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Beyond Cholesterol: Novel Risk Factors for Atherosclerotic Disease

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Based upon data from the Framingham Heart Study,the American Heart Association has advocated a risk-factor prediction algorithm that takes into account age, total and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, smoking history, diabetes, and evidence of left ventricular hypertrophy.[1] This traditional approach to the prediction of myocardial infarction (MI) risk is clinically effective and provides an important avenue for patient education and behavioral and pharmacologic intervention. Thus, in daily clinical practice, coronary artery disease (CAD) risk assessment typically includes a careful history and a physical examination accompanied by lipid screening.

Many patients with few traditional risk factors, however, develop life-threatening acute coronary syndromes with no prior symptoms of vascular insufficiency. Screening studies have shown that hyperlipidemia, hypertension, smoking, family history, and diabetes might predict less than half of all future cardiovascular events.[2,3] Other studies indicate that, in patients with premature atherosclerosis, the predictive value of traditional cardiovascular risk factors might be quite limited.

In an attempt to better predict risk of first MI, several epidemiologic studies have looked beyond cholesterol and explored a series of novel risk factors for atherosclerotic disease (refer to table 1).[4] In general, what these novel risk factors have in common is that they relate directly or indirectly to thrombus formation and dissolution and to the processes of atherosclerotic initiation and progression. Evolving data in the epidemiology of hemostasis and thrombosis indicates that, on a population basis, there are individuals "prone to thrombose" as well as those "prone to hemorrhage." Moreover, evidence is accruing that abnormalities related to these novel parameters could explain at least some of the coronary events that occur among people who are otherwise at apparently low risk.

Among the novel risk factors for arterial thrombosis outlined in the table,five have attracted the most clinical attention and are reviewed in this presentation. They are plasma concentrations of fibrinogen, homocysteine,tissue-type plasminogen activator (tPA),lipoprotein(a), and C-reactive protein.

Plasma fibrinogen concentration

Plasma fibrinogen concentration is the most extensively studied non-traditional marker of vascular risk.While fibrinogen is part of the acute-phase response and thus, to some extent, reflects underlying inflammation, it is also a major factor in blood viscosity,is a critical element in the process of fibrin deposition and atherosclerotic progression, and is associated with hypercoagulability. It is therefore not surprising that several cross-sectional studies have found that high plasma fibrinogen concentration correlates with prevalence of CAD and that fibrinogen levels are elevated among people with angina pectoris

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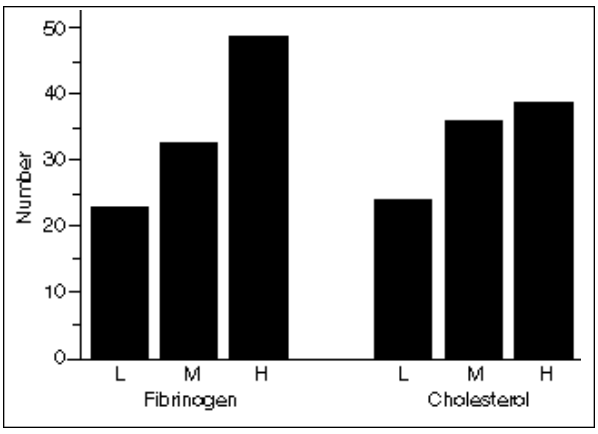
Table 1: Potential hemostatic and thrombotic markers of atherothrombotic risk. (From Ridker PM. Association of hemostatic and thrombotic factors with cardiovascular risk. In: Schafer AI (editor) *Molecular Mechanisms of Hypercoagulable States;* 1997; Landes Bioscience).

Concentration Markers	
	Fibrinogen
	Tissue type plasminogen activator (t-PA)
	Plasminogen activator inhibitor (PAI-1)
	Factor V, VII, VIII
	Lipoprotein(a)
	Homocysteine
	von Willebrand factor antigen
Process Markers	
	t-PA/PAI-1 complex
	Plasmin-Alpha-2-Antiplasmin (PAP) complex
	Prothrombin Fragment 1+2
	Thrombin-Antithrombin III (TAT) complex
	Fibrinopeptide A
	Fibrin Degradation Products
	D-dimer
Functional Markers	
	Activated Protein C Resistance (APC-R)
	Factor VIIc and VIIa
	Thrombin
Global Markers	
	Clot lysis time
Inflammatory Markers	
	C-Reactive Protein
	Interleukins
	Vascular Adhesion Molecules
Platelet Markers	
	Platelet Size and Volume
	Platelet Aggregation, Activity and Function

and acute infarction. Fibrinogen concentration has also been reported to correlate with extent of both peripheral and cerebral atherosclerosis.[5]

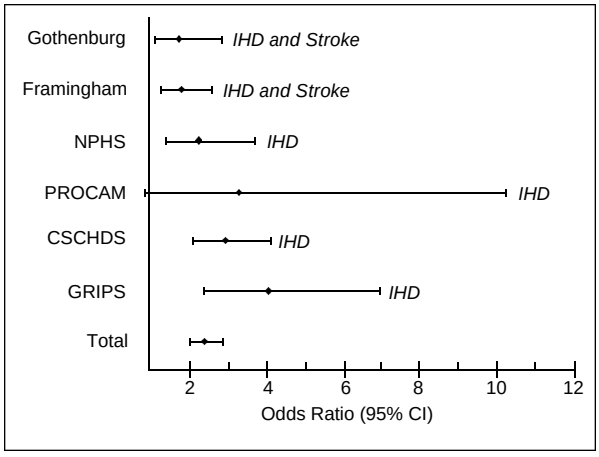
From a clinical perspective, the most important data relating fibrinogen to cardiovascular risk derive from prospective cohort studies in which plasma concentration was measured at baseline and was then related to the risk of future disease. Individuals in the Northwick Park Heart Study who subsequently died of cardiovascular disease or suffered a nonfatal ischemic event during the follow-up period had significantly higher fibrinogen levels than those who remained free of disease.[6] In this important prospective study, subjects with the highest levels of plasma fibrinogen concentration had relative risks of future CAD comparable to or greater than those associated with elevated levels of total cholesterol (figure 1).

Figure 1: Ischemic heart disease events occurring in the Northwick Park Heart Study as a function of low, middle and high tertiles of fibrinogen and total cholesterol. (Adapted from Meade TW et al. Haemostatic function and ischemic heart disease: Principal results of the Northwick Park Heart Study. *Lancet* 1986;2:533–537.)



Corroborative evidence indicating that fibrinogen is an important risk factor for cardiovascular disease is available from several studies, including the Gothenburg Heart Study,[7] the Framingham Heart Study,[8] the Caerphilly and Speedwell Collaborative Studies,[9] and the recent European Concerted Action on Thrombosis (ECAT)[10] and PROCAM[11] studies. The latter two have also provided data indicating that assessment of fibrinogen levels adds to the predictive value of total or low-density lipoprotein (LDL) cholesterol in predicting vascular risk. Moreover, data are available showing that fibrinogen level is a predictor of all-cause mortality as well as of thromboembolic stroke.[7] In a recent meta-analysis, individuals with fibrinogen levels in the upper third of the control distribution were found to have a relative risk of future cardiovascular disease 2.3 times higher than that of individuals with levels in the lowest third (figure 2).[5]

Figure 2: Odds ratios of ischemic heart disease and stroke for patients with fibrinogen level in the upper third of the distribution in six prospective studies of fibrinogen and cardiovascular disease. (Adapted from Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: A meta-analysis and review of the literature. *Ann Intern Med* 1993;118:956–963.)



Plasma fibrinogen level is partly under genetic control, but it is also affected by several environmental determinants, the most critical being cigarette consumption. The Framingham investigators estimated that almost 50% of the cardiovascular risk attributable to smoking was mediated through the adverse effects of fibrinogen.[12] From a clinical perspective, this issue is important for patient care, as the relationship between smoking and fibrinogen is dose-related and reversible.[13] Fibrinogen levels in women are also hormonally determined, and recent evidence suggests that estrogen replacement therapy can significantly reduce plasma fibrinogen concentration.[14]

While fibrinogen screening has been advocated by some preventive cardiologists,no clinical trial data available have indicated that specific efforts to reduce fibrinogen lead to improved cardiovascular health. However, this is being examined in several clinical trials now under way, and the role of fibrinogen levels as a tool for vascular screening and targeted intervention is likely to be clarified in the near future.

Mild-to-moderate hyperhomocysteinemia

It has been known for several years that patients with homocystinuria,an inherited disorder characterized by high levels of homocysteine (>100 mmol/L), have a markedly increased predilection for premature atherothrombosis. However, more recent data indicate that even mild elevations of homocysteine are associated with increased thrombotic risk. A large series of cross-sectional and retrospective case-control studies indicates that mild-to-moderate hyperhomocysteinemia (>15 mmol/L) is associated with increased risks of CAD, peripheral artery disease, stroke, and venous thromboembolism.[15] In addition, a growing number of prospective studies indicates that level of homocysteine is a graded predictor of future vascular events, among both currently healthy individuals and those with known angina pectoris (figure 3).[16–19]

Very recent data reveal the importance of mild-to-moderate homocysteinemia as a prognostic factor among patients with CAD.In a prospective study involving 587 patients with angiographically confirmed coronary disease who were followed over a four-year period, cardiovascular mortality was 4.5 times higher for those with homocysteine levels in excess of 20.0 μmol/L as for those with the lowest levels (<9.0 μmol/L).[20] Moreover, estimated survival in this study population was related to plasma level of homocysteine in a direct, graded manner (figure 4). These data are remarkably consistent,and prior overviews have suggested that elevated homocysteine is associated with increased vascular risk in a graded fashion such that up to 10% of the population risk for coronary disease might be attributable to homocysteine concentration.[15]

Figure 3: Meta-analysis of cross-sectional, case-control, and cohort studies relating total plasma homocysteine level to cardiovascular risk. Odds ratios are on a log scale based upon a 5 μmol/L increase in homocysteine level. (Adapted from Boushey et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *JAMA* 1995;274:1049–1057.)

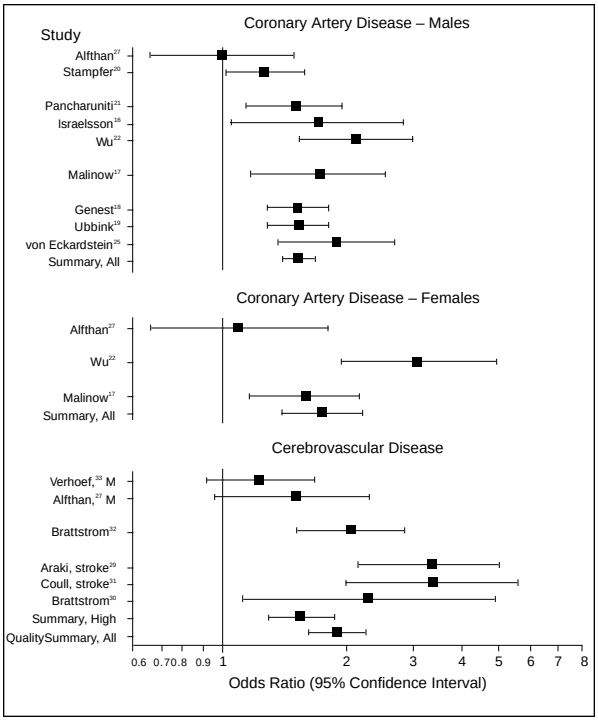
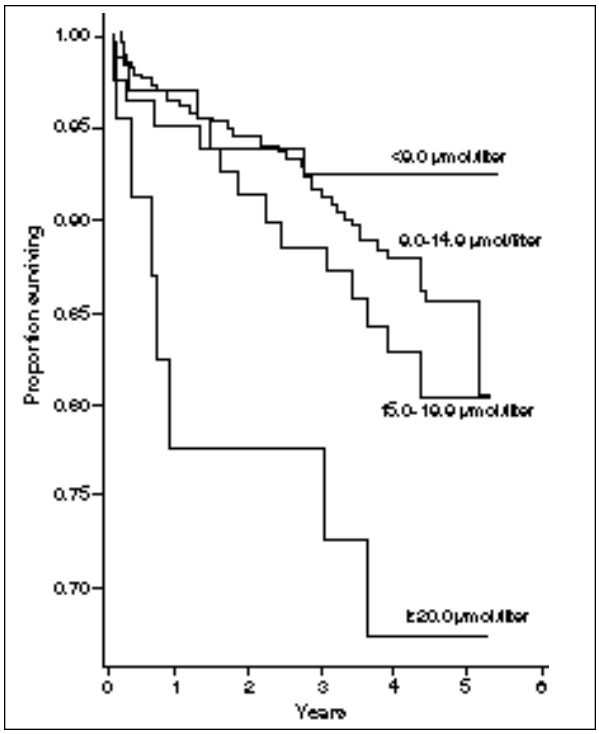


Figure 4: Estimated survival among patients with coronary artery disease, according to plasma total homocysteine levels. (Adapted from Nygard O, et al. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 997;33:230–236.)



The primary cause of mild-to-moderate homocysteinemia is poor dietary intake of folate,[21] although there are also common genetic polymorphisms that can affect plasma levels.[22] Folate is highly effective in reducing elevated homocysteine levels,and use of this agent has been advocated for reducing the risk of CAD. Indeed,if such an approach is proven effective, increased folate intake might lead to the annual prevention of 20,000 to 50,000 premature coronary deaths.[15] Several well-designed clinical trials are currently being organized to critically evaluate the issue. In the meantime, the United States has implemented folate fortification of cereal products, because increased intake reduces the incidence of first-trimester neural-tube defects. This supplementation,however,might not be sufficient to adequately reduce coronary risk.

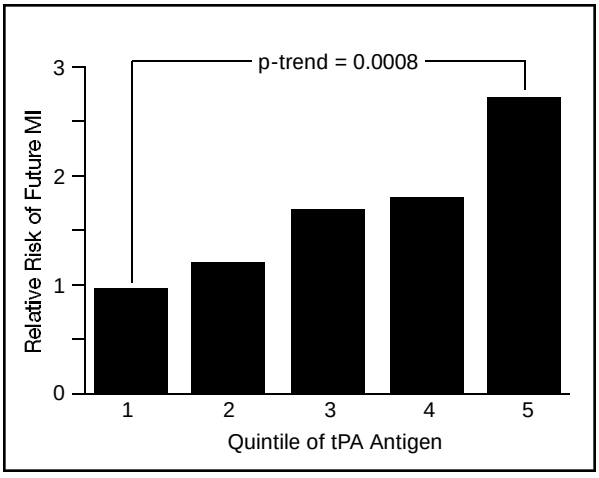
Hyperhomocysteinemic patients who have suffered unexplained thromboses might have a second defect of hemostasis. This issue is particularly relevant to venous thromboembolism; for example, recent data indicate that individuals affected both by hyperhomocysteinemia and by a common mutation in the gene coding for coagulation factor V (factor V Leiden) are at markedly increased risk of thrombosis when compared to individuals with only one of these defects.[23]

Impaired fibrinolysis: tPA and PAI-1

Perhaps the strongest direct evidence supporting the hypothesis that there are individuals prone to thrombosis derives from epidemiologic studies of impaired fibrinolysis and cardiovascular risk. In broad terms, the function of the intrinsic fibrinolytic system reflects a balance between endothelial-derived proteins (tissue-type plasminogen activator [tPA], for example) capable of dissolving thrombi and those (such as plasminogen-activator inhibitor type 1 [PAI-1])—capable of inhibiting the clot-dissolving process. Several prospective studies[24–28] have now demonstrated that elevated levels of both these substances are associated with increased thrombotic risk. Two other factors associated with impaired fibrinolysis, cross-linked fibrin degradation products (D-dimer)[29] and clot lysis times,[30] have also been found to predict future ischemic heart disease.

Activity levels of both tPA and PAI-1 are difficult to measure, unfortunately, and assessment of impaired fibrinolysis can be a complex process. However, standardized assays for antigen levels of tPA are now available, and they indicate tPA to be a strong marker of vascular risk. The predictive value of tPA antigen among patients free of coronary disease was initially demonstrated in the Physicians' Health Study, a large-scale survey involving nearly 15,000 apparently healthy men who provided baseline plasma samples and were then followed for the future occurrence of MI.[26] In this study, baseline concentrations of tPA antigen were significantly higher among men who subsequently suffered a first-ever MI compared with those who remained healthy during the follow-up period. Moreover, the risk associated with increasing levels of tPA antigen rose in a graded manner such that those with the highest levels at study initiation had relative risk of future MI approximately three times that of subjects with lower levels (figure 5). The risk of future thromboembolic stroke among the seemingly healthy subjects also rose with increasing levels of tPA antigen, a finding that was independent of other vascular risk factors.[27]

Figure 5: Relative risks of future MI associated with baseline levels of tPA antigen among currently healthy men. (Adapted from Ridker et al. Endogenous tissue-type plasminogen activator and risk of MI. *Lancet* 1993;341:1165–1168.)



The clinical utility of tPA antigen assay has also been demonstrated among patients with angina pectoris. For example, in the previously mentioned ECAT study of patients with chronic stable angina,[10,28] tPA antigen levels at study entry were associated with a step-wise increase in risk of future MI and sudden death. Of perhaps greater importance, the standardized relative risks associated with tPA antigen concentration in the ECAT study were greater in magnitude than for any other hemostatic or thrombotic parameter measured, including PAI-1 antigen, PAI-1 activity, and von Willebrand factor antigen.

Intrinsic fibrinolytic function might, in part, be genetically determined. However, as with fibrinogen and homocysteine, intrinsic fibrinolytic function is modified by several environmental and behavioral factors including smoking, obesity, estrogen, lipid levels, and alcohol consumption.[31–33]

Recent evidence also indicates a potentially important interaction between tPA, PAI-1, and the renin-angiotensin system.[34] In one recent study, for example, the use of the angiotensin-converting enzyme (ACE) inhibitor ramipril was found to favorably affect the balance between tPA and PAI-1 among patients with recent anterior MI.[35] Whether this effect has long-term clinical benefit remains uncertain; however, it is intriguing to speculate that the effects of ACE inhibitors on fibrinolytic function might partly explain the observation that long-term therapy with either captopril[36] or enalapril[37] appears to reduce rates of recurrent MI as well as mortality.

Testing for impaired fibrinolysis is generally available in academic centers equipped with specialized hemostasis laboratories. From an epidemiologic perspective, tPA-antigen screening has several practical advantages over measuring other factors of fibrinolysis in that levels tend to be stable over time, are readily measured with low coefficients of variation in standardized assays, and can be evaluated in clinical samples collected without specialized techniques. However, whether assessment of tPA antigen adds to the ability to predict risk over and above that achievable with standard lipid testing remains uncertain. Thus, while data regarding both tPA and PAI-1 provide insight into the pathophysiology of acute MI, the clinical utility of these measures is unknown.

Lipoprotein(a)

Although technically a lipid, lipoprotein(a) is often considered a marker of thrombosis since the apolipoprotein component of lipoprotein(a) shares homology with plasminogen. This unique lipid appears to play a regulatory role in atherothrombosis;[38] indeed, unlike other lipid molecules, which primarily participate in atherosclerotic progression, lipoprotein(a) has been hypothesized to compete with plasminogen in binding to fibrin, resulting in a potential direct inhibition of endogenous fibrinolysis.

Clinical data supporting a role for lipoprotein(a) in coronary disease come from a series of cross-sectional and retrospective case-control studies.[38] There have also been several prospective studies relating baseline level of lipoprotein(a) to future vascular risk. However, while several of these prospective studies have been positive,[4,39–42] others have found little—if any—association between lipoprotein(a) and subsequent risk.[43–45] Moreover, even among the positive studies, the absolute magnitude of association between baseline level of lipoprotein(a) and subsequent risk appears to be modest.

It is possible that the lack of consistency in the prospective studies of lipoprotein(a) reflects controversy regarding the best method of measuring it and the fact that different isoforms of the apo(a) component of lipoprotein(a) might have different atherothrombotic effects. It has also been hypothesized that the predictive value of lipoprotein(a) levels might be useful only in patients with hyperlipidemia.[41,46] Furthermore, lipoprotein(a) levels might well differ in different populations and between the sexes. Unfortunately, all of these limitations tend to reduce the utility of lipoprotein(a) as a marker for clinical thrombosis.

Approaches for screening lipoprotein(a) vary considerably. In some centers, screening for this unique lipid parameter is commonly undertaken in an effort to determine vascular risk; however, other centers rarely use lipoprotein(a) screening. This latter approach likely reflects the fact that there is no current therapy that specifically reduces lipoprotein(a) concentration, and there is no evidence that such an effect leads to improved vascular health. It is also important to recognize that methods for lipoprotein(a) evaluation vary and that the most promising approaches to lipoprotein(a) screening—such as sinking-pre-beta electrophoresis, apo(a) size determination, and polymorphism analysis—are generally not available in most clinical settings.[47,48]

C-reactive protein

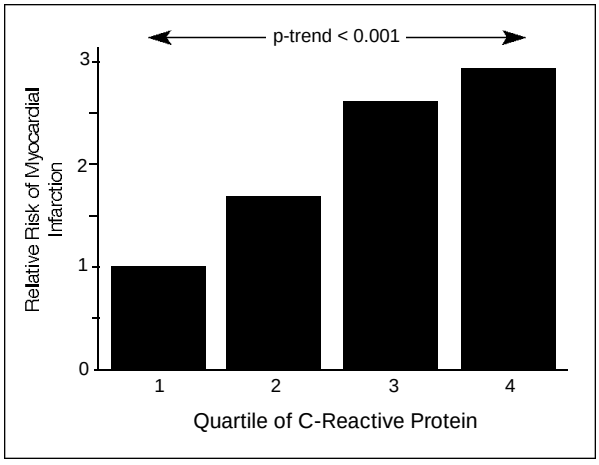
The most recently described risk factor for atherothrombotic disease is C-reactive protein, an acute-phase reactant whose plasma levels are determined largely by effects of inflammatory cytokines on hepatic production. Until recently, clinical tests for C-reactive protein were relatively insensitive. With the introduction of increased sensitivity tests, C-reactive protein assay can now be used as a method of evaluating systemic microinflammation, a process hypothesized to play a critical role in the initiation and progression of atherosclerosis and, perhaps, in the conversion of stable atherosclerotic plaque to unstable thrombus-prone lesions.

Clinical evidence relating C-reactive protein to thrombosis is rapidly accumulating. In cross-sectional studies, levels of C-reactive protein are associated with several other vascular risk factors including cigarette consumption, hyperlipidemia, obesity, blood pressure, and diabetes.[49] Recent studies also indicate that levels of C-reactive protein are elevated among patients with stable and unstable angina as well as acute MI.[50,51] However, since C-reactive protein increases following acute ischemia, it is uncertain whether these effects are a cause or a result of acute coronary insufficiency.

Two recently presented prospective studies demonstrate that the level of C-reactive protein is indeed elevated many years in advance of coronary occlusion. Among high-risk patients participating in the MRFIT study,[52] levels of C-reactive protein measured at study entry were associated with significantly increased risks of fatal coronary disease. This observation, however, was applicable only to smokers. Since smoking is known to increase levels of C-reactive protein and is itself a fundamental cardiovascular risk factor, the possibility that the relationship between C-reactive protein and vascular risk observed in the MRFIT study is due primarily to cigarette consumption cannot be excluded.

The role of C-reactive protein as an important vascular risk factor has recently been clarified in data from the Physicians' Health Study.[53] In this study of apparently healthy men, baseline levels of C-reactive protein were found to predict future risk of MI and thromboembolic stroke, both

Figure 6: Relative risks of future myocardial infarction among apparently healthy men, according to baseline level of C-reactive protein. (Adapted from Ridker et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973–979.)



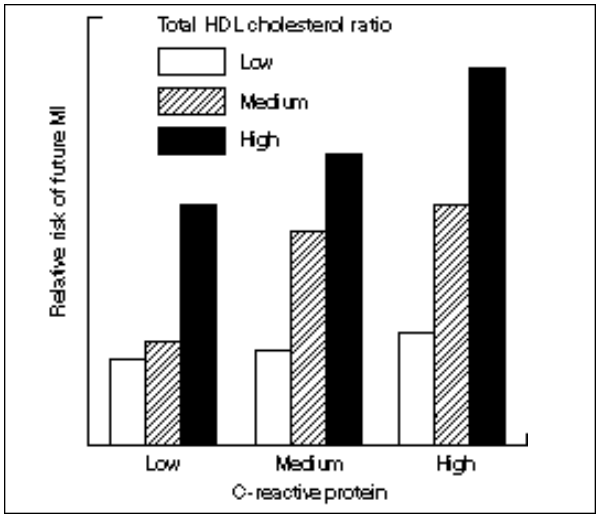
among all study participants and among non-smokers. For example, healthy men with baseline levels of C-reactive protein greater than 2.1 mg/L (the 75th percentile of the control distribution) were found to have three times the risk of future MI (relative risk=2.9, P< 0.001) and two times the risk of future ischemic stroke (relative risk=1.9, P=0.02) compared to those with lower levels[53] (figure 6).

From a clinical perspective,this study's data also suggest that assessment of C-reactive protein might well add to our ability to predict future vascular disease events.

- First, risk estimates associated with increased C-reactive protein were stable over long periods, implying that the effects of inflammation are probably mediated through a chronic process directly associated with atherogenesis.
- Second, the risk of future MI associated with C-reactive protein was independent of total and HDL cholesterol, triglycerides, lipoprotein(a), tPA antigen, homocysteine, D-dimer, fibrinogen, body mass index, diabetes, hypertension, and a family history of premature atherosclerosis.[53]
- Subsequent analyses from this study showed that predictive models incorporating lipid and C-reactive protein levels provided significantly better risk assessment than did models using lipid levels alone.In fact, the relative risks of future MI among subjects with high levels of lipids and C-reactive protein were greater than the product of the individual risks associated with elevations of either factor alone (figure 7).
- Furthermore, levels of C-reactive protein were predictive of future MI risk even in those subgroups of patients with "low-risk" lipid profiles.

It is intriguing to consider the possibility that infectious organisms such as *Chlamydia pneumoniae*, herpesvirus, or cytomegalovirus could be a cause of the chronic inflammation detected in studies of C-reactive protein and vascular risk. In this regard,the hypothesis has been raised that antimicrobial therapy might have a role in the prevention of atherothrombosis.[54] This hypothesis will require direct testing in randomized clinical trials.

Figure 7: Interrelation of C-reactive protein and the total cholesterol to HDL cholesterol ratio in the prediction of future MI. (Adapted from Ridker et al, Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–979.)



The primary prevention of MI

While factors such as fibrinogen, homocysteine, tPA antigen, lipoprotein(a),and C-reactive protein all appear to be associated with future vascular risk, the clinical decision to screen for any of them is complex. First, with the possible exception of fibrinogen and C-reactive protein, data are limited describing whether these factors add to our ability to predict risk over and above that available with traditional methods. Second, with the exception of homocysteine, simple methods to reduce levels of these factors are not readily available. Third, for factors such as lipoprotein(a) and perhaps tPA antigen, the associated risk might be limited to individuals with hyperlipidemia. Finally, clinical trial data demonstrating that reduction of any of these factors leads to a net clinical benefit are currently lacking.

At the same time,because acute cardiovascular events will continue to occur among conventionally low-risk individuals, clinical interest in novel markers of atherothrombosis is likely to increase. Indeed, despite substantial gains over the past 20 years, CAD remains the single most important cause of morbidity and mortality in the United States, accounting for approximately one in every four fatalities.[55] From the perspective of primary prevention, tactics such as smoking cessation, dietary discretion, lipid reduction, moderate exercise, and blood-pressure control will remain the most important means of reducing vascular risk well into the 21st century.[56] Knowledge that a given individual is at increased coronary risk even when conventional risk factors are absent is likely to improve compliance with behavioral interventions. Moreover, the pathophysiologic implications of these novel markers will undoubtedly lead to new therapeutic approaches to cardiovascular disorders.

This Brigham and Women's Hospital Cardiovascular Grand Rounds summary includes information previously presented in detail in the following publications:

Ridker PM. Fibrinolytic and inflammatory markers for arterial occlusion: The evolving epidemiology of thrombosis and hemostasis. *Thromb Haemost* 1997;78:53–59.

Ridker PM. Association of hemostatic and thrombotic factors with cardiovascular risk. In Schafer AI (editor), *Molecular mechanisms of hypercoagulable states;* 1997; Landes Bioscience.

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Dr. Ridker's primary research interests involve the epidemiology of hemostasis and thrombosis as it relates to the prediction of future myocardial infarction, stroke, and venous thromboembolism, and to the primary prevention of cardiovascular diseases. Areas of particular interest include population-based prospective studies of biochemical markers for arterial and venous thrombosis, inflammatory parameters of atherosclerotic risk, and genetic polymorphisms associated with atherothrombosis. In general, Dr. Ridker's studies of these novel risk factors apply traditional large-scale epidemiologic techniques to areas of emerging biochemical research within the field of vascular biology. Dr. Ridker's research efforts are supported by the National Heart, Lung, and Blood Institute as well as the American Heart Association. Dr. Ridker has been the recipient of a Sinclair-Kennedy Fellowship from Harvard University, an NRSA from the National Institutes of Health, a Clinician Scientist Award from the American Heart Association, and a Faculty Development Award from SmithKline Beecham.