



TITLE: **Assessing Cardiovascular Disease Risk with HS-C-reactive Protein**

AUTHOR: **Judith Walsh, M.D., MPH**
Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

PUBLISHER: **California Technology Assessment Forum**

DATE OF PUBLICATION: **June 17, 2009**

PLACE OF PUBLICATION: **San Francisco, CA**



ASSESSING CARDIOVASCULAR DISEASE RISK WITH HS-C REACTIVE PROTEIN

A Technology Assessment

INTRODUCTION

The California Technology Assessment forum was asked to assess the evidence for the use of high sensitivity C reactive protein (CRP) for prediction of coronary heart disease (CHD) risk. This topic is being reviewed now because of the recently published results of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, where individuals with elevated CRP but without hyperlipidemia were treated with statins with the goal of reducing CHD risk.¹

BACKGROUND

Coronary artery disease (CAD) is the number one cause of death in men and women. Many risk factors increase an individual's risk for CHD, including family history of premature CHD, smoking, hypertension, diabetes and hyperlipidemia. Many risk models have been created that estimate an individual's risk of cardiovascular disease based on an individual's age and other cardiovascular risk factors. For example, the Framingham model estimates an individuals' ten year risk of cardiovascular disease based on age, blood pressure, smoking status and cholesterol levels [www.nhlbi.gov/guidelines/cholesterol/risk]

Besides the established CHD risk factors, other factors have been explored as risk factors for CHD. Inflammatory processes appear to be involved in the development of atherosclerosis and several biomarkers of inflammation have been studied. CRP is the one that has been most extensively studied.

CRP is an acute phase protein that is produced in the liver under the influence of cytokines including interleukin (IL)-6 and tumor necrosis factor-alpha. CRP is elevated in many conditions including infections and inflammatory disorders. When these assays were initially developed, for use in these conditions, they were developed with a detection limit of 3-5 mg/l, which is higher than the level seen in most healthy individuals. Subsequently high sensitivity measurements for CRP have developed (hs-CRP) that can detect levels down to 0.3 mg/dl. The hs-CRP assays are

needed for cardiovascular risk stratification since it is based on the discrimination of levels below 3 mg/L. For determination of cardiovascular risk, the following values have been defined: (low risk <1 mg/L), average risk (1-3 mg/L) and high risk (>3.mg/L). These values correspond approximately to tertiles of the general population. Because hsCRP levels can fluctuate, it has been recommended that two measurements obtained two weeks apart be averaged to provide a more stable estimate.)². Values of >10 mg/l suggest the possibility of infection or inflammation.

Many established CHD therapies also affect CRP levels. For example, statins result in a reduction in CRP levels by about 20-30%,³ The reduction in CRP appears to be independent of the effect on LDL cholesterol.^{4,5} In addition, the Dietary Approaches to Stop Hypertension(DASH) style diet has been associated with a reduction in CHD mortality and stroke risk as well as a reduction in CRP.⁶

The effect of aspirin on CHD may also be mediated by its anti-inflammatory effect. Among men in the Physicians' Health Study, the CHD risk reduction seen with aspirin was much greater for men with CRP in the upper quartile than for those with CRP in the lowest quartile (56 % versus 14%).⁷ Beta blockers have also been associated with a reduction in CRP in individuals with CHD.⁸

The potential goal of using hs-CRP would be to determine whether or not it adds additional prognostic value to conventionally measured cardiovascular risk factors including blood pressure, blood glucose, lipoproteins, and also whether or not treating individuals with elevated hs-CRP affects clinical outcomes. Thus, the following questions are relevant: 1) Is elevated hs-CRP associated with CHD risk? 2) Does measuring hs-CRP add prognostic value to measurement of conventional CHD risk factors in individuals without CHD? 3) Does treatment of elevated hs-CRP in individuals without CHD change clinical outcomes? 4) Does screening for elevated hs-CRP affect CHD outcomes?

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies

Many CRP assays have been approved by the FDA through the 510(k) process. In 2005 the FDA Office of In Vitro Diagnostic Device Evaluation and Safety (OVID) published a guidance document

which differentiates between the types of CRP assays, CRP, high-sensitivity CRP (hsCRP) and cardiac CRP (cCRP), and the requirements for identifying each and its use. While cCRP assays are the only ones approved by the FDA for use in cardiovascular risk assessment/stratification, the FDA recognizes that the hsCRP may be the more generic term used.⁹

TA criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Search Methods: We searched Medline, the Cochrane clinical trials database, Cochrane reviews, database and the Database of Abstracts of Reviews of Effects (DARE) using the search terms of cardiovascular disease or heart disease or coronary disease or carotid artery diseases cross referenced with C reactive protein. In addition, we searched the bibliographies of the identified articles and other reviews to identify primary data sources and search strategies to ensure a complete review of the relevant literature. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Studies were included if they included the use of hs-CRP in predicting cardiovascular disease in primary prevention population based studies, if they assessed the impact of treating elevated CRP on clinical outcomes or if they assessed the impact of screening for CHD on clinical outcomes.

Inclusion criteria:

- Study had to assess a clinical outcome
- Study had to measure high sensitivity CRP
- Study had to independently assess CRP as a predictor of CHD risk in a primary prevention population based cohort or assess the impact of treatment of elevated CRP on clinical outcomes or assess the impact of screening for elevated hs-CRP on clinical outcomes
- Included only humans
- Published in English as a peer reviewed article

Studies were excluded if they only focused on non-clinical outcomes such as lipid levels or other metabolic parameters. Because we were focusing on assessing CHD risk in healthy individuals in the general population, we did not include individuals with known CHD nor did we focus on

retrospective case-control studies. We identified relevant published articles: we identified seven prospective population based cohort studies and one randomized controlled trial. The outcomes evaluated included myocardial infarction (MI), CHD mortality, revascularization, angina, and total mortality. The observational studies assessed the role of hs-CRP in predicting cardiovascular outcomes. The clinical trial addressed whether treatment of elevated hs-CRP affected cardiovascular outcomes. No studies were identified that evaluated the impact of screening for hs-CRP and the effect on clinical outcomes.

Search Results

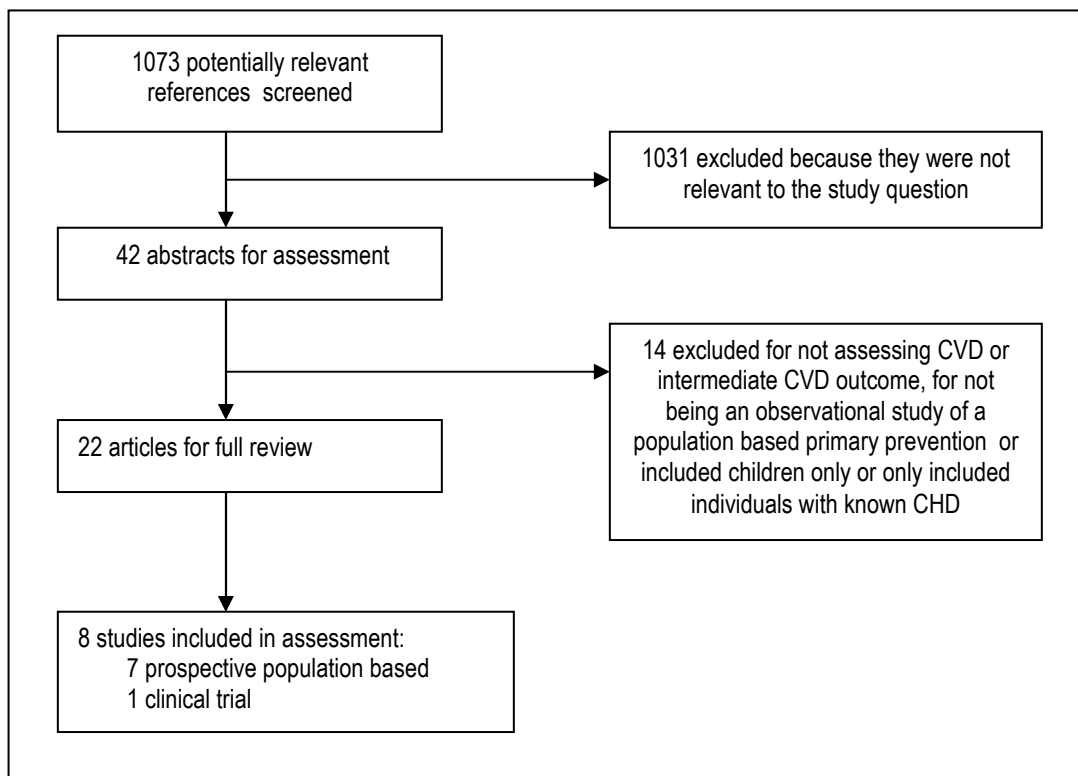


Figure 1. Study Selection

Is hs-CRP a predictor of CHD and does it add additional prognostic value to traditional cardiac risk factors?

Multiple prospective observational studies in primary prevention populations including over 50,000 participants have assessed whether or not hs-CRP was a predictor of CHD outcomes. (Table 1) In



most of these primary prevention population observational studies, hs-CRP was a predictor of CHD outcomes.



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TABLE 1: Prospective Cohort Studies of Primary Prevention Populations Assessing CRP as a Predictor of CHD Outcomes

Study	N	% Women	Length of follow-up	Comparison	Outcome	Multivariate Risk Ratios
Framingham ¹⁰	4444	56%	8 years	hs-CRP <1 mg/L, 1-3 mg/L and >3 mg/dl	Total CVD Major CVD Major CHD	RR 1.6 (95% c.i. 1.19, 2.14) for CRP >3 mg/l
Strong Heart Study ¹¹	3277	64%	6 years	hs-CRP <1 mg/L, 1-4 mg/L and >h mg/dl	CVD events	RR 1.63 (1.00-2.67) for hs-CRP >4 mg/L
Helsinki Aging ¹²	455	49%	10 years	CRP ,5 mg/L vs. >5 mg/L	Total mortality CV mortality	RR 1.20 (1.08, 1.32) for total mortality RR 1.22 (1.10, 1.35) for CV mortality
Health ABC, ¹³	2225	55%	3.6 years	Highest vs. lowest tertile of CRP		RR 2.6 (1.45-4.67) for CHF events RR 1.20 (0.83-1.75) for CHD events
Women's Health Study ¹⁴	27,939	100%	8 years	Quintiles of CRP	MI, ischemic stroke, revascularization, CV death	RR CV events each quintile compared with lowest quintile 1.4, 1.6, 2.0, 2.3 (p<0.001)
Kuopio ¹⁵	1476	0%	14.6 years	CRP <1.0 mg/L vs. 1.0-2.9 mg/L vs. 3.0-10 mg/L	All cause and cardiovascular mortality	RR CV mortality 4.1 (2.1, 8.2) for highest vs. lowest CRP
Cardiovascular Health Study ¹⁶	5020	60%	11 years	CRP <1.0 mg/L vs. 1.0-2.9 mg/L vs. 3.0 mg/L or greater	MI , stroke, CVD death, all cause mortality	RR 1.33 (1.11, 1.60) for MI CRP > 3 mg/L compared with <1 mg/L. RR 1.38 (1.25, 1.53) for all cause mortality
MONICA ¹⁷	3620	0%	7.1 years	CRP <1.0 mg/L vs. 1.0-2.9 mg/L vs. 3.0 mg/L or greater	Total mortality, CVD mortality, CHD mortality,	HR total mortality 1.88 91.41, 2.52) highest vs. lowest
PROSPER ¹⁸	3,165 (primary prevention group)	52% (entire cohort)	3.2 years	Tertiles of CRP	Composite endpoint CHD death, nonfatal MI or fatal or nonfatal stroke	RR 1.51 91.17, 1.95) for highest vs. lowest tertile

Hs-CRP is a predictor of CHD risk and may add additional value beyond that provided by usual cardiovascular risk factors. In some of the prospective studies, CRP added prognostic value when added to a model that included traditional cardiovascular risk factors in estimating CHD risk.^{14, 19} However, in other studies, measuring hs-CRP did not add additional prognostic value.^{10, 12}

A recent AHA Scientific Statement set forth criteria for the evaluation of novel markers of cardiovascular risk²⁰. The novel risk factor is added to standard risk markers and is evaluated. Then the discrimination of the new marker is reported. Finally the accuracy of the new marker is reported. The observed vs. the expected event rates across the range of risks are reported for models with and without the risk marker.

A new cardiac risk algorithm was developed and validated based on the Framingham risk calculator. The new model includes two additional risk factors- family history of CHD and hsCRP and was developed separately for men and women^{21, 22}. In the model for women, a total of 24,558 women were followed for 10.2 years for incident cardiovascular disease (CVD). Data from two-thirds of the women (the derivation cohort) were used to develop the risk algorithm. This algorithm was subsequently tested in a validation cohort to compare observed and expected outcomes. These new models were compared with Framingham models in women for predicting cardiovascular risk. They first assessed the discrimination of the models and then assessed their ability to reclassify individuals' cardiac risk. In a model that included age, systolic blood pressure, glycohemoglobin if diabetic, smoking, total and HDL cholesterol, hs-CRP and parental history of MI before the age of 60, 44% of women with a ten year risk of CHD of five percent to ten percent as predicted by the Framingham model were reclassified to a higher or lower risk category, and 45% of those with a Framingham risk of 10-20% were reclassified to a higher or lower risk category. This prediction algorithm, known as the Reynolds Risk Score can reclassify a fair number of individuals to higher or lower cardiovascular risk categories and could have important implications for pharmacotherapy.²¹ In other cohorts including men,²²⁻²⁵ the use of hs-CRP reclassifies 20-30% of intermediate-risk asymptomatic individuals to a different risk category.

Does treatment of elevated hs-CRP affect clinical outcomes?

There has been one randomized controlled trial (RCT) which assessed whether or not treating

individuals with elevated hs-CRP but normal LDL- cholesterol with statins could decrease the rate of first cardiovascular events. The JUPITER trial was a randomized double-blind placebo controlled multi-center trial conducted in 26 countries. Participants were 17,802 men aged 50 and older and women aged 60 and older without CHD who had an LDL cholesterol <130 mg/L and an hs-CRP of 2.0 mg/L or more. Participant characteristics at baseline are described in Table 2. At baseline participants had a mean body mass index (BMI) of 28.3, 16% were smokers, 11% had a family history of premature CHD, and 17% were on aspirin. At baseline participants' median LDL-C was 108 mg/dl and median SBP was 134 mm HG and median DBP was 80 mm Hg. They were randomized to receive rosuvastatin 20 mg versus placebo. Individuals with inflammatory conditions were excluded; individuals taking immunosuppressants were also excluded. Potential participants underwent a four week run in period to ensure compliance. The primary endpoint was MI, stroke, arterial revascularization, hospitalization for unstable angina or death from cardiovascular causes. The trial was planned to continue for four years of follow-up, but was stopped early after 1.9 years of follow up when the data safety and monitoring board noted a significant reduction in the primary end point among participants receiving rosuvastatin. LDL-cholesterol was lowered by 50% and CRP levels were decreased by 37%. There were 142 events in the treatment group versus 251 in the placebo group for a hazard ratio was 0.56 (95% C.I. 0.46, 0.69). Similar reductions were seen for the individual end point of MI, stroke, death from cardiovascular causes and the combined outcome of revascularization or stable angina. In terms of absolute risk, 1.8% of participants in the placebo group had an event compared with 0.9% in the rosuvastatin group resulting in a number needing to treat (NNT) of 120 for 1.9 years to prevent one CHD event.

Table 2: Baseline Characteristics of JUPITER Participants

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Age (mean)	66.0	66.0
% Female	38.5%	37.9%
Mean BMI (kg/m ²)	28.3	28.4
Median SBP (mmHg)	134	134
Median DBP (mmHg)	80	80
Current Smokers (%)	15.7%	16.0%
Hs-CRP (mean) mg/L	4.2	4.2
LDL Cholesterol (mg/dl) median	108	108
HDI Cholesterol (mg/dl) median	49	49

Although the JUPITER trial showed a significant reduction in cardiovascular events among the individuals included, there are several potential limitations. First, the group of included individuals was a relatively select one. Individuals with prior use of lipid lowering therapy, diabetes, elevated creatinine, recent cancer and uncontrolled hypertension, hepatic dysfunction or elevated creatine phosphokinase (CPK) were excluded as were individuals who did not have LDL cholesterol or hsCRP in the target range. Secondly, participants who met original inclusion criteria then underwent a run in and only those who were compliant at four weeks were included. Thus, of over 89,000 individuals initially screened, over 72,000 were ineligible. Third, participants were a relatively high risk group with a mean BMI of 28.3, and a fairly high prevalence of other cardiovascular risk factors. Finally, there is no information on long term safety of lowering LDL to such a low level as with rosuvastatin in the participants. There was a slight increased rate of physician diagnosed diabetes mellitus in rosuvastatin treated participants of unclear significance. Long term safety is particularly important given that individuals without disease would have to be treated for many years to achieve potential benefit.

In conclusion, among healthy individuals without CHD, but with a moderate prevalence of cardiovascular risk factors, without hyperlipidemia, but with elevated CRP levels, rosuvastatin treatment can reduce the risk of major cardiovascular events.

Does screening for elevated hs-CRP lead to improvement in CHD outcomes?

No studies have addressed whether or not screening for elevated hs-CRP and then treating based on hs-CRP results affects clinical outcomes.

Level of Evidence 1, 3

TA Criteria 1 is met for hs-CRP as a predictor of CHD events

TA Criteria 2 is met for whether treatment of elevated hs-CRP affects clinical outcomes

TA criteria 2 is not met for whether screening for elevated hs-CRP leads to improved clinical outcomes compared with no screening

TA Criteria 3: The technology must improve net health outcomes

Does treating individuals with an elevated hs-CRP with statins improve net health outcomes?

In the JUPITER trial, individuals with elevated hs-CRP and normal cholesterol levels who were treated with statins had improved cardiac outcomes compared with those who were not treated. Thus in this group of individuals, health outcomes were improved.

Does screening for hs-CRP to identify those at high risk improve net health outcomes?

For a diagnostic test, ideally there should be evidence that use of the test would result in improved medical management in a way that would benefit the patient. Therefore, once CRP elevation has been identified, there should be evidence that identification of elevated CRP leads to a reduction in CHD outcomes that would not happen if an elevated CRP was not elevated.

Although the JUPITER trial showed that treating individuals without hyperlipidemia and with elevated CRP reduces the incidence of major cardiovascular events, it was a study of statin therapy, not a study of hs-CRP testing. A randomized trial in which some individuals received treatment based on hs-CRP test results and others received therapy independent of hs-CRP results could answer the question of whether or not measuring hs-CRP affects clinical outcomes, but this has not been done.

An important question is whether identifying an elevated hs-CRP can help a physician in determining whether or not the patient should take statins. Screening with hs-CRP to identify those at high risk has not been compared to not screening with respect to CHD outcomes. The ideal study would allocate some patients to treatment based on an elevated hs-CRP, whereas others would receive treatment independent of hs-CRP results. This has not been done.

It has been suggested that testing those at intermediate risk may be helpful. Measurement of hs-CRP is an independent marker of risk and in those judged at intermediate risk by global risk assessment (10-20% risk of CHD per ten years) at the discretion of the physician, may help direct

further evaluation and therapy in the primary prevention of CVD. The results of such therapy based on this strategy remain uncertain.²

To date, testing for hs-CRP has not been shown to improve net health outcomes, compared with not testing for hs-CRP.

TA Criterion 3 is met for whether treatment of individuals without CHD with elevated hs-CRP improves net health outcomes

TA Criterion 3 is not met for whether or not screening for elevated hs-CRP will improve net health outcomes

TA Criterion 4: The technology must be as beneficial as any of the established alternatives.

The main alternative to hs-CRP testing and treatment based on hs-CRP results is not using hs-CRP in decision making about the use of statins or other cardiac risk reduction therapy. Often clinicians use assessment of an individual's risk for CHD to decide about risk reducing therapies, such as the use of statins for hyperlipidemia or initiation of drug therapy for hypertension. Sometimes clinicians use the Framingham risk score to calculate an individual's ten year risk of CHD to aid in the decision about initiation of drug therapy. The Reynolds risk score, which includes hs-CRP level to assess CHD risk, may be a more accurate way to classify CHD risk.²¹ However, even if it is a more accurate way to assess CHD risk, whether or not using hs-CRP as part of cardiac risk assessment improves cardiac outcomes compared with not using hs-CRP has not been shown. Thus, it is not known whether or not use of hs-CRP is as beneficial as any of the established alternatives.

TA Criterion 4 is not met

TA Criterion 5: The improvement must be attainable outside the investigational settings.

Treating high risk individuals with elevated hs-CRP with statins has been shown to reduce CHD risk in the investigational setting, but has not been evaluated outside of this setting. Whether the use of hs-CRP in addition to other markers of CHD risk results in a reduction in CHD events



compared with not using hs-CRP has not been demonstrated in the investigational setting and therefore it cannot be considered attainable outside this setting.

TA Criterion 5 is not met.

SUMMARY

In summary, hs-CRP is being evaluated for use in screening for CHD risk and for decision making about the use of statins. Elevated hs-CRP is associated with CHD risk, and treatment of individuals with elevated hs-CRP but normal LDL cholesterol for 1.9 years leads to a reduction in cardiovascular outcomes. However, we do not know how a strategy where treatment decisions are guided by hs-CRP compares with a strategy where treatment decisions are not influenced by hs-CRP levels. There is no evidence regarding whether or not screening for elevated hs-CRP will affect clinical outcomes.

RECOMMENDATION

Measurement of hs-CRP does not meet CTAF criteria 3-5 for improvement in health outcomes compared with no testing.

June 17, 2009

This is the first time this topic is being assessed by the California Technology Assessment Forum.

The California Technology Assessment Forum voted to accept the recommendation as presented.



RECOMMENDATIONS OF OTHERS

Blue Shield and Blue Cross Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) produced a special report regarding this technology in 2003.

Centers for Medicare and Medicaid Services (CMS)

A specific reference to use of this technology was not found on the CMS web site.

American College of Cardiology – California Chapter (CA ACC)

The CA ACC has provided a statement supporting the use of this technology. A representative attended the meeting to provide testimony.

American Heart Association (AHA)

The AHA has posted this document discussing CRP to their web site:
<http://www.americanheart.org/presenter.jhtml?identifier=4648>

ABBREVIATIONS USED

CRP	C-reactive protein
CHD	Coronary heart disease
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
CAD	Coronary artery disease
IL	Interleukin
DASH	Dietary Approaches to Stop Hypertension
OVID	Office of In Vitro Diagnostic Device Evaluation and Safety
hsCRP	High sensitivity C reactive protein
cCRP	Cardiac CRP
DARE	Databases of Abstracts of Reviews of Effects
MI	Myocardial infarction
CVD	Cardiovascular disease
EPIC	European Prospective Investigation into Cancer and Nutrition
RCT	Randomized controlled trial
BMI	Body Mass Index
NNT	Number needing to treat
CPK	Creatine phosphokinase
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure

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