Evaluation of Four Automated High-Sensitivity C-Reactive Protein Methods: Implications for Clinical and Epidemiological Applications

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Background: C-reactive protein (CRP) can provide prognostic information about the risk of developing atherosclerotic complications in apparently healthy patients. This new clinical application requires quantification of CRP concentrations below those traditionally measured in the clinical laboratory.

Methods: The Dade Behring BN II, the Abbott IMx, the Diagnostic Products Corporation IMMULITE, and the Beckman Coulter IMMAGE are four automated analyzers with high-sensitivity CRP (hs-CRP) methods. We evaluated these assays for precision, linearity, and comparability with samples from 322 apparently healthy blood donors.

Results: The imprecision (CV) of the BN II, IMx, IMMULITE, and IMMAGE methods was <7.6%, <12%, <9.8%, and <9.7% at 3.5 mg/L, respectively. The BN II, IMx, IMMULITE, and IMMAGE methods were linear down to <0.30, <0.32, <0.85, and 2.26 mg/L, respectively. CRP concentrations demarcating each quartile in a healthy population were method dependent. The IMx method gave results comparable to the BN II method for values in the reference interval. The IMMULITE method had a positive intercept compared with the BN II method. The IMMAGE method demonstrated more scatter and a positive intercept compared with the BN II method, which may reflect the fact that it is a less sensitive assay.

Conclusions: The four hs-CRP methods exhibited differences in results for a healthy population. Additional standardization efforts are required to ensure that hs-CRP results can be related to large-scale epidemiologic studies.

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C-Reactive protein (CRP) is an acute phase reactant produced by the liver under the control of interleukin-6. Its serum concentration can increase 1000-fold with acute inflammatory events such as infection, trauma, and surgery. Persistent increases in CRP can also occur in chronic inflammatory disorders, including autoimmune diseases and malignancy. Traditionally, CRP has been used clinically for monitoring infection and autoimmune disorders. Automated methods with detection limits of 3–5 mg/L are routinely available in the clinical laboratory for this purpose.

Chronic inflammation is an important component in the development of atherosclerosis [for recent reviews, see Refs. (1, 2)]. CRP concentrations have been shown to correlate with markers of endothelial dysfunction (3, 4). Numerous recent studies have demonstrated that CRP can be used to help predict the risk of acute events in patients with atherosclerosis. Included in this list are several studies conducted in large populations of apparently healthy men and women who subsequently developed coronary artery disease, cerebrovascular disease, or peripheral arterial disease (5–10). CRP has also been shown to predict risk of future events in patients with acute coronary syndromes and in patients with stable angina and coronary artery stents (11–17).

A variety of different methods for quantifying the CRP concentration in serum have been used. When studies...
have been conducted with apparently healthy individuals, high-sensitivity CRP (hs-CRP) methods that can accurately divide results within the reference intervals into quartiles or quintiles have been required. These high-sensitivity methods usually have used ELISA methodology, and a single in-house ELISA assay was used for several epidemiologic studies (5, 6). This methodology is primarily for research use and generally is not routinely available in clinical laboratories. Standard CRP methods in the clinical laboratory have limits of detection of 3–5 mg/L and are unsuitable for these applications. Recently, several automated hs-CRP assays have been developed that are suitable for routine use in the clinical laboratory. They possess greater precision at low concentrations of CRP. We evaluated the performance characteristics of four of these, including method comparability, using samples from 322 apparently healthy adult blood donors.

Materials and Methods

Samples

A total of 322 serum samples were collected from 204 male and 118 female blood donors. The median age of the entire group was 32 years with a range of 17–80 years. The median ages of the male and female donors were 37 and 24 years, respectively. Serum was separated from the red cells and stored at −70 °C until analysis. In addition, a total of 50 samples were collected from patients with CRP concentrations >8 mg/L. All studies with samples from human subjects were approved by the Institutional Review Board of the University of Utah Health Sciences Center.

Apparatus

The BN II nephelometer was from Dade/Behring, the IMx analyzer was from Abbott Diagnostics, the IMMULITE analyzer was from Diagnostics Products Corporation, and the IMMAGE nephelometer was from Beckman/Coulter.

Assay Procedures

All four methods used the manufacturers’ reagents as directed. The BN II N High Sensitivity CRP assay utilizes a monoclonal antibody coated to polystyrene particles and fixed-time kinetic nephelometric measurements (18). The BN II nephelometer makes a 1:400 dilution to measure CRP concentrations between 3.5 and 210 mg/L and a 1:20 dilution below 3.5 mg/L. The IMx assay uses an automated microparticle capture enzyme immunoassay with two mouse anti-CRP monoclonal antibodies (19). A 1:50 manual dilution provides a measurable range of 0.05–30 mg/L. The IMx hs-CRP method is not and has never been commercially available. The IMMULITE assay is a two-site chemiluminescent enzyme immunoassay with one monoclonal and one polyclonal anti-CRP antibody. A 1:100 manual dilution provides a measurable range of 0.1–500 mg/L. The IMMAGE assay uses a polyclonal anti-CRP antibody coated to latex particles and rate nephelometric measurements. The IMMAGE nephelometer makes a 1:36 dilution for values up to 80 mg/L and a 1:216 dilution for higher concentrations. The limits of detection were 0.01 mg/L [zero calibrator + 3 SD (18)], 0.05 mg/L [zero calibrator + 3 SD (2)], 0.1 mg/L [zero calibrator + 2 SD; manufacturer's claim], and 1.0 mg/L (linearity study; manufacturer's claim) for the BN II, IMx, IMMULITE, and IMMAGE methods, respectively. Results below the detection limits of the assays were reported as the detection limits of the assays. All methods except the IMx have been approved by the Food and Drug Administration (FDA) for clinical use in the United States. Only the N High Sensitivity CRP assay has been approved by the FDA for use in assessing the risk of cardiovascular and peripheral vascular disease.

Samples for linearity and precision studies were prepared from two serum pools. The low pool was prepared by combining samples from blood donors with hs-CRP concentrations in the lowest quartile. The high pool was prepared by combining patient samples with hs-CRP concentrations of ~10 mg/L. The high pool was diluted with the low pool to the following final percentage of high pool: 100%, 75%, 50%, 30%, 20%, 10%, 5%, and 0%. Samples were assayed in duplicate on 10 different days.

Data Analysis

EP Evaluator release 3 software (David G. Rhoads Associates) was used for Deming regression analysis, calculation of r, and S_{y|x}. hs-CRP concentrations were skewed rightward in samples from blood donors; therefore, percentile values were estimated and hs-CRP concentrations were log transformed for method comparison plots.

Results

To examine the precision and linearity of the four methods in the CRP concentration range of the reference interval, serum pools were prepared as described in Materials and Methods. The precision of each method was assessed using these pools (Table 1). The BN II method demonstrated the best precision across the range of concentrations. The IMx and IMMULITE methods showed comparable precision, and the IMMAGE showed the poorest precision of the methods evaluated, with a CV >20% at a CRP concentration of 2.26 mg/L. The BN II, IMx, and IMMULITE methods were linear down to the lowest concentration tested, which was a pool of the samples from the lowest quartile of hs-CRP concentrations from blood donors (Fig. 1). The IMMAGE method was linear down to a concentration corresponding to the median value of the group of blood donors. The BN II, IMMULITE, and IMMAGE methods gave comparable results of 9.79, 9.71, and 10.13 mg/L, respectively, for the high pool, whereas the IMx method gave a value of 13.73 mg/L. The BN II and IMx methods gave comparable results of 0.30 and 0.32 mg/L, respectively, for the low pool, whereas the IMMULITE method gave a value of 0.85 mg/L. Regression analysis of the data yielded intercepts that were comparable to the measured values for the low
The hs-CRP concentrations of 322 serum samples collected from apparently healthy adult blood donors were measured by the BN II, IMx, IMMULITE, and IMMAGE methods simultaneously. Inspection of the data revealed a highly skewed population. Therefore, values for the 25th,

### Table 1. Summary of precision data.

<table>
<thead>
<tr>
<th>Pool</th>
<th>BN II Mean, mg/L</th>
<th>CV, %</th>
<th>IMx Mean, mg/L</th>
<th>CV, %</th>
<th>IMMULITE Mean, mg/L</th>
<th>CV, %</th>
<th>IMMAGE Mean, mg/L</th>
<th>CV, %</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>5.7</td>
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<td>8.22</td>
<td>1.9</td>
<td>10.06</td>
<td>7.3</td>
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<td>6.9</td>
<td>8.28</td>
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<td>8.0</td>
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<td>8.1</td>
<td>6.25</td>
<td>4.4</td>
</tr>
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<td>3.3</td>
<td>5.02</td>
<td>9.2</td>
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<td>5.0</td>
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<td>5</td>
<td>2.35</td>
<td>3.9</td>
<td>3.08</td>
<td>9.8</td>
<td>2.60</td>
<td>7.4</td>
<td>3.50</td>
<td>9.7</td>
</tr>
<tr>
<td>6</td>
<td>1.30</td>
<td>3.1</td>
<td>1.63</td>
<td>6.7</td>
<td>1.73</td>
<td>9.5</td>
<td>2.26</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>0.80</td>
<td>2.8</td>
<td>0.95</td>
<td>6.7</td>
<td>1.29</td>
<td>9.8</td>
<td>&lt;1.00</td>
<td>ND²</td>
</tr>
<tr>
<td>8</td>
<td>0.30</td>
<td>7.6</td>
<td>0.32</td>
<td>11</td>
<td>0.85</td>
<td>9.7</td>
<td>&lt;1.00</td>
<td>ND²</td>
</tr>
</tbody>
</table>

*ND, not determined.

The hs-CRP linearity at concentrations <14 mg/L.

Samples were prepared as described in Materials and Methods and run in duplicate on 10 different days. The mean values for each sample were plotted vs the dilution, and linear regression was performed. Regression analysis for the BN II method (A) gave a slope of 9.87, an intercept of 0.42, and an r of 0.997. For the IMx method (B), the slope was 13.33, the intercept was 0.48, and r was 0.997. For the IMMULITE method (C), the slope was 8.86, the intercept was 0.84, and r was 1.000. For the IMMAGE method (D), the slope was 8.59, the intercept was 1.75, and r was 0.997.
50th, 75th, 90th, 95th, and 97.5th percentiles were determined for each method (Table 2). The BN II and IMx methods yielded comparable results for the 25th through the 95th percentiles. The IMMULITE gave slightly higher values than the BN II method for the 25th and 50th percentiles, and comparable values for the 75th through 95th percentiles. The IMMAGE method gave substantially higher values than the other methods for the 50th and 75th percentiles, whereas the 25th percentile value for this group of samples was below the detection limit of the assay. The BN II, IMMULITE, and IMMAGE methods gave comparable results for the 97.5th percentile, whereas the IMx value was higher.

When percentiles were determined by gender, values for the 25th and 50th percentiles were comparable, whereas values for the 75th, 90th, and 95th percentiles were nearly twice as high for women as for men. Because of the limited sample size, the 97.5th percentile was not determined by gender. When the relationship between age and hs-CRP was examined using the BN II method, the Pearson correlation coefficient \( r \) was 0.238 (\( P < 0.001 \)).

The agreement of the four methods with samples from blood donors was assessed graphically (Fig. 2). The BN II method previously had been compared with an in-house ELISA method that was used in several hs-CRP epidemiologic studies and has been validated clinically (18, 20). Furthermore, it is the only method approved by the FDA for cardiovascular and peripheral vascular risk assessment. Therefore, it was chosen as the comparative method when evaluating the other three methods. Deming regression analysis was performed on all data before log transformation. A comparison of the BN II and IMx methods gave a slope of 0.99 ± 0.01, an intercept of 0.09 ± 0.03, and a \( S_{\text{or}} \) of 0.55 (\( r = 0.991 \)). A comparison of the BN II and IMMULITE methods gave a slope of 0.93 ± 0.01, an intercept of 0.39 ± 0.01, and a \( S_{\text{or}} \) of 0.32 (\( r = 0.997 \)). A comparison of the BN II and IMMAGE methods gave a slope of 0.97 ± 0.01, an intercept of 1.04 ± 0.04, and \( S_{\text{or}} \) of 0.59 (\( r = 0.989 \)). Statistical analysis of the agreement between the BN II comparative method and the other three methods for each quartile was performed (21). The results (Table 3) indicate that the mean differences and SDs of the differences for the lowest three quartile were lowest between IMx and the comparative method, intermediate between the IMMULITE and the comparative method, and highest for the IMMAGE. For the highest quartile, these values were lowest for the IMMULITE method, followed by the IMx and then the IMMAGE method. All methods showed statistically significant differences from the comparative method (\( P < 0.05 \)) except for the IMMAGE method with the highest quartile.

The four methods were compared using samples with increased concentrations of CRP (Fig. 3). All methods showed excellent agreement at CRP concentrations up to 50 mg/L. Above this concentration, there appeared to be considerably more scatter in the data. Both the IMx and IMMULITE methods showed differences with the BN II method >2 SD at concentrations >150 mg/L that could not be explained by proportional bias alone.

**Discussion**

The analytic performance characteristics of CRP assays are changing as new clinical applications are being developed. hs-CRP assays are required for atherosclerotic risk prediction in apparently healthy adults. Both accuracy and precision issues need to be addressed. CRP results will most likely be interpreted in quartiles or quintiles for risk assessment. Therefore, hs-CRP assays will also need to be standardized for CRP concentrations of 0.2–10 mg/L so that results obtained in large population studies can be applied to individual patients. A definition of functional assay sensitivity similar to that used for thyroid-stimulating hormone measurement is required to ensure that assays have the requisite precision at low CRP concentrations. We propose that for risk stratification for cardiovascular, cerebrovascular, and peripheral vascular disease, the hs-CRP assay imprecision should be <10% at a concentration of 0.2 mg/L.

Several previous studies that examined serum CRP concentrations in apparently healthy populations, using highly sensitive ELISA, nephelometric, and turbidimetric methods, have found median values ranging from 0.58 to 1.13 mg/L (5, 18, 19, 22–26). The median values deter-

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**Table 2. CRP concentrations at selected percentiles in adult blood donors.**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>BN II</th>
<th>IMx</th>
<th>IMMULITE</th>
<th>IMMAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Male</td>
<td>Female</td>
<td>All</td>
</tr>
<tr>
<td>25th</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>50th</td>
<td>0.8</td>
<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>75th</td>
<td>1.9</td>
<td>1.4</td>
<td>3.1</td>
<td>2.0</td>
</tr>
<tr>
<td>90th</td>
<td>4.1</td>
<td>2.9</td>
<td>7.6</td>
<td>4.9</td>
</tr>
<tr>
<td>95th</td>
<td>8.0</td>
<td>4.9</td>
<td>9.5</td>
<td>8.6</td>
</tr>
<tr>
<td>97.5th</td>
<td>12.5</td>
<td>ND</td>
<td>ND</td>
<td>17.3</td>
</tr>
</tbody>
</table>

*CRP was quantified in samples from 322 blood donors. Of these, 118 were female and 204 were male.

ND, not determined.
mined by the BN II, IMx, and IMMULITE methods were 0.8, 0.8, and 1.1 mg/L, respectively, consistent with these earlier studies. Four of these studies found 75th percentile values ranging from 1.44 to 2.10 mg/L, whereas we found values of 1.9, 2.0, and 2.2 mg/L for the BN II, IMx, and IMMULITE methods, respectively, again consistent with the earlier studies (5, 23, 25, 26). Two previous studies found a 90th percentile hs-CRP concentration of 3 mg/L, whereas we found values of 4.1–5.3 mg/L for the four methods we investigated (19, 23). The basis for this difference in the 90th percentiles observed could be attributable to either differences in the populations studied or the methodologies used. The median age of our population was 32 years, whereas the median ages of the two previous studies reporting values for the 90th percentile were not given. A weak positive correlation between age and hs-CRP concentration has been demonstrated (24), and we found a similar correlation. This indicates that younger ages are associated with lower hs-CRP values; however, it is unlikely that the previous studies had a median age substantially younger than 32 years. The good agreement between our data and those generated in previous studies for the median and 75th percentiles indicates similar assay calibration and suggests that population differences may explain the higher values we observed for the 90th percentile.

When our results were examined after segregation by gender, differences became noticeable at the 75th, 90th, and 95th percentiles. Previous studies that looked at the effect of gender failed to find a significant difference (23, 24). However, a recent study found that estrogen replacement therapy caused a large sustained increase in

<table>
<thead>
<tr>
<th>Method &amp; percentile</th>
<th>Mean, mg/L</th>
<th>Mean difference, a mg/L</th>
<th>SD of difference, mg/L</th>
<th>P b</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMx</td>
<td>0–25th</td>
<td>0.19</td>
<td>-0.04</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>25–50th</td>
<td>0.48</td>
<td>-0.04</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>50–75th</td>
<td>1.26</td>
<td>0.08</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>75–100th</td>
<td>6.38</td>
<td>0.32</td>
<td>1.08</td>
</tr>
<tr>
<td>IMMULITE</td>
<td>0–25th</td>
<td>0.59</td>
<td>0.36</td>
<td>0.16</td>
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<tr>
<td></td>
<td>25–50th</td>
<td>0.88</td>
<td>0.35</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>50–75th</td>
<td>1.54</td>
<td>0.36</td>
<td>0.15</td>
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<td></td>
<td>75–100th</td>
<td>5.87</td>
<td>-0.05</td>
<td>0.71</td>
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<td>IMMAGE</td>
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<td>1.17</td>
<td>0.94</td>
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</tr>
<tr>
<td></td>
<td>75–100th</td>
<td>7.05</td>
<td>1.09</td>
<td>0.91</td>
</tr>
</tbody>
</table>

a Samples were assigned to a quartile based on their BN II result. The mean and SD of the difference between each method and the BN II method were calculated for each quartile.

b A two-tailed t-test was performed to determine whether the means of each quartile were statistically significantly different from those obtained by the BN II method.

Fig. 2. Concordance of hs-CRP methods with samples from blood donors.

Samples collected from 322 adult blood donors were analyzed by all four methods, and the 25th, 50th, 75th, and 90th percentiles were determined. Results were rounded to the nearest 0.1 mg/L. Consequentially, individuals points, particularly at lower concentrations on the graphs, may represent values from several patient samples. A log scale was used for both the ordinate and abscissa in each panel. Results >10 mg/L were excluded from each plot. (A), comparison of the results of the IMx and BN II methods; (B), comparison of the results of the IMMULITE and BN II methods; (C), comparison of the results of the IMMAGE and BN II methods.
Fig. 3. Comparison of methods with 50 samples from patients with increased CRP concentrations.

(A, C, and E). Deming regression analysis. The solid line indicates the regression line, and the dashed line indicates unity. Statistical outliers >4 SD from the regression line are indicated as (□) and were excluded from the Bland-Altman plots in B and D. (B, D, and F). Bland-Altman analyses. The solid line indicates the mean difference between methods, and the 95% confidence intervals for the difference are indicated by dashed lines. (A), slope = 1.10 (95% confidence interval, 1.06–1.14); intercept = −4.1 (95% confidence interval, −7.6 to −0.5); $S_{yx} = 8.4; r = 0.991$. (B), mean bias and SD, 2.3 and 9.7 mg/L, respectively. (C), slope = 1.06 (95% confidence interval, 1.02–1.10); intercept = −4.4 (95% confidence interval, −7.7 to −1.1); $S_{yx} = 7.7; r = 0.991$. (D), mean bias and SD, −0.6 and 8.0 mg/L, respectively. (E), slope = 0.92 (95% confidence interval, 0.89–0.95); intercept = −0.9 (95% confidence interval, −3.6 to 1.8); $S_{yx} = 6.4; r = 0.992$. (F), mean bias and SD, 6.0 and 7.9 mg/L, respectively.
the hs-CRP concentrations in postmenopausal women (27, 28). The basis for the gender differences observed, particularly as it affects results primarily in higher hs-CRP percentiles in our population, is uncertain, but it may reflect hormonal differences.

All of the methods we investigated have been standardized against the WHO International Reference Standard for CRP Immunoassay 85/506 (29). Agreement between all methods for concentrations above the upper limit of the reference interval was acceptable. The BN II and IMx methods showed excellent agreement across the whole range of hs-CRP concentrations encountered in adult blood donors. The IMMULITE showed acceptable agreement with the BN II method for hs-CRP concentrations at or above the 75th percentile, whereas the IMMAGE method showed good agreement only with hs-CRP concentrations above the 90th percentile. Harmonization of hs-CRP results at concentrations below these values will require further work. For clinical risk stratification and epidemiologic studies, there needs to be agreement between methods across the reference interval down to hs-CRP concentrations of 0.2 mg/L. The BN II and IMx methods currently meet this goal, whereas the IMMAGE and IMMULITE methods do not.

The recoveries observed for the IMx method for serum pools prepared from healthy donors were ~30% higher than the other three methods (Table 1 and Fig. 1). However, the percentile values for the donor population determined using the IMx were very similar to the other methods with the exception that the IMx gave the highest values of the methods tested for the 95th and 97.5th percentiles, which were 10–30% higher than the other methods. The IMx method also showed a slope of 1.10 compared with the BN II method for samples from patients with increased CRP concentrations. The intercept observed for the IMMULITE method when measured recoveries were plotted vs dilution for donor serum pools (Fig. 1) was higher (~0.4 mg/L) than those for the BN II and IMx methods. This was also reflected in higher values for the 25th, 50th, and 75th percentiles. The modest proportional and constant biases observed for the IMx and IMMULITE methods, respectively, likely result from differences in calibration. A previous comparison between the BN II and Hemagen ELISA methods showed a slope of 0.75 and an intercept of ~0.25 mg/L (18). Although these two hs-CRP methods have been standardized with the same WHO CRP reference material, they exhibit significant differences in the values obtained (24). These authors concluded that although the exact source of differences was uncertain, it was probably attributable to inadequate standardization. We have confirmed this observation with a different group of hs-CRP assays. Further effort is required for the standardization of hs-CRP assays at concentrations comparable to those seen in healthy subjects.

Another issue that merits discussion is the precision of the methods evaluated. The BN II and IMMAGE methods have automated dilutions, whereas the IMx and IMMULITE methods both require a manual dilution prepared off-line. The BN II method was the most precise, whereas the IMx and IMMULITE methods showed comparable precision with values in the reference interval. The IMMAGE method showed the worst precision at low concentrations of CRP, although acceptable precision with CVs <10% was observed at a CRP concentrations above the 75th percentile of a healthy population. Given the relatively large within-subject variability (CV = 42%), analytical CVs of 10% or less should be adequate for both clinical and epidemiologic studies (24).

In conclusion, the four hs-CRP methods we evaluated exhibited some differences in results for a healthy population. Additional standardization efforts are required to ensure that results obtained by automated hs-CRP methods used in the clinical laboratory can be related to large-scale epidemiologic studies. Once standardization has been achieved, hs-CRP assays can provide useful data for atherosclerotic risk stratification in apparently healthy individuals.

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References

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