Point High-Sensitivity C-Reactive Protein and Cardiac C-Reactive Protein Assays: Is There a Need to Differentiate?

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Recent evidence has shown that inflammation plays a pivotal role in the inception and progression of atherosclerosis, and population studies have demonstrated a strong and independent association between baseline concentrations of inflammatory biomarkers and future coronary events. Because the majority of individuals who develop coronary events are not in a high-risk group according to the Framingham risk assessment of traditional risk factors for coronary heart disease (CHD),⁶ and because one half of those who suffer myocardial infarctions have normal lipid values, measurement of inflammatory markers has been suggested as an adjunct to lipid testing to better identify individuals at increased risk (1).

Of the inflammatory markers evaluated by a CDC and American Heart Association (AHA) Panel in 2002 (2, 3), only C-reactive protein (CRP) met the analytical requirements for outpatient clinical use and, therefore, has been studied intensely over the past decade.

More than 25 prospective epidemiologic studies have shown that CRP is a strong and independent predictor of future myocardial infarction, ischemic stroke, peripheral arterial disease, and sudden cardiac death in apparently healthy men and women (4). Furthermore, 9 studies to date have demonstrated that CRP provides additional prognostic value to the Framingham Risk Score (4).

Guidelines regarding the potential usefulness of CRP in primary and secondary prevention settings have been issued by the CDC and AHA (2). Physicians have become accustomed to use of the “high-sensitivity CRP (hsCRP)” terminology when considering measurement of CRP for vascular disease risk stratification, as opposed to the use of standard CRP assays that monitor infections and other inflammatory conditions.

To assess CHD risk, CRP must be measured by highly sensitive methods (hsCRP) that are capable of reliably measuring concentrations within the healthy reference interval. Currently, more than 30 such methods are available world-wide, many of which have been cleared by the US Food and Drug Administration (FDA). On September 22, 2005, the FDA issued new guidelines for industry and FDA staff regarding this analyte, entitled Review Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP) and Cardiac C-Reactive Protein (cCRP) Assays (5). As the title of the document indicates, the FDA introduced a new category or classification for this analyte, “cardiac CRP (cCRP)”.

For the reasons articulated below, we believe that such a step is unnecessary and may cause confusion.

- The expected performance criteria of hsCRP and cCRP methods are identical. Therefore, analytically, there is no valid rationale to create 2 different names for the same assay, because it may be used for more than 1 clinical application.
- The new FDA guidelines stipulate that cCRP assays should be standardized to Certified Reference Material 470, whereas the hsCRP assays, at minimum, should be traceable to Certified Reference Material 470. Fundamentally, there is no difference between standardizing

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Nonstandard abbreviations: CHD, coronary heart disease; AHA, American Heart Association; CRP, C-reactive protein; hsCRP, high-sensitivity CRP; FDA, US Food and Drug Administration; and cCRP, cardiac CRP.
Another potentially confusing issue is the fact that the hsCRP methods were first introduced, the FDA required demonstration of comparability of the new assays to a predicate device, in this case the Dade Behring assay. Such a step was absolutely necessary at the time to demonstrate the ability of the new assays to perform adequately at low CRP concentrations and to assure comparability among the high-sensitivity methods (7, 8). However, according to the new guidelines, any manufacturer of an existing hsCRP reagent that seeks to have its assay labeled as cCRP must perform a “bridging study”. This entails a repeat of the method-comparison study with the Dade Behring assay, for example, which is now also labeled as cCRP. According to the FDA, this action will ensure that the 2 methods are clinically comparable. It is unclear how such a step will lead to improvement of performance, considering that neither of the 2 methods has changed analytically. Furthermore, these additional studies will burden the manufacturers, and eventually the healthcare system, with unnecessary cost.

The introduction of the term cCRP and its defined use are not only unnecessary but unclear. The regulation stipulates that hsCRP be used in “the evaluation of conditions thought to be associated with inflammation in otherwise healthy individuals”, whereas cCRP is to be used “as an aid in the identification and stratification of individuals at risk for future cardiovascular disease. When used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, cCRP may be useful as an independent marker of prognosis for recurrent events in patients with stable coronary disease or acute coronary syndrome” (5). These statements could be construed to mean that hsCRP should be used in assessing CHD risk in the primary prevention setting because atherosclerosis is a condition associated with inflammation, whereas cCRP should be used in risk stratification in the secondary prevention setting, in patients with acute coronary syndromes. Another potential interpretation of these rules is that hsCRP should be used in conditions other than cardiovascular disease, where overt infection or inflammation is absent, whereas cCRP should be used in risk assessment of heart disease. By this definition, it is unclear what the future usefulness of hsCRP might be. One can only imagine the potential confusion among clinicians over which of these 2 assays to choose for the same analyte.

Another potentially confusing issue is the fact that the term “cardiac CRP”, proposed by the FDA, is very similar to the trademarked term used by Quest Diagnostics, “cardio CRP™”, for their hsCRP assay. We believe the use of such a term by the FDA will inadvertently appear to be an endorsement by the agency of one particular assay, a stance we believe inconsistent with agency policy and one likely to further confuse the clinical community.

Although we disagree with the premise of the FDA guidelines, we applaud the agency for requesting that all CRP results, regardless of the assay used, should be reported in milligrams per liter. This recommendation is consistent with the earlier CDC/AHA guidelines (2, 3).

Introducing these regulatory changes for hsCRP at this time, for no apparent gain in quality of testing, is unwarranted. It is important to note that considerable efforts have been made, on the part of the federal government and various national organizations, to educate clinicians and laboratorians about the differences between the traditional CRP and hsCRP methods and about their clinical utility. Furthermore, most publications about the utility of CRP in risk prediction of cardiovascular disease have used the term hsCRP. To our knowledge, none have used cCRP.

We hope that the FDA will reverse its action and join the other federal agencies and national scientific organizations in educating the medical and laboratory communities about the potential usefulness of hsCRP in the prediction of cardiovascular disease. The most important issue regarding hsCRP has been confusion among clinicians as to the difference between older methods of CRP evaluation and the newer hsCRP methods required for cardiovascular risk detection. We urge the FDA to help the clinical chemistry community achieve consistency in the use of these terms rather than create an even greater confusion for practicing physicians.

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References
Dr. Rifai and coauthors seem to have misunderstood the guidance proffered by the US Food and Drug Administration (FDA) and the laboratory safety tip addressing the issue of matching claims with performance data for C-reactive protein (CRP) assays. The FDA believes that different claims for CRP require very different data sets and different performance criteria to support differing intended uses.

FDA premarket guidance proposals are written to benefit companies and FDA reviewers regarding recommendations for studies that support premarket submissions for medical devices in the United States. They are not meant to be clinical practice guidelines; however, FDA guidelines are meant to be based on sound science, committed to truth in labeling, and intended to help to ensure the safety and effectiveness of medical devices for the promotion of public health.

The driving force behind FDA premarket assay reviews is based on the indications for use of a given assay. For regulatory purposes, the distinction between CRP assays, high-sensitivity (hs)CRP assays, and cardiac (c)CRP assays lies with the Indications for Use. In the Guidance for Industry and FDA Staff: Criteria for Assessment of C-Reactive Protein (CRP), High Sensitivity C-Reactive Protein (hsCRP), and Cardiac C-Reactive Protein (cCRP) Assays (1), the discussion on indications for use can be found in Section 5: Types of CRP Assays. This section states that, although all CRP assays start with the same basic indications for use (i.e., general evaluation of infection, tissue injury, and inflammatory disorders), hsCRP assays and cCRP assays have additional claims.

hsCRP assays are intended for more sensitive detection of inflammatory states, whereas cCRP assays are intended for use in cardiovascular risk assessment. FDA data requirements differ for each of these 2 intended uses. The regulatory distinctions in both claims and data requirements have been established to assist manufacturers, FDA staff, and laboratory users to understand the different types of performance data gathered to support a particular assay.

The hsCRP assay indication is based on data demonstrating the ability to analytically measure a lower CRP concentration than the traditional or older CRP assays. When compared with traditional assays, this increased analytical reliability may be useful in the clinical investigation of conditions associated with inflammation. This