Abstract—This article summarizes epidemiological studies of inflammation markers, particularly C-reactive protein, and cardiovascular disease as of early 2002. Gaps in the research and the public health practice implications are also discussed. Although considerable work has been published since this review was completed, the perspectives and issues presented are still useful in evaluating the use of inflammation markers for risk stratification and prevention. (Circulation. 2004;110:e554-e559.)

Key Words: AHA Scientific Statements ■ atherosclerosis ■ inflammation ■ population ■ risk factors

The Centers for Disease Control and Prevention/American Heart Association (CDC/AHA) Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice was convened on March 14 and 15, 2002, in Atlanta, Ga, to examine the selection and use of inflammatory markers to predict cardiovascular disease (CVD) risk. Three discussion groups on issues related to laboratory, clinical, and population science were organized. The present report contains the discussions and recommendations of the population science discussion group.

Recommendation for Public Health Practice
The screening of entire populations for elevated high-sensitivity C-reactive protein (hsCRP) for use in primary prevention is not justified at this time (Class III, Level of Evidence: C).

Recommendations for Research
1. If possible, pool prospective population studies with multiple adjustment for other cardiovascular disease (CVD) risk factors to better describe the independent association between hsCRP and CVD end points, including different CVD subgroups, and to explore possible interactions with other CVD risk factors, including age, race, and ethnicity.
2. Pool population study data to better describe the distribution and determinants of inflammatory markers in the general population and in population subgroups.
3. Study existing and new cohorts to examine the distribution and determinants of hsCRP and other inflammation markers and their association with CVD across a broader range of ethnic subgroups; studies of African American and Hispanic populations are particularly needed.
4. Study the distribution and determinants of hsCRP and other inflammation markers in children, young adults, and older adults.
5. Study the cost-effectiveness of hsCRP screening.

Discussion
The Population Science Discussion Group focused on questions related to the determinants of the population burden of atherosclerosis. This perspective also applies to the potential for using inflammation markers in some clinical settings. We attempted to answer a series of questions about inflammation in CVD. Inflammation can be measured by an array of serum or plasma markers, but
we focused on CRP, which is measured with high-sensitivity assays, because CRP was the main topic of the workshop and this marker appears to be a stable analyte and has been subject to numerous recent studies. A given inflammatory marker may or may not estimate all aspects of the underlying inflammatory processes, especially as an inflammatory marker may or may not estimate all aspects of the underlying inflammatory processes, especially as

### TABLE 1. Abbreviated Results From Regular Cohort Studies Examining Relationship Between CRP and CVD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>No.</th>
<th>Age, y</th>
<th>Follow-Up, y</th>
<th>End Point</th>
<th>No.</th>
<th>CRP Comparisons</th>
<th>OR (95% CI)</th>
<th>Adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agewall et al17</td>
<td>Goteborg, Sweden</td>
<td>131 men</td>
<td>56–77</td>
<td>3.0</td>
<td>Fatal &amp; nonfatal MI, SCD</td>
<td>16</td>
<td>Per mg/L</td>
<td>1.16 (1.06–1.29)</td>
<td>Age, smoking, SBP, DM, CVD organ damage, intervention group</td>
</tr>
<tr>
<td>Koenig et al18</td>
<td>MONICA (Augsburg, Germany)</td>
<td>936 men</td>
<td>45–64</td>
<td>8.2</td>
<td>Fatal or nonfatal AMI</td>
<td>53</td>
<td>&gt;6.573 vs ≤0.402</td>
<td>2.70(1.39–5.27)</td>
<td>Age, BMI, TC, HDL, smoking, alcohol, SBP, DBP, education, LTLA, DM</td>
</tr>
<tr>
<td>Harris et al24</td>
<td>Iowa 65+ Rural Health Study, US</td>
<td>279 men, 396 women</td>
<td>77.8</td>
<td>4.6</td>
<td>CVD death ICD 410–414, 430–438, 440–442</td>
<td>74</td>
<td>≥2.78 vs &lt;0.91</td>
<td>1.8 (0.9–3.6)</td>
<td>Age, sex, prevalent CVD, smoking, DM, BMI</td>
</tr>
<tr>
<td>Jager et al25</td>
<td>Hoom Study, the Netherlands</td>
<td>631 men &amp; women</td>
<td>50–75</td>
<td>5</td>
<td>CVD death ICD 390–458</td>
<td>24</td>
<td>≥2.84 vs ≤2.84</td>
<td>1.32 (0.52–3.35)</td>
<td>Age, sex, IGT, DM, smoking, hypertension, low HDL, TC, HDL, PAD, obesity, TC</td>
</tr>
<tr>
<td>Mendall et al19</td>
<td>Caerphilly Prospective Heart Disease Study, UK</td>
<td>1239 men</td>
<td>45–59</td>
<td>13.7</td>
<td>First fatal or nonfatal IHD</td>
<td>249*</td>
<td>≥3.88 vs ≤0.82</td>
<td>1.53 (0.83–2.82)</td>
<td>Plate, age, BMI, smoking, height, FEV1, alcohol use, SES, father’s SES</td>
</tr>
<tr>
<td>Lowe et al20</td>
<td>Speedwell Study, UK</td>
<td>1595 men</td>
<td>49–67</td>
<td>6.25</td>
<td>First fatal or nonfatal IHD</td>
<td>162†</td>
<td>≥4.3 vs ≤0.6</td>
<td>1.60 (0.90–2.83)</td>
<td>Age, thawing status, smoking, BMI, DBP, TC, ischemia</td>
</tr>
<tr>
<td>Ridker et al21</td>
<td>Air Force/Texas Coronary Atherosclerosis Prevention Study, US</td>
<td>5742 men &amp; women</td>
<td>45–73</td>
<td>5</td>
<td>Nonfatal MI, UA, SCD</td>
<td>216</td>
<td>Per quartile</td>
<td>1.17 (1.03–1.33)</td>
<td>Age, sex, smoking, hypertension, FH, lipid levels</td>
</tr>
<tr>
<td>Rost et al22</td>
<td>Framingham Heart Study, US</td>
<td>591 men 871 women</td>
<td>69.1 70.2</td>
<td>12–14</td>
<td>First ischemic stroke, TIA</td>
<td>82 men</td>
<td>114 women</td>
<td>≥6.90 vs 1.08 men</td>
<td>1.6 (0.87–3.13)</td>
</tr>
<tr>
<td>Pirro et al23</td>
<td>Quebec Cardiovascular Study, Canada</td>
<td>2037 men</td>
<td>45–76</td>
<td>5.2</td>
<td>Angina, CI, nonfatal MI, coronary death</td>
<td>105</td>
<td>≥3.80 vs ≤0.85</td>
<td>1.0 (0.5–1.8)</td>
<td>Age, smoking, DM, medication use, SBP, BMI</td>
</tr>
<tr>
<td>Strandberg &amp; Tilvis24</td>
<td>Helsinki Aging Study, Finland</td>
<td>326 women</td>
<td>75, 80, 85</td>
<td>10</td>
<td>CVD mortality (ICD 401–442)</td>
<td>147</td>
<td>Per 10 mg/L</td>
<td>1.22 (1.10–1.35)</td>
<td>Age, sex</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; SCD, sudden cardiac death; SBP, systolic blood pressure; DM, type 2 diabetes mellitus; CVD, cardiovascular disease; AMI, acute myocardial infarction; BMI, body mass index (wt/h²); TC, total cholesterol; HDL, high-density lipoprotein-cholesterol; DBP, diastolic blood pressure; LTPA, leisure time physical activity; ICD, International Classification of Diseases, 9th revision; IGT, impaired glucose tolerance; TG, triglyceride; IHD, ischemic heart disease; PAD, peripheral arterial disease; FEV1, forced expiratory volume at 1 s; SES, socioeconomic status; UA, unstable angina; FH, family history of CHD; TIA, transient ischemic attack; and CI, coronary insufficiency. Other abbreviations as in text.

*No. of events reported for 1395 participants.
†No. of events reported for 1690 participants.
Two additional studies demonstrated significant associations between hsCRP and stroke.

Six traditional (not nested) cohort studies (Table 1) have examined the relationship between CRP and CHD. In addition, 1 cohort study focused on stroke as the sole outcome of interest, and 3 cohort studies used combined CVD end points. Of the 6 cohort studies of CHD, 3 did not find a significant association between CRP concentration and CHD after adjustment for various potential confounders. Three studies reported significant independent associations between CRP and CVD. Two of 3 cohort studies failed to find significant associations between CRP concentration and death from CVD. One cohort study described a significant association between CRP concentration and stroke among both men and women.

Significant associations between CRP concentration and smoking status (present and past), blood pressure, lipid concentrations, body mass index or other anthropometric variables, plasma glucose level and type 2 diabetes mellitus, and physical activity have been described. In addition, age is positively correlated with CRP concentration. Thus, in studying the potential relationship of hsCRP to CVD after traditional risk factors are measured, a minimal set of covariates should include age, smoking status, blood pressure, lipid concentrations, glucose level, and body mass index or other anthropometric variables. Only 2 nested case-control studies and no cohort study of CHD included these 6 variables as matching or confounding variables. Relatively few nested case-control studies of CHD or CVD have adjusted for type 2 diabetes mellitus, and only 2 studies have used measurements of fasting glucose concentration or fructosamine. Only 2 studies have adjusted for physical activity. Because studies have generally shown substantial attenuation of risk ratios as the number of covariates has increased, the risk estimates demonstrated by many of the nested case-control studies may overestimate the independent risk ratios. Studies also need to consider medication use carefully because estrogen replacement and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors raise and lower hsCRP, respectively.

Danesh and colleagues described a risk ratio of 1.7 for the highest tertile of CRP (>2.4 mg/L) as compared with the lowest CRP tertile (1.0 mg/L). In their updated meta-analysis published in 2000, which included both nested case-control and full cohort studies, the authors calculated a risk ratio of 2.0 (95% CI 1.6 to 2.5) for the top tertile as compared with the bottom tertile. A superficial examination of the full cohort study data, in which to date the control for confounding appears to be more complete, suggests that the risk ratio is likely lower (Table 2). With data from 4 studies that reported a measure of relative risk for the top quartile or quintile that was maximally adjusted except for other inflammatory markers such as fibrinogen, the estimates are 2.6, 1.53, 1.60, and 1.18–20. Furthermore, in the Air Force/Texas Coronary Atherosclerosis Prevention Study, the relative risk per quartile of CRP was 1.17. This number would suggest that participants in that trial with a CRP in the highest quartile would have a risk of 1.60, which is consistent with the median risk of the other studies.

The present discussion group was asked to address the following 6 questions:

1. What is the distribution of inflammatory markers in the general population (in contrast to clinical populations)?
   a. Do distributions of inflammatory markers vary among groups defined by age, sex, ethnicity, and prevalence of diseases?

2. What is the population-attributable risk and the population-attributable risk fraction for CVD using high-risk levels of inflammatory markers? What proportion of clinical events, deaths, or both from CVD might be predicted in the population?

It is premature to calculate population-attributable risk because the association between inflammatory markers and CVD has not been shown to be causal. Also, as discussed above, the strength of the association between hsCRP and CVD end points, when fully adjusted for other established CVD risk factors, is still somewhat uncertain, as is the proportion of the population who should be defined as high risk. If we ignore these caveats and use the range of relative risks from the published studies and use a high-risk definition of the top quintile, then it appears that the population-attributable risk would be between 10% and 25%.

3. Do inflammatory markers correlate with other risk factors and behaviors in population-based studies? Do these differ from those observed in clinical popula-
TABLE 2. Abbreviated Results From Nested Case-Control Studies Examining Relationship Between CRP and CVD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
<th>Age, y</th>
<th>Follow-Up, y</th>
<th>End Point</th>
<th>CRP Comparisons</th>
<th>OR (95% CI)</th>
<th>Adjusted for</th>
<th>Matched on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al</td>
<td>Physician’s Health Study, US</td>
<td>97 men</td>
<td>192</td>
<td>40–84</td>
<td>17</td>
<td>SCD</td>
<td>0.2–0.5</td>
<td>(0.14–0.29)</td>
<td>Age, smoking, length of follow-up</td>
<td></td>
</tr>
<tr>
<td>Danesh et al</td>
<td>24 British towns, UK</td>
<td>506 men</td>
<td>1025</td>
<td>40–59</td>
<td>9.5</td>
<td>Fatal CHD, nonfatal MI</td>
<td>&gt;2.4 vs &lt;0.9</td>
<td>2.13</td>
<td>(1.38–3.28)</td>
<td>Age, town of residence</td>
</tr>
<tr>
<td>Folsom et al</td>
<td>ARIC</td>
<td>615 men &amp; women</td>
<td>590</td>
<td>45–64</td>
<td>3.6–4.3</td>
<td>MI, CHD death, revascularization</td>
<td>&gt;6.09 vs &lt;0.83</td>
<td>1.5 (0.8–2.7)</td>
<td>Age, sex, race, TC, HDL, SBP, smoking, DM</td>
<td></td>
</tr>
<tr>
<td>Gram et al</td>
<td>Glaxo, Denmark</td>
<td>133 men &amp; women</td>
<td>258</td>
<td>≥40</td>
<td>7–15</td>
<td>MI, CHD</td>
<td>Per log mg/L</td>
<td>1.13</td>
<td>(1.0–2.3)</td>
<td>Controls-stratified sample (age, sex, carotid IMT)</td>
</tr>
<tr>
<td>Guseklo et al</td>
<td>Leiden 85-Plus Study, the Netherlands</td>
<td>80 men &amp; women</td>
<td>83</td>
<td>≥85</td>
<td>≤5</td>
<td>Stroke death (SD 430–438)</td>
<td>&gt;20 vs ≤5</td>
<td>11 (2.4–45)</td>
<td>Age, sex, smoking, NSAID use, TC, HTN, DM, CVD</td>
<td></td>
</tr>
<tr>
<td>Kervinen et al</td>
<td>Helsinki Heart Study, Finland</td>
<td>150 men</td>
<td>150</td>
<td>40–55</td>
<td>≤8.5</td>
<td>MI or coronary death</td>
<td>≥2.7 vs ≤2.7</td>
<td>Unspecified</td>
<td>Age, smoking</td>
<td></td>
</tr>
<tr>
<td>Kuller et al</td>
<td>Multiple Risk Factor Intervention Trial, US</td>
<td>148 men</td>
<td>296</td>
<td>35–57</td>
<td>≤17</td>
<td>CHD mortality</td>
<td>≥3.3 vs ≤1.2</td>
<td>2.8 (1.4–5.4)</td>
<td>Age, DBP, smoking, TG, LDL, HDL</td>
<td></td>
</tr>
<tr>
<td>Ravnainen et al</td>
<td>Helsinki Heart Study, Finland</td>
<td>98 men</td>
<td>195</td>
<td>6–7</td>
<td>Nonfatal MI</td>
<td>≥3.3 vs ≤1.2</td>
<td>0.8 (0.4–1.7)</td>
<td>Age, smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packard et al</td>
<td>West of Scotland Coronary Prevention Study, UK</td>
<td>580 men</td>
<td>1160</td>
<td>56.8 (SD 5.2)</td>
<td>≤6</td>
<td>Fatal CHD, nonfatal MI</td>
<td>&lt;0.76</td>
<td>1.0</td>
<td>Age, SBP, TG, LDL, HDL</td>
<td></td>
</tr>
<tr>
<td>Ridker et al</td>
<td>Physican’s Health Study, US</td>
<td>246 men</td>
<td>543</td>
<td>40–84</td>
<td>≤14</td>
<td>MI</td>
<td>≥2.11 vs ≤0.55</td>
<td>2.9 (1.8–4.6)</td>
<td>Age, smoking, randomization time</td>
<td></td>
</tr>
<tr>
<td>Roivainen et al</td>
<td>Women’s Health Study, US</td>
<td>122 women</td>
<td>244</td>
<td>59.3 (SD 6.4)</td>
<td>≤3</td>
<td>MI, stroke, PTCA, CABG, CVD death</td>
<td>&gt;7.3 vs ≤1.5</td>
<td>4.1 (1.7–9.9)</td>
<td>Age, smoking</td>
<td></td>
</tr>
<tr>
<td>Sakkinen et al</td>
<td>Honolulu Heart Program, US</td>
<td>369 men</td>
<td>1348</td>
<td>45–68</td>
<td>20</td>
<td>MI</td>
<td>&gt;1.0 vs ≤0.33</td>
<td>1.6 (1.1–2.2)</td>
<td>Age, HTN, DM, smoking, TC, BMI, alcohol</td>
<td></td>
</tr>
<tr>
<td>Tice et al</td>
<td>Study of Osteoporotic Fractures, US</td>
<td>52 women</td>
<td>342</td>
<td>≥65</td>
<td>6</td>
<td>CVD death</td>
<td>1.2–3.0</td>
<td>Age, HTN, LDL, HDL, BMI, smoking, estrogen use, site, education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracy et al</td>
<td>Cardiovascular Health Study, US</td>
<td>89 men</td>
<td>89</td>
<td>65–79</td>
<td>≤3</td>
<td>MI, CHD death</td>
<td>≥2.79 vs ≤0.96</td>
<td>1.07 (0.52–2.22)</td>
<td>Age, sex, subclinical disease, time</td>
<td></td>
</tr>
<tr>
<td>Rural Health Promotion Project, US</td>
<td>80 men</td>
<td>80</td>
<td>65–79</td>
<td>≤3</td>
<td>MI, CHD death</td>
<td>Q5 vs Q1–4</td>
<td>2.0 (0.82–4.87)</td>
<td>Not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witherell et al</td>
<td>KPHC Multisite Health Checkup System, US</td>
<td>100 men &amp; women</td>
<td>161</td>
<td>4.8</td>
<td>MI</td>
<td>Per log mg/L</td>
<td>1.4 (1.0–1.9)</td>
<td>Smoking, HTN, ECO, obesity, TC, Helicobacter pylori infection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hcy, homocysteine; HTN, hypertension history; PA, physical activity; BP, blood pressure; IMT, intima-media thickness; t-PA, tissue-type plasminogen activator; NSAID, nonsteroidal antiinflammatory drug; LDL, low-density lipoprotein-cholesterol; PTCA, angioplasty; CABG, coronary artery bypass graft; AP, angina pectoris; and ECG, electrocardiogram. Other abbreviations as in Table 1 or in text.
tions? Can inflammatory markers be used as surrogates for or additives to risk-calculation equations?

There appear to be strong correlations between inflammatory markers, particularly fibrinogen and hsCRP, and the elements of the metabolic syndrome; ie, people with obesity, central adiposity, physical inactivity, and type 2 diabetes mellitus have higher levels of inflammatory markers. In addition, smoking and hormone replacement therapy elevate hsCRP. There are also early indications that weight loss lowers levels of inflammatory markers.

Inflammation, as measured (imperfectly) by fibrinogen, WBC, and hsCRP, appears to be an independent risk factor in middle-aged white men and women. More data exist for fibrinogen and WBC, but hsCRP also appears to be independent and clearly is more easily and reliably measured than is fibrinogen. More data are needed on younger populations and in multiple ethnic groups, especially African Americans and Hispanics. The control for other risk factors has been incomplete in some of the published studies, and the matching design also has limitations. The early population-wide studies do indicate independence, but the strength of the association appears weaker than indicated in the earlier studies (with a relative risk about 2.0 or below in fully adjusted models). Thus, the degree of improvement of global risk prediction by the addition of inflammatory markers is not yet well established. Improvements in the area under the receiver-operating curve may be rather modest across entire populations, but it is important to note that this does not mean that inflammatory markers would not be useful predictors of CVD in selected populations, especially those at intermediate risk. The addition of inflammatory markers to global risk prediction in patients at intermediate risk could result in a significant increase in the “posttest probability” of CVD, which would be useful clinically. The use of hsCRP for screening cannot be recommended with confidence until this strategy meets more of the usual criteria for screening. It is shown to reduce morbidity and mortality in a clinical trial, or both. The nonspecificity of elevated CRP may be particularly problematic in applying the population-level results to individual patients, with the possibility of necessitating multiple determinations and potentially expensive searches for noncardiovascular causes of elevated CRP.

The present group thought that additional prospective studies of more diverse populations, including a full range of potential confounding variables, would be helpful at this juncture. It is likely that a number of these studies are already in progress, but new studies may be needed to broaden the number of ethnic subgroups studied.

4. What is the role of inflammatory factors in the causal pathway? Do inflammatory factors predict risk independently, spuriously because of confounding, or nonindependently as intermediary steps through which other risk factors act?

Clearly, there is confounding between inflammatory markers and other established risk factors, but there is also an independent component of the association. The number of positive studies to date makes it unlikely that this association is spurious; however, the role of inflammatory markers in the causal pathway is still unclear, which does not necessarily detract from the usefulness of inflammatory markers as risk markers. Inflammation may play a role in any of the developmental stages of CVD, including the initiation and progression of atherosclerosis, plaque formation, plaque rupture, and thrombosis. A wealth of nonepidemiological data indicate that inflammation is an important cause of the development of atherosclerosis and thus CVD. Causality has not been demonstrated for specific markers in experimental epidemiological studies (ie, randomized controlled trials). Thus, it is unknown whether any specific marker is involved in the causal chain, mediating the effects of other risk factors (eg, diabetes or obesity) or merely reflecting the presence of undiagnosed atherosclerosis. Additional basic and clinical research will likely shed more light on these issues, as will clinical trials once appropriate interventions are identified.

5. Do inflammatory markers or clusters of inflammatory markers identify high-risk subjects in a cost-effective manner? What is the cost per newly identified high-risk subject with inflammatory markers relative to standard means of risk estimation (eg, individual risk factors, multiple risk scores)?

Until the ability of hsCRP to improve risk stratification is better established, it is premature to speculate on cost-effectiveness. CRP can be measured at relatively low cost, even with the high-sensitivity assay, particularly when compared with the imaging studies that also have been advocated for primary screening (carotid ultrasound and coronary calcium quantification by computed x-ray tomography). In addition, hsCRP measurement could be less prone than imaging studies to stimulate expensive and perhaps unnecessary clinical testing and even coronary catheterization.

6. Do infections and other inflammatory disease cause CVD through increases in inflammatory mediators?

This question could be important in determining the population-level contribution of inflammation to CVD burden; however, the question cannot be answered at this time. Studies of the relationship between infectious burden and CVD have been limited by measures of previous infection rather than long-term, persistent, or active infection. In addition, the role of infection in stimulating inflammation and therefore atherosclerosis is not established.

References
4. Witherell HL, Smith KL, Ley C, Friedman GD, Orentreich N, Vogelman JH. Helicobacter pylori infection, C-reactive protein, and risk for myo-


CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: Report From the Population Science Discussion Group

Stephen P. Fortmann, Earl Ford, Michael H. Criqui, Aaron R. Folsom, Tamara B. Harris, Yuling Hong, Thomas A. Pearson, David Siscovick, Frank Vinicor and Peter F. Wilson

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