Should We Use C-Reactive Protein or Other Novel Markers for CHD Risk Stratification?

Folsom AR, Chambless LE, Ballantyne CM, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: The Atherosclerosis Risk in Communities Study. Arch Intern Med 2006;166:1368–73.

Study Overview

Objective. To examine whether C-reactive protein (CRP) or other novel risk markers for coronary heart disease (CHD) add to the predictive value of current CHD risk prediction models.

Design. Case-control study within a prospective cohort study (case-cohort design).

Setting and participants. 15,792 patients aged 45 to 74 years who were sampled from 4 U.S. communities from 1987 to 1989 in the Atherosclerosis Risk in Communities (ARIC) study [1]. The case-cohort design involved all incident CHD cases compared with a stratified random sample of the ARIC cohort. Sampling was restricted to white and African-American patients. Patients with CHD, stroke, or transient ischemic attack at baseline were excluded. Hazard rate ratios were calculated for novel risk factors to assess for associations with incident CHD.

Main outcome measures. Additional contribution of individual novel risk markers to CHD prediction beyond that of traditional risk factors as measured by the area under the receiver operating characteristic curve (AUC).

Main results. Of the 19 novel risk markers, only lipoprotein-associated phospholipase A_2 ($LpPLA_2$) offered a small but statistically significant increase in the predictive value of risk models that included traditional risk factors. CRP and 17 other novel risk markers (eg, vitamin B_6, folate, D-dimer, homocysteine) did not significantly improve the prediction of incident CHD beyond that of traditional risk factors.

Conclusion. At this time, routine measurement of novel risk markers for CHD appears unjustified.

Commentary

CRP is an acute phase reactant mainly produced by hepatocytes under the regulation of cytokines and is the most widely studied marker of inflammation in cardiovascular disease. Previous research has demonstrated that CRP has a statistically significant association with CHD [2]. Recently, there has been an interest in whether novel markers such as CRP can improve CHD prediction models. This study by Folsom et al is the latest to address the value of CRP and other markers of inflammation in predicting coronary events beyond that of known risk factors.

Folsom et al examined 19 novel risk factors, using AUC (ie, the probability that a person who had an incident event within a specified time [5 years] had a higher risk score than a person who did not have an event by that time) to measure individual risk prediction. While many of the novel risk markers had a statistically significant age-adjusted association with incident CHD, only 1 of 19 risk markers ($LpPLA_2$)

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marginally improved the prediction of models that also employed traditional risk factors. For example, when CRP was added to the basic risk model (including the traditional risk markers of age, race, sex, total cholesterol, high-density lipoprotein level, systolic blood pressure, antihypertensive medication, smoking status), the AUC increased from 0.767 to 0.770, an incremental increase that was not statistically significant ($P > 0.05$).

This study does not suggest that novel risk markers are unimportant; however, it remains a question whether these markers can be clinically useful. There is clear evidence that modifying traditional risk factors, which are easily assessed in an office visit, reduces the risk for CHD. Furthermore, while CRP is associated with CHD, it is unclear whether this marker is an actual risk factor that contributes to the pathogenesis of the disease or a by-product of the inflammation already initiated by the presence of traditional risk factors [3]. There is currently no evidence to show that decreasing CRP levels increases survival or reduces coronary events [4].

Applications for Clinical Practice

Twenty-one percent of Americans smoke [5] and 60 million Americans have hypertension [6]. One third of patients with hypertension are never diagnosed and another third are undertreated. In addition, 6% to 8% of the U.S. population has documented diabetes [7]. At this time, public health efforts that focus on the diagnosis and modification of these known risk factors for CHD promise the greatest benefit. Routine screening for novel coronary artery disease risk markers is probably not warranted at this time.

—Review by Khashayar Hematpour, MD, (St. Luke's-Roosevelt Hospital Center, New York, NY) and Salomeh Keyhani, MD, MPH

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