White Blood Cell Count Predicts Reduction in Coronary Heart Disease Mortality With Pravastatin

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**Background**—Elevated serum inflammatory marker levels are associated with a greater long-term risk of cardiovascular events. Because 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (statins) may have an antiinflammatory action, it has been suggested that patients with elevated inflammatory marker levels may have a greater reduction in cardiovascular risk with statin treatment.

**Methods and Results**—We evaluated the association between the white blood cell count (WBC) and coronary heart disease mortality during a mean follow-up of 6.0 years in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study, a clinical trial comparing pravastatin (40 mg/d) with a placebo in 9014 stable patients with previous myocardial infarction or unstable angina. An increase in baseline WBC was associated with greater coronary heart disease mortality in patients randomized to placebo (hazard ratio for 1×10⁹/L increase in WBC, 1.18; 95% CI, 1.12 to 1.25; P<0.001) but not pravastatin (hazard ratio, 1.02; 95% CI, 0.96 to 1.09; P=0.56; P for interaction=0.004). The numbers of coronary heart disease deaths prevented per 1000 patients treated with pravastatin were 0, 9, 30, and 38 for baseline WBC quartiles of <5.9, 6.0 to 6.9, 7.0 to 8.1, and >8.2×10⁹/L, respectively. WBC was a stronger predictor of this treatment benefit than the ratio of total to high-density lipoprotein cholesterol and a global measure of cardiac risk. There was also a greater reduction (P=0.052) in the combined incidence of cardiovascular mortality, nonfatal myocardial infarction, and stroke with pravastatin as baseline WBC increased (by quartile: 3, 41, 61, and 60 events prevented per 1000 patients treated, respectively).

**Conclusions**—These data support the hypothesis that individuals with evidence of inflammation may obtain a greater benefit from statin therapy. *(Circulation. 2005;111:1756-1762.)*

**Key Words:** coronary disease ■ inflammation ■ leukocytes ■ mortality ■ statins
The aim of the present study was to determine whether a higher WBC predicted a greater treatment benefit from pravastatin in subjects with known stable coronary heart disease (CHD) who participated in the Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study.12

Methods

The LIPID Study was a randomized, placebo-controlled clinical trial of cholesterol-lowering treatment with pravastatin involving 9014 Australians and New Zealanders.12 Men and women 31 to 75 years of age with a history of acute myocardial infarction or hospitalization for unstable angina within the previous 3 months to 3 years were eligible for enrollment. Exclusion criteria included significant illness during the previous 3 months, unavailability for long-term follow-up, significant cardiac failure (New York Heart Association class III or IV), and treatment with lipid-lowering drugs. After a run-in phase, patients with a fasting total serum cholesterol level in the range of 4.0 to 7.0 mmol/L (155 to 271 mg/dL) and a serum triglyceride level of ≤5.0 mmol/L (≤445 mg/dL) were randomly assigned to receive either pravastatin (40 mg/d) or a matching placebo. All patients received dietary and general lifestyle advice. Patient care was otherwise under the direction of their usual doctors.

WBC was measured at the local laboratory before randomization, after 1 and 5 years of follow-up, and at the end of the study. Serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured at a central laboratory. Baseline data and a previously described multivariate model13 were used to calculate a “global risk score” for each patient to rank the risk of CHD mortality or nonfatal myocardial infarction. Independent predictors of risk used to calculate the global risk score were total and HDL cholesterol levels, age, gender, smoking status, myocardial infarction or unstable angina as the qualifying event, previous coronary revascularization procedures, diabetes mellitus, hypertension, and previous stroke.

Information on deaths, myocardial infarction, and stroke was obtained from hospital records, death certificates, autopsy reports, and physicians’ notes and was reviewed by the Outcome Assessment Committee, which was blinded to the patients’ treatment allocation. As in the LIPID Study,12 the primary end point of this analysis was CHD mortality. In addition, an expanded end point that included cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke was used. Cardiovascular mortality was defined as death from a cardiac cause, from cerebrovascular disease, or from peripheral vascular disease. Hospital admissions for unstable angina or coronary revascularization procedures during follow-up were documented but not reviewed by the Outcome Assessment Committee.

Patients were randomized between June 1990 and December 1992, and final patient follow-up visits occurred during 1997. The vital status of all but 1 patient was ascertained.

Statistical Analysis

All analyses in this study were performed on an intention-to-treat basis, and probability values were 2 sided. Estimates of relative risk reduction and 95% CIs were made with the Cox proportional-hazard model.14 Assessment of variation between subgroups in the effects of treatment on all outcomes was based on tests of trend for interaction in the Cox model. All probability values reported in the tables were unadjusted for multiple comparisons.

Analyses of the associations between WBC and outcomes were adjusted for baseline risk factors identified previously by Marschner et al.13 Relative risks were based on hazard ratio (HR) estimates with 95% CIs. Tests of trend for baseline risk factors were based on χ² tests.

Results

Clinical Characteristics Stratified by Baseline WBC

Table 1 shows the patients’ baseline demographics, cardiovascular risk factors, and clinical measures of cardiovascular disease stratified by WBC quartiles. Subjects with a higher WBC were more likely to be current or ex-smokers, to be obese, or to have diabetes, a low HDL cholesterol level, or a high serum triglyceride level. They were also more likely to have clinical evidence of more severe cardiovascular disease, including previous stroke, previous myocardial infarction, and symptoms of angina, dyspnea, and claudication. There was a weak association between an increased WBC and hypertension, but there was no association between WBC and LDL cholesterol level, previous smoking, age, gender, or country of residence.

Association Between WBC and Cardiovascular Outcomes

For every increase of 1×10⁹/L in baseline WBC, there was a progressive increase in CHD mortality (HR, 1.15; 95% CI, 1.10 to 1.19; P<0.001; Table 2). This increase in risk was observed for both sudden CHD mortality (HR, 1.12; 95% CI, 1.06 to 1.18; P<0.001) and nonsudden CHD mortality (HR, 1.19; 95% CI, 1.12 to 1.26; P<0.001). A higher WBC was also associated with increased risks of nonfatal myocardial infarction (HR, 1.09; 95% CI, 1.05 to 1.13; P<0.001) and stroke (HR, 1.10; 95% CI, 1.05 to 1.16; P<0.001). The strength of these associations was only partly accounted for by the association between WBC and other predictors of cardiovascular risk (Table 2). The rates of hospitalization for unstable angina and referral for coronary revascularization procedures during follow-up did not increase as the WBC increased.

Cardiovascular Event Rates Stratified by WBC and Treatment Allocation

Table 3 shows the associations of baseline WBC with CHD mortality and with the combined risk of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke in both treatment groups. The increase in CHD mortality observed with an increase in the WBC was greater in patients randomized to placebo than in those randomized to pravastatin (interaction P=0.004 for trend). After adjustment for all other baseline predictors of mortality, including serum lipid levels, this association remained significant in the placebo group, as did the interaction between WBC, pravastatin treatment, and CHD mortality. The increase in the combined risk of cardiovascular mortality, nonfatal myocardial infarction, and stroke observed with an increase in WBC was also greater in patients randomized to placebo than in those randomized to pravastatin. These associations were not influenced by the time from the qualifying event to measurement of WBC at the baseline visit.

Comparison With Other Indicators of Cardiovascular Risk

Table 4 shows the risk of CHD mortality in both treatment groups stratified by quartiles of WBC, ratio of total to HDL cholesterol, and global risk score. The absolute mortality reduction observed with pravastatin increased progressively as the baseline WBC quartile increased (P=0.017). In contrast, neither the ratio of total to HDL cholesterol (P=0.4) nor global risk score (P=0.6) predicted a greater absolute reduc-
tion in mortality with pravastatin treatment. Table 5 shows the combined risk of cardiovascular mortality, nonfatal myocardial infarction, and stroke in both treatment groups stratified by quartiles of WBC, ratio of total to HDL cholesterol, and global risk score. There was a trend toward a greater overall reduction in these events with pravastatin as the baseline WBC quartile increased (\(P < 0.001\)).

Figure 1 shows the cumulative CHD mortality rate, and Figure 2 the cumulative cardiovascular event rate during 6 years of treatment with pravastatin compared with placebo in patients with WBC above and below the median value (7.0 \(\times 10^9/L\)) for the study population at the baseline assessment.

**Change in WBC During Pravastatin Treatment**

Figure 3 shows the median WBC of both treatment groups at baseline, after 1 and 5 years of follow-up, and at the end of the study. On average, WBC decreased between the baseline and end of the study.

### TABLE 1. Baseline Characteristics of Study Population Stratified by WBC Quartile

<table>
<thead>
<tr>
<th>WBC Quartile (% of Subjects With Characteristic)</th>
<th>Median, 5.3 (\times 10^9/L) (Range, 2.5–5.9 (\times 10^9/L))</th>
<th>Median, 6.5 (\times 10^9/L) (Range, 6.0–6.9 (\times 10^9/L))</th>
<th>Median, 7.5 (\times 10^9/L) (Range, 7.0–8.1 (\times 10^9/L))</th>
<th>Median, 9.1 (\times 10^9/L) (Range, 8.2–19.9 (\times 10^9/L))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (interquartile range), y</td>
<td>62 (55–67)</td>
<td>62 (55–67)</td>
<td>63 (56–68)</td>
<td>62 (54–67)</td>
<td></td>
</tr>
<tr>
<td>Age ≥65 years</td>
<td>39</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>0.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>83</td>
<td>84</td>
<td>85</td>
<td>82</td>
<td>0.3</td>
</tr>
<tr>
<td>Australian (vs New Zealander)</td>
<td>67</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>0.4</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39</td>
<td>42</td>
<td>42</td>
<td>43</td>
<td>0.006</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>7</td>
<td>10</td>
<td>11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index &gt;30 kg/m²</td>
<td>14</td>
<td>17</td>
<td>19</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4</td>
<td>6</td>
<td>9</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>61</td>
<td>65</td>
<td>67</td>
<td>62</td>
<td>0.3</td>
</tr>
<tr>
<td>LDL cholesterol (\geq 3.5 \text{ mmol/L})</td>
<td>69</td>
<td>72</td>
<td>69</td>
<td>70</td>
<td>0.8</td>
</tr>
<tr>
<td>HDL cholesterol (&lt;1.0 \text{ mmol/L})</td>
<td>58</td>
<td>61</td>
<td>65</td>
<td>67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (\geq 1.5 \text{ mmol/L})</td>
<td>47</td>
<td>54</td>
<td>56</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction as qualifying event</td>
<td>61</td>
<td>65</td>
<td>64</td>
<td>65</td>
<td>0.007</td>
</tr>
<tr>
<td>Myocardial infarction before qualifying event</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac and vascular symptoms at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>7</td>
<td>10</td>
<td>10</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyspnea (NYHA class 1+)</td>
<td>43</td>
<td>49</td>
<td>49</td>
<td>54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angina (CCS class 1+)</td>
<td>34</td>
<td>36</td>
<td>38</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society.

### TABLE 2. Association Between Baseline WBC and Cardiovascular Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patients With Event, n</th>
<th>Unadjusted HR (95% CI)</th>
<th>Unadjusted P</th>
<th>Adjusted HR (95% CI)*</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD mortality</td>
<td>660</td>
<td>1.15 (1.10–1.19)</td>
<td>&lt;0.001</td>
<td>1.11 (1.06–1.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sudden</td>
<td>393</td>
<td>1.12 (1.06–1.18)</td>
<td>&lt;0.001</td>
<td>1.08 (1.02–1.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>Nonsudden</td>
<td>267</td>
<td>1.19 (1.12–1.26)</td>
<td>&lt;0.001</td>
<td>1.15 (1.08–1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>714</td>
<td>1.09 (1.05–1.13)</td>
<td>&lt;0.001</td>
<td>1.05 (1.01–1.10)</td>
<td>0.019</td>
</tr>
<tr>
<td>Stroke†</td>
<td>373</td>
<td>1.10 (1.05–1.16)</td>
<td>&lt;0.001</td>
<td>1.08 (1.02–1.14)</td>
<td>0.010</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>1293</td>
<td>1.00 (0.97–1.04)</td>
<td>0.81</td>
<td>0.99 (0.96–1.02)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>2111</td>
<td>1.02 (1.00–1.05)</td>
<td>0.06</td>
<td>1.01 (0.98–1.03)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Results shown are for patients randomized to pravastatin and placebo combined. Estimates were made with the Cox proportional-hazards model. Baseline WBC was analyzed as a continuous variable.

*Adjusted for other baseline risk predictors.

†419 strokes occurred in 373 patients, including 31 hemorrhagic strokes.
and 1-year follow-up assessments and then remained stable. Median WBC did not differ between treatment groups at any visit.

**Discussion**

In this large randomized clinical trial of patients with a history of myocardial infarction or hospitalization for unstable angina, the reduction in CHD mortality observed with pravastatin treatment was greater in patients with a higher baseline WBC than in those with a lower baseline WBC. Patients with a higher WBC had a higher absolute risk of sudden or nonsudden CHD mortality during a mean follow-up period of 6 years. In addition, the findings support the hypothesis that pravastatin may decrease the risk of CHD mortality by some action on inflammatory pathways.

Our finding that an increased baseline WBC was associated with diabetes, obesity, hypertriglyceridemia, and a low HDL cholesterol level is consistent with previous observations that inflammation is part of the metabolic syndrome.\(^{15}\) WBC was also associated with other predictors of CHD mortality, including smoking and clinical evidence of more severe cardiac, cerebrovascular, and peripheral vascular disease; however, the interaction between WBC and the treatment benefit of pravastatin persisted after adjustment for these and other conventional risk factors, although confounding from other factors that were not measured cannot be excluded. In addition, the beneficial effect of pravastatin on CHD mortality did not increase with an increase in the risk score calculated from multiple baseline variables.\(^{13}\) These observations suggest that WBC provides additional information on the likely benefit of statin treatment beyond that obtained from an assessment of absolute cardiac risk.

Although previous clinical trials have not assessed WBC as a predictor of statin treatment benefit, several studies have assessed the predictive value of C-reactive protein in this setting. In the Cholesterol and Recurrent Events Study,\(^6\) elevated levels of the inflammatory markers serum amyloid A and/or C-reactive protein were associated with an increased risk of cardiac mortality or nonfatal myocardial infarction during follow-up in patients randomized to placebo but not in

### TABLE 3. Association Between WBC and Primary Outcomes Stratified by Treatment Allocation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>(P) for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD mortality</td>
<td>373</td>
<td>287</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>1.21 (1.15–1.27)</td>
<td>1.07 (1.01–1.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular mortality, nonfatal myocardial infarction, or stroke</td>
<td>897</td>
<td>710</td>
<td>0.069</td>
</tr>
<tr>
<td></td>
<td>1.13 (1.10–1.17)</td>
<td>1.10 (1.06–1.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&lt;0.001)</td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.08 (1.04–1.13)</td>
<td>1.05 (1.00–1.09)</td>
<td>(0.06, 0.033)</td>
</tr>
</tbody>
</table>

Estimates were made with the Cox proportional-hazards model. Baseline WBC was analyzed as a continuous variable.

*Adjusted for other baseline risk predictors.

### TABLE 4. Incidence of CHD Mortality in Patients Randomized to Pravastatin or Placebo Stratified by Quartile of WBC, Ratio of Total to HDL Cholesterol, and Global Cardiovascular Risk Score Assessed at Baseline

<table>
<thead>
<tr>
<th>Median (Range)</th>
<th>Subjects, n</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>HR (95% CI)</th>
<th>Heterogeneity P for Trend</th>
<th>CHD Deaths Avoided Per 1000 Patients Treated With Pravastatin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, 10^9/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3 (2.5–5.9)</td>
<td>2167</td>
<td>59 (5.4)</td>
<td>59 (5.5)</td>
<td>1.03 (0.72–1.48)</td>
<td>0.027</td>
<td>0</td>
</tr>
<tr>
<td>6.5 (6.0–6.9)</td>
<td>2190</td>
<td>74 (6.8)</td>
<td>65 (5.9)</td>
<td>0.87 (0.62–1.20)</td>
<td>0.033</td>
<td>9</td>
</tr>
<tr>
<td>7.5 (7.0–8.1)</td>
<td>2263</td>
<td>102 (9.2)</td>
<td>72 (6.2)</td>
<td>0.66 (0.49–0.89)</td>
<td>0.033</td>
<td>30</td>
</tr>
<tr>
<td>9.1 (8.2–19.9)</td>
<td>2392</td>
<td>138 (11.5)</td>
<td>91 (7.7)</td>
<td>0.65 (0.50–0.85)</td>
<td>0.033</td>
<td>38</td>
</tr>
<tr>
<td>Ratio of total to HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5 (2.2–5.1)</td>
<td>2253</td>
<td>85 (7.5)</td>
<td>53 (4.7)</td>
<td>0.63 (0.45–0.88)</td>
<td>0.35</td>
<td>28</td>
</tr>
<tr>
<td>5.6 (5.1–6.1)</td>
<td>2253</td>
<td>82 (7.2)</td>
<td>63 (5.6)</td>
<td>0.77 (0.56–1.07)</td>
<td>0.16</td>
<td>16</td>
</tr>
<tr>
<td>6.6 (6.1–7.1)</td>
<td>2253</td>
<td>97 (8.7)</td>
<td>83 (7.3)</td>
<td>0.83 (0.62–1.11)</td>
<td>0.14</td>
<td>14</td>
</tr>
<tr>
<td>8.0 (7.1–13.9)</td>
<td>2253</td>
<td>109 (9.7)</td>
<td>88 (7.8)</td>
<td>0.78 (0.59–1.03)</td>
<td>0.19</td>
<td>19</td>
</tr>
<tr>
<td>Risk score</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.49 (0.65–1.88)</td>
<td>2209</td>
<td>39 (3.6)</td>
<td>19 (1.7)</td>
<td>0.46 (0.26–0.79)</td>
<td>0.037</td>
<td>19</td>
</tr>
<tr>
<td>2.17 (1.88–2.49)</td>
<td>2247</td>
<td>68 (6.2)</td>
<td>54 (4.7)</td>
<td>0.76 (0.53–1.08)</td>
<td>0.15</td>
<td>15</td>
</tr>
<tr>
<td>2.93 (2.49–3.44)</td>
<td>2293</td>
<td>94 (8.0)</td>
<td>62 (5.6)</td>
<td>0.69 (0.50–0.95)</td>
<td>0.24</td>
<td>24</td>
</tr>
<tr>
<td>4.37 (3.47–16.3)</td>
<td>2265</td>
<td>172 (15.0)</td>
<td>152 (14.0)</td>
<td>0.89 (0.72–1.11)</td>
<td>0.10</td>
<td>10</td>
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</tbody>
</table>

*Test for trend association between CHD mortality and WBC quartile, \(P=0.017\); ratio of total to HDL cholesterol, \(P=0.4\); risk score, \(P=0.6\).
those randomized to pravastatin. In contrast, the risk of coronary events in patients without elevated inflammatory marker levels was similar in the placebo and pravastatin treatment groups. In the Air Force/Texas Coronary Atherosclerosis Prevention Study, subjects with a below-average LDL cholesterol level combined with an above-average C-reactive protein level had a significant reduction in acute coronary events if randomized to lovastatin rather than placebo, whereas the event rates did not differ significantly between treatment groups in subjects with below-average levels of both LDL cholesterol and C-reactive protein. Nonrandomized cohort studies have also suggested that the reduction in cardiovascular mortality observed with statin treatment is greater in patients with higher C-reactive protein levels.

In the present study, WBC was not decreased by pravastatin treatment. This suggests that an increased WBC is a marker for increased cardiovascular risk related to inflammation but that serial measurements of WBC would not be useful for assessing the treatment efficacy of statins. Previous studies have demonstrated that statins (including pravastatin) reduce serum C-reactive protein levels. It has been suggested that the greater benefit observed with some high-dose

<table>
<thead>
<tr>
<th>Median (Range)</th>
<th>Subjects, n</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>HR (95% CI)</th>
<th>Heterogeneity</th>
<th>Events Avoided</th>
<th>Per 1000 Patients Treated With Pravastatin*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, 10^9/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3 (2.5–5.9)</td>
<td>2167</td>
<td>163 (14.8)</td>
<td>155 (14.5)</td>
<td>0.98 (0.78–1.22)</td>
<td>0.052</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6.5 (6.0–6.9)</td>
<td>2190</td>
<td>200 (18.3)</td>
<td>156 (14.2)</td>
<td>0.76 (0.62–0.93)</td>
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<tr>
<td>7.5 (7.0–8.1)</td>
<td>2263</td>
<td>240 (21.7)</td>
<td>181 (15.6)</td>
<td>0.69 (0.57–0.84)</td>
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<tr>
<td>9.1 (8.2–19.9)</td>
<td>2392</td>
<td>294 (24.4)</td>
<td>218 (18.4)</td>
<td>0.73 (0.61–0.87)</td>
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<tr>
<td>Ratio of total to HDL cholesterol</td>
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<tr>
<td>4.5 (2.2–5.1)</td>
<td>2253</td>
<td>188 (16.6)</td>
<td>143 (12.8)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.85</td>
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<tr>
<td>5.6 (5.1–6.1)</td>
<td>2253</td>
<td>217 (19.1)</td>
<td>166 (14.9)</td>
<td>0.76 (0.62–0.92)</td>
<td></td>
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<tr>
<td>6.6 (6.1–7.1)</td>
<td>2253</td>
<td>237 (21.3)</td>
<td>204 (17.9)</td>
<td>0.82 (0.68–0.99)</td>
<td></td>
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<tr>
<td>8.0 (7.1–13.9)</td>
<td>2253</td>
<td>255 (22.8)</td>
<td>197 (17.4)</td>
<td>0.73 (0.61–0.88)</td>
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<tr>
<td>Risk score</td>
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<tr>
<td>1.49 (0.65–1.88)</td>
<td>2209</td>
<td>121 (11.2)</td>
<td>82 (7.2)</td>
<td>0.63 (0.48–0.84)</td>
<td>0.36</td>
<td>40</td>
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<tr>
<td>2.17 (1.88–2.49)</td>
<td>2247</td>
<td>170 (15.5)</td>
<td>156 (13.6)</td>
<td>0.87 (0.70–1.08)</td>
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<tr>
<td>2.93 (2.49–3.44)</td>
<td>2293</td>
<td>241 (20.4)</td>
<td>172 (15.5)</td>
<td>0.73 (0.60–0.89)</td>
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<tr>
<td>4.37 (3.47–16.3)</td>
<td>2265</td>
<td>365 (31.9)</td>
<td>300 (26.8)</td>
<td>0.82 (0.70–0.95)</td>
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</table>

*Test for trend for association between cardiovascular events and WBC quartile, $P=0.09$; ratio of total to HDL cholesterol, $P=0.4$; risk score, $P=0.44$.

**Figure 1.** Cumulative CHD mortality during 6 years of treatment with pravastatin vs placebo in patients with baseline WBC above or below median value ($7.0 \times 10^9$/L) for the study population at the baseline assessment.

**Figure 2.** Cumulative cardiovascular events (cardiovascular mortality, nonfatal myocardial infarction, and stroke) during 6 years of treatment with pravastatin vs placebo in patients with baseline WBC above or below median value ($7.0 \times 10^9$/L) for the study population at the baseline assessment.
statins after an acute coronary syndrome may be related to a
greater reduction in C-reactive protein levels.\textsuperscript{18} Statins may have
additional antinflammatory effects. By inhibiting
HMG-CoA reductase, they decrease synthesis of isoprenoids,
which have multiple functions related to cell membrane
signaling. Statins have also been reported to reduce binding
of leukocytes to intercellular adhesion molecule-1 by directly
inhibiting the main \( \beta_2 \) integrin,\textsuperscript{19,20} and they have additional
immunomodulatory effects not related to inhibition of HMG-
CoA reductase.\textsuperscript{19}

It is not known whether WBC and C-reactive protein level
predict cardiovascular risk by common or different pathways.
The association between elevated C-reactive protein levels
and cardiovascular events may be related to the degree of
plaque inflammation and instability\textsuperscript{21}; however, in
the present study, there was no association between an
increased WBC and subsequent hospitalization for unstable
angina or coronary revascularization. This suggests that the
WBC may not be associated with an increased rate of
progression of CHD. Previous studies have described an
association between an increased WBC, measured early after
hospitalization for myocardial infarction, and an increased
risk of heart failure, cardiogenic shock, and cardiac mortality.\textsuperscript{22–24} WBC increases with time from symptom onset to
presentation with acute myocardial infarction, suggesting that
it is influenced by the inflammatory response to myocardial
necrosis.\textsuperscript{25} The present study provides evidence that an
increased WBC measured 5 months to 3 years after myocar-
dial infarction or unstable angina is also associated with a
greater long-term cardiovascular risk.

The ratio of total to HDL cholesterol was chosen for this
analysis because it was the strongest lipid predictor of
coronary events in the LIPID Study\textsuperscript{26}; however, the reduction in
CHD morality and cardiovascular events with pravastatin
treatment was similar in patients with higher and lower ratios
of total to HDL cholesterol. This finding is consistent with
those of other large statin trials in which the relative risk
reduction was similar in subjects with high, average, and low
LDL cholesterol levels.\textsuperscript{27–29} In the present study, there was no
association between WBC and LDL cholesterol, which is
consistent with studies that found no association between
C-reactive protein and LDL cholesterol.\textsuperscript{4–6} These observa-
tions are consistent with the hypothesis that WBC and LDL
cholesterol level influence cardiac risk by different pathways.

This study has a number of limitations. Because the
analysis was post hoc and multiple comparisons were under-
taken, the possibility of a statistically significant but spurious
interaction resulting from chance cannot be excluded. It is not
clear why the interaction between baseline WBC and the
treatment benefit of pravastatin was strong for CHD mortality
but weaker for the combined end point of cardiovascular
mortality, nonfatal myocardial infarction, and stroke. These
observations are novel, and the explanation for them is
uncertain, but they have important implications for clinical
practice. They therefore need to be confirmed by analyses
from other large statin trials. The LIPID Study excluded
patients with a baseline total cholesterol level of <4.0 or
>7.0 mmol/L (<155 or >271 mg/dL), and the predictive
power of serum lipid levels and WBC might be different in a
population that included the full range of cholesterol levels.
Because the white blood cell differential was not available for
this analysis, it was not possible to determine which compo-
nent of WBC was most important for predicting CHD risk.
C-reactive protein levels also were not available for the
present analysis, and further studies are needed to compare
the predictive values of the WBC, C-reactive protein levels,
and other inflammatory markers. The use of inflammatory
markers to target statin treatment may have more relevance in
the general population than in patients with known CHD, for
whom the benefits of statins are widely accepted. Additional
information from primary prevention trials is needed to
strengthen the hypothesis that inflammatory markers should
be used to target statin therapy in persons without known
CHD.\textsuperscript{30}

In conclusion, the findings of this study suggest that
patients with evidence of inflammation, including an
increased WBC, may obtain a greater benefit from statin
therapy.

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