

Evaluating Novel Cardiovascular Risk Factors: Can We Better Predict Heart Attacks?

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Myocardial infarction often occurs among persons without traditional risk factors, and it has been hypothesized that assessment of "novel" markers may help identify persons who are prone to premature atherothrombosis. However, when considering the clinical utility of screening for any new marker for cardiovascular disease, physicians should consider whether there is a standardized and reproducible assay for the marker of interest; whether there is a consistent series of prospective epidemiologic studies indicating that baseline elevations of the novel marker predict future risk; and whether assessment of the novel marker adds to the predictive value of other plasma-based risk factors, specifically, the ratio of total cholesterol to high-density lipoprotein cholesterol. In this article, these criteria are used to evaluate five promising markers of cardiovascular risk: lipoprotein(a), total plasma homocysteine, fibrinolytic capacity, fibrinogen, and high-sensitivity C-reactive protein. Background is also provided to assist physicians in deciding whether one or more of these novel markers deserve clinical consideration in general outpatient settings.

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Ann Intern Med. 1999;130:933-937.

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Hyperlipidemia has proven to be an important modifiable cardiovascular risk factor for myocardial infarction, but many myocardial infarctions occur among persons with normal lipid values who otherwise appear to be at low clinical risk. In an attempt to better predict future myocardial infarction, epidemiologic studies have explored a series of novel risk factors for coronary disease, many of which are important for specific individuals (1). Of these factors, lipoprotein(a) levels; total plasma homocysteine levels; fibrinolytic function, as assessed by levels of tissue-type plasminogen activator and plasminogen activator inhibitor antigens; and inflammatory markers, such as fibrinogen and high-sensitivity C-reactive protein, have received the most attention (**Table 1**). However, when considering the clinical utility of any new marker for cardiovascular disease in currently healthy persons, three important issues must be considered.

First, there must be consensus among clinical chemists and research scientists on a sensitive and specific diagnostic test for the marker of interest. If assay characteristics are unacceptable or if controversy over the best way to measure a given marker is ongoing, it is unlikely that a clinically useful recommendation for screening to detect high risk can be made. For example, despite many years of research, there is no consensus on the appropriate method for lipoprotein(a) evaluation, and standardization of lipoprotein(a) testing in several commercially available kits remains inadequate (2). Efforts to standardize clinical assays for fibrinogen are improving, but intra-assay and interassay coefficients of variation for this marker remain high when different measurement methods are compared. By contrast, World Health Organization standards have been set for high-sensitivity assessment of C-reactive protein, and testing for high-sensitivity C-reactive protein seems to provide consistent and reproducible results (3, 4). Accurate assessment of fibrinolytic function requires standardized phlebotomy conditions, an issue that limits the utility of this approach. Furthermore, fibrinolytic markers have wide diurnal and seasonal variations (5, 6). With regard to total plasma homocysteine, the labor and expertise required for high-pressure liquid chromatography reduce the application of this technique for general screening.

Second, there must be a consistent series of prospective epidemiologic studies indicating that the novel marker of interest can be detected in apparently healthy persons before the onset of clinical disease. Prospective studies (in which exposure is ascertained before the onset of thrombosis) are critical in determining the validity of any proposed relation between a novel risk factor and subsequent myocardial infarction or stroke. Several markers, including lipoprotein(a) and total plasma homocysteine levels, may increase after acute myocardial infarction (7-10), whereas fibrinogen and C-reactive protein are part of the acute phase response. Thus, caution should be used when interpreting data from retrospective studies (in which exposure is ascertained after the onset of thrombosis). It is important to recognize that retrospective evaluations of novel

markers cannot exclude the possibility that the marker of interest is a result rather than a cause of acute vascular occlusion. Meta-analyses of retrospective studies, even when carefully performed, do not reduce the possibility of such bias (11, 12).

To date, consistent prospective data are available for fibrinogen (13–17), high-sensitivity C-reactive protein (16, 18–24), and the fibrinolytic markers tissue-type plasminogen activator and plasminogen activator inhibitor (16, 25–29). For each of these substances, several large-scale studies have been completed in diverse patient populations, indicating both consistency and generalizability. In contrast, prospective studies for lipoprotein(a) and total plasma homocysteine are inconsistent—both positive and negative results have been reported in high-quality prospective studies. For example, several prospective studies of total plasma homocysteine have reported modest positive associations (30–34), but results of other studies have been null (35–38). Furthermore, one prospective study of homocysteine provided evidence of association with short-term (30) but not long-term (39) follow-up. Similarly, although several prospective studies of lipoprotein(a) have provided evidence of a positive association (40–44), other large-scale studies have not (45–47). Thus, the clinical utility of population-based assessment of lipoprotein(a) and homocysteine remains controversial.

Third, there must be evidence that assessment of

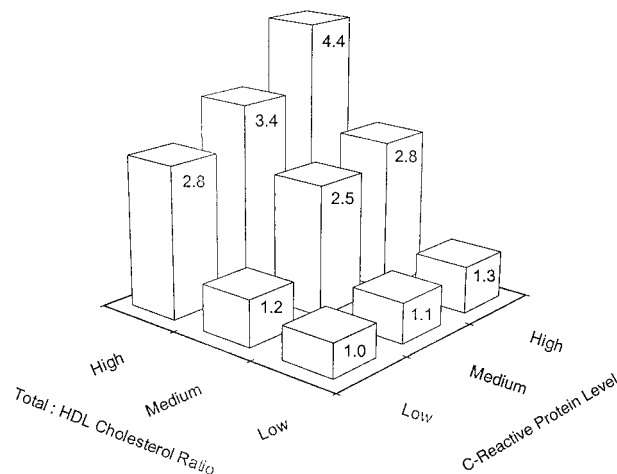


Figure 1. Relative risk for future myocardial infarction on the basis of simultaneous assessment of high-sensitivity C-reactive protein and the lipid profile. Data are stratified into low, middle, and high tertiles for both high-sensitivity C-reactive protein and the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol. From Ridker and colleagues [49].

a novel marker adds to our ability to predict risk over and above that already achievable through the use of established cardiovascular risk factors. The demonstration that a given marker has predictive value in univariate analysis is not sufficient to recommend clinical use because the observed association may be the result of confounding by other, traditional risk factors. Thus, fibrinolytic markers, such as tissue-type plasminogen activator and plasminogen activator inhibitor, both of which predict future cardiovascular disease in univariate analysis, may be of limited clinical utility for screening because the predictive value in multivariate analysis appears marginal (1). Of perhaps greater importance is the demonstration that the novel marker is at least additive in terms of risk prediction to that of established coronary risk factors (48). In particular, the clear clinical demonstration that a given marker improves the predictive value of total and high-density lipoprotein (HDL) cholesterol levels is critical because assessment of these markers is unlikely to be replaced by any new marker. To date, data demonstrating the additive value of lipoprotein(a) and homocysteine measurement are inconsistent. By contrast, measurement of fibrinogen (16, 17) or high-sensitivity C-reactive protein (22, 49) in addition to lipid measurement has been shown to cause significant improvement in clinical prediction models based on lipids alone in both men and women. An example of this additive effect for high-sensitivity C-reactive protein, a sensitive marker of chronic low-grade vascular inflammation, is shown in **Figure 1**.

Although it is not critical for risk prediction per se, an additional issue to consider is whether a given marker is modifiable and whether such modification

Table 1. Potential Markers of Risk for Vascular Occlusion*

Concentration markers	
Fibrinogen	
tPA	
PAI-1	
Factor V, VII, and VIII	
Lipoprotein(a)	
Homocysteine	
von Willebrand factor antigen	
Process markers	
tPA/PAI-1 complex	
Plasmin- α_2 -antiplasmin complex	
Prothrombin fragment 1 + 2	
Thrombin-antithrombin III complex	
Fibrinopeptide A	
Fibrin degradation products	
D-dimer	
Functional markers	
Activated protein C resistance	
Factor VIIc and VIIa	
Thrombin	
Global marker	
Clot lysis time	
Inflammatory markers	
High-sensitivity C-reactive protein	
Serum amyloid A	
Interleukins	
Vascular and cellular fibrinogen adhesion molecules	
Platelet markers	
Platelet size and volume	
Platelet aggregation, activity, and function	

* PAI-1 = plasminogen activator inhibitor; tPA = tissue-type plasminogen activator. Adapted from Ridker PM. Association of hemostatic and thrombotic factors with cardiovascular risk. In: Schafer AJ, ed. *Molecular Mechanisms of Hypercoagulable States*. Austin, TX: Landes Bioscience; 1997.

reduces cardiovascular risk. No completed randomized trials indicate that specific therapies designed to reduce levels of any novel marker lead to reduced cardiovascular event rates. Several studies indicate, however, that folate replacement reduces homocysteine levels (50, 51), and ongoing trials of folate therapy will help to determine the clinical utility of homocysteine screening. Recently, the U.S. supply of cereals and grains was fortified with folic acid to reduce the risk for neural tube defects. Although the impact of such fortification on cardiovascular risk is unknown, preliminary data indicate that the overall population distribution of homocysteine has been significantly reduced. Thus, food fortification may have further reduced the utility of generalized screening for mild to moderate hyperhomocystinemia.

Such agents as niacin and bezafibrate are reported to have some efficacy in reducing lipoprotein(a) and fibrinogen levels, respectively, but the magnitude and specificity of these effects are uncertain. No currently available therapies specifically reduce high-sensitivity C-reactive protein levels, although it is of interest that baseline concentrations of high-sensitivity C-reactive protein seem to modulate the efficacy of two preventive therapies, low-dose aspirin and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition. For example, data from double-blind, randomized clinical trials suggest that the relative efficacy of these two commonly used therapies may be greater in persons with evidence of underlying inflammation as assessed by high-sensitivity C-reactive protein (19, 52). Moreover, preliminary data suggest that long-term 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibition reduces high-sensitivity C-reactive protein levels in a manner that is relatively independent of low-density lipoprotein cholesterol levels. Taken to-

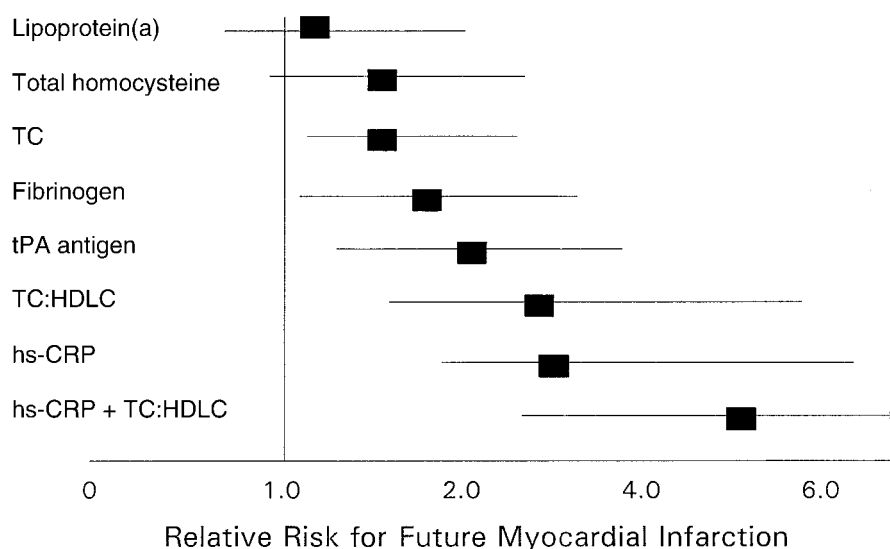
Table 2. Assessment of the Clinical Utility of Novel Markers of Cardiovascular Risk

Marker	Assay Conditions Standardized?	Prospective Studies Consistent?	Additive to Total and High-Density Lipoprotein Cholesterol?
Lipoprotein(a)	No	Yes/No	Yes/No
Total homocysteine	Yes/No	Yes	Yes/No
Tissue-type plasminogen activator and plasminogen activator inhibitor	Yes/No	Yes	Yes
Fibrinogen	Yes/No	Yes	Yes
High-sensitivity C-reactive protein	Yes	Yes	Yes

gether, these data raise the possibility that novel markers may also have a role in monitoring preventive therapies.

As shown in **Table 2**, the criteria outlined above for assay characteristics, consistency of prospective epidemiologic studies, and the ability of a given marker to add to the predictive value of total and HDL cholesterol can assist clinicians in deciding whether a “novel” marker of risk deserves clinical consideration in general outpatient settings. For specific patients who have known metabolic disorders or have a personal or family history of unexplained premature atherothrombosis, a more aggressive approach to evaluation of novel risk markers may be warranted. In addition, markers that help with disease prognostication may not necessarily be the most relevant markers for understanding disease pathophysiology. For example, recent prospective data concerning specific cytokines and cellular adhesion molecules help explain the inflammatory processes underlying atherosclerosis (53, 54), but the prognostic value of these markers in clinical settings is uncertain compared with more easily measured

Figure 2. Relative risk for future myocardial infarction among apparently healthy middle-aged men in the Physicians' Health Study according to baseline levels of lipoprotein(a), total plasma homocysteine, total cholesterol (TC), fibrinogen, tissue-type plasminogen activator (tPA) antigen, the ratio of total cholesterol to high-density lipoprotein cholesterol (HDL), and high-sensitivity C-reactive protein (hs-CRP). For consistency, risks are computed for men in the top compared with the bottom quartile for each marker.



markers of inflammation, such as high-sensitivity C-reactive protein.

Few studies have systematically evaluated the relative efficacy of different novel risk factors on coronary prediction in the same patient population. Thus, quantitative data formally addressing the sensitivity, specificity, and additive predictive value of novel markers are currently limited (16, 48, 49). Nonetheless, in one prospective study of apparently healthy middle-aged U.S. men, evaluations of total and HDL cholesterol, lipoprotein(a), total plasma homocysteine, fibrinogen, tissue-type plasminogen activator antigen, and high-sensitivity C-reactive protein levels have been presented (19, 27, 30, 39, 45, 55, 56). The relative efficacy of each of these markers for predicting future myocardial infarction is shown in **Figure 2**. Such data are encouraging because they raise the possibility that measurement of novel coronary markers may significantly improve our ability to predict heart attack risk. In contrast, similar prospective data are not available for screening techniques designed to directly detect preclinical atherosclerosis, such as electron-beam computed tomography. Thus, the cost and relative efficacy of imaging technologies currently under investigation must be carefully compared with those of several plasma-based markers that have already been shown in prospective cohort studies to predict coronary events.

Grant Support: Dr. Ridker is supported by an Established Investigator Award from the American Heart Association, Dallas, Texas.

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I have added . . . a parcel of my own particular asafetida. It is imported for me by a Turkey merchant; and as you perhaps have noticed in spite of the sturgeon's bladder in which it is enclosed it is by far the most pungent, the most truly fetid, variety known to man. For you must know, gentlemen, that when the mariner is dosed, he likes to know that he has been dosed; with fifteen grains or even less of this valuable substance scenting him and the very air about him there can be no doubt of the matter; and such is the nature of the human mind that he experiences a far greater real benefit than the drug itself would provide, were it deprived of its stench.

Patrick O'Brian
The Commodore
 W.W. Norton; 1995

Submitted by:
 Joel E. Gallant, MD, MPH
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