year follow-up when compared with patients who continued smoking. In analyses adjusted for baseline characteristics, the persistent smokers had a greater relative risk (RR) of death from all causes (RR 1.68 [95% confidence interval 1.33 to 2.13]) and cardiac death (RR 1.75 [1.30 to 2.37]) as compared with patients who stopped smoking for at least one year after surgery. The estimated benefit of survival for the quitters increased from 3% at five years to 14% at 15 years. The quitters were less likely to undergo repeat CABG or a percutaneous coronary angioplasty procedure (RR 1.41 [1.02 to 1.94]).

CONCLUSIONS
Patients who continued to smoke after CABG had a greater risk of death than patients who stopped smoking. They also underwent repeat revascularization procedures more frequently. Cessation of smoking is therefore strongly recommended after CABG. Clinicians are encouraged to start or to continue smoking-cessation programs in order to help smokers to quit smoking, especially after CABG.

Circulation 2000;102: 1227-1232
Plasma Homocysteine Predicts Mortality Independently of Traditional Risk Factors and C-Reactive Protein in Patients With Angiographically Defined Coronary Artery Disease


Background-Plasma homocysteine (tHCY) has been associated with coronary artery disease (CAD). We tested whether tHCY also increases secondary risk, after initial CAD diagnosis, and whether it is independent of traditional risk factors, C-reactive protein (CRP), and methylenetetrahydrofolate reductase (MTHFR) genotype. Methods and Results-Blood samples were collected from 1412 patients with severe angiographically defined CAD (stenosis≥70%). Plasma tHCY was measured by fluorescence polarization immunoassay. The study cohort was evaluated for survival after a mean of 3.0±1.0 years of follow-up (minimum 1.5 years, maximum 5.0 years). The average age of the patients was 65±11 years, 77% were males, and 166 died during follow-up. Mortality was greater in patients with tHCY in tertile 3 than in tertiles 1 and 2 (mortality 15.7% versus 9.6%, P=0.001 [log-rank test], hazard ratio [HR] 1.63). The relative hazard increased 16% for each 5-μmol/L increase in tHCY (P<0.001). In multivariate Cox regression analysis, controlling for univariate clinical and laboratory predictors, elevated tHCY remained predictive of mortality (HR 1.64, P=0.009), together with age (HR 1.72 per 10-year increment, P<0.0001), ejection fraction (HR 0.84 per 10% increment, P=0.0001), diabetes (HR 1.98, P=0.001), CRP (HR 1.42 per tertile, P=0.004), and hyperlipidemia. Homozygosity for the MTHFR variant was weakly predictive of tHCY levels but not mortality. Conclusions-In patients with angiographically defined CAD, tHCY is a significant predictor of mortality, independent of traditional risk factors, CRP, and MTHFR genotype. These findings increase interest in tHCY as a secondary risk marker and in secondary prevention trials (ie, with folate/B vitamins) to determine whether reduction in tHCY will reduce risk.

Circulation, 2000;102:1107-1113

Prospective Study Correlating Fibrinopeptide A, Troponin I, Myoglobin, and Myosin Light Chain Levels With Early and Late Ischemic Events in Consecutive Patients Presenting to the Emergency Department With Chest Pain

Ali Sonel, Brett M. Sasseen, Naomi Fineberg, Nils Bang, and Robert L. Wilensky
Background—Although thrombus formation plays a major role in acute coronary syndromes, few studies have evaluated a thrombus marker in risk stratification of patients with chest pain. Furthermore, the relation between markers that reflect myocardial injury and thrombus formation that may predict events in a heterogeneous patient population is unknown. This study correlated markers of thrombus and myocardial injury with early and late ischemic events in consecutive patients with chest pain.

Methods and Results—Serum troponin I (TnI), myoglobin, and myosin light chain levels were obtained from 247 patients and urinary fibrinopeptide A (FPA) from 178 of the 247. By multivariate analysis, patients with an elevated FPA level were 4.82 times more likely to die or have myocardial infarction, unstable angina, and coronary revascularization at 1 week (P=0.002, 95% CI 1.78, 13.03), whereas those with an elevated TnI (>0.2 ng/mL) were 9.41 times more likely (P<0.001, 95% CI 2.84, 31.17). At 6 months (excluding the index event), an elevated FPA level was an independent predictor of events, with an odds ratio of 9.57 (P<0.001, CI 3.29, 27.8), and was the only marker to predict a shorter event-free survival (P<0.001). The other markers did not independently correlate with cardiac events, although MLC incrementally increased early predictive accuracy in combination with the FPA and TnI.

Conclusions—Elevated FPA and TnI correlated with cardiac events during the initial week in patients presenting to the Emergency Department with chest pain. FPA predicted adverse events and a shorter event-free survival at 6 months.
abnormalities) cardiac complications.

Results Patients free from major complications until day 7 (44% of all patients) were found to constitute a very low risk group and thus would qualify for discharge at day 7. Of the 39% of patients with an uncomplicated infarction (low risk) in the validation group, 31% were discharged at day 7, while 8% stayed longer because of non-cardiac co-morbidity, for social reasons or logistic problems. No major adverse event occurred within 7 days after hospital discharge and only 1.8% developed complications within 1 month. The median duration of hospital stay for all in-hospital survivors was 7 days compared to 10 days in the control group.

Conclusion Prospective application of the early discharge decision rule, based upon simple clinical variables and without the need for additional non-invasive and invasive tests, resulted in a significant reduction of hospital stay. The decision rule correctly classified patients into high and low risk groups and appeared feasible and safe. Its efficacy was demonstrated by its ability to identify a large group of post infarction survivors at low risk for complications during follow-up. Copyright 2000 The European Society of Cardiology

Journal of the American College of Cardiology, 36:2056-2063

Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the U.S. from 1990 through 1999: The National Registry of Myocardial Infarction 1, 2 and 3

William J. Rogers, John G. Canto, Costas T. Lambrew, Alan J. Tiefenbrunn, Becky Kinkaid, David A. Shoultz, Paul D. Frederick, Nathan Every for the Investigators in the National Registry of Myocardial Infarction 1 2 and 3

OBJECTIVES We sought to determine trends in the treatment of myocardial infarction from 1990 through 1999 in the U.S. and to relate these trends to current guidelines.

BACKGROUND Limited data are available to show how recent clinical trials and clinical guidelines have impacted treatment of myocardial infarction.

METHODS Temporal trends in myocardial infarction treatment and outcome were assessed by using data from 1,514,292 patients in the National Registry of Myocardial Infarction (NRMI) 1, 2 and 3 from 1990 through 1999. Results During this interval, the use of intravenous thrombolytic therapy declined from 34.3% to 20.8%, but the use of primary angioplasty increased from 2.4% to 7.3% (both P = 0.0001). The median floor-to-drug time among thrombolytic therapy recipients fell from 61.8 to 37.8 min (p = 0.0001), primarily owing to shorter floor-to-data and data-to-decision times. The prevalence of non-Q wave infarctions increased from 45% in 1994 to
63% in 1999 (p = 0.0001). From 1994 through 1999, there was increased usage of beta-blockers, aspirin and angiotensin-converting inhibitors, both during the first 24 h after admission and on hospital discharge (all P = 0.0001). Between 1990 and 1999, the median duration of hospital stay fell from 8.3 to 4.3 days, and hospital mortality declined from 11.2% to 9.4% (both P = 0.0001).

CONCLUSIONS The NRMI data from 1990 through 1999 demonstrate that the recommendations of recent clinical trials and published guidelines are being implemented, resulting in more rapid administration of intravenous thrombolytic therapy, increasing use of primary angioplasty and more frequent use of adjunctive therapies known to reduce mortality, and may be contributing to the higher prevalence of non-Q wave infarctions, shorter hospital stays and lower hospital mortality.


Relation of Race and Sex to the Use of Reperfusion Therapy in Medicare Beneficiaries with Acute Myocardial Infarction


Background. There are few reports describing the combined influence of the race and sex of a patient on the use of reperfusion therapy for acute myocardial infarction.

Methods. To determine the relation of race and sex to the receipt of reperfusion therapy for myocardial infarction in the United States, we reviewed the medical records of 234,769 Medicare patients with myocardial infarction. From these records we identified 26,575 white or black patients who met strict eligibility criteria for reperfusion therapy. We then performed bivariate and multivariate analyses of prevalence ratios to determine predictors of the use of reperfusion therapy in four subgroups of patients categorized according to race and sex: white men, white women, black men, and black women.

Results. Among eligible patients, white men received reperfusion therapy with the highest frequency (59 percent), followed by white women (56 percent), black men (50 percent), and black women (44 percent). After adjustment for differences in demographic and clinical characteristics, white women were as likely as white men to receive reperfusion therapy (prevalence ratio, 1.00; 95 percent confidence interval, 0.98 to 1.03). Likewise, black women were as likely as black men to receive reperfusion therapy (prevalence ratio, 1.00; 95 percent confidence interval, 0.89 to 1.13). However, black women were significantly less likely to receive...
reperfusion therapy than white men (prevalence ratio, 0.90; 95 percent confidence interval, 0.82 to 0.98), as were black men (prevalence ratio, 0.85; 95 percent confidence interval, 0.78 to 0.93).

Conclusions. After adjustment for differences in clinical and demographic characteristics and clinical presentation, differences according to sex in the use of reperfusion therapy are minimal. However, blacks, regardless of sex, are significantly less likely than whites to receive this potentially lifesaving therapy.

Journal of the American College of Cardiology, 35:6:1516-1524

Relationship between corrected TIMI frame counts at three weeks and late survival after myocardial infarction


OBJECTIVES To evaluate the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (CTFC) as a predictor of late survival after myocardial infarction.

BACKGROUND Thrombolysis in Myocardial Infarction flow grades predict late survival after myocardial infarction. The CTFC provides a more reproducible measurement of infarct-related artery blood flow than the TIMI flow grade, and has been linked to 30-day outcomes, but it has not yet been established how the CTFC correlates with late survival.

METHODS Of 1,001 patients with acute myocardial infarction presenting within 4 h of symptom onset, 882 underwent angiography at approximately three weeks. Infarct artery flow was assessed, blinded to clinical outcomes, according to the CTFC and TIMI flow grade. Late cardiac mortality and survival were determined in 97.5% of patients.

RESULTS The mean CTFC was 40 ± 29 in 644 patent infarct arteries (median, 34 [interquartile range, 24 to 47]). The CTFC, assessed as a continuous univariate variable, was found to be a predictor of five-year survival, as was the TIMI flow grade (both p < 0.001). On multivariate analysis, factors associated with five-year survival included the ejection fraction or end-systolic volume index (both p < 0.001), exercise duration (p = 0.005), age (p = 0.008), diabetes (p = 0.02) and CTFC (p = 0.02) or TIMI flow (p = 0.02). The same factors, except for the CTFC and TIMI flow grade, were predictors of 10-year survival.
CONCLUSIONS The CTFC three weeks after myocardial infarction was an independent predictor of five-year survival, but not 10-year survival. Although the CTFC provided additional prognostic information within TIMI flow grades, its superiority was not demonstrated.

Circulation, 2000;102: 642-648

Race, Sex, Poverty, and the Medical Treatment of Acute Myocardial Infarction in the Elderly

Saif S. Rathore, Alan K. Berger, Kevin P. Weinfurt, Manning Feinleib, William J. Oetgen, Bernard J. Gersh, and Kevin A. Schulman

Background-Race, sex, and poverty are associated with the use of diagnostic cardiac catheterization and coronary revascularization during treatment of acute myocardial infarction (AMI). However, the association of sociodemographic characteristics with the use of less costly, more readily available medical therapies remains poorly characterized.

Methods and Results-We evaluated 169,079 Medicare beneficiaries ≥65 years of age treated for AMI between January 1994 and February 1996 to determine the association of patient race, sex, and poverty with the use of medical therapy. Multivariable regression models were constructed to evaluate the unadjusted and adjusted influence of sociodemographic characteristics on the use of 2 admission (aspirin, reperfusion) and 2 discharge therapies (aspirin, β-blockers) indicated during the treatment of AMI. Therapy use varied by patient race, sex, and poverty status. Black patients were less likely to undergo reperfusion (RR 0.84, 95% CI 0.78, 0.91) or receive aspirin on admission (RR 0.97, 95% CI 0.96, 0.99) and β-blockers (RR 0.94, 95% CI 0.88, 1.00) at discharge. Female patients were less likely to receive aspirin on admission (RR 0.98, 95% CI 0.97, 0.99) and discharge (RR 0.98, 95% CI 0.96, 0.99). Poor patients were less likely to receive aspirin (RR 0.97, 95% CI 0.96, 0.98) or reperfusion (RR 0.97, 95% CI 0.93, 1.00) on admission and aspirin (RR 0.98, 95% CI 0.96, 1.00), or β-blockers (RR 0.95, 95% CI 0.91, 0.99) on discharge.

Conclusions-Medical therapies are currently underused in the treatment of black, female, and poor patients with AMI.

Journal of the American College of Cardiology, 35:112-118
Seropositivity to chlamydial lipopolysaccharide and chlamydia pneumoniae, systemic inflammation and stable coronary artery disease: Negative results of a case-control study

Albrecht Hoffmeister, Dietrich Rothenbacher, Peter Wanner, Guenter Bode, Kenneth Persson, Hermann Brenner, Vinzenz Hombach, Wolfgang Koenig

OBJECTIVES We investigated the association between seropositivity to chlamydial lipopolysaccharide (cLPS) or Chlamydia pneumoniae (CP) and angiographically documented coronary artery disease (CAD), and we examined the relationship between serostatus and markers of systemic inflammation.

BACKGROUND The potential contribution of CP to atherogenesis is still a matter of debate, and inflammation has been suggested to represent the link between infection and atherosclerotic disease.

METHODS Subjects age 40 to 68 years were recruited for this case-control study between October 1996 and November 1997: 312 patients with at least one coronary stenosis >50% and 479 age- and sex-matched blood donors without manifest CAD or history of angina. Antibodies against cLPS and CP, C-reactive protein (CRP), fibrinogen, plasma viscosity, leukocytes and neutrophils were determined. The study had a power of >80% to detect an odds ratio (OR) of 1.55 or above for the prevalence of immunoglobulin (IgG) antibodies against cLPS at a significance level of alpha = 0.05.

RESULTS Prevalence of IgG antibodies against cLPS was not different between cases and controls (61% vs. 62%; p = 0.7). The adjusted OR for the presence of CAD given positive IgG serostatus against cLPS was 0.9 (95% CI; 0.6 to 1.3). Similarly, no difference in the prevalence of IgG antibodies against CP was seen (88% vs. 87%; p = 0.6); the adjusted OR was 1.0 (95% CI; 0.6 to 1.6). Markers of inflammation did not show any statistically significant difference between cLPS seropositives and seronegatives.

CONCLUSIONS Our results indicate no strong association between CP and CAD, and increased systemic inflammation in patients with CAD does not seem to be due to seropositivity to cLPS or CP.

Circulation, 2000;101: 2557-2567

Predictors of Outcome in Patients With Acute Coronary Syndromes Without Persistent ST-Segment Elevation: Results From an International Trial of 9461 Patients

Eric Boersma, Karen S. Pieper, Ewout W. Steyerberg, Robert G. Wilcox, Wei-Ching Chang, Kerry L. Lee, K.
Background-Appropriate treatment policies should include an accurate estimate of a patient’s baseline risk. Risk modeling to date has been underutilized in patients with acute coronary syndromes without persistent ST-segment elevation.

Methods and Results-We analyzed the relation between baseline characteristics and the 30-day incidence of death and the composite of death or myocardial (re)infarction in 9461 patients with acute coronary syndromes without persistent ST-segment elevation enrolled in the PURSUIT trial [Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy]. Variables examined included demographics, history, hemodynamic condition, and symptom duration. Risk models were created with multivariable logistic regression and validated by bootstrapping techniques. There was a 3.6% mortality rate and 11.4% infarction rate by 30 days. More than 20 significant predictors for mortality and for the composite end point were identified. The most important baseline determinants of death were age (adjusted $\beta=95$), heart rate (2=32), systolic blood pressure (2=20), ST-segment depression (2=20), signs of heart failure (2=18), and cardiac enzymes (2=15). Determinants of mortality were generally also predictive of death or myocardial (re)infarction. Differences were observed, however, in the relative prognostic importance of predictive variables for mortality alone or the composite end point; for example, sex was a more important determinant of the composite end point ($2=21$) than of death alone ($2=10$). The accuracy of the prediction of the composite end point was less than that of mortality (C-index 0.67 versus 0.81).

Conclusions-The occurrence of adverse events after presentation with acute coronary syndromes is affected by multiple factors. These factors should be considered in the clinical decision-making process.

Circulation, 2000;102:833-839

Infections, Immunity, and Atherosclerosis : Associations of Antibodies to Chlamydia pneumoniae, Helicobacter pylori, and Cytomegalovirus With Immune Reactions to Heat-Shock Protein 60 and Carotid or Femoral Atherosclerosis

Manuel Mayr, Stefan Kiechl, Johann Willeit, Georg Wick, and Qingbo Xu
Background-Atherogenesis involves inflammatory processes in which infections are incriminated as possible contributors.

Methods and Results-We evaluated cardiovascular risk factors as well as seropositivity to Chlamydia pneumoniae, Helicobacter pylori, and cytomegalovirus in a population-based study. A significant association between prevalence and severity of atherosclerosis in carotid and femoral arteries and IgA antibodies to C pneumoniae was demonstrated that was not substantially altered after adjustment for established risk factors. For anti-H pylori IgG antibodies, significant correlations to vascular disease were restricted to low social status and lesions in carotid arteries. In addition, the study design allowed us to monitor lesion progression over time. In this prospective analysis, C pneumoniae seropositivity emerged as a significant risk predictor. Antibody titers against cytomegalovirus were not a marker for prevalence or incidence of atherosclerosis in this population. Further infection parameters added to the predictive value of chlamydial serology in risk assessment: Mean odds ratios for the prevalence of carotid atherosclerosis were 4.2 and 6.3 for seropositive subjects with elevated C-reactive protein levels and clinical evidence for chronic respiratory infection, respectively. For subjects with all 3 infection parameters, the odds ratio of carotid atherosclerosis reached 10.3 (P<0.0001). Concomitantly, serum antibodies to mycobacterial heat-shock protein 65 (mHSP65) correlated with seropositivity to C pneumoniae and H pylori but not to cytomegalovirus.

Conclusions-This prospective population-based study provides strong evidence for a potential atherogenic role of persistent bacterial infection, especially C pneumoniae, as indicated by serological and clinical data and demonstrates a correlation between immune reactions to mHSP65 and bacterial infections in atherogenesis.

Circulation, 2000;102: 1014-1019

Impact of Diabetes on Long-Term Prognosis in Patients With Unstable Angina and Non-Q-Wave Myocardial Infarction: Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry

Klas Malmberg, Salim Yusuf, Hertzel C. Gerstein, Joanne Brown, Feng Zhao, David Hunt, Leopoldo Piegas, James Calvin, Matyas Keltai, Andrzej Budaj, and for the OASIS Registry Investigators

Background-Although unstable coronary artery disease is the most common reason for admission to a coronary care unit, the long-term prognosis of patients with this diagnosis is unknown. This is particularly true for patients with diabetes mellitus, who are known to have a high morbidity and mortality after an acute...
myocardial infarction.

Methods and Results—Prospectively collected data from 6 different countries in the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry were analyzed to determine the 2-year prognosis of diabetic and nondiabetic patients who were hospitalized with unstable angina or non-Q-wave myocardial infarction. Overall, 1718 of 8013 registry patients (21%) had diabetes. Diabetic patients had a higher rate of coronary bypass surgery than nondiabetic patients (23% versus 20%, P<0.001) but had similar rates of catheterization and angioplasty. Diabetes independently predicted mortality (relative risk [RR], 1.57; 95% CI, 1.38 to 1.81; P<0.001), as well as cardiovascular death, new myocardial infarction, stroke, and new congestive heart failure. Moreover, compared with their nondiabetic counterparts, women had a significantly higher risk than men (RR, 1.98; 95% CI, 1.60 to 2.44; and RR, 1.28; 95% CI, 1.06 to 1.56, respectively). Interestingly, diabetic patients without prior cardiovascular disease had the same event rates for all outcomes as nondiabetic patients with previous vascular disease.

Conclusions—Hospitalization for unstable angina or non-Q-wave myocardial infarction predicts a high 2-year morbidity and mortality; this is especially evident for patients with diabetes. Diabetic patients with no previous cardiovascular disease have the same long-term morbidity and mortality as nondiabetic patients with established cardiovascular disease after hospitalization for unstable coronary artery disease.


Markers of Myocardial Damage and Inflammation in Relation to Long-Term Mortality in Unstable Coronary Artery Disease

Bertil Lindahl, Henrik Toss, Agneta Siegbahn, Per Venge, Lars Wallentin, for the FRISC Study Group

Background. In patients with unstable coronary artery disease, there is a relation between the short-term risk of death and blood levels of troponin T (a marker of myocardial damage) and C-reactive protein and fibrinogen (markers of inflammation). Using information obtained during an extension of the follow-up period in the Fragmin during Instability in Coronary Artery Disease trial, we evaluated the usefulness of troponin T, C-reactive protein, and fibrinogen levels and other indicators of risk as predictors of the long-term risk of death from cardiac causes.

Methods. Levels of C-reactive protein and fibrinogen at enrollment and the maximal level of troponin T during the first 24 hours after enrollment were analyzed in 917 patients included in a clinical trial of low-molecular-
weight heparin in unstable coronary artery disease. The patients were followed for a mean of 37.0 months (range, 1.6 to 50.6).

Results. During follow-up, 1.2 percent of the 173 patients with maximal blood troponin T levels of less than 0.06 µg per liter died of cardiac causes, as compared with 8.7 percent of the 367 patients with levels of 0.06 to 0.59 µg per liter and 15.4 percent of the 377 patients with levels of at least 0.60 µg per liter (P=0.007 and P=0.001, respectively). The rates of death from cardiac causes were 5.7 percent among the 314 patients with blood C-reactive protein levels of less than 2 mg per liter, 7.8 percent among the 294 with levels of 2 to 10 mg per liter, and 16.5 percent among the 309 with levels of more than 10 mg per liter (P=0.29 and P=0.001, respectively). The rates of death from cardiac causes were 5.4 percent among the 314 patients with blood fibrinogen levels of less than 3.4 g per liter, 12.0 percent among the 300 with levels of 3.4 to 3.9 g per liter, and 12.9 percent among the 303 with levels of at least 4.0 g per liter (P=0.004 and P=0.69, respectively). In a multivariate analysis, levels of troponin T and C-reactive protein were independent predictors of the risk of death from cardiac causes.

Conclusions. In unstable coronary artery disease, elevated levels of troponin T and C-reactive protein are strongly related to the long-term risk of death from cardiac causes. These markers are independent risk factors, and their effects are additive with respect to each other and other clinical indicators of risk.

Circulation, 2000;102:2031-2037

TIMI Risk Score for ST-Elevation Myocardial Infarction: A Convenient, Bedside, Clinical Score for Risk Assessment at Presentation : An Intravenous nPA for Treatment of Infarcting Myocardium Early II Trial Substudy

David A. Morrow, Elliott M. Antman, Andrew Charlesworth, Richard Cairns, Sabina A. Murphy, James A. de Lemos, Robert P. Giugliano, Carolyn H. McCabe, and Eugene Braunwald

Background-Considerable variability in mortality risk exists among patients with ST-elevation myocardial infarction (STEMI). Complex multivariable models identify independent predictors and quantify their relative contribution to mortality risk but are too cumbersome to be readily applied in clinical practice.

Methods and Results-We developed and evaluated a convenient bedside clinical risk score for predicting 30-day mortality at presentation of fibrinolytic-eligible patients with STEMI. The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI was created as the simple arithmetic sum of independent predictors of mortality weighted according to the adjusted odds ratios from logistic regression analysis in the Intravenous nPA for Treatment of Infarcting Myocardium Early II trial (n=14 114). Mean 30-day mortality was 6.7%. Ten baseline variables, accounting for 97% of the predictive capacity of the multivariate model, constituted the TIMI risk score. The risk score showed a >40-fold graded increase in mortality, with scores ranging from 0 to ≥8
mortality was <1% among patients with a score of 0. The prognostic discriminatory capacity of the TIMI risk score was comparable to the full multivariable model (c statistic 0.779 versus 0.784). The prognostic performance of the risk score was stable over multiple time points (1 to 365 days). External validation in the TIMI 9 trial showed similar prognostic capacity (c statistic 0.746).

Conclusions-The TIMI risk score for STEMI captures the majority of prognostic information offered by a full logistic regression model but is more readily used at the bedside. This risk assessment tool is likely to be clinically useful in the triage and management of fibrinolytic-eligible patients with STEMI.

PTX3, A Prototypical Long Pentraxin, Is an Early Indicator of Acute Myocardial Infarction in Humans

Giuseppe Peri, Martino Introna, Domenico Corradi, Giuseppe Iacuitti, Stefano Signorini, Fausto Avanzini, Fabrizio Pizzetti, Aldo P. Maggioni, Tiziano Moccetti, Marco Metra, Livio Dei Cas, Pietro Ghezzi, Jean D. Sipe, Gianpietro Re, Giorgio Olivetti, Alberto Mantovani, and Roberto Latini

Background-Inflammation is an important component of ischemic heart disease. PTX3 is a long pentraxin whose expression is induced by cytokines in endothelial cells, mononuclear phagocytes, and myocardium. The possibility that PTX3 is altered in patients with acute myocardial infarction (AMI) has not yet been tested.

Methods and Results-Blood samples were collected from 37 patients admitted to the coronary care unit (CCU) with symptoms of AMI. PTX3 plasma concentrations, as measured by ELISA, higher than the mean±2 SD of age-matched controls (2.01 ng/mL) were found in 27 patients within the first 24 hours of CCU admission. PTX3 peaked at 7.5 hours after CCU admission, and mean peak concentration was 6.94±11.26 ng/mL. Plasma concentrations of PTX3 returned to normal in all but 3 patients at hospital discharge and were unrelated to AMI site or extent, Killip class at entry, hours from symptom onset, and thrombolysis. C-reactive protein peaked in plasma at 24 hours after CCU admission, much later than PTX3 (P<0.001). Patients >64 years old and women had significantly higher PTX3 concentrations at 24 hours (P<0.05). PTX3 was detected by immunohistochemistry in normal but not in necrotic myocytes.

Conclusions-PTX3 is present in the intact myocardium, increases in the blood of patients with AMI, and disappears from damaged myocytes. We suggest that PTX3 is an early indicator of myocyte irreversible injury in ischemic cardiomyopathy.
Long-term prognosis of diabetic patients with myocardial infarction: relation to antidiabetic treatment regimen

I. Gustafsson, P. Hildebrandt, M. Seibæk, T. Melchior, C. Torp-Pedersen, L. Køber, P. Kaiser-Nielsen

Aims The present study was performed to evaluate pre-admission history, presentation, initial treatment and long-term mortality in patients with myocardial infarction and diabetes.

Methods and Results Between 1990 and 1992, 6676 patients with acute myocardial infarction were screened for entry into the Trandolapril Cardiac Evaluation (TRACE) study. In this cohort 719 (11%) of the patients had a history of diabetes. Among the diabetic patients 19% were treated with insulin, 52% with oral hypoglycaemic agents and 29% with diet only. The diabetic patients were slightly older, more likely to be female and had a higher prevalence of known cardiovascular disease. Even though the diabetic patients had the same frequency of ST-segment elevation on the electrocardiogram and the same admission delay, treatment with thrombolysis and aspirin was less frequently prescribed to the diabetic patients than to patients without diabetes. The mortality rate was significantly increased in the diabetic patients, 7-year mortality being 79% in insulin-treated, 73% in tablet-treated and 62% in diet-treated diabetic patients compared with 46% in patients without diabetes. In a multivariate analysis only diabetic patients treated with oral hypoglycaemic agents or with insulin had an increased mortality compared with non-diabetic patients.

Conclusions Patients with diabetes mellitus and myocardial infarction are treated with thrombolysis to a lesser extent than non-diabetic patients. Diabetic patients treated with oral hypoglycaemic agents or insulin, but not those treated with diet alone, have a significantly increased mortality following acute myocardial infarction compared with non-diabetic patients. Copyright 2000 The European Society of Cardiology

Prognostic value of cardiac troponin-I levels following catheter-based coronary interventions

Shmuel Fuchs, Ran Kornowski, Roxana Mehran, Alexandra J. Lansky, Lowell F. Satler, Augusto D. Pichard, Kenneth M. Kent, Chester E. Clark, Gregg W. Stone, Martin B. Leon
This study has examined the prognostic significance of troponin-I (Tn-I) levels after catheter-based coronary interventions in coronary arteries and saphenous vein grafts lesions. Tn-I and creatine kinase-MB (CK-MB) fraction levels were measured at 6 and 18 to 24 hours after catheter-based coronary intervention in 1,129 consecutive patients with normal preintervention plasma levels of Tn-I, and CK-MB levels below the cutoff for myocardial infarction. Patients were stratified according to maximal postangioplasty Tn-I levels. Group I (n = 784) had no elevated Tn-I (<0.15 ng/ml), group II (n = 170) had Tn-I at 0.15 to 0.45 ng/ml, and group III (n = 175) had Tn-I elevation >0.45 ng/ml. Major in-hospital complications (death, Q-wave infarction, and emergent coronary bypass grafting) and out-of-hospital intermediate-term (8 months) outcomes were compared between the 3 groups. Tn-I elevation >0.45 ng/ml was associated with increased risk of mortality (group III, 1.6%; group II, 0.6%; and group I, 0.1%; p = 0.019) and major in-hospital complications (3.2%, 1.7%, and 0.5%; p = 0.004). There was no difference in death (1.8%, 3.2%, and 2.4%; p = 0.74), Q-wave infarction (0.6%, 0%, and 0.3%; p = 0.66), or target lesion revascularization (10.1%, 9.0%, and 9.3%; p = 0.86) between the 3 groups at follow-up. Cardiac event-free survival was similar between groups (p = 0.3). By multivariate analysis, Tn-I >0.45 ng/ml was an independent predictor for major in-hospital complications (odds ratio 2.1, 95% confidence interval 1.2 to 3.9, p = 0.01). The degree of risk was also associated with the conjoint elevation of Tn-I and CK-MB levels (odds ratio 1.1, 95% confidence interval 1.02 to 1.2, p = 0.01). We conclude that Tn-I levels >3 times the normal limit and conjoint elevation of Tn-I and CK-MB levels after coronary angioplasty are associated with increased risk of major in-hospital complications, but have no incremental risk of adverse intermediate-term (8 months) clinical outcomes.

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Hyperhomocysteinemia Increases Risk of Death, Especially in Type 2 Diabetes : 5-Year Follow-Up of the Hoorn Study

Ellen K. Hoogeveen, Pieter J. Kostense, Cornelis Jakobs, Jacqueline M. Dekker, Giel Nijpels, Robert J. Heine, Lex M. Bouter, and Coen D. A. Stehouwer

Background-A high serum total homocysteine (tHcy) concentration is a risk factor for death, but the strength of
the relation in patients with type 2 (non-insulin-dependent) diabetes mellitus compared with nondiabetic subjects is not known. A cross-sectional study suggested that the association between tHcy and cardiovascular disease is stronger in diabetic than in nondiabetic subjects. We therefore prospectively investigated the combined effect of hyperhomocysteinemia and type 2 diabetes on mortality.

Methods and Results—Between October 1, 1989, and December 31, 1991, serum was saved from 2484 men and women, 50 to 75 years of age, who were randomly selected from the town of Hoorn, The Netherlands. Fasting serum tHcy concentration was measured in 171 subjects who died (cases; 76 of cardiovascular disease) and in a stratified random sample of 640 survivors (control subjects). Mortality risks were calculated over 5 years of follow-up by means of logistic regression. The prevalence of hyperhomocysteinemia (tHcy >14 \( \mu \text{mol/L} \)) was 25.8%. After adjustment for major cardiovascular risk factors, serum albumin, and HbA1c, the odds ratio (95% CI) for 5-year mortality was 1.56 (1.07 to 2.30) for hyperhomocysteinemia and 1.26 (1.02 to 1.55) per 5-\( \mu \text{mol/L} \) increment of tHcy. The odds ratio for 5-year mortality for hyperhomocysteinemia was 1.34 (0.87 to 2.06) in nondiabetic subjects and 2.51 (1.07 to 5.91) in diabetic subjects (P=0.08 for interaction).

Conclusions—Hyperhomocysteinemia is related to 5-year mortality independent of other major risk factors and appears to be a stronger (1.9-fold) risk factor for mortality in type 2 diabetic patients than in nondiabetic subjects.

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Hormone replacement therapy and distensibility of carotid arteries in postmenopausal women: a randomized, controlled trial

Peter Angerer, Wolfgang Kothny, Stefan Stork, Clemens von Schacky

OBJECTIVES
The study objective was to clarify in a randomized, controlled, observer-blind trial whether hormone replacement therapy (HRT) improves elastic properties of the common carotid artery in women with signs of subclinical atherosclerosis, especially in subgroups with increased risk, and whether less progestin enhances the effect.

BACKGROUND
Previous observational studies have yielded conflicting results on the influence of HRT on central arteries. Some studies reported improvement of distensibility by estrogen alone or in the subgroup of smokers.
METHODS
A total of 321 postmenopausal women were randomized to 1 mg 17βestradiol plus 0.025 mg gestodene for 12 days every month (HRT 1), or 1 mg 17βestradiol plus 0.025 mg gestodene for 12 days every third month (HRT 2), or no-HRT, during 48 weeks. In 173 women, distensibility of the common carotid artery was determined before and after therapy by M-mode ultrasound and brachial blood pressure measurement.

RESULTS
Change of distensibility was small and similar in the three treatment groups. In the subgroup of current smokers, HRT 2 (low progestin) increased distensibility by 32% (HRT 2: 8.2 ± 11.7; HRT 1: 0.6 ± 6.0; no HRT: -1.8 ± 6.8 × 10^-3 kPa, P = 0.025 for no-HRT vs. HRT 2). In the subgroups with elevated blood pressure, high low density lipoprotein (LDL) cholesterol, or high age, no effect of HRT was detected.

CONCLUSIONS
This randomized intervention study demonstrates that long-term HRT with estrogen and progestin does not substantially influence distensibility of central arteries. Yet, in currently smoking postmenopausal women, HRT with low progestin seems to improve distensibility; this merits further study in a specifically designed trial.


Effects of Estrogen Replacement on the Progression of Coronary-Artery Atherosclerosis

David M. Herrington, David M. Reboussin, K. Bridget Brosnihan, Penny C. Sharp, Sally A. Shumaker, Thomas E. Snyder, Curt D. Furberg, Glen J. Kowalchuk, Thomas D. Stuckey, William J. Rogers, David H. Givens, David Waters

Background. Heart disease is a major cause of illness and death in women. To understand better the role of estrogen in the treatment and prevention of heart disease, more information is needed about its effects on coronary atherosclerosis and the extent to which concomitant progestin therapy may modify these effects.

Methods. We randomly assigned a total of 309 women with angiographically verified coronary disease to receive 0.625 mg of conjugated estrogen per day, 0.625 mg of conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate per day, or placebo. The women were followed for a mean (±SD) of 3.2±0.6 years. Base-line and follow-up coronary angiograms were analyzed by quantitative methods.

Results. Estrogen and estrogen plus medroxyprogesterone acetate produced significant reductions in low-
density lipoprotein cholesterol levels (9.4 percent and 16.5 percent, respectively) and significant increases in high-density lipoprotein cholesterol levels (18.8 percent and 14.2 percent, respectively); however, neither treatment altered the progression of coronary atherosclerosis. After adjustment for measurements at base line, the mean (±SE) minimal coronary-artery diameters at follow-up were 1.87±0.02 mm, 1.84±0.02 mm, and 1.87±0.02 mm in women assigned to estrogen, estrogen plus medroxyprogesterone acetate, and placebo, respectively. The differences between the values for the two active-treatment groups and the value for the placebo group were not significant. Analyses of several secondary angiographic outcomes and subgroups of women produced similar results. The rates of clinical cardiovascular events were also similar among the treatment groups. Conclusions. Neither estrogen alone nor estrogen plus medroxyprogesterone acetate affected the progression of coronary atherosclerosis in women with established disease. These results suggest that such women should not use estrogen replacement with an expectation of cardiovascular benefit.

Circulation, 2000; 102: 1893-1900

Effect of Pravastatin on Coronary Disease Events in Subgroups Defined by Coronary Risk Factors: The Prospective Pravastatin Pooling Project

Background-Previous trials have had insufficient numbers of coronary events to address definitively the effect of lipid-modifying therapy on coronary heart disease in subgroups of patients with varying baseline characteristics.

Methods and Results-The data from 3 large randomized trials with pravastatin 40 mg were pooled and analyzed with the use of a prospectively defined protocol. Included were 19 768 patients, 102 559 person-years of follow-up, 2194 primary end points (coronary death or nonfatal myocardial infarction), and 3717 expanded end points (primary end point, CABG, or PTCA). Pravastatin significantly reduced relative risk in younger (<65 years) and older (≥65 years) patients, men and women, smokers and nonsmokers, and patients with or without diabetes or hypertension. The relative effect was smaller, but absolute risk reduction was similar in patients with hypertension compared with those without hypertension. Relative risk reduction was significant in predefined categories of baseline lipid concentrations. Tests for interaction were not significant between relative risk reduction and baseline total cholesterol (5% to 95% range 177 to 297 mg/dL, 4.6 to 7.7 mmol/L), HDL cholesterol (27 to 58 mg/dL, 0.7 to 1.5 mmol/L), and triglyceride (74 to 302 mg/dL, 0.8 to 3.4 mmol/L)
concentrations, analyzed as continuous variables. However, for LDL cholesterol, the probability values for interaction were 0.068 for the prespecified primary end point and 0.019 for the expanded end point. Relative risk reduction was similar throughout most of the baseline LDL cholesterol range (125 to 212 mg/dL, 3.2 to 5.5 mmol/L) with the possible exception of the lowest quintile of CARE/LIPID (<125 mg/dL) (relative risk reduction 5%, 95% CI 19% to -12%).

Conclusions-Pravastatin treatment is effective in reducing coronary heart disease events in patients with high or low risk factor status and across a wide range of pretreatment lipid concentrations.

Circulation, 2000;102: 2165-2168

Direct Proinflammatory Effect of C-Reactive Protein on Human Endothelial Cells

Vincenzo Pasceri, James T. Willerson, and Edward T. H. Yeh

Background-The acute-phase reactant C-reactive protein (CRP) is an important risk factor for coronary heart disease. However, the possible effects of CRP on vascular cells are not known.

Methods and Results-We tested the effects of CRP on expression of adhesion molecules in both human umbilical vein and coronary artery endothelial cells. Expression of vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM-1), and E-selectin was assessed by flow cytometry. Incubation with recombinant human CRP (10 \( \mu \)g/mL) for 24 hours induced a 10-fold increase in expression of ICAM-1 and a significant expression of VCAM-1, whereas a 6-hour incubation induced significant E-selectin expression. Adhesion molecule induction was similar to that observed in endothelial cells activated with interleukin-1\( \beta \). In coronary artery endothelial cells, induction of ICAM-1 and VCAM-1 was already present at 5 \( \mu \)g/mL and reached a maximum at 50 \( \mu \)g/mL, at which point a substantial increase in expression of E-selectin was also evident. The CRP effect was dependent on presence of human serum in the culture medium, because no effect was seen in cells cultured with serum-free medium. In contrast, interleukin-1\( \beta \) was able to induce adhesion molecule expression in the absence of human serum.

Conclusions-CRP induces adhesion molecule expression in human endothelial cells in the presence of serum. These findings support the hypothesis that CRP may play a direct role in promoting the inflammatory component of atherosclerosis and present a potential target for the treatment of atherosclerosis.
Effect of Plasma Homocysteine Concentration on Early and Late Events in Patients With Acute Coronary Syndromes

Peter J. Stubbs, Mohamed K. Al-Obaidi, Ronan M. Conroy, MusB, Paul O. Collinson, MRCPath, Ian M. Graham, FRCPI, and Mark I. M. Noble

Background—Although a raised plasma homocysteine is a risk factor for vascular disease, it is not known whether it is associated with an adverse cardiac outcome in patients admitted with acute coronary syndromes. We evaluated the relationship between plasma homocysteine and short-term (28 days) and long-term (median 2.5 years) prognosis in acute coronary syndromes.

Methods and Results—We evaluated the relationship of quintiles of homocysteine to fatal and nonfatal coronary disease early (28 days) and late (29 days to a median of 2.5 years) after admission to a single unit of patients with unstable angina (n=204) and myocardial infarction (n=236). The end points studied were cardiac death (n=67) and/or myocardial (re)infarction (n=30). Cox regression and logistic regression were used to estimate the relationship of homocysteine to coronary events. The event rate within the first 28 days (22 cardiac deaths and 5 nonfatal infarctions) was not related to the admission homocysteine level. In the 203 unstable angina and 214 myocardial infarction survivors, an apparent threshold effect was seen on long-term follow-up, with a significant step-up in the frequency of events between the lowest 3 quintiles (14 cardiac deaths and 11 nonfatal infarctions) and the upper 2 quintiles (31 fatal and 12 nonfatal events). Patients in the upper 2 quintiles (>12.2 μmol/L) had a 2.6-fold increase in the risk of a cardiac event (95% CI, 1.5 to 4.3, P<0.001).

Conclusions—Elevated total homocysteine levels on admission strongly predict late cardiac events in acute coronary syndromes.
OBJECTIVES
This study was designed to document the inflammatory response up to one year after acute presentation with unstable angina (UA) and non-Q wave infarction (NQMI) as reflected by the expression of soluble cell adhesion molecules (CAMs).

BACKGROUND
Coronary plaque inflammation is a key component in the pathogenesis of acute coronary syndromes. Cell adhesion molecules are critical mediators of the inflammatory process. Soluble forms of these molecules are detectable in serum and are elevated acutely in patients with UA and NQMI.

METHODS
Patients presenting with UA and NQMI had serum samples taken at presentation and then after three, six and 12 months. A control group of similar age and gender distribution was used for comparison. Levels of soluble inter-cellular adhesion molecule-1, vascular cell adhesion molecule-1, endothelial-selectin and platelet-selectin were measured using an ELISA technique.

RESULTS
We studied 91 patients (M/F = 73/18, mean age 62 ± 11 years, 56 UA and 35 NQMI) and 24 controls (M/F = 18/6, mean age 56 ± 12 years). Levels of all four soluble CAMs were significantly elevated in both UA and NQMI patients at presentation, three and six months in comparison with controls. Levels in UA and NQMI groups fell between six and 12 months after initial presentation.

CONCLUSIONS
The results suggest that the inflammatory stimulus triggering expression of CAMs is sustained for up to six months after presentation with either UA or NQMI and then returns toward control values over the following six months.

Circulation, 2000 ;102: 2058-2062
Epidemiological and Genetic Associations of Activated Factor XII Concentration With Factor VII Activity, Fibrinopeptide A Concentration, and Risk of Coronary Heart Disease in Men

Francesco Zito, Felicity Drummond, Sarah R. Bujac, M. Peter Esnouf, James H. Morrissey, Steve E. Humphries, and George J. Miller
Background-The relations of plasma activated factor XII (FXIIa) concentration and a common polymorphism (C46T) of the factor XII gene with hemostatic status and risk of coronary heart disease (CHD) were examined by prospective surveillance.

Methods and Results-Genotyping for the C46T variant was performed in 2624 men 50 to 61 years of age who were free of CHD at baseline. The genotype distribution was as follows: CC, 56.7%; CT, 36.9%; and TT, 6.6%. Plasma FXIIa was measured by ELISA on 1745 samples collected 1 year after baseline; median levels were (ng/mL) CC, 2.0; CT, 1.4; and TT, 0.8 (P<0.0001). Respective values for plasma fibrinopeptide A (FPA, nmol/L) were 1.52, 1.35, and 1.15 (P<0.0001); for factor VII coagulant activity (FVIIc, % standard), 114.5, 116.2, and 109.3 (P=0.02). Group differences in FVIIc were unchanged by adjustment for body mass index and serum triglycerides. Whereas CHD incidence did not differ significantly by genotype, rates (per 1000 person-years) by thirds of FXIIa distribution were for <1.5 ng/mL, 7.2; for 1.5 to 2.0 ng/mL, 7.2; and for >2.0 ng/mL, 13.6. Respective hazard ratios with the low third as reference group were 1.01 and 1.96 (P=0.007), which were essentially unchanged after allowance for genotype, blood lipids, blood pressure, body mass index, FVIIc, and FPA.

Conclusions-The C46T polymorphism is a determinant of FXIIa, FPA, and possibly FVIIc, suggesting that FXII influences the activity state of the coagulation pathway and FPA cleavage from fibrinogen in vivo. Plasma FXIIa is increased in middle-aged men at high risk of CHD.

JAMA, 2000;284:1799-1805

Differences in Prognostic Factors and Outcomes Between Women and Men Undergoing Coronary Artery Stenting

Julinda Mehilli; Adnan Kastrati; Josef Dirschinger; Hildegard Bollwein; Franz-Josef Neumann; Albert Schomig

Context Women with coronary artery disease (CAD) are believed to have a higher risk for adverse outcomes than men after conventional coronary interventions. The increasing use of coronary stenting has improved the outcome of patients undergoing coronary interventions, but little is known about the nature of outcomes in men vs women after this procedure.

Objective To examine whether there are sex-based differences in prognostic factors and in early and late outcomes among CAD patients undergoing coronary stent placement.

Design, Setting, and Patients Inception cohort study, at 2 tertiary referral institutions in Germany. Consecutive series of 1001 women and 3263 men with symptomatic CAD who were treated with stenting between May 1992 and December 1998. Patients who underwent stenting in the setting of acute myocardial infarction were
Main Outcome Measure The combined event rates of death and nonfatal myocardial infarction, assessed at 30 days and 1 year after stenting and compared by sex.

Results Compared with men, women undergoing coronary stenting were significantly older (mean age, 69 vs 63 years) and more likely to present with diabetes, arterial hypertension, or hypercholesterolemia. Women had less extensive CAD, a less frequent history of myocardial infarction and better preserved left ventricular function than men. Women presented an excess risk of death or nonfatal myocardial infarction only during the early period after stenting: the 30-day combined event rate of death or myocardial infarction was 3.1% in women and 1.8% in men (P = .02) and the multivariate-adjusted hazard ratio (HR) for women was 2.02 (95% confidence interval [CI], 1.27-3.19). At 1 year, the outcome was similar for both women and men (combined event rate for women, 6.0%, and for men, 5.8% (P = .77); multivariate-adjusted HR for women, 1.06 [95% CI, 0.75-1.48]). There was a sex difference in the prognostic value of baseline characteristics: the strongest prognostic factors were diabetes in women and age in men.

Conclusions The results of this study indicate that 1-year outcomes of women with CAD undergoing coronary artery stenting are similar to those of men. Despite the similarity in outcomes, there are several sex-specific differences in baseline characteristics, clinical course after the intervention, and relative weight of prognostic factors.

Circulation, 2000;102: 1639-1644

Development of Antibody Against Epitope of Lipoprotein(a) Modified by Oxidation : Evaluation of New Enzyme-Linked Immunosorbent Assay for Oxidized Lipoprotein(a)

Shingo Yamada, Ryuichi Morishita, Shigefumi Nakamura, Toshio Ogihara, Yoshiaki Kusumi, Isamu Sakurai, Nobuhiko Kubo, and Ikunosuke Sakurabayashi

Background-Recently, the biological effects of oxidized lipoprotein(a) [Lp(a)] have been reported to be more potent than Lp(a), the arteriosclerosis-relevant lipoprotein. Thus, investigations with oxidized Lp(a) are expected to provide viewpoints different from the conventional ones based on Lp(a).

Methods and Results-An anti-Lp(a) monoclonal antibody (161E2) was produced against synthetic peptide antigen (Arg-Asn-Pro-Asp-Val-Ala-Pro). This epitope was characterized as having various properties because its external exposure was induced as a result of oxidative modification. Using 161E2 antibody, we developed a
new enzyme-linked immunosorbent assay to measure Lp(a) modified by oxidative stress. The present data demonstrated that oxidized Lp(a) that contains the epitope of 161E2 antibody was present in the serum of humans. Therefore, we used this new enzyme-linked immunosorbent assay to evaluate the role of oxidized Lp(a) in patients with hypertension, which induces oxidative stress. Interestingly, hypertensive patients with complications showed a significantly higher level of oxidized Lp(a) in serum than did normotensive subjects (P<0.01), whereas there was no significant difference in native Lp(a) between normotensive and hypertensive subjects. Importantly, positive immunostaining with 161E2 monoclonal antibody was found in the human arteriosclerotic tissue.

Conclusions-We developed a new antibody against an epitope in Lp(a) as a result of oxidation treatment but not in native Lp(a). The present data demonstrated in vivo the presence of oxidized Lp(a) in the atherosclerotic tissue and its elevation in hypertensive patients. The presence of oxidized Lp(a) may be important in understanding the role of Lp(a) in cardiovascular disease.

Eur Heart J, 2000;21:911-8

Gender differences in diagnosis and treatment of coronary artery disease from 1981 to 1997. No evidence for the Yentl syndrome


Aims The aim of the present clinical study was to evaluate whether gender-related differences existed as regards the extent and localization of coronary artery lesions in patients with angiographically documented coronary artery disease, and whether these angiographic findings would lead to differences in further management.

Methods and results Over a 16-year period (1981-1997) we evaluated 1894 patients (1526 men, 368 women) with angiographically documented coronary artery disease (luminal stenosis >=60%). For each patient the coronary angiographic results and subsequent revascularization procedures (percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery) were analysed. The study period was divided into the early angioplasty years (1981 to 1989) and the current angioplasty years (1990-1997). No gender differences in extent and localization of coronary angiographic lesions were observed. In men and women the incidence of single-vessel disease was 42% and 40%, two-vessel disease 27% and 27%, three-vessel disease 26% and 24%,
and left main disease 5% and 8%, respectively (P=ns). Localization of disease in men and women was 36% and 39% for the left anterior descending coronary artery, 34% and 32% for the right coronary artery, and 27% and 26% for the left circumflex coronary artery, respectively (P=ns). There was a significant shift from multi-vessel disease towards single-vessel disease in both men and women (both P<0.001). As to subsequent management, a significant gender difference in favour of women was observed (P=0.021). Over time, the number of angioplasty procedures increased significantly from 11.6% to 23.2% for men (P<0.001), and for women from 17.6% to 28.0% (P=0.025), whereas the number of coronary artery bypass procedures decreased in men from 34.9% to 29.5% (P=0.024) and in women from 42.6% to 30.6% (P=0.019). Referral to angioplasty (n=535) and coronary artery bypass surgery (n=616) in relation to the extent of the disease did not show any gender bias in favour of men.

Conclusions Our angiographic findings did not show significant gender differences as regards the extent and localization of coronary artery disease in patients with angiographically documented coronary artery disease. More importantly, no substantial evidence could be found for under-referral of women to subsequent therapeutic management. Therefore our study questions the presence of Yentl syndrome in the current era.

Circulation, 2000;102: 2180-2184

Coronary Composition and Macrophage Infiltration in Atherectomy Specimens From Patients With Diabetes Mellitus

Pedro R. Moreno, Alvaro M. Murcia, Igor F. Palacios, Miltiadis N. Leon, Victor H. Bernardi, Valentin Fuster, and John T. Fallon

Background-Lipid-rich, inflamed atherosclerotic lesions are associated with plaque rupture and thrombosis, which are the most important causes of death in patients with diabetes mellitus. This study was designed to quantify lipid composition and macrophage infiltration in the coronary lesions of patients with diabetes mellitus.

Methods and Results-A total of 47 coronary atherectomy specimens from patients with diabetes mellitus were examined and compared with 48 atherectomy specimens from patients without diabetes. Plaque composition was characterized by trichrome staining. Macrophage infiltration was characterized by immunostaining. Clinical and demographic data were similar in both groups. The percentage of total area occupied by lipid-rich atheroma was larger in specimens from patients with diabetes (7±2%) than in specimens from patients without diabetes (2±1%; P=0.01), and the percentage of total area occupied by macrophages was larger in specimens
from patients with diabetes (22±3%) than in specimens from patients without diabetes (12±1%; P=0.003). The incidence of thrombus was also higher in specimens from patients with diabetes than in specimens from patients without diabetes (62% versus 40%; P=0.04). Plaque composition, macrophage infiltration, and thrombus were similar in lesions from diabetic patients treated with insulin compared with lesions from patients treated with sulfonylureas or diet.

Conclusions—Coronary tissue from patients with diabetes exhibits a larger content of lipid-rich atheroma, macrophage infiltration, and subsequent thrombosis than tissue from patients without diabetes. These differences suggest an increased vulnerability for coronary thrombosis in patients with diabetes mellitus.

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Association of Fibrinogen With Cardiovascular Risk Factors and Cardiovascular Disease in the Framingham Offspring Population

James J. Stec, Halit Silbershatz, Geoffrey H. Tofler, Travis H. Matheney, Patrice Sutherland, Izabela Lipinska, Joseph M. Massaro, Peter F.W. Wilson, James E. Muller, and Ralph B. D’Agostino, Sr

Background—Fibrinogen has been identified as an independent risk factor for cardiovascular disease and associated with traditional cardiovascular risk factors. Also, the role of elevated fibrinogen in thrombosis suggests that it may be on the causal pathway for certain risk factors to exert their effect. These associations remain incompletely characterized. Moreover, the optimal fibrinogen assay for risk stratification is uncertain.

Methods and Results—In 2632 subjects from cycle 5 of the Framingham Offspring Population, fibrinogen levels were determined with a newly developed immunoprecipitation test (American Biogenetic Sciences) and the functional Clauss method. With the immunoprecipitation method, there were significant linear trends across fibrinogen tertiles (P<0.001) for age, body mass index, smoking, diabetes mellitus, total cholesterol, HDL cholesterol, and triglycerides in men and women. The Clauss method had significant results (P<0.030), except for triglycerides in men. Fibrinogen levels were higher for those with compared with those without cardiovascular disease. After covariate adjustment, fibrinogen remained significantly higher in those with cardiovascular disease with the use of the immunoprecipitation test (P=0.035 and P=0.018 for men and women, respectively) but not with the Clauss method.

Conclusions—Fibrinogen was associated with traditional cardiovascular risk factors. Elevation of fibrinogen may provide a mechanism for risk factors to exert their effect. Also, fibrinogen levels were higher among subjects
with cardiovascular disease compared with those without disease. The immunoprecipitation test showed a stronger association with cardiovascular disease than the Clauss method, suggesting that it may be a useful screening tool to identify individuals at increased thrombotic risk.


C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women

Paul M. Ridker, Charles H. Hennekens, Julie E. Buring, Nader Rifai

Background. Since inflammation is believed to have a role in the pathogenesis of cardiovascular events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events.

Methods. We conducted a prospective, nested case-control study among 28,263 apparently healthy postmenopausal women over a mean follow-up period of three years to assess the risk of cardiovascular events associated with base-line levels of markers of inflammation. The markers included high-sensitivity C-reactive protein (hs-CRP), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 (sICAM-1). We also studied homocysteine and several lipid and lipoprotein measurements. Cardiovascular events were defined as death from coronary heart disease, nonfatal myocardial infarction or stroke, or the need for coronary-revascularization procedures.

Results. Of the 12 markers measured, hs-CRP was the strongest univariate predictor of the risk of cardiovascular events; the relative risk of events for women in the highest as compared with the lowest quartile for this marker was 4.4 (95 percent confidence interval, 2.2 to 8.9). Other markers significantly associated with the risk of cardiovascular events were serum amyloid A (relative risk for the highest as compared with the lowest quartile, 3.0), sICAM-1 (2.6), interleukin-6 (2.2), homocysteine (2.0), total cholesterol (2.4), low-density lipoprotein (LDL) cholesterol (2.4), apolipoprotein B-100 (3.4), high-density lipoprotein (HDL) cholesterol (0.3), and the ratio of total cholesterol to HDL cholesterol (3.4). Prediction models that incorporated markers of inflammation in addition to lipids were significantly better at predicting risk than models based on lipid levels alone (P<0.001). The levels of hs-CRP and serum amyloid A were significant predictors of risk even in the subgroup of women with LDL cholesterol levels below 130 mg per deciliter (3.4 mmol per liter), the target for primary prevention established by the National Cholesterol Education Program. In multivariate analyses, the only plasma markers that independently predicted risk were hs-CRP (relative risk for the highest as compared
with the lowest quartile, 1.5; 95 percent confidence interval, 1.1 to 2.1) and the ratio of total cholesterol to HDL cholesterol (relative risk, 1.4; 95 percent confidence interval, 1.1 to 1.9).

Conclusions. The addition of the measurement of C-reactive protein to screening based on lipid levels may provide an improved method of identifying women at risk for cardiovascular events.

Journal of the American College of Cardiology, 2000;36:1812-1817

Clinical study: acute coronary syndromes
Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy

David A. Morrow, Elliott M. Antman, Milenko Tanasijevic, Nader Rifai, James A. de Lemos, Carolyn H. McCabe, Christopher P. Cannon, Eugene Braunwald

Objectives We sought to evaluate cardiac troponin I (cTnI) for predicting early clinical outcomes and the efficacy of enoxaparin among patients with non-ST segment elevation acute coronary syndrome (ACS) and negative creatine kinase, MB fraction (CK-MB) levels.

Background Cardiac TnI identifies patients with unstable angina who are at higher risk of death or myocardial infarction (MI) by 30 days. The utility of cTnI for predicting very early clinical events, including recurrent ischemia, and the efficacy of enoxaparin are not yet established.

Methods At baseline and 12 h to 24 h after enrollment in the Thrombolysis in Myocardial Infarction (TIMI)-11B trial, samples were collected for cTnI determination.

Results Among 359 patients with negative serial CK-MB values, 50.1% had a cTnI result >0.1 ng/ml within the first 24 h. Patients with elevated cTnI were at higher risk of death or MI at 48 h (3.9 vs. 0%, P = 0.01) and 14 days (13.9 vs. 2.2%, p < 0.0001). Elevated cTnI also correlated with higher risk of recurrent ischemia requiring urgent revascularization by 48 h (10.0 vs. 1.7%, P = 0.001) and 14 days (20.6 vs. 5.6%, p ≤0.0001). Enoxaparin had a greater benefit among patients with elevated vs. normal cTnI (p = 0.03), achieving a 47% reduction in the risk of death, MI or urgent revascularization by 14 days in cTnI-positive patients (p = 0.007).

Conclusions Elevation of cTnI among patients with non-ST segment elevation ACS and negative levels of CK-MB identifies those at higher risk for very early adverse outcomes, including severe recurrent ischemia. Treatment with enoxaparin reduces the risk associated with elevated cTnI.
Apolipoprotein E genotypes and response of plasma lipids and progression-regression of coronary atherosclerosis to lipid-lowering drug therapy

Christie M. Ballantyne, J. Alan Herd, Evan A. Stein, Laura L. Ferlic, J. Kay Dunn, Antonio M. Gotto, Jr., Ali J. Marian

OBJECTIVES We sought to examine the association of apolipoprotein (apo) E genotypes with baseline plasma lipid levels and severity of coronary artery disease (CAD), as well as the response to treatment with fluvastatin in the Lipoprotein and Coronary Atherosclerosis Study (LCAS).

BACKGROUND Apo E genotypes have been associated with plasma lipid levels and CAD. However, the influence of apo E genotypes on the response of plasma lipids and CAD progression or regression to statin treatment in patients with mildly to moderately elevated cholesterol remains unknown.

METHODS Apo E genotypes were determined by polymerase chain reaction and restriction mapping. Plasma lipids were measured at baseline and 12 weeks after therapy with fluvastatin or placebo in 320 subjects. In 287 subjects, quantitative coronary angiography was performed at baseline and after 2.5 years of treatment.

RESULTS Subjects with the 3/3 genotype had greater reductions in total cholesterol (20.4% vs. 15.4%, \( P = 0.01 \)) and low density lipoprotein (LDL) cholesterol (28.8% vs. 22.7%, \( P = 0.03 \)) than did the subjects with the 3/4 or 4/4 genotype. In contrast, subjects with the 2/3 genotype (n = 10) had a greater increase in high density lipoprotein cholesterol (19.1%) than did the subjects with the 3/3 genotype (4.3%, \( P = 0.002 \)) and those with the 3/4 or 4/4 genotype (7.0%, \( P = 0.02 \)). Subjects with the 3/4 or 4/4 genotype had an increased frequency of previous angioplasty, but other measures of baseline CAD severity and baseline lipids did not differ significantly among the genotypes, nor did CAD progression or clinical events.

CONCLUSIONS Although subjects with the \( \epsilon4 \) allele had less reduction in LDL cholesterol with fluvastatin, they had similar benefit in terms of CAD progression.
Background—A proportion of patients who present with suspected acute coronary syndrome (ACS) are found to have insignificant coronary artery disease (CAD) during coronary angiography, but these patients have not been well characterized.

Methods and Results—Of the 5767 patients with non-ST-segment elevation ACS who were enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide) Therapy (PURSUIT) trial and who underwent in-hospital angiography, 88% had significant CAD (any stenosis >50%), 6% had mild CAD (any stenosis >0% to 50%), and 6% had no CAD (no stenosis identified). The frequency of death or nonfatal myocardial infarction at 30 days was reduced with eptifibatide treatment in patients with significant CAD (18.3% versus 15.6% for placebo, P=0.006) but not in those with mild CAD (6.6% versus 5.4%, P=0.62) and with no CAD (3.0% versus 1.2%, P=0.28). We identified independent baseline predictors of insignificant CAD (mild or no CAD) and used them to develop a simple predictive nomogram of the probability of insignificant CAD for use at hospital presentation. This nomogram was validated in a separate population of patients with non-ST-segment elevation ACS.

Conclusions—Patients with suspected ACS found to have insignificant CAD have a low risk of adverse outcomes, do not appear to benefit from treatment with eptifibatide, and can be predicted with a simple nomogram drawn from baseline characteristics. Because patients with significant CAD appear to have an enhanced benefit from eptifibatide treatment, the predictive nomogram developed can be used to determine indications for glycoprotein IIb/IIIa blockade.


Enrollment of Women in Cardiovascular Clinical Trials Funded by the National Heart, Lung, and Blood Institute

David J. Harris, Pamela S. Douglas

Background. With the recognition that certain aspects of cardiovascular disease are specific to sex, the U.S.
government has sought to ensure that federally funded clinical research yields adequate high-quality information about heart disease in women.

Methods. We tabulated the numbers of men and women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute (NHLBI) between 1965 and 1998, recording both total numbers and the numbers for each type of cardiovascular disease. We analyzed the data according to the sex-specific prevalence of disease and assessed changes in enrollment over time. We performed a similar analysis after excluding all single-sex trials.

Results. A total of 398,801 subjects (215,796 women and 183,005 men) were enrolled in NHLBI-funded studies of cardiovascular disease. The overall enrollment rate for women (54 percent) exceeded the prevalence of cardiovascular disease in women in the general population (49 percent) and increased over time (P=0.002). With single-sex trials excluded, the enrollment rate for women was 38 percent, which did not change significantly over time. In studies of coronary artery disease and hypertension the rates of enrollment of women were similar to or exceeded the prevalence of these disorders in women. The enrollment rate increased significantly over time in studies of coronary artery disease (P<0.001) but not in studies of hypertension or arrhythmia. Women were underenrolled in studies of heart failure, and the rate of enrollment did not change significantly over time. When single-sex trials were excluded from the analysis of enrollment rates according to the prevalence of disease, the results were similar. There was no change in enrollment rates over time for any category of disease.

Conclusions. Federal efforts to increase the representation of women in clinical trials have been moderately successful primarily because of the institution of a small number of large, single-sex trials involving coronary artery disease. There has been no change in the sex composition of cohorts in the majority of studies of cardiovascular disease.

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Ability of troponin I to predict cardiac events in patients admitted from the emergency department

Michael C. Kontos, F. Philip Anderson, Ramin Alimard, Joseph P. Ornato, James L. Tatum, Robert L. Jesse

OBJECTIVES We sought to determine the predictive ability of troponin I (TnI) in a heterogeneous group of patients with chest pain admitted from the emergency department (ED) for exclusion of myocardial infarction (MI).
BACKGROUND Previous studies in high-risk patients demonstrated that troponin elevations are associated with increased cardiac events. Little information is available on its predictive ability in more heterogeneous, lower risk patients.

METHODS Consecutive patients admitted from the ED for possible MI underwent serial myocardial marker sampling of TnI and creatine kinase, CK-MB over an 8-h period. Patients with ST segment elevation were excluded. End points included MI, death, significant complications (e.g., cardiac or respiratory arrest, intra-aortic balloon pump, pulmonary artery catheter or pacemaker placement, revascularization or inotropic infusion) and significant disease.

RESULTS Events occurred in 513 (27%) of the 1,929 patients evaluated: MI in 175 (9.1%) and death in 34 (1.8%); an additional 248 patients (13%) without MI had complications, and 323 (17%) without MI had significant disease. Sensitivity of TnI for MI was high (96%). Patients without MI who were TnI-positive were more likely to have complications (43% vs. 12%) or significant disease (41% vs. 17%) as compared with those who were TnI-negative; however, the sensitivity of TnI for these two end points was low (14% and 21%, respectively). Predictive values were unchanged after excluding patients with ischemic electrocardiograms.

CONCLUSIONS Troponin I had a high sensitivity for MI when used as part of a rapid rule-in protocol; however, the sensitivity for other end points was low. Use of TnI alone failed to identify the majority of patients who had either significant disease or complications.

Eur Heart J, 2000;21:975-80

Cell adhesion molecules in relation to simvastatin and hormone replacement therapy in coronary artery disease


Aims To assess the effect of simvastatin, hormone replacement therapy and their combination on soluble cell adhesion molecules and plasma lipids, in hypercholesterolaemic post-menopausal women with coronary artery disease.

Methods We studied 16 post-menopausal women with coronary artery disease and hypercholesterolaemia (total cholesterol >200mg.dl⁻¹ and LDL cholesterol >130mg.dl⁻¹). We compared simvastatin (20mg daily) with hormone replacement therapy (0.625mg conjugated oestrogen and 2.5mg medroxyprogesterone acetate daily) and their combination, in a randomized, crossover, placebo controlled study. Each treatment period was 8 weeks long with a 4 week washout interval between treatments. Circulating cell adhesion molecules and
plasma lipids were evaluated at the end of each treatment period.

Results All three active treatments—simvastatin, hormone replacement therapy and the combination therapy—significantly reduced total and LDL cholesterol, compared to placebo (P<0·001). Only hormone replacement therapy, alone and in combination with simvastatin, significantly decreased lipoprotein(a) when compared to placebo (P<0·05), whereas simvastatin had no significant effect. Likewise, hormone replacement therapy and the combination therapy significantly reduced the intercellular adhesion molecule (ICAM-1) plasma levels (P=0·03 and P=0·02, respectively), while simvastatin, which was superior to hormone replacement therapy in lowering total and LDL cholesterol, did not modify ICAM-1 levels; the combination therapy was not more effective than hormone replacement therapy alone in ICAM-1 reduction. Neither the effect, on any treatment when compared to placebo, of VCAM-1 nor E-selectin levels differed significantly.

Conclusions Hormone replacement therapy may limit the inflammatory response to injury by modulating the expression of cell adhesion molecules from the endothelial cells, possibly in association with lipoprotein (a) reduction. Copyright 2000 The European Society of Cardiology

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Effect of Niacin on Lipid and Lipoprotein Levels and Glycemic Control in Patients With Diabetes and Peripheral Arterial Disease
The ADMIT Study: A Randomized Trial

Marshall B. Elam; Donald B. Hunninghake; Kathryn B. Davis; Rekha Garg; Craig Johnson; Debra Egan; John B. Kostis; David S. Sheps; Eliot A. Brinton; for the ADMIT Investigators

Context Although niacin increases low levels of high-density lipoprotein cholesterol (HDL-C), which frequently accompany diabetes, current guidelines do not recommend use of niacin in patients with diabetes because of concerns about adverse effects on glycemic control; however, this is based on limited clinical data.

Objective To determine the efficacy and safety of lipid-modifying dosages of niacin in patients with diabetes.

Design and Setting Prospective, randomized placebo-controlled clinical trial conducted in 6 clinical centers from August 1993 to December 1995.

Participants A total of 468 participants, including 125 with diabetes, who had diagnosed peripheral arterial disease.

Interventions After an active run-in period, participants were randomly assigned to receive niacin (crystalline
nicotinic acid), 3000 mg/d or maximum tolerated dosage (n = 64 with diabetes; n = 173 without diabetes), or placebo (n = 61 with diabetes; n = 170 without diabetes) for up to 60 weeks (12-week active run-in and 48-week double-blind).

Main Outcome Measures Plasma lipoprotein, glucose, hemoglobin A1c (HbA1c), alanine aminotransferase, and uric acid levels; hypoglycemic drug use; compliance; and adverse events, in patients with diabetes vs without who were receiving niacin vs placebo.

Results Niacin use significantly increased HDL-C by 29% and 29% and decreased triglycerides by 23% and 28% and low-density lipoprotein cholesterol (LDL-C) by 8% and 9%, respectively, in participants with and without diabetes (P<.001 for niacin vs placebo for all). Corresponding changes in participants receiving placebo were increases of 0% and 2% in HDL-C and increases of 7% and 0% in triglycerides, and increases of 1% and 1% in LDL-C. Glucose levels were modestly increased by niacin (8.7 and 6.3 mg/dL [0.4 and 0.3 mmol/L]; P = .04 and P<.001) in participants with and without diabetes, respectively. Levels of HbA1c were unchanged from baseline to follow-up in participants with diabetes treated with niacin. In participants with diabetes treated with placebo, HbA1c decreased by 0.3% (P = .04 for difference). There were no significant differences in niacin discontinuation, niacin dosage, or hypoglycemic therapy in participants with diabetes assigned to niacin vs placebo.

Conclusions Our study suggests that lipid-modifying dosages of niacin can be safely used in patients with diabetes and that niacin therapy may be considered as an alternative to statin drugs or fibrates for patients with diabetes in whom these agents are not tolerated or fail to sufficiently correct hypertriglyceridemia or low HDL-C levels.

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Influence of diabetes mellitus on early and late clinical outcomes in saphenous vein graft stenting

Javed M. Ahmed, Mun K. Hong, Roxana Mehran, George Dangas, Gary S. Mintz, Augusto D. Pichard, Lowell F. Satler, Kenneth M. Kent, Hongsheng Wu, Gregg W. Stone, Martin B. Leon

OBJECTIVES The purpose of this study was to compare early and late clinical outcomes in diabetic and nondiabetic patients after stent implantation in saphenous vein grafts (SVG).

BACKGROUND Patients with diabetes mellitus have less favorable acute and long-term outcomes after stent implantation in native coronary arteries. The impact of diabetes on SVG stenting, however, is not known.
METHODS We studied 908 consecutive patients (1,366 SVG lesions) treated with Palmaz-Schatz stents. In-hospital and late clinical outcomes (death, Q-wave myocardial infarction and repeat revascularization rates at one year) were compared between diabetic (n = 290) and nondiabetic (n = 618) patients.

RESULTS In-hospital mortality was significantly higher in diabetic as compared with nondiabetic patients (2.2% vs. 0.3%, p = 0.003). At one-year follow-up, target lesion revascularization (TLR) was 16.6% in diabetic and 12.3% in nondiabetic patients (p = 0.03). Overall cardiac event-free survival (freedom from death, Q-wave myocardial infarction and any coronary revascularization procedure) at one year was significantly lower in the diabetic (68%) compared with the nondiabetic patients (79%, p = 0.0003). By Cox regression analysis, diabetes mellitus was an independent predictor of both TLR (relative risk: 1.23; confidence interval: 0.96 to 1.58; p = 0.004) and late cardiac events (relative risk: 1.40; confidence interval: 1.05 to 1.86; p = 0.02).

CONCLUSIONS Patients with diabetes undergoing stent implantation in SVG have: 1) higher in-hospital and late mortality, 2) higher one-year TLR rates, and 3) significantly lower one-year cardiac event-free survival. Thus, diabetic patients have less favorable acute and late clinical outcomes after stent implantation in SVG lesions.

Circulation, 2000;102: 1082-1085

Lipoprotein(a) and Coronary Heart Disease: Meta-Analysis of Prospective Studies

John Danesh, Rory Collins, and Richard Peto

Background-Studies of the association between the plasma concentration of lipoprotein(a) [Lp(a)] and coronary heart disease (CHD) have reported apparently conflicting findings. We report a meta-analysis of the prospective studies with at least 1 year of follow-up published before 2000.

Methods and Results-The following information was abstracted for each study: geographical location of study, size, type of cohort (population-based or selected because of previous disease), mean age, follow-up duration, blood storage temperature and duration, assay methods, degree of adjustment for potential confounders, and relationship of baseline Lp(a) measurement with subsequent CHD risk. There were 5436 deaths from CHD or nonfatal myocardial infarctions during a weighted mean follow-up of 10 years in the 27 eligible studies. Comparison of individuals in the top third of baseline plasma Lp(a) measurements with those in the bottom third in each study yielded a combined risk ratio of 1.6 (95% CI 1.4 to 1.8, 2P<0.0001), with similar findings when the analyses were restricted to the 18 studies of general populations (combined risk ratio 1.7, 95% CI 1.4
to 1.9; 2P<0.00001). Despite differences among studies in blood storage techniques and assay methods, there was no significant heterogeneity among the results from the 18 population-based studies or among those from the 9 studies of patients with previous disease. Lp(a) was only weakly correlated with classical vascular risk factors, and adjustment for those that had been recorded made little difference to the reported risk ratios.

Conclusions-These prospective studies demonstrate a clear association between Lp(a) and CHD, but further studies are needed to determine the extent to which this is causal.

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17ß-Estradiol Decreases Endothelin-1 Levels in the Coronary Circulation of Postmenopausal Women With Coronary Artery Disease

Carolyn M. Webb, PhD; Mohammad A. Ghatei, PhD; John G. McNeill; DCRR; Peter Collins, MD, FRCP

Background
Estrogen reverses acetylcholine-induced coronary vasoconstriction via the possible facilitation of endothelium-derived NO. Estrogen also affects endothelium-derived constrictor factors. We therefore investigated the effects of 17ß-estradiol on coronary vasomotor responses to substance P (SP), and coronary sinus endothelin-1 and NO metabolite levels in postmenopausal women with coronary heart disease.

Methods and Results
We studied 20 women; 14 received estrogen (mean age 65±2 years) and 6 served as ethanol control subjects (age 63±3 years). Intracoronary infusions of papaverine (8 mg) and SP were administered before and 20 minutes after 50 pg/min 17ß-estradiol or 0.2 μL/min control. Coronary blood flow was calculated from the diameter, as measured with quantitative coronary angiography, and flow velocity, as measured with intracoronary Doppler. Coronary sinus plasma endothelin-1 and nitrite/nitrate (NO2/NO3) were measured at baseline, at peak velocity response to each infusion, and every 5 minutes during the estradiol infusion. Endothelin-1 levels were decreased after 20 minutes of estradiol (1.12±0.18 versus 0.86±0.17 pmol/L baseline2 versus estradiol, P=0.05). Endothelin-1 levels to SP decreased after 17ß-estradiol (1.29±0.18 versus 1.04±0.15 and 1.3±0.16 versus 0.99±0.17 pmol/L for before versus after estradiol, 10 and 25 pmol/min SP; both P<0.05). NO2/NO3 levels did not change. There was no change in vasomotor responses to estradiol alone or to papaverine or SP before versus after estradiol.

Conclusions
Short-term intracoronary 17ß-estradiol administration decreases coronary endothelin-1 levels. There was no enhancement of vasomotor responses to SP after the administration of estrogen, suggesting that the effects of estrogen on coronary acetylcholine responses may be a specific and not a generalized effect on coronary vasoreactivity.

J Am Coll Cardiology, 2000;36:1500-6

A randomized trial of the effects of early cardiac serum marker availability on reperfusion therapy in patients with acute myocardial infarction: The serial markers, acute myocardial infarction and rapid treatment trial (SMARTT)

W. Brian Gibler, James W. Hoekstra, W. Douglas Weaver, Mitchell W. Krucoff, Alfred P. Hallstrom, Raymond E. Jackson, Michael R. Sayre, James Christenson, George L. Higgins, Grant Innes, Richard J. Harper, Gary P. Young and Nathan R. Every for the SMARTT Investigators

OBJECTIVES
The purpose of this study was to assess whether the immediate availability of serum markers would increase the appropriate use of thrombolytic therapy.

BACKGROUND
Serum markers such as myoglobin and creatine kinase, MB fraction (CK-MB) are effective in detecting acute myocardial infarction (AMI) in the emergency setting. Appropriate candidates for thrombolytic therapy are not always identified in the emergency department (ED), as 20% to 30% of eligible patients go untreated, representing 10% to 15% of all patients with AMI. Patients presenting with chest pain consistent with acute coronary syndrome were evaluated in the EDs of 12 hospitals throughout North America.

METHODS
In this randomized, controlled clinical trial, physicians received either the immediate myoglobin, CK-MB results at 0 and 1 h after enrollment (stat) or conventional reporting of myoglobin, CK-MB 3 h or more after hospital admission (control). The primary end point was the comparison of the proportion of patients within the stat group versus control group who received appropriate thrombolytic therapy. Secondary end points included the emergent use of any reperfusion treatment in both groups, initial hospital disposition of patients (coronary care unit, monitor or nonmonitor beds) and the proportion of patients appropriately discharged from the ED.
RESULTS
Of 6,352 patients enrolled, 814 (12.8%) were diagnosed as having AMI. For patients having AMI, there were no statistically significant differences in the proportion of patients treated with thrombolytic therapy between the stat and control groups (15.1% vs. 17.1%, P = 0.45). When only patients with ST segment elevation on their initial electrocardiogram were compared, there were still no significant differences between the groups. Also, there was no difference in the hospital placement of patients in critical care and non-critical care beds. The availability of early markers was associated with more hospital admissions as compared to the control group, as the number of patients discharged from the ED was decreased in the stat versus control groups (28.4% vs. 31.5%, P = 0.023).

CONCLUSIONS
The availability of 0- and 1-h myoglobin and CK-MB results after ED evaluation had no effect on the use of thrombolytic therapy for patients presenting with AMI, and it slightly increased the number of patients admitted to the hospital who had no evidence of acute myocardial necrosis.


Cardiac Troponin T Predicts Mortality in Patients With End-Stage Renal Disease

Jutta Dierkes, Ute Domrose, Sabine Westphal, Andreas Ambrosch, Hans-Peter Bosselmann, Klaus Hinrich Neumann, and Claus Luley

Background-Patients with end-stage renal disease have a high risk of premature death, mainly as the result of cardiovascular disease (CVD), which is not sufficiently explained by the conventional risk factors. We therefore prospectively investigated total mortality and cardiovascular events in 102 patients on hemodialysis and assessed the prognostic value of baseline disease status and laboratory variables including total homocysteine and cardiac troponin T.

Methods and Results-Patients were followed for 2 years or until their first event of CVD (for outcome variable cardiovascular events, n=33) or death (for outcome variable total mortality, n=28). Survival was computed by the Kaplan-Meier method. Cox proportional hazards model was used to determine independent predictors of CVD events or total mortality. Cardiac troponin T emerged as the most powerful predictor of mortality, resulting in an almost 7-fold risk increase at concentrations $\geq 0.10$ ng/mL (hazard ratio 6.85, 95% CI 3.04 to 15.45). Total homocysteine level greater than median was also associated with mortality (hazard ratio 2.44, 95% CI 1.10
to 5.40). These hazard ratios did not change substantially after adjustment for other risk factors. Significant predictors for CVD events were baseline diabetes, cerebrovascular disease, serum glucose, and triglycerides. After adjustment, only glucose and triglycerides remained significantly related to CVD events (hazard ratio with 95% CI 1.33 [1.12 to 1.57] and 1.14 [1.04 to 1.26], respectively, for a 1-mmol/L increase in concentration).

Conclusions—We conclude that total homocysteine and particularly cardiac troponin T are important predictors of mortality in patients with end-stage renal disease, whereas other laboratory variables and baseline disease status have less prognostic value.

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Utilization of coronary angiography and revascularization after acute myocardial infarction in men and women risk stratified by the American College of Cardiology/American Heart Association guidelines

Prasad K. Kilaru, Russell F. Kelly, James E. Calvin, Joseph E. Parrillo

OBJECTIVES We sought to determine whether men and women are equally likely to receive coronary angiography and revascularization after acute myocardial infarction (AMI) when they are risk stratified according to American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines for post-MI care.

BACKGROUND Several previous studies have suggested that women may undergo angiography and revascularization procedures less frequently than men.

METHODS In 439 consecutive patients admitted to a public hospital with AMI, rates of coronary angiography and revascularization were compared in men and women categorized, according to ACC/AHA practice guidelines, as having strong (class I or IIa) or weaker (class IIb) indications for angiography.

RESULTS Women were older and more likely to be diabetic or hypertensive, but men and women were equally likely to meet class I/IIa criteria for post-MI angiography (both 51%). Angiography rates were nearly identical in men and women overall (63% vs. 64%), as well as in patients in class I/IIa (80% vs. 82%) and class IIb (46% vs. 46%) (all p > 0.80, with >80% power to detect important differences); the only multivariate predictors of post-MI angiography were age and ACC/AHA class. Significant coronary artery disease was equally prevalent in men and women undergoing angiography, and men and women were equally likely to undergo revascularization, whether they were in class I/IIa (both 55%, p = 0.90) or class IIb (59% vs. 58%, p = 0.88). No significant differences in mortality were noted between men and women.
CONCLUSIONS Despite being older and having more risk factors than men, women were equally likely to undergo coronary angiography and revascularization procedures after AMI, and they had in-hospital clinical outcomes that were at least as favorable.

Divergent effects of hormone therapy on serum markers of inflammation in postmenopausal women with coronary artery disease on appropriate medical management


OBJECTIVES
The goal of our study was to determine whether hormone therapy alters markers of inflammation in postmenopausal women with chronic stable coronary artery disease (CAD) on appropriate medical management.

BACKGROUND
Hormone therapy reduces some markers of inflammation associated with atherosclerosis risk (cell adhesion molecules) but increases levels of another marker of inflammation-C-reactive protein-in healthy postmenopausal women.

METHODS
Ten women (average age 66 years; range 59 to 76 years) with CAD on medical management (including aspirin [9], statin lipid-lowering therapy [7], angiotensin-converting enzyme inhibitors [3]) were randomly assigned to conjugated equine estrogens 0.625 mg (combined with medroxyprogesterone acetate 2.5 mg daily in five women with uterus intact) or placebo(s) daily for one month with crossover to the alternate therapy after one month off of hormone treatment in a double-blind study. At the end of each treatment phase, the following markers of inflammation were measured in serum: interleukin-6, C-reactive protein, E-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and matrix metalloproteinase-9.

RESULTS
Hormone therapy significantly lowered serum levels of cell adhesion molecules E-selectin (46.9 ± 18.3 vs. 56.3 ± 20.6 ng/mL, P = 0.006), intercellular adhesion molecule-1 (282 ± 74 vs. 304 ± 78 ng/mL, P = 0.013) and vascular cell adhesion molecule-1 (605 ± 218 vs. 657 ± 214 ng/mL, P = 0.01) but increased levels of matrix
metalloproteinase-9 (648 ± 349 vs. 501 ± 285 ng/mL, P = 0.02). Interleukin-6 (4.33 ± 4.78 vs. 3.04 ± 1.47 pg/mL, P = 0.283) and C-reactive protein (0.88 ± 1.13 vs. 0.61 ± 0.50 mg/dL, P = 0.358) were not significantly elevated on hormone therapy compared with placebo values.

CONCLUSIONS

Hormone therapy has divergent effects on serum markers of inflammation in women with CAD. Reduction in levels of cell adhesion molecules may reduce attachment of white blood cells to the vessel wall, but increases in matrix metalloproteinase-9 within the vessel wall could digest and weaken fibrous caps of vulnerable plaques, thus provoking thrombosis.

Circulation, 2000; 102: 1086-1092
Tissue Endothelin-Converting Enzyme Activity Correlates With Cardiovascular Risk Factors in Coronary Artery Disease

Frank Ruschitzka, Ueli Moehrlen, Thomas Quaschning, Mario Lachat, Georg Noll, Sidney Shaw, Zhihong Yang, Daniel Teupser, Thomas Subkowski, Marko I. Turina, and Thomas F. Luscher

Background-Endothelin-converting enzymes (ECEs) are the key enzymes in endothelin-1 (ET-1) generation. However, their pathophysiological role in patients with cardiovascular disease remains elusive.

Methods and Results-Vascular reactivity to big endothelin-1 (bigET-1; 10-9 to 10-7 mol/L) and ET-1 (10-9 to 10-7 mol/L) were examined in the internal mammary artery (IMA, n=33) and saphenous vein (SV, n=27) of patients with coronary artery disease with identified cardiovascular risk factors. Vascular ECE activity was determined by conversion of exogenously added bigET-1 to ET-1. Tissue contents of bigET-1 and ET-1 were measured by radioimmunoassay. In addition, the effects of LDL and oxidized LDL on ECE-1 protein levels were determined by Western blot analysis in human IMA endothelial cells. In the IMA, vascular ECE activity showed an inverse correlation with serum LDL levels (r=-0.76; P<0.01) and systolic and diastolic blood pressure and a positive correlation with fibrinogen (r=0.58; P<0.05). In the SV, fibrinogen was the only parameter to be correlated with vascular ECE activity. Vascular tissue content of bigET-1 was attenuated in the IMA of patients with hyperfibrinogenemia but increased in patients with elevated systolic blood pressure and increased serum LDL levels (P<0.05). Most interestingly, LDL and oxidized LDL downregulated ECE-1 protein levels in human IMA endothelial cells (P<0.05).

Conclusions-These data demonstrate, for the first time, that vascular ECE activity is (1) inversely correlated with serum LDL levels and blood pressure and (2) positively associated with fibrinogen in human vascular
tissue. Hence, ECE-1 activity may modulate cardiovascular risk in patients with coronary artery disease.

Thromb Haemost, 83(3):404-7, 2000

Prospective analysis after coronary-artery bypass grafting: platelet GP IIIa polymorphism (HPA-1b/PIA2) is a risk factor for bypass occlusion, myocardial infarction, and death.
Zotz RB; Klein M; Dauben HP; Moser C; Gams E; Scharf RE

Recently, we have demonstrated that human platelet antigen 1b (HPA-1b or P1A2) is a hereditary risk factor for platelet thrombogenicity leading to premature myocardial infarction in preexisting coronary artery disease. However, HPA-1b does not represent a risk factor for coronary artery disease itself. The aim of our present study was to evaluate the role of HPA-1b on the outcome in patients after coronary-artery bypass surgery. We prospectively determined the HPA-1 genotype in 261 consecutive patients prior to saphenous-vein coronary-artery bypass grafting. The patients were followed for one year. Among patients with bypass occlusion, myocardial infarction, or death more than 30 days after surgery, the prevalence of HPA-1b was significantly higher than among patients without postoperative complications (60 percent, 6/10, vs. 24 percent, 58/241, p <0.05, odds ratio 4.7). Using a stepwise logistic regression analysis with the variables HPA-1b, age, sex, body mass index, smoking (pack-years), hypertension, diabetes, cholesterol and triglyceride concentration, only HPA-1b had a significant association with bypass occlusion, myocardial infarction, or death after bypass surgery (p = 0.019, odds ratio 4.7). This study shows that HPA-1b is a hereditary risk factor for bypass occlusion, myocardial infarction, or death in patients after coronary-artery bypass surgery.

Atherosclerosis, 150(2):381-7, 2000

Comparison of various lipid, lipoprotein, and bilirubin combinations as risk factors for predicting coronary artery disease.

Schwertner HA; Fischer JR Jr
Studies were performed to determine if serum bilirubin, when combined with various lipid and lipoprotein risk factors, enhances our ability to predict coronary artery disease (CAD). This hypothesis was tested in a retrospective study of 644 middle-aged males who had undergone coronary angiography. The traditional risk factors of cholesterol, high density lipoprotein cholesterol (HDL-C), cholesterol/HDL-C ratios, triglycerides, age, cigarette smoking, and systolic blood pressure were tested by discriminant analysis, as were various cholesterol/bilirubin, cholesterol/(HDL-C+bilirubin), and low-density lipoprotein cholesterol (LDL-C)/(HDL-C+bilirubin) ratios. Each of these bilirubin-containing ratios was found to be an independent risk predictor when tested with the traditional risk factors. When the LDL-C/(HDL-C+bilirubin) ratio was included with the traditional risk predictors, it improved the prediction of severe CAD from 28.4 to 35.3% and the overall correct classification of CAD from 68.3 to 71.1%. When the 75th percentile was used as a cut-point, the diagnostic sensitivities obtained with cholesterol/(HDL-C+bilirubin) ratios (52.1%) and LDL-C/(HDL-C+bilirubin) ratios (51.7%) were better than those obtained with cholesterol/HDL-C ratios (40.4%) (P=0.033 and 0.048, respectively). LDL-C/(HDL-C+bilirubin) ratios also improved the prediction of severe CAD over those obtained with LDL-C/HDL-C ratios (43.4%); however, the changes were not statistically significant (P=0.096). If confirmed in other populations, serum bilirubin may be combined with LDL-C/HDL-C ratios, cholesterol/HDL-C ratios, cholesterol, or with various apolipoproteins to improve the prediction of CAD.

Can J Cardiol, 16 Suppl A(-HD-):5A-10A, 2000

Coronary artery disease and women: applying the guidelines for risk factor management.

McPherson R

Coronary artery disease (CAD) is the leading cause of death for women. In large part because of increased age at presentation and a greater frequency of concomitant morbidities, women who develop CAD have a poorer prognosis than do men. Although the long term outcome of revascularization procedures is good, the associated procedural morbidity and mortality in women is high. More emphasis should be placed on the primary and secondary prevention of CAD in women. Although women respond well to risk factor modification, including lipid-lowering therapies, recent data indicate that their awareness of risk factors and prevention strategies is poor. Physician risk factor assessment and adherence to current guideline recommendations are essential in preventing the development or progression of CAD in women.
Hereditary dyslipidemias and combined risk factors in children with a family history of premature coronary artery disease.

Sveger T; Flodmark CE; Nordborg K; Nilsson-Ehle P; Borgfors N

AIM: Schoolchildren aged 10-11 with a family history of premature coronary artery disease (CAD), were examined in order to identify children with genetically determined dyslipidemias and a combination of risk factors. METHODS: A total of 4000 questionnaires were distributed by the school; 55% of the families answered and returned the questionnaire. Blood lipids, apolipoprotein B, and Lp(a) lipoprotein were analysed in high risk children and their parents. RESULTS: A family history of premature CAD in parents or grandparents was identified in 208 families; 175 agreed to take part in a clinical examination and laboratory tests. Normal blood lipid tests were found in 89 children. Another 48 had an isolated increase of Lp(a) lipoprotein of minor clinical importance. Of the remaining 38 children, 23 had non-hereditary abnormalities of low (LDL) or high density lipoprotein (HDL) cholesterol or apolipoprotein B. Fifteen children were suspected to have genetically determined dyslipidemias or a combination of risk factors: in four, possible familial hypercholesterolaemia (FH); in five, possible familial combined hyperlipidaemia; in three, hereditary low HDL cholesterol; and in three a combination of high LDL cholesterol and Lp(a) lipoprotein concentrations. In addition, possible FH was detected in eight of the parents. CONCLUSION: It is worthwhile asking parents about the occurrence of premature CAD among their child’s closest relatives.

Analysis of risk factors for myocardial infarction and cardiac mortality after major vascular surgery.

Sprung J; Abdelmalak B; Gottlieb A; Mayhew C; Hammel J; Levy PJ; O’Hara P; Hertzer NR

BACKGROUND: Patients undergoing vascular surgical procedures are at high risk for perioperative myocardial infarction (PMI). This study was undertaken to identify predictors of PMI and in-hospital death in
major vascular surgical patients. METHODS: From the Vascular Surgery Registry (6,948 operations from January 1989 through June 1997) the authors identified 107 patients in whom PMI developed during the same hospital stay. Case-control patients (patients without PMI) were matched at a 1:1 ratio with index cases according to the type of surgery, gender, patient age, and year of surgery. The authors analyzed data regarding preoperative cardiac disease and surgical and anesthetic factors to study association with PMI and cardiac death. RESULTS: By using univariable analysis the authors identified the following predictors of PMI: valvular disease ($P = 0.007$), previous congestive heart failure ($P = 0.04$), emergency surgery ($P = 0.02$), general anesthesia ($P = 0.03$), preoperative history of coronary artery disease ($P = 0.001$), preoperative treatment with beta-blockers ($P = 0.003$), lower preoperative ($P = 0.03$) and postoperative ($P = 0.002$) hemoglobin concentrations, increased bleeding rate (as assessed from increased cell salvage; $P = 0.025$), and lower ejection fraction ($P = 0.02$). Of the 107 patients with PMI, 20.6% died of cardiac cause during the same hospital stay. The following factors increased the odds ratios for cardiac death: age ($P = 0.001$), recent congestive heart failure ($P = 0.01$), type of surgery ($P = 0.04$), emergency surgery ($P = 0.02$), lower intraoperative diastolic blood pressure ($P = 0.001$), new intraoperative ST-T changes ($P = 0.01$), and increased intraoperative use of blood ($P = 0.005$). Patients who underwent coronary artery bypass grafting, even more than 12 months before index surgery, had a 79% reduction in risk of death if they had PMI ($P = 0.01$). Multivariable analysis revealed preoperative definitive diagnosis of coronary artery disease ($P = 0.001$) and significant valvular disease ($P = 0.03$) were associated with increased risk of PMI. Congestive heart failure less than 1 yr before index vascular surgery ($P = 0.0002$) and increased intraoperative use of blood ($P = 0.007$) were associated with cardiac death. The history of coronary artery bypass grafting reduced the risk of cardiac death ($P = 0.04$) in patients with PMI. CONCLUSIONS: The in-hospital cardiac mortality rate is high for patients who undergo vascular surgery and experience clinically significant PMI. Stress of surgery (increased intraoperative bleeding and aortic, peripheral vascular, and emergency surgery), poor preoperative cardiac functional status (congestive heart failure, lower ejection fraction, diagnosis of coronary artery disease), and preoperative history of coronary artery bypass grafting are the factors that determine perioperative cardiac morbidity and mortality rates.

Am Heart J, 139(6):971-8, 2000

Clinical importance of risk factors and exercise testing for prediction of significant coronary artery stenosis in women recovering from unstable coronary artery disease: the Stockholm Female Coronary Risk Study.

Al-Khalili F ; Svane B ; Wamala SP ; Orth-Gomér K ; Ryd L ; Schenck-Gustafsson K
BACKGROUND: The objectives of this study were to investigate the relation between coronary risk factors, exercise testing parameters, and the presence of angiographically significant coronary artery disease (CAD) (> or =50% luminal stenosis) in female patients previously hospitalized for an acute CAD event. METHODS AND RESULTS: All women younger than age 66 years in the greater Stockholm area in Sweden who were hospitalized for acute coronary syndromes during a 3-year period were recruited. Besides collection of clinical parameters, coronary angiography and a symptom-limited exercise test were performed in 228 patients 3 to 6 months after the index hospitalization. The mean age was 56 +/- 7 years. Angiographically nonsignificant CAD (stenosis <50%) was verified in 37% of the patients; significant CAD was found in 63%. The clinical parameters that showed the strongest relation with the presence of significant CAD after adjusting for age were history of myocardial infarction (odds ratio [OR] 4.91, 95% confidence interval [CI] 2.35 to 7.49), history of diabetes mellitus (OR 3.83, 95% CI 1.63 to 14.31), serum high-density lipoprotein cholesterol <1.4 mmol/L (OR 2.11, 95% CI 1.20 to 3.72), and waist-to-hip ratio >0.85 (OR 1.78, 95% CI 1.02 to 3.10). A low exercise capacity and associated low change of rate-pressure product from rest to peak exercise were the only exercise testing parameters that were significantly related to angiographically verified significant CAD (<90% of the predicted maximal work capacity adjusted for age and weight, OR 1.91, 95% CI 1.04 to 3.50). CONCLUSIONS: In female patients recovering from unstable CAD, exercise capacity was the only exercise testing parameter of value in the prediction of significant CAD. The consideration of certain clinical characteristics and coronary risk factors offer better or complementary information when deciding on further coronary assessment.

Table V. Associations of exercise test variables and coronary angiographic findings
Table VI. Clinical determinants of significant CAD (>=50% stenosis)

J Womens Health Gend Based Med, 8(5):617-22, 1999

Coronary risk factors in women one year after coronary artery bypass grafting.

Allen JK

Given the importance of risk factor management to long-term outcome following coronary artery bypass grafting (CABG) and the paucity of information on risk factor changes in women, a study was undertaken to examine the coronary risk factor status of women before and 1 year after CABG. This study was a prospective investigation of 130 women who underwent first-time, isolated CABG between February 1992 and October
Lipid profiles, blood pressure, weight, smoking status, and other lifestyle behaviors were measured at the time of surgery and again 12 months later. The sample was 24% African American and had a mean age of 65 years and an average of 11 years of education. Substantial favorable changes in risk factor status occurred in the prevalence of smoking and the number of cigarettes smoked per day among smokers. Although the women experienced weight loss, 58% continued to be obese, and the self-reported dietary intake of fat, saturated fat, and cholesterol remained above the recommended levels of the National Cholesterol Education Program’s Step II diet. Mean systolic and diastolic blood pressures significantly increased, and a substantial number of patients (54%) continued to exhibit hypertension at 1 year. No significant changes in plasma lipid concentrations were observed. At 1 year, one third of the women exceeded recommended levels for triglycerides, 78% for total cholesterol, and 92% for low-density lipoproteins. These findings indicate that women continue to have multiple coronary risk factors after CABG, putting them at high risk for future coronary heart disease events. Healthcare professionals need to target these women for effective secondary prevention.

Arch Pathol Lab Med, 123(12):1219-22, 1999

An overview of genetic factors influencing plasma lipid levels and coronary artery disease risk.

Ozturk IC ; Killeen AA

BACKGROUND: Coronary artery disease (CAD) is a major cause of morbidity and mortality in most Western countries and its origin involves a significant genetic component. METHODS: Genetic and epidemiologic studies have been performed to identify factors that influence the CAD risk in the population. RESULTS: The primary loci that have been demonstrated to be associated with increased CAD risk owing to genetic mutations include the low-density lipoprotein receptor, apolipoprotein B-100, and lipoprotein(a). Additional implicated loci include lipoprotein lipase, apolipoprotein CII, cholesteryl ester transfer protein, apolipoprotein AI, and lecithin-cholesterol acyl transferase. CONCLUSIONS: Numerous mutations in known genes exert a major effect on CAD risk in some patients. However, in most patients with CAD, the genetic component is believed to be attributable to the aggregate effect of loci that, individually, exert only a minor influence on lipoprotein levels.
Lipoprotein(a) is a risk factor for occurrence of acute myocardial infarction in patients with coronary vasospasm.

Miwa K; Nakagawa K; Yoshida N; Taguchi Y; Inoue H

OBJECTIVES: The purpose of this study is to determine whether lipoprotein(a) (Lp[a]) is an independent risk factor for coronary spasm and occurrence of acute myocardial infarction (AMI) in patients with coronary spasm. BACKGROUND: Although elevated serum Lp(a) levels are known to be associated with coronary atherosclerosis and AMI, the association between the elevated level of this lipoprotein and coronary spasm remains to be elucidated. METHODS: Serum Lp(a) levels were measured using a latex immunoassay in 77 patients with coronary spasm but without a significant (>75%) fixed coronary stenosis, including 16 with prior myocardial infarction (MI), in 177 patients with a fixed stenosis but without rest angina, including 114 with prior MI and in 81 control subjects without coronary artery disease. RESULTS: The serum Lp(a) level in patients with coronary spasm (median; 17 mg/dl) was higher (p < 0.01) than in control subjects (12 mg/dl) but lower (p < 0.01) than in patients with a fixed stenosis (23 mg/dl). The incidence of subjects with higher (>25 mg/dl) serum Lp(a) levels was higher in patients with a fixed stenosis (46%, p < 0.01) but not in patients with coronary spasm (27%), compared with control subjects (21%). Among the patients with coronary spasm, the incidence of higher Lp(a) levels was higher in patients with than in those without a history of prior MI (56% vs. 21%, p <0.05). The patients with higher Lp(a) levels had a higher incidence of prior MI than those without (41% vs. 13%, p < 0.05). The multivariate analysis confirmed that higher serum Lp(a) level is an independent determinant for prior MI in these patients (odds ratio, 4.19; 95%, confidence interval, 1.03 to 17.00). CONCLUSIONS: Elevated serum level of Lp(a) was found to be associated with a history of prior MI in patients with coronary spasm, suggesting that Lp(a) may play an important role in the genesis of thrombotic coronary occlusion and the occurrence of AMI subsequent to coronary spasm.
Impaired endothelial function has been reported to be the initial step in atherosclerosis. Some coronary risk factors independently relate to impaired endothelial function. However, few studies have examined the association between coronary risk factors and endothelial function in patients who have multiple risk factors without clinical atherosclerosis. This study was undertaken to elucidate the relationship between accumulation of coronary risk factors and vascular endothelial dysfunction. We examined 101 subjects with one or more coronary risk factors 56.8 +/- 1.0 years old and 40 age-matched control subjects without coronary risk factors. We measured brachial artery diameter non-invasively using a 7.5-MHz ultrasound machine at rest, during reactive hyperemia caused by endothelium-dependent vasodilatation, and after sublingual administration of nitroglycerin, which causes endothelium-independent vasodilatation. The percentage change in flow-mediated diameter (%FMD; deltaD/D x 100), in subjects with one or more coronary risk factors was significantly lower than that in control subjects(4.8 +/- 0.3% vs. 6.7 +/- 0.5%, p < 0.01). Endothelium-independent vasodilatation by nitroglycerin did not differ between the two groups. Endothelial function was impaired according to the accumulation of coronary risk factors. On multiple regression analysis, the number of risk factors, age, and brachial artery diameter at rest showed significant correlation with %FMD. Our results suggest that an accumulation of coronary risk factors was significantly related to impairment of endothelial function.
Cardiac-specific troponin I levels and risk of coronary artery disease and graft failure following heart transplantation.

Labarrere CA; Nelson DR; Cox CJ; Pitts D; Kirlin P; Halbrook H

CONTEXT: Previous studies have yielded conflicting data regarding whether a relationship exists between elevated cardiac troponin levels and acute allograft rejection in patients who have received heart transplants. OBJECTIVE: To determine whether cardiac troponin I levels after heart transplantation were associated with a procoagulant microvasculature and long-term allograft outcome. DESIGN: Prospective cohort study with a mean (SE) follow-up of 45.1 (2.5) months. Serum troponin I levels were measured 9.9 (0.2) times per patient during the first 12 months after heart transplantation. SETTING: Heart transplant center in the United States. PATIENTS: A total of 110 consecutive patients who received a heart transplant between 1989 and 1997 and survived at least 1 year after transplantation. MAIN OUTCOME MEASURES: Histological and immunohistochemical biopsy findings, development of coronary artery disease (CAD), and graft failure in patients with vs without elevated serum cardiac troponin I levels. RESULTS: All recipients had elevated troponin I levels during the first month after transplantation. Troponin I levels remained persistently elevated during the first 12 months in 56 patients (51%) and became undetectable in 54 patients (49%). Persistently elevated troponin I levels were associated with increasing fibrin deposits in microvasculature and cardiomyocytes (P<0.001). Patients with persistently elevated levels of troponin I had significantly increased risk for subsequent development of CAD (odds ratio [OR], 4.3; 95% confidence interval [CI], 1.8-10.1; P<0.001) and graft failure (OR, 3.4; 95% CI, 1.2-9.7; P=0.02), and also developed more severe CAD (OR, 4.2; 95% CI, 1.9-9.3; P<0.001) and showed more disease progression (OR, 3.7; 95% CI, 1.3-10.4; P=0.009). CONCLUSION: In this study, elevated cardiac troponin I levels, which are considered to be a noninvasive surrogate marker of a procoagulant microvasculature, identified a subgroup of patients with high risk for developing CAD and graft failure after cardiac transplantation. JAMA. 2000;284:457-464

Relation of Helicobacter pylori infection and angiographically demonstrated coronary artery disease.
Conventional coronary risk factors explain only part of the variation in the incidence of cases of coronary heart disease. Recently H. pylori genomic material has been demonstrated in the coronary arteries of myocardial infarct. In searching for additional coronary risk factors, the potential role of H. pylori infection deserves to be investigated. To clarify if H. pylori infection is associated with an increased risk of coronary heart disease, a series of patients admitted to the Cardiac Catheterization Laboratory for coronary angiography were recruited prospectively. Cases (N = 165) were defined as those who had at least one coronary artery lesion occupying at least 50% of the luminal diameter on coronary angiography. Patients who had normal coronary angiography were selected as controls (N = 127). Demographic data, cardiovascular risk factors, and socioeconomic status were measured in both of the patients and controls. Stored serum specimens from both groups were tested for the presence of serum IgG antibody to H. pylori using enzyme-linked immunosorbent assay; 69.1% of the cases and 77.2% of the controls were seropositive for H. pylori (odds ratio 0.66, 95% CI 0.38-1.16, P = 0.12). After adjustment for age, gender, cardiovascular risk factors, and socioeconomic class, this remained nonsignificant (odds ratio 0.59, 95% CI 0.32-1.09, P = 0.09). H. pylori seropositivity was not associated with several coronary risk factors in either cases or controls. The proportion of H. pylori-positive patients was higher among the cases with triple vessel disease (77.5%) than those with double vessel disease (67.3%) and single vessel disease (65.7%); however, the differences were not statistically significant (odds ratio 0.57, 95% CI 0.23-1.4, P = 0.19). In this study no increase was found in H. pylori seropositivity in subjects with coronary artery disease. This minor association suggests that previous H. pylori infection, reflecting the early childhood environment, may not be important in determining the risk of coronary heart disease.

Atherosclerosis, 150(2):381-7, 2000

Comparison of various lipid, lipoprotein, and bilirubin combinations as risk factors for predicting coronary artery disease.

Schwertner HA; Fischer JR Jr

Studies were performed to determine if serum bilirubin, when combined with various lipid and lipoprotein
risk factors, enhances our ability to predict coronary artery disease (CAD). This hypothesis was tested in a retrospective study of 644 middle-aged males who had undergone coronary angiography. The traditional risk factors of cholesterol, high density lipoprotein cholesterol (HDL-C), cholesterol/HDL-C ratios, triglycerides, age, cigarette smoking, and systolic blood pressure were tested by discriminant analysis, as were various cholesterol/bilirubin, cholesterol/(HDL-C+bilirubin), and low-density lipoprotein cholesterol (LDL-C)/(HDL-C+bilirubin) ratios. Each of these bilirubin-containing ratios was found to be an independent risk predictor when tested with the traditional risk factors. When the LDL-C/(HDL-C+bilirubin) ratio was included with the traditional risk predictors, it improved the prediction of severe CAD from 28.4 to 35.3% and the overall correct classification of CAD from 68.3 to 71.1%. When the 75th percentile was used as a cut-point, the diagnostic sensitivities obtained with cholesterol/(HDL-C+bilirubin) ratios (52.1%) and LDL-C/(HDL-C+bilirubin) ratios (51.7%) were better than those obtained with cholesterol/HDL-C ratios (40.4%) (P=0.033 and 0.048, respectively). LDL-C/(HDL-C+bilirubin) ratios also improved the prediction of severe CAD over those obtained with LDL-C/HDL-C ratios (43.4%); however, the changes were not statistically significant (P=0.096). If confirmed in other populations, serum bilirubin may be combined with LDL-C/HDL-C ratios, cholesterol/HDL-C ratios, cholesterol, or with various apolipoproteins to improve the prediction of CAD.


Lack of association of a common polymorphism of the plasminogen activator inhibitor-1 gene with coronary artery disease and myocardial infarction.

Anderson JL; Muhlestein JB; Habashi J; Carlquist JF; Bair TL; Elmer SP; Davis BP

OBJECTIVES: The study was done to assess whether the common polymorphic allele (4G) of the plasminogen activator inhibitor-1 (PAI-1) gene is associated with coronary artery disease (CAD) or myocardial infarction (MI). BACKGROUND: Impaired fibrinolytic function has been associated with CAD and MI. Plasminogen activator inhibitor-1 plays a central role in intravascular thrombosis and thrombolysis; the common insertion/deletion polymorphism (4G/5G) of PAI-1 has been correlated with altered PAI-1 levels and proposed as a coronary risk factor. METHODS: Blood was drawn and DNA extracted from 1,353 consenting patients undergoing coronary angiography. The 4G and 5G alleles of PAI-1 were amplified using specific primers.
Amplified products were visualized by staining with ethidium bromide after electrophoresis in 1.5% agarose.

RESULTS: Patient age averaged 63.5 (SD 11.7) years; 70% were men, 28% had a history of MI, 66% had severe CAD (>60% stenosis), and 23% had no CAD or MI. Overall, the frequency of the 4G allele was 54.2%, and 78% of patients were 4G carriers. Genotypic distributions were: 4G/4G = 30.1%, 4G/5G = 47.9%, and 5G/5G = 21.8%. Neither carriage of 4G (CAD odds ratio [OR] = 1.08 [0.80 to 1.46], MI OR = 1.11 [0.83 to 1.49]) nor 4G/4G homozygosity (CAD OR = 1.07, MI OR = 0.98) was associated with CAD or MI. In multivariate analyses, risk factors associated with CAD were (in order): gender, age, smoking, diabetes, cholesterol, and hypertension; for MI, they were gender, smoking, and cholesterol. CONCLUSIONS: A common PAI-1 polymorphism (4G) was not importantly associated with angiographic CAD or history of MI in a Caucasian population. Modest risk (i.e., OR <1.5), especially for MI, or risk in association with other factors, cannot be excluded.

CMAJ, 163(1):49-56, 2000

Emerging relations between infectious diseases and coronary artery disease and atherosclerosis.

Fong IW

Cardiovascular disease is the leading cause of death in developed countries. The cause is multifactorial. A substantial proportion of patients with coronary artery disease (CAD) do not have traditional risk factors. Infectious diseases may play a role in these cases, or they may intensify the effect of other risk factors. The association of CAD and Chlamydia pneumoniae infection is firmly established, but causality is yet to be proven. The link with other infectious agents or conditions, such as cytomegalovirus, herpes simplex virus, Helicobacter pylori and periodontitis, is more controversial. Cytomegalovirus infection is more strongly linked than native CAD to coronary artery restenosis after angioplasty and to accelerated CAD after cardiac transplantation. However, new data on this topic are appearing in the literature almost every month. The potential for novel therapeutic management of cardiovascular disease and stroke is great if infection is proven to cause or accelerate CAD or atherosclerosis. However, physicians should not “jump the gun” and start using antibiotic therapy prematurely for CAD. The results of large randomized clinical trials in progress will help establish causality and the benefits of antimicrobial therapy in CAD.
Independent association of serum squalene and noncholesterol sterols with coronary artery disease in postmenopausal women.

Rajaratnam RA; Gylling H; Miettinen TA

OBJECTIVES: The purpose of the study was to investigate whether cholesterol metabolism is associated with coronary artery disease (CAD) in postmenopausal women. BACKGROUND: Although hypercholesterolemia, a predominant risk factor of CAD, is related to cholesterol metabolism, the association between cholesterol metabolism and CAD is not well known. METHODS: In addition to conventional coronary risk factors, fasting serum squalene, delta8-cholestenol, desmosterol, lathosterol (indicators of cholesterol synthesis), cholestanol, campesterol and sitosterol (indicators of cholesterol absorption) were measured in 48 50- to 55-year-old consecutive women with angiographically verified CAD and in 61 age-matched healthy controls. RESULTS: The coronary patients had elevated ratios of squalene (p < 0.001), desmosterol (p = 0.005), campesterol (p = 0.028) and sitosterol (p = 0.022) to cholesterol, but had lower respective lathosterol value (p = 0.041) compared with the controls, despite similar serum cholesterol levels. Adjusted for age, body mass index, family history of CAD, smoking, hypertension, serum triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol level and glycosylated hemoglobin A1c% (GHbA1c), the ratios of squalene (odds ratio, 1.36; 95% confidence interval, 1.17 to 1.57), lathosterol (0.98; 0.97 to 0.99), campesterol (1.01; 1.00 to 1.01) and sitosterol (1.01; 1.00 to 1.03) were significantly associated with the risk of CAD. In addition, family history of CAD and GHbA1c% were also independently related to the presence of CAD. CONCLUSIONS: The results suggest that women with elevated ratios of serum squalene, campesterol and sitosterol to cholesterol and low respective lathosterol values have enhanced risk for CAD. Thus, enhanced absorption and reduced synthesis of cholesterol may be related to coronary atherosclerosis.

HPA-1 and HPA-3 polymorphisms of the platelet fibrinogen receptor and coronary artery disease and myocardial infarction.

Kastrati A; Koch W; Mehilli J; Seidl H; von Beckerath N
Platelet fibrinogen receptor (glycoprotein [GP] IIb/IIIa) plays a fundamental role in atherothrombosis. The human platelet antigen (HPA) -1 and the HPA-3 are the most extensively studied polymorphisms of GPIIIa and GPIIb, respectively. This study was designed to test, in a large population, the hypothesis that these polymorphisms represent a risk factor for the occurrence of coronary artery disease (CAD) and myocardial infarction (MI). Consecutive, angiographically examined patients with significant coronary stenoses but without symptoms or signs of old or acute MI constituted the group with CAD (CAD, n = 998) and those with old or acute MI constituted the group with MI (MI, n = 793). As controls served subjects, matched with patients for age and sex, with neither angiographic CAD nor symptoms or signs of MI (matched controls [MC], n = 340) as well as a group of blood donors without cardiac symptoms or signs of CAD (BD, n = 104). Genotype distribution was similar across the groups; HPA-1a/a: HPA-1a/b: HPA-1b/b was 75.0%: 22.1%: 2.9% in BD, 72.6%: 24.7%: 2.6% in MC, 70.5%: 26.8%: 2.7% in CAD, and 70.7%: 26.4%: 2.9% in MI; HPA-3a/a: HPA-3a/b: HPA-3b/b was 39.4%: 40.4%: 20.2% in BD, 33.5%: 50.0%: 16.5% in MC, 35.0%: 46.4%: 17.0% in CAD, and 37.1%: 48.0%: 16.5% in MI. There was no interaction between these polymorphisms, nor between each of these polymorphisms and other risk factors. Thus, the HPA-1 and HPA-3 polymorphisms are neither separately nor in concert associated with any measurable increase of the risk for CAD or MI in angiographically evaluated subjects.

Clin Cardiol, 23(5):335-40 ,2000

Angiotensin-converting enzyme and apolipoproteins genes polymorphism in coronary artery disease.

Mansur AP ; Annicchino-Bizzacchi J ; Favarato D ; Avakian SD ; C sar LA ; Ramires JA

BACKGROUND: Association between angiotensin-converting enzyme (ACE) as well as apolipoprotein (apo) AI, B, and E polymorphisms and dyslipidemia and coronary artery disease (CAD) is controversial. HYPOTHESIS: This study assessed the distribution of ACE insertion/deletion, apo AI A>G mutation, apo B signal peptide insertion/deletion, apo B XbaI restriction fragment length, and apo E polymorphisms in 388 nondiabetic patients. METHODS: The study population included 112 patients with stable CAD, 139 patients with acute myocardial infarction (AMI), and 137 age-matched control subjects. RESULTS: Univariate analysis
showed higher prevalence of XbaI X+/X+ genotype in patients with CAD (p = 0.02). Angiotensin-converting enzyme and apo polymorphisms were not associated with lipid levels or severity of CAD. When all genotypes known to be related to CAD; such as ACE DD, apo AI GG, apo B del/del, and XbaI X+X+, and E4 allele of apo E, were pooled, again no significant differences among groups were seen. Multivariate regression analysis disclosed traditional risk factors and elevated levels of apo B for men and reduced levels of apo AI for women as independent variables for CAD. CONCLUSIONS: In addition to traditional coronary risk factors, apo B and AI could be considered predictors of CAD. No association between either form of CAD and polymorphisms was noted.

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