Predictive Value of Elevated White Blood Cell Count in Patients With Preexisting Coronary Heart Disease

The Bezafibrate Infarction Prevention Study

Moti Haim, MD; Valentina Boyko, MSc; Uri Goldbourt, PhD; Alexander Battler, MD; Solomon Behar, MD

Background: Inflammation is implicated in the pathogenesis of atherosclerosis and acute coronary syndromes. White blood cell (WBC) count increases during infections and inflammatory illnesses and has been shown to predict coronary heart disease (CHD) independent of traditional cardiovascular risk factors. This apparent association may reflect a relationship between the WBC count and other coronary risk factors. Studies in patients with CHD are scarce and give conflicting results. The aim of the present study was to investigate the association between WBC count and subsequent coronary events and total mortality in a large cohort of patients with CHD.

Methods: We evaluated the relationship between WBC count and 6-year risk of coronary events and mortality in a large cohort of patients with chronic CHD who were enrolled in a secondary prevention study of bezafibrate.

Results: In univariate analysis, WBC count was associated with an elevated 6-year risk of myocardial infarction, cardiac death, and total mortality. On multivariate adjustment, the positive association with risk of myocardial infarction and cardiac death was eliminated, but WBC count remained predictive of total mortality: relative risk, 1.47; 95% confidence interval, 1.13 to 1.92, in the upper tertile of WBC count (as compared with the lowest). For every 1000/µL increase in WBC count, risk of total death increased by 6% (relative risk, 1.06; 95% confidence interval, 1.03-1.10).

Conclusions: Elevated WBC count in patients with CHD was associated with higher long-term risk of all-cause mortality. This excess risk of mortality was not due to cardiac causes.

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Inflammation is implicated in the pathogenesis of atherosclerosis and acute coronary syndromes, and inflammatory markers may aid in the detection of persons at risk for atherosclerosis and its complications.1-5

The white blood cell (WBC) count, which rises during infections and inflammatory illnesses, predicts coronary heart disease (CHD) morbidity and mortality in large-scale community studies6-15 and among patients at risk for CHD.16,17 independent of traditional cardiovascular risk factors. However, this finding may be biased by confounding owing to the strong link between WBC count and other coronary risk factors, such as smoking, hypertension, obesity, elevated triglyceride levels, and insulin resistance.18-24 Indeed, in 2 recent community studies that adjusted for such coronary risk factors, the WBC count was no longer associated with elevated CHD risk.25,26

Of the few studies that have addressed this issue in patients with preexisting CHD, some found a positive association between WBC count and coronary risk,27-29 whereas others did not.30

The aim of the present study was to investigate the association between WBC count and subsequent long-term risk of mortality and coronary events in a large cohort of patients with CHD.

STUDY SAMPLE AND END POINTS

The study population consisted of participants in the Bezafibrate Infarction Prevention Study, a placebo-controlled, randomized, secondary prevention trial that evaluated the efficacy of the lipid-lowering drug bezafibrate in reducing death and nonfatal myocardial infarction in 3090 patients with CHD.31 In this study, CHD was defined as a history of myocardial infarction for more than 6 months but less than 5 years before enrollment in the study, or a history of angina pectoris confirmed by positive findings on coronary angiography, nuclear scintigraphy, or an exercise test.31 The primary end points of the study were fatal myo-

From the Department of Cardiology, Rabin Medical Center, Petah Tikva, Israel (Drs Haim and Battler), and Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel (Ms Boyko and Drs Goldbourt and Behar), both affiliated with Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. The authors have no relevant financial interest in this article.
cardiac infarction, nonfatal myocardial infarction, and sudden death. The end points were reviewed and confirmed by an independent critical events committee whose members were blinded to the treatment assignment of the study participants. Mean duration of follow-up was 6.2 years (range, 4.7-7.6 years). Details of the study results have been published.31

LABORATORY PROCEDURES

Blood samples for measurement of serum lipids, fibrinogen, blood chemistry, and complete blood cell count were collected at randomization (baseline) and thereafter at regular intervals. All laboratory analyses were performed in a single central laboratory by means of standard automated procedures with commercial kits. For the purpose of the present study, we evaluated the entire Bezafibrate Infarction Prevention Study cohort according to the WBC count taken at baseline, before randomization to bezafibrate treatment.

DATA ANALYSIS

Baseline characteristics were compared according to WBC count at baseline before randomization to bezafibrate or placebo treatment. The χ² and analysis of variance tests were used for comparison of categorical and continuous variables, respectively.

We assessed the univariate association between baseline WBC count and the other baseline characteristics with total death, cardiac death, myocardial infarction, sudden cardiac death, and the combined primary end point of myocardial infarction and sudden cardiac death.

Multivariate analyses adjusting for confounders associated with WBC count and coronary outcomes or total death were performed by means of the Cox proportional hazards model. In these models, WBC count was introduced as a continuous variable and additional analyses were done according to tertiles of WBC count, with patients in the lowest tertile of WBC count serving as a reference. A test based on a defined time-dependent covariate was used for assessing the proportionality of hazards. The results of the test did not contradict the proportional hazards assumption for variables included in the models.

The Bezafibrate Infarction Prevention Study included 3090 patients with CHD. Complete baseline WBC counts were not available for 147 patients (4.8%), and they were excluded from the present analysis. Four hundred forty-three patients reached the primary end points, with no difference in rate between the placebo and bezafibrate groups.31

In univariate analysis, WBC count was significantly associated with total death (P<.001), cardiac death (P=.03), myocardial infarction (P=.04), and the combined end point of sudden death and myocardial infarction (P=.03), but not with sudden cardiac death (P=.62). Other univariate predictors are given in Table 1. Increase in WBC count was associated with an increased age-adjusted risk of myocardial infarction, cardiac death, and total death, but not sudden cardiac death (Table 2). After multivariate adjustment, WBC count was associated only with increased risk of total death (Table 2).

BASELINE CHARACTERISTICS

Patients with CHD and an elevated WBC count had a higher rate of coronary risk factors: hypertension, diabetes mellitus, smoking, history of previous myocardial infarction, high body mass index, and high serum concentrations of triglycerides, fasting glucose, and fibrinogen (Table 3). Concentration of high-density lipoprotein cholesterol was lower in the patients with a higher baseline WBC count.

MYOCARDIAL INFARCTION AND SUDDEN DEATH

The incidence rate of myocardial infarction during follow-up was significantly higher in patients with a higher

<table>
<thead>
<tr>
<th>Table 1. Univariate Association (P Values) Between Baseline Characteristics and Study End Points</th>
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<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>White blood cell count</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>SBP</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>PAD</td>
</tr>
<tr>
<td>Previous stroke</td>
</tr>
<tr>
<td>Previous MI</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>NYHA class ≥II</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Serum glucose</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>HDL-C</td>
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<tr>
<td>Triglycerides</td>
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<tr>
<td>Fibrinogen</td>
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</tbody>
</table>

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral arterial disease; SBP, systolic blood pressure.
WBC count at baseline (Table 4). Both the unadjusted and the age-adjusted relative risk of myocardial infarction were significantly higher among patients in the highest WBC tertile compared with those in the lowest tertile (Table 4). However, multivariate adjustment eliminated this association (Table 4). The rate and the relative risk of sudden cardiac death were not significantly different between the lowest and highest tertiles of WBC count. The rate and the age-adjusted risk of the combined end point of myocardial infarction and sudden death were associated with WBC count at baseline (Table 4). On adjustment, this association disappeared and did not reach statistical significance (Table 4).

CARDIAC MORTALITY

Rate of death from cardiac causes was significantly higher in the highest WBC tertile compared with the lowest (Table 5). However, adjustment for multiple confounders eliminated this association (Table 5).

TOTAL DEATH

Total death rate increased from 8% in the lowest WBC count tertile to 14% in the highest WBC tertile (Table 6). The corresponding unadjusted and age-adjusted relative risks increased in a graded manner in the patients in the second and third WBC tertiles compared with patients in the lowest tertile. Adjustment for multiple confounders (including also levels of total cholesterol, high-density lipoprotein cholesterol, triglycerides, and fibrinogen) did not reduce the relative risk (Table 6). Finally, a model (model 3 in Table 6) that also included other comorbidities associated with total death (see the “Methods” section) generated a hazards ratio of 1.47 in the third tertile of WBC count compared with the first, which was statistically significant.

COMMENT

MAIN FINDINGS

In the present study of patients with CHD in stable condition, a single baseline measurement of elevated WBC count was associated with increased long-term all-cause mortality risk. This finding was not due to an increased risk of cardiac death, myocardial infarction, or sudden cardiac death, which were not influenced by the WBC count at baseline. The univariate association with the incidence of myocardial infarction and cardiac death, observed before adjustment, was eliminated after adjustment for baseline cardiovascular confounders.

WBC COUNT AND CORONARY RISK FACTORS

A large number of studies have demonstrated that elevated WBC count is related to other coronary risk factors. Multivariate adjustment for baseline cardiovascular confounders eliminated this association (Table 4). However, multivariate adjustment eliminated this association (Table 4). The rate and the relative risk of sudden cardiac death were not significantly different between the lowest and highest tertiles of WBC count. The rate and the age-adjusted risk of the combined end point of myocardial infarction and sudden death were associated with WBC count at baseline (Table 4). On adjustment, this association disappeared and did not reach statistical significance (Table 4).

The adjustment for coronary risk factors completely eliminated the association in the present series of elevated WBC count with higher incidence of myocardial infarction and death from cardiac causes. Previous studies have found that elevated WBC count was an independent predictor of CHD and cardiovascular mortality. However, most of these were community studies that included a majority of patients without evidence of prevalent CHD at baseline. Furthermore, most of them did not adjust for triglycerides or fibrinogen—both of which were associated with WBC count in the present analysis and were previously shown in our study population to predict CHD, stroke, and death. In other community studies, the apparent association between WBC count and coronary risk was attenuated or completely disappeared after adjustment for coronary risk factors, including lipid...
levels\(^\text{25}\) and inflammatory markers such as fibrinogen, von Willebrand factor, and C-reactive protein.\(^\text{26,30,38}\) It is possible that elevated WBC count is associated with early development of atherosclerosis in healthy persons, but once established coronary atherosclerotic disease is present, it does not influence risk of recurrent events.

The association between WBC count and risk of recurrent cardiovascular events in patients with preexist-
Table 5. Incidence and Risk of Cardiac Mortality According to WBC Count at Baseline

<table>
<thead>
<tr>
<th>WBC Count</th>
<th>Cardiac Death</th>
</tr>
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<tbody>
<tr>
<td>≤5970/µL</td>
<td>(n = 970)</td>
</tr>
<tr>
<td>Rate, No. (%)</td>
<td>54 (5.6)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1</td>
</tr>
<tr>
<td>Age-adjusted risk</td>
<td>1</td>
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<tr>
<td>Multivariate adjusted‡</td>
<td>1</td>
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<tr>
<td>Multivariate adjusted§</td>
<td>1</td>
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</tbody>
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Abbreviation: WBC, white blood cell.
*Values in parentheses are 95% confidence intervals unless otherwise specified.
†P value for comparison between third and first tertiles of WBC count.
‡Model 1 was adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, smoking, New York Heart Association (NYHA) functional class, body mass index (BMI), fasting glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.
§Model 2 was adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, smoking, NYHA functional class, BMI, fasting glucose, and fibrinogen.

Table 6. Incidence and Risk of Total Death According to WBC Count at Baseline

<table>
<thead>
<tr>
<th>WBC Count</th>
<th>Total Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5970/µL</td>
<td>(n = 970)</td>
</tr>
<tr>
<td>Rate, No. (%)</td>
<td>82 (8.5)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>1</td>
</tr>
<tr>
<td>Age-adjusted risk</td>
<td>1</td>
</tr>
<tr>
<td>Multivariate adjusted‡</td>
<td>1</td>
</tr>
<tr>
<td>Multivariate adjusted§</td>
<td>1</td>
</tr>
<tr>
<td>Multivariate adjusted§</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviation: WBC, white blood cell.
*Values in parentheses are 95% confidence intervals unless otherwise specified.
†P value for comparison between third and first tertiles of WBC count.
‡Model 1 was adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, smoking, New York Heart Association (NYHA) functional class, body mass index (BMI), fasting glucose, total cholesterol, high-density lipoprotein cholesterol, and triglycerides.
§Model 2 was adjusted for age, sex, diabetes mellitus, hypertension, previous myocardial infarction, smoking, NYHA functional class, BMI, fasting glucose, and fibrinogen.
||Model 3 was adjusted for age, sex, previous myocardial infarction, NYHA functional class, hypertension, diabetes mellitus, smoking, BMI, presence of chronic obstructive pulmonary disease, peripheral arterial disease, and history of stroke.

Although CHD has been evaluated in very few studies, and the conclusions drawn were conflicting. Amaro et al27 and Ikata et al,29 in 2 small, independent studies, reported a positive association of WBC count with severity of findings on coronary angiography and with risk of coronary events. Held et al28 reported that WBC count could predict future incidence of coronary events independent of other confounders of coronary risk; however, they failed to adjust for lipid and fibrinogen levels. In another recent study in patients with CHD, a higher incidence of CHD events was found in those with elevated WBC count at baseline, but adjustment for lipoprotein levels, left ventricular function, and inflammatory markers diminished this association.30 It is therefore possible that an elevated WBC count in patients with CHD reflects a state of high risk of recurrent CHD events that is due to the presence of traditional risk factors. Accordingly, elevated levels of other inflammatory mediators more specifically related to the pathogenesis of atherothrombotic complications, such as C-reactive protein13 and soluble adhesion molecules,30-41 may be more suitable to assess the risk of CHD events, in addition to traditional risk factors, in this patient population.

TOTAL MORTALITY

In the present study, the rate of all-cause mortality was significantly higher in the patients with CHD who had an elevated WBC count. This association, described by other investigators as well,9,14,26 remained significant even after adjustment for other comorbid conditions associated with WBC count and mortality. It could not be explained in our series by an increased risk of cardiac events and cardiac death, and was attributed to noncardiac causes of death. Whether WBC count is a nonspecific marker of increased mortality risk or a marker of long-term mortality from specific causes requires further evaluation. Although this apparent independent association may be coincidental, the fact that it was found in various subgroups at risk makes coincidence unlikely.
LIMITATIONS

Our series has several limitations. We used a single baseline measurement of WBC count without addressing the change in WBC count over time, which might influence the results. We did not measure C-reactive protein concentration, which seems to be the most important inflammatory predictor of coronary risk, nor did we measure other inflammatory variables, except fibrinogen. Be that as it may, taking into account other inflammatory measures or markers in this study of the relationship between WBC count and coronary risk would not add much to the value of the findings, since the association with cardiac morbidity and mortality disappeared on adjustment for fibrinogen alone. On the other hand, the strengths of the present study are its long follow-up period, its large sample size, and the reliability of the outcome data, which were collected in the setting of a controlled clinical trial.

CONCLUSIONS

Total WBC count is apparently not independently associated with long-term risk of myocardial infarction or cardiac death in patients with CHD. However, increased WBC count is independently associated with total mortality risk in this patient population.

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Corresponding author: Moti Haim, MD, Department of Cardiology, Rabin Medical Center, Beilinson Campus, Petah Tikva 49100, Israel (e-mail: motih@netvision.net.il).

REFERENCES


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**Announcement**

New Editor and New Address for Editorial Correspondence

Effective January 2004, Philip Greenland, MD, succeeded James E. Dalen, MD, MPH, as Editor of the ARCHIVES. Editorial correspondence should be sent to the new address: Philip Greenland, MD, Editor, Archives of Internal Medicine, 680 N Lake Shore Dr, Suite 1102, Chicago, IL 60611; phone: 312-503-5387; fax: 312-503-5388; e-mail: archinternmed@jama-archives.org. Manuscript submissions should be sent to Dr Greenland’s attention via e-mail attachment to archinternmed@jama-archives.org.