C-Reactive Protein as a Risk Predictor
Do Race/Ethnicity and Gender Make a Difference?
Michelle A. Albert, MD, MPH; Paul M Ridker, MD, MPH

Case presentation: M.A. is a 43-year-old female African-American airline pilot with a family history of stroke and insulin-dependent diabetes who comes to the cardiovascular clinic for a routine yearly physical required by her employer. She is asymptomatic and physically active as the mother of 2 young sons (aged 3 and 8 years). She is concerned about her risk for stroke and a heart attack because of her mother’s death from a stroke at age 55. She also has a 49-year-old brother who was recently hospitalized with heart failure. She has no significant past medical history and takes no medications. M.A. does not smoke, drink alcohol, or use illicit drugs.

On physical examination, she has a systolic blood pressure of 160 mm Hg and a diastolic blood pressure of 95 mm Hg bilaterally. Her heart rate is 86, and respirations and oxygen saturation are within normal limits. Her weight is 170 lb and height is 6 ft. The remainder of her physical examination is also within normal limits.

Testing performed included a 12-lead ECG that demonstrates sinus rhythm at 86 beats per minute and left ventricular hypertrophy and fasting lipid profile that shows a total cholesterol level of 208 mg/dL, LDL cholesterol level of 135 mg/dL, HDL cholesterol level of 52 mg/dL, and triglycerides of 142 mg/dL. Her highsensitivity C-reactive protein (hs-CRP) level is 4.5.

What advice would you give to M.A. with regard to her concerns about her risk for cardiovascular disease?

Background
Morbidity and mortality from cardiovascular disease (CVD) differ significantly on the basis of race/ethnicity and gender. In the United States, where CVD accounts for nearly 40% of all deaths,1 black men have the highest mortality rate from CVD, and Asian women have the lowest (Figure 1).2 These race/ethnicity and gender differences are likely related to differences in risk factor burden, differential clustering of risk factors, access to healthcare, and socioeconomic variables. Moreover, it is unclear whether strategies such as improved lipid screening and treatment of CVD risk factors, which are no doubt responsible for some of the recent progress in reducing CVD mortality in the United States, are effectively implemented across different ethnic groups. It is also uncertain whether all persons at high risk for CVD are adequately identified solely by results of traditional risk factor profiling. Approximately 40% of persons who develop CVD have only 1 traditional CVD risk factor, whereas almost 20% have none of these risk factors.3 The pathogenesis of atherosclerosis is understood to involve inflammation as a core element4;5; markers of vascular inflammation have shown promise for improved risk prediction. Of inflammatory markers currently available, hs-CRP has been studied the most extensively. It is thus important to understand how or if inflammation is influenced by race/ethnicity or gender status.

hs-CRP and Cardiovascular Risk
hs-CRP is the most extensively studied and validated measure of vascular inflammation to date. An acute-phase reactant consisting of 5 identical, non-covalently bonded 23-kDa subunits,6 CRP was first described by Tillett and Francis as a marker of pneumococcal infections.7 CRP is produced by the liver and by the smooth muscle cells of
coronary arteries in response to inflammatory stimuli. Long-term levels of CRP as measured by high-sensitivity assays (hs-CRP) can predict the risk of future vascular disease. Multiple prospective cohort studies have demonstrated that hs-CRP predicts future CVD risk in both men and women.

hs-CRP appears to be valuable in the clinical setting for several reasons: It can be measured with an inexpensive, standardized high-sensitivity commercial assay; it lacks seasonal and diurnal variation; and it provides additive predictive information to both the lipid profile and the Framingham Cardiovascular Risk Score (FCRS). The finding that hs-CRP is minimally associated with most of the individual components of the FCRS suggests that hs-CRP and the FCRS might be measuring different aspects of CVD risk. Guidelines proposed by the American Heart Association and the Centers for Disease Control and Prevention on the use of hs-CRP in the clinical setting recommend that physicians consider measuring hs-CRP levels in addition to lipid levels in men and women at intermediate risk for coronary heart disease (CHD) and categorize patients as at low, average, or high risk according to the following levels of hs-CRP: <1 mg/L (low risk), 1 to 3 mg/L (average risk), and >3 mg/L (high risk).

**hs-CRP and Cardiovascular Risk Prediction Among Women**

A large number of studies on hs-CRP and CVD risk prediction have been performed in cohorts comprising women. Although data from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) show that hs-CRP levels increase with age and were noted to be significantly higher among women than among men aged >15 years, hs-CRP levels are comparable among men and middle-aged women not taking hormone replacement therapy (HRT), with a median hs-CRP level between 1.5 and 2.0 mg/L for both. On average, hs-CRP levels in postmenopausal women taking conventional oral HRT are higher than among those not taking HRT. This effect appears to be present for women taking estrogen alone as well as estrogen plus progesterone, at least at standard doses (Figure 2). These data may have clinical implications with regard to conventional HRT use.
and CVD risk and support the findings of the Heart and Estrogen/progestin Replacement Study Follow-up (HERS II) and the Women’s Health Initiative, which reported significantly increased risk of CVD events among HRT users. Whether an increase in inflammatory mediators such as hs-CRP confers a heightened risk of CVD in these women is uncertain. By contrast, studies of women taking lower doses of estrogen have found little or no effect on hs-CRP levels, and women taking selective estrogen receptor modulators as an alternative to conventional oral HRT appear to experience no adverse effects on hs-CRP levels. Transvaginal estrogen use also has no impact on hs-CRP levels.

Data from apparently healthy, middle-aged, postmenopausal women participating in the Women’s Health Study show that whereas hs-CRP, serum amyloid A and interleukin-6 all significantly predict CVD risk, hs-CRP had the highest cardiovascular risk correlation and, as noted, added predictive information to the FCRS (Figure 3). Importantly, hs-CRP differentiated high- and low-risk women even among those considered to be at low risk on the basis of LDL cholesterol levels <130 mg/dL. Among these women, the relative risks of CVD increased progressively in increasing quartiles of hs-CRP (1.0, 2.4, 2.9, and 4.1; P for trend=0.005). Moreover, hs-CRP added prognostic information at all levels of LDL cholesterol even after we controlled for other traditional CVD risk factors (Figure 4).

Research from the Nurses’ Health Study also demonstrates that elevated levels of hs-CRP designate heightened risk of CHD, a relationship that withstood adjustment for the major CVD risk factors. In this cohort of apparently healthy women at baseline who developed CHD during 8 years of follow-up, hs-CRP was a better predictor of CHD than other inflammatory markers in low-risk subgroups that included women with a body mass index (BMI) <25 kg/m², LDL cholesterol <130 mg/dL, and no history of hypertension. Likewise, results from the multiethnic Atherosclerosis Risk in Communities study show that hs-CRP is associated with the development of CHD after full multivariable adjustment. Subjects with high hs-CRP levels (>3 mg/L) were noted to have a greater CHD risk (hazard ratio, 1.72; 95% CI, 1.24 to 2.39) than subjects with average hs-CRP levels (1 to 3 mg/L; hazard ratio, 1.31; 95% CI, 0.96 to 1.80). Data from the Reykjavik Study that consisted of almost 30% women also indicate a similar relationship between hs-CRP and CHD risk prediction. After adjustment for established risk factors and socioeconomic factors, the odds ratio for CHD was 1.45 (95% CI, 1.25 to 1.68) in participants in the highest tertile of hs-CRP compared with the lowest tertile; the odds ratio over the first 10 years of follow-up was 1.8, virtually identical to data in women from the United States. Research from a cohort of older men and women indicates that hs-CRP is a powerful predictor of CVD in both men and women.
adults (aged ≥65 years) also found a relationship between hs-CRP >3 mg/L and CHD risk that was of similar strength to the Reykjavik data (adjusted relative risk 1.45; 95% CI, 1.14 to 1.86; \( P = 0.004 \)). However, these older men and women with elevated hs-CRP had high event rates and an estimated population-attributable CHD risk of 11%, suggesting potential benefit of lowering hs-CRP levels. In the Rotterdam Study, which examined the value of hs-CRP in predicting CHD risk in men and women aged ≥55 years, hs-CRP failed to add information to the Framingham risk algorithm. The 2-fold increase in risk of myocardial infarction for participants in the highest quartile of hs-CRP compared with those in the lowest quartile (odds ratio, 2.0; 95% CI, 1.1 to 3.4) largely disappeared after adjustment for traditional risk factors (odds ratio, 1.2; 95% CI, 0.6 to 2.2). However, this latter finding might reflect the variable nature of risk factor distribution, sample size, and relative importance of different risk factors in different populations.

### hs-CRP and Race/Ethnicity

In contrast to data on women, information about the relationship between race/ethnicity and hs-CRP is scarce. Because hs-CRP predicts CVD risk, and CVD morbidity and mortality vary widely by self-described race/ethnicity in the United States and Europe, it is possible that differences in levels of inflammation among racial/ethnic groups might influence outcome. Research from the 1999–2000 NHANES show that black and Mexican women and children have higher CRP levels than white women and children. However, after taking into account potential confounders of the relationship between hs-CRP and race/ethnicity, NHANES found no significant difference between the hs-CRP levels of white and black women.

Women’s Health Study data reveal that blacks have higher hs-CRP levels than their white, Hispanic, and Asian counterparts (Figure 5). Whereas black women had the highest hs-CRP levels, Asian women had the lowest. Specifically, median hs-CRP levels for black women were 2.96 mg/L (interquartile range [IQR], 1.19 to 5.86) compared with 2.06 mg/L (IQR, 0.88 to 4.88) for Hispanic women, 2.02 mg/L (IQR, 0.81 to 4.37) for white women, and 1.12 mg/L (IQR, 0.48 to 2.25) for Asian women. hs-CRP levels were influenced by BMI, a finding consistent with the role of adipose tissue in the production of interleukin-6, an upstream progenitor of hs-CRP. Importantly, this observed difference in hs-CRP levels by racial/ethnic group was not entirely explained by traditional CVD risk factors, suggesting that environmental or genetic influences may also be operative.

Significant race/ethnic differences in the distribution of hs-CRP levels were also found in the multiethnic, population-based Dallas Heart Study. Median hs-CRP levels were 30% higher in blacks than in whites (me-
In contrast to previous data, hs-CRP levels were nearly twice as high in women as in men (median, 3.3 versus 1.8 mg/L; P<0.001) and higher in black women than in black men. In this unselected urban cohort, these hs-CRP differences remained despite exclusion of those participants taking statin or HRT therapy and adjustment for CVD risk factors such as BMI. After sample-weight adjustment, the proportion of participants with high hs-CRP levels (≥3 mg/L) was 30.9% of white men, 39.7% of black men, 51.2% of white women, and 57.5% of black women (P<0.05 for each of the last 3 groups versus white men).

South Asians living in Great Britain have a higher vascular disease burden than whites and are reported in some studies to have higher hs-CRP levels than European whites. Among South Asian women, because hs-CRP was strongly associated with central obesity even after adjustment for BMI and percent body fat, elevated hs-CRP levels likely reflect the higher prevalence of the metabolic syndrome. Additional data from Canada also show that South Asians and Aboriginals have significantly higher hs-CRP levels than do persons of European or Chinese ancestry. After adjustment for sex and age, mean CRP levels were 3.74 mg/L for Aboriginals and 2.59 mg/L for South Asians compared with 2.06 mg/L among Europeans and 1.18 mg/L among Chinese (overall, P<0.0001). These differences in hs-CRP correlated closely with the metabolic syndrome and were independently associated with CVD prevalence such that every 10% increase in hs-CRP was associated with a 3% odds increase of CVD.

Other data demonstrate that Japanese tend to have lower hs-CRP levels than US and European populations. In a study of >6000 Japanese men and women, mean hs-CRP levels were 0.83 and 0.59 mg/L, respectively, even after BMI was taken into account. Notably, <30% of the Japanese population is classified as overweight/obese. To further evaluate the relationship between body size and hs-CRP among healthy Japanese, Saijo and colleagues demonstrated that hs-CRP was associated more tightly with measures of visceral obesity such as waist circumference and waist-to-hip ratio than with BMI. More data are needed on the relationship between race/ethnicity and hs-CRP and on investigations seeking whether variation in levels of hs-CRP correlate with observed differences in cardiovascular risk.

### Race/Ethnicity, Gender, and Modification of hs-CRP Levels

To be an effective marker of risk, it is not necessary to fulfill Koch’s postulates; it is only important to demonstrate that the biomarker of interest consistently predicts risk in different patient populations. In this regard, whether lowering hs-CRP per se will reduce cardiovascular risk remains unknown and is a question undergoing intense investigation. Clinically, reductions in hs-CRP can be achieved through both behavioral and medical approaches. Risk factor modification techniques such as increased physical activity, moderate alcohol intake, weight loss, and smoking cessation all lower hs-CRP. Of the pharmacological agents, the ability of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to reduce CRP levels has been studied extensively and is a class effect. Data related to statin therapy and hs-CRP exist for both men and women. In a post hoc analysis of the Cholesterol and Recurrent Events (CARE) trial, hs-CRP levels decreased with pravastatin therapy compared with placebo (−21.6%; P=0.007) at 5 years of follow-up among patients with a history of myocardial infarction. Importantly, the magnitude of change in hs-CRP levels was unrelated to any change in lipid levels.

The Pravastatin Inflammation/CRP Evaluation (PRINCE) trial was designed to prospectively examine the effect of pravastatin compared with placebo on hs-CRP levels in persons with and without a history of CVD. hs-CRP levels were decreased by 16.9% after 6 months of pravastatin therapy, whereas almost no change occurred in the placebo group (P<0.001). This result was replicated among all subgroups regardless of age, gender, smoking status, presence or absence of diabetes mellitus, lipid parameters, BMI, or medication use. Similar to CARE, there was a minimal relationship between changes in LDL cholesterol and hs-CRP, implying that the antiinflammatory effects of statin therapy may be independent of lipid lowering.

Further data from the primary prevention Air Force/Texas Coronary Atherosclerosis Prevention Study of 5742 men and women demonstrated a significant 14.8% reduction in hs-CRP with lovastatin therapy (P<0.001). Moreover, lovastatin was beneficial in preventing future cardiovascular events among individuals with below median lipid levels who had above median levels of hs-CRP. These data suggest that hs-CRP might be useful in conjunction with lipid screening as a method to identify potentially high-risk individuals with average lipid levels who might nonetheless benefit from statin therapy. Data related to hs-CRP modification in race/ethnic US minorities are limited. The Comparison of Efficacy and Safety of Rosuvastatin versus Atorvastatin in African-American Patients (ARIES) study showed that among 708 black hypercholesterolemic participants (>60% of whom were women) treated with rosuvastatin or atorvastatin, statistically significant decreases in hs-CRP were noted in both drug treatment groups at 6 weeks of follow-up. Notably, >66% of the population had at least moderate (>2.0 mg/L) hs-CRP levels at baseline consistent with the observed trend of higher hs-CRP levels among blacks. Furthermore, as statistically expected, hs-CRP reductions were larger in this group than in those with lower baseline levels of hs-CRP. Data on the effect of statin therapy on
hs-CRP concentrations remain scant for Hispanic Americans.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial evaluated the effects of lipid lowering with atorvastatin 80 mg/d versus pravastatin 40 mg/d on recurrent risk of myocardial infarction or death from coronary causes in patients with acute coronary syndromes.47 Twenty-two percent of the participants were women. Both statins lowered levels of LDL cholesterol and hs-CRP, but participants who achieved levels of LDL cholesterol <70 mg/dL and hs-CRP <2 mg/L had the greatest benefit over 2.5 years of follow-up (age-adjusted event rates per 100 person-years: LDL cholesterol ≥70 mg/dL, hs-CRP ≥2 mg/L=4.6; LDL cholesterol <70 mg/dL, hs-CRP ≥2 mg/L=3.1; LDL cholesterol ≥70 mg/dL, hs-CRP <2 mg/L=3.2; LDL cholesterol <70 mg/dL, hs-CRP <2 mg/L=2.4). Cumulative rates of recurrent myocardial infarction and coronary death for the PROVE IT–TIMI 22 trial according to achieved levels of LDL cholesterol and hs-CRP are shown in Figure 6.47 Similar to the minimal correlation between changes in LDL cholesterol and hs-CRP observed in PRINCE, <3% of the variation in achieved hs-CRP levels in PROVE IT could be accounted for by the variation in achieved LDL cholesterol levels.

Data from the Reversal of Atherosclerosis with Aggressive Lipid-Lowering (REVERSAL) trial corroborate the PROVE IT–TIMI 22 results. In REVERSAL, intravascular ultrasound demonstrated that decreases in both LDL cholesterol and hs-CRP that were greater than the median were associated with significantly slower rates of atherosclerosis progression than were decreases in both parameters that were less than the median.48 Approximately 18% of the participants were women, and 11% were nonwhite.

It is not known whether lowering hs-CRP levels in persons with no prior history of CVD will result in a reduction in cardiovascular risk. One ongoing study seeking to evaluate this question is the Justification for the Use of Statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). Begun in 2003, JUPITER is a prospective, randomized, international trial that will examine the effect of rosuvastatin 20 mg/d or placebo in preventing first major cardiovascular events in 15,000 apparently healthy men and women with low LDL cholesterol (<130 mg/dL) who are considered to be at high cardiovascular risk because of elevated levels of hs-CRP (≥2 mg/L).49

Case Follow-Up

M.A.’s family history of premature CVD places her at heightened risk for cardiovascular events. Her family and personal history are disturbing and consistent with the higher prevalence of hypertension, stroke, and heart failure among blacks compared with other race/ethnic groups in the United States with death rates that average ≈30% higher for CVD. The average life expectancy, based on 2002 US Department of Health and Human Services data, of a black woman is 75.6 years (all races, 77.3 years; male, 74.5 years; female, 79.9 years; white female, 80.3 years; and white male, 75.1 years). M.A.’s calculated 10-year Framingham Cardiovascular Risk (developed in a primarily white population) is estimated to be low at 1%.50 Although risk prediction data by race/ethnicity related to hs-CRP levels are lacking, it is probably reasonable to note that on the basis of her family history of premature CVD and elevated hs-CRP level, her 10-year risk of CVD is more likely to be intermediate and, most importantly, both her age-related relative and lifetime risks of CVD are high.51 She should therefore be counseled about appropriate diet and exercise therapy in real time. Antihypertensive therapy should also be initiated because of the evidence of stage II hypertension and “possible” end-organ effects as evidenced by left ventricular hypertrophy on her ECG. Indeed, it is likely that she might need >1 blood pressure–lowering agent to control her hypertension. Additionally, consideration should be given to the initiation of low-dose aspirin and statin therapy if behavioral interventions do not result in appropriate reductions in her LDL cholesterol level.
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