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Review

Brief review and critical examination of the use of hs-CRP for cardiac risk assessment with the conclusion that it is premature to use this test

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Abstract

Background: Inflammation appears to be an important ingredient in the process of atherosclerosis that leads to coronary artery disease. Some have designed an algorithm for assessing risk of coronary artery disease using the inflammatory marker hs-CRP in conjunction with lipoprotein lipid risk factors.
Aim: I contend that because of its poor discrimination for coronary risk in clinical trials, until its utility is better proven, hs-CRP should not be recommended for defining risk.
Review: Published articles and reassessment of papers previously published.
Conclusions: After adjustment for conventional risk factors, hs-CRP discriminates poorly between persons with coronary disease and those without over a range of from about 0.6 to 7 mg/L which includes most apparently well people. Nor does the evidence indicate that hs-CRP adds significant predictive value to the clinical traits that define metabolic syndrome.

Keywords: hs-CRP; Low density lipoprotein cholesterol; High density lipoprotein cholesterol; Predictive values

Contents

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1. Introduction

It is hypothesized that endothelial dysfunction, lipoprotein oxidation and inflammation are the major physiological mechanisms that lead to acute ischemic syndromes [1–4]. Historically, automated analysis of CRP in clinical laboratories uses turbidimetry or nephelometry with sensitivities just below about 8 mg/L for identifying and monitoring acute or chronic conditions associated with infection and autoimmune disease [5], above which level this nonspecific marker for inflammation is useful when the prevalence of disease based on symptoms is high. Data indicate that CRP at lower concentrations, so called, high sensitivity C-reactive protein (hs-CRP) and other inflammatory markers are associated with atherosclerosis and that inflammatory markers decrease with lipoprotein altering therapy [6–8]. These are important findings that support the inflammatory disease hypothesis of atherosclerosis.

Moreover, it was suggested that hs-CRP could be used to assess risk of coronary heart disease (CHD) for clinical purposes [9], even for global assessment in apparently healthy persons where the prevalence of CHD is low. It is the usefulness of hs-CRP for these purposes that I question in this article. Problems related to sample collection, methodological variation, standardization, precision and quality control parameters have been carefully reviewed in detail recently [10] and will not be discussed here. Here, I will focus on the poor discrimination that this marker has shown in clinical trials that I believe makes its use for clinical purposes dubious.

2. Background information

Ridker and associates showed that hs-CRP added to the prediction by relative risk or odds ratio (RR) when tertiles or quartiles were used in conjunction with the ratio of total cholesterol/high density lipoprotein cholesterol (HDLC) or total cholesterol alone [9,11]. Rifai and Ridker suggested an algorithm for assessing RR of CHD using hs-CRP in conjunction with the ratio of HDLC to total cholesterol concentration [12]. Presumably, because ratios are difficult to use in clinical practice, the algorithm was modified to use cutoffs of hs-CRP (mg/L) <1, 1–3, >3 in conjunction with LDLC concentration or Framingham 10 year risk assessment [13]. More recently, Ridker, Wilson and Grundy suggested extending the cutoff points to <0.5, 0.5 to <1, 1–3, >3 to 10 and >10 [14].

3. hs-CRP is nonspecific with a poor positive predictive value and poorly defined clinical decision points

hs-CRP is an extremely nonspecific marker that varies with the status of inflammation in any person. Thus, besides being very elevated in acute infections and chronic diseases, at lower levels, it appears to vary with smoking (6), hormone replacement therapy (HRT) [15], obesity [16,17], age [18], diabetes [19] and atrial arrhythmias [20]. We estimated a very poor Bayesian positive predictive value of 0.86% in the highest RR quartile when hs-CRP was used alone as a marker for predicting CHD [21]. A recent article indicated that 40% of women between ages 30–39 have hs-CRP concentrations >3.3 mg/L, and that this high percentage was similar in normal women and those treated with HRT [22], which would be consistent with the poor predictive value that we calculated [21].

In addition, appropriate clinical decision points remain unclear. In one study, apparently healthy women on HRT, without CHD, showed an average hs-CRP of 3.75 mg/L [23] that would put these normal women into the highest quintile associated with disease in another study [11]. Men who smoke