Emerging Use of Inflammatory Biomarkers in Assessing Risk for Cardiovascular Disease

Case Study and Commentary, Jan Laws Houghton, MD

Abstract
- **Objective:** To review the role of C-reactive protein (CRP) levels in assessing cardiovascular risk.
- **Methods:** Qualitative assessment of the literature.
- **Results:** Slowly progressive coronary heart disease (CHD) frequently remains asymptomatic for decades, and its presence can only be inferred by the recognition of risk factors, including advanced age, hypertension, hypercholesterolemia, diabetes mellitus, tobacco use, and family history of premature atherosclerosis. Recent studies support the concept that vascular inflammation is an early step in the pathogenesis of atherosclerosis. CRP is produced in small quantities as a byproduct of vascular inflammation through the formation of its precursor, interleukin-6. Levels of CRP measured using a high-sensitivity assay (hs-CRP) have been shown to be predictive of future cardiovascular events. Prediction of CHD risk can be performed using the Framingham risk scoring system, which defines high-, intermediate-, and low-risk subsets; risk status is then used to determine recommended low-density lipoprotein cholesterol goals. Observational studies have shown that hs-CRP provides additive prognostic information, which allows further refinement of risk status, especially among those at intermediate risk.
- **Conclusion:** Because the determinants of atherosclerosis include complex genetic, environmental, and evolutionary forces, all of which are integrated through production of hs-CRP, this biomarker may prove to be uniquely positioned for the task of global risk prediction. A benefit from initiation of certain therapies, including cholesterol-lowering drugs, in response to hs-CRP elevation, has not yet been demonstrated in a randomized placebo-controlled clinical trial.

Cardiovascular disease (CVD) is the leading cause of death among men and women in westernized societies and is projected to emerge as the leading cause of death and disability worldwide by the year 2020 [1]. In 2001, CVD was responsible for nearly 39% of all deaths in the United States, claiming more lives than the next 5 causes combined [2]. In 2004, the estimated annual direct health care cost related to CVD among Americans was $226.7 billion. When including indirect costs related to lost productivity from cardiovascular morbidity and mortality, the estimated total was $368.4 billion. By comparison, in 2003, the estimated direct and indirect cost of all cancers was $189 billion [3].

One of the hallmarks of CVD presentation is its unpredictable nature. Half of all cardiac deaths are sudden and unexpected [4], and more than half of those dying suddenly of coronary heart disease (CHD) have no previous symptoms. Many of those presenting with acute myocardial infarction (MI) die in the first hour due to cardiogenic shock or fatal arrhythmias, not surviving to hospitalization [5,6]. Because of the unpredictable and lethal nature of CVD, clinical practice guidelines advise more aggressive detection of early, even subclinical, disease among patients judged to be at intermediate and high risk based on well-established risk factors [7]. One emerging method for detection of subclinical disease involves testing for vascular inflammation, an early step in the pathophysiology of atherosclerosis [8]. The introduction of novel serum biomarkers for vascular inflammation, especially high-sensitivity C-reactive protein (hs-CRP), is reported to improve risk assessment and represents a promising approach in achieving earlier detection of CHD [9–12]. Early detection and intensified primary prevention, in keeping with recent clinical practice guidelines, are of great importance in the effort to reduce CVD morbidity and mortality.

**CASE STUDY**
**Initial Presentation**

A 52-year-old woman presents to her primary care physician for a general medical examination.

**History**
The patient was last seen 5 years earlier and in the interim has felt well. Her gynecologist continues to renew blood pressure medication initiated by her primary physician. During her most recent yearly gynecologic examination, the

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patient complained of severe menopausal symptoms, and the physician discussed the advantages and disadvantages of hormone replacement therapy (HRT) with her. Her gynecologist recommended that she make an appointment with her primary care physician for a general medical examination prior to a final decision about HRT.

Upon seeing her internist, the patient describes recent onset of shortness of breath during usual activities. She attributes these symptoms to her smoking habit of one-half pack per day over the previous 30 years. She denies any exertional chest discomfort but admits having chest pressure with associated tightness in her neck and throat during stressful situations. Her major complaints include severe hot flashes and night sweats and unusual difficulty sleeping. She continues to have menstural periods but in an irregular pattern, averaging every 6 to 8 weeks with an occasional missed cycle. Gynecologic examinations and mammograms are up to date and normal. When questioned about risk factors, the patient denies diabetes mellitus and hypercholesterolemia. However, she has not had screening blood work done since her last primary care visit. She remembers being told that her cholesterol was minimally elevated 5 years earlier and was counseled to reduce dietary cholesterol and fats. She subsequently eliminated most fried foods and red meat from her diet. She has been treated for hypertension since age 45 years and is currently maintained on diltiazem XR 180 mg/day. She works full-time as a data entry clerk and engages in no routine leisure activity. The patient is adopted and has no knowledge of her birth parents.

Physical Examination

The patient is a healthy-appearing, moderately overweight, middle-aged white woman. Weight and height are 170 lb and 5’4” (body mass index [BMI], 29 kg/m²). Waist circumference is 37 inches. Blood pressure is 138/85 mm Hg. Pulse is 85 bpm in a regular rhythm. Chest and cardiovascular examination are normal, and no carotid or abdominal bruits are appreciated. Distal pulses are patent.

Laboratory Testing

An electrocardiogram reveals normal sinus rhythm with normal waveforms and intervals. Fasting blood glucose is 112 mg/dL. Hemoglobin A₁c is 6.4% (normal, 4.1%–6.5%). Fasting lipid profile is as follows: total cholesterol, 220 mg/dL; high-density lipoprotein (HDL) cholesterol, 39 mg/dL; low-density lipoprotein (LDL) cholesterol, 146 mg/dL; and triglycerides, 175 mg/dL.

Table 1. Cardiac Risk Factors Used to Modify Low-Density Lipoprotein Cholesterol Goals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>LDL Cholesterol Goal</th>
</tr>
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<tbody>
<tr>
<td>Tobacco use</td>
<td>≥ 140/90 mm Hg or on medication</td>
</tr>
<tr>
<td>Hypertension</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Family history of premature coronary heart disease</td>
<td>First-degree relative, male &lt; 55 years or female &lt; 65 years</td>
</tr>
</tbody>
</table>

Age

- Men ≥ 45 years; women ≥ 55 years

Risk for CHD can be predicted by traditional risk factors established by the Framingham Heart Study. This long-term follow-up study begun in 1949 found that advanced age, male gender (under age 65 years), tobacco use, hypertension, diabetes mellitus, and hypercholesterolemia were predictive of CHD risk [13]. This list has been refined over time to specify that men aged 45 years or older and women aged 55 years or older and those with a family history of premature atherosclerosis (defined as heart disease in male first-degree relatives younger than 55 years and in female first-degree relatives younger than 65 years) are at risk. The case patient has several traditional risk factors, including hypertension, tobacco use, and dyslipidemia, so she clearly is not a low-risk patient. Until recently, further stratification of risk was frequently subjective and not standardized.

The 3 adult treatment panels (ATP) convened by the National Cholesterol Education Program (NCEP) have issued clinical practice guidelines for primary and secondary prevention of CHD. The most recent panel described mechanisms for assigning low-, intermediate-, and high-risk prognosis in patients based on history of CVD and presence of cardiac risk factors (Table 1) [14]. Assigned risk is then used to determine recommended LDL cholesterol goals. LDL cholesterol is not included as a risk factor because the central purpose of the risk classification system is to modify the treatment of LDL. Patients with CHD or those with CHD “risk equivalents” are considered to be in the high-risk category. CHD risk equivalents include diabetes mellitus, peripheral vascular disease, abdominal aortic aneurysm, and symptomatic carotid artery disease; these conditions carry a risk for major coronary events equivalent to that of established CHD (ie, > 20% risk over 10 years).

In patients with 2 or more risk factors, risk is estimated using the Framingham scoring system (Figure 1). Points are
Figure 1. Risk assessment algorithm for determining the 10-year risk of developing coronary heart disease using Framingham risk scoring. CHD = coronary heart disease; HDLC = high-density lipoprotein cholesterol; SBP = systolic blood pressure; TCHOL = total cholesterol. (Adapted from Executive summary of The Third Report of The National Cholesterol Education Program [NCEP] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]. JAMA 2001;285:2497.)
assigned based on age, gender, total cholesterol, smoking status, HDL cholesterol, and systolic blood pressure. Patients with 2 or more risk factors and a calculated Framingham score associated with greater than 20% risk over 10 years are also considered to be in the high-risk category. Patients in the intermediate-risk category have 2 or more risk factors and generally have a 10% to 20% risk of a CHD event over the next 10 years. Patients in the lowest risk category have a less than 10% risk of a CHD event in 10 years and usually have 0 to 1 risk factor.

The calculated Framingham risk score for the case patient is 20 points, which correlates with a 10-year event risk of 11%, an intermediate risk category. The patient has 3 major NCEP risk factors.

• How does this risk affect the patient’s treatment goals?

Regardless of CHD risk category, smoking cessation should be strongly encouraged because of the pervasive health threat smoking poses. The patient should be referred to a smoking cessation program or supplied with appropriate medications to enhance success. ATP III specified LDL cholesterol goals and cut-points for therapeutic lifestyle changes (TLC) and drug therapy based on risk category. LDL goals are < 160 mg/dL for low-risk patients, < 130 mg/dL for intermediate-risk patients, and < 100 mg/dL for high-risk patients. TLC is recommended for all patients who are not at their LDL goal. TLC consists of a reduced cholesterol (< 200 mg/day) and reduced saturated fat (< 7% of total calories) diet, weight reduction, and increased physical activity. According to ATP III, LDL-lowering drugs should be considered in low-risk patients with LDL ≥ 190 mg/dL and in intermediate-risk patients with LDL ≥ 130 mg/dL (unless their 10-year risk is < 10%, in which case their cutpoint for drug therapy is ≥ 160 mg/dL). For high-risk patients, drug therapy should be considered in patients with LDL ≥ 130 mg/dL, although the panel allowed that drug therapy is optional for high-risk patients with LDL 100 to 129 mg/dL.

Since the publication of ATP III, several randomized placebo-controlled clinical trials have concluded that the optimal LDL cholesterol level in high-risk patients is on the order of < 70 mg/dL [15,16]. Based on this finding, updated ATP III guidelines [17] recommend an LDL cholesterol goal of < 70 mg/dL in patients with acute coronary syndromes and in those at very high risk, described as presence of established CVD plus any of the following: multiple major risk factors, especially diabetes; severe and poorly controlled risk factors, especially continuing tobacco use; and multiple features of the metabolic syndrome, especially triglyceride level ≥ 200 mg/dL plus non-HDL cholesterol ≥ 130 mg/dL and HDL cholesterol < 40 mg/dL. Furthermore, in those at intermediate risk such as the case patient, the updated ATP III guidelines state that a LDL cholesterol goal of < 100 mg/dL is a therapeutic option at the physician’s discretion. This option is felt to be particularly appropriate in the setting of advanced age, presence of more than 2 risk factors, continuing tobacco use, strongly positive family history of premature atherosclerosis, triglyceride level ≥ 200 mg/dL plus non-HDL cholesterol ≥ 160 mg/dL and HDL cholesterol < 40 mg/dL, the metabolic syndrome, and/or the presence of emerging risk factors (eg, hs-CRP > 3 mg/L). Finally, the update recommends that when cholesterol-lowering medications are used in both intermediate- and high-risk patients, LDL cholesterol should be reduced by 30% to 40%.

Based on ATP III, the case patient’s LDL cholesterol goal is 130 mg/dL. However, her LDL cholesterol goal is adjusted down to 100 mg/dL, according to the ATP III update [17], based on her ongoing tobacco use, low HDL cholesterol, and the presence of the metabolic syndrome. This syndrome is a disorder characterized by an inflammatory and atherogenic phenotype [18] and is diagnosed when at least 3 of 5 characteristic findings are present (waist circumference > 35 inches in women, triglyceride level ≥ 150 mg/dL, HDL cholesterol < 50 mg/dL in women, blood pressure ≥ 130/85 mm Hg, and fasting blood glucose ≥ 110 mg/dL). Our patient fulfills all 5 of the diagnostic criteria. ATP III recognized the metabolic syndrome as a secondary target for therapy, recommending initiation of TLC.

• What characteristics in this patient can modify the Framingham estimation of risk?

There are several factors that are concerning with regard to this patient’s estimated risk. First, she has both hypertension and hypercholesterolemia. The coexistence of these disorders causes a risk synergism whereby the attributable risk is greater than summation of the individual risks [19]. In addition, her family history is unknown. Although Framingham risk scoring does not utilize family history of CVD in assignment of points for determination of 10-year event risk, knowledge of family medical history often provides compelling insight into an individual patient’s likelihood of disease processes [20]. Finally, since she meets all 5 criteria for the metabolic syndrome, her derived risk using any currently approved algorithm, including the Framingham scoring system, is likely to be underestimated.

• Are there additional factors which may prove useful in estimating this patient’s cardiovascular risk?
A number of plasma markers have been shown to predict cardiovascular risk, including total cholesterol, LDL cholesterol, apolipoprotein B, homocysteine, total cholesterol/HDL cholesterol ratio, hs-CRP, and LDL and HDL cholesterol particle size phenotype [9–12,21,22]. In the Women’s Health Study (WHS), a case-control analysis of the 122 women having cardiovascular events over 3 years of follow-up showed that the relative risk of a cardiovascular event was best predicted by hs-CRP, followed by the total cholesterol/HDL cholesterol ratio (Figure 2). The predictive value of these 2 parameters in combination yielded the best results, with an average sixfold increase in relative risk when both parameters were elevated into the highest quartile subgroup [23]. Following these findings, hs-CRP and LDL cholesterol were measured in participants with usable stored baseline blood samples, and the results were used to construct survival curves. This study found that in a large population-based sample of women, CRP was a stronger predictor of cardiovascular events than LDL cholesterol over 8 years’ mean follow-up and that it provided additional and independent risk prediction when compared with the Framingham risk score [24]. Population-based surveys have revealed the expected distribution of hs-CRP and total cholesterol/HDL cholesterol measurements stratified by increasing quintiles of risk (Table 2) [24,25]. Each quintile is associated with defined risk of a cardiovascular event from lowest to highest risk. Risk assessment algorithms using both parameters have been proposed for assigning a relative risk score [26].

In addition, in the WHS 24.3% of the 14,719 participants had the metabolic syndrome at study entry [27]. Median hs-CRP levels increased progressively as the number of criteria for metabolic syndrome increased. The median hs-CRP level was 5.75 mg/L in women satisfying all 5 criteria, a value that places such women in the highest risk category for occurrence of a cardiovascular event (Table 2). In fact, women with metabolic syndrome who had hs-CRP levels in the highest tertile had a doubling of cardiovascular risk when compared with those with hs-CRP levels in the lowest tertile. This information was not published at the time the ATP III guidelines were released. Accordingly, in metabolic syndrome, hs-CRP adds to the prognostic information supplied through the Framingham risk scoring system.

- What is the relationship between hs-CRP and CHD?

A number of studies have been performed to investigate the relationship between CRP and cardiovascular morbidity and mortality in primary and secondary prevention populations. A cross-sectional study examined this relationship in a randomly selected group of 388 British men aged 50 to 69 years drawn from general practices in 3 Health Authority Districts in South London [28]. This study was the first to demonstrate an increase in prevalence of CHD in association with doubling of CRP within the normal range. Another cross-sectional study (the Monitoring Trends and Determinants in Cardiovascular Disease Augsburg, Germany [MONICA] cohort study) was conducted in 936 healthy men aged 45 to 64 years randomly sampled from the general population of over 280,000 inhabitants in 1984 and 1985 with

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**Table 2. hs-CRP and Total Cholesterol:HDL Cholesterol in Cardiovascular Risk Assessment**

<table>
<thead>
<tr>
<th>Quintile of Risk</th>
<th>Level of Risk</th>
<th>hs-CRP Level (mg/L)</th>
<th>TC/HDL Cholesterol Ratio (Women)</th>
<th>TC/HDL Cholesterol Ratio (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lowest</td>
<td>0.1–0.6</td>
<td>&lt;3.4</td>
<td>&lt;3.4</td>
</tr>
<tr>
<td>2</td>
<td>Low</td>
<td>0.7–1.1</td>
<td>3.4–4.1</td>
<td>3.4–4.0</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>1.2–1.9</td>
<td>4.1–4.7</td>
<td>4.0–4.7</td>
</tr>
<tr>
<td>4</td>
<td>High</td>
<td>2.0–3.8</td>
<td>4.7–5.8</td>
<td>4.7–5.5</td>
</tr>
<tr>
<td>5</td>
<td>Highest</td>
<td>3.9–15.0</td>
<td>&gt;5.8</td>
<td>&gt;5.5</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; hs-CRP = high-sensitivity assay of C-reactive protein; TC = total cholesterol. (Data from Rifai N, Ridker P. High-sensitivity C-reactive protein: a novel and promising marker of coronary heart disease. Clin Chem 2001;47:403–11.)

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**Figure 2.** Relative risk of future cardiovascular events associated with baseline elevation of the highest quartile for markers of inflammation and lipids. HDLC = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein. (Adapted with permission from Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836.)
follow-up performed over 8 years [29]. This study found that modest elevations in baseline serum CRP concentration were predictive of incident nonfatal and fatal coronary events. In 1982, the Physicians’ Health Study enrolled over 22,000 male physicians aged 40 to 84 years with no history of MI, stroke, transient ischemic attack, or cancer. The nested case-control design was used to examine the relationship between baseline plasma concentration of CRP in 543 initially healthy men who had MI or ischemic stroke and in 543 controls who remained healthy during 8-year follow-up [30]. Men with hs-CRP in the highest quartile had 3 times the risk of MI and 2 times the risk of ischemic stroke when compared with those having hs-CRP in the lowest quartile.

The Cholesterol and Recurrent Events (CARE) study was a randomized, double-blind, placebo-controlled trial testing statin therapy in the secondary prevention of cardiovascular events among 4159 patients with prior history of MI [31]. The nested case-control design was used to compare CRP levels in prerandomization blood samples from 391 participants in CARE who developed new nonfatal or fatal coronary events and in an equal number of age- and sex-matched participants who remained free of new cardiac events during follow-up [32]. Those with CRP levels in the highest quintile had a relative risk of recurrent events 77% higher than those with levels in the lowest quintile. The Multiple Risk Factor Intervention Trial (MRFIT) was a randomized primary prevention trial that enrolled over 12,800 men aged 35 to 57 years with at least 1 of the 3 risk factors: hypertension, hypercholesterolemia, and tobacco use [33]. A nested case-control study was conducted among 148 participant cases and 148 controls in order to study the relationship between level of CRP and CHD mortality over 17 years’ follow-up [34]. This analysis found that those with baseline CRP in quartile 4 had a nearly 3 times higher risk of mortality when compared with those in quartile 1. Finally, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a primary prevention trial of lovastatin or placebo in over 6000 men and women with average levels of total and LDL cholesterol and below-average levels of HDL cholesterol [35]. After an average follow-up of 5.2 years, there was a 37% reduction in nonfatal and fatal CHD events in the lovastatin-treated group when compared with placebo. Blood samples obtained at the time of randomization and at 1 year were frozen and assayed for hs-CRP during a later post-hoc analysis. This analysis showed that an increase in coronary events correlated with an increase in baseline CRP. Treatment with lovastatin was found to reduce coronary events in patients with increased total cholesterol/HDL cholesterol ratio regardless of CRP and in patients with decreased total cholesterol/HDL cholesterol ratio when CRP was elevated; the latter finding suggests the independent importance of CRP [36]. Lovastatin treatment reduced the CRP level by nearly 15%. Thus, multiple observational and post hoc analysis studies in both primary and secondary prevention cohorts have demonstrated the utility of CRP prediction of cardiovascular events. To date, there are no published reports from randomized placebo-controlled trials that address the possible linkage between therapies that reduce CRP and improvement in event rates.

The Pravastatin Inflammation/CRP Evaluation (PRINCE) trial was a prospective study with primary and secondary prevention cohorts designed to study the effect of pravastatin on CRP levels [37]. In both cohorts, CRP was reduced by 13% to 17% at 12 to 24 weeks of therapy. Because there is no prospective trial data showing that reduction in hs-CRP results in reduction of cardiovascular risk, a large multicenter, randomized, placebo-controlled trial (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin [JUPITER]) is underway to evaluate the use of rosuvastatin, a potent lipid-lowering statin drug, in the primary prevention of cardiovascular events in healthy men and women without a history of CVD or hyperlipidemia (LDL cholesterol < 130 mg/dL) but with elevated hs-CRP [38]. This study will address whether measurement of hs-CRP should be routinely used in a primary care population to pinpoint those likely to benefit from statin therapy despite having a normal or low LDL cholesterol level.

- Which patients should have hs-CRP measured?

The American Heart Association and Centers for Disease Control and Prevention jointly issued a scientific statement regarding the usefulness of cardiac biomarkers [39]. For risk stratification, determination of hs-CRP was judged a class IIa indication (Conflicting Evidence/Opinion: Weight in favor of usefulness/efficacy) in those at intermediate risk (10%-20% CHD event rate over 10 years) in order to help direct further evaluation and therapy, including use of stress testing, for the purpose of primary prevention of CVD. In general, CRP testing is not recommended in individuals at low predicted risk (<10% over 10 years) because testing is unlikely to result in identification of high-risk status. However, if the Framingham risk prediction is suspected to be falsely low, for example, in a patient with a strong family history of premature atherosclerosis or compelling clinical presentation, it would appear to be reasonable to perform CRP testing for confirmation of risk status. In those at high predicted risk (>20% over 10 years), intensive medical therapy is indicated on clinical grounds; therefore, it is felt CRP testing will add little. Despite this, CRP testing may provide prognostic information and may be useful in counseling and
motivation of high-risk patients. Finally, the consensus paper recommended stratification of cardiovascular risk by tertiles of hs-CRP as follows: low risk, < 1.0 mg/L; intermediate risk, 1.0-3.0 mg/L; and high risk, > 3.0 mg/L.

Determination of hs-CRP is not recommended as a screening tool for risk assessment in the entire adult population; however, it is acknowledged that it may be useful in some patients to assist in global risk assessment at the discretion of the treating physician. Plasma levels of other inflammatory biomarkers such as soluble intercellular adhesion molecule type 1, serum amyloid A, and interleukin (IL)-6 correlate with increased relative risk of cardiovascular events in research studies but are not currently recommended for use in determination of risk in clinical practice.

Additional Laboratory Data

Testing shows a total cholesterol/HDL cholesterol ratio of 5.6:1 and an hs-CRP level of 4.1 mg/L. Based on Table 2, the total cholesterol/HDL cholesterol ratio places the patient in quintile 4, which is defined as high risk for a cardiovascular event during follow-up. Similarly, the hs-CRP measurement places her in quintile 5, the highest risk category. Using a composite total cholesterol:HDL cholesterol and hs-CRP algorithm derived from population-based surveys, the patient has a sixfold in relative risk when compared with lowest risk patients [26].

- What is the role of CRP in cardiovascular inflammation?
- How is hs-CRP measured?

Recent studies support the concept that vascular inflammation is an early step in the pathogenesis of atherosclerosis [40–43]. This work acknowledges the seminal contribution of white blood cells and, in particular, the monocyte in plaque evolution obeing the “response to injury” directive. During this process, monocytes enter the subendothelial space and in doing so become macrophages and ultimately cholesterol-laden foam cells. These and activated T-lymphocyte cells release cytokines, including IL-6, which promote further inflammatory activity. Circulating IL-6 results in hepatic production of CRP and serum amyloid A [44]. It is now evident that CRP is not only a marker but also a mediator of vascular wall inflammation [45,46]. Because of ease of measurement and reproducibility in the absence of transient systemic inflammatory conditions, CRP appears to be a useful adjunctive biomarker in assessment of cardiovascular risk [47,48].

Hs-CRP, also known as cardio-CRP, is a polypeptide molecule with acute phase reactant properties [11]. CRP was originally named because of its appearance in plasma in response to the C-polysaccharide of Streptococcus pneumoniae and was used to follow disease activity in response to acute or chronic inflammatory conditions, including bacterial pneumonia, inflammatory bowel disease, rheumatoid arthritis, or collagen vascular diseases. In such diseases, when acute or active, CRP levels rise markedly, typically 100 times or greater. These changes are measured using the traditional assay in mg/L. A high-sensitivity assay was subsequently developed that measures CRP in mg/L and affords greater than twentyfold improved sensitivity, allowing measurement of normal range and mildly elevated CRP, formerly undetectable using the traditional assay. This is the range that is associated with cardiovascular inflammation.

Hs-CRP levels remain remarkably stable in the absence of clinically obvious inflammatory processes. Accordingly, in order to avoid false-positive elevations in hs-CRP, it is recommended that the patient be free of any obvious active infectious or inflammatory process at the time of phlebotomy and that a second specimen be tested 2 to 4 weeks later for confirmation. Unlike lipid fractions, CRP may be measured non-fasting. CRP levels increase with age, obesity, sedentary behavior, tobacco use, hypercholesterolemia, insulin resistance states, oral contraceptive use, and HRT [11,12].

- Is there a genetic basis for hs-CRP plasma concentration?

CHD tends to cluster in families, as do lifestyle choices. This is consistent with the observation that both genetics and environment are responsible for disease expression. A monozygotic twin study enrolling 68 male and 87 female pairs found that the within-pair correlation coefficient for hs-CRP was 0.4 [49]. However, CRP also correlated significantly with blood pressure, BMI, and some lipid parameters, all of which may be influenced by both genetic and lifestyle contributions. In order to estimate heritability more rigorously, a second study compared within-pair correlation coefficient of baseline CRP in 146 monozygotic and 164 dizygotic healthy female twin pairs [50]. These were closely matched for height, weight, BMI, blood pressure, and lifestyle variables, and none had chronic disease or intercurrent illness. Within-pair correlation coefficient for CRP was 0.49 in monozygotic twins and 0.28 in dizygotic twins. Statistical modeling estimated that heritability of baseline CRP expression is 52%. Thus, current information suggests that hs-CRP level is associated with a substantial degree of inheritance.

- Is there an evolutionary basis for elevated CRP?
One plausible explanation may involve primordial physiologic directives. This term refers to survival mechanisms in one age that may become risk factors for mortality in another. Between 70,000 and 100,000 years ago, at the peak of the last Ice Age, extreme climatic conditions nearly resulted in the extinction of Homo sapiens [51]. This created a genetic bottleneck in which a small number of genes were passed ultimately to a large population, as we have now [52]. On the verge of man’s near extinction, successful survival mechanisms would have addressed the main causes of death, namely infection, trauma, malnutrition, starvation, and prolonged fasting [53]. Therefore, enhanced immunity, inflammatory and healing responses, enhanced ability to sustain gluconeogenesis, and robust endogenous cholesterol production may have allowed an advantage for survival in prehistoric times [54]. Changes in lifespan and lifestyle explain the physiologic consequences of genes that averted our extinction but now contribute to CVD and diabetes.

Initiation of Risk Reduction Interventions

Although formal Framingham risk scoring places the case patient in an intermediate risk category, the presence of multiple cardiac risk factors, the metabolic syndrome, and a high-risk hs-CRP score suggests that she is at high risk and mandates an aggressive diagnostic and therapeutic regimen. Her history of dyspnea could be an anginal equivalent. Thus, the physician orders a radionuclide exercise stress test. The patient exercises using a Bruce protocol to her target heart rate. She has no chest discomfort, and there is no evidence of ischemia based on electrocardiogram changes or nuclear perfusion scans. The physician counsels the patient about risk reduction, including tobacco cessation, weight loss, and incorporation of routine exercise into her lifestyle. She is referred to a nutritionist for education about a reduced fat, reduced cholesterol diet with calorie limits. She is offered nicotine replacement therapy or bupropion to assist with tobacco cessation. She elects to try a transdermal nicotine patch 14 mg/day. The physician recommends that she purchase a pedometer with a goal of 10,000 steps per day most days but at least 5 days of the week. She increases the diltiazem XR to 240 mg/day to improve blood pressure control, and advises the patient to begin aspirin 81 mg/day. The patient is given an appointment to return in 6 weeks and is instructed to have a fasting lipid profile and hs-CRP measurement done before the visit. At the time of her follow-up visit, the patient reports that she has made changes in her diet, has lost 5 lb, and is walking 1 hour a day. Unfortunately, she is still smoking 3 to 5 cigarettes per day. Follow-up lipid profile and hs-CRP in the recommended diet are as follows: total cholesterol, 215 mg/dL; HDL cholesterol, 37 mg/dL; LDL cholesterol, 144 mg/dL; triglycerides, 170 mg/dL; and hs-CRP, 4.0 mg/L. Although the patient has made progress with weight loss and an exercise routine, she is still smoking (although at a reduced rate), and her lipid profile remains above target. This second hs-CRP value confirms significant elevation of the biomarker. The LDL cholesterol goal remains < 100 mg/dL based on the recent ATP III update. The patient is prescribed bupropion CR 300 mg/day to use in addition to the nicotine patch. When questioned, she says it is unlikely she could improve her diet further. Therefore, rather than advancing diet therapy for an additional 6 weeks as recommended by ATP-III, statin drug therapy is initiated with follow-up planned in 6 weeks.

- Is this patient a candidate for HRT, and does her hs-CRP level affect this decision?

This patient’s main complaint was of perimenopausal symptoms that included severe hot flashes and sleep disturbance. HRT is an effective agent for relief of constitutional and affective symptoms associated with the perimenopausal state. Before 2 recent landmark studies, HRT was considered a protective strategy for primary and secondary prevention of CHD. The Heart and Estrogen/Progestin Replacement Study (HERS), a randomized placebo-controlled trial in postmenopausal women with established CHD, found that treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce CHD events over an average follow-up period of 4.1 years [55]. After unblinding, HERS II followed the surviving consenting subjects for an additional 2.7 years and confirmed lack of any late cardiac benefit undetected in the earlier portion of the study [56]. This study concluded that postmenopausal HRT is not indicated for secondary prevention in women with CHD. The Women’s Health Initiative (WHI), a randomized controlled trial in healthy postmenopausal women, consisted of 2 arms, estrogen plus progestin in women with an intact uterus and estrogen alone in those without [57]. The combined hormone therapy arm was discontinued prematurely after 5.2 years mean follow-up because of a trend suggesting an increase in invasive breast cancer. The initial analysis revealed excess risk not only of breast cancer but also of CHD events, stroke, and pulmonary emboli in subjects randomized to combination HRT. The estrogen alone study was recently stopped prematurely after an average follow-up of almost 7 years [58]. Estrogen alone HRT did not affect incidence of CHD or breast cancer but increased the risk of stroke.

HRT use is known to cause an increase in hs-CRP level. In order to investigate whether this apparent up-regulation of vascular inflammation in users of HRT is associated with occurrence of CHD events, a nested case-control study within the WHI observational study was performed [59]. This
study examined the relationships among HRT use, baseline levels of hs-CRP and IL-6, and occurrence of CHD events in 304 cases and 304 controls matched for age, smoking status, ethnicity, and follow-up time. Three major findings were reported. First, baseline levels of hs-CRP and its predominant inflammatory precursor, IL-6, were independently associated with twofold increases in risk of cardiac events. Second, HRT use was associated with increases in hs-CRP but not in IL-6, suggesting that the CRP elevation occurred through an IL-6-independent pathway. Third, CRP levels at baseline were independently predictive of CHD events regardless of HRT status. Thus, the actual level of CRP at baseline, not HRT use, was the primary determinant of risk.

Although the case patient has no major contraindications to HRT use (eg, abnormal bleeding, history of venous or arterial thrombosis, breast cancer or other estrogen-sensitive cancer, or liver disease), she has an intermediate-risk Framingham score, a high-risk hs-CRP value, and multiple cardiac risk factors, including hypertension and tobacco use. It is currently unknown if intermediate- or high-risk status suggested by Framingham scoring and/or CRP value is a contraindication to HRT, but it seems reasonable to consider alternative medical therapies. For example, isoflavones (ie, plant estrogens) are found in soy and red clover products and have been reported to be effective in prevention of hot flashes [60]. However, this effect has not been confirmed by randomized placebo-controlled clinical trials. Limited trials have found other agents to be effective, including black cohosh, dong quai, evening primrose oil, Chinese herbs, vitamin E, and acupuncture [60]. Finally, the prescription drugs megestrol, clonidine, and the selective serotonin reuptake inhibitors have been shown to be effective in limited trials [60].

What treatments or interventions result in reduction of elevated hs-CRP?

Reduction in hs-CRP levels occurs after weight loss, routine exercise, improved diet, and tobacco cessation [25]. Lipid-lowering therapy with statin drugs has been shown to reduce hs-CRP by 15% to 25% over a 3- to 6-month treatment phase [25]. Other lipid-lowering agents, including niacin, fibrates, and gemfibrozil, have also been reported to lower hs-CRP. The insulin-sensitizing drug class, thiazolidinediones, and angiotensin II-modulating drugs reduce hs-CRP plasma levels [25,61]. Aspirin and clopidogrel lower cardiovascular risk but do not appear to lower CRP, although this remains controversial [12]. There is no definitive evidence to date that reducing CRP will lead to reduction in cardiovascular event rates. Thus, randomized clinical trials are needed to further refine the approach to use of hs-CRP and other inflammatory biomarkers in the primary prevention of cardiovascular disease and events.

Summary

CVD is the leading cause of death in both men and women in westernized societies. Because CVD is an unpredictable and lethal disease, improved methodology for detection of early or subclinical disease is of utmost importance in the effort to reduce cardiovascular morbidity and mortality. One proposed way to detect early disease is to measure a byproduct of vascular inflammation, an early stage in the development of atherosclerosis. Recently, novel CVD biomarkers have been introduced into the clinical arena as a way to improve assessment of risk. One of these, hs-CRP, a polypeptide molecule produced in response to inflammatory cytokines released by the vascular endothelium, has shown great promise to date in prediction of cardiovascular events. However, the evidence, although compelling, was obtained through observational trials or post hoc analyses; thus, the scientific community awaits further evidence from randomized trials. For now, use of hs-CRP to enhance CVD risk assessment is a reasonable adjunct to the traditional risk factor and Framingham risk scoring approach in a primary prevention population at intermediate risk and in those whose risk assessment is felt to be underestimated on clinical grounds.

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