C-Reactive Protein and the Prediction of Cardiovascular Events Among Those at Intermediate Risk
Moving an Inflammatory Hypothesis Toward Consensus

Paul M Ridker, MD, MPH, FACC
Boston, Massachusetts

Over 20 large-scale prospective studies show that the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) is an independent predictor of future cardiovascular events that additionally predicts risk of incident hypertension and diabetes. In many studies, the relative impact of hsCRP is at least as large as that individually of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure, or smoking, and knowledge of hsCRP correctly reclassifies a substantial proportion of “intermediate-risk” individuals into clinically relevant higher- or lower-risk categories. Other studies show the relative benefit of statins to be greater among those with increased hsCRP and that achieved hsCRP levels after statin therapy predict recurrent event rates as much as achieved levels of low-density lipoprotein cholesterol. Nonetheless, it remains controversial whether the time has come to modify traditional algorithms used for global risk detection. As described here, 6 areas of controversy regarding hsCRP are resolvable with a consensus position that focuses in primary prevention on selective use among individuals with 5% to 20% 10-year risk as estimated by Adult Treatment Panel III, and focuses in secondary prevention on high-risk patients being treated with statin therapy. Forthcoming trial data could expand or contract this “screen selectively” policy, and investigators should be open to the possibility that second-generation inflammatory biomarkers may be developed that supplant hsCRP altogether. In the meantime, however, this consensus position on hsCRP should be one to which both advocates and critics of the inflammatory hypothesis of atherosclerosis can adhere because it is one that can immediately improve patient care.

Exactly 10 years ago it was reported that the inflammatory biomarker C-reactive protein, when measured in blood with a high-sensitivity assay (hsCRP), is a strong, independent predictor of future myocardial infarction and stroke among apparently healthy asymptomatic men, and that the magnitude of this effect was similar to that of cholesterol and blood pressure (1,2). That work showed that inflammation, as reflected in the concentration of hsCRP, preceded the onset of cardiovascular events rather than being a result of ischemia or smoking as previously assumed (3–6), and thus provided evidence confirming the hypothesis that atherothrombosis was, in part, an inflammatory disorder (7–9).

Since that report from the Physicians Health Study in 1997, the ability of hsCRP to predict myocardial infarction, ischemic stroke, and vascular death has been confirmed in more than 20 diverse population cohorts including the Women’s Health Study (10–12), a general population cohort from Britain (13), the WHI (Women’s Health Initiative)-observational cohort (14), the Honolulu Heart Study (15), the NHS (Nurses Health Study) (16), the HPFUS (Health Professionals Follow-Up Study) (16), the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease)-Augsberg cohort (17,18), the ARIC (Atherosclerosis Risk in Communities) study (19), the CHS (Cardiovascular Health Study) (20), the SHS (Strong Heart Study) (21), the Kuopio Ischemic Heart Disease Risk Factor Study (22), and the EPIC (Evaluation for Prevention of Ischemic Complications)-Norfolk cohort (23). Further work has shown elevated hsCRP to modify risk associated with metabolic syndrome (24–26) and to predict incident type 2 diabetes (27–29) as well as hypertension (30,31). In 2002, on the basis of data from 27,939 initially healthy women followed up over a decade, plasma levels of hsCRP <1 mg/l, 1 to 3 mg/l, and >3 mg/l were established as
representing lower, average, or higher relative vascular risk when added to traditional risk factors (12). After a comprehensive assay standardization program was completed by the Centers for Disease Control and Prevention, a panel of prevention experts presented in 2003 the first guidelines for use of commercial hsCRP tests as an adjunct to global risk prediction (32).

More recently, the addition of hsCRP to traditional risk factors has been shown to reclassify up to 30% of individuals at “intermediate risk” into clinically relevant higher- or lower-risk categories, and that the relative impact of hsCRP on prediction is at least as large as that individually of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, or smoking (33). In fact, as shown in the recently published Reynolds Risk Score (34), 2 key biomarkers, hsCRP (reflecting inflammation) and family history (reflecting genetic predisposition), not only reclassify nearly 50% of all women with Adult Treatment Panel III (ATP-III) estimated 5% to 10% and 10% to 20% 10-year risk into higher- or lower-risk categories, but do so with markedly improved accuracy (35). Other data show that hsCRP is effective at predicting incident peripheral arterial disease in the general population (36,37) as well as vascular complications among diabetic patients (38,39), those undergoing hemodialysis and peritoneal dialysis (40–42), and those undergoing bypass surgery or percutaneous coronary angioplasty (43,44). Many additional studies confirm the utility of hsCRP for prediction of ischemic stroke, a condition in which lipid levels are less effective (15,45–48). Because hsCRP has been implicated in progression of carotid and cortical small vessel disease (49,50), these observations suggest an even larger role for inflammation in the cerebral vasculature. Finally, hsCRP levels track with abdominal obesity, insulin resistance, and the number of components of the metabolic syndrome that are present. Yet, despite this concordance, multiple studies show that individuals formally qualifying for metabolic syndrome by current criteria who have hsCRP >3 mg/l are at higher risk for future cardiovascular events and diabetes compared with those with metabolic syndrome who have hsCRP <1 mg/l, a risk relationship almost identical to that for hsCRP among individuals without metabolic syndrome (24–26).

Based on this consistent body of evidence, many physicians measure hsCRP as an adjunct to global cardiovascular risk prediction, and an intensive search has been initiated for targeted vascular anti-inflammatory agents that might have efficacy in the treatment and prevention of coronary disease. However, there is ongoing debate regarding whether or not the time has come to modify traditional algorithms used for the global detection of vascular risk (51). Over the past decade, 6 areas of controversy have framed much of this debate. As will be described, these controversies are largely resolvable such that a consensus position on hsCRP can be reached that both advocates and critics of the inflammation hypothesis can adhere to and will ultimately improve patient care.

### Resolving the Framingham Heart Study and Reykjavik Heart Study Controversies

Figure 1 shows the predictive value in 14 apparently healthy populations with baseline hsCRP levels of <1 mg/l, 1 to 3 mg/l, and >3 mg/l after adjustment for traditional risk factors. All show similar efficacy with no evidence of heterogeneity. Nonetheless, reports from 2 of these cohorts generated controversy because they did not seem to affirm these data, at least as initially published. Of these, the Framingham Heart Study data are the most important because they represent a cohort that is the basis for most global risk prediction models.

Three presentations from the Framingham investigators are highlighted here. In the first, Rost et al. (46) published Framingham data in which risk of stroke or transient ischemic attack for men and women with baseline CRP levels in the top quartile were 2.0 and 2.7 times higher, respectively, when compared with those in the lowest quartile, effects that remained significant for both genders after adjustment for smoking, total:HDL cholesterol, systolic blood pressure, and diabetes. This article was followed in 2005 by a second Framingham manuscript that again found CRP to be an important predictor of cardiovascular risk in age- and gender-adjusted models, but was interpreted less optimistically because these effects were attenuated and no longer significant after full multivariate adjustment (52). Although often cited as a null paper, that analysis unfortunately was performed with a non–high-sensitivity assay for CRP, and thus a true test of the inflammation hypothesis in Framingham required repeat testing with an appropriate hsCRP assay. That re-analysis was presented as an abstract at the November 2006 meeting of the American Heart Association. As reported, the age- and gender-adjusted relative risks in Framingham for hard cardiovascular events among individuals with baseline blood levels of hsCRP <1 mg/l, 1 to 3 mg/l, and >3 mg/l were 1.0 (referent), 1.5, and 2.9, highly significant observations entirely consistent with earlier work. Moreover, this re-analysis showed that the fully adjusted relative risks among those with increasing levels of hsCRP were 1.0 (referent), 1.2, and 1.7, again a highly significant finding (53). Thus, had an appropriate high-sensitivity assay been used originally, there would never have been any controversy between data from the Framingham Heart Study and data presented by earlier investigators.

A second cohort that generated controversy at the time of its publication was the Reykjavik Heart Study (54). This
Icelandic cohort began in 1967 in a population with high lipid levels and thus is a comparison of hsCRP with usual risk factors in an era that preceded effective public health recommendations to reduce fat intake. The investigators of the Reykjavik Heart Study did not report outcomes by hsCRP levels of <1 mg/l, 1 to 3 mg/l, and >3 mg/l, but did report multivariate adjusted evidence showing that individuals with hsCRP in the highest tertile were significantly more likely to suffer future vascular events when compared with those in the lowest tertile (relative odds 1.5, 95% confidence interval [CI] 1.3 to 1.7). Despite this statistically significant result, the Reykjavik report concluded that hsCRP was not clinically meaningful as this effect was “modest” in magnitude. However, in the same report, the multivariate adjusted odds ratio for systolic blood pressure was also 1.5 (95% CI 1.3 to 1.7). Further, for those with hsCRP in the top fifth of the distribution (a level that should correlate closely with hsCRP >3 mg/l), the multivariate adjusted odds ratio for hsCRP was 1.7 with 95% CIs completely overlapping the risk associated with smoking (1.4 to 2.0). Thus, the impact of hsCRP in the Reykjavik data is in fact identical in magnitude to the impact of hypertension and smoking in that population.

Subsequent to the Reykjavik data, 2 other European cohorts presented prospective data on hsCRP in populations with more contemporary lipid levels, and both reported affirmative data. In the EPIC-Norfolk prospective population (23), the fully adjusted odds ratio for future vascular events among those with baseline hsCRP levels >3 mg/l was 1.8 (95% CI 1.4 to 2.3), whereas the Kuopio Ischemic Heart Disease Risk Factor Study of vascular mortality reported a fully adjusted odds ratio of 2.9 (95% CI 1.5 to 5.9) (22). Both of these contemporary European cohorts found the impact of hsCRP to be at least as large as that of most usual risk factors, data fully consistent with other reports (55).

Resolving the C-Statistic Controversy

Despite the data in Figure 1, the impact of adding hsCRP to model fit as measured by area under the receiver-operator characteristic (ROC) curve (and summarized by the C-statistic) is small, an observation that has led some to conclude that hsCRP (and potentially other novel risk factors for that matter) has little role in vascular disease prediction (56–58). However, a careful analysis of the C-statistic and its role in prediction modeling suggests that this is an incorrect conclusion and that the use of the C-statistic as a method of selecting variables for risk prediction models may be ill advised (59).

The C-statistic is a technique designed to discriminate between cases and noncases in the setting of diagnostic testing where disease already exists and where sensitivity and specificity are of clinical importance. The C-statistic,
however, is a far less effective tool for selecting prediction variables when faced with a healthy population in which the task is to identify future disease where none currently exists. As Cook (59) has recently shown, this technique can lead to erroneous conclusions when applied to risk prediction in prospective cohort data, particularly those involving healthy individuals at risk for common disorders such as myocardial infarction or stroke.

By way of example, for an individual risk factor to provide adequate discrimination on its own as judged by the C-statistic, it must have a hazard ratio of 16.0 or greater (60). This fact, however, should not be construed to imply that biomarkers with smaller hazard ratios are without clinical utility. For example, a biomarker with an adjusted hazard ratio of 3.0 may be incapable of moving the C-statistic, yet that same biomarker could in theory increase a specific individual’s estimated 10-year risk from 8% to 24%, a reclassification of risk with major implications for treatment decisions. Moreover, other than age, no component of the Framingham risk score has an adjusted hazard ratio >3.0 (most, in fact, are between 1.6 and 2.0). As such, proponents of the C-statistic as the sole basis for selecting risk factors would, by necessity, also eliminate lipids, blood pressure, and perhaps even smoking from consideration as clinically important. This paradox is particularly true for cholesterol, the core basis for pharmacologic interventions proven to lower cardiovascular risk; were the same criteria applied to total, LDL, and HDL cholesterol that are now being applied to hsCRP, each of these would have erroneously been eliminated as a risk factor for heart disease.

A more tenable position would be to acknowledge that the C-statistic is an insensitive tool for selecting variables to be included in risk prediction models based on prospective cohort data of currently healthy individuals. Statisticians have suggested that additional methods can be used to evaluate model fit in this setting, including global measures such as the Bayes Information Criteria, Brier score, Yates slope, and entropy (59,61). They also have emphasized that more attention should be paid in this setting to calibration and to reclassification (59,62–64).

Using these techniques, large and clinically important differences between prediction models with and without hsCRP have been found, despite minimal effects on the C-statistic (33,35,53). This turns out to be of greatest importance for reclassifying individuals at intermediate global risk using ATP-III criteria. For example, as shown in Figure 2, for a representative population of 100,000 U.S. women without diabetes (80,000 at 5% to 10% 10-year risk and 20,000 at 10% to 20% 10-year risk by ATP-III), additional knowledge of hsCRP and family history would place 13,500 of these women at low risk, 48,500 at low to moderate risk, 32,500 at moderate to high risk, and 5,400 at high risk. Moreover, in a direct comparison of estimated to actual event rates, this reclassification of risk has been shown to be correct for well over 95% of those reclassified, despite only marginal effects on the C-statistic (35).

**Figure 2** Risk Reclassification Using hsCRP and Parental History

Impact of high-sensitivity C-reactive protein (hsCRP) (representing inflammation) and family history (representing genetics) on estimates of global cardiovascular risk for a representative population of 100,000 U.S. women at 5% to 10% and 10% to 20% 10-year risk according to the Adult Treatment Panel III (ATP-III). Data adapted from references 34 and 35. BP = blood pressure; CVD = cardiovascular disease; HDLC = high-density lipoprotein cholesterol; TC = total cholesterol.
Resolving the Statin Controversy

In collaboration with the CARE (Cholesterol And Recurrent Events) Investigators, it was reported in 1998 that post-MI patients with elevated hsCRP levels had a greater relative clinical benefit from statin therapy in secondary prevention when compared with those with lower hsCRP levels (65). Soon thereafter, it was reported that statins reduce plasma levels of hsCRP in a manner largely independent of LDL reduction (66–68). Further, in collaboration with the AFCAPS/TexCAPs (Air Force/Texas Coronary Atherosclerosis Prevention Study) Investigators, the observation was made in primary prevention that individuals with elevated levels of hsCRP seemed to benefit from statin therapy even when LDL cholesterol levels were not elevated (69).

Although initially controversial, the observation that statins lower hsCRP has been confirmed by multiple investigators (70–74) and provides clinical support for the hypothesis that in addition to lowering LDL cholesterol, statins might also have clinically relevant anti-inflammatory effects (75,76). On this basis, many physicians use hsCRP as a “tie-breaker” method to decide on statin use among patient groups in which lipid-lowering therapy is considered optional by current ATP-III guidelines. In primary prevention, such patients typically include those with LDL cholesterol between 130 and 160 mg/dl who also have 10% to 20% 10-year risks and are not diabetic. The use of hsCRP for this purpose seems to provide a method of better targeting statins to the most appropriate higher-risk individuals, an effect that would both maximize benefit and minimize risk.

A second statin controversy was raised when investigators in the PROVE-IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22) trial presented a prespecified analysis addressing whether best clinical outcomes were obtained among acute coronary syndrome patients treated with statins who had LDL cholesterol reduced below 70 mg/dl or who had hsCRP levels reduced below 2 mg/l, the approximate median values for both variables after 30 days of therapy (77). In that analysis of 3,745 patients, rates of recurrent myocardial infarction or cardiovascular death were lowest when both of these target goals was achieved (Fig. 3, left). However, when only the LDL cholesterol <70 mg/dl target or only the hsCRP <2 mg/l target was achieved, risk reductions were less impressive (and the worst outcomes were observed when neither target was attained). These effects were independent of other determinants of outcome including age, gender, smoking, diabetes, hypertension, obesity, HDL cholesterol, peak creatine kinase leak, Killip class, use of early revascularization, and left ventricular ejection fraction. On this basis, it was hypothesized that among very-high-risk patients undergoing statin therapy, the dual goals of LDL and hsCRP reduction should be considered a new clinical target for therapy (78). In a follow-up analysis of PROVE-IT–TIMI-22, achieving low levels of hsCRP after initiation of statin therapy was further found to be associated with reduced risks of stroke (79).
As with any controversial hypothesis, these data required independent confirmation. Recently, the A to Z (Aggrastat to Zocor) Investigators also found that achieving the dual goal of LDL cholesterol <70 mg/dl and hsCRP <2 mg/l was associated with the best clinical outcomes among 3,813 acute coronary syndrome patients initiating statin therapy (80); as shown in Figure 3 (right), this effect in the A to Z trial was virtually identical to that found in PROVE-IT–TIMI-22. Moreover, in an analysis of the REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering Therapy) trial that used intravascular ultrasound to measure disease progression over 18 months of statin therapy, individuals who achieved below median levels of both LDL and hsCRP achieved the greatest coronary atheroma regression (81). This surrogate biomarker data supports hard end point data from PROVE-IT–TIMI-22 and A to Z, as well as data showing that those in whom both LDL cholesterol and hsCRP are reduced on statin therapy are also those with the least progression of carotid intimal medial thickness (82). These confirmations show that initial observations regarding statins and hsCRP are reproducible and consistent (83). Not all LDL-lowering therapies reduce hsCRP. For example, ezetimibe given as monotherapy has no impact on hsCRP, although when given concomitantly with a statin it seems to augment CRP reduction.

For primary prevention patients with LDL cholesterol below 130 mg/dl who are at increased risk on the basis of elevated hsCRP, it remains unproven whether statin therapy will effectively reduce vascular event rates. To address this issue, the multinational JUPITER (Justification for the Use of statins in Primary prevention: an International Trial Evaluating Rosuvastatin) trial was launched in 2003 comparing rosuvastatin with placebo among 17,800 primary prevention patients with LDL cholesterol <130 mg/dl who also have hsCRP >2 mg/l (84). This trial has completed enrollment and is designed to complete at approximately 500 end points have accrued.

Resolving the Biological Variation Controversy

Plasma levels of hsCRP acutely increase during stress, whether ischemic or because of major trauma or infection. This biological variance has led some critics to suggest that hsCRP measurement cannot be an effective clinical tool. Below is a summary of evidence addressing this concern.

First, marked variation in hsCRP levels would have imposed a major bias toward the null hypothesis in all of the aforementioned early epidemiologic studies in which only a single baseline hsCRP measure was obtained. As such, the observed relative risks consistently seen in these studies will, if anything, be underestimates of the true relative risk associated with inflammation in the vascular disease process. Moreover, as suggested in the 2003 American College of Cardiology/American Heart Association guidelines for inflammatory biomarker use (32), evaluating hsCRP on 2 occasions separated by a few weeks (as is also recommended for lipids) greatly reduces any such variation in usual clinical practice.

Second, hsCRP levels are stable over long periods of time. In the CARE trial, the age-adjusted correlation coefficient for hsCRP measured at baseline and after 5 years of follow-up among individuals allocated to placebo was 0.60, a level of correlation greater than that of total cholesterol, LDL cholesterol, or triglycerides (66). Similarly, for 2,834 participants in the AFCAPS/TexCAPs trial treated with placebo, there was no difference between median hsCRP levels at baseline and after 1 year of follow-up (69). Finally, among 379 participants in the Reykjavik Heart Study who provided paired samples over a decade apart, the within-person correlation coefficient for hsCRP was 0.59, identical to that of total cholesterol (0.60) (54). In all of these studies, the reported correlation coefficients for repeated hsCRP levels were similar to if not superior to that of repeated blood pressure measurements, another risk marker commonly used in global prediction models.

Despite this consistency of hsCRP levels over time, the potential for biologic variation has led to misunderstanding regarding the predictive value of chronically high levels of hsCRP. Published data indicate that individuals with very high levels of hsCRP (ranging between 10 and 60 mg/l on a chronic basis) are in fact at markedly high risk for future vascular events, and that the impact of hsCRP on risk is linear across a full range of hsCRP levels in a manner analogous to that of LDL cholesterol (85). Thus, although it is appropriate to repeat hsCRP testing for values in excess of 5 mg/l (and to use the lower of the 2 measurements for clinical decision making), individuals with substantially increased levels on a chronic basis should not be considered false-positive because they are at high risk for future cardiovascular events.

Resolving the “Marker or Mechanism” Controversy

Controversy exists regarding whether CRP is only a clinically useful determinant of disease, or whether it also may play a causal role in the atherothrombotic process (86,87). Those who have proposed a causal role for CRP note that CRP promotes endothelial cell activation and dysfunction, has substantive effects on vascular smooth muscle cells and neointimal formation, and directly affects monocyte and macrophage activity as well as matrix metalloproteinase function (88–93). Further, human CRP infusion studies show both proinflammatory and prothrombotic effects (94), whereas in transgenic mouse models, CRP seems to increase thrombosis rates after vascular injury (95). From a genetic perspective, CHS investigators have found that specific polymorphisms in the CRP gene associate with plasma levels of CRP and predict future events, data suggesting a potentially causal link between CRP and atherothrombosis.
The CRP also may block the effect of leptin on satiety and weight gain, suggesting a novel mechanism for leptin resistance (97). Some of these findings are controversial, however, and those who argue that CRP is not a causal determinant of atherosclerosis correctly note that no data directly showing that CRP reduction reduces vascular risk are yet available. Further, because the liver is a major source of CRP production and because CRP levels will increase with secretion of cytokines such as interleukin-6 from several tissues including adipocytes, CRP may only be a secondary messenger of the inflammatory process.

The “marker versus mechanism” debate remains open and is an area with a need for more research. Most importantly, there is a need to develop novel CRP inhibitors that can be used to test directly whether CRP reduction results in reduced event rates. One such agent has been described and, at least in animal models, has shown promise (98).

That being said, it is not necessary for any particular biomarker to fulfill the Koch postulates before being useful in a clinical setting. Even if CRP proves not to be causally related to atherosclerosis, it could remain a highly effective adjunctive method for the detection of cardiovascular risk, particularly when LDL cholesterol levels are normal or low. By way of example, physicians routinely measure HDL cholesterol to assist in risk detection despite a lack of evidence that increasing HDL improves clinical outcomes. Debate concerning mechanistic properties of CRP should have little bearing on its utility as a clinically effective biomarker for risk detection.

Moving Toward a Consensus: Resolving the “Screen Everyone” Versus “Screen Those at Intermediate Risk” Controversy

Half of all heart attacks and strokes in the U.S. occur among those without hyperlipidemia, and between 15% and 20% occur among individuals who additionally do not smoke or suffer from hypertension or diabetes (99). These data, along with the observation that higher levels of hsCRP predict vascular risk even when lipid levels are low, have led to an additional controversy in the hsCRP literature that relates to the selection of whom to screen. In essence, that controversy can be summarized as “screen everyone” versus “screen selectively” focusing on those at intermediate global risk.

Those who advocate a “screen everyone” position note that because current guidelines suggest screening all individuals for total cholesterol and HDL cholesterol as well as blood pressure, the same should hold for hsCRP because the magnitude of risk is similar and equally independent. Further, the finding of an isolated but persistently marked elevation of hsCRP should raise clinical concern regarding vascular risk in a manner analogous to that of isolated hyperlipidemia or hypertension. A “screen everyone” approach may also be cost-effective because the test itself is far less expensive than a return physician visit to review initial lipid findings (100). From a patient perspective, this approach would eliminate the need for a second phlebotomy (and third physician contact) before risk level is computed. Because risk assessment should ultimately occur in the primary care physician’s office, these issues have spurred interest in on-site finger stick evaluation for hsCRP analogous to that currently available for total cholesterol and HDL cholesterol.

A more conservative view that I favor is a “screen selectively” policy for hsCRP that focuses on primary prevention for those at 5% to 20% 10-year risk as estimated by ATP-III risk factors, and focuses on secondary prevention for high-risk patients being treated with statins when achievement of low hsCRP levels along with low levels of LDL cholesterol portend best outcomes. Each of these positions has the advantage of being fully evidence based, and they are modest extensions of the intermediate-risk and high-risk recommendations made in 2003 by the American Heart Association/Centers for Disease Control and Prevention panel at a time when far less data were available (32). Forthcoming data such as that from the JUPITER trial could expand or contract a “screen selectively” policy. Investigators should also be open to the possibility that second-generation inflammatory biomarkers may be developed that supplant hsCRP altogether.

Clear policy statements endorsing selective hsCRP use among these intermediate-risk and high-risk groups would contribute to consensus building in the epidemiology and clinical community, as critics of the “screen everyone” approach have agreed that selective screening of intermediate-risk individuals is an evidence-based position (101). After all, if the primary purpose of risk prediction is to better inform our patients about their respective needs for dietary discretion, smoking cessation, exercise, and appropriate pharmacologic intervention, a more accurate scoring system should not be objectionable as long as it is inexpensive and leaves the locus of control in the hands of the primary care physician. Because those with 5% to 20% 10-year risk by current ATP-III algorithms represent the group in which clinical decision making is most complex, both patients and primary care providers stand to benefit from such a middle-ground position at this time.

Reprint requests and correspondence: Dr. Paul M Ridker, Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, 900 Commonwealth Avenue East, Boston, Massachusetts 02215. E-mail: pridker@partners.org.

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