Triglyceride Concentration and Ischemic Heart Disease
An Eight-Year Follow-up in the Copenhagen Male Study

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Background—The role of triglycerides as a risk factor of ischemic heart disease (IHD) remains controversial. For the present study, we examined the relation between fasting triglycerides and risk of IHD in the Copenhagen Male Study.

Methods and Results—Baseline measurements of fasting lipids and other IHD risk factors were obtained for 2906 white men (age range, 53 to 74 years) who were initially free of overt cardiovascular disease. During an 8-year follow-up period, 229 men had a first IHD event. Crude cumulative incidence rates of IHD were 4.6% for the lowest, 7.7% for the middle, and 11.5% for the highest third of triglyceride levels (P for trend <.001). Compared with the lowest third level and adjusted for age, body mass index, alcohol, smoking, physical activity, hypertension, non–insulin-dependent diabetes mellitus, social class, and LDL and HDL cholesterol, relative risks of IHD (95% confidence interval) were 1.5 (1.0 to 2.3; P=.05) and 2.2 (1.4 to 3.4; P<.001) for the middle and highest third of triglyceride levels, respectively. When triglyceride levels were stratified by HDL cholesterol levels (triglyceride third multiplied by HDL cholesterol third), a clear gradient of risk of IHD was found with increasing triglyceride levels within each level of HDL cholesterol, including high HDL cholesterol level, which are thought to provide protection against IHD.

Conclusions—In middle-aged and elderly white men, a high level of fasting triglycerides is a strong risk factor of IHD independent of other major risk factors, including HDL cholesterol. (Circulation. 1998;97:1029-1036.)

Key Words: coronary disease ■ lipids ■ lipoproteins ■ risk factors

The role of serum TG as a screening test and a risk factor of IHD remains controversial.1–3 Although in most epidemiological studies a positive relationship has been found between TG level and the risk of IHD, the usefulness of measuring TG in general screening strategies has been questioned because multivariate analysis control for HDL-C usually eliminates or substantially diminishes the role of TG as a predictor of IHD.1–3 However, the interpretation of multivariate models that include TG and HDL-C is complex and associated with several problems.1–3 TG and HDL-C are closely associated both in general screening strategies has been questioned because multivariate analysis control for HDL-C usually eliminates or substantially diminishes the role of TG as a predictor of IHD.1–3 However, the interpretation of multivariate models that include TG and HDL-C is complex and associated with several problems.1–3 TG and HDL-C are closely associated both

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distinct roles of TG and HDL-C in IHD in standard multivariate analysis.1–3 In addition, in comparison with HDL-C, the distribution of TG levels is markedly skewed, requiring logarithmic transformation for distribution-dependent analyses such as standard regression analysis, a statistical maneuver that may not provide an appropriate representation of underlying biological processes.1 Finally, adding to the complexity, some individuals with very high TG levels, such as those with lipoprotein phenotype I or V, appear to have no increased risk of IHD.4 With these problems kept in mind, the purpose of the present study was to present an analysis of data from the CMS to determine the effect of TG versus that of HDL-C on the risk of IHD.

Methods

Participants

The CMS was started in 1970 as a prospective cardiovascular study.3,5 The prospective male participants were derived from 14 workplaces in Copenhagen: the air force, army, navy, emergency management agency, postal service, customs service, a railroad company, national bank, a telephone company, three municipal service centers (for electricity and engineering and a fire brigade), a pharmaceutical company, and a building contractor company. All eligible 6125 men were employed and aged 40 to 59 years (mean age, 48 years); a total of 5249 men (87%) participated.

In 1985 through 1986, a new baseline was established, which was used for the present prospective study. All survivors from the 1970 study were traced by means of the Danish Central Population Register. Between June 1985 and June 1986, all survivors (4505 except 34 emigrants) from the original cohort were invited to take part in this study. Three thousand three hundred eighty-seven men (75%) agreed and gave informed consent. Their mean age was 63 years (age range, 53 to 74 years). The study took place at The Glostrup Population Study, Glostrup Hospital, University of Copenhagen (Denmark). Each subject was interviewed by a physician (H.O.H.) regarding a previously completed questionnaire and examined, with height, weight, and blood pressure measurements taken. A venous blood sample was taken after the subjects had fasted for ≥12 hours for the measurement of serum concentrations of lipids.

Criteria of Exclusion

Men who at baseline had a history of acute myocardial infarction, angina pectoris, stroke, or intermittent claudication were excluded.
Triglycerides and Ischemic Heart Disease

Selected Abbreviations and Acronyms

CMS = Copenhagen Male Study
HDL-C = HDL cholesterol
IHD = ischemic heart disease
LDL-C = LDL cholesterol
NIDDM = non–insulin-dependent diabetes mellitus
TG = triglyceride(s)

Total weekly consumption of alcohol was calculated with the use of questionnaire items regarding average alcohol consumption on weekdays and weekends. Intakes of beer, wine, and spirits were reported separately. Most of the alcohol consumed was beer. One drink corresponded to 10 to 12 g ethanol. The men classified themselves as never smokers, previous smokers, or current smokers. Current tobacco consumption was calculated on the basis of information about the number of cigarettes, cheroots, or cigars or the weight of pipe tobacco smoked daily. One cigarette was taken as equal to 1 g tobacco, 1 cheroot as equal to 3 g tobacco, and 1 cigar as equal to 4 g tobacco. As previously estimated on the basis of serum cotinine level, the validity of tobacco reporting was high.14

With respect to leisure-time physical activity, the men classified themselves as sedentary, slightly active (<4 hours of activity per week), or physically more active based on the following question: Which description most precisely covers your pattern of physical activity in leisure time? (1) You are almost entirely sedentary or perform light physical activity for <2 hours per week. (2) You perform light physical activity for 2 to 4 hours per week. (3) You perform light physical activity for >4 hours per week or vigorous activity for 2 to 4 hours per week. (4) You perform highly vigorous physical activity for >4 hours per week or regular exercise or competitive sports several times per week. For analytical purposes, those responding as being in group 3 or 4 were pooled and are referred to as the “high physical activity group,” and those responding as being in group 1 or 2 were pooled and are referred to as the “low physical activity group,” with <4 hours of activity per week.

According to the system of Svalastoga,1 the men were divided into five social classes based on level of education and job profile. Strata were defined as follows: social class I, self-employed subjects with ≥21 employees and white collar workers with ≥51 subordinates or subjects with academic degrees (typical jobs in the study cohort were officer, civil engineer, office executive, and department head); social class II, self-employed administrators with 6 to 20 employees and white collar workers with 11 to 50 subordinates or an intermediate education (typical jobs were head clerk, engineer, and nonacademic architect); social class III, self-employed subjects with 1 to 5 employees and white collar workers with 1 to 10 subordinates (typical jobs were engine driver and train guard); social class IV, self-employed subjects without employees, white collar workers without subordinates or without qualified work, and skilled blue collar workers (typical jobs were machine fitter in a telephone company and station foreman); and social class V, unskilled blue collar workers (typical jobs were unskilled laborer, mechanic, and driver). For analytical purposes, those corresponding to social class IV or V were pooled and are referred to as the “low social class.”

End Points

In 1995, a register follow-up was carried out on morbidity and mortality rates for 1985/1986 and December 31, 1993. All men who had taken part in the 1985/1986 examination were traced from registers. Information was obtained on hospital admissions and death certificate diagnoses within the follow-up period. We used the diagnoses from official national registers; ischemic heart disease diagnoses were codes 410 through 414 from the International Classification of Diseases, 8th Revision. Previous studies have demonstrated a high validity for Danish national registers.16-20

Statistical Analysis

Variables of interest are expressed as mean±SD values or frequencies (in percentages). Differences between groups were tested using ANOVA or Kendall’s τ B test for trend. The simultaneous contributions of several factors to the risk of IHD were analyzed with the use of multiple logistic regression models and the maximum likelihood ratio method. All calculations were performed with SPSSPC+ basic and advanced statistical software, version 3.1.22 A probability value of ≤0.05 was taken as significant unless otherwise stated.

The study was approved by the Ethics Committee for Medical Research in the County of Copenhagen.

from the follow-up study. For all who reported admission to hospital because of acute myocardial infarction before the start of the study, hospital records were checked. The diagnosis of acute myocardial infarction was accepted if at least two of the following symptoms or signs were recorded: retrosternal pain lasting ≥20 minutes, typical serial ECG changes in more than two ECG measurements, and increases in the serum concentration of relevant enzymes (alanine aminotransferase, lactate dehydrogenase, or creatinine phosphokinase—MB). Information regarding angina pectoris, stroke, and intermittent claudication was established with the questionnaire. Three hundred forty-two men (10.1%) were excluded due to cardiovascular diseases, and 139 men (4.1%) were excluded due to missing data or conflicting answers; therefore, 2906 men were eligible for the prospective study.

Measurements

Serum concentrations of total cholesterol, TG, and HDL-C were analyzed with the use of standard methods.4,5 Fasting lipids were measured only once in each subject. Fasting lipids were not subjected to ultracentrifugation, and the amount of possible chylomicronemia was not determined. The fasting TG measurements were performed using the Fully Enzymatic Method (Boehringer-Mannheim Biochemicals) and standardized in accordance with the World Health Organization Collaborating Center for Blood Lipid Research in Atherosclerosis and Ischemic Heart Disease at the Institute for Clinical and Experimental Medicine/IKEM (Prague, Czechoslovakia). All standard deviations were <0.05 mmol/L, including between-day and within-day measurements, and all coefficients of variation were <3.5%. LDL-C was determined indirectly according to Friedewald’s formula.1 Approximately 1.5% of the study population had a TG level of >4.5 mmol/L, a level at which the indirect LDL-C calculation becomes unreliable. However, the exclusion from the study of subjects with a TG level of >4.5 mmol/L did not materially affect the relation found between LDL-C and IHD, so we continued to use Friedewald’s formula in subjects with a TG level of >4.5 mmol/L and did not directly measure LDL-C.

The study population was divided into equal thirds according to TG levels. Cut points were 1.09 and 1.60 mmol/L. The population was further divided into nine subgroups when each TG third was stratified by HDL-C thirds (TG thirds multiplied by HDL-C thirds). Cut points for HDL-C were ≥1.18 and ≥1.48 mmol/L. The reason for selecting TG thirds as the major cut points in the present study was to provide data comparable to data from the Framingham Heart Study, in which basically the TG values shown above were used to subdivide the Framingham population.12

Self-reported NIDDM was accepted, provided the diagnosis had previously been verified by a physician. None of the participants had insulin-dependent diabetes mellitus. No measurements of plasma glucose and insulin were performed in the present cohort. The presence or absence of glucosuria was recorded after the subjects hadfasted for ≥12 hours. Of the 2906 men, 1.4% had glucosuria. Of subjects with known NIDDM, 24.5% had glucosuria, whereas only 0.8% of subjects without known NIDDM had glucosuria. With a manometer developed by London School of Hygiene,13 blood pressure was measured on the right arm with the subject seated. The definition of hypertension was based on questionnaire information and blood pressure measurements; the criteria were self-reported use of antihypertensive treatment or systolic blood pressure of ≥150 mm Hg and diastolic blood pressure of ≥100 mm Hg. Body mass index (kg/m²) was calculated on the basis of weight and height measurements.

Cut points for HDL-C were ≥1.48 mmol/L. The reason for selecting HDL-C thirds (TG thirds multiplied by HDL-C thirds) was to provide data comparable to data from the Framingham Heart Study, in which basically the TG values shown above were used to subdivide the Framingham population.12

Selected Abbreviations and Acronyms

CMS = Copenhagen Male Study
HDL-C = HDL cholesterol
IHD = ischemic heart disease
LDL-C = LDL cholesterol
NIDDM = non–insulin-dependent diabetes mellitus
TG = triglyceride(s)
Results

Lipid and nonlipid IHD risk factor characteristics according to thirds of fasting serum TG concentrations are summarized in Table 1; only ∼1.5% of the study population had a TG level of >4.5 mmol/L. The higher the TG concentration, the higher were the total cholesterol and LDL-C concentrations and the lower was the HDL-C concentration. In addition, individuals with higher TG concentrations were less physically active and had a higher body mass index, higher systolic and diastolic blood pressures, and a higher prevalence of hypertension, NIDDM, and glucosuria than those with lower concentrations. Thus, a high fasting serum TG concentration appeared to be a marker of the presence of several IHD risk factors in a group of middle-aged and elderly men.

During the follow-up period, 229 men had a first IHD event; 163 events were nonfatal, and 66 events were fatal. In total, 426 men died from all causes. Crude cumulative incidence rates of IHD and all-cause mortality during the 8-year follow-up period according to thirds of fasting serum TG concentrations, both overall and stratified on thirds of HDL-C levels, are summarized in Table 2. A clear association was found between TG levels and the risk of IHD, both overall and stratified on thirds of HDL-C levels, with cut points of 6.0 and ≥6.9 mmol/L. Finally, Table 2 shows that no clear association was found between TG levels and all-cause mortality, although individuals in the lowest third of TG levels tended to have a lower all-cause mortality rate.

The relative risks of IHD during the 8-year follow-up period according to thirds of fasting serum TG concentrations, both overall and stratified on thirds of HDL-C levels, are summarized in Table 3. The relation between risk of IHD and TG was assessed by successive adjustment for age only and for age and other potentially confounding factors and covariates. Overall, a clear gradient of risk of IHD was found with increasing thirds of TG levels; compared with the lowest third of TG level, the risk of IHD was 50% higher (P=.001) in the middle third and 120% higher (P<.001) in the highest third of TG level after control for the other major risk factors of IHD, including LDL-C and HDL-C. In addition, within each third of HDL-C level, a gradient of risk of IHD was found with increasing thirds of TG levels, and the difference in the risk of IHD remained significant or borderline significant in the highest third of TG level after control for the other major risk factors of IHD. If total cholesterol instead of LDL-C was

| TABLE 1. Characteristics of Men With Different Fasting Serum TG Concentrations Divided Into Thirds |
|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Characteristic                                    | TG Levels, thirds                               |                                                  |                                                  |                                                  |
|                                                  | 0.88 mmol/L (0.44–1.09) (n=982)                  | 1.33 mmol/L (1.10–1.59) (n=973)                  | 2.45 mmol/L (1.60–22.4) (n=951)                  |                                                  |
| Serum lipids, mmol/L                              |                                                  |                                                  |                                                  |                                                  |
| Total cholesterol                                 | 6.08±0.96                                       | 6.51±1.04                                        | 6.89±1.12                                        | <.001                                           |
| LDL-C                                            | 4.11±0.92                                       | 4.54±1.00                                        | 4.57±1.12                                        | <.001                                           |
| HDL-C                                            | 1.56±0.36                                       | 1.35±0.31                                        | 1.16±0.27                                        | <.001                                           |
| Lifestyle factor                                  |                                                  |                                                  |                                                  |                                                  |
| Alcohol use, beverages/week                       | 17.4±13.6                                       | 17.4±13.8                                        | 18.6±14.9                                        | .06                                             |
| Tobacco, g/d                                      | 7.8±10.0                                        | 8.9±9.8                                          | 8.5±9.8                                          | .16                                             |
| Physical activity, (<4 h/week), %                 | 36.8                                            | 46.5                                             | 58.7                                             | <.001                                           |
| Clinical/paraclinical factor                     |                                                  |                                                  |                                                  |                                                  |
| Body mass index, kg/m²                            | 24.4±2.9                                        | 25.6±3.0                                         | 27.0±2.9                                         | <.001                                           |
| Systolic blood pressure, mm Hg                    | 119±17                                          | 120±18                                           | 124±16                                           | <.001                                           |
| Diastolic blood pressure, mm Hg                   | 71±11                                           | 72±12                                            | 75±11                                            | <.001                                           |
| Hypertension, %                                   | 8.0                                              | 8.8                                              | 19.9                                             | <.001                                           |
| NIDDM, %                                          | 1.1                                              | 1.5                                              | 3.0                                              | .001                                            |
| Glucosuria, %                                     | 0.7                                              | 1.0                                              | 2.4                                              | <.001                                           |
| Other characteristic                              |                                                  |                                                  |                                                  |                                                  |
| Low social class (classes IV and V), %            | 47                                               | 51                                               | 53                                               | .004                                            |
| Age, y                                            | 62.0±5.2                                        | 63.0±5.4                                         | 62.3±4.9                                         | .03                                             |

Values are mean±SD or frequency (in percentage).
*By ANOVA or Kendall’s τ B test for trend.
include in the regression model, all results given in Table 3 were basically the same (not shown).

Cardiovascular drugs, especially β-blockers and diuretics, are known to affect the lipoprotein profile. In addition, subjects with a history of cancer may have modified their lifestyles and lifestyle-related risk factors because of their illness. To eliminate any interference from these two conditions, 96 men with a history of cancer during the period of 1943 through December 31, 1986, and 438 men taking any kind of cardiovascular drugs (for practical purposes, men who received β-blockers and diuretics for hypertension) were excluded from the analysis presented in Table 4. Restriction of the analysis to men not taking cardiovascular drugs and without a history of cancer did not materially affect the relation between risk of IHD and TG; if anything, the slope of the gradient, both overall and within each third of HDL-C levels, appeared to get steeper.

To provide results that could be compared with those obtained by other investigators, we subjected our data to a standard logistic regression analysis. To express the relative risk of IHD/1.0 mmol/L change in TG level, we used the antilogarithm on the primary results from the standard logistic regression analyses. In univariate analysis, relative risk of IHD (95% confidence interval) associated with a 1.0-mmol/L change in TG level was 1.4 (0.8 to 2.1); in multivariate analysis with control for age and HDL-C, the relative risk of IHD associated with a 1.0-mmol/L change in TG level was 1.0 (0.2 to 1.8).

Discussion

Main Results

The present study provides some major new findings strongly suggestive of a role of fasting serum TG as a risk factor of IHD. This study appears to be the first to show in men that a clear gradient of risk of IHD can be found with increasing TG levels within each level of HDL-C, also after controlling for the other major risk factors of IHD, including total cholesterol or LDL-C. This study also appears to be the first in which the TG risk issue was studied with control for the potentially confounding effects of antihypertensive drugs, level of physical activity, alcohol use, and social class. Finally, our results identified a small subgroup of men with high TG levels who

TABLE 2. Crude Cumulative Incidence, % (n/total), of IHD and All-Cause Mortality from 1985 through 1986 to December 31, 1993, According to Level of Fasting Serum TG and HDL-C Divided Into Thirds

<table>
<thead>
<tr>
<th>HDL-C Level, mmol/L (thirds)</th>
<th>TG Level, thirds</th>
<th>IHD</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.88 mmol/L (0.44–1.09)</td>
<td>(n=982)</td>
<td>1.33 mmol/L (1.10–1.59)</td>
</tr>
<tr>
<td>1.00 (0.29–1.18)</td>
<td>6.5% (7/108)</td>
<td>9.3% (28/301)</td>
<td>12.2% (70/574)</td>
</tr>
<tr>
<td>1.32 (1.19–1.47)</td>
<td>4.0% (14/346)</td>
<td>8.0% (29/362)</td>
<td>9.5% (26/273)</td>
</tr>
<tr>
<td>1.76 (1.48–3.46)</td>
<td>4.5% (24/528)</td>
<td>5.8% (18/310)</td>
<td>12.5% (13/104)</td>
</tr>
<tr>
<td>Overall</td>
<td>4.6% (45/982)</td>
<td>7.7% (75/973)</td>
<td>11.5% (109/951)</td>
</tr>
</tbody>
</table>

Values are mean mmol/L (range).

*By Kendall's τ B test for trend.

P values for Cox proportional hazards regression analyses are adjusted for age only and for age and other potentially confounding factors. In all analyses, the lowest third of TG is regarded as reference category and set to 1.

*P<.02, †P<.05, ‡P<.01, §P<.001.

TABLE 3. Relative Risk With 95% Confidence Limits for IHD From 1985/1986 Through December 31, 1993, According to Level of Fasting Serum TG and HDL-Cholesterol Divided into Thirds

<table>
<thead>
<tr>
<th>HDL-C Level, mmol/L (thirds)</th>
<th>TG Level, thirds</th>
<th>IHD adjusted for age</th>
<th>IHD adjusted for age and potential confounders†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.88 mmol/L (0.44–1.09)</td>
<td>(n=982)</td>
<td>1.33 mmol/L (1.10–1.59)</td>
</tr>
<tr>
<td>1.00 (0.29–1.18)</td>
<td>1.4 (0.6–3.4)</td>
<td>2.0 (0.9–4.4)*</td>
<td>1.6 (0.6–4.0)</td>
</tr>
<tr>
<td>1.32 (1.19–1.47)</td>
<td>2.1 (1.1–4.0)†</td>
<td>2.4 (1.2–4.7)‡</td>
<td>1.8 (0.9–3.6)*</td>
</tr>
<tr>
<td>1.76 (1.48–3.46)</td>
<td>1.3 (0.7–2.4)†</td>
<td>3.1 (1.5–6.4)‡</td>
<td>1.1 (0.6–2.2)†</td>
</tr>
<tr>
<td>Overall</td>
<td>1.7 (1.2–2.5)†</td>
<td>2.7 (1.5–6.4)‡</td>
<td>1.5 (1.0–2.3)†</td>
</tr>
</tbody>
</table>

Values are mean mmol/L (range).

P values for Cox proportional hazards regression analyses are adjusted for age only and for age and other potentially confounding factors. In all analyses, the lowest third of TG is regarded as reference category and set to 1.

*P<.02, †P<.05, ‡P<.01, §P<.001.

†LDL-C, HDL-C, alcohol use (beverages/week), tobacco (g/d), physical activity (<4 h/week), body mass index, systolic blood pressure, diastolic blood pressure, hypertension, NIDDM, glucosuria, and low social class.
had a high risk of IHD despite their high HDL-C levels, which are thought to provide protection against IHD.

Our Approach
As discussed by Austin and Garber and Avins, the role of the TG level as a risk factor of IHD has long been controversial. However, it also is well recognized that the statistical characteristics of the distribution of TG levels, variability of TG measurements, and statistical and metabolic relations between TG and other risk factors (in particular, HDL-C) may reduce the ability to detect an association between TG and risk of IHD in standard multivariate analysis. To compensate for the ability to detect an association between TG and other risk factors (in particular, HDL-C) may reduce variability of TG measurements, and statistical and metabolic relations between TG and other risk factors, (in particular, HDL-C) may reduce the ability to detect an association between TG and risk of IHD.

However, it also is well recognized that the statistical characteristics of the distribution of TG levels, variability of TG measurements, and statistical and metabolic relations between TG and other risk factors (in particular, HDL-C) may reduce the ability to detect an association between TG and risk of IHD. On the basis of the problems described above, we used categorical transformation and divided the study population into subgroups stratifying TG levels by HDL-C levels, and in this context it should be remembered that in accordance with most but not all previous studies, we could not identify fasting hypertriglyceridemia as a risk factor of IHD after adjustment for HDL-C in our conventional multivariate analysis.

To compensate for the problems described above, we used categorical transformation and divided the study population into subgroups stratifying TG levels by HDL-C levels, and in this context it should be remembered that in accordance with most but not all previous studies, we could not identify fasting hypertriglyceridemia as a risk factor of IHD after adjustment for HDL-C in our conventional multivariate analysis. By working with categorically transformed TG data in relatively large subgroups, the effect of the large variability in TG measurements was smoothed out, and the effect was minimized of the apparent paradox that the highest TG levels are not necessarily associated with the highest risk of IHD. This may explain why in the present study, we were able to identify fasting hypertriglyceridemia as a strong independent risk factor of IHD.

On the basis of our categorically transformed data and adjustments for HDL-C, subjects with TG levels of ≥2.0 mmol/L had a >100% increase in risk of IHD compared with subjects with TG levels of ≥1.0 mmol/L, a substantially higher value than the 14% increase in risk found in a recent meta-analysis study of TG, HDL-C, and risk of IHD with a 1.0 mmol/L increase in TG level. In addition, because in our analysis we stratified for HDL-C levels, it was possible to demonstrate a clear effect of TG on the risk of IHD distinct from that of HDL-C.

Special Subgroups
In the present study, we identified a small subgroup of hypertriglyceridemic men who had a high risk of IHD although they had a high HDL-C level, which was thought to be cardioprotective. We further characterized this subgroup to determine whether the presence of other risk factors could account for the high incidence of IHD in this subgroup. The most distinct and consistent difference between the high TG/high HDL-C subgroup and the other subjects in the highest third of TG levels was that basically all of the high TG/high HDL-C subjects had a TG level of 1.6 to 2.5 mmol/L, an interval of TG levels associated with the highest risk of IHD in our study. This subgroup also had a higher alcohol intake (27.8 beverages/week), a lower body mass index (25.8 kg/m²), more subjects with low social class (60%), but no subjects with a diagnosis of NIDDM, but none of these differences are obvious explanations for the unexpected high risk in the high TG/high HDL-C subgroup. There were no significant differences in the other variables listed in Table 1. We did not measure HDL subpopulations, and because different HDL subpopulations may differ in their ability to protect against IHD, we speculate that this subgroup had a preponderance of HDL particles without the ability to protect against an increased risk of IHD. In this context, it is relevant to point out that other subgroups, such as patients with IDDM, have an increased risk of IHD despite a raised HDL-C level.

In the present study, we found that subjects with TG levels of ≥2.5 mmol/L had a lower risk of IHD than subjects with TG levels of 1.6 to 2.5 mmol/L. We further characterized this subgroup to determine whether the presence of other risk factors...
factors could account for this observation, but this subgroup in general seemed to have a higher prevalence of other IHD risk factors. Compared with subjects with a TG level of 1.6 to 2.5 mmol/L, they had a higher total cholesterol level (0.39 mmol/L), lower HDL-C level (0.18 mmol/L), higher body mass index (1.5 kg/m²), higher systolic blood pressure (2.5 mm Hg), higher diastolic blood pressure (2.3 mm Hg), higher prevalence of hypertension (26% versus 17%), higher prevalence of NIDDM (4.2% versus 2.8%), higher prevalence of glucosuria (5.1% versus 1.3%), and more physically inactive subjects (62% versus 52%). The decrease in risk of IHD with TG levels of >2.5 mmol/L was seen in both younger and older subjects, and the mortality was the same as that in subjects with TG levels of 1.6 to 2.5 mmol/L.

Biological Plausibility
Because fasting hypertriglyceridemia can been identified as an independent risk factor of IHD, what is the pathogenetic link between hypertriglyceridemia and IHD? In this question may be hidden another possible explanation for the TG controversy that involves the existence of different kinds of TG-rich lipoproteins, some of which are atherogenic and some of which are not. Although total cholesterol is a reasonable substitute for LDL cholesterol, total TG sometimes inadequately represents the atherogenic TG-containing lipoproteins. This paradox is underscored by the observation that subjects with lipoprotein phenotypes I and V have no increased risk of IHD despite very high TG levels, whereas the hypertriglyceridemic state in phenotype IIB is associated with a remarkably increased risk. As discussed by Castelli, the TG-rich lipoproteins that appear not to be atherogenic are chylomicrons and very large VLDL particles, whereas smaller VLDL particles, in particular VLDL remnants and chylomicron remnants, are highly atherogenic, as shown in vitro with high uptake into macrophages, leading to foam cell formation, and in vivo with progression of coronary artery lesions. Although we did not perform ultracentrifugation, our results clearly suggest that TG-rich lipoproteins with differing atherogenic potential also were clinically significant in the CMS. Subjects with TG levels of >2.5 mmol/L appeared to have less atherogenic TG-rich lipoproteins than subjects with TG levels of 1.6 to 2.5 mmol/L, and they indeed appeared to be protected from IHD despite the fact that they had a higher prevalence of several other risk factors of IHD. This interesting finding is supported by the results of studies in animals: thus, the cholesterol-fed diabetic rabbit has high cholesterol and high TG levels and very large TG-rich lipoproteins but no atherosclerosis. In addition, it could be hypothesized that subjects with TG levels of 1.6 to 2.5 mmol/L had such atherogenic TG-rich lipoproteins that even high levels of cardioprotective HDL-C are unable to protect against IHD.

In addition to a direct atherogenic effect of TG-rich lipoproteins, high TG levels appear to be a marker of a series of other potentially atherogenic and prothrombotic changes. High TG levels have an effect on LDL particle size, density distribution, and composition, leading to a smaller, denser, more atherogenic LDL particle, and through plasminogen activator inhibitor–1, TG are associated with deficient fibrinolysis. High TG levels also are closely associated with insulin resistance and hyperinsulinemia; although the independent role of insulin in the pathogenesis of IHD is controversial, a high fasting insulin concentration was recently identified as an independent risk factor in the Quebec Cardiovascular Study. Thus, there is substantial biological support for the association found in our study between fasting hypertriglyceridemia and risk of IHD.

TG and Glucose Tolerance
In the CMS, fasting plasma glucose levels were not measured; thus, it was not possible to present direct evidence that hypertriglyceridemia was a risk factor of IHD independent of glucose tolerance and glucose control. This point is of significant relevance; (1) in the CMS, probands with a high TG level were characterized by an increased prevalence of NIDDM and glucosuria. (2) Criqui et al did not find TG to be an independent risk factor when fasting glucose levels were included in multivariate data analysis. However, on the basis of our global findings and the medical literature, we do not think adjustment for undiagnosed or uncontrolled diabetes would have changed our results. Of the 2906 men, 1.4% had glucosuria. Of subjects with known NIDDM, 24.5% had glucosuria, whereas only 0.8% of subjects without known NIDDM had glucosuria. The absence of glucosuria does not rule out mild or biochemical diabetes (diagnosed only with an oral glucose tolerance test), but it seems reasonable to conclude that the vast majority of the present study population did not have clinically significant diabetes. This conclusion is supported by data from another Danish study from the greater Copenhagen area, the Glostrup Population Study, in which <5% of the men aged 60 to 70 years had fasting glucose levels of >6.8 mmol/L. In addition, in the subgroup with high TG/high HDL-C levels, no subjects had a diagnosis of NIDDM and only 1 of the 104 subjects had glucosuria, yet there was a clear gradient of risk with increasing TG levels within the subjects with the highest levels of HDL-C. In the medical literature, TG level has been reported to be a stronger risk factor of IHD than glucose level and other measures of glucose control in subjects with impaired glucose tolerance or diabetes, and TG-rich lipoproteins have been related to the progression of coronary atherosclerosis in nondiabetic subjects. Finally, in a 10-year follow-up in the Glostrup Population Study of elderly men, hypertriglyceridemia was identified as a risk factor of cardiovascular events and cardiovascular mortality after control for the other major risk factors, including impaired glucose tolerance and diabetes, in that Danish study, HDL-C was not measured.

TG as a Screening Test
Should the fasting TG level be used as a screening test? So far, no primary prevention trials have been designed to specifically evaluate TG lowering in relation to risk of IHD. However, there is evidence from some cholesterol-lowering trials that subjects with hypertriglyceridemia will benefit most from treatment. In the Helsinki Heart Study, most of the risk of IHD and nearly all the benefits of drug treatment...
were confined to persons with high concentrations of both TG and cholesterol. In the West of Scotland Coronary Prevention Study, when the subjects were divided into groups according to lipid levels at baseline, men with TG levels above the median (≥1.6 mmol/L) experienced a greater treatment benefit in absolute terms than did men with total cholesterol levels above the median (≥7.0 mmol/L). In the present study, fasting hypertriglyceridemia was associated with an increased risk of IHD at all levels of HDL-C, including high HDL-C levels thought to provide protection against IHD, and fasting hypertriglyceridemia was a stronger risk factor than total cholesterol. It also is interesting that the TG levels found to be associated with an increased risk in the present study were within a range generally considered to be without clinical significance. Thus, fasting serum TG levels appear to be a relevant screening test and should be included in risk factor profiles; in preventive medicine, more attention to fasting TG levels of 1.6 to 2.5 mmol/L appears to be warranted.

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