Clinical Usefulness of Very High and Very Low Levels of C-Reactive Protein Across the Full Range of Framingham Risk Scores

Paul M Ridker, MD, MPH; Nancy Cook, ScD

Background—High-sensitivity C-reactive protein (hsCRP) is a strong independent risk factor for cardiovascular events, and levels of hsCRP of <1, 1 to <3, and ≥3 mg/L have been suggested to define low-, moderate-, and high-risk groups. However, the positive predictive value of very low (<0.5 mg/L) and very high levels of hsCRP (>10.0 mg/L) is uncertain.

Methods and Results—Baseline levels of hsCRP were evaluated among 27 939 apparently healthy women who were followed up for myocardial infarction, stroke, coronary revascularization, or cardiovascular death. Crude and Framingham Risk Score (FRS)—adjusted relative risks (RRs) of incident cardiovascular events were calculated across a full range of hsCRP levels. Cardiovascular risks increased linearly from the very lowest (referent) to the very highest levels of hsCRP. Crude RRs for those with baseline hsCRP levels of <0.5, 0.5 to <1.0, 1.0 to <2.0, 2.0 to <3.0, 3.0 to <4.0, 4.0 to <5.0, 5.0 to <10.0, 10.0 to <20.0, and ≥20.0 mg/L were 1.0, 2.2, 2.5, 3.1, 3.7, 4.2, 4.9, 6.3, and 7.6, respectively (P for trend <0.001). After adjustment for FRS, these risks were 1.0, 1.6, 1.6, 1.7, 1.9, 2.2, 2.3, 2.8, and 3.1 (P for trend <0.001). All risk estimates remained significant in analyses stratified by FRS and after control for diabetes. Of the total cohort, 15.1% had hsCRP <0.50 mg/L, and 5.4% had hsCRP >10.0 mg/L.

Conclusions—Both very low (<0.5 mg/L) and very high (>10 mg/L) levels of hsCRP provide important prognostic information on cardiovascular risk. hsCRP is clinically useful for risk prediction across a full range of values and across a full range of FRS. (Circulation. 2004;109:1955-1959.)

Key Words: risk factors ■ prevention ■ epidemiology ■ inflammation ■ C-reactive protein

High-sensitivity C-reactive protein (hsCRP) has emerged as a strong independent risk factor for future cardiovascular events that adds prognostic information at all levels of LDL cholesterol, at all levels of the Framingham Risk Score (FRS), and at all levels of the metabolic syndrome.1 On the basis of published data from large, prospective cohorts,2-9 the Centers for Disease Control and Prevention and the American Heart Association (CDC/AHA) in January of 2003 issued the first set of clinical guidelines for hsCRP as a part of global risk prediction and suggested that levels of hsCRP of <1, 1 to <3, and ≥3 mg/L be used to represent low, moderate, and high vascular risk.10 However, as clinicians have begun using hsCRP on a regular basis, questions about the usefulness of both very high and very low levels of hsCRP have emerged. In particular, some physicians have raised concern that very high levels of hsCRP (>10 mg/L) may represent nonspecific inflammation and therefore lack positive predictive value. At the same time, others have voiced concern that very low levels of hsCRP might give patients a false sense of security, particularly when other traditional risk factors are present. We addressed these clinical issues in the large-scale Women’s Health Study, in which baseline levels of hsCRP as well as FRS were measured among 27 939 apparently healthy women who were followed up over a 9-year period for the occurrence of first cardiovascular events.

Methods

The Women’s Health Study is an ongoing trial of aspirin and vitamin E in primary prevention being conducted among American women age ≥45 years with no previous history of cardiovascular disease or cancer. Participants were enrolled between November 1992 and July 1995, at which time they provided detailed information on demographic, lifestyle, and behavioral risk factors. Among women enrolled, 28 345 provided a baseline blood sample, of which 27 939 underwent successful measurement of LDL cholesterol, HDL cholesterol, and hsCRP.9 As described elsewhere, all women have been followed up for incident cardiovascular events, including nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures, and cardiovascular death.9

Received December 15, 2003; revision received February 3, 2004; accepted February 3, 2004.
Because hormone replacement therapy (HRT) is known to elevate relative risks adjusted for the FRS and additionally for diabetes.

For all models, we computed both crude relative risks and used to compute relative risks across the full spectrum of hsCRP levels. In each instance, Cox proportional-hazards models were then used to compute relative risks for those with baseline hsCRP levels of <1, 1 to <3, and ≥3 mg/L. Cox proportional-hazards models were then used to compute relative risks across the full spectrum of hsCRP levels. In each instance, Cox proportional-hazards models were used to compute relative risks across the full spectrum of hsCRP levels. For all models, we computed both crude relative risks and relative risks adjusted for the FRS and additionally for diabetes. Because hormone replacement therapy (HRT) is known to elevate hsCRP levels, we repeated all analyses for the subgroup of women not using these agents at study entry.

Table 1 presents the crude and FRS-adjusted relative risks of future cardiovascular events in analyses in which baseline hsCRP values were defined according to clinically useful cutpoints of hsCRP rather than strict deciles. Again, in analyses of both the total cohort and those not taking HRT, a highly significant relationship between hsCRP and risk was observed across the full spectrum of hsCRP levels. Specifically, the very lowest risk was observed among those in the referent group with hsCRP levels <0.5 mg/L, whereas risk was almost 8-fold higher among those with levels of hsCRP in excess of 20 mg/L (crude relative risk, 7.6; 95% CI, 4.7 to 12.1). These effects were even stronger in the non–HRT-using subgroup, in which the crude relative risk for those with hsCRP levels ≥20 mg/L was increased nearly 10-fold. All findings remained statistically significant after adjustment for FRS and additionally for diabetes (P for trend across groups <0.001 for both the total cohort and non–HRT users).

Table 3 presents crude and adjusted relative risks of future cardiovascular events in analyses in which baseline hsCRP levels were classified into 10 groups based on exact decile cutpoints. As shown, there is a strong and highly significant linear association between baseline hsCRP and future cardiovascular risk across the full spectrum of hsCRP levels. Specifically, crude relative risks from the very lowest (referent) to very highest deciles of baseline hsCRP were 1.0, 1.3, 2.6, 2.2, 3.0, 3.4, 3.6, 4.2, 5.1, and 6.3 (P for trend across groups <0.001).

Following guidelines issued by CDC/AHA,10 we initially classified all study participants into 3 groups on the basis of baseline hsCRP levels of <1, 1 to <3, and ≥3 mg/L. Cox proportional-hazards models were then used to compute relative risks of future cardiovascular events across these 3 study groups. We then addressed the issue of whether very high or very low levels of hsCRP have clinical relevance for risk prediction in 2 stages. First, to avoid the possibility of data-derived findings, we initially reclassified all participants into 1 of 10 groups based on increasing deciles of the distribution of hsCRP. Second, to increase clinical usefulness, we repeated these analyses after classifying all participants into 1 of 10 groups based on increasing deciles of the distribution of hsCRP. Because hormone replacement therapy (HRT) is known to elevate hsCRP levels, we repeated all analyses for the subgroup of women not using these agents at study entry.

Results

The risk factor profile of participants in the Women’s Health Study is similar to that of the general population in terms of both lipid levels and the proportion having metabolic syndrome.11 Among the 27 939 women evaluated in this analysis, 12% were smokers at study entry, 2.5% had diabetes, and 25% had a history of hypertension. The mean body mass index was 25.9 kg/m². Between study initiation and time of this analysis, 698 first cardiovascular events were reported and confirmed by the end-points committee.

Table 1 presents the crude and FRS-adjusted relative risks of future cardiovascular events according to the clinical cutpoints set by the CDC/AHA guidelines. Compared with women with baseline levels of hsCRP <1 mg/L, the crude relative risk for those with baseline hsCRP levels between 1 and <3 mg/L was 1.7 (95% CI, 1.4 to 2.2), whereas the relative risk for those with baseline hsCRP levels ≥3 mg/L was 3.0 (95% CI, 2.4 to 3.7) (P for trend across groups <0.001). As expected, these risks were attenuated but remained statistically significant in models adjusted for FRS and additionally for diabetes. As also shown in Table 1, these effects remained statistically significant in the subgroup analysis of those 15 745 women not taking HRT at study entry (P for trend across groups <0.001).

Table 2 presents crude and FRS-adjusted relative risks of future cardiovascular events in analyses in which hsCRP levels were classified into 10 groups based on exact decile cutpoints. As shown, there is a strong and highly significant linear association between baseline hsCRP and future cardiovascular risk across the full spectrum of hsCRP levels. Specifically, crude relative risks from the very lowest (referent) to very highest deciles of baseline hsCRP were 1.0, 1.3, 2.6, 2.2, 3.0, 3.4, 3.6, 4.2, 5.1, and 6.3 (P for trend across groups <0.001). After adjustment for FRS, these risk estimates were 1.0, 0.9, 1.7, 1.3, 1.7, 1.6, 1.7, 1.9, 2.1, and 2.4 (P for trend across groups <0.001). Almost identical findings were observed in the subgroup not taking HRT at study entry (P for trend <0.001).

Table 3 presents crude and adjusted relative risks of future cardiovascular events in analyses in which baseline hsCRP values were defined according to clinically useful cutpoints of hsCRP rather than strict deciles. Again, in analyses of both the total cohort and those not taking HRT, a highly significant relationship between hsCRP and risk was observed across the full spectrum of hsCRP values. Specifically, the very lowest risk was observed among those in the referent group with hsCRP levels <0.5 mg/L, whereas risk was almost 8-fold higher among those with levels of hsCRP in excess of 20 mg/L (crude relative risk, 7.6; 95% CI, 4.7 to 12.1). These effects were even stronger in the non–HRT-using subgroup, in which the crude relative risk for those with hsCRP levels ≥20 mg/L was increased nearly 10-fold. All findings remained statistically significant after adjustment for FRS and additionally for diabetes (P for trend across groups <0.001 for both the total cohort and non–HRT users).

Figure 1 presents the relative impact of both very high and very low levels of hsCRP on future vascular risk using clinically relevant cutpoints for hsCRP. For comparison, the CDC/AHA cutpoints of <1, 1 to <3, and ≥3 mg/L used to determine low, moderate, and high risk are also shown. Figure 2 shows the predictive value of hsCRP levels among those with calculated 10-year Framingham Risks above and below 10%.

Finally, because diabetes is often considered a coronary risk equivalent, we repeated our analyses for those women free of diabetes at study entry. Among such women, the relative risks for those with baseline hsCRP levels <0.5, 0.5 to <1.0, 1.0 to <2.0, 2.0 to <3.0, 3.0 to <4.0, 4.0 to <5.0, 5.0 to <10.0, 10.0 to <20.0, and ≥20.0 mg/L were 1.0, 2.1, 2.6, 3.0, 3.6, 4.0, 4.6, 5.0, and 7.4, respectively (P for trend <0.001).
In all analyses, virtually identical results were obtained when individual components of the FRS were used.

**Discussion**

These prospective data indicate that the predictive value of hsCRP for future cardiovascular events is linear across a full range of values. Most importantly, these data demonstrate that both very high (>10 mg/L) and very low (<0.5 mg/L) levels of hsCRP provide important prognostic information on vascular risk across a full range of FRS. These observations were consistent in analyses using deciles of hsCRP as well as clinically relevant cutpoints and were present in the total cohort as well as in the subgroups of those not taking HRT and those without diabetes.

The present data have both clinical and pathophysiologically relevant. From a clinical perspective, these data demonstrate that the predictive value of hsCRP is strongly linear across the full range of values. Thus, not only is there no evidence in these data of any threshold effect, but there is also no evidence that unusually low or unusually high values represent false-positive findings. Quite to the contrary, these data indicate that there is considerable predictive value of hsCRP levels beyond the ranges suggested by the recent CDC/AHA guidelines for use of hsCRP. Thus, in addition to the "high-risk" group defined by the CDC/AHA as having levels of hsCRP between 3 and 10 mg/L, there appears to be a "very-high-risk" group with levels of hsCRP in excess of 10 mg/L (which in our study represented 5.5% of the total

### TABLE 2. Crude and FRS-Adjusted Relative Risks of First Cardiovascular Events According to Increasing Deciles of hsCRP With Cutpoints Also Provided

<table>
<thead>
<tr>
<th>Decile</th>
<th>hsCRP, mg/L</th>
<th>Events, n</th>
<th>Crude RR</th>
<th>FRS-Adjusted RR</th>
<th>FRS + DM-Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;0.36</td>
<td>22</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>2</td>
<td>0.36–&lt;0.64</td>
<td>28</td>
<td>1.3 (0.7–2.2)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td>3</td>
<td>0.64–&lt;1.00</td>
<td>55</td>
<td>2.6 (1.6–4.3)</td>
<td>1.7 (1.0–2.8)</td>
<td>1.7 (1.0–2.8)</td>
</tr>
<tr>
<td>4</td>
<td>1.00–&lt;1.46</td>
<td>49</td>
<td>2.2 (1.4–3.7)</td>
<td>1.3 (0.8–2.2)</td>
<td>1.3 (0.8–2.2)</td>
</tr>
<tr>
<td>5</td>
<td>1.46–&lt;2.02</td>
<td>65</td>
<td>3.0 (1.9–4.9)</td>
<td>1.7 (1.0–2.7)</td>
<td>1.7 (1.0–2.7)</td>
</tr>
<tr>
<td>6</td>
<td>2.02–&lt;2.74</td>
<td>72</td>
<td>3.4 (2.1–5.5)</td>
<td>1.6 (1.0–2.6)</td>
<td>1.6 (1.0–2.6)</td>
</tr>
<tr>
<td>7</td>
<td>2.75–&lt;3.71</td>
<td>76</td>
<td>3.6 (2.2–5.7)</td>
<td>1.7 (1.0–2.7)</td>
<td>1.7 (1.0–2.7)</td>
</tr>
<tr>
<td>8</td>
<td>3.71–&lt;5.17</td>
<td>90</td>
<td>4.2 (2.6–6.7)</td>
<td>1.9 (1.2–3.0)</td>
<td>1.9 (1.2–3.0)</td>
</tr>
<tr>
<td>9</td>
<td>5.17–&lt;7.73</td>
<td>108</td>
<td>5.1 (3.2–8.0)</td>
<td>2.1 (1.3–3.4)</td>
<td>2.1 (1.3–3.4)</td>
</tr>
<tr>
<td>10</td>
<td>≥7.73</td>
<td>133</td>
<td>6.3 (4.0–9.8)</td>
<td>2.4 (1.5–3.9)</td>
<td>2.4 (1.5–3.9)</td>
</tr>
</tbody>
</table>

**P** for trend <0.001 <0.001 <0.001

### TABLE 3. Crude and FRS-Adjusted Relative Risks of First Cardiovascular Events Across a Full Range of Clinically Set hsCRP Cutpoints

<table>
<thead>
<tr>
<th>hsCRP, mg/L</th>
<th>Events, n</th>
<th>Crude RR</th>
<th>FRS-Adjusted RR</th>
<th>FRS + DM-Adjusted RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.50</td>
<td>34</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>0.50–&lt;1.0</td>
<td>71</td>
<td>2.2 (1.4–3.2)</td>
<td>1.6 (1.1–2.4)</td>
<td>1.6 (1.1–2.5)</td>
</tr>
<tr>
<td>1.0–&lt;2.0</td>
<td>111</td>
<td>2.5 (1.7–3.7)</td>
<td>1.6 (1.1–2.4)</td>
<td>1.6 (1.1–2.4)</td>
</tr>
<tr>
<td>2.0–&lt;3.0</td>
<td>91</td>
<td>3.1 (2.1–4.6)</td>
<td>1.7 (1.1–2.5)</td>
<td>1.7 (1.1–2.5)</td>
</tr>
<tr>
<td>3.0–&lt;4.0</td>
<td>79</td>
<td>3.7 (2.5–5.6)</td>
<td>1.9 (1.3–2.9)</td>
<td>1.9 (1.2–2.8)</td>
</tr>
<tr>
<td>4.0–&lt;5.0</td>
<td>63</td>
<td>4.2 (2.8–6.4)</td>
<td>2.2 (1.4–3.3)</td>
<td>2.0 (1.3–3.1)</td>
</tr>
<tr>
<td>5.0–&lt;10.0</td>
<td>169</td>
<td>4.9 (3.4–7.1)</td>
<td>2.3 (1.5–3.3)</td>
<td>2.0 (1.4–3.0)</td>
</tr>
<tr>
<td>10.0–&lt;20.0</td>
<td>44</td>
<td>6.3 (4.0–9.8)</td>
<td>2.8 (1.7–4.4)</td>
<td>2.4 (1.5–3.8)</td>
</tr>
<tr>
<td>≥20</td>
<td>36</td>
<td>7.6 (4.7–12.1)</td>
<td>3.1 (1.9–5.1)</td>
<td>2.4 (1.5–4.0)</td>
</tr>
</tbody>
</table>

**P** for trend <0.001 <0.001 <0.001 <0.001 <0.001

Abbreviations as in Table 1. Values represent RR (95% CI) compared with the referent (ref) group. Data are shown for the total cohort (n=27 939) and for those women not taking HRT (n=15 745).
Moreover, although levels of hsCRP ≥ 20 mg/L were rare (2.2% of the total population), these individuals were observed to have the very highest risk of future vascular events. By contrast, risk appeared to be very low for individuals at the other end of the spectrum with hsCRP levels < 0.5 mg/L (15.1% of the study population). Indeed, this group appeared to have very low risk even when compared with those with hsCRP levels between 0.5 and 1.0 mg/L. As shown in our multivariate analyses, this was true even when other risk factors were present and after adjustment for the FRS and additionally for diabetes.

From a pathophysiological perspective, these analyses also raise several intriguing issues. First, the observation that individuals with exceptionally low levels of hsCRP have very low risks of future cardiovascular events provides clinical support for the concept that CRP itself may have a direct role in atherothrombosis and raises the possibility that a virtual absence of CRP may in fact be protective. For example, mice transgenic for human CRP not only begin to express elevated CRP levels for the first time but also have increased rates of arterial thrombosis, at least compared with wild-type mice that minimally express CRP. Recent work further indicates that CRP can be produced within the vascular smooth muscle of diseased coronary arteries and that this production may directly lead to the expression of several mediators of the atherothrombotic process, including adhesion molecule induction, reduced NO production, and altered fibrinolytic function. Thus, individuals without expressed CRP levels may largely be free of these proatherogenic responses. Conversely, our observation that individuals with very high levels of hsCRP are at very high vascular risk is consistent with the hypothesis that CRP may have direct arterial effects or be a surrogate for these effects. In this regard, rather than suggesting that markedly elevated levels of hsCRP represent a false-positive response, the current clinical data raise the possibility that chronic inflammation from any of several causes may well increase vascular risk. As such, these data are consistent with reports suggesting that several chronic conditions including arthritis, periodontal disease, and chronic low-grade infection may all predispose to atherothrombotic events.

Our data also reinforce the need to use high-sensitivity assays for the evaluation of CRP. Although older assays for CRP might be able to reliably detect levels in excess of 10 mg/L (the very-high-risk group), it is only with use of hsCRP assays that clinical detection across a full range can be assessed. As demonstrated in these data, that range must include those at high risk (hsCRP between 3 and 10 mg/L) as well as those at very low risk (<0.5 mg/L) and intermediate risk (hsCRP between 1.0 and 3.0 mg/L), all levels undetectable without high-sensitivity assays.

An important limitation of our study is that we evaluated hsCRP levels only once at baseline and thus cannot eliminate the possibility that some of the marked elevations observed might well reflect a clinically silent acute-phase response. However, this potential misclassification bias among those with high levels of hsCRP can lead only to an underestimation of true effects, not a falsely high risk estimate. Thus, the magnitude of predictive values found here for hsCRP are, if anything, likely to be underestimates of true effects. Clinicians can largely avoid this difficulty by simply measuring hsCRP twice whenever levels are in excess of 10 mg/L. This
practice is consistent with the recent CDC/AHA guidelines and, as has been found in several reports, greatly reduces any residual variation in levels that may be observed in outpatient clinical use. Finally, absolute event rates within the Women’s Health Study are low in comparison to the general population because of the “healthy cohort effect” and the fact that our participants are healthcare providers. However, the fact that hsCRP has been shown to predict vascular risk with similar magnitude in multiple other studies of men and women suggests that the relative risks described here are generalizable.

Acknowledgments
This study was funded by grants from the National Heart, Lung, and Blood Institute with additional support from the Donald W. Reynolds Foundation (Las Vegas, Nev), the Doris Duke Charitable Foundation (New York, NY), and the Leducq Foundation (Paris, France).

References
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Circulation. 2004;109:1955-1959; originally published online March 29, 2004;
doi: 10.1161/01.CIR.0000125690.80303.A8
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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