CASE DESCRIPTION

A 72-year-old white woman underwent a routine annual physical examination. She had no history of diabetes, cardiovascular disease, cancer, or chronic inflammatory condition. She smoked, had hypertension (systolic blood pressure 145 mm Hg), and was being treated with an angiotensin-converting–enzyme inhibitor. She was on no other medications. Physical examination was unremarkable. She was thin with a body mass index of 23 kg/m².

Screening laboratory evaluation included total cholesterol [5.59 mmol/L (216 mg/dL)], LDL cholesterol (LDL-C)² [2.69 mmol/L (104 mg/dL)], and HDL-C [2.12 mmol/L (82 mg/dL)]. Her primary care physician considered her lipid concentrations “optimal,” and the patient’s calculated Framingham 10-year risk for cardiovascular disease was 7% or low risk, despite her age and smoking history. However, the patient had a family history that included myocardial infarction in her father at age 58 years as well as bypass surgery in a brother at age 62 years. Her high-sensitivity C-reactive protein (hsCRP) was increased at 7.7 mg/L (repeat value 2 weeks later 7.4 mg/L). With these data, the patient’s calculated 10-year risk according to the Reynolds Risk Score was 23.2%, or very high risk.

Preventive therapy recommendations for this patient were based on Framingham guidelines, so no pharmacologic intervention was provided. Four months later the patient was admitted with acute myocardial infarction and substantial loss of ventricular function. Coronary angiography revealed stenoses in the left anterior descending and circumflex arteries. She was treated with drug-eluting stents and prescribed simvastatin 40 mg, aspirin, and Plavix; 30 days after lipid-lowering therapy was initiated, LDL-C was 2.02 mmol/L (78 mg/dL) and hsCRP was 4.8 mg/L.

Both the patient and her physician wondered why myocardial infarction occurred despite excellent lipid concentrations, and both sought information regarding whether the patient’s achieved LDL-C and hsCRP concentrations were adequate for long-term care.

DISCUSSION

LIMITATIONS OF TRADITIONAL RISK-PREDICTION ALGORITHMS

Epidemiologic investigators in Framingham, MA, have defined age, hypertension, smoking, diabetes, and hyperlipidemia as the major coronary risk factors. Over time, these risk markers were codified into global risk prediction scores, which are often used by primary care physicians to assess cardiovascular risk. Largely on the basis of these risk algorithms, treatment guidelines for prevention of myocardial infarction, stroke, and cardiovascular death recommend statin therapy for patients with established vascular disease, diabetes, and overt hyperlipidemia. This approach is insufficient, however, because half of all myocardial infarction and stroke events occur among apparently healthy men and women with average or even low concentrations of cholesterol, and 20% occur in the absence of any major risk factor. As demonstrated in this case, myocardial infarction often occurs among apparently healthy men and women with LDL-C concentrations considered optimal, well below the therapeutic target of 3.37 mmol/L (130 mg/dL) suggested in current treatment guidelines.

INFLAMMATION AND hsCRP

In the 40 years that have passed since the establishment of the major cardiac risk factors, our understanding of the biology of atherothrombosis has markedly advanced. All major textbooks now describe coronary artery disease not only as a disorder of lipid deposition but also as a disorder of underlying low-grade systemic inflammation. Inflammation plays crucial roles in the early cell adhesion that initiates atherosclerosis and in the expansion and rupture of otherwise stable atherothrombotic plaques. This later process leads to acute...
ischemia and downstream necrosis, resulting in myocardial infarction, stroke, or vascular death (1).

Clinically, this enhanced inflammatory response is easily measured by using high sensitivity assays for hsCRP that have been cleared by the US Food and Drug Administration for use in ascertainment of global cardiovascular risk and in prediction of stroke. In guidelines issued by the American Heart Association and the CDC in 2003, hsCRP was recommended as an adjunct to global risk prediction with concentrations of hsCRP <1, 1–3, and >3 mg/L corresponding with lower, moderate, and higher relative risk categories, respectively (2).

In more than 20 prospective epidemiologic studies performed among apparently healthy men and women worldwide, hsCRP concentrations have repeatedly proven to serve as independent predictors of future vascular events, with a magnitude of effect comparable to global risk prediction with concentrations of hsCRP <1, 1–3, and >3 mg/L corresponding with lower, moderate, and higher relative risk categories, respectively (2).

In emergency room settings, increased hsCRP concentrations also predict instability among chest pain patients. Among acute coronary syndrome patients, increased hsCRP is closely associated with increased vascular mortality, even when biomarkers of myocardial necrosis such as troponin are negative. hsCRP is also a powerful predictor of incident stroke, an observation of clinical importance because in this setting LDL-C is less effective as a risk predictor.

SPECIFICITY AND CLINICAL USE OF hsCRP

hsCRP is an acute-phase reactant that increases during major infection or trauma, and thus some clinicians have raised concern about the specificity of hsCRP in clinical practice. Data from multiple large studies demonstrate, however, that among otherwise healthy individuals, hsCRP concentrations are stable over long periods of time and that the year-to-year and decade-to-decade variations in hsCRP show comparable intraclass correlations to those of cholesterol and blood pressure. Furthermore, hsCRP has proven specific as a predictor of vascular events, incident diabetes (a disorder characterized by premature atherothombosis), and cardiovascular death. As a result, hsCRP concentrations are a strong predictor of total mortality.

To improve the predictive accuracy of hsCRP measurements, the American Heart Association/CDC guidelines suggest that concentrations be measured twice and an average value used for prediction, a recommendation also made for cholesterol. In practice, this protocol is unnecessary for the majority of patients, for whom a single evaluation suffices, particularly if the initial test is <3 mg/L. When values exceed 3 mg/L, repeat measurement in 2–3 weeks is advised, and the lower of the values (rather than the average) should be used for risk prediction.

In most studies, hsCRP concentrations do not predict cancer or other inflammatory conditions. As such, there is no reason to pursue work-up for these diagnoses in asymptomatic patients if the physical examination and other routine testing are normal.

Although the major determinants of hsCRP are diet, exercise, obesity, and smoking, recently reported genomewide association studies have shown that loci in chromosomal regions known to have an impact on insulin resistance, obesity, thrombosis, and premature atherosclerosis all impact plasma hsCRP concentrations (4).

Most relevant to the case we describe, hsCRP concentrations predict vascular risk even when cholesterol concentrations are low. In a prospective cohort of 28,000 initially healthy women, cardiac event-free survival was worse among those with increased hsCRP and low LDL-C than among those with low hsCRP and increased LDL-C (5).

THE REYNOLDS RISK SCORES

Recognizing the need to move beyond traditional risk markers, investigators supported by the Donald W. Reynolds Foundation measured a panel of 34 putative behavioral, environmental, and biochemical determinants of vascular risk in the Women’s Health Study and used these data to derive and validate a new global risk prediction score (6). A core issue in developing the Reynolds Risk Score was to derive the most parsimonious prediction model in a statistically unbiased manner. Thus, although multiple biomarkers such as fibrinogen, homocysteine, apolipoproteins A-I and B, creatinine clearance, hemoglobin A1c, and soluble intercellular adhesion molecule 1 were all independent predictors of future vascular risk in this evaluation, only 2 novel biomarkers—hsCRP (representing inflammatory risk) and parental history of myocardial infarction before age 60 (representing genetic risk)—were demonstrated to improve overall risk assessment.

When compared to the Framingham Risk Score, the Reynolds Risk Score reclassified between 20% and 30% of those at “intermediate risk” into clinically relevant higher or lower risk categories and did so with improved accuracy. Although discrimination was only marginally improved when hsCRP and parental history were added to traditional risk factors, other parameters...
of the global model fit as well as calibration, and reclassification did improve substantially. A comparable Reynolds Risk Score for men has recently been developed. The Reynolds Risk Score for both men and women can be freely accessed at www.ReynoldsRiskScore.org.

As demonstrated in the case we describe, knowledge of inflammatory and genetic risk—the 2 parameters that the Reynolds Risk Score adds to traditional Framingham covariates—can shift risk prediction for selected patients. For individuals lacking an enhanced innate immune response or for those without a family history, relatively little is gained by using the Reynolds algorithm rather than the Framingham algorithm.

STATIN THERAPY AND THE CONCEPT OF DUAL TARGETS FOR BOTH ACHIEVED LDL-C AND ACHIEVED hsCRP

The most important interventions for vascular risk reduction are diet, exercise, and smoking cessation. All of these interventions not only reduce hsCRP concentrations but are also proven to reduce vascular risk. A primary aim of global risk prediction with either the Framingham Risk Score or the Reynolds Risk Score is to motivate individuals to change lifestyle practices before the onset of vascular disease.

Unfortunately, diet, exercise, and smoking cessation are necessary but insufficient interventions for risk reduction in many patients, and pharmacologic therapies are needed. For almost all cases, the first pharmacologic intervention to be considered is treatment with statins, agents proven to reduce vascular risk 20% to 25% when given to those with hyperlipidemia, vascular disease, or diabetes.

Statins are highly effective, and paradoxes uncovered in major trials suggest that these agents may do more than reduce cholesterol. For example, the magnitude of benefit of statin therapy is not closely correlated with LDL-C concentrations, and statins have beneficial effects within weeks of therapy initiation, long before lipid reduction should impact on plaque morphology. In addition to being potent inhibitors of the 3-hydroxy-3-methyl-glutaryl-CoA reductase pathway, statins reduce inflammatory cell adhesion and monocyte recruitment at the endothelial level, alter smooth muscle migration in developing plaques, and favorably impact on several mediators of plaque stability, all functions considered to be antiinflammatory (7).

All statins reduce hsCRP concentrations in a manner largely independent of LDL-C reduction, although on a population basis more effective statins derive ben-
efit from more aggressive LDL-C reduction as well as more aggressive hsCRP reduction. Several clinical trials including CARE (Cholesterol and Recurrent Events), AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22), A to Z (Aggrastat to Zocor), and REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) have shown not only that statin therapy reduces hsCRP but that among healthy individuals, stable coronary disease patients, and those with acute coronary syndrome, the magnitude of benefit associated with statin therapy correlates in part to achieved hsCRP concentrations.

In both the PROVE IT–TIMI 22 and A-to-Z trials (Fig. 1), patients achieving hsCRP concentrations <2 mg/L after initiating statin therapy had better clinical outcomes compared to patients who did not, regardless of the LDL-C response (8, 9). In both trials, best clinical outcomes accrued among those who achieved the dual targets of LDL-C <1.81 mmol/L (70 mg/dL) and hsCRP <2 mg/L. On this basis, physicians often increase statin dose (or change to a more potent statin) to achieve these dual targets of both lipid and inflammatory reduction.

**THE JUPITER TRIAL AND ITS IMPLICATIONS FOR PATIENTS WITH LOW CONCENTRATIONS OF CHOLESTEROL AND INCREASED CONCENTRATIONS OF hsCRP**

Despite data demonstrating that individuals with low LDL-C but increased hsCRP are at high risk, whether to treat such individuals with statin therapy has until recently been uncertain.

In a hypothesis-generating analysis of the AFCAPS/TexCAPS trial published in 2001, lovastatin was
found to benefit those with low LDL-C and high hsCRP, whereas no benefit was observed in low LDL-C, low hsCRP patients (10). On this basis, the justification for the use of statins in prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to directly evaluate whether rosuvastatin 20 mg daily would decrease cardiovascular events among apparently healthy men and women with LDL-C concentrations <3.37 mmol/L (130 mg/dL) who were at increased risk owing to hsCRP ≥2 mg/L.

As recently reported, the 17 802–patient JUPITER trial was stopped by its Data and Safety Monitoring Board because rosuvastatin use among low LDL-C/high hsCRP patients was associated with a 44% reduction in the primary trial endpoint (P < 0.00001), a 54% reduction in myocardial infarction (P = 0.0002), a 48% reduction in stroke (P = 0.002), a 47% reduction in hospitalization for unstable angina or arterial revascularization (P < 0.00001) and a 20% reduction in mortality (P = 0.02) (Fig. 2) (11). A 37% reduction in the primary endpoint was observed among those with increased concentrations of hsCRP and no other major risk factor other than age (P = 0.015). These effects were present although the median LDL-C at study entry was 2.8 mmol/L (108 mg/dL) and the median HDL-C was 1.27 mmol/L (49 mg/dL). Regarding cost-effectiveness, the number-needed-to-treat in JUPITER was 25, a value if anything superior to that observed in primary prevention trials using statin therapy among hyperlipidemic patients.

JUPITER also provides data for previously under-studied groups including women and minority patients. With regard to case we report, rosuvastatin reduced rates of myocardial infarction, stroke, revascularization, and cardiovascular death 46% among women (P < 0.001). Preliminary analyses also confirm that apparently healthy men and women who achieve low concentration of both LDL-C [<3.37 mmol/L (<70 mg/dL)] and hsCRP (<2 mg/L) have the greatest benefit from statin therapy, supporting the dual-target hypothesis. Thus, JUPITER provides additional evidence that hsCRP, as an indicator of the intensity of underlying inflammation, may serve not only as a prognostic tool but also as a measure of the success of treatment with statin therapy.

CASE FOLLOW-UP

The patient described would have qualified for JUPITER; had she been enrolled and allocated to rosuvastatin 20 mg daily, she would have had a nearly 50% lower risk of suffering myocardial infarction. In this case, use of the Reynolds Risk Score rather than the Framingham Risk Score would have led to earlier initiation of preventive therapy. It has been estimated that application of the screening and prevention strategy tested in JUPITER could prevent more than 50 000 vascular events annually in the US alone.

After infarction, the patient was started on simvastatin 40 mg, but this choice was insufficient to achieve the dual targets of LDL-C <1.81 mmol/L (70 mg/dL) and hsCRP <2 mg/L. The patient was thus switched to a more potent statin at a higher dose. She also entered a cardiac rehabilitation program, started a daily exercise regimen, and, most importantly, stopped her lifelong smoking habit.

POINTS TO REMEMBER

- More than 50% of those who develop coronary events have either none or only one of the traditional risk factors.
- When hsCRP and family history of cardiovascular disease are added to the Framingham Risk Score, patients are classified with higher accuracy into risk categories.
- The greatest benefit from statin therapy, for both primary and secondary prevention, is achieved using both LDL-C and hsCRP as target goals for therapy.
- Patients with low LDL-C and high hsCRP are at a higher risk of future coronary events than those with high LDL- and low hsCRP.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: P.M. Ridker has received consulting fees and/or lecture fees from Astra-Zeneca, Novartis, Merck-Schering Plough, Roche, Sanofi-Aventis, ISIS, and Vascular Biogenics.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: P.M. Ridker received investigator-initiated research grant support from the National Heart Lung and Blood Institute, the National Cancer Institute, the Donald W Reynolds Foundation, the Leducq Foundation, Astra-Zeneca, Novartis, Merck, Abbott, Roche, and Sanofi-Aventis.
Expert Testimony: None declared.
Other Disclosures: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation or approval of manuscript.
Clinical Case Study

CRP is an acute-phase protein that is produced primarily in the liver but may also be produced in atherosclerotic plaques. CRP is a calcium-dependent ligand-binding pentamer that activates the complement system, induces adhesion molecule expression, enhances macrophage phagocytosis, and may well play a direct role in the pathogenesis of atherosclerosis.

Sensitive and reproducible hsCRP assays are now available. Increased hsCRP is an independent predictor of cardiovascular disease (CVD), and hsCRP concentrations are often increased in obese and diabetic patients. hsCRP is now incorporated into CVD risk scores available. Increased hsCRP is an independent predictor of cardiovascular disease (CVD), and hsCRP concentrations are often increased in obese and diabetic patients. hsCRP is now incorporated into CVD risk scores for both men and women. Statins inhibit cholesterol production, and treatment with statins, especially rosvastatin and atorvastatin, has been shown to reduce LDL-C and hsCRP concentrations. In the recent JUPITER trial, 17,802 individuals (men older than 50 and women older than 60 years) with LDL-C concentrations ≥3.37 mmol/L (130 mg/dL) and hsCRP concentrations >2 mg/L were randomized to rosvastatin 20 mg/day or placebo. The trial was stopped early in favor of the rosvastatin arm and demonstrated significant reductions in heart disease, stroke, and total mortality associated with rosvastatin treatment.

The case patient described here was a 72-year-old woman with a history of hypertension and current cigarette smoking, as well as a positive family history of premature heart disease. She had a body mass index of 23 kg/m², and her laboratory values were: LDL-C 69 mmol/L (104 mg/dL), HDL-C 2.12 mmol/L (82 mg/dL), and hsCRP 7.7 and 7.2 mg/L. Despite excellent lipid values, 4 months after her examination the patient suffered a myocardial infarction and was documented to have significant coronary heart disease requiring angioplasty and stent placement. Ridker has made a compelling case for the use of hsCRP in patient risk stratification and selection for aggressive lifestyle and risk-factor modification and statin therapy for the prevention of CVD in middle-aged and elderly people.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: E.J. Schaefer has received consulting fees and/or lecture fees from Abbott, AstraZeneca, Boston Heart Laboratory, Merck, Merck Schering, Pfizer, Roche, Schering, and Unilever.
Stock Ownership: None declared.
Honoraria: None declared.

References

The Adult Treatment Panel III guidelines place the 72-year-old female in the category of multiple risk factors (age, hypertension, smoking, family history) and thus recommend calculating her 10-year risk. In using the Framingham Risk Score, the physician was correct in classifying the patient as having "low" cardiovascular risk (<10% over 10 years), and with an LDL cholesterol concentration of 2.67 mmol/L, she thus would not be considered for pharmacologic treatment.

Why Did This Strategy Fail for This Patient?

First, the Framingham model fails to include components of inflammatory and genetic risk. The patient’s risk as calculated with the Reynolds Risk Score, which includes high-sensitivity C-reactive protein (hs-CRP) and family history, is 23.2% over 10 years, which is in the high-risk category; she would therefore be eligible for statin therapy.

Second, the definition of intermediate risk, which is currently 10%–20%, should be lowered to 5%–20%. Most women have a <10% risk. Statins have been shown to be effective in this range, and tests such as hs-CRP measurement or imaging improve risk stratification in the 5%–20% category.

Alternatively, a simpler approach would be to count traditional risk factors, especially hypertension, as well as age, smoking, and family history. On the basis of these risk factors and ASCOT-LLA findings, a clinician could justify starting the patient on statin therapy along with therapeutic lifestyle changes, including smoking cessation. The current approach of calculating 10-year risk with an equation is not used frequently in clinical practice. Finally, a new approach would be to incorporate the findings of JUPITER into practice. Before telling men older than 50 years or women older than 60 years that they would not benefit from statin therapy, a physician could measure hs-CRP. If the hs-CRP concentration is ≥2 mg/L, then statin therapy could be offered on the basis of evidence from JUPITER, in which high-efficacy statin therapy that reduced LDL cholesterol by approximately 50% and hs-CRP by 37% reduced events by almost 50%.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

Authors’ Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:

Employment or Leadership: None declared.
Consultant or Advisory Role: C.M. Ballantyne, Abbott Laboratories, AstraZeneca, Atherogenics, GlaxoSmithKline, Merck, Merck/Schering-Plough, Novartis, Pfizer, Sanofi-Synthelabo, Schering-Plough, and Takeda.
Stock Ownership: None declared.
Honoraria: C.M. Ballantyne, Abbott Laboratories, AstraZeneca, Atherogenics, GlaxoSmithKline, Merck, Merck/Schering-Plough, Novartis, Pfizer, Sanofi-Synthelabo, Schering-Plough, and Takeda.
Research Funding: C.M. Ballantyne, Abbott Laboratories, AstraZeneca, GlaxoSmithKline, Merck, Pfizer, Sanofi-Synthelabo, Schering-Plough, and Takeda.
Expert Testimony: None declared.
Role of Sponsor: The funding organizations played a direct role in the final approval of the manuscript.