C-Reactive Protein as a Predictor of Cardiovascular Risk in a Population With a High Prevalence of Diabetes
The Strong Heart Study

Lyle G. Best, MD; Ying Zhang, PhD; Elisa T. Lee, PhD; Jean-Liang Yeh, PhD; Linda Cowan, PhD; Vittorio Palmieri, MD; Mary Roman, MD; Richard B. Devereux, MD; Richard R. Fabsitz, PhD; Russell P. Tracy, PhD; David Robbins, MD; Michael Davidson, MD; Aftab Ahmed, MD; Barbara V. Howard, PhD

Background—High-sensitivity C-reactive protein (CRP) has been investigated extensively as a marker for predicting the risk of cardiovascular disease (CVD). CVD accounts for a large proportion of mortality and morbidity in American Indians; we sought to test the association of CRP and CVD in a population-based American Indian cohort 45 to 74 years old.

Methods and Results—Of 3277 participants who were CVD-free at baseline, 542 had CRP >10 mg/L and were excluded from analysis; 50.1% of those included had diabetes. There were 343 CVD events among this cohort during a median follow-up of 6.2 years. Multiple CVD risk factors were used as covariates in Cox proportional-hazard models. After exclusions, the median CRP (3.2 mg/L) was higher than reported in many other populations. CRP predicted CVD in models adjusted for traditional risk factors, but not when albuminuria and fibrinogen were included. In subgroup analysis, CRP was strongly related to incident CVD among nondiabetic women participants, even after adjustment for traditional CVD risk factors and other indicators of inflammation. Conversely, CRP was elevated beyond the useful range of the American Heart Association/Centers for Disease Control and Prevention clinical guidelines in 16% of this population, and CRP was not predictive of CVD in important subgroups, such as those with diabetes.

Conclusions—CRP was a predictor of CVD in this American Indian population with a high prevalence of diabetes and other risk factors. The predictive ability of CRP varies considerably among subgroups with different risk factor profiles.

(Circulation. 2005;112:1289-1295.)

Key Words: inflammation ■ epidemiology ■ risk factors ■ cardiovascular diseases ■ diabetes mellitus

Theories incorporating inflammation in the pathogenesis of atherosclerosis have existed since 1823, when Rayer and later Virchow compared the inflammatory process and atherosclerosis.1 Many authors have elaborated on the concept and on our current understanding of the role of inflammation in the pathogenesis of atherosclerosis.2

Markers of physiological inflammatory response have been shown to predict atherosclerotic complications in a variety of healthy populations, such as middle-aged men,3 women,4 the elderly5 (in the United States), and in European cohorts.6 Controlled trials are beginning to demonstrate reduced risk for cardiovascular disease (CVD) among subjects treated with agents influencing the inflammatory response, as well as other physiological pathways.3,7

C-reactive protein (CRP) has been investigated extensively as a marker of inflammatory response that is useful in predicting the risk for CVD. Newer high-sensitivity (hsCRP) assays developed in the early 1990s8 have allowed detection of more subtle changes in values.

CVD accounts for a large proportion of mortality and morbidity in American Indian communities.9 Because the prevalences of obesity and diabetes are high in this population, it is important to explore the relation between inflammation and CVD. High-sensitivity CRP has been shown to provide risk information independent of HDL, total cholesterol, and other typical cardiovascular risk factors.10 We sought to test the usefulness of hsCRP in a population-based American Indian cohort.

Methods
The American Indian communities participating in the Strong Heart Study and the study design, survey methods, and laboratory techniques have been described previously.11,12 Approval was obtained from relevant institutional review boards, and all participants gave informed consent.

Received July 24, 2004; revision received May 23, 2005; accepted May 31, 2005.
From Missouri Breaks Industries Research Inc, Timber Lake, SD (L.G.B.); University of Oklahoma Health Sciences Center, Oklahoma City (Y.Z., E.T.L., J.-L.Y., L.C.); Cornell Medical Center, New York, NY (V.P., M.R., R.B.D.); National Heart Lung and Blood Institute, Bethesda, Md (R.R.F.); Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington (R.P.T.); and Medstar Research Institute, Washington, DC (D.R., M.D., A.A., B.V.H.).
Correspondence to Lyle Best, MD, #1 Airport Rd, RR1, Box 88, Rolette, ND 58366. E-mail sbest@utma.com
© 2005 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.104.489260

Epidemiology

C-Reactive Protein as a Predictor of Cardiovascular Risk in a Population With a High Prevalence of Diabetes
The Strong Heart Study

Lyle G. Best, MD; Ying Zhang, PhD; Elisa T. Lee, PhD; Jean-Liang Yeh, PhD; Linda Cowan, PhD; Vittorio Palmieri, MD; Mary Roman, MD; Richard B. Devereux, MD; Richard R. Fabsitz, PhD; Russell P. Tracy, PhD; David Robbins, MD; Michael Davidson, MD; Aftab Ahmed, MD; Barbara V. Howard, PhD

Background—High-sensitivity C-reactive protein (CRP) has been investigated extensively as a marker for predicting the risk of cardiovascular disease (CVD). CVD accounts for a large proportion of mortality and morbidity in American Indians; we sought to test the association of CRP and CVD in a population-based American Indian cohort 45 to 74 years old.

Methods and Results—Of 3277 participants who were CVD-free at baseline, 542 had CRP >10 mg/L and were excluded from analysis; 50.1% of those included had diabetes. There were 343 CVD events among this cohort during a median follow-up of 6.2 years. Multiple CVD risk factors were used as covariates in Cox proportional-hazard models. After exclusions, the median CRP (3.2 mg/L) was higher than reported in many other populations. CRP predicted CVD in models adjusted for traditional risk factors, but not when albuminuria and fibrinogen were included. In subgroup analysis, CRP was strongly related to incident CVD among nondiabetic women participants, even after adjustment for traditional CVD risk factors and other indicators of inflammation. Conversely, CRP was elevated beyond the useful range of the American Heart Association/Centers for Disease Control and Prevention clinical guidelines in 16% of this population, and CRP was not predictive of CVD in important subgroups, such as those with diabetes.

Conclusions—CRP was a predictor of CVD in this American Indian population with a high prevalence of diabetes and other risk factors. The predictive ability of CRP varies considerably among subgroups with different risk factor profiles.

(Circulation. 2005;112:1289-1295.)

Key Words: inflammation ■ epidemiology ■ risk factors ■ cardiovascular diseases ■ diabetes mellitus

Theories incorporating inflammation in the pathogenesis of atherosclerosis have existed since 1823, when Rayer and later Virchow compared the inflammatory process and atherosclerosis.1 Many authors have elaborated on the concept and on our current understanding of the role of inflammation in the pathogenesis of atherosclerosis.2

Markers of physiological inflammatory response have been shown to predict atherosclerotic complications in a variety of healthy populations, such as middle-aged men,3 women,4 the elderly5 (in the United States), and in European cohorts.6 Controlled trials are beginning to demonstrate reduced risk for cardiovascular disease (CVD) among subjects treated with agents influencing the inflammatory response, as well as other physiological pathways.3,7

C-reactive protein (CRP) has been investigated extensively as a marker of inflammatory response that is useful in predicting the risk for CVD. Newer high-sensitivity (hsCRP) assays developed in the early 1990s8 have allowed detection of more subtle changes in values.

CVD accounts for a large proportion of mortality and morbidity in American Indian communities.9 Because the prevalences of obesity and diabetes are high in this population, it is important to explore the relation between inflammation and CVD. High-sensitivity CRP has been shown to provide risk information independent of HDL, total cholesterol, and other typical cardiovascular risk factors.10 We sought to test the usefulness of hsCRP in a population-based American Indian cohort.

Methods
The American Indian communities participating in the Strong Heart Study and the study design, survey methods, and laboratory techniques have been described previously.11,12 Approval was obtained from relevant institutional review boards, and all participants gave informed consent.

Received July 24, 2004; revision received May 23, 2005; accepted May 31, 2005.
From Missouri Breaks Industries Research Inc, Timber Lake, SD (L.G.B.); University of Oklahoma Health Sciences Center, Oklahoma City (Y.Z., E.T.L., J.-L.Y., L.C.); Cornell Medical Center, New York, NY (V.P., M.R., R.B.D.); National Heart Lung and Blood Institute, Bethesda, Md (R.R.F.); Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington (R.P.T.); and Medstar Research Institute, Washington, DC (D.R., M.D., A.A., B.V.H.).
Correspondence to Lyle Best, MD, #1 Airport Rd, RR1, Box 88, Rolette, ND 58366. E-mail sbest@utma.com
© 2005 American Heart Association, Inc.
Circulation is available at http://www.circulationaha.org
DOI: 10.1161/CIRCULATIONAHA.104.489260
The study enrolled 4549 individuals, 45 to 74 years old, for their first examination between July 1989 and January 1992. Participation rates of all eligible tribe members averaged 64%. Nonparticipants were similar to participants in age and self-reported frequency of diabetes. Retention of cohort members for the second examination (July 1993 to December 1995) averaged 88% of survivors.

At each examination, the evaluation consisted of an interview, a physical examination, and a fasting venipuncture. Serum was separated from clotted blood and stored at −80°C. CRP analysis was first performed on samples collected during the second examination.

From 1988 until the present, deaths have been ascertained through tribal and medical records, by death certificates, or by direct contact with participants and their families. These materials are reviewed independently by physician members of the Strong Heart Study Morbidity and Mortality Review Committee for assignment of cause of death using standardized case definition criteria.13

Trained medical record abstractors ascertained nonfatal cardiovascular events by reviewing medical records for potential events or interventions, including procedures diagnostic of CVD (eg, coronary angiography). Using this information and standard criteria, a physician member of the Morbidity and Mortality Review Committee determined the specific CVD diagnosis.13,14 Quality control procedures, including blinded review of abstracted records by a second physician panel member, have shown a diagnostic concordance rate >90%.

There were 3638 participants enrolled at the second examination. Of this group, 270 were excluded from the present analysis because of a history of definite coronary heart disease (CHD), myocardial infarction (MI), or cerebrovascular accident (CVA) before 1993. CVD events included definite/possible fatal MI, definite/possible fatal CVA, definite/possible fatal CHD, definite sudden death caused by CHD, or definite nonfatal MI (by medical record review or ECG evidence of definite MI by Minnesota code since the baseline examination), CHD, or CVA. Definite cases of MI were defined as those with a verified history of MI after review of pertinent records or Minnesota ECG codes of 1.1 and most of the 1.2 codes.13,14 Participants with evidence of coronary artery bypass grafting, coronary angioplasty, or coronary angiography showing clinically significant obstruction, as well as certain other combinations of evidence, were categorized as definite coronary heart disease.13,14 Possible cases of MI, CHD, and CVA were defined using similar but more inclusive criteria.13,14 Because CRP measurement was first performed during the second examination, only those events ascertained between 1993 and December 31, 2000, were included in this analysis. Separate analyses that included only coronary events between 1993 and December 31, 2000, were included in this analysis. The Figure shows the distribution of CRP among those with values in the range for CVD risk assessment.17 In keeping with these recommendations, those participants with values >10 mg/L were excluded from the primary analysis. Descriptive statistics for the various covariates are shown as either percentages or means with SDs. If a mean was not appropriate to describe the distribution, then the median was calculated and the minimum and maximum values given. The comparisons of these variables between those who were excluded and those included were performed using a t test or χ² test for continuous or categorical variables. The rank-sum test was used to compare total triglycerides and plasminogen activator inhibitor-1 because of skewed distributions. Multivariable regression was used to investigate associations between CRP and age, sex, diabetes, nonsteroidal antiinflammatory drug (NSAID) use, smoking, and obesity.

CRP measurements were categorized according to AHA/CDC recommendations12 for the primary analysis and with a higher upper cut point of 4 mg/L and as a continuous variable in secondary analyses. The upper cut point value, >4 mg/L, was chosen arbitrarily to reflect a slightly higher value than that recommended by the AHA/CDC (>3 mg/L) because of the higher distribution of CRP values in these communities. The Cox proportional-hazard model was used to analyze the association between CVD events and CRP, controlling for confounding variables. Multivariable models were constructed by adding similar groups of commonly accepted risk factors for CVD as covariates. Stepwise procedures were used to eliminate those factors not contributing significantly (P>0.05) to predictive power, both in preliminary models and in the maximally adjusted model, which initially included all covariates. Analyses stratified by sex, diabetic status, and other factors were also performed using a consistent set of covariates to examine the data for possible interactions of these variables on CVD risk.

Results

After those with prevalent CVD at baseline had been excluded, there were 3277 participants with CRP values, at risk for CVD and under surveillance between 1993 and the end of 2000. From the remaining participants, an additional 542 (16.5%) were excluded because of CRP values >10 mg/L. The minimum, first quartile, median, third quartile, and maximum length of follow-up were 0.03, 5.4, 6.2, 6.8, and 8.1 years, respectively, from the time of hsCRP determination. A total of 343 cohort members who met the criteria for CVD were identified with events during the follow-up interval. These events included nonfatal MI, 41%; definite CHD (angiographic intervention or evidence of CHD), 23%; nonfatal CVA, 14%; fatal CHD 20%; and fatal CVA, 2%.

The Figure shows the distribution of CRP among those included in the analysis (with CRP ≤10 mg/L). Of those with CRP >10 mg/L, 219 (40.4%) had values between 10 and 15 mg/L, 106 (19.6%) had values between 15 and 20 mg/L, 122 (22.5%) had values between 20 and 30 mg/L, and 95 (17.5%) had values ranging from 30 to 123 mg/L. The characteristics
of those excluded because of elevated CRP levels are summarized in Table 1. Those excluded were more likely to be female, hypertensive, diabetic, albuminuric, and to have higher body mass index and lower levels of total and LDL cholesterol. Fibrinogen and plasminogen activator inhibitor-1 levels, which are typically correlated with CRP, were significantly elevated in those with high levels of CRP. The incidence of CVD morbidity and mortality was not higher in those with CRP levels $>10$ mg/L than in those with lower levels.

Table 2 shows the results of multivariable regression analysis of CRP values with selected covariates. Female sex, diabetes, and obesity are all independently related to higher CRP values, whereas older age is associated with lower levels, after adjustment for other variables.

By use of Cox proportional-hazard models with CRP as a continuous independent variable and adjustment for the traditional risk factors of sex, age, smoking, LDL cholesterol (LDL-C), HDL-C, hypertension, and diabetes, the risk of incident CVD was increased 6% for every 1-mg/L increase in CRP (hazard ratio $=1.06$; 95% CI, 1.01 to 1.11), although LDL-C and HDL-C were not significant covariates. A similar model including fibrinogen and microalbuminuria/macroalbuminuria continued to show significant association with CVD risk (hazard ratio $=1.06$; 95% CI, 1.01 to 1.12); but LDL-C, HDL-C, fibrinogen, and microalbuminuria were not retained in the final model as independent predictors.

Results of Cox proportional-hazard models are shown in Table 3. CRP was entered using AHA/CDC categories as $<1$ mg/L, 1 to 3 mg/L, and $>3$ mg/L, with a distribution of 226, 1075, and 1434 participants, respectively. Univariate and minimally adjusted models (models 1 and 2) show relative risks (RRs) of up to 2.09 (95% CI, 1.29 to 3.4) for the highest category of CRP. Adjusting for the traditional CVD risk factors of sex, age, smoking, LDL cholesterol (LDL-C), HDL-C, hypertension, and diabetes, the risk of incident CVD was increased 6% for every 1-mg/L increase in CRP (hazard ratio $=1.06$; 95% CI, 1.01 to 1.11), although LDL-C and HDL-C were not significant covariates. A similar model including fibrinogen and microalbuminuria/macroalbuminuria continued to show significant association with CVD risk (hazard ratio $=1.06$; 95% CI, 1.01 to 1.12); but LDL-C, HDL-C, fibrinogen, and microalbuminuria were not retained in the final model as independent predictors.
factors (hypertension, diabetes, lipoproteins) in model 3 attenuates the RR to approximately 1.6 (95% CI, 1.00 to 2.67). The addition of fibrinogen and albuminuria to model 3 causes CRP to lose its independent relationship with CVD (data not shown). When only participants with CRP measurements above the 95th percentile (cut point = 22.8 mg/L) were excluded from the analysis, CRP was predictive of CVD when adjusted for demographic variables but not when adjusted for traditional risk factors (hazard ratio = 1.60; 95% CI, 0.98 to 2.61, P = 0.06 for those with CRP > 3 mg/L). Results were similar when the analysis included all participants (n = 3277), regardless of CRP values.

Analyses were performed stratified by sex, diabetes status, NSAID use, and obesity status using the AHA/CDC categories of CRP. The association of CRP and CVD is very strong among female participants with statistically significant RRs (CRP > 3 versus CRP < 1) in all models. When adjusted for all possible covariates, including traditional CVD risk factors, fibrinogen, and albuminuria, CRP has an RR of 4.37 (95% CI, 1.07 to 17.86). Stratifying by male sex failed to show any significant results. The interaction between NSAID use and CRP is statistically significant (NSAID use increases the RR of CVD with increasing CRP), whereas the interactions between CRP and all other covariates were not statistically significant. Analyses using CHD end points gave results essentially the same as those using CHD and CVA end points, but using CVA end points alone led to nonsignificant results, perhaps because of lack of power.

The high average level of CRP in this population (mean = 3.7 mg/L, SD = 2.3 mg/L) suggested that an alternative upper cut point might provide more meaningful analyses. Secondary analyses were conducted using CRP categories of < 1 mg/L, 1–4 mg/L, and > 4 mg/L, with a distribution of 226, 1501, and 1008 participants, respectively. As noted in Table 4, the RR estimates were generally higher than in comparable models using the AHA/CDC categories. Indeed, model 3 now shows that CRP is a significant risk factor for CVD, even while adjusting for traditional risk factors alone, or in addition to fibrinogen and albuminuria (RR = 1.7; 95% CI, 1.02–2.86). When all participants (regardless of CRP level) (n = 3277) were included in this secondary analysis, significant results were obtained for model 3, including

### Table 3: Cox Proportional-Hazard Models for the Prediction of CVD, Based on AHA/CDC Categories of CRP

<table>
<thead>
<tr>
<th>Model*</th>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CRP1† (&lt;1 mg/L)</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Unadjusted model</td>
</tr>
<tr>
<td></td>
<td>CRP2 (1–3 mg/L)</td>
<td>1.49</td>
<td>0.91–2.44</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3 (&gt;3 mg/L)</td>
<td>1.78</td>
<td>1.10–2.88</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CRP1</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Sex‡, age‡, SHS center</td>
</tr>
<tr>
<td></td>
<td>CRP2</td>
<td>1.60</td>
<td>0.97–2.62</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3</td>
<td>2.09</td>
<td>1.29–3.40</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CRP1</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Sex‡, age‡, smoking‡, LDL-C, HDL-C, hypertension‡, diabetes‡</td>
</tr>
<tr>
<td></td>
<td>CRP2</td>
<td>1.35</td>
<td>0.82–2.22</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3</td>
<td>1.63</td>
<td>1.00–2.67</td>
<td>0.05</td>
<td></td>
</tr>
</tbody>
</table>

*The model was reduced by stepwise selection. CRP was forced into the model. All covariates were candidates for removal. Only those covariates remaining significant (P < 0.05, marked by ‡) stayed in the model. †CRP1 is the referent level.‡Covariates remaining significant.

### Table 4: Cox Proportional-Hazard Models for the Prediction of CVD, Based on Alternative Categories of CRP

<table>
<thead>
<tr>
<th>Model*</th>
<th>Variables</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CRP1† (&lt;1 mg/L)</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Unadjusted model</td>
</tr>
<tr>
<td></td>
<td>CRP2 (1–4 mg/L)</td>
<td>1.46</td>
<td>0.90–2.38</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3 (&gt;4 mg/L)</td>
<td>1.95</td>
<td>1.19–3.17</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>CRP1</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Sex‡, age‡, SHS center</td>
</tr>
<tr>
<td></td>
<td>CRP2</td>
<td>1.60</td>
<td>0.99–2.61</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3</td>
<td>2.32</td>
<td>1.42–3.80</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>CRP1</td>
<td>1.0</td>
<td></td>
<td></td>
<td>Sex‡, age‡, smoking‡, LDL-C, HDL-C, hypertension‡, diabetes‡</td>
</tr>
<tr>
<td></td>
<td>CRP2</td>
<td>1.34</td>
<td>0.82–2.19</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRP3</td>
<td>1.78</td>
<td>1.08–2.92</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*The model was reduced by stepwise selection. CRP was forced into the model. All covariates were candidates for removal. Only those covariates remaining significant (P < 0.05, marked by ‡) stayed in the model. †CRP1 is the referent level.‡Covariates remaining significant.
traditional risk factors (RR = 1.7; 95% CI, 1.03–2.74). Stratified analyses showed RR estimates and significance for these models that were similar to those using AHA/CDC categories among female participants (RR = 4.4; 95% CI, 1.07–18.07, model 4) but no significant results for males.

Results of additional stratified analyses are presented in Table 5. The same model entering CRP as a continuous variable and including all covariates was used in these analyses. CRP was a significant predictor of CVD in non-diabetic (non-DM) participants (RR = 1.10 per mg/L; 95% CI, 1.02 to 1.19, P = 0.02), and particularly in the female, non-DM participant (RR = 1.15 per mg/L; 95% CI, 1.02 to 1.31, P = 0.02). Evaluation of models with and without CRP using the comparison of Akaike’s information criterion and log-likelihood values indicate that the addition of CRP increased the explanatory value of all models in Table 5 for which CRP is statistically significant, ie, including either all participants or those stratified by female sex, non-DM, obese, and female non-DM status.

Finally, results showing similar models comparing quintiles of all cohort members, including those with CRP > 10 mg/L, are given in Table 6. Note that the uppermost quintile begins at 8.7 mg/L, corresponding closely to those excluded in previous analyses (CRP > 10 mg/L). There is a significant association between CRP and CVD in the 2 highest quintiles when adjusted only for sex and age, but after further adjustment for the additional risk factors of smoking, diabetes, and hypertension, statistical significance is no longer present.

**Discussion**

Multiple prospective studies have determined that mild elevations of CRP predict future CVD events in groups with varying demographic characteristics and no apparent CVD, those with significant risk factors for CVD, and those with known CVD at baseline. To date, there have been no prospective studies that did not observe a univariate association between CRP and clinical CVD events. In several studies, however, the relation has disappeared after adjustment for other CVD risk factors. The fact that modification of the inflammatory response by statins appears to reduce the risk of CVD, independently of their lipid-lowering effects, further suggests a causal role for CRP or some very closely associated physiological factor.

Although the AHA/CDC recommendations regarding CRP were developed in consideration of numerous published reports, many of these data are from populations with markedly lower prevalences of diabetes, obesity, and other...
risk factors. This fact and the possibility of variation in absolute accuracy in CRP determinations may make the application of the AHA/CDC guidelines undependable in some populations. The use of recommended AHA/CDC categories in this population showed a marginal association of CRP with CVD when adjusted for traditional risk factors and no independent association when fibrinogen and albuminuria were included in models. Secondary analyses using slightly higher cut points showed increased RRs, even after adjustment for traditional risk factors alone, or in addition to fibrinogen and albuminuria. Models using CRP as a continuous variable appeared to have increased power and had results similar to analyses with the alternative categories. CRP was also shown by Akaike information criterion and log-likelihood values to enhance the explanatory value of many models described in Table 5.

The exclusion of those with CRP values >10 mg/L might be questioned, because this removes a relatively large fraction of this population from consideration, but this is the recommendation of the AHA/CDC. A recent report from the Women’s Health Study showed significant associations of CRP and CVD, even at levels of 10 to 20 mg/L and in those >20 mg/L;25 however, in the present study using AHA/CDC criteria, CRP was not a significant risk factor in multivariable analyses, including those with values >10 mg/L. Analysis using quintiles of CRP (the uppermost of which represented almost all of those with CRP >10 mg/L) also failed to show a statistically significant association with CVD after adjustment for traditional risk factors. It is also important to note that the Women’s Health Study population has a very different prevalence of risk factors (diabetes 2.5%, hypertension 25%, body mass index 25.9 kg/m², and higher socioeconomic status) compared with this cohort.

The median value of CRP in this cohort (before exclusion of values >10 mg/L) was 3.8 mg/L; the mean CRP of those with values <10 mg/L was 3.2 mg/L. This is in contrast to median values in other population-based studies of 2.1 mg/L (National Health and Nutrition Examination Survey26), 2.67 mg/L (Cardiovascular Health Study27), and 1 to 2 mg/L (depending on age) in Europe.28 The only population-based median (3.49 mg/L) to approach that of the present cohort is from the subgroup of 230 women taking unopposed estrogen replacement therapy in the Cardiovascular Health Study.29

Possible reasons for the higher CRP values in this population include a very high prevalence of diabetes mellitus (54%) and obesity. Diabetes and high body mass index are associated with elevated CRP,30,31 and in 1 study limited to diabetic participants, the median CRP values were 4.13 mg/L for the control group and 4.97 mg/L for those assigned to postmenopausal hormone replacement therapy.32 In contrast, a Japanese investigation of CRP as a risk factor of CVD in type 2 diabetic individuals found rather low values of CRP, with means of 2.9 and 1.1 mg/L in those with and without CVD, respectively.33 Consistent with the literature,26–28 multivariable analysis of our data shows CRP to be higher among women, and this Strong Heart Study population consisted of 64% women. The prevalence in this cohort of hormone replacement therapy, which raises CRP values, is low (15.2%) compared with other studies,34 and thus, the high CRP values cannot be attributed to estrogen use. Finally, there may be an increased burden of infectious diseases in this population,35,36 raising the average value of CRP. The intensity of smoking (cigarettes per day) in this cohort is relatively low,34 which may explain the lack of relationship with CRP in this cohort. Most previous reports have found an increase in CRP at older ages; the opposite effect in this population may be because of a survival effect. A study in the Netherlands found that CRP levels predicted CVD when models were minimally adjusted for age, sex, and glucose tolerance, but not when further adjusted for hypertension, smoking, and lipids.37 Among a cohort of 350 Japanese type 2 diabetic individuals, CRP was found to predict CVD in multivariable analyses adjusted for traditional risk factors similar to those in model 3 of this study.31 In the present study, even models that treated CRP as a continuous variable did not show an association with risk of CVD in diabetic participants. Because 70% of the CVD events in this study occurred among those with diabetes, and approximately 50% of the population has diabetes, it is surprising that CRP retained predictive power on a total population basis.

The primary strengths of this study are its prospective design, the careful confirmation of incident events, and the testing of this risk factor in a population that differs in important respects from those previously examined. A limitation of the present study is the inclusion of some participants with “possible” CVD at baseline, which could increase the apparent predictive effect of CRP if those with milder manifestations of CVD also had higher CRP values at baseline. The findings from subgroup analyses should also be considered preliminary until confirmed by additional studies, because false-positive results from testing multiple hypotheses and false-negative results from small sample size often affect subgroup analyses.

In conclusion, CRP was an independent predictor of CVD in this American Indian population, in which there is a high prevalence of risk factors. The magnitude of this association is rather modest, with adjusted RRs generally being <2.0. Sixteen percent of this population had single CRP levels >10 mg/L and thus beyond the range of applicability of the AHA/CDC clinical recommendations. In addition, the predictive ability of the AHA/CDC-recommended CRP risk categories was not uniform, and in some subgroups, such as those with diabetes, CRP was not associated with CVD risk. These results have important considerations for implementing the clinical use of CRP as an aid in the risk stratification of patients.

Acknowledgments
This work was supported by cooperative agreement grants U01-HL-65520, U01-HL-41642, U01-HL-41652, U01-HL-41654, and U01-HL-65521 from the National Heart, Lung, and Blood Institute, Bethesda, Md. We thank the Strong Heart Study participants, Indian Health Service facilities, and participating tribal communities for their extraordinary cooperation and involvement, which has contributed to the success of the Strong Heart Study. The views expressed in this article are those of the authors and do not necessarily reflect those of the Indian Health Service.
C-Reactive Protein: The Strong Heart Study

Best et al

References


C-Reactive Protein as a Predictor of Cardiovascular Risk in a Population With a High Prevalence of Diabetes: The Strong Heart Study
Lyle G. Best, Ying Zhang, Elisa T. Lee, Jeun-Liang Yeh, Linda Cowan, Vittorio Palmieri, Mary Roman, Richard B. Devereux, Richard R. Fabsitz, Russell P. Tracy, David Robbins, Michael Davidson, Aftab Ahmed and Barbara V. Howard

Circulation. 2005;112:1289-1295; originally published online August 22, 2005; doi: 10.1161/CIRCULATIONAHA.104.489260

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/9/1289

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/