Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)—Can C-Reactive Protein Be Used to Target Statin Therapy in Primary Prevention?

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The most important action of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) is their ability to lower levels of low-density lipoprotein (LDL) cholesterol. Statins have proved highly effective in reducing the risk of cardiovascular events in both primary and secondary prevention studies. However, the magnitude of risk reduction associated with statins is greater than that predicted on the basis of LDL cholesterol lowering alone. A likely explanation for this effect is the anti-inflammatory action of statins. Following the observation that high-sensitivity C-reactive protein (hs-CRP) is a powerful predictor of cardiovascular events, investigators in the Cholesterol and Recurrent Events (CARE) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trials demonstrated that the magnitude of risk reduction associated with statin therapy was higher among those with elevated hs-CRP levels. In addition, there is accumulating evidence that statins lower plasma levels of hs-CRP in a manner largely independent of LDL cholesterol lowering. In contrast, little benefit has been demonstrated for statin therapy in the absence of both hyperlipidemia and inflammation. Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is a large multinational, long-term, double-blind, placebo-controlled, randomized clinical trial designed to assess directly whether statin therapy (rosuvastatin 20 mg/day) should be given to apparently healthy individuals with low LDL cholesterol levels but elevated hs-CRP levels—a critical issue for the prevention of cardiovascular disease. Support for the concept behind the JUPITER trial is also now available from several recent trials comparing different intensities of statin therapy on disease progression as well as clinical end points. These studies indicate that the hs-CRP level achieved after initiation of statin therapy may be as important as the LDL cholesterol level achieved. All of these data raise the possibility that hs-CRP could be used to target high-risk patients who may benefit from early statin use. Ongoing work will determine whether hs-CRP reduction, independent of LDL cholesterol reduction, results in a net clinical benefit. **(Am J Cardiol 2006; 97[suppl]:33A–41A)**

Numerous avenues of research ranging from basic experimental evidence to population-based observational studies have led to the recognition that cardiovascular disease (CVD) involves a systemic inflammatory process.[1] Large epidemiologic studies carried out in diverse populations have repeatedly documented the association between high-sensitivity C-reactive protein (hs-CRP), an indicator of inflammation, and CVD outcomes, independent of traditional cardiovascular risk factors.[2] However, it remains uncertain whether therapies that lower hs-CRP levels would also result in lower cardiovascular event rates.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the most widely studied lipid-lowering agents and the most effective low-density lipoprotein (LDL) cholesterol–lowering medications. Statins lower LDL cholesterol and total cholesterol levels by approximately 20% to 50% and have a lesser effect on lowering triglycerides (≈10% to 40%) and raising high-density lipoprotein (HDL) cholesterol (≈5% to 15%) levels. Most studies of the effect of statins on outcomes have shown that for approximately every 1% reduction in LDL cholesterol level, there is an associated 1% reduction in risk of clinical cardiovascular events.[3]

Data from multiple large-scale randomized clinical trials

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Paul M Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease.

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support a similar relative risk reduction with statin therapy for cardiovascular outcomes in both the primary and the secondary prevention of CVD. This has led to the development of current international guidelines that focus on LDL cholesterol lowering as the primary target of therapy, tailoring the level of optimal LDL cholesterol reduction to the individual's level of cardiovascular risk.[3] Several risk prediction models, such as the Framingham risk equations and the European Systematic Coronary Risk Evaluation (SCORE), use traditional risk factors to estimate global CVD risk in asymptomatic individuals.[4,5] However, most US women and a large proportion of US men are classified as low risk when the Framingham risk score, as recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, is used to estimate risk in the primary prevention setting. Current US population estimates from the National Health and Nutrition Examination Survey (NHANES) found that <1% of women had high-risk Framingham scores (10-year estimated risk for hard coronary events of >20%) and only 4% of women had intermediate-risk scores (10% to 20%), compared with 5% and 29% in men, respectively.[6] Meanwhile, the lifetime risk of developing CVD for both men and women is substantially higher—approximately 1 in 3 for women and 1 in 2 for men.[7]

To improve cardiovascular risk stratification and detection, an expert panel assembled by the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) provided a scientific statement on hs-CRP summarizing how it may be applied for clinical cardiovascular risk assessment in primary prevention populations.[8] This report termed hs-CRP an independent marker of cardiovascular risk and endorsed its use as part of global risk prediction in asymptomatic individuals, particularly those deemed at intermediate risk for CVD by traditional risk factors.[8] The panel also established a set of cut points to be used in clinical practice, with hs-CRP levels of <1 mg/L considered low risk and >3 mg/L, high risk.

The Cholesterol And Recurrent Events (CARE) trial first demonstrated that statin therapy also lowers plasma levels of hs-CRP.[9] This has since been shown to be a class effect, with an approximate statin-mediated reduction of hs-CRP levels of 20% to 30%.[9,10] However, the beneficial value of lowering hs-CRP that is independent of lowering LDL cholesterol is not so clear.

The critical question then becomes whether inflammatory markers, such as hs-CRP, can be clinically useful in selecting patients who may benefit from statin therapy despite having normal LDL cholesterol values. This is the hypothesis driving Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a long-term, multinational, randomized, double-blind, placebo-controlled study to assess rosuvastatin 20 mg in the primary prevention of cardiovascular events in 15,000 subjects with low LDL cholesterol levels and elevated levels of hs-CRP.

Role of Inflammation in Cardiovascular Disease

Multiple large-scale prospective studies performed in a variety of populations have demonstrated that hs-CRP is a strong and independent predictor of CVD events, including myocardial infarction (MI), ischemic stroke, sudden cardiac death, and diabetes mellitus.[11–22] In the Physicians' Health Study, an epidemiologic study of >22,000 healthy middle-aged men with no clinical evidence of disease, increasing levels of hs-CRP at study entry were associated with up to a 3-fold increase in risk of incident MI and a 2-fold increase in risk of ischemic stroke.[12] When directly compared with other novel risk factors—including homocysteine, lipoprotein(a), interleukin-6, intercellular adhesion molecule–1, and serum amyloid A—and standard lipid measures, hs-CRP has proved to be the single strongest predictor of cardiovascular risk in apparently healthy women. This is demonstrated in the Women's Health Study (Figure 1), with a relative risk ratio of 4.4 for the highest versus lowest quartile of hs-CRP.

Moreover, the addition of hs-CRP to traditional cholesterol screening enhanced cardiovascular risk prediction and proved to be independent of LDL cholesterol, suggesting that elevated hs-CRP levels may be particularly useful for identifying asymptomatic individuals who may be at high risk for future cardiovascular events but who have average cholesterol levels. As shown in Figure 2, the poorest event-free survival in women was among those with high LDL cholesterol and high hs-CRP levels, and the best event-free survival was among those with low LDL cholesterol and low hs-CRP levels. Notably, individuals with low LDL cholesterol levels but high hs-CRP levels were at higher risk than those with high LDL cholesterol levels but low hs-CRP levels. This important finding of higher risk associated with high hs-CRP/low LDL cholesterol is among the motivating factors behind the JUPITER trial because this population of apparently healthy individuals—usually missed by current screening guidelines—is being prospectively studied for the first time.

Levels of hs-CRP add important prognostic information on cardiovascular risk not only at all levels of LDL cholesterol but also at all levels of the Framingham risk score (Figure 3). With increasing levels of global coronary risk (Figure 3, left), there was a graded and consistent relation with increasing levels of hs-CRP in a dose-response manner. This additional prognostic information is most clinically relevant for those asymptomatic individuals who are at intermediate risk for CVD based on their traditional risk factor profile (Framingham risk estimate of 5% to 20% for developing coronary artery disease over a 10-year period). Currently, these individuals are not considered eligible for aggressive risk factor modification with statin therapy because their LDL cholesterol levels are below the current therapeutic target of 3.36 mmol/L (130 mg/dL).[3] The JUPITER trial was designed to study just this population. The ability of hs-CRP to add prognostic information on

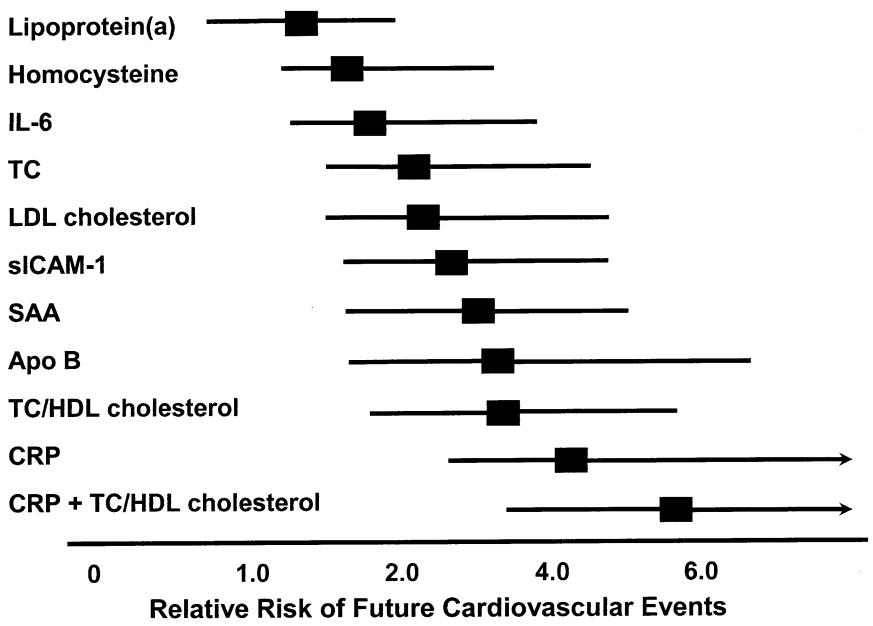

Figure 1. Risk factors for future cardiovascular events in apparently healthy women in the Women's Health Study. Apo B = apolipoprotein B; CRP = C-reactive protein; HDL = high-density lipoprotein; IL-6 = interleukin-6; LDL = low-density lipoprotein; SAA = serum amyloid A; sICAM-1 = soluble intercellular adhesion molecule–1; TC = total cholesterol. (Reprinted with permission from *N Engl J Med*.[14])

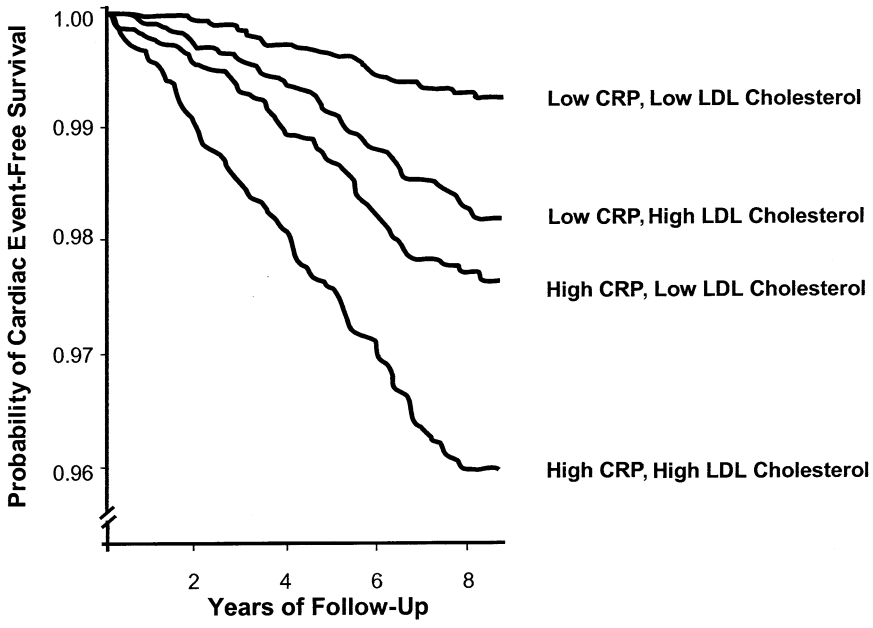

Figure 2. Kaplan-Meier curves depicting cardiovascular event-free survival according to 4 groups based on high or low levels of C-reactive protein (CRP) and low-density lipoprotein (LDL) over 8 years of follow-up in the Women's Health Study. Low CRP was defined as beneath the study median of 1.52 mg/L and low LDL as beneath the study median of 3.2 mmol/L (123.7 mg/dL). (Reprinted with permission from *N Engl J Med*.[15])

global cardiovascular risk after adjustment for all Framingham risk factors has been confirmed in 9 major prospective studies (Figure 4).

The hs-CRP marker has also been found to modify the risk associated with the metabolic syndrome, which encompasses a number of proatherogenic, prothrombotic, and proinflammatory risk factors (abdominal obesity, elevated triglycerides, low HDL cholesterol levels, high blood pressure, and high fasting glucose levels).[16] This finding may be because of the active role that adipocytes play in inflammatory vascular processes, particularly in central or abdominal tissue. The metabolic syndrome has been associated with increased cardiovascular risk and thus was identified as a target of therapy in NCEP ATP III.[3] Individuals with the metabolic syndrome are more likely to have high hs-CRP levels, and those with 1 or 2

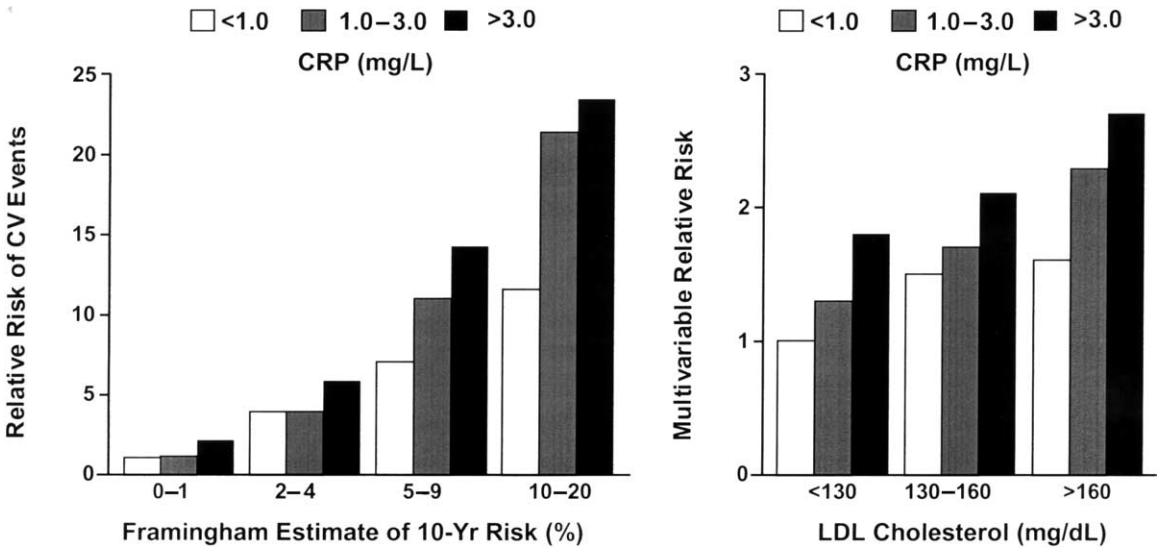

Figure 3. C-reactive protein (CRP) adds independent prognostic information at all levels of the Framingham risk score (*left*) and all levels of low-density lipoprotein (LDL) cholesterol (*right*). CV = cardiovascular. (Reprinted with permission from *N Engl J Med*.[15])

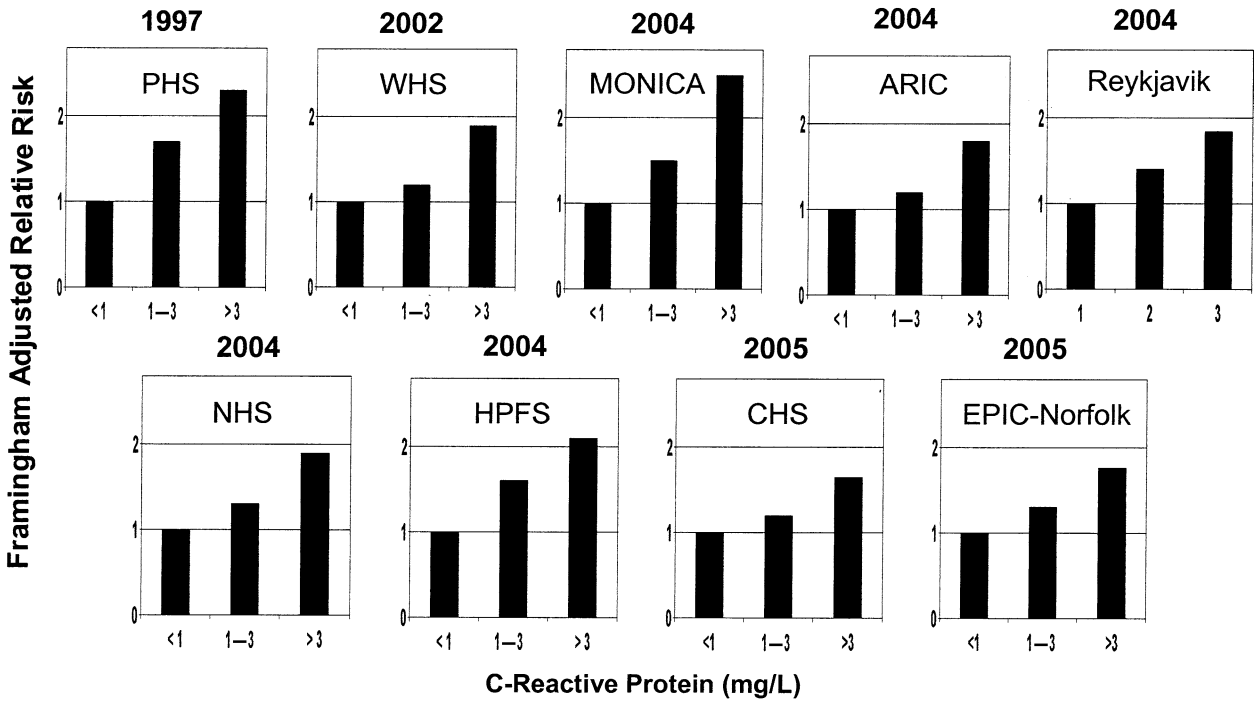

Figure 4. C-reactive protein was an independent predictor of cardiovascular risk in 9 large prospective studies across diverse populations. ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; EPIC = European Prospective Investigation into Cancer and Nutrition; HPFS = Health Professionals Follow-up Study; MONICA = Monitoring Trends and Determinants in Cardiovascular Disease; NHS = Nurses' Health Study; PHS = Physicians' Health Study; WHS = Women's Health Study.

criteria for the metabolic syndrome have higher hs-CRP levels than those with none.

In a study of >14,000 apparently healthy women, median hs-CRP levels for those with 0, 1, 2, 3, 4, or 5 criteria for the metabolic syndrome were 0.68, 1.09, 3.01, 3.88, and 5.75 mg/L, respectively.[16] In individuals who met NCEP ATP III criteria for the metabolic syndrome, those with high levels of hs-CRP (≥3 mg/L) had worse event-free survival than those with low hs-CRP levels (<3 mg/L). Figure 5 shows cardiovascular event-free survival in analyses stratified by hs-CRP levels of <1, 1 to 3, and >3 mg/L, which are cutoffs chosen to correspond with CDC recommendations for differentiating low-, intermediate-, and high-risk groups.[8] As clearly shown, hs-CRP levels added information at all levels of the metabolic syndrome, just as prior data had demonstrated that hs-CRP added important prog-

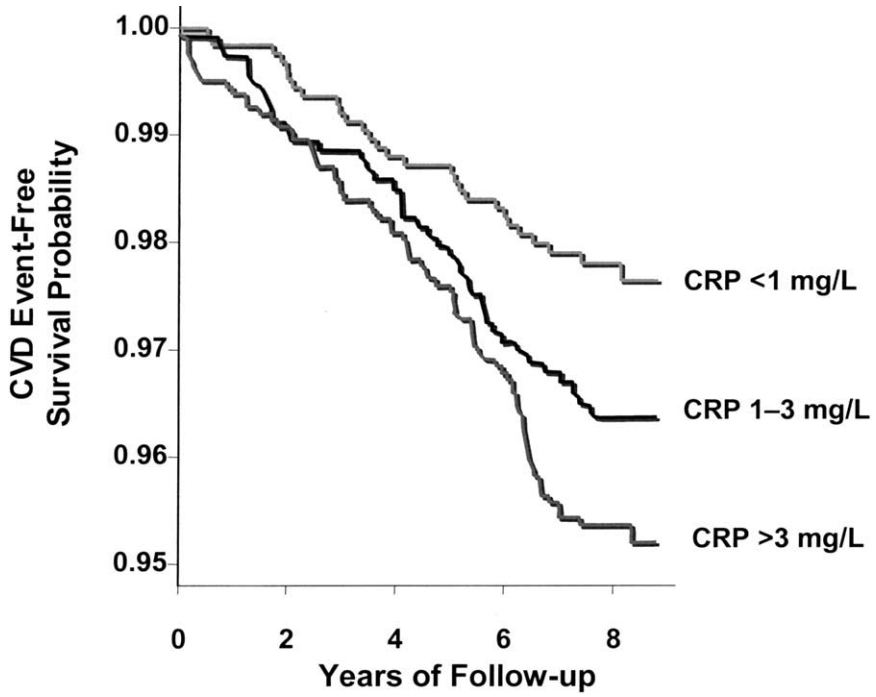

Figure 5. C-reactive protein (CRP) adds important predictive value to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) metabolic syndrome. CVD = cardiovascular disease. (Reprinted with permission from *Circulation*.[16])

nostic information at all levels of LDL cholesterol and at all levels of the Framingham risk score.

Although a number of different markers of inflammation can provide useful information for predicting cardiovascular risk, acute-phase reactant hs-CRP is currently the most accurate marker.[23] Inflammatory markers, such as soluble intercellular adhesion molecule–1 and interleukin-6, are not readily measured in clinical settings, partly because of their instability and partly because of measurement error. In contrast, several commercial assays with acceptable coefficients of variation are available for the measurement of CRP, and a program to standardize CRP testing is currently being developed by the CDC.[8]

Emerging evidence also suggests that hs-CRP may not only be a useful marker of inflammation but may also play an active role in the pathogenesis of atherosclerosis (Figure 6). Specifically, CRP appears to be directly involved in augmenting the innate inflammatory response; inducing prothrombotic factors, such as plasminogen activator inhibitor–1, proinflammatory adhesion molecules, and monocyte chemoattractant protein–1; and interfering with endothelial nitric oxide synthase.[24–27] Recent studies have shown that CRP is produced not only in the liver, as previously believed, but also locally in other tissues, including smooth muscle cells from normal coronary arteries and diseased coronary artery bypass grafts.[28,29] Moreover, CRP transgenic mice that were made to overexpress the human CRP gene developed significant thrombosis after arterial damage, suggesting that hs-CRP may be more than just a marker for atherosclerosis.

C-Reactive Protein–Lowering Effects of Statins in Acute Coronary Syndromes

Until recently, it was not known whether the hs-CRP–lowering action of statins provided any clinical benefit beyond their LDL cholesterol–lowering action. In 2 studies published recently—the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) and the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) studies—the strongest evidence to date is provided for the independent cardiovascular benefits associated with statin-induced hs-CRP lowering.[30,31] These 2 trials compared the effects of high-dose atorvastatin with those of low-dose pravastatin, demonstrating that lowering hs-CRP levels through intensive statin therapy reduced progression of coronary plaque and risk of recurrent clinical events in patients with acute coronary syndromes. In PROVE IT–TIMI 22, there was a highly significant relative reduction of CVD events (16%) favoring high-dose statin therapy at a 2.5-year follow-up—although the benefit was seen as early as 30 days from the start of therapy.[31]

A prespecified analysis of PROVE IT–TIMI 22 revealed similar and statistically independent relations between hs-CRP reduction and risk of recurrent coronary events and between LDL cholesterol reduction and risk of such events. When patients were divided into categories on the basis of final hs-CRP and LDL cholesterol levels achieved, those with hs-CRP levels reduced to <2 mg/L had fewer recurrent events, regardless of the LDL cholesterol level achieved by statin therapy. As shown in Figure 7, the patients at highest

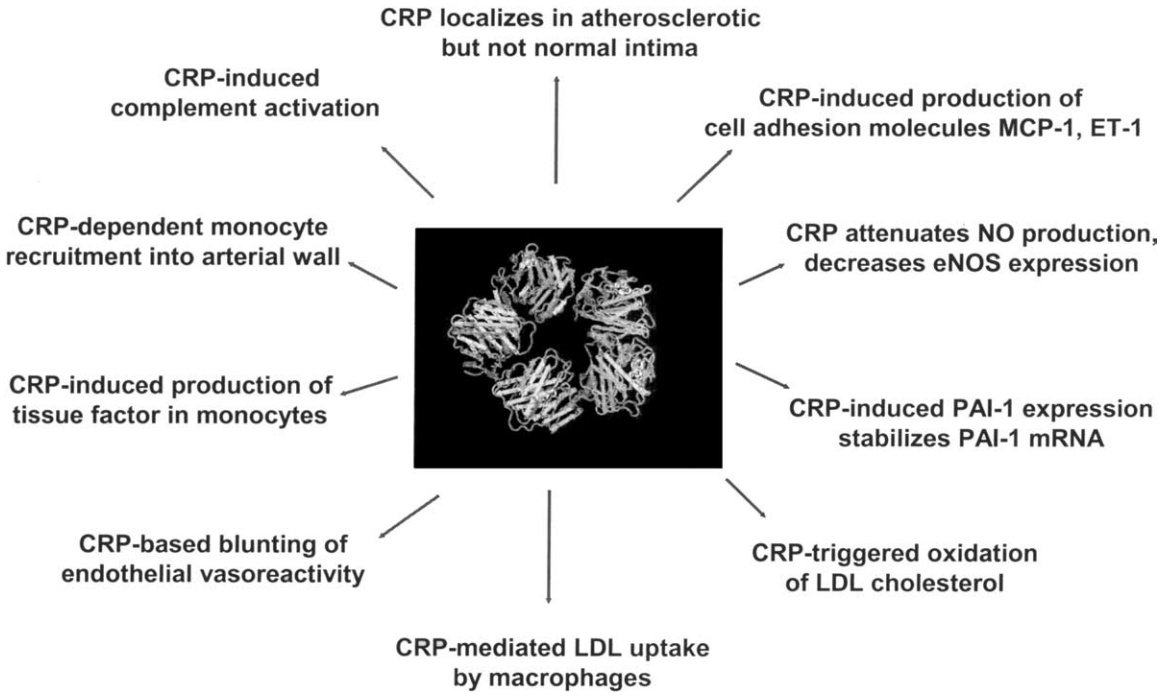

Figure 6. C-reactive protein (CRP) is likely more than just a marker for atherosclerosis, playing an active role in the pathogenesis of atherosclerosis. eNOS = endothelial nitric oxide synthase; ET-1 = endothelin-1; LDL = low-density lipoprotein; MCP-1 = monocyte chemoattractant protein–1; mRNA = messenger ribonucleic acid; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor–1.

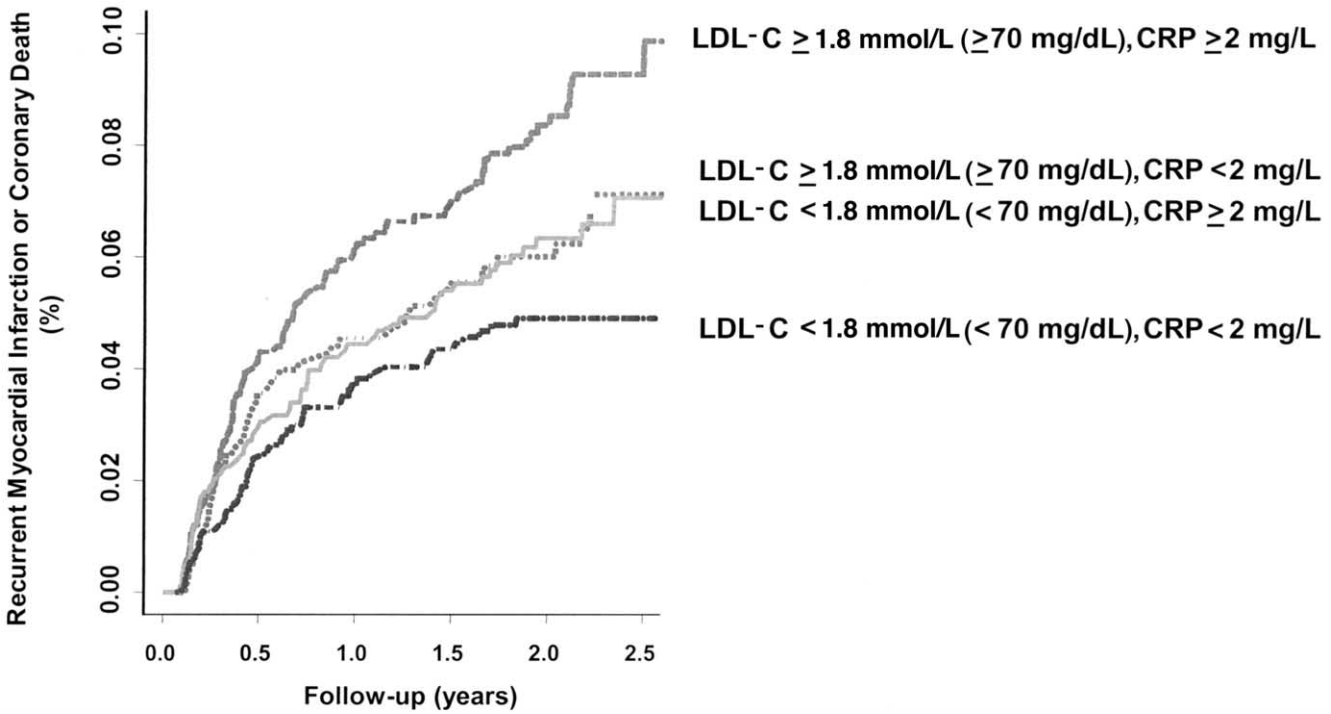

Figure 7. Cumulative incidence of recurrent coronary events in patients with acute coronary syndromes according to levels of C-reactive protein (CRP) and low-density lipoprotein cholesterol (LDL-C) achieved by statin therapy over a 2.5-year follow-up period. (Reprinted with permission from *N Engl J Med*.[31])

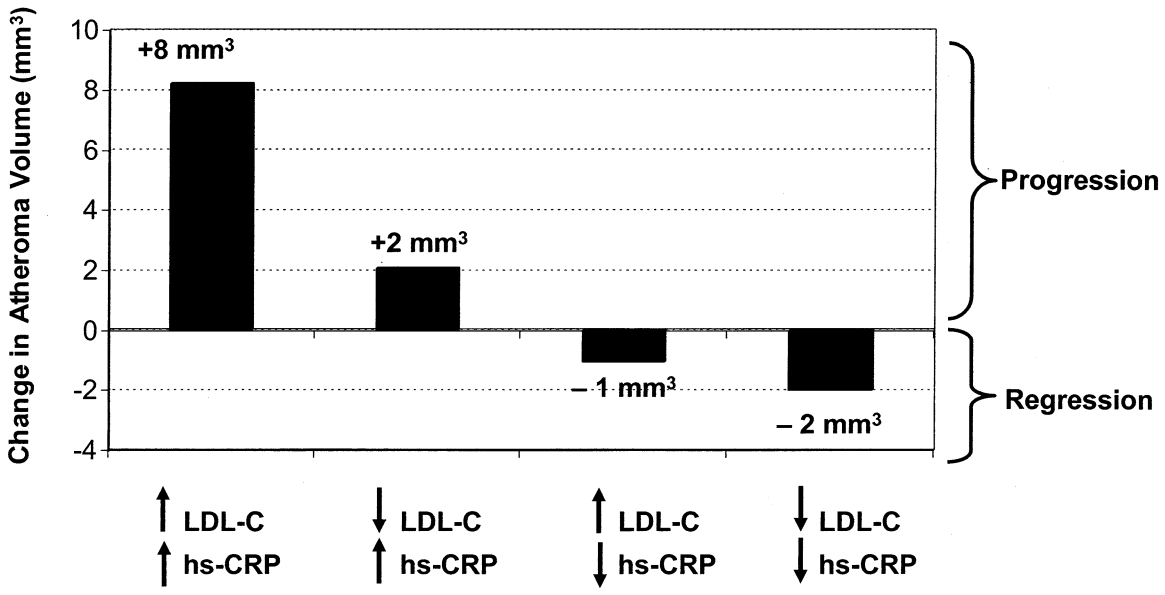

Figure 8. High-sensitivity C-reactive protein (hs-CRP) lowering with aggressive statin therapy slowed atherosclerotic progression and resulted in regression of atheroma volume as measured by intravascular ultrasonography in patients with coronary disease in the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial. ↓ = reduction greater than study median; ↑ = reduction less than study median; LDL-C = low-density lipoprotein cholesterol. (Based on data from *N Engl J Med*.[30])

risk were those in whom both LDL cholesterol and hs-CRP remained elevated despite statin therapy. In patients whose LDL cholesterol was lowered to below study median (<1.8 mmol/L [<70 mg/dL]) with statin use, those whose hs-CRP levels remained elevated had significantly higher recurrent event rates than those whose CRP levels were reduced to <2 mg/L. Moreover, the correlation between hs-CRP reduction and LDL cholesterol reduction achieved by statin use was small in both trials (correlation coefficient, 0.1 to 0.2). These findings suggest that the beneficial effects of statin therapy for secondary prevention of cardiovascular events may be as much a result of lowering hs-CRP levels as lowering LDL cholesterol levels.

REVERSAL demonstrated that lowering hs-CRP levels in patients with coronary disease by intensive statin therapy resulted in reduced atherosclerotic lesion progression; in some patients there was even atheromatous regression, as measured by intravascular ultrasonography (Figure 8). These findings suggest that to maximize the benefit of statin therapy, physicians may need to monitor hs-CRP levels in addition to LDL cholesterol levels for secondary prevention of CVD. JUPITER will clarify whether such monitoring could also be beneficial for primary prevention.

Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)

Because inflammation is an integral part of the underlying pathophysiology of atherosclerosis and hs-CRP is a useful clinical marker of this inflammatory process, an important unresolved question is whether hs-CRP screening combined with traditional lipid screening would provide an improved strategy for statin use in primary prevention of CVD. The JUPITER trial was designed to answer this question. Several factors governed the design. First, statin therapy has been repeatedly demonstrated to lower the risk of CVD events. Second, several studies have now shown statins to have a greater impact on lowering CVD risk in individuals with higher levels of inflammation.[32,33] As already noted, for example, investigators in the CARE trial of secondary prevention found that the benefit of pravastatin was greater among subjects with elevated hs-CRP levels.[32] Similarly, in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of primary prevention with lovastatin, the event reduction among those with low LDL cholesterol but high hs-CRP was virtually identical to that seen in patients with high LDL cholesterol.[33] Third, more than half of CVD events occur in individuals with LDL cholesterol levels that current guidelines do not consider eligible for therapy. And finally, because of the hs-CRP–lowering effects of statins, treating individuals with high hs-CRP levels but normal LDL cholesterol levels may extend the benefit of prophylactic statins.

The primary objective of the JUPITER trial is to determine whether statin therapy (rosuvastatin 20 mg/day) will reduce the rate of first major cardiovascular events, defined as the combined primary end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or arterial revascularization among healthy individuals with low LDL cholesterol levels (<3.36

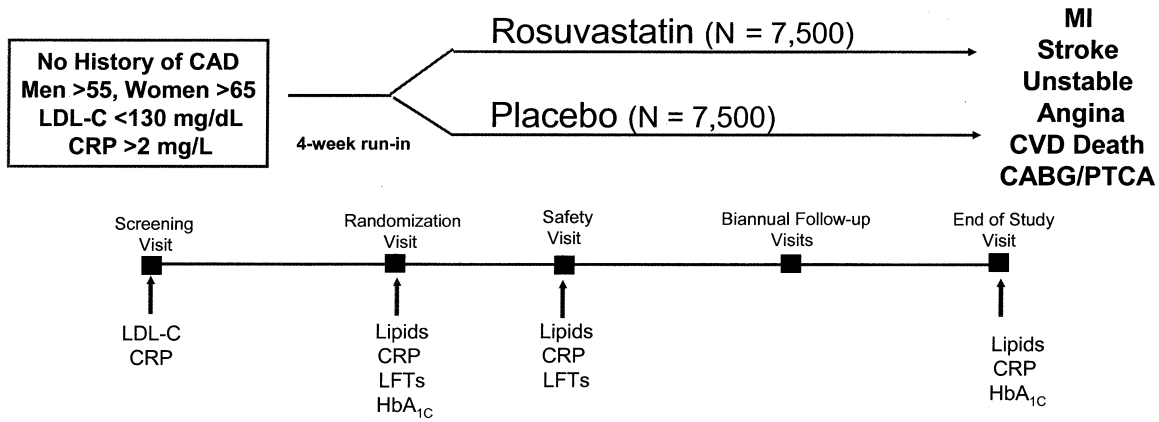

Figure 9. Schematic of the basic trial design for Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), a large multicenter trial to answer definitively whether those with low cholesterol levels but high C-reactive protein (CRP) levels should be treated aggressively with statin therapy to prevent cardiovascular events. CABG/PTCA = coronary artery bypass graft surgery/percutaneous transluminal coronary angioplasty; CAD = coronary artery disease; CVD = cardiovascular disease; HbA_{1c} = hemoglobin A_{1c}; LDL-C = low density lipoprotein cholesterol; LFTs = liver function tests; MI = myocardial infarction.

mmol/L [130 mg/dL]) but high hs-CRP levels (≥2 mg/L).[34]

Figure 9 shows the basic JUPITER trial design. Asymptomatic individuals (men aged >55 years, women aged >65 years) who have no prior history of MI, stroke, or myocardial revascularization and who on initial screening are found to have LDL cholesterol levels <3.36 mmol/L (130 mg/dL) and hs-CRP levels ≥2.0 mg/L are randomized in a double-blind manner to either rosuvastatin 20 mg/day or placebo. All study participants are then observed over a period of 3 to 4 years for the development of a first cardiovascular event. JUPITER has been designed to answer definitively whether those with average or low LDL cholesterol levels but high hs-CRP levels should be treated aggressively with statin therapy to lower their risk of CVD events.

Secondary objectives of JUPITER are to evaluate whether rosuvastatin therapy lowers the incidence of type 2 diabetes mellitus, bone fractures, and venous thromboembolism. Given the large sample size and the inclusion of a large number of women and minorities, the study will also provide an important tool for evaluating the safety of long-term rosuvastatin use in various racial and ethnic groups.

Conclusion

The JUPITER trial is the first large-scale, multinational, double-blind, placebo-controlled clinical trial to investigate the effects of statins in the primary prevention of cardiovascular events in individuals with low levels of LDL cholesterol who may be at risk because of their elevated hs-CRP levels. Trial results could provide an evidence base for the use of hs-CRP in addition to LDL cholesterol to guide statin therapy in primary prevention. Because of its potential impact on public health, this trial represents an extremely important step in understanding the links among inflammation, statin therapy, and CVD prevention—knowledge that could lead to substantial alterations in our approach to cardiovascular prophylaxis and treatment.

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