Reviews

Should We Measure C-reactive Protein on Earth or Just on JUPITER?

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ABSTRACT

Evidence for the role of inflammation in the pathogenesis of atherosclerosis is compelling and has generated interest in high-sensitivity C-reactive protein (hs-CRP) as a marker of cardiovascular risk. Data regarding hs-CRP and cardiovascular risk, though largely consistent, is of unclear clinical relevance. Most recently, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial has led to further debate regarding the utility of hs-CRP. This article provides a comprehensive review of the data regarding cardiovascular risk and hs-CRP with an emphasis on the JUPITER trial and concludes with an evidence-based analysis of the current role of hs-CRP in cardiovascular risk assessment.

Introduction and Background

It is now widely accepted that inflammation plays a key role in the pathogenesis of all stages of atherosclerosis from the development of the initial fatty streak to acute plaque rupture and thrombosis. Despite major advances in treatment, coronary heart disease remains a major cause of morbidity and mortality worldwide. Therefore accurate assessment of cardiovascular risk in individuals and populations is of paramount importance to decrease the global burden of coronary heart disease. Conventionally, the first step in the assessment of cardiovascular risk is an appraisal of traditional risk factors via the use of a global risk score. Among the criticisms of algorithms such as the Framingham risk score is that for patients with intermediate risk, estimated to be between 25% to 40% of the population,[1] there is limited guidance regarding appropriate therapy. This gap has prompted the investigation of novel markers with the potential to improve cardiovascular risk prediction. Data support that high-sensitivity C-reactive protein (hs-CRP) may be such an independent marker. Recently, the release of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial[2] has generated new interest in this marker and provoked considerable debate about the potential role and utility of hs-CRP testing in the general population.

C-reactive Protein

C-reactive protein (CRP) was originally discovered in 1930 and named for its binding to the pneumococcal C-polysaccharide. It is a major acute phase reactant produced in the liver in response to numerous inflammatory cytokines. Any form of infection, tissue injury, or inflammation may be associated with an increase in circulating CRP. C-reactive protein levels generally increase 6 hours after an acute stimulus and peak within 48 hours.[3] In contrast to other markers of inflammation, the relatively long half-life of CRP (approximately 19 hrs) allows for its levels to remain stable long enough to render random measurements clinically relevant.[4]

The biologic function of CRP remains debatable—data supporting its role in the pathogenesis of inflammation is confined to in vitro and animal studies. In addition to binding to the pneumococcal C-polysaccharide, CRP binds to numerous other molecules including oxidized phospholipids, modified low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and platelet activating factor.[5–7] It is believed that CRP binds to and precipitates soluble ligands, aggregates particulate ligands, and activates the classical complement pathway, thus contributing to both host defense against infection and enhancing inflammatory tissue damage.[8] However, skeptics argue that the dramatic rise in CRP, up to a 1000-fold increase in conditions such as sepsis, is simply a reflection of the underlying pathophysiology and does not directly cause any adverse effects locally or systemically. It has also been noted that the injection of large amounts of human CRP into animals produces no observable adverse inflammatory or tissue damaging effects.[9] A recent human genetic study found that CRP gene polymorphisms associated with higher plasma levels of CRP were not associated with higher rates of ischemic heart and cerebrovascular events, suggesting that CRP is not a direct mediator of vascular events.[10] Thus, whether CRP is a critical, active component of the inflammatory cascade or simply a marker of inflammation remains controversial.

CRP and Cardiovascular Risk

Regardless of whether or not CRP plays a causal role in atherosclerosis, numerous studies suggest its role

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in predicting cardiovascular events. The term "high-sensitivity" CRP refers to the measurement of CRP in serum or plasma samples using immunoassay methods with sufficient sensitivity to quantify CRP throughout its normal range. This stands in contrast to older assays that had detection limits in the range of 2 to 10 mg/L, rendering them useful for the detection of the acute phase response of CRP, but of limited utility in the measurement of baseline values. Studies measuring CRP in the general adult population in the United States have found median values of approximately 0.8 mg/L with 33% of subjects between 3 and 10 mg/L.[11,12] One criticism of CRP as a marker of cardiovascular risk is, due to its nonspecific nature, is that levels may increase sporadically unrelated to any cardiac pathology. One study found that in patients with stable coronary artery disease (CAD), when stratifying their CRP level as low, average, and high-risk, the change from the first to second measurement of CRP adjusted the patients risk category in 40% of patients.[13] However, perhaps more importantly, other studies evaluating the stability of serial measurements of CRP have reported no significant difference in variability of CRP as compared to that seen in the measurement of blood pressure or serum cholesterol.[14–16]

High-sensitivity C-reactive protein may provide prognostic value in a wide variety of clinical scenarios, from asymptomatic subjects to patients hospitalized for acute coronary syndromes. Most data regarding the utility of hs-CRP in cardiovascular risk assessment is derived from observational studies. More than 15 large observational studies have been published demonstrating the utility of elevated hs-CRP for predicting adverse cardiovascular events after multivariate adjustment for a variety of conventional cardiovascular risk factors (Table 1). A smaller number of studies have also been published demonstrating a trend towards an association of elevated hs-CRP for the prediction of adverse cardiovascular events that did not reach statistical significance after multivariate adjustment (Table 2). It must be acknowledged that a majority of the studies reaching statistical significance for hs-CRP are either entirely male or include a large majority of males (11/17), whereas a majority of the studies not reaching statistical significance for hs-CRP enrolled a majority of female patients (7/8). Also, as most of these studies were performed in Europe and America, most did not enroll large numbers of minorities. Finally, there is also considerable variation in these studies in the correction factors utilized in the multivariate adjustment and the number of patients in whom the actual CRP and cardiovascular outcomes analysis was carried out. However, taken as a whole these data suggest that increased hs-CRP is associated with a significant risk of incident cardiovascular events after correcting for traditional risk factors. A large meta-analysis including many of the previously mentioned studies supports this conclusion and found that patients in the top quartile of hs-CRP have an odds ratio (OR) of 1.45 for major cardiovascular events compared to patients in the lowest quartile after correcting for traditional cardiovascular risk factors.[14] Furthermore, studies have also shown that the relative impact of elevated hs-CRP on the prediction of cardiovascular events is as large, individually, as that of LDL cholesterol, HDL cholesterol, blood pressure, and smoking.[37,38]

Statins and CRP

Hydroxymethylglutaryl-CoA reductase inhibitors (statins) are the most widely studied cholesterol-lowering medications. In addition to their potent LDL lowering capabilities, laboratory studies have suggested they may have anti-inflammatory effects. Consistent with this observation, several studies have demonstrated the efficacy of statin in lowering CRP, and further, that this is independent of cholesterol-lowering effects.[15,39] These data, combined with the realization that 20% of coronary events occur in patients with no major risk factors,[40] served as the impetus for using CRP to identify additional at-risk patients who might benefit from statin therapy. Post hoc analysis from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) trial, a study randomizing patients without cardiovascular disease with average LDL and low high-density lipoprotein (HDL) levels to lovastatin or placebo, found that patients with a high CRP (defined as a CRP level above the median value of 1.6 mg/L) benefited from statin therapy whereas those with a low CRP (defined as a CRP level below the median value of 1.6 mg/L) did not.[16] Post hoc analysis from the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial comparing pravastatin (40 mg) to atorvastatin (80 mg) in patients following acute coronary syndromes, demonstrated that patients who achieved low levels of LDL (<70 mg/dL) and low CRP levels (<2 mg/dL) after statin therapy had less recurrent events than those who achieved low levels of LDL without a concomitant decrease in CRP.[41] The authors concluded that elevated CRP, irrespective of LDL level, was a marker of increased cardiovascular risk. Collectively, these observational data suggest that patients with low LDL but elevated CRP have higher cardiovascular risk and that statins may reduce the rate of cardiovascular events in this population. The JUPITER trial was conducted to prospectively test this hypothesis.

JUPITER Trial

The JUPITER trial was a large, multi-national, double-blind, placebo-controlled trial including more than 17 000 men and women. The trial was designed to assess whether statin therapy would reduce cardiovascular events (with the primary end point defined as the composite of cardiovascular death,

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Table 1. Studies Demonstrating Statistically Significant Correlation Between hs-CRP and Adverse Cardiovascular Events

Study (Year Published)	Population	Time of Initial Survey	Total No.of Participants	Nested Case-Cohort Analysis	Age Range	Male (%)	Mean Follow-Up (Yrs)	End Point	RR or OR (95% CI)
PHS (1997)[17]	Men	1982	22 071	1068 534 cases 534 controls	40–84	100	8	MI	2.6 (1.6–4.4) highest vs lowest quartile
BRHS (2000)[18]	Men	1978–1980	5661	1531 506 cases 1025 controls	40–59	100	16	MI, cardiac death	2.13 (1.38–3.28) highest tertile vs lowest tertile
AFCAPS-TEXCAPS (2001)[16]	Men/Women	1990–1993	6605	None	45–73	85	5	MI, cardiac death, unstable angina	1.17(1.03–1.33) per quartile increase
HONOLULU (2002)[19]	Men	1967–1970	8006	1717 369 cases 1348 controls	45–68	100	20	MI	1.6 (1.1–2.2) highest vs lowest quartile
WHI (2002)[20]	Women	1994–1998	75 343	608 304 cases 304 controls	50–79	0	3	MI, cardiac death	2.1 (1.1–4.1) highest vs lowest quartile
WHS (2002)[21]	Women	1992–1995	27 939	None	>44	0	8	MI, ischemic stroke, coronary revascularization, cardiac death	2.3 (1.6–3.4) highest vs lowest quintile
PRIME (2003)[22]	Men	1991–1994	9758	926 317 cases 609 controls	50–59	100	5	MI, cardiac death	2.16 (1.26–3.72) highest vs lowest tertile
SOF (2003)[23]	Women	1986–1988	9704	492 92 cases 400 controls	>64	0	6	Cardiac death	8.0 (2.2–2.9) highest vs lowest quartile

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Table 1. (*Continued*)

Study (Year Published)	Population	Time of Initial Survey	Total No.of Participants	Nested Case-Cohort Analysis	Age Range	Male (%)	Mean Follow-Up (Yrs)	End Point	RR or OR (95% CI)
ARIC (2004)[24]	Men/Women	1990–1992	12 819	1348 608 cases 740 controls	45–64	43	6	Incident CHD	1.72 (1.24–2.39) highest tertile vs lowest tertile
Caerphilly + Spee = dwater (2004)[25]	Men	1979–1983	3213	None	49–66	100	8	MI, cardiac death	1.72 (1.14–2.58) highest quintile vs lowest quintile
HPFUS (2004)[26]	Men	1993–1995	18 225	794 265 cases 529 controls	40–75	100	6	MI, cardiac death	2.55 (1.40–4.65) highest vs lowest quintile
Reykjavik (2004)[14]	Men/Women	1967–1991	18 569	6428 2459 cases 3969 controls	33–59	71	20	MI, cardiac death	1.45 (1.25–1.68) highest vs lowest tertile
WOSCOP (2004)[27]	Men	1989–1991	6595	1419 485 cases 934 controls	45–64	100	5	MI, cardiac death, revascularization	1.49 (1.00–2.22)
CHS (2005)[28]	Men/Women	1989–1990	3971	None	>64	43	10	MI, cardiac death	1.45 (1.14–1.86) CRP >3 mg/dL vs CRP <1 mg/dL
KIHD (2005)[29]	Men	1984–1989	2321	None	42–60	100	15	Cardiac death	1.71 (1.16–2.54) highest vs lowest tertile
MONICA-Augsburg (2006)[30]	Men	1984–1995	5382	1304 295 cases 1009 control	35–74	100	11	MI, cardiac death	1.89 (1.28–2.77) highest vs lowest tertile

[a] Studies: AFCAPS/TEXCAPS; ARIC - Atherosclerosis Risk in Communities; BRHS - British Regional Heart Study; Caerphilly and Speedwell Studies; CHS - Cardiovascular Health Study; HONOLULU - Honolulu Heart Study; HPFUS - Health Professionals Follow-up Study; KIHD - Kuopio Ischemic Heart Disease Risk Factor Study; MONICA-Augsburg - Monitoring Cardiovascular Disease Augsburg Cohort Study; PHS - Physicians' Health Study; PRIME - Prospective Epidemiological Study of Myocardial Infarction; Reykjavik - Reykjavik Study; SOF - Study of Osteoporotic Fractures; WHI - Women's Health Initiative; WHS - Women's Health Study; WOSCOP - West of Scotland Coronary Prevention Study.
[b] CAD - Coromary Artery Disease; MI - Myocarcial Infarction; OR - Odds Ratio; RR - Risk Ratio.

continued

Table 2. Studies Demonstrating Nonstatistically Significant Correlation Between hs-CRP and Adverse Cardiovascular Events

Study (Year Published)	Population	Time of Initial Survey	Total No. of Participants	Nested Case-Cohort Analysis	Age Range	Male (%)	Mean Duration of Follow-Up (Yrs)	End Point	RR or OR (95% CI)
Hoorn Study (1999)[31]	Men/Women	1989–1992	631	None	50–75	48	5	Cardiovascular death	1.32 (0.52–3.35) highest vs lowest tertile
Iowa 65+ (1999)[32]	Men/Women	1987–1989	1293	675 subjects 176 cases 499 controls	>64	41	5	Cardiovascular death	1.8 (0.9–3.6) highest vs lowest quartile
Quebec Cardiovascular Study (2001)[33]	Men	1985	2037	None	35–64	100	5	Stable or unstable angina, MI, cardiac death	1.1 (0.7–1.6) higher half vs lower half
Health-ABC (2003)[34]	Men/Women	1997–1998	2225	None	70–79	45	3.6	Incident CHD	1.2 (0.83–1.75)
Rotterdam Study (2003)[35]	Men/Women	1990–1993	7983	657 subjects 100 cases 557 controls	>54	46	5	MI	1.2 (0.6–2.2) highest vs lowest quartile
FHS (2005)[36]	Men/ Women	1980–1995	4446	None	Avg = 59	44	8	MI, cardiac death	1.22 (0.81–1.84)
MONICA-Augsburg (2006)[30]	Women	1984–1995	5336	1058 subjects 87 cases 971 control	35–74	0	11	MI, cardiac death	1.35 (0.64–2.84) highest vs lowest tertile

[a] Studies: FHS - Framingham Heart Study; Health-ABC - Health, Aging, and Body Composition Study; Hoom Study; Iowa 65+ - Iowa 65+ Rural Health Study; MONICA-Augsburg - Monitoring Cardiovascular Disease Augsburg Cohort Study; Quebec Cardiovascular Study; Rotterdam Study - The Rotterdam Study.
[b] CAD - Coronary Artery Disease; MI - Myocardial Infarction; OR - Odds Ratio; RR - Risk Ratio.

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myocardial infarction, stroke, hospitalization for unstable angina, or arterial revascularization) in individuals with normal LDL cholesterols (<130 mg/dL) but elevated CRP levels (>2.0 mg/L). The trial included males over the age of 50 and females over the age of 60 with no history of cardiovascular disease, stroke, or diabetes, and randomized patients meeting the above criteria to rosuvastatin (20 mg) or placebo. It should be noted that the principal investigator holds a patent on the use of CRP assay for cardiovascular risk assessment, and the manufacturer of rosuvastatin, AstraZeneca, funded the study.

The median LDL at the initiation of the trial was 108 mg/dL and the median CRP was 4.3 mg/L. Approximately 40% of patients met the criteria for the metabolic syndrome at baseline, 16% used tobacco, 11% had a family history of heart disease, and the average age was 66. The trial screened more than 90 000 patients to enroll the 17 802 subjects. Half of the excluded patients had an LDL >130 mg/dL, another 40% had CRP levels less than 2.0 mg/L.

As expected, among patients treated with rosuvastatin, LDL levels decreased by approximately 50%, from a median of 108 mg/dL to 55 mg/dL at 12 months. C-reactive protein levels were similarly reduced, from an average of 4.2 mg/L at baseline to 2.2 mg/L at 12 months. These effects persisted over the course of the study.

The JUPITER trial was stopped early after a mean of 1.9 years of follow-up by an independent data and safety monitoring board due to a significant reduction in the combined primary end point in the rosuvastatin arm of the study. The primary end point was reduced by 44% in the rosuvastatin arm with a 20% reduction in all-cause mortality. The absolute risk reduction was 1.2%, with the primary end point occurring in 2.8% of patients in the placebo arm vs 1.6% of patients in the rosuvastatin arm. The benefit of rosuvastatin therapy was found to be consistent for each of the individual components of the primary end point, and was consistent across all subgroups including analyses based on age, race, and gender.

A recently published abstract at the American Stroke Association International Stroke Conference focused on the 48% reduction in nonfatal stroke, similar to the 55% reduction in nonfatal myocardial infarction (MI).[42] Importantly, the ischemic stroke rate was reduced without a coincident increase in hemorrhagic stroke, a notable finding given the potential anticoagulant effects of statins. Similar to the combined cardiovascular end points in the study, the reduction in stroke was consistent across all subgroups. A recently released analysis also demonstrated that patients achieving a low CRP and low LDL after 1 year of therapy had lower event rates than patients with high CRP and low LDL.[43] Analysis of secondary end points from the JUPITER study also found that venous thromboembolic events (VTE) were reduced in the statin arm of the study.[44] Interestingly, the reduction in VTE events by approximately 50% was similar in degree to the reduction in cardiovascular events. The reduced incidence of VTE did not correlate with lipid levels—this may highlight the importance of anti-inflammatory effects of statins in reducing events in both the arterial and venous beds.

There was no significant difference in serious reported adverse events between the rosuvastatin and placebo groups, though interestingly, there was a clinically modest but statistically significantly higher incidence of diabetes in the rosuvastatin arm of the study. The etiology for this difference in the statin arm is unclear.

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C-reactive protein had been reported in post hoc analyses to predict cardiovascular risk in a number of primary and secondary prevention trials. The JUPITER trial suggests elevated CRP may identify a subgroup of patients who do not otherwise meet guideline criteria for statin therapy, but nonetheless appear to benefit. What then is the potential role of measuring CRP in clinical practice in light of the JUPITER findings? Should we acknowledge its potential benefits in a low risk population and immediately advocate its routine measurement in this population? Alternatively, would it be useful to incorporate hs-CRP formally into a risk score similar to the Framingham risk calculator and use its results to selectively identify patients in whom statin therapy will be both therapeutic and cost-effective? Or should we continue to follow the CDC/AHA guidelines for the clinical application of CRP, which suggest that it should be measured only in patients deemed to be at intermediate risk by the use of conventional risk factors in whom the decision regarding the intensification of therapy is unclear?[45]

An important concern regarding the application of the JUPITER findings to the general population in the midst of expanding healthcare costs and a nationwide recession is the cost-effectiveness of treating a large number of patients with elevated CRP but normal cholesterol levels. A recently published analysis suggests that more than 11 million new patients in the United States may become candidates for statin therapy by applying the JUPITER criteria to the population at large.[46] At a projected cost of $1200/year for rosuvastatin, given a number needed to treat of 95 patients for 2 years, the cost to prevent 1 primary end point from occurring is $228 000. If one assumes 5 persons need to be screened to find 1 candidate meeting the study criteria, then to find 95 subjects, one would need to screen an additional 475 subjects. At a cost of $20 per CRP test, this would add another $10 000 to the cost of preventing 1 cardiovascular event from occurring. Thus, the costs of implementing such a broad pharmacological primary prevention program needs to be considered closely prior to advocating such a strategy.

It also must be acknowledged that the study design of JUPITER does not specifically prove that we should measure CRP. Because the JUPITER trial excluded patients with LDL

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<130 mg/dL and CRP <2 mg/L, it did not prove that CRP can be used to differentiate patients who would or would not benefit from statin therapy. Perhaps men over 50 and women over 60 with hs-CRP <2 mg/L would also have benefited from statin therapy? Unfortunately, the JUPITER trial does not answer this question so we simply do not know if testing for hs-CRP differentiates a person who will and will not benefit from statin therapy. Rather, it may be argued that JUPITER joins several other studies, such as PROVE-IT TIMI 22, in demonstrating that lowering LDL reduces cardiovascular events, with the caveat that JUPITER extends these findings to patients without known CAD or CAD equivalents.

Should we consider CRP as an additional marker of risk, and embrace new risk-prediction models that incorporate CRP? The Reynolds risk score, incorporating family history and CRP into a cardiovascular risk model, was reported to be a better predictor of cardiovascular events than the Framingham risk score in both men and women.[47,48] However, even the application of the Reynolds risk score to an intermediate risk group of men resulted in the reclassification of only 20% to a low or high risk category.[47] Moreover, the same study found that family history was at least as strong a predictor of cardiovascular risk as CRP. Only at the extremes of CRP (<0.5 mg/L or >10 mg/L) did CRP add to the prognostic value gained by including family history. This raises the question whether a simple, thorough history rather than lab tests with added costs might result in similar improvements in cardiovascular risk prediction.

What about the impact of JUPITER on CDC/AHA guidelines for CRP use? As stated above, the current recommendations state that hs-CRP levels may be useful in patients at intermediate risk, defined as a 10-year Framingham risk of >10% and <20%,[45] and that "clinical judgment is required whether to adjust risk within this risk category by measurement of hs-CRP." At the time of its writing in 2003, the guidelines state as to the question of when and in whom hs-CRP should be measured:

> "No clinical trials have been completed in which a population has been randomly allocated to screening for hs-CRP and compared with a control population not allocated to hs-CRP screening and both groups followed up prospectively to determine the benefits and harms of the screening. In particular, there continue to be few data on the cost-effectiveness of screening with inflammatory markers, taking into account further testing and treatment of persons classified as having high risk for CVD or the possibility of reduced testing and treatment of persons classified as being at low-risk. . .Such trials, however, are a recognized area for needed research."

Despite its impressive results, the JUPITER trial still does not address these key questions—namely a trial comparing statin therapy for primary prevention patients with patients with low and high hs-CRP levels and the cost effectiveness questions raised previously. The importance of answering these key questions is again reiterated by reviewing the status of hs-CRP in the context of a recently released expert scientific statement from the AHA addressing the evaluation of novel markers of cardiovascular risk.[49] The article outlines 6 important elements for evaluating new cardiovascular risk markers prior to advocating their routine use, including proof concept, prospective validation, incremental value beyond established standard risk markers, clinical utility, clinical outcomes, and cost effectiveness. As outlined, hs-CRP meets only 4 of the 6 criteria, as the clinical outcomes and cost effectiveness data for hs-CRP is still lacking. Thus, we would argue that the JUPITER trial has still not addressed the key questions about hs-CRP raised more than 5 years ago by the guidelines, and thus should not change the recommendations made in the guidelines substantially. However, in patients at intermediate risk in whom the decision regarding the initiation of statins is unclear, JUPITER would seem to establish a hs-CRP level above 2 mg/L as a reasonable cut-off above which a more aggressive primary prevention with statin therapy would be reasonable.

Conclusion

The data linking elevated hs-CRP and cardiovascular disease continue to grow and was added to substantially by the JUPITER trial. However, we believe that until a true randomized clinical trial including both low- and high–hs-CRP patients is conducted and a careful assessment of the cost-effectiveness of CRP testing is performed, advocating the widespread use of hs-CRP would be premature. While acknowledging the contribution of JUPITER to preventive cardiology and its potential role in realigning our criteria for statin therapy, we recommend the selective approach to CRP measurement only in intermediate-risk individuals advocated by the CDC/AHA should remain the standard of care until more information regarding CRP is available.

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