Am J Cardiol (2004);93:313-7
Usefulness of periprocedural creatinine phosphokinase-MB release to predict adverse outcomes after intracoronary radiation therapy for in-stent restenosis
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We aimed to analyze periprocedural creatinine phosphokinase (CPK)-MB elevation in patients treated with intracoronary radiation therapy (IRT) for in-stent restenosis (ISR) to risk stratify these patients. The clinical significance of periprocedural CPK-MB elevation after IRT for ISR is unknown. An elevated CPK-MB has been associated with increased mortality after conventional angioplasty. We evaluated 1,326 patients who were enrolled in radiation trials for ISR at the Washington Hospital Center using gamma- and beta-emitters. Patients were analyzed according to degree of CPK-MB increase within 24 hours of the index IRT procedure (normal CPK-MB, CPK-MB 1 to 3 times the upper limit of normal, or CPK-MB >3 times the upper limit of normal). Patients with CPK-MB >3 times the upper limit of normal were older (64 +/- 12 years, p = 0.04), more likely to be smokers (64%, p = 0.04), hypertensive (85%, p <0.01), and diabetic (49%, p = 0.04). The cohort with the highest CPK-MB release (CPK-MB >3 times the upper limit of normal) had significantly higher rates of adverse clinical events at 12 months (major adverse cardiac events 40%, p <0.01), including death (9.3%, p <0.01) and late thrombosis (6.3%, p <0.01). Periprocedural CPK-MB elevation is of prognostic importance in patients treated with IRT for ISR, and its analysis appears to be mandatory to risk stratify these patients. The impact of glycoprotein IIb/IIIa antagonists in reducing periprocedural CPK-MB release awaits evaluation.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14759380

Am Heart J (2004);147:239-45
High fasting glucose levels as a predictor of worse clinical outcome in patients with coronary artery disease: results from the Bezafibrate Infarction Prevention (BIP) study
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BACKGROUND: A high fasting glucose level may be a marker not only for microvascular complications, but also for macrovascular complications. We evaluated the clinical significance of a high fasting glucose level (> or =110 mg/dL), detected either at baseline or during follow-up, in the Bezafibrate Infarction Prevention (BIP) study. METHODS: The BIP study was a secondary prevention prospective double-blind study comparing bezafibrate to placebo. A total of 3122 patients with documented coronary artery heart disease who were aged 45 to 74 years and had a total cholesterol level between 180 and 250 mg/dL, low-density lipoprotein cholesterol level < or =180 mg/dL, a high-density lipoprotein cholesterol level < or =45 mg/dL, a triglyceride level < or =300 mg/dL, and a fasting glucose < or =160 mg/dL were randomized to receive 400 mg of bezafibrate daily or placebo. RESULTS: The primary end point of the BIP study was fatal myocardial infarction, non-fatal myocardial infarction, or sudden death. Secondary end points included hospitalization for unstable angina, percutaneous transluminal coronary angioplasty, and coronary artery bypass grafting. At baseline, 330 patients (11%) had diabetes mellitus, and 293 patients (9%) had an impaired fasting

blood glucose level (IFG). During 6.2 years of follow-up, diabetes mellitus developed in 186 patients (6%), IFG developed in 366 patients (12%), and 62% of patients remained with normal fasting glucose levels (NFG). Patients with diabetes mellitus and IFG both at baseline or developing during follow-up had a significantly higher rate of secondary end points than paients with NFG (P <.0001). Bezafibrate treatment reduced secondary end points only in patients with NFG (P =.04). CONCLUSION: Diabetes mellitus and IFG were common in the BIP study and were predictive of a worse clinical outcome that was not attenuated with bezafibrate treatment.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14760320

Circulation (2004);109:837-42
Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study
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BACKGROUND: Measuring C-reactive protein (CRP) has been recommended to identify patients at high risk for coronary heart disease (CHD) with low LDL cholesterol (LDL-C). Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a proinflammatory enzyme associated primarily with LDL. METHODS AND RESULTS: In a prospective, case cohort study in 12 819 apparently healthy middle-aged men and women in the Atherosclerosis Risk in Communities study, the relation between Lp-PLA2, CRP, traditional risk factors, and risk for CHD events over a period of approximately 6 years was examined in a proportional hazards model, stratified by LDL-C. Lp-PLA2 and CRP levels were higher in the 608 cases than the 740 noncases. Both Lp-PLA2 and CRP were associated with incident CHD after adjustment for age, sex, and race with a hazard ratio of 1.78 for the highest tertile of Lp-PLA2 and 2.53 for the highest category of CRP versus the lowest categories. Lp-PLA2 correlated positively with LDL-C (r=0.36) and negatively with HDL-C (r=-0.33) but not with CRP (r=-0.05). In a model adjusted for traditional risk factors including LDL-C, the association of Lp-PLA2 with CHD was attenuated and not statistically significant. For individuals with LDL-C below the median (130 mg/dL), Lp-PLA2 and CRP were both significantly and independently associated with CHD in fully adjusted models. For individuals with LDL-C <130 mg/dL, those with both Lp-PLA2 and CRP levels in the highest tertile were at the greatest risk for a CHD

Inflammation is a recognized key component of acute c[redacted]ndromes. Such pathogenetic achievement has led to the use of inflamm[redacted] and proteins as prognostic markers in these syndromes. A number of m[redacted]e been proposed, including proinflammatory cytokines such as interleukin-[redacted]kin-1RA, and tumor necrosis factor-alpha, adhesion molecules such as intra[redacted]hesion molecule-1 and vascular adhesion molecule-1 and markers of cell activation. Although all are of scientific interest, the clinical use of these markers is limited by their high cost, low availability, and unfavorable biological profile. Conversely, common markers of inflammation such as C-reactive protein (CRP), the prototypic acute phase protein, and to a lesser extent fibrinogen, have been proven to be reliable and important markers of risk in ischemic heart disease. CRP, in particular, has been found to be associated with short- and long-term prognosis in acute coronary syndromes, including ST-elevation myocardial infarction, and in stable angina, and to predict the risk of restenosis and major events, including death, after revascularization procedures. CRP has been consistently found to be independent from other risk factors and to have an incremental value beyond the common risk factors and biochemical markers of risk, including troponin. Whether CRP also should be used as a guide to therapy is still a matter of discussion that deserves further, properly designed studies.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15611382

Circulation (2004);110:1592-7
Elevations in troponin I after percutaneous coronary interventions are associated with abnormal tissue-level perfusion in high-risk patients with non-ST-segment-elevation acute coronary syndromes
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BACKGROUND: In the setting of non-ST-segment-elevation (NSTE) acute coronary syndromes (ACS), the pathophysiological mechanisms underlying post-percutaneous coronary intervention (PCI) cardiac troponin I (cTnI) elevation remain unclear.
METHODS AND RESULTS: We evaluated the relationship between troponin elevation and tissue-level perfusion using the TIMI flow grade, corrected TIMI frame count, TIMI myocardial perfusion grade (TMPG), and myocardial contrast enhancement by intracoronary myocardial contrast echocaTIM.ie-0.ow

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15353489

Eur Heart J (2004);25:1675-8
Isoprostanes, emerging biomarkers and potential mediators in cardiovascular diseases
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15451144

N Engl J Med (2004);350:1387-97
C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease
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BACKGROUND: C-reactive protein is an inflammatory marker believed to be of value in the prediction of coronary events. We report data from a large study of C-reactive protein and other circulating inflammatory markers, as well as updated meta-analyses, to evaluate their relevance to the prediction of coronary heart disease. METHODS: Measurements were made in samples obtained at base line from up to 2459 patients who had a nonfatal myocardial infarction or died of coronary heart disease during the study and from up to 3969 controls without a coronary heart disease event in the Reykjavik prospective study of 18,569 participants. Measurements were made in paired samples obtained an average of 12 years apart from 379 of these participants in order to quantify within-person fluctuations in inflammatory marker levels. RESULTS: The long-term stability of C-reactive protein values (within-person correlation coefficient, 0.59; 95 percent confidence interval, 0.52 to 0.66) was similar to that of both blood pressure and total serum cholesterol. After adjustment for base-line values for established risk factors, the odds ratio for coronary heart disease was 1.45 (95 percent confidence interval, 1.25 to 1.68) in a comparison of participants in the top third of the group with respect to base-line C-reactive protein values with those in the bottom third, and similar overall findings were observed in an updated meta-analysis involving a total of 7068 patients with coronary heart disease. By comparison, the odds ratios in the Reykjavik Study for coronary heart disease were somewhat weaker for the erythrocyte sedimentation rate (1.30; 95 percent confidence interval, 1.13 to 1.51) and the von Willebrand factor concentration (1.11; 95 percent confidence interval, 0.97 to 1.27) but generally stronger for established risk factors, such as an increased total cholesterol concentration (2.35; 95 percent confidence interval, 2.03 to 2.74) and cigarette smoking (1.87; 95 percent confidence interval, 1.62 to 2.16). CONCLUSIONS: C-reactive protein is a relatively moderate predictor of coronary heart disease. Recommendations regarding its use in predicting the likelihood of coronary heart disease may need to be reviewed.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15070788

J Am Coll Cardiol (2004);44:1812-8
Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis
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OBJECTIVES: We sought to evaluate the association between plasma levels of monocyte chemoattractant protein (MCP)-1 and the risk for subclinical atherosclerosis. BACKGROUND: Monocyte chemoattractant protein is a chemokine that recruits monocytes into the developing atheroma and may contribute to atherosclerotic disease development and progression. Plasma levels of MCP-1 are independently associated with prognosis in patients with acute coronary syndromes, but few population-based data are available from subjects in earlier stages of atherosclerosis. METHODS: In the Dallas Heart Study, a population-based probability sample of adults in Dallas County </=65 years old, plasma levels of MCP-1 were measured in 3,499 subjects and correlated with traditional cardiovascular risk factors, high-sensitivity C-reactive protein (hs-CRP), and coronary artery calcium (CAC) measured by electron beam computed tomography. RESULTS: Higher MCP-1 levels were associated with older age, white race, family history of premature coronary disease, smoking, hypertension, diabetes, hypercholesterolemia, and higher levels of hs-CRP ($p < 0.01$ for each). Similar associations were observed between MCP-1 and risk factors in the subgroup of participants without detectable CAC. Compared with the subjects in the lowest quartile of MCP-1, the odds of prevalent CAC (CAC score >/=10) for subjects in the second, third, and fourth quartiles were 1.30 (95% confidence interval [CI] 0.99 to 1.73), 1.60 (95% CI 1.22 to 2.11), and 2.02 (95% CI 1.54 to 2.63), respectively. The association between MCP-1 and CAC remained significant when adjusted for traditional cardiovascular risk factors, but not when further adjusted for age. CONCLUSIONS: In a large population-based sample, plasma levels of MCP-1 were associated with traditional risk factors for atherosclerosis, supporting the hypothesis that MCP-1 may mediate some of the atherogenic effects of these risk factors. These findings support the

significantly reduced baseline FBF (2.2 +/- 0.5 vs. 1.9 +/- 0.5 mL/min/100 mL of forearm tissue, P < 0.001) and acetylcholine-stimulated FBF responses (AUC: 35.0 +/- 16.0 vs. 25.9 +/- 11.9; P < 0.001). CRP serum levels were inversely correlated with L-NMMA-induced decreases in baseline as well as acetylcholine-stimulated FBF responses. Co-infusion of the oxygen-derived free radical scavenger vitamin C significantly increased baseline FBF from 2.0 +/- 0.5 to 2.5 +/- 0.7 (mL/min/100 mL forearm tissue (P < 0.001)) and acetylcholine-stimulated FBF responses in patients with elevated CRP, but not in patients with low CRP serum levels. Vitamin C-induced increases in baseline FBF and in acetylcholine-stimulated FBF responses were significantly correlated with CRP serum levels. By multivariable analysis, CRP serum levels remained the only statistically significant independent predictor of NO bioavailability in the systemic circulation of patients with CAD. CONCLUSIONS: In patients with CAD, low grade systemic inflammation is associated with increased in vivo oxidative stress leading to impaired systemic bioavailability of NO, which might significantly contribute to the transition from stable coronary artery disease to acute coronary syndromes.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15321699

J Am Coll Cardiol (2004);44:44-9
Interleukin-10 serum levels and systemic endothelial vasoreactivity in patients with coronary artery disease
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OBJECTIVES: Because the endothelium is a major target for inflammatory cytokines, we investigated whether elevated interleukin (IL)-10 serum levels are associated with improved endothelial vasoreactivity in patients with coronary artery disease (CAD). BACKGROUND: Chronic inflammation plays a pivotal role in the progression of atherosclerosis. Interleukin-10 is an anti-inflammatory cytokine that exerts important protective effects on atherosclerotic lesion development in experimental animals. METHODS: Vasoreactivity was assessed in 65 male patients with documented CAD by measuring endothelium-dependent (acetylcholine [ACh] 10 to 50 microg/min) and endothelium-independent (sodium nitroprusside [SNP] 2 to 8 microg/min) forearm blood flow (FBF) responses using venous occlusion plethysmography. RESULTS: Serum levels of IL-10 were significantly correlated with ACh-induced FBF responses (r = 0.31, p < 0.02), but not with SNP responses. Importantly, if IL-10 serum levels were increased in patients with elevated C-reactive protein (CRP) levels, no impairment of ACh-stimulated FBF response was observed. On multivariate analysis, including low-density lipoprotein cholesterol, smoking, hypertension, diabetes, clinical status of the patients, and statin and/or angiotensin-converting enzyme inhibitor treatment, only IL-10 (p < 0.02) and CRP serum levels (p < 0.02) were significant independent predictors of ACh-induced FBF responses. CONCLUSIONS: Thus, increased IL-10 serum levels are associated with improved systemic endothelial vasoreactivity in patients with elevated CRP serum levels, demonstrating that the balance between pro- and anti-inflammatory mediators is a major determinant of endothelial function in patients with CAD.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15234404

Am Heart J (2004);147:42-8
Elevated leukocyte count and adverse hospital events in patients with acute coronary syndromes: findings from the Global Registry of Acute Coronary Events (GRACE)
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OBJECTIVE: To examine the association between elevated leukocyte count and hospital mortality and heart failure in patients enrolled in the multinational, observational Global Registry of Acute Coronary Events (GRACE). BACKGROUND: Elevated leukocyte count is associated with adverse hospital outcomes in patients presenting with acute myocardial infarction (AMI). The association of this prognostic factor with hospital mortality and heart failure in patients with other acute coronary syndromes (ACS) is unclear. METHODS: We examined the association between admission leukocyte count and hospital mortality and heart failure in 8269 patients presenting with an ACS. This association was examined separately in patients with ST-segment elevation AMI, non-ST-segment elevation AMI, and unstable angina. Leukocyte count was divided into 4 mutually exclusive groups (Q): Q1 <6000, Q2 = 6000-9999, Q3 = 10,000-11,999, Q4 >12,000. Multiple logistic regression analysis was performed to examine the association between elevated leukocyte count and hospital events while accounting for the simultaneous effect of several potentially confounding variables. RESULTS: Increasing leukocyte count was significantly associated with hospital death (adjusted odds ratio [OR] 2.8, 95% CI 2.1-3.6 for Q4 compared to Q2 [normal range])

median NT-proBNP level was 353 ng/L (107 to 1357 ng/L). Compared with the lowest quartile, patients in the second, third, and fourth quartiles had a relative risk of subsequent death of 2.94 (95% CI, 1.15 to 7.52), 5.32 (95% CI, 2.19 to 12.91), and 11.5 (95% CI, 4.90 to 26.87), respectively. The NT-proBNP was independently associated with death in a logistic regression model, which included clinical variables, ECG, and troponin T in patients either with (OR of highest versus lowest quartile, 7.0; 95% CI, 1.9 to 25.6) or without (OR of highest versus lowest quartile, 4.1; 95% CI, 1.1 to 14.6) persistent ST-segment elevation. NT-proBNP was also an independent predictor of severe heart failure. CONCLUSIONS: The measurement of NT-proBNP on admission improves the early risk stratification of patients with ACS, suggesting the need for the development of targeted therapeutic strategies.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15197143

Am J Cardiol (2004);93:88-90
Comparison of ischemia-modified albumin levels in patients undergoing percutaneous coronary intervention for unstable angina pectoris with versus without coronary collaterals
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This study compared ischemia-modified albumin levels, a marker of ischemia in patients undergoing percutaneous coronary intervention. Ischemia-modified albumin levels were significantly lower in patients with collateral circulation compared with those without collateral circulation.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14697474

J Am Coll Cardiol (2004);44:1210-4
Differential mortality risk of postprocedural creatine kinase-MB elevation following successful versus unsuccessful stent procedures
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OBJECTIVES: This study was designed to evaluate the effect of periprocedural myocardial infarction (MI) on mortality according to success of the stent procedure.

1.7%, p = 0.01), but the effect was significant only for type 3 MI (4.7% vs. 1.7%, p = 0.008). Moreover, the mortality difference for any MI was confined to patients with unsuccessful procedures (13.1% vs. 0%, p = 0.03), with no significant effect among patients with otherwise successful procedures (2.1% vs. 1.7%, p > 0.20). The independent predictors of mortality were unsuccessful procedure (p < 0.001), diabetes mellitus (p = 0.001), history of prior MI (p = 0.003), multivessel disease (p = 0.006), and advancing age (p < 0.001), but not periprocedural MI. CONCLUSIONS: The association of periprocedural MI with increased mortality during the first year following stent placement was confined to patients with unsuccessful procedures.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15364321

Circulation (2004);109:726-32
Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE)
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BACKGROUND: Serum amyloid-alpha (SAA) is a sensitive marker of an acute inflammatory state. Like high-sensitivity C-reactive protein (hs-CRP), SAA has been linked to atherosclerosis. However, prior studies have yielded inconsistent results, and the independent predictive value of SAA for coronary artery disease (CAD) severity and cardiovascular events remains unclear. METHODS AND RESULTS: A total of 705 women referred for coronary angiography for suspected myocardial ischemia underwent plasma assays for SAA and hs-CRP, quantitative angiographic assessment, and follow-up evaluation. Cardiovascular events were death, myocardial infarction, congestive hear-6l6lCD7%, p = 0.01), but the effect was significant only for type 3 MI (4.7% vs. 1.7%, 0.008). Moreover, the mortality difference for any MI was confined to patients with unsuccessful procedures (13.1% vs. 0%, p = 0.03), with no significant effect among patients with otherwise successful procedures (2.1% vs. 1.7%, p > 0.20). The independent predictors of mortality were unsuccessful procedure (p < 0.001), diabetes mellitus (p = 0.001), history of prior MI (p = 0.003), multivessel disease (p = 0.006), and advancing age (p < 0.001), but not periprocedural MI. CONCLUSIONS: The association of periprocedural MI with increased mortality during the first year following stent placement was confined to patients with unsuccessful procedures.
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OBJECTIVES: We compared outcomes in patients with non-ST-segment elevation acute coronary syndromes (ACS) according to the degree of cardiac troponin I (cTnI) elevation. BACKGROUND: Controlled trials of high-risk patients have found that troponin elevations identify an even higher risk subset. It is unclear whether outcomes are similar among a lower risk, heterogeneous patient group. Also, few studies have reported outcomes other than myocardial infarction (MI) or death, based on the peak troponin value. METHODS: Consecutively, admitted patients without ST-segment elevation on the initial electrocardiogram underwent serial marker sampling using creatine kinase (CK), CK-MB fraction, and cTnI. Patients were grouped according to peak cTnI: negative = no detectable cTnI; low = peak greater than the lower limit of detectability but less than the optimal diagnostic value; intermediate = peak greater than or equal to the optimal diagnostic value but less than the manufacturer's suggested upper reference limit (URL); and high = peak greater than or equal to the URL. Thirty-day outcomes included cardiac death, MI based on CK-MB, revascularization, significant disease, and a reversible defect on stress testing. Six-month mortality was also determined. Negative evaluations for ischemia included nonsignificant disease, no reversible stress defect, and negative rest perfusion imaging. RESULTS: Of the 4,123 patients admitted, 893 (22%) had detectable cTnI values. Cardiac events and positive test results at 30 days and 6-month mortality increased significantly with increasing cTnI values. Negative evaluations for ischemia were significantly and inversely related to peak cTnI values. Although adverse events were significantly more common in patients with a low cTnI value than in those with negative cTnI, negative evaluations for ischemia were frequent. CONCLUSIONS: Increased cTnI values are associated with worse outcomes. Although low cTnI values are associated with adverse events, they do not have the same implication as higher cTnI values, and nonischemic evaluations are frequent.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15028350

Chest (2004);126:1032-9
Risk stratification and prognostic implication of plasma biomarkers in nondiabetic patients with stable coronary artery disease: the role of high-sensitivity C-reactive protein
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STUDY OBJECTIVES: To evaluate the implication of plasma biomarkers to future cardiovascular events in nondiabetic patients with stable coronary artery disease (CAD).Designs and settings: Prospective, follow-up study at a tertiary referral center.Patients and measurement: Serial plasma biomarkers including high-sensitivity C-reactive protein (hsCRP), homocysteine, soluble adhesion molecules, von Willebrand factor, and lipid profiles were determined before coronary angiograms in a series of nondiabetic CAD patients with stable angina. Among them, 75 consecutive patients who

CVD. There was no significant change in IL-6 levels in both patient groups. CONCLUSIONS: Intensive multifactorial risk management can reduce high levels of sCD40L but can only partially correct abnormal platelet activation, inflammation, and coagulation in diabetes, particularly in patients with overt CVD.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15136493

J Am Coll Cardiol (2004);44:1945-56
Leukocyte count and coronary heart disease: implications for risk assessment
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Inflammation is a key feature of atherosclerosis and its clinical manifestations. The leukocyte count is a marker of inflammation that is widely available in clinical practice. This paper reviews the available epidemiologic evidence for a relationship between the leukocyte count and coronary heart disease (CHD). Numerous epidemiologic and clinical studies have shown leukocytosis to be an independent predictor of future cardiovascular events, both in healthy individuals free of CHD at baseline and in patients with stable angina, unstable angina, or a history of myocardial infarction. This relationship has been observed in prospective and retrospective cohort studies, as well as in case-control studies. It is strong, consistent, temporal, dose-dependent, and biologically plausible. The relationship persists after adjustment for multiple CHD risk factors, including smoking. Elevated differential cell counts, including eosinophil, neutrophil, and monocyte counts, also predict the future incidence of CHD. Leukocytosis affects CHD through multiple pathologic mechanisms that mediate inflammation, cause proteolytic and oxidative damage to the endothelial cells, plug the microvasculature, induce hypercoagulability, and promote infarct expansion. In summary, leukocytosis has been consistently shown to be an independent risk factor and prognostic indicator of future cardiovascular outcomes, regardless of disease status. The leukocyte count is inexpensive, reliable, easy to interpret, and ordered routinely in inpatient and outpatient settings. However, its diagnostic and prognostic utility in CHD is widely unappreciated. Further studies are needed to assess the true impact of leukocytosis on CHD, compare it with other inflammatory markers such as C-reactive protein and lipoprotein phospholipase A(2) levels, and promote its use in CHD prediction.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15542275

J Am Coll Cardiol (2004);44:1510-20
Effect of granulocyte-macrophage colony-stimulating factor inducer on left ventricular remodeling after acute myocardial infarction
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OBJECTIVES: We sought to determine the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF) induction on post-myocardial infarction (MI) remodeling, especially in relation to the inflammatory response and myocardial fibrosis.

BACKGROUND: Granulocyte-macrophage colony-stimulating factor modifies wound healing by promoting monocytopoiesis and infiltration of monocytes and macrophages into injured tissue; however, the effect of GM-CSF induction on the infarct healing process and myocardial fibrosis is unclear. METHODS: A model of MI was produced in Wistar rats by ligation of the left coronary artery. The MI animals were randomized to receive GM-CSF inducer (romurtide 200 microg/kg/day for 7 consecutive days) (MI/Ro) or saline (MI/C). RESULTS: Echocardiographic and hemodynamic studies on day 14 revealed increased left ventricular (LV) end-diastolic dimension, decreased fractional shortening, elevated LV end-diastolic pressure, and decreased LV maximum rate of isovolumic pressure development in MI/Ro compared with MI/C. Immunoblotting showed that expression of transforming growth factor (TGF)-beta1 in the infarcted site on day 3 after MI was decreased in MI/Ro compared with MI/C. In the infarcted site, TGF-beta1, collagen type I and type III messenger ribonucleic acid (mRNA) expression on day 3, and collagen content on day 7 were reduced in MI/Ro compared with MI/C, in association with marked infarct expansion. In MI/Ro, monocyte chemoattractant protein-1 mRNA level and the degree of infiltration of monocyte-derived macrophages (ED-1-positive)were greater in the infarcted site on day 7 than those in MI/C. CONCLUSIONS: The GM-CSF induction by romurtide facilitated infarct expansion in association with the promotion of monocyte recruitment and inappropriate collagen synthesis in the infarcted region during the early phase of MI.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15464336

J Am Coll Cardiol (2004);44:451-7
Plasma level of oxidized low-density lipoprotein is an independent determinant of coronary macrovasomotor and microvasomotor responses induced by bradykinin
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OBJECTIVES: We examined the relationship between coronary endothelium-dependent vasodilation in response to bradykinin (BK) and plasma levels of oxidized low-density lipoprotein (oxLDL) in subjects with normal coronary arteries. BACKGROUND: It is unclear whether the plasma oxLDL level is a determinant of coronary endothelial function. Bradykinin plays an important role in regulating resting coronary tone and flow-mediated coronary vasomotion. METHODS: Coronary blood flow (CBF) in the left anterior descending (LAD) coronary artery was assessed by quantitative angiography and a Doppler flow wire in 94 consecutive subjects with normal coronary arteries. The plasma oxLDL level was measured by enzyme-linked immunosorbent assay using DLH3R, a specific antibody against oxLDL. RESULTS: Plasma levels of oxLDL in diabetic subjects (n = 13) were higher than those in non-diabetic subjects (n = 81). Plasma levels of oxLDL correlated with body mass index (BMI). Bradykinin at doses of 0.2, 0.6, and 2.0 microg/min caused dose-dependent increases in diameter and CBF in the LAD coronary artery. By a univariate analysis, oxLDL levels significantly correlated with epicardial ($r = -0.30$, $p < 0.0001$) and resistant ($r = -0.36$, $p = 0.003$) coronary vasodilator responses to BK at 2.0 microg/min, whereas total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides were not associated with these coronary responses. In a stepwise multivariate analysis, oxLDL

levels were significantly correlated with epicardial and resistant coronary vasomotor responses to BK, independent of age, gender, smoking status, other lipid levels, BMI, hypertension, and diabetes. CONCLUSIONS: The plasma level of oxLDL is an appropriate surrogate for assessing coronary endothelial-dependent vasomotor function as estimated by responses to BK compared with conventional risk factors for atherosclerosis.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15261947

J Am Coll Cardiol (2004);44:335-9
B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction: an ENTIRE-TIMI-23 substudy
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OBJECTIVES: We sought to evaluate B-type natriuretic peptide (BNP), alone and in comparison to cardiac troponin I (cTnI) and high-sensitivity C-reactive protein (hs-CRP), for risk assessment at initial presentation with ST-segment elevation myocardial infarction (STEMI). BACKGROUND: Elevated levels of BNP drawn two to four days after acute myocardial infarction are associated with higher mortality. Sparse data are available on its use at first presentation with STEMI. METHODS: We obtained samples from 438 patients presenting within 6 h of STEMI enrolled in the Enoxaparin Tenecteplase-Tissue-Type Plasminogen Activator With or Without Glycoprotein IIb/IIIa Inhibitor as Reperfusion Strategy in ST-Segment Elevation Myocardial Infarction (ENTIRE)-Thrombolysis In Myocardial Infarction (TIMI)-23 trial. Outcomes were assessed through 30 days. RESULTS: Median BNP was higher in patients who died (89 pg/ml, 25th to 75th percentile: 40 to 192), compared with survivors (15 pg/ml, 25th to 75th percentile: 8.8 to 32, $p < 0.0001$). Patients with BNP >80 pg/ml were at significantly higher risk of death (17.4% vs. 1.8%, $p < 0.0001$). Cardiac troponin established a gradient of mortality between the highest and lowest quartile (7.9% vs. 0%, $p = 0.007$). C-reactive protein was not associated with outcome. After adjustment for cTnI, hs-CRP, and major clinical predictors, including age, heart failure, anterior myocardial infarction location, heart rate, and blood pressure, a BNP level >80 pg/ml was associated with a seven-fold higher mortality risk (odds ratio 7.2, 95% confidence interval 2.1 to 24.5, $p = 0.001$). Patients with BNP >80 pg/ml were also more likely to have impaired coronary flow ($p = 0.049$) and incomplete resolution of ST-segment elevation ($p = 0.05$). CONCLUSIONS: Increased concentrations of BNP at initial presentation of patients with STEMI are associated with impaired reperfusion after fibrinolysis and higher short-term risk of mortality. These data support the value of combining markers of hemodynamic stress with traditional approaches to risk assessment in acute myocardial infarction.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15261928

Jama (2004);292:2824-5
Biomarkers for coronary heart disease: predictive value or background noise?
M. Mitka
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15598900

Heart (2004);90:528-33
Implications of plasma concentrations of adiponectin in patients with coronary artery disease
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OBJECTIVE: To investigate whether concentrations of plasma adiponectin constitute a significant coronary risk factor, with particular focus on the relation between plasma concentrations of adiponectin and the development of acute coronary syndrome (ACS). SUBJECTS AND METHODS: Plasma concentrations of adiponectin were measured in 123 patients with coronary artery disease (CAD) and in 17 control participants. Patients were divided into three groups according to condition type: acute myocardial infarction (AMI) group (n = 59), unstable angina pectoris (UAP) group (n = 28), and stable angina pectoris (SAP) group (n = 36). RESULTS: Plasma concentrations of adiponectin correlated negatively with body mass index ($r = -0.18$, $p < 0.05$), serum triglyceride ($r = -0.25$, $p < 0.01$), and fasting glucose concentrations ($r = -0.21$, $p < 0.05$), but correlated positively with age ($r = 0.26$, $p < 0.01$), high density lipoprotein cholesterol concentrations ($r = 0.35$, $p < 0.01$), and low density lipoprotein particle size ($r = 0.37$, $p < 0.01$). Plasma concentrations of adiponectin in patients with ACS, in both the AMI and UAP groups, were significantly lower than those in patients with SAP and in the control group (ACS, 6.5 (3.0) microg/ml; SAP, 11.3 (5.9) micro g/ml; control 12.8 (4.3) microg/ml; $p < 0.01$). Additionally, plasma concentrations of adiponectin in patients with CAD (7.9 (4.6) microg/ml, $p < 0.01$) were significantly lower than in the control group. There were, however, no significant differences between patients with SAP and the control group ($p = 0.36$). Multiple logistic regression analysis showed that smoking, fasting glucose concentration, and low log adiponectin concentration correlated independently with the development of an ACS. CONCLUSIONS: The findings suggest that measurement of plasma concentrations of adiponectin may be of use for assessing the risk of CAD and may be related to the development of ACS.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15084551

Am J Cardiol (2004);93:750-3
Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions
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The objectives of this study were to investigate the incidence, predictors, and clinical significance of isolated postprocedural troponin-I elevations in a consecutive series of patients who underwent percutaneous coronary intervention. We observed, in a series of 1,128 patients, that isolated troponin-I elevations without concomitant creatine kinase elevations occurred in 17% of patients after percutaneous coronary intervention, and that even troponin-I elevations 5 times above the upper limit of normal did not predict events after hospital discharge.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15019884

(diagnostic threshold, 0.1 ng/mL). Using angioscopy at the culprit lesions, we examined the presence of coronary thrombus, yellow plaque, and complex plaque. Moreover, we compared the preinterventional angiographic parameters (thrombus and complexity of the culprit lesion, and TIMI flow) between the two groups. Twenty-two patients were troponin-positive and 35 patients were troponin-negative. Univariate analyses indicated that the TIMI flow and the incidence of coronary thrombus detected with angioscopy correlate with the elevated troponin T levels. A multivariate logistic regression analysis showed the presence of coronary thrombus detected with angioscopy to be the only independent factor associated with elevated troponin T levels in patients with NSTE-ACS (odds ratio, 22.1; 95% CI, 2.59 to 188.42; P=0.0046). CONCLUSIONS: Using angioscopy, the elevated troponin T levels in NSTE-ACS were confirmed to be strongly associated with the presence of coronary thrombus.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14732748

Am Heart J (2004);148:405-15
Clinical significance of a single measurement of troponin-I and C-reactive protein at admission in 1773 consecutive patients with acute coronary syndromes
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BACKGROUND: The clinical significance of biochemical markers of myocardial damage or inflammation has not been prospectively established in populations representing the whole spectrum of acute coronary syndromes. We investigated whether the elevation of these biomarkers at admission has a prognostic value that is independent and incremental to baseline clinical variables and quantitative electrocardiographic ischemia. METHODS: We measured blood levels of cardiac troponin I (cTnI) and C-reactive

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BACKGROUND: Few studies have simultaneously investigated the role of soluble tumor necrosis factor alpha (TNF-alpha) receptors types 1 and 2 (sTNF-R1 and sTNF-R2), C-reactive protein, and interleukin-6 as predictors of cardiovascular events. The value of these inflammatory markers as independent predictors remains controversial. METHODS: We examined plasma levels of sTNF-R1, sTNF-R2, interleukin-6, and C-reactive protein as markers of risk for coronary heart disease among women participating in the Nurses' Health Study and men participating in the Health Professionals Follow-up Study in nested case-control analyses. Among participants who provided a blood sample and who were free of cardiovascular disease at baseline, 239 women and 265 men had a nonfatal myocardial infarction or fatal coronary heart disease during eight years and six years of follow-up, respectively. Using risk-set sampling, we selected controls in a 2:1 ratio with matching for age, smoking status, and date of blood sampling. RESULTS: After adjustment for matching factors, high levels of interleukin-6 and C-reactive protein were significantly related to an increased risk of coronary heart disease in both sexes, whereas high levels of soluble TNF-alpha receptors were significant only among women. Further adjustment for lipid and nonlipid factors attenuated all associations; only C-reactive protein levels remained significant. The relative risk among all participants was 1.79 for those with C-reactive protein levels of at least 3.0 mg per liter, as compared with those with levels of less than 1.0 mg per liter (95 percent confidence interval, 1.27 to 2.51; P for trend <0.001). Additional adjustment for the presence or absence of diabetes and hypertension moderately attenuated the relative risk to 1.68 (95 percent confidence interval, 1.18 to 2.38; P for trend = 0.008). CONCLUSIONS: Elevated levels of inflammatory markers,

disease (CHD) and stroke, respectively, were recorded. After adjustment for major cardiovascular risk factors, participants grouped in the highest fifth of triglyceride levels had a 70% (95% CI, 47 to 96) greater risk of CHD death, an 80% (95% CI, 49 to 119) higher risk of fatal or nonfatal CHD, and a 50% (95% CI, 29% to 76%) increased risk of fatal or nonfatal stroke compared with those belonging to the lowest fifth. The association between triglycerides and CHD death was similar across subgroups defined by ethnicity, age, and sex. CONCLUSIONS: Serum triglycerides are an important and independent predictor of CHD and stroke risk in the Asia-Pacific region. These results may have clinical implications for cardiovascular risk prediction and the use of lipid-lowering therapy.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15492305

J Am Coll Cardiol (2004);43:35-8
Early interleukin-1 receptor antagonist elevation in patients with acute myocardial infarction
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OBJECTIVES: We sought to evaluate interleukin-1 receptor antagonist (IL-1Ra) levels in patients with ST-segment elevation acute myocardial infarction (AMI) upon emergency department (ED) admission in order to assess the sensitivity of such a determination by comparison with common markers of myocardial necrosis. BACKGROUND: Inflammatory markers are elevated in patients with unstable coronary syndromes, but IL-1Ra levels during the early phases of AMI have not been previously investigated. METHODS: Levels of IL-1Ra were measured in 44 consecutive patients with AMI and compared with creatine kinase (CK), CK-MB, troponin I, myoglobin, and C-reactive protein (CRP). RESULTS: Upon admission, 82% of patients had elevated (>230 pg/ml) IL-1Ra levels, compared with 41% of patients with raised CK ($p = 0.001$), CK-MB (45%, $p = 0.002$), troponin I (57%, $p = 0.027$), myoglobin (48%, $p = 0.004$), and CRP (57%, $p = 0.019$) levels. The IL-1Ra values were significantly higher in patients with heralded AMI than in those without pre-infarction angina (671 vs. 320 pg/ml, $p = 0.013$). The sensitivity of IL-1Ra determination increased to 86% when chest pain duration was < or =3 h and to 91% if heralded infarction occurred. CONCLUSIONS: Our study indicates that, unlike markers of necrosis, an increase of IL-1Ra levels occurs early in patients with AMI, is more significant in those with heralded infarction and symptom onset < or =3 h, and precedes the release of markers of necrosis. Thus, IL-1Ra determination may be an important early adjuvant toward the diagnosis of AMI in the ED.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14715179

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BACKGROUND: Low-level cardiac troponin-I (cTn-I) elevations predict adverse cardiovascular outcomes in patients with definite acute coronary syndromes (ACS), as defined by the presence of chest pain accompanied by ischemic electrocardiographic changes. However, their prognostic value in other clinical situations remains unclear. METHODS: We studied 366 patients with suspected myocardial infarction (MI) but without definite ACS, including 57 patients with low-level cTn-I elevations (1.0 to 3.0 ng/mL) and 309 patients with cTn-I <1.0 ng/mL. All cTn-I measurements were made with the Dade Stratus II analyzer. We determined the adjusted 1-year risk of nonfatal MI or death from coronary heart disease (CHD death) in each group by using Cox proportional hazards models. RESULTS: Among patients with cTn-I elevations between 1.0 and 3.0 ng/mL, 6 (11%) had a nonfatal MI or CHD death at 1 year compared with 12 (4%) patients in the cTn-I <1.0 ng/mL group [hazard ratio (HR), 3.5; 95% CI, 1.4 to 8.8]. After adjusting for baseline clinical characteristics, cTn-I levels between 1.0 and 3.0 ng/mL remained strongly associated with nonfatal MI or CHD death (adjusted HR, 3.4; 95% CI, 1.3 to 9.4). This association persisted even in the 215 patients who presented without chest pain (adjusted HR, 4.3; 95% CI, 1.4 to 13). CONCLUSIONS: Low-level cTn-I elevations identify a subset of patients at increased risk for future cardiovascular events, even when obtained outside the context of definite ACS or presentation with chest pain.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15523306

Jama (2004);291:1730-7
Plasma adiponectin levels and risk of myocardial infarction in men
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CONTEXT: Adiponectin, a recently discovered adipocyte-derived peptide, is involved in the regulation of insulin sensitivity and lipid oxidation and, purportedly, in the development of atherosclerosis and coronary heart disease in humans. OBJECTIVE: To assess prospectively whether plasma adiponectin concentrations are associated with risk of myocardial infarction (MI). DESIGN, SETTING, AND PARTICIPANTS: Nested case-control study among 18 225 male participants of the Health Professionals Follow-up Study aged 40 to 75 years who were free of diagnosed cardiovascular disease at the time of blood draw (1993-1995). During 6 years of follow-up through January 31, 2000, 266 men subsequently developed nonfatal MI or fatal coronary heart disease. Using risk set sampling, controls were selected in a 2:1 ratio matched for age, date of blood draw, and smoking status (n = 532). MAIN OUTCOME MEASURE: Incidence of nonfatal MI and fatal coronary heart disease by adiponectin level.

adjustment for low- and high-density lipoprotein cholesterol levels modestly attenuated this association (RR, 0.56; 95% CI, 0.32-0.99; P for trend =.02). CONCLUSIONS: High plasma adiponectin concentrations are associated with lower risk of MI in men. This relationship can be only partly explained by differences in blood lipids and is independent of inflammation and glycemic status.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15082700

Circulation (2004);110:292-300
Tissue plasminogen activator antigen and D-dimer as markers for atherothrombotic risk among healthy postmenopausal women
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BACKGROUND: Plasma markers of fibrinolytic function are associated with incident coronary events among several, but not all, prospective epidemiologic investigations of healthy individuals. Few studies have evaluated this relationship in women. In addition, although menopausal hormone therapy (HT) may alter markers of fibrinolytic function, the relevance of this effect for coronary risk assessment has not been studied. METHODS AND RESULTS: In a prospective, nested case-control study among 75 343 postmenopausal women without prior cardiovascular disease or cancer, we evaluated the relationships of elevated tissue plasminogen activator (tPA) antigen and D-dimer with subsequent first coronary heart disease events over a median period of 2.9 years. Baseline levels of both biomarkers were higher among 304 cases compared with 304 controls matched on age, smoking status, ethnicity, and length of follow-up; median values were 9.0 versus 7.4 ng/mL (P<0.001) for tPA antigen and 27.6 versus 23.4 ng/mL (P=0.001) for D-dimer. In matched-pairs analyses, the odds ratio in the highest versus lowest quartile of tPA antigen was 3.5 (95% CI, 2.1 to 5.8; P trend <0.001) and for D-dimer was 2.0 (95% CI, 1.2 to 3.2; P trend=0.005). After adjustment for lipid and nonlipid risk factors, including C-reactive protein, tPA antigen remained a significant predictor. Multivariable-adjusted associations for D-dimer, although attenuated, largely remained statistically significant. When stratified by HT, the relationship between tPA

blood occurs in a variety of vascular disorders. The purpose of this study was to evaluate the utility of circulating endothelial cell (CEC) count as a diagnostic marker of non-ST-elevation acute coronary syndromes (ACSs). METHODS AND RESULTS: CEC counts were determined immediately (H0), 4 hours (H4), and 8 hours (H8) after admission in 60 patients with documented non-ST-elevation ACS and 40 control patients with no evidence of coronary artery disease. A total of 32 patients in the ACS group had elevated CEC counts (>3 cells/mL) in relation to early admission and single-episode chest pain. Patients from the control group had normal CEC counts. The interval between the chest pain episode and elevation was significantly shorter for CEC than troponin I. No correlation was found between the 2 markers. Interestingly, a subgroup of ACS patients with initially normal troponin I levels had high CEC counts, thus allowing early diagnosis in 30% more cases. At H0, the mean area under the receiver operating characteristic curve was significantly higher with the CEC count than with the troponin I level. At H4 and H8, the combined use of CEC and troponin was significantly better as a marker of ACS than CEC alone or troponin I alone. CONCLUSIONS: This study demonstrates that CEC count can be used as an early, specific, independent diagnostic marker for non-ST-elevation ACS. A combined strategy using CEC count and troponin I level could provide an effective diagnostic tool.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15364807

Circulation (2004);109:294-5
Renal disease, homocysteine, and cardiovascular complications
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14744952

Eur Heart J (2004);25:313-21
Creatine kinase-MB elevation after percutaneous coronary intervention predicts adverse outcomes in patients with acute coronary syndromes
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AIM: To study the relationship between outcomes and peak creatine kinase (CK)-MB levels after percutaneous coronary intervention (PCI) in patients with non-ST-segment elevation acute coronary syndromes (NSTE ACS). METHODS AND RESULTS: Peak CK-MB ratios (peak CK-MB level/upper limit of normal [ULN]) after PCI were analysed in 6164 patients with NSTE ACS from four randomized trials who underwent in-hospital PCI. We excluded 696 patients with elevated CK or CK-MB levels <24h before PCI; the

The continuous peak CK-MB ratio after PCI significantly predicted adjusted 6-month mortality (risk ratio, 1.06 per unit increase above ULN; 95% confidence interval, 1.01-1.11; P=0.017). CONCLUSIONS: Greater CK-MB elevation after PCI is independently associated with adverse outcomes in NSTE ACS. These results underscore the adverse implications of elevated CK-MB levels after PCI in this high-risk population.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14984920

Circulation (2004);110:380-5
C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study
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BACKGROUND: Inflammation (assessed by C-reactive protein [CRP]) and the metabolic syndrome (MetS) are associated with cardiovascular disease (CVD), but population-based data are limited. METHODS AND RESULTS: We assessed the cross-sectional relations of CRP to the MetS (National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Adult Treatment Panel III definition) in 3037 subjects (1681 women; mean age, 54 years) and the utility of CRP and the MetS to predict new CVD events (n=189) over 7 years. MetS (> or =3 of 5 traits) was present in 24% of subjects; mean age-adjusted CRP levels for those with 0, 1, 2, 3, 4, or 5 MetS traits were 2.2, 3.5, 4.2, 6.0, or 6.6 mg/L, respectively (P trend <0.0001). In persons with MetS, age-adjusted CRP levels were higher in women than men (7.8 versus 4.6 mg/L; P<0.0001). MetS and baseline CRP were individually related to CVD events (for MetS: age-sex-adjusted hazard ratio [HR], 2.1; 95% CI, 1.5 to 2.8; for highest versus lowest CRP quartile: HR, 2.2; 95% CI, 1.4 to 3.5). Greater risk of CVD persisted for MetS and CRP even after adjustment in a model including age, sex, MetS (HR, 1.8; 95% CI, 1.4 to 2.5), and CRP (HR, 1.9; 95% CI, 1.2 to 2.9). The c-statistic associated with the age- and sex-adjusted model including CRP was 0.72; including MetS, 0.74; and including CRP and MetS, 0.74. CONCLUSIONS: Elevated CRP levels are related to insulin resistance and the presence of the MetS, especially in women. Although discrimination of subjects at risk of CVD events using both MetS 2.ot.

status between diabetic and non-diabetic patients. Prospective cohort analysis of C reactive protein concentration, fibrinogen concentration, and leucocyte count as predictors of cardiovascular death in diabetic patients. SETTING: Coronary care unit in Spain. PARTICIPANTS: 83 diabetic patients with non-ST elevation acute coronary syndrome and 83 sex and aged matched patients selected from 361 non-diabetic patients with non-ST elevation acute coronary syndrome. MAIN OUTCOME MEASURES: Plasma concentrations of C reactive protein and fibrinogen, and leucocyte count. Investigators contacted patients to assess clinical events. RESULTS: Concentrations of C reactive protein and fibrinogen, and leucocyte count on admission were higher in diabetic than in non-diabetic patients (7 mg/l v 5 mg/l, p = 0.020; 3.34 g/l v 2.90 g/l, p = 0.013; and 8.8 x 10(9)/l v 7.8 x 10(9)/l, p = 0.040). Among diabetic patients, these values were also higher in those who died during the 22 month follow up (13 mg/l v 6 mg/l, p = 0.001; 3.95 g/l v 3.05 g/l, p < 0.001; and 11.4 x 10(9)/l v 8.4 x 10(9)/l, p = 0.005). After adjustment for confounding factors, diabetic patients in the highest tertile of C reactive protein had a hazard ratio for cardiovascular death of 4.51 (95% confidence interval (CI) 1.62 to 12.55). Similar hazard ratios were for fibrinogen 3.74 (95% CI 1.32 to 10.62) and for leucocyte count 3.64 (95% CI 1.37 to 9.68). CONCLUSIONS: Inflammation appears more evident in diabetic than in non-diabetic patients with acute coronary syndrome. C reactive protein concentration, fibrinogen concentration, and leucocyte count constitute independent predictors of cardiovascular death in diabetics with unstable coronary disease.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14966041

Am Heart J (2004);148:34-40
Homocysteine and cardiovascular disease: biological mechanisms, observational epidemiology, and the need for randomized trials
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Basic research indicates that homocysteine causes endothelial dysfunction and damage, accelerates thrombin formation, inhibits native thrombolysis, promotes lipid peroxidation through free radical formation, and induces vascular smooth muscle proliferation and monocyte chemotaxis. Most, but not all, observational epidemiological studies indicate that individuals with higher homocysteine levels have increased risks of cardiovascular disease. The magnitude ranges from approximately 20% in prospective studies to approximately 80% in retrospective case-control studies. In all observational epidemiological studies, however, the amount of uncontrolled and uncontrollable confounding is as large as the postulated small to moderate effect size. Thus, the totality of evidence should include randomized trials of sufficient sample size and duration with clinical end points. Folic acid reduces levels of homocysteine, but at present, despite several plausible biological mechanisms and a large body of observational epidemiological data, it is unclear whether supplementation will reduce risks of cardiovascular disease. It is also unclear whether any benefit of folic acid is attributable to lowering homocysteine levels. The current evidence is necessary, but not

decision-making for individual patients and policy decisions for the health of the general public.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15215789

Circulation (2004);109:2850-6
Relations of plasma matrix metalloproteinase-9 to clinical cardiovascular risk factors and echocardiographic left ventricular measures: the Framingham Heart Study
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BACKGROUND: Plasma levels of matrix metalloproteinase-9 (MMP-9), a key determinant of extracellular matrix degradation, are increased in heart failure and in acute coronary syndromes. We investigated cross-sectional relations of plasma MMP-9 to vascular risk factors and echocardiographic left ventricular (LV) measurements.
METHODS AND RESULTS: We studied 699 Framingham Study participants (mean age, 57 years; 58% women), free of heart failure and previous myocardial infarction, who underwent routine echocardiography. We examined sex-specific distributions of LV internal dimensions (LVEDD) and wall thickness (LVWT) and sampled persons with both LVEDD and LVWT below the sex-specific median (referent, n=299), with increased LVEDD (LVEDD > or =90th percentile, n=204) and increased LVWT (LVWT > or =90th percentile, n=221) in a 3:2:2 ratio. Plasma MMP-9 was detectable in 138 persons (20%). In multivariable models, increasing heart rate (OR per SD, 1.41; 95% CI, 1.17 to 1.71) and antihypertensive treatment (OR, 1.63; 95% CI, 1.06 to 2.50) were key clinical correlates of detectable plasma MMP-9. In multivariable-adjusted models, detectable plasma MMP-9 was associated with increased LVEDD (OR, 2.84; 95% CI, 1.13 to 7.11), increased LVWT (OR, 2.54; 95% CI, 1.00 to 6.46), and higher LV mass (P=0.06) in men

with women, and increased with age, body mass index and total/HDL-cholesterol ratio, but decreased with alcohol intake. Plasma TIMP-1 was also directly related to smoking, diabetes and use of anti-hypertensive treatment. Adjusting for age, sex and height, plasma TIMP-1 was positively associated with LV mass, wall thickness, relative wall thickness, end-systolic diameter, and left atrial diameter and the risk of having increased LV end-diastolic diameter or increased wall thickness, and negatively correlated with fractional shortening. Additional adjustment for clinical covariates attenuated the relations of plasma TIMP-1 to most echocardiographic measures. CONCLUSIONS: In our cross-sectional investigation, plasma total TIMP-1 was related to major cardiovascular risk factors and to indices of LV hypertrophy and systolic dysfunction. This raises the possibility that cardiovascular risk factors may influence cardiovascular remodelling via extracellular matrix degradation, which may be reflected in plasma TIMP-1 levels.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15342170

Circulation (2004);110:1387-91
Plasma level of B-type natriuretic peptide as a prognostic marker after acute myocardial infarction: a long-term follow-up analysis
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BACKGROUND: Circulating levels of B-type natriuretic peptide (BNP), a cardiac hormone, reflect the severity of cardiac dysfunction. Because the plasma BNP level changes dramatically during the period after the onset of acute myocardial infarction (AMI), identification of a suitable sampling time is problematic. There have been several reports indicating that the plasma BNP level obtained in the acute phase of AMI can be used as a prognostic marker. We examined whether the plasma BNP level measured 3 to 4 weeks after the onset of AMI represents a reliable prognostic marker for patients with AMI. METHODS AND RESULTS: We analyzed 145 consecutive patients with AMI. Plasma BNP levels were measured during the 3 to 4 weeks after onset of AMI. Of those patients, 23 experienced fatal cardiac events during this study. The mean follow-up period was 58.6 months. Log BNP, left ventricular end-diastolic pressure, and pulmonary vascular resistance were all significantly higher in the cardiac death group, and there were more men and more patients with a history of heart failure in the cardiac death group. A Cox proportional hazards model analysis showed that log BNP was an independent predictor of cardiac death. The survival rate was significantly higher in

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BACKGROUND: Thrombin plays an important role in the development of atherosclerosis and restenosis after percutaneous coronary intervention. Because heparin cofactor II (HCII) inhibits thrombin action in the presence of dermatan sulfate, which is abundantly present in arterial wall, HCII may affect vascular remodeling by modulating thrombin action. We hypothesized that patients with high plasma HCII activity may show a reduced incidence of in-stent restenosis (ISR). METHODS AND RESULTS: Sequential coronary arteries (n=166) with NIR stent (Boston Scientific Corp) implantation in 134 patients were evaluated before, immediately after, and at 6 months after percutaneous coronary intervention. Patients were divided into the following groups: high HCII (> or =110%, 45 lesions in 36 patients), normal HCII (> or =80% and <110%, 81 lesions in 66 patients), and low HCII (<80%, 40 lesions in 32 patients). Percent diameter stenosis at follow-up in the high-HCII group (18.7%) was significantly lower (P=0.046) than that in the normal-HCII group (30.3%) or the low-HCII group (29.0%). The ISR rate in the high-HCII group (6.7%) was significantly lower than that in the low-HCII group (30.0%) (P=0.0039). Furthermore, multivariate analysis demonstrated that high plasma HCII activity is an independent factor in reducing the incidence of angiographic restenosis (odds ratio, 0.953/1% increase of HCII; 95% CI, 0.911 to 0.998). CONCLUSIONS: The results demonstrate that HCII may have a hitherto unrecognized effect in inhibiting ISR. The effect of HCII may be mediated by inactivating thrombin in injured arteries, thereby inhibiting vascular smooth muscle cell migration and proliferation.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14744972

Circulation (2004);109:3164-70
Percutaneous coronary intervention results in acute increases in oxidized phospholipids and lipoprotein(a): short-term and long-term immunologic responses to oxidized low-density lipoprotein
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BACKGROUND: This study was performed to assess whether oxidized low-density lipoprotein (OxLDL) levels are elevated after percutaneous coronary intervention (PCI). METHODS AND RESULTS: Patients (n=141) with stable angina pectoris undergoing PCI had serial venous blood samples drawn before PCI, after PCI, and at 6 and 24 hours, 3 days, 1 week, and 1, 3, and 6 months. Plasma levels of OxLDL-E06, a measure of oxidized phospholipid (OxPL) content on apolipoprotein B-100 detected by antibody E06, lipoprotein(a) [Lp(a)], autoantibodies to malondialdehyde (MDA)-LDL and copper-oxidized LDL (Cu-OxLDL), and apolipoprotein B-100-immune complexes (apoB-IC) were measured. OxLDL-E06 and Lp(a) levels significantly increased immediately after PCI by 36% (P<0.0001) and 64% (P<0.0001), respectively, and returned to baseline by 6 hours. In vitro immunoprecipitation of Lp(a) from selected plasma samples showed that almost all of the OxPL detected by E06 was bound to Lp(a) at all time points, except in the post-PCI sample, suggesting independent release and subsequent reassociation of OxPL with Lp(a) by 6 hours. Strong correlations were

noted between OxLDL-E06 and Lp(a) (r=0.68, P<0.0001). MDA-LDL and Cu-OxLDL autoantibodies decreased, whereas apoB-IC levels increased after PCI, but both returned to baseline by 6 hours. Subsequently, IgM autoantibodies increased and peaked at 1 month and then returned to baseline, whereas IgG autoantibodies increased steadily over 6 months. CONCLUSIONS: PCI results in acute plasma increases of Lp(a) and OxPL and results in short-term and long-term immunologic responses to OxLDL. OxPL that are released or generated during PCI are transferred to Lp(a), suggesting that Lp(a) may contribute acutely to a protective innate immune response. In settings of enhanced oxidative stress and chronically elevated Lp(a) levels, the atherogenicity of Lp(a) may stem from its capacity as a carrier of proinflammatory oxidation byproducts.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15184281

Circulation (2004);110:1940-5
Growth factors in the collateral circulation of chronic total coronary occlusions: relation to duration of occlusion and collateral function
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BACKGROUND: Despite extensive animal experimental evidence, there are few data on the relation of growth factors and collateral function in humans. METHODS AND RESULTS: In 104 patients with a chronic total coronary occlusion (CTO; >2 weeks'

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OBJECTIVES: This study was designed to evaluate the relationship between plasma leptin and prognosis in patients with angiographically confirmed coronary atherosclerosis. BACKGROUND: Experimental studies suggest that leptin, an adipose tissue-derived hormone, exerts important cardiovascular effects. METHODS: Study subjects were recruited prospectively from a cohort of patients undergoing clinically indicated coronary angiography (n = 382). The median duration of follow-up was four years. Follow-up information was available for 361 patients. RESULTS: The combined end point of cardiac death, myocardial infarction (MI), cerebrovascular accident, or re-vascularization occurred in 44 subjects. In the simple Cox model, leptin had a significant ($p < 0.001$) non-linear/cubic univariate relationship with the combined end point. Other variables associated with prognosis in the univariate analysis were body mass index (BMI), prior MI, insulin resistance, C-reactive protein (CRP), fibrinogen, and number of coronary vessels with >50% stenosis. A positive relationship between leptin and prognosis was also seen when leptin levels were split by quintiles, with a hazard ratio of 6.46 for the highest quintile. The only two variables significantly associated with the combined end point in the multivariate Cox model were leptin ($p = 0.004$) and number of coronary vessels with >50% stenosis ($p < 0.001$). A similar relationship between leptin and prognosis was observed when leptin was adjusted for BMI. CONCLUSIONS: In patients with angiographically confirmed coronary atherosclerosis, leptin is a novel predictor of future cardiovascular events independent of other risk factors, including lipid status and CRP.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15519013

Eur Heart J (2004);25:2006-12
Troponin is more useful than creatine kinase in predicting one-year mortality among acute coronary syndrome patients
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AIMS: To compare the long-term prognostic value of troponins (Tn) vs. conventional cardiac biomarker creatine kinase (CK) and CK-MB across the spectrum of acute coronary syndromes (ACS). METHODS AND RESULTS: In the prospective, observational Canadian ACS Registry, 4627 patients with ACS were enrolled from 51 centres. The CK, CK-MB, Tn samples were analysed in each hospital clinical laboratory

mortality after stratification by Tn status. In multivariable analysis controlling for other known prognosticators including creatinine, abnormal Tn (adjusted OR 1.78; 95% CI 1.30-2.44; P<0.001) but not CK/CK-MB was independently associated with increased one-year mortality. CONCLUSIONS: Elevated Tn was independently associated with worse outcome at one-year, while CK or CK-MB status did not provide incremental prognostic information. Our findings support the use of Tn in the risk stratification of unselected ACS patients.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15541836

Eur Heart J (2004);25:1049-56
Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies
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AIMS: We compare the predictive values of plasma lipids (total and HDL-cholesterol, triglycerides) and three haemostatic/inflammatory risk markers for subsequent ischaemic heart disease (IHD). METHODS AND RESULTS: Two UK populations totalling 4860 men were screened for evidence of IHD between 1979 and 1983. Men were followed over 10 years and validated coronary events were recorded. Risk estimates were made using relative odds, receiver operating characteristic (ROC) curves and deciles of risk. Regression dilution effects were also examined. By 10 years, 525 men had a coronary event (fatal, non-fatal or silent myocardial infarction, MI). Two alternative multivariate models were compared - a lipid model (total, HDL-cholesterol, triglyceride) and a haemostatic/inflammatory model (fibrinogen, viscosity and white cell count). 'Correction' for regression dilution increased relative odds for most risk factors. In the distribution of predicted risk, using established risk factors in conjunction with either lipid or haemostatic/inflammatory factors, the deciles of risk analysis showed that

inflammatory process and are not due to acute myocardial damage. We hypothesized that the serum CRP level, which would abnormally elevate thereafter, is followed by a plaque rupture in the clinical setting of AMI. METHODS AND RESULTS: CRP was prospectively measured by high-sensitivity CRP assay (hs-CRP) in 157 consecutive patients (106 patients within 6 h, and 51 patients >/= 6 h but < 12 h after the onset of AMI) with ST-segment elevation AMI undergoing primary percutaneous coronary intervention (PCI). Serum levels of hs-CRP were also measured in 30 patients with stable angina undergoing elective PCI and in 30 healthy control subjects. The serum level of hs-CRP was significantly higher in patients with an onset of AMI < 6 h than in patients with angina pectoris (2.7 +/- 2.3 mg/L vs 1.4 +/- 0.7 mg/L, p < 0.0001 [mean +/- SD]) and in healthy subjects (2.7 +/- 2.3 mg/L vs 1.0 +/- 0.6 mg/L, p < 0.0001). There were no significant differences in serum levels of hs-CRP in patients with an onset of AMI </= 3 h than in those patients with an onset of AMI > 3 h but < 6 h (2.7 +/- 2.5 mg/L vs 2.7 +/- 2.2 mg/L, p = 0.87). However, the serum level of hs-CRP was significantly higher in patients with an onset >/= 6 h than in patients with an onset < 6 h (14.1 +/- 16.5 mg/L vs 2.7 +/- 2.3 mg/L, p < 0.0001). CONCLUSIONS: Serum levels of hs-CRP were significantly higher in patients with an onset of AMI < 6 h than in healthy subjects and in patients with angina pectoris undergoing PCI. The inflammatory process has been proved as one of the mechanisms causing plaque rupture. Elevated serum hs-CRP levels in patients with AMI < 6 h may portend vulnerable plaque rupture.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15539707

Heart (2004);90:419-24
C Reactive protein, moderate alcohol consumption, and long term prognosis after successful coronary stenting: four year results from the GENERATION study
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OBJECTIVES: To determine the impact of moderate alcohol consumption on long term prognosis after successful coronary stenting, and whether it could be related to preprocedural plasma C reactive protein (CRP). DESIGN:er(l)oigo4.9(G)6eog,u.8(er3m-8.8.1(PCs)5.1

this effect is positively related to preprocedural inflammatory status. An anti-inflammatory action of moderate alcohol consumption cannot be excluded.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15020518

Circulation (2004);110:1747-53
Markers of inflammation and rapid coronary artery disease progression in patients with stable angina pectoris
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BACKGROUND: Both endothelial cell activation and macrophage activation play a significant role in atherogenesis and atheromatous plaque vulnerability and may determine rapid coronary artery disease (CAD) progression. We sought to assess the association between serum inflammatory markers and rapid CAD progression in patients with chronic stable angina pectoris. METHODS AND RESULTS: We studied 124 chronic stable angina pectoris patients (84 men; mean age, 61+/-10 years) who were on a waiting list for coronary angioplasty for a mean time of 4.8+/-2.4 months. CAD progression was defined as > or =10% diameter reduction of a pre-existing stenosis > or =50%, > or =30% diameter reduction of a stenosis <50%, development of a new stenosis > or =30% in a previously normal segment, or progression of any stenosis to total occlusion. CAD progression occurred in 35 patients (28%). After adjustment with binary logistic regression, neopterin (P<0.001), high-sensitivity C-reactive protein (P=0.017), matrix metalloproteinase-9 (P=0.002), soluble intercellular adhesion molecule 1 (P<0.001), and previous history of unstable angina (P=0.01) were

were stored and who were free of previous acute myocardial infarction (AMI) at the 1968/1969 baseline. Homocysteine was analyzed in 2001 with frozen serum from the baseline study and related to AMI incidence and mortality during 24 years of follow-up. Cox regression analyses were used with adjustment for age, traditional risk factors, and tHcy modifiers. For the fifth tHcy quintile, relative risk was 1.86 (95% CI 1.06 to 3.26) for AMI and 5.14 (95% CI 2.22 to 11.92) for death due to AMI. Age-standardized Kaplan-Meier plots for the fifth tHcy quintile versus others showed significant differences both for AMI and for death due to AMI that were apparent after 15 years of follow-up. CONCLUSIONS: Homocysteine in middle-aged women is an independent risk factor for myocardial infarction and in particular mortality due to myocardial infarction. The study illustrates that long-term prospective studies might be necessary to show effects of homocysteine levels on AMI morbidity and mortality in women.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14769681

Eur Heart J (2005);26:107-9
An evolving story of lipoprotein-associated phospholipase A2 in atherosclerosis and cardiovascular risk prediction
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15618064

N Engl J Med (2005);352:20-8
C-reactive protein levels and outcomes after statin therapy
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BACKGROUND: Statins lower the levels of low-density lipoprotein (LDL) cholesterol and C-reactive protein (CRP). Whether this latter property affects clinical outcomes is unknown. METHODS: We evaluated relationships between the LDL cholesterol and CRP levels achieved after treatment wi.6(eatmtSchoddl(B)-e-a0.9(4(g)-4.6( )]wom Enis.4( )5.1(widep

atorvastatin was more likely than pravastatin to result in low levels of LDL cholesterol and CRP, meeting these targets was more important in determining the outcomes than was the specific choice of therapy. Patients who had LDL cholesterol levels of less than 70 mg per deciliter and CRP levels of less than 1 mg per liter after statin therapy had the lowest rate of recurrent events (1.9 per 100 person-years). CONCLUSIONS: Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. Strategies to lower cardiovascular risk with statins should include monitoring CRP as well as cholesterol.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15635109