Elevated Serum Triglyceride Levels and Long-Term Mortality in Patients With Coronary Heart Disease

The Bezafibrate Infarction Prevention (BIP) Registry

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**Background**—The association between elevated blood triglyceride levels and subsequent mortality risk in patients with established coronary heart disease (CHD) has been investigated rarely. The aim of the present study was to investigate this association.

**Methods and Results**—We evaluated mortality over a mean follow-up time of 5.1 years among 9033 male and 2499 female CHD patients who were screened for participation in the Bezafibrate Infarction Prevention (BIP) Study. A stepwise increase in mortality with increasing serum triglyceride levels was observed in patients with desirable or elevated serum total cholesterol levels and in patients with either desirable or abnormally low HDL cholesterol levels. Multivariate adjustment for factors other than HDL cholesterol yielded a slightly increased adjusted mortality risk with a 1-natural-log-unit elevation of triglyceride levels in men (hazard ratio [HR] 1.14, 95% CI 1.00 to 1.30) and women (HR 1.37, 95% CI 1.04 to 1.88). Excess covariate-adjusted risk was noted among patients with elevated total and LDL cholesterol and in women with HDL cholesterol levels 45 mg/dL. After additional adjustment for HDL cholesterol, the risk of mortality with a 1-natural-log-unit elevation of triglycerides declined in men (HR 1.09, 95% CI 0.94 to 1.26) and in women (HR 1.10, 95% CI 0.80 to 1.50). A trend for increased mortality risk remained in patients with elevated total and LDL cholesterol and in women with HDL cholesterol >45 mg/dL.

**Conclusions**—Elevated triglyceride levels were associated with a small, independent increased mortality risk in CHD patients. This risk may be increased among subgroups of patients with elevated total cholesterol and LDL cholesterol levels. (Circulation. 1999;100:475-482.)

**Key Words:** coronary disease ■ lipoproteins ■ mortality

The consequences of elevated blood triglyceride levels are controversial, and the benefit of reducing these levels has not been established clearly. Several studies conducted in healthy persons, mostly men, showed that elevated triglyceride levels were associated with increased risk for coronary heart disease (CHD). In most of these studies, the positive relation between triglyceride levels and CHD risk persisted after adjustment for possible confounders but disappeared after HDL cholesterol was introduced into the multivariate model. Several investigators reasoned that the introduction of both HDL cholesterol and triglycerides as independent covariates was inappropriate owing to multicollinearity and an intimate link between these variables in lipid metabolism. In a few studies, triglyceride levels did remain predictive of subsequent development of CHD after adjustment for HDL cholesterol, which suggests a possible role for triglycerides in the development of CHD.

The association between elevated triglyceride levels and subsequent mortality risk in patients with established CHD has been investigated rarely. Therefore, we undertook the present study to evaluate the association between elevated triglyceride levels and subsequent mortality in a large cohort of male and female patients (n=11 575) with proven CHD.

**Methods**

**Study Sample**

A total of 15 524 patients considered eligible for participation in the Bezafibrate Infarction Prevention (BIP) Study were examined between February 1990 and October 1992. The design and rationale of BIP have been published previously. The screened population included patients aged 40 to 74 years with a diagnosis of CHD based on one of the following: (1) documented myocardial infarction (MI) in the previous 3 years; (2) symptomatic stable angina pectoris and either a positive exercise test, positive myocardial ischemia by radionuclear scintigraphy, or ≥80% stenosis of 1 of the major coronary arteries.
coronary arteries demonstrated by coronary angiography; or (3) documented PTCA or CABG operation in the preceding 6 months.

Patients enrolled to participate in the BIP study (n=3122) were excluded from the present analysis to avoid the possible modification of bezafibrate treatment on the association between triglyceride levels and subsequent mortality. Among the remaining patients, information on date, site, and underlying cause of death according to the ninth version of the International Classification of Disease (ICD-9) codes was available for 11 575 patients, who constitute the study sample. The present analysis provides mortality data after a mean follow-up of 5.1 years (range 2 days to 6.8 years). The underlying cause of death was classified as coronary if coded 410 to 414 of the ICD-9 code.

Data Acquisition
During the first visit, records were obtained concerning previous and current illnesses and medications used by the patient, and a complete physical examination was performed. The patients were assigned a functional class according to the New York Heart Association (NYHA) classification, and severity of angina was scored by the Canadian Cardiovascular Society classification.

Laboratory Examination
Laboratory measurements were performed in a central laboratory (Physiological and Hygiene Laboratory at the Wolfson Medical Center, Holen, Israel). All analyses were performed with a Boehringer-Hitachi 704 random-access analyzer with Boehringer diagnostic kits. Accuracy and precision were under periodic surveillance by the Centers for Disease Control and Prevention service in Atlanta, Ga. For 6772 patients whose total cholesterol, HDL cholesterol, and triglyceride levels were within specified limits, a second blood sample was drawn 2.5 months after the first sample. Blood samples were taken after ≥12 hours of fast. Between February 1990 and January 1994, we determined triglyceride levels by subtracting the free glycerol level (determined by using a separate enzymatic kit [Sigma Chemical]) from the total triglyceride value. Since January 1994, we calculated triglyceride levels by subtracting 4.5 mg/dL (mean value of free glycerol level).

Laboratory results were monitored throughout the study period. A drift in triglyceride levels was identified in the study period that lowered the triglyceride levels by an average of 11.25% for specimens drawn between October 16, 1990, and February 8, 1991, due to differences between different batches of analytical kits supplied by Boehringer-Mannheim. To ensure comparability of measurements throughout the study period, adjustment was made by reanalysis of frozen sera collected during the period the drift was detected with kits used routinely at the time of reanalysis and by application of linear regression analysis to obtain an estimation of the old values on the new scale. All triglyceride levels for the above period (from January 1994, we calculated triglyceride levels by subtracting 4.5 mg/dL (mean value of free glycerol level).

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Statistical Analysis
Data were analyzed with SAS software. Age-adjusted mortality rates per 1000 person-years were computed with an SAS macro. Multivariate analysis of mortality was performed with the Cox proportional hazards model (PHREG procedure) to account for differing lengths of follow-up and to adjust for covariates predictive of mortality. The covariates were age, HDL cholesterol, LDL cholesterol, glucose, diabetes mellitus, hypertension, NYHA class, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, angina pectoris, current smoking, and past smoking. Because the distribution of triglyceride was skewed, a natural log of triglyceride was introduced into the model. The significance levels for entering and removing an explanatory variable were set at 0.15 and 0.10, respectively.

A single measurement of triglycerides is subject to random fluctuation due to laboratory measurement and biological fluctuations. Because 6772 patients attended the second screening visit, at which another triglyceride measurement was performed, we estimated the reliability of serum triglyceride measurements using the values of the first and second visits. We recomputed the hazard ratios by multiplying the Cox regression coefficients by a regression dilution factor. The regression factor was calculated as follows: we divided the difference in mean triglyceride level between the lowest and highest quartiles, computed from the first measurement, by the difference in mean triglyceride level at the second measurement in similarly defined lowest and highest quartiles. The effect of incorporating the regression dilution bias is to provide an estimate of mortality risk associated with triglyceride increment, correcting for regression to the mean.

Results
Among 11 575 patients included in the present study, triglyceride levels were available for only 11 546 patients. In addition, medical history data were incomplete for 14 patients who were excluded from the present analysis.

Baseline Characteristics
The study sample comprised 9033 men and 2499 women (Table 1). The women in this sample were older, had a higher frequency of coronary risk factors at baseline, and their symptoms were usually more severe, as reflected by their NYHA and angina class, compared with men (Table 1).

| Table 1. Baseline Characteristics of Men and Women With CHD in the BIP Registry |
|---------------------------------|---------------------|---------------------|
|                                | Men (n=9033), n (%) | Women (n=2499), n (%) |
| Age, y                         | 59.2±7.2            | 61.8±6.0            |
| Diabetes mellitus              | 1838 (20)           | 649 (26)            |
| Hypertension                   | 2712 (30)           | 1164 (46)           |
| Angina pectoris                | 5288 (59)           | 1674 (67)           |
| Smoking                        | 1115 (12)           | 200 (8)             |
| BMI, kg/m²                     | 2.65±0.34           | 2.71±0.43           |
| NYHA class                     |                     |                     |
| I                              | 2797 (53)           | 798 (48)            |
| II                             | 2262 (43)           | 779 (46)            |
| III + IV                       | 222 (4)             | 95 (6)              |
| Previous stroke                | 173 (2)             | 43 (2)              |
| PVD                            | 308 (4)             | 85 (3)              |
| Total cholesterol, mg/dL       | 221±41              | 241±44              |
| LDL cholesterol, mg/dL         | 152±36              | 164±39              |
| HDL cholesterol, mg/dL         | 36.9±9.7            | 45.1±12.1           |
| Triglycerides, mg/dL           | 166±104             | 162±94              |
| 5-Year all-cause mortality     | 1243 (14)           | 327 (13)            |
| 5-Year CHD mortality           | 630 (51)            | 158 (48)            |

PVD indicates peripheral vascular disease.

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Triglyceride Levels and Other Comorbid Conditions
In both men and women, diabetes mellitus and hypertension were associated with elevated triglyceride levels (Table 2).
Total cholesterol, LDL cholesterol, and plasma fibrinogen levels tended to be elevated in patients with elevated triglyceride levels. Serum HDL cholesterol was inversely related to triglycerides. The correlation coefficients were $-0.43$ and $-0.48$ for men and women, respectively.

### Five-Year Mortality in Relation to Triglyceride Level

Age-adjusted all-cause mortality rates per 1000 person-years increased in a stepwise fashion with increasing triglyceride quintile values in both men (from 21.2 to 33.5) and women (from 17 to 37.6) (Figures 1 and 2, respectively). Age-adjusted CHD mortality rates showed a similar trend in men (from 9.2 to 16.9) and women (from 8.4 to 18.7). Among men, the age-adjusted all-cause and CHD mortality hazard ratios in the fifth quintile (versus the first quintile) were 1.54 (95% CI 1.29 to 1.84) and 1.77 (95% CI 1.36 to 2.30), respectively. Among women, the corresponding values were 2.19 (95% CI 1.52 to 3.16) for all-cause mortality and 2.09 (95% CI 1.25 to 3.50) for CHD mortality.

Among men and women, mortality increased with increasing triglyceride levels in patients with or without angina pectoris, diabetes mellitus, or hypertension and in patients with low, intermediate, and elevated body mass index (Figure 3). Mortality was elevated in male and female patients with increased triglyceride levels who also had desirable or elevated total and LDL cholesterol levels and in patients of either sex with desirable or abnormally low HDL cholesterol levels (Figure 4).

### Table 2: Frequency of Comorbid Conditions and Means of Other Biochemical Variables in Tertiles of Serum Triglycerides in Male and Female Patients With CHD

<table>
<thead>
<tr>
<th></th>
<th>Tertile 1 (≤113.2 mg/dL)</th>
<th>Tertile 2 (113.2–176 mg/dL)</th>
<th>Tertile 3 (&gt;176 mg/dL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>15</td>
<td>19</td>
<td>26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women</td>
<td>19</td>
<td>24</td>
<td>35</td>
<td>&lt;0.01</td>
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<tr>
<td>Hypertension, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>29</td>
<td>29</td>
<td>32</td>
<td>0.05</td>
</tr>
<tr>
<td>Women</td>
<td>44</td>
<td>45</td>
<td>50</td>
<td>0.02</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>204 (36)</td>
<td>223 (39)</td>
<td>237 (43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>224 (38)</td>
<td>239 (39)</td>
<td>260 (47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42.6 (10.1)</td>
<td>36.7 (8.3)</td>
<td>31.5 (7.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women</td>
<td>52.7 (12.4)</td>
<td>44.9 (10.1)</td>
<td>37.8 (8.9)</td>
<td>&lt;0.001</td>
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<td>LDL cholesterol, mg/dL, mean (SD)</td>
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<td></td>
<td></td>
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<tr>
<td>Men</td>
<td>144 (32)</td>
<td>158 (36)</td>
<td>155 (39)</td>
<td>&lt;0.001</td>
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<tr>
<td>Women</td>
<td>154 (35)</td>
<td>165 (36)</td>
<td>172 (43)</td>
<td>&lt;0.001</td>
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<tr>
<td>Fibrinogen, mg/dL, mean (SD)</td>
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<tr>
<td>Men</td>
<td>338 (75)</td>
<td>349 (80)</td>
<td>349 (80)</td>
<td>0.004</td>
</tr>
<tr>
<td>Women</td>
<td>371 (85)</td>
<td>378 (76)</td>
<td>378 (75)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

**Figure 1.** Age-adjusted all-cause and CHD mortality rates (per 1000 person-years) by quintiles of triglyceride levels in male coronary patients. I <94.3, II 94.3 to 124.4, III 124.4 to 160.7, IV 160.7 to 217, and V >217 mg/dL.

**Figure 2.** Age-adjusted all-cause and CHD mortality rates (per 1000 person-years) by quintiles of triglyceride levels in female coronary patients. Triglyceride values are the same as in Figure 1.
Multivariate Analysis

Table 3 provides the adjusted mortality hazard ratios associated with an elevation of 1 natural log unit of triglyceride levels. Adjustment was made for confounders known to be associated with elevated mortality in CHD patients (see Methods). Triglyceride levels were predictive of mortality in both men and women, but after HDL cholesterol was added to the model, the relative risk was of borderline significance only, with a 95% CI that crossed unity (Table 3).

Elevated triglyceride levels appeared to be associated with increased mortality in female and male patients with elevated total and LDL cholesterol levels but not in their counterparts with total and LDL cholesterol values within the desirable range. The results are also consistent with a predictive role for triglycerides in men and women without previous MI. When HDL cholesterol was added to the model, a trend remained for increased subsequent mortality in male and female patients with elevated total or LDL cholesterol, in males without previous MI, and in females with HDL cholesterol levels $>45$ mg/dL. No synergism of low HDL cholesterol and elevated triglycerides in affecting mortality was apparent in this study.

Regression Dilution Correction

The computed regression dilution factor was 1.26 in men and 1.28 in women. Correction for this factor (see Methods) did not modify the adjusted hazard ratio substantially. For example, the adjusted hazard ratios for mortality with each elevation of 1 natural log unit of triglyceride levels were increased from 1.09 to 1.11 in men and from 1.10 to 1.12 in women. Application of similar corrections in the other tested subgroups did not change the hazard ratios appreciably.

Discussion

Most previous studies have evaluated the relationship between elevated triglyceride levels and subsequent risk in subjects free of CHD. In the present study, we describe the association between elevated triglyceride levels and mortality in patients with established CHD.

The main findings of the present study were as follows: (1) elevated triglyceride levels were associated with increased prevalence of other coronary risk factors, including diabetes mellitus, hypertension, and elevated total cholesterol, LDL cholesterol, and serum fibrinogen levels, and with subnormal levels of HDL cholesterol; (2) there was a strong stepwise increase in age-adjusted mortality with increasing triglyceride levels in both men and women and in several clinical subsets of patients; (3) on adjustment by age and other covariates, elevated triglyceride levels were associated with increased mortality primarily in women, in male and female patients with elevated total and LDL cholesterol, and in patients with angina but without previous MI; (4) adjustment for HDL cholesterol levels reduced the above associations, but elevated triglyceride levels remained predictive for mortality in CHD patients with elevated LDL and total cholesterol levels; and (5) elevated triglyceride levels were associated with increased mortality risk in the subgroup of patients with elevated HDL cholesterol but not in patients with decreased HDL cholesterol levels.

Concurrent elevated triglyceride levels, hypertension, diabetes mellitus, obesity, and other dyslipidemias are consistent with previously published studies in healthy subjects. This aggregate of metabolic and clinical abnormalities was named “syndrome X,” and it was suggested that a single abnormality (insulin resistance and hyperinsulinemia) is the underlying cause of this cluster. These associations, in particular the inverse association with HDL cholesterol, complicate analyses designed to evaluate the independent contribution of elevated triglyceride levels to subsequent morbidity and mortality in these subjects. Most
studies of subjects without clinically evident CHD have demonstrated a univariate relation between elevated triglyceride levels and subsequent CHD. However, adjustment for other coronary risk factors, and in particular HDL cholesterol, usually reduced or eliminated the independent association between triglycerides and CHD risk. Several authors have questioned whether it is judicious to adjust for HDL cholesterol levels when the relation between triglyceride levels and CHD morbidity and mortality is being assessed. Triglyceride and HDL cholesterol levels are usually inversely related (including in the present study), with a correlation coefficient of $\approx -0.4$ to $-0.6$, implying multicollinearity. Therefore, it is possible that by adjusting for HDL cholesterol, we are overadjusting and therefore underestimating the true risk inherent to elevated levels of triglycerides in coronary patients. However, we did not observe any increase in the risk of mortality associated with triglycerides in the subgroups of men and women with low serum HDL cholesterol.

In the present analysis, elevated triglyceride levels were predictive of subsequent mortality in male and female patients with elevated total and LDL cholesterol levels. These observations are derived from post hoc analysis and require confirmation by additional studies designed to examine this issue. However, they may have important practical application, because CHD patients with elevated total and LDL cholesterol are recognized candidates for cholesterol-lowering therapy with HMG-CoA reductase inhibitors. A substantial proportion of these patients have elevated triglyceride levels. For example, in the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) study, 25% of the patients had baseline serum triglyceride levels $>193$ mg/dL, and in the CARE (Cholesterol And Recurrent Events) study, 50% of the patients had triglyceride levels $>144$ mg/dL. These triglyceride levels are similar to those of the present study population.

Results of Observational Studies
Criqui et al demonstrated that elevated triglyceride levels were predictive of subsequent occurrence of CHD and all-cause mortality in healthy men and women, but adjustment for HDL cholesterol and fasting serum glucose eliminated the independent relation between triglyceride levels and CHD mortality. In contrast with our results in CHD patients, triglycerides remained predictive for mortality in the subgroups of subjects free of CHD with low LDL cholesterol levels but not in subjects with high LDL cholesterol levels. In the PROspective Cardiovascular Munster (PROCAM) study, conducted among healthy men, elevated triglyceride levels were independently associated with subsequent development of CHD even after adjustment for HDL cholesterol. In the PROCAM study and other studies, elevated triglyceride levels were most predictive for subsequent CHD when accompanied by elevated total and LDL cholesterol. In the placebo group of the Helsinki Heart Study, an elevated triglyceride level was predictive of future CHD events, but this excess risk was halved after adjustment for HDL cholesterol. The results were consistent with the increased risk
associated with elevated triglyceride levels in the subgroups of men with high total and LDL cholesterol levels, as well as in men with HDL cholesterol <35 mg/dL.

In the studies of Jeppesen et al. and Ganziano et al., a high triglyceride/HDL cholesterol ratio was a powerful predictor of morbidity and mortality. Likewise, in the Honolulu Heart Program and in the Helsinki Heart Study, triglycerides were associated with elevated morbidity in conjunction with decreased HDL cholesterol levels.5,6,19 These studies involved follow-up of CHD-free individuals. In the present study, conducted among CHD patients, the results are consistent with an absence of low HDL cholesterol/high triglyceride synergism. In fact, among female patients with serum HDL cholesterol ≥45 mg/dL, the mortality hazard was increased ≥1.5-fold. This discrepancy could be explained by different study samples (healthy subjects versus CHD patients), different lipid profiles, different outcome measures, and chance, reflecting a post hoc finding. No clear-cut explanation is readily available, and confirmation in an independent investigation is required before this surprising observation can be understood. However, similar to our results, Jeppesen et al. in an 8-year follow-up study of healthy men, observed the highest relative risk associated with elevated triglycerides in the subgroup of persons in the highest tertile of HDL cholesterol.

Previous studies have not examined the possible bias created by use of a single measurement of serum triglyceride levels, which are subject to considerable intraindividual and interindividual variability. Therefore, repeated measurements provide a more accurate estimate of the “true” level of triglycerides in each study subject. Criqui et al. used the average of 2 measurements as the estimate for triglyceride levels in their subjects. We have adjusted for the possible regression dilution bias caused by repeated measurements of triglyceride levels with a previously reported method.18 This correction did not alter the results.

Data From Intervention Studies

The efficacy of reducing blood levels of triglycerides in reducing the incidence of coronary events or mortality has not been substantiated. In the Helsinki Heart Study, conducted among asymptomatic healthy men, gemfibrozil reduced triglyceride levels by 35% and produced a 34% reduction in the incidence of CHD,28 mainly among obese patients with elevated triglyceride levels and reduced HDL cholesterol levels.29 This was statistically ascribed primarily to elevation of HDL cholesterol.

In the BECAIT study (Bezafibrate Coronary Atherosclerosis Intervention Trial), conducted among young post-MI
male patients, bezafibrate (200 mg TID) reduced serum triglyceride levels by 31% and plasma fibrinogen by 12% and increased serum HDL cholesterol levels by 9%. This was accompanied by a reduction in the luminal diameter of coronary arteries and by a concomitant lower coronary event rate in the bezafibrate group.\textsuperscript{30,31}

In the Stockholm secondary prevention study,\textsuperscript{32} survivors of MI were assigned to either a combination of clofibrate and nicotinic acid or to placebo. CHD mortality was significantly lower in the treatment group, mainly in the subgroup of patients with elevated triglycerides and among patients showing the greatest triglyceride reduction by the study medication.\textsuperscript{32}

**Study Limitations**

Our study is limited by its post hoc observational design. Thus far, the evidence regarding the role of triglycerides in CHD patients has been scant. Our observation sheds some light on this role and suggests synergism with elevated total and LDL cholesterol levels; however, this needs to be verified through clinical trials. Another limitation, common to many observational studies, is the absence of information concerning potential spontaneous or therapy-induced changes in triglycerides and other parameters of blood chemistry during the follow-up period.

In conclusion, elevated triglyceride levels are associated with the risk of mortality in CHD patients, possibly more so in women than in men. It is unclear how much of this risk is due to low serum HDL cholesterol levels. Post hoc analysis raises the possibility that the association in men is restricted to patients with angina but not with previous MI. More research is required to address this speculation. Post hoc analysis is also consistent with an association between triglycerides and mortality in patients with increased LDL cholesterol, who are established candidates for LDL cholesterol-lowering treatment.\textsuperscript{33} The results of clinical trials that specifically evaluate the efficacy of the triglyceride-lowering and HDL cholesterol–raising medications bezafibrate and gemfibrozil in CHD patients\textsuperscript{14,34} should help clarify the role of elevated triglyceride levels and triglyceride-reduction therapy on the incidence of coronary events and mortality in patients with CHD.

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