Do Triglycerides Provide Meaningful Information About Heart Disease Risk?

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Background: Prior research suggests that adding triglyceride determinations to measurements of total cholesterol and cholesterol subfractions may improve the prediction of coronary heart disease (CHD).

Objective: To determine the additional value of measuring triglyceride levels, in addition to cholesterol levels and subfractions, for predicting CHD.

Study Design: A set of secondary analyses of previously reported studies.

Methods: We performed secondary analyses of data from the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Coronary Primary Prevention Trial, and the Lipid Research Clinics Prevalence and Mortality Follow-Up Study. Predictor variables included the levels of fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and fasting blood glucose; age; blood pressure; cigarette smoking; body mass index; and postmenopausal estrogen use. Analytic methods included Cox proportional hazards models, calculation of stratified crude incidence rates, and measurement of the area under the receiver operating characteristic curve.

Main Outcome Measures: Outcome variables were fatal and nonfatal myocardial infarctions.

Results: With few exceptions, no significant interactions between cholesterol subfractions and triglyceride levels were found and receiver operating characteristic curve analyses revealed that triglyceride measurements did not improve discrimination between those subjects who did and did not suffer CHD events. In men, categorical analyses employing both triglyceride and cholesterol levels were similar to those using cholesterol categories alone. In the one study of women, those subjects with both a high-risk cholesterol profile and high triglyceride levels were more likely to have a CHD event, though this finding was based on fewer subjects and CHD events.

Conclusion: These data suggest that, in men, measurement of serum triglyceride levels does not provide clinically meaningful information about CHD risk beyond that obtainable by measurement of serum cholesterol subfractions alone.

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The relation between serum triglyceride levels and coronary heart disease (CHD) has remained enigmatic despite 40 years of research. Because numerous statistical and biological problems plague the analysis of an independent association between triglyceride levels and CHD, attention has recently focused on the value of triglyceride levels, when combined with the measurement of other lipid levels, in predicting the development of CHD.

Several studies have suggested interactions between triglyceride and cholesterol levels in the prediction of CHD (ie, the magnitude of the cholesterol-CHD association is dependent on the triglyceride level). In the most notable example, an elegant post hoc analysis of the Helsinki Heart Study found that cholesterol levels were not strongly predictive of CHD in the absence of hypertriglyceridemia. Similar interactions were reported for men in the Prospective Cardiovascular Munster (PROCAM) study. These observations have been widely cited as evidence that triglyceride measurement plays an important role in the clinical assessment of CHD risk.

While such observations raise intriguing questions about the clinical use of triglyceride measurement, these analyses also have potentially serious analytic...
MATERIALS AND METHODS

We identified and obtained the raw data from 3 large prospective US studies that measured all necessary baseline variables and that were in the public domain (Table 1); detailed descriptions of each have been published previously. These studies are the Multiple Risk Factor Intervention Trial (MRFIT),19,20 the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),21,22 and the Lipid Research Clinics Prevalence and Mortality Follow-Up Study (LRC-PFU).23,24 The end points used in these analyses were definite fatal or nonfatal myocardial infarction (LRC-CPPT and MRFIT) and definite or suspected CHD death (LRC-PFU). All analyses were repeated for the MRFIT and LRC-CPPT data sets, using CHD death as the outcome; the results were similar to the analyses using fatal or nonfatal myocardial infarction as the end point, so only the latter are presented here.

STUDY DESCRIPTIONS

The Multiple Risk Factor Intervention Trial

The MRFIT was a randomized, controlled trial of dietary modification, antihypertensive therapy, and smoking cessation counseling for primary prevention of CHD in men.19,20 Subjects, aged 35 to 57 years, were required to be at high risk for CHD based on their levels of 3 cardiac risk factors: cigarette smoking, hypertension, and/or hypercholesterolemia. The first of 12866 subjects was enrolled in 1973, and subjects were followed up for an average of 6.1 years. The 6340 control subjects with sufficient data were analyzed in this study. The mean age of subjects in this group was 46.5 years; 90% of the subjects were white and 7% were African American. The mean TC, LDL, and HDL values were 6.52 mmol/L (252 mg/dL), 4.14 mmol/L (160 mg/dL), and 1.09 mmol/L (42 mg/dL), respectively.

All analyses with the MRFIT data set were adjusted for the enrollment criteria variables (ie, the number of cigarettes smoked, diastolic blood pressure, and TC level), since failure to account for the sampling method could result in biased estimates of effect.21 Low-density lipoprotein level was not substituted for TC level, since there was only a moderate correlation between these variables in this data set (r=0.59, P<.001). Models using LDL instead of TC level were also examined; these analyses showed stronger adjusted associations between triglyceride levels and CHD, but no differences in discrimination analyses.

The Lipid Research Clinics Coronary Primary Prevention Trial

The LRC-CPPT was a randomized, double-blind, placebo-controlled clinical trial of cholestyramine for the primary prevention of CHD.21,22 Beginning in 1973, 3806 men, between the ages of 35 and 59 years, who were free of symptomatic CHD, and who had levels of low-density lipoprotein cholesterol of 4.9 mmol/L or more (≥190 mg/dL) and triglycerides of 3.4 mmol/L or less (≤130 mg/dL) were enrolled in the study and followed up for an average of 7.4 years. Subjects in both groups were instructed on a cholesterol-lowering diet. Only data from the placebo group (n=1899) were used in these analyses. Among these subjects, the average age was 47.4 years; 96% of these subjects were white and 3% were African American. The mean TC, LDL, and HDL values were 7.21 mmol/L (279 mg/dL), 5.27 mmol/L (204 mg/dL), and 1.14 mmol/L (44 mg/dL), respectively.

The Lipid Research Clinics Prevalence and Mortality Follow-Up Study

The LRC-PFU was a prospective cohort study performed in 10 US centers.23,24 Recruitment occurred between 1972 and 1976 and resulted in the enrollment of 60502 subjects at baseline for a cross-sectional study of hyperlipidemia. A 15% random sample, and all subjects with elevated lipid levels, were enrolled in a prospective mortality study, with an average follow-up of 12.2 years. Subjects from one clinic were excluded from the public-use data set, so that data were available on 8681 subjects. After excluding subjects who were pregnant, reported angina, or had a history of myocardial infarction, took antiarrhythmic medications or digitalis, had a positive treadmill stress test for myocardial ischemia, or who had fasted less than 9 hours prior to providing blood samples at the second screening visit, 4136 men and 3505 women remained for analysis.

Analyses are reported separately for men and women (the LRC-CPPT and MRFIT had only male participants). Among the male subjects, the mean age at enrollment was 45.5 years; 97% of these subjects were white and 3% were African American. The mean TC, LDL, and HDL values for this group were 5.74 mmol/L (222 mg/dL), 3.80 mmol/L (147 mg/dL), and 1.16 mmol/L (45 mg/dL), respectively. Among female participants, the mean age on enrollment was 47.8 years; 93% of these subjects were white and 4% were African American. The mean values for TC, LDL, and HDL were 5.77 mmol/L (223 mg/dL), 3.73 mmol/L (145 mg/dL), and 1.53 mmol/L (59 mg/dL), respectively.

All statistical modeling procedures accounted for the sampling design of the prospective cohort.24 An analysis of the independent association between triglyceride levels and CHD events in this study has been published previously.2

ANALYTIC APPROACH

Several approaches were used to assess the value of triglyceride levels in predicting CHD. Analysis of Cox proportional hazards models was performed, using CHD death as the end point, since this is the most common outcome for subjects with hyperlipidemia. We used time-varying covariates to account for changes in lipid levels. We included lipid values at baseline as well as the most recent lipid values available for each subject up to the time of death or the end of follow-up. Triglyceride and cholesterol levels and other lipid values were also included as time-dependent covariates.

Role of chance effects. Finally, such observations may be owing, in part, to residual confounding: since the triglyceride level is correlated with levels of total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), triglyceride levels may serve more as a proxy for cholesterol levels and cholesterol sub-

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[Table 1: Details of the studies mentioned in the text.]
hazards models, crude incidence rates, and receiver operating characteristic (ROC) curves were performed with all data sets.

Log-transformed triglyceride levels were used in all modeling procedures, since models employing this transformation were found to be much less sensitive to the presence of very high triglyceride levels. Single measurements of each lipid variable were used for the baseline values. No adjustments were made for multiple comparisons. All analyses were performed with Stata Statistical Software, version 5.0.

COX PROPORTIONAL HAZARD MODELS

To examine the independent association of triglyceride levels with CHD and to test for the presence of significant interactions, Cox proportional hazards models were fit using lipid levels (including the cholesterol ratios) as continuous variables and as 4 categorical subgroups (described below). The other covariates in the full models were age, current cigarette smoking status, systolic blood pressure, fasting blood glucose level, LDL/HDL ratio (or TC/HDL ratio in the MRFIT analysis), body mass index, and estrogen replacement therapy (for the LRC-PFU women). Likelihood ratio statistics were used to test the statistical significance of the log-transformed triglyceride levels and interaction terms. All lower-order terms were included in models in which interaction terms were present.

ANALYSIS OF CRUDE INCIDENCE RATES

Crude (unadjusted) incidence rates were examined within 4 subgroups, defined in 2 different ways (Table 2). First, subjects were divided into 4 subgroups, using the criteria of the Helsinki and PROCAM studies. These groups were defined by dichotomous categories of triglyceride levels (≤2.3 mmol/L [≤200 mg/dL], >2.3 mmol/L [>200 mg/dL]), and the LDL/HDL ratio (≤3, >3) in the Lipid Research Center analyses or the TC/HDL ratio (≤6, >6) in the MRFIT analyses. In the second approach, subjects were divided into 4 different subgroups, defined solely by groups of the LDL/HDL ratio or the TC/HDL ratio ("cholesterol ratios"). Simple quartiles of the cholesterol ratios were not used, since the distribution of subjects in cholesterol quartiles would be very different from the distribution of subjects in subgroups defined by the combination of triglyceride and LDL/HDL ratio values. To make the distributions of subjects similar with the 2 methods, the cut-off values for the LDL/HDL ratio groups were set to keep the same numbers of subjects in each of the corresponding strata as for those defined by the triglyceride and LDL/HDL ratios method (Table 2). For example, in the LRC-CPPT data set, the stratum defined by low triglyceride levels and low LDL/HDL ratio (stratum A in Table 2) contained 977 subjects (52% of the total number of subjects); to define a similarly populated low cholesterol ratio stratum, the upper limit of the LDL/HDL ratio for this stratum was set to 4.7. The other 3 LDL/HDL ratio strata were constructed similarly. Tests for homogeneity of the incidence rates for the 4 categorical strata were performed with log rank tests for equality of the corresponding survivor functions.

For the Lipid Research Center data sets, crude incidence rates for each of these categories were calculated by dividing the number of events by the total person-time at risk in each subgroup. Confidence intervals were constructed assuming a Poisson distribution of outcome events. In the MRFIT data set, incidence rates were estimated by fitting exponential failure-time models to the data, which permitted adjustment for the enrollment-criteria variables, as noted earlier. In these models, the mean values for diastolic blood pressure (91 mm Hg), TC (6.5 mmol/L [252 mg/dL]), and daily number of cigarettes smoked (19 cigarettes) were used to estimate the incidence rates.

ROC CURVE ANALYSES

The analyses described above test for the independent association between triglyceride levels and CHD or the presence of significant interactions between triglyceride and other lipid levels. From the clinician's viewpoint, a crucial issue is whether triglyceride levels are useful in classifying patients' risk of CHD. To examine this issue directly, ROC curves were constructed to examine the additional value of triglyceride levels (beyond that of cholesterol) in discriminating between subjects who did or did not suffer a cardiac endpoint.

Three sets of models were compared. The first set compared the outcome discrimination of the 2 sets of 4 subgroup classifications (the 4 subgroups defined by triglyceride and cholesterol ratio cutpoints compared with the 4 categories defined by cholesterol ratios only, as described earlier). The second set of models compared the added discrimination ability of triglyceride levels with the cholesterol ratios alone, both used as continuous variables. The third set compared the additional discrimination of triglyceride levels with a multivariate logistic function including adjustment for age, baseline cigarette smoking status, systolic blood pressure, fasting blood glucose level, body mass index, cholesterol ratio, and estrogen replacement therapy use (for LRC-PFU women only). The area under the ROC curve was the primary outcome for these analyses. The area under the ROC curve provides a global estimate of the discriminative ability of each model and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). Ninety-five percent bias-corrected confidence intervals for the difference in the area under the ROC curves for each pair of models were determined by bootstrap methods.

fractions rather than providing substantial independent information. For example, when subjects are first dichotomized into "high-cholesterol" and "low-cholesterol" subgroups, which are then further dichotomized by the presence or absence of elevated triglyceride levels, the predictive information about CHD risk obtained with this method may be similar to that provided by simply dividing subjects into 4 groups using cholesterol levels alone.

To gain further insight into this issue, we performed a set of secondary analyses of previously reported studies. These analyses were designed to specifically examine the
potential value of the triglyceride level, beyond that of cholesterol subfractions, in predicting CHD.

**RESULTS**

**COX PROPORTIONAL HAZARD ANALYSES**

Univariate analyses showed a significant association between triglyceride levels and CHD in all data sets except MRFIT (Table 3). However, when adjusted for other known predictors of CHD, the triglyceride level–CHD association was markedly attenuated and was no longer statistically significant (with all $P$ values $> .2$ in all data sets).

There was low to moderate correlation between the LDL/HDL ratio and the triglyceride level in all data sets. The Spearman rank correlations for the LRC data sets were 0.22 in the LRC-CPPT, 0.36 for the LRC-PFU (Men), and 0.28 for the LRC-PFU (Women).

<table>
<thead>
<tr>
<th>Study Type</th>
<th>No. of Subjects</th>
<th>Mean TG Level, mmol/L (mg/dL)</th>
<th>Mean Follow-up Time, y</th>
<th>Outcome (No. of Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRFIT 19,20</td>
<td>RCT/pl 6340</td>
<td>4.99 (193)</td>
<td>32</td>
<td>F/NF MI (426)</td>
</tr>
<tr>
<td>LRC-CPPT 21,22</td>
<td>1899</td>
<td>3.96 (153)</td>
<td>18</td>
<td>F/NF MI (187)</td>
</tr>
<tr>
<td>LRC-PFU 23,24</td>
<td>Men Cohort 4136</td>
<td>4.71 (182)</td>
<td>28</td>
<td>CHD death (116)</td>
</tr>
<tr>
<td></td>
<td>Women Cohort 3505</td>
<td>3.33 (129)</td>
<td>13</td>
<td>CHD death (60)</td>
</tr>
</tbody>
</table>

* TG indicates triglyceride; MRFIT, Multiple Risk Factor Intervention Trial; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; LRC-PFU, Lipid Research Clinics Prevalence and Mortality Follow-Up Study; RCT/pl, randomized controlled trial (placebo group only); F/NF MI, fatal or nonfatal myocardial infarction; and CHD, coronary heart disease.

Table 3. Summary of Data Sets Used in Analyses*

<table>
<thead>
<tr>
<th>Study Type</th>
<th>No. of Subjects</th>
<th>Mean TG Level, mmol/L (mg/dL)</th>
<th>% With TG $\geq 5.17$ mmol/L ($\geq 200$ mg/dL)</th>
<th>Mean Follow-up Time, y</th>
<th>Outcome (No. of Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRFIT 19,20</td>
<td>RCT/pl 6340</td>
<td>4.99 (193)</td>
<td>32</td>
<td>6.1</td>
<td>F/NF MI (426)</td>
</tr>
<tr>
<td>LRC-CPPT 21,22</td>
<td>1899</td>
<td>3.96 (153)</td>
<td>18</td>
<td>7.4</td>
<td>F/NF MI (187)</td>
</tr>
<tr>
<td>LRC-PFU 23,24</td>
<td>Men Cohort 4136</td>
<td>4.71 (182)</td>
<td>28</td>
<td>12.2</td>
<td>CHD death (116)</td>
</tr>
<tr>
<td></td>
<td>Women Cohort 3505</td>
<td>3.33 (129)</td>
<td>13</td>
<td>12.2</td>
<td>CHD death (60)</td>
</tr>
</tbody>
</table>

* TG indicates triglyceride; MRFIT, Multiple Risk Factor Intervention Trial; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; LRC-PFU, Lipid Research Clinics Prevalence and Mortality Follow-Up Study; RCT/pl, randomized controlled trial (placebo group only); F/NF MI, fatal or nonfatal myocardial infarction; and CHD, coronary heart disease.

Table 2. Definition of Cutoff Points for LRC Studies and MRFIT*^

<table>
<thead>
<tr>
<th>Stratum</th>
<th>TG-Cholesterol Definition</th>
<th>LRC-CPPT</th>
<th>LRC-PFU (Men)</th>
<th>LRC-PFU (Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>LDL/HDL $\leq 5$, TG $\geq 5.17$ mmol/L (200 mg/dL)</td>
<td>$&lt;4.7$ (52)</td>
<td>$&lt;3.8$ (66)</td>
<td>$&lt;3.9$ (85)</td>
</tr>
<tr>
<td>B</td>
<td>LDL/HDL $\leq 5$, TG $&lt;5.17$ mmol/L (200 mg/dL)</td>
<td>$&gt;4.7$ to $&lt;5.0$ (9)</td>
<td>$&gt;3.8$ to $&lt;5.0$ (24)</td>
<td>$&gt;3.9$ to $&lt;5.0$ (11)</td>
</tr>
<tr>
<td>C</td>
<td>LDL/HDL $&lt;5$, TG $\geq 5.17$ mmol/L (200 mg/dL)</td>
<td>$&gt;5.0$ to $&lt;6.7$ (30)</td>
<td>$&gt;5.0$ to $&lt;6.1$ (7)</td>
<td>$&gt;5.0$ to $&lt;6.0$ (3)</td>
</tr>
<tr>
<td>D</td>
<td>LDL/HDL $&gt;5$, TG $\geq 5.17$ mmol/L (200 mg/dL)</td>
<td>$&gt;6.7$ (9)</td>
<td>$&gt;6.1$ (4)</td>
<td>$&gt;6.0$ (2)</td>
</tr>
</tbody>
</table>

* Definition of cutoff points in each dataset for 2 sets of lipid subgroups (the first defined by both triglyceride levels and the low-density lipoprotein/high-density lipoprotein [LDL/HDL] ratio; the second defined by 4 groups of LDL/HDL ratios only), with cutoff points set to keep the same number of subjects in each group. The ratio of total cholesterol to HDL-cholesterol was used in the MRFIT analysis. See Table 1 for an explanation of the other (study) abbreviations. TC indicates total cholesterol.

Table 3. Cox Proportional Hazard Ratios (HR) for Triglyceride (TG) Levels and Interaction Terms*^

<table>
<thead>
<tr>
<th>Term†</th>
<th>MRFIT HR 95% CI</th>
<th>LRC-CPPT HR 95% CI</th>
<th>LRC-PFU (Men) HR 95% CI</th>
<th>LRC-PFU (Women) HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>lnTG  (univariate)</td>
<td>1.15 (0.97-1.37)</td>
<td>1.60 (1.11-2.30)</td>
<td>1.63 (1.15-2.30)</td>
<td>2.62 (1.58-4.32)</td>
</tr>
<tr>
<td>lnTG</td>
<td>1.03 (0.83-1.24)</td>
<td>1.33 (0.86-2.07)</td>
<td>0.97 (0.54-1.72)</td>
<td>0.91 (0.39-2.09)</td>
</tr>
<tr>
<td>lnTG-LDL interaction</td>
<td>0.99 (0.99-1.00)</td>
<td>0.99 (0.98-1.00)</td>
<td>1.00 (0.99-1.01)</td>
<td>1.00 (0.99-1.02)</td>
</tr>
<tr>
<td>lnTG-HDL-C interaction</td>
<td>1.02 (0.98-1.01)</td>
<td>0.97 (0.92-1.06)</td>
<td>0.96 (0.94-0.97)</td>
<td>0.98 (0.95-1.01)</td>
</tr>
<tr>
<td>lnTG-LDL/HDL-C interaction</td>
<td>0.96 (0.90-1.03)</td>
<td>0.82 (0.64-1.06)</td>
<td>0.95 (0.88-1.02)</td>
<td>1.23 (0.78-1.96)</td>
</tr>
</tbody>
</table>

* In multivariate models (except as noted); outcome variables and study abbreviations defined in the asterisk footnote of Table 1. TG indicates triglyceride; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; and CI, confidence interval.
† Hazard ratios (HRs) refer to term listed at left. All models adjusted for age, baseline cigarette smoking status, systolic blood pressure, fasting blood glucose level, body mass index, LDL-C level, HDL-C level, and estrogen replacement therapy (LRC-PFU women only); total cholesterol level was substituted for LDL-C in MRFIT analysis.
PFU men, and 0.45 for the LRC-PFU women. In MRFIT the rank correlation between triglyceride level and the TC/HDL ratio was 0.52 (P < .001 for all correlations).

INTERACTION ANALYSES

For each data set, interaction terms were added to the multivariate models that included the lipid measurements as continuous variables. In general, no consistent evidence of an interaction between triglyceride and other lipid levels was present (Table 3). In the LRC-PFU study, a significant interaction was found between triglyceride and HDL levels in men (as suggested by a prior study), and a significant interaction was identified between triglycerides and TC levels in the MRFIT data set. No other significant interaction terms were present in any of the adjusted models.

The subjects in each study were divided into 4 lipid strata, defined first by dichotomizing the data by the ratio of LDL/HDL (or TC/HDL ratio for the MRFIT data), as defined earlier. These 2 strata were then further dichotomized by the triglyceride level and crude (unadjusted) incidence rates were calculated for each stratum. These rates were compared with the crude incidence rates calculated within 4 strata defined by 4 categories of LDL/HDL (or TC/HDL ratios), as described earlier (Figure).

In all data sets, the crude incidence rates varied across the strata, and statistical testing revealed significant heterogeneity of the rates (all P values < .001). In analyses involving male subjects, however, the trends identified in the strata defined by a combination of triglyceride and other lipid levels were similar, though not identical, to the trends identified by the strata defined solely by LDL/HDL ratios (Figure). Thus, the 2 methods of grouping provided similar information. Among women, the incidence rate for the group defined by a high triglyceride level and high LDL/HDL ratio was much higher than any other stratum; this pattern was inconsistent with the trends observed in the subgroups defined only by LDL/HDL categories (Figure).

ROC CURVE ANALYSES

In addition to testing associations between triglyceride levels and CHD, ROC curves were constructed to examine the incremental benefit of measuring triglyceride levels, beyond that of measuring cholesterol subfractions alone, in discriminating between subjects who had a cardiac event and those who did not. These ROC curves were created for pairs of models, with one member of each pair excluding triglyceride levels, the other including triglyceride levels. In each case, triglyceride levels added very little discriminative power to models containing the LDL/HDL ratio variables alone (Table 4). Regardless of how the lipid values were used (ie, categorical or continuous variables), the differences between the models containing triglyceride levels and those that did not were within 2% and almost all were statistically nonsignificant.
The possibility that knowledge of the triglyceride level might provide useful information for assessing an individual's risk of CHD has been a tempting hypothesis. If determining the triglyceride level provided meaningful information, triglyceride levels may have important clinical use even if a clear consensus on the value of treating hypertriglyceridemia is lacking.

These analyses were specifically designed to examine the question of how much additional predictive information is gained by measuring triglyceride levels in addition to determining the cholesterol subfractions generally recommended for assessing CHD risk. Analysis of Cox proportional hazard models, calculation of crude incidence rates, and construction of ROC curves were all used to study whether combining triglyceride and cholesterol measurements was superior to using cholesterol measurements alone.

In men, the evidence suggests that triglyceride measurement provides little clinically useful information. While the subgroup of men with high triglyceride levels and high LDL/HDL ratios tended to have higher CHD rates than other subgroups, this pattern was similar to that observed by using groupings defined by LDL/HDL ratios alone (Figure). Multivariate survival analyses found few significant interactions between triglyceride and other lipid levels; ie, the association between cholesterol subfractions and CHD was not materially affected by the triglyceride level (Table 3). Finally, ROC curve analyses found no additional discriminative value of adding triglyceride variables to values of TC or cholesterol subfractions alone (Table 4).

There are several possible explanations for the discrepancy between these findings and those of other investigators. As noted earlier, the Helsinki Heart Study analyses were performed post hoc and may be more susceptible to chance effects; however, the PROCAM study found similar, though less striking, interactions. Second, both the Helsinki and PROCAM studies were carried out in Europe and all studies used in these analyses were performed in the United States; the relation between lipid levels and CHD may not be the same in the different populations. For example, the association between hypertriglyceridemia and CHD seems to be stronger and more consistent in Scandinavian countries than in the United States. Finally, the LRC-PFU study contained data on CHD deaths only; both fatal and nonfatal cardiac events were included in the Helsinki and PROCAM studies. However, both the LRC-CPPT and the MRFIT included nonfatal as well as fatal outcomes but did not show the same types of interactions as observed in the 2 European studies.

Most importantly, the Figure indicates that, in men, the patterns identified by combining dichotomous classifications of cholesterol subfractions and triglyceride levels provided similar information as analysis of the cholesterol levels alone. These analyses suggest that, rather than adding useful independent information, the triglyceride level functions, in part, as a proxy for the cholesterol measurements commonly used in clinical practice, and do not provide meaningful additional information.

In women, analysis of crude incidence rates found a significant interaction between triglyceride levels and cholesterol subfractions that was similar to that observed among men in the Helsinki and PROCAM studies. In the LRC-PFU study, those women with an LDL/HDL ratio greater than 5 and a triglyceride level higher than 2.3 mmol/L (>200 mg/dL) were approximately 4 times more likely to die of CHD than were women without these levels of hyperlipidemia (Figure). However, these results should be interpreted with caution: the 95% confidence interval for the mortality rate of this stratum (2.6-18.8 per 1000 person-years) included the point estimates in the next 2 lower strata. Also, these estimates are crude, unadjusted, incidence rates. These intriguing results require careful validation in other data sets before firm conclusions can be drawn.

**Table 4. Areas Under the Receiver Operating Characteristic (ROC) Curves**

<table>
<thead>
<tr>
<th>Model</th>
<th>MRFIT</th>
<th>LRC-CPPT</th>
<th>LRC-PFU (Men)</th>
<th>LRC-PFU (Women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol-ratio subgroups</td>
<td>0.56</td>
<td>0.58</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td>Cholesterol-ratio/TG subgroups</td>
<td>0.57</td>
<td>0.57</td>
<td>0.61</td>
<td>0.57</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>0.01 (−0.002, 0.03)</td>
<td>−0.008 (−0.03, 0.03)</td>
<td>−0.01 (−0.06, 0.04)</td>
<td>−0.008 (−0.08, 0.05)</td>
</tr>
<tr>
<td>Continuous variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL/HDL ratio†</td>
<td>0.60</td>
<td>0.59</td>
<td>0.65</td>
<td>0.67</td>
</tr>
<tr>
<td>LDL/HDL ratio + TG</td>
<td>0.60</td>
<td>0.61</td>
<td>0.65</td>
<td>0.66</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>−0.00004 (−0.003, 0.003)</td>
<td>0.02 (−0.0002, 0.06)</td>
<td>−0.001 (−0.03, 0.01)</td>
<td>−0.008 (−0.04, −0.001)</td>
</tr>
<tr>
<td>Full model‡</td>
<td>0.64</td>
<td>0.63</td>
<td>0.84</td>
<td>0.85</td>
</tr>
<tr>
<td>Full model + TG</td>
<td>0.64</td>
<td>0.63</td>
<td>0.83</td>
<td>0.85</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>0.0009 (−0.001, 0.009)</td>
<td>0.004 (−0.0009, 0.03)</td>
<td>0.0005 (−0.003, 0.008)</td>
<td>0.0 (−0.005, 0.004)</td>
</tr>
</tbody>
</table>

*Areas under the ROC curves for the models shown, and difference between pairs of models (without and with triglyceride [TG] levels) and the associated 95% confidence intervals (CIs). “Categorical Variables” refer to lipid subgroups as defined in Table 2; “Continuous Variables” models use lipid variables without grouping into categories. Study abbreviations defined in the asterisk footnote of Table 1. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

†The ratio of total cholesterol to HDL was used in the MRFIT analysis.

‡The full model included baseline age, current cigarette smoking status, systolic blood pressure, fasting blood glucose level, LDL/HDL ratio or total cholesterol/HDL ratio (in the MRFIT analysis), body mass index, and estrogen replacement therapy (for the LRC-PFU women).
reached regarding a useful role for triglyceride measurement in estimating CHD risk in women. While the analysis of crude incidence rates identified a uniquely high-risk subgroup (with high triglyceride levels and a high LDL/HDL ratio), the ROC curve analyses did not find important discriminative value of triglyceride measurement. This apparent discrepancy is most likely because of the fact that the high-risk subgroup represented only a very small proportion of all women and events in the cohort.

Several investigators have searched for evidence of a triglyceride-cholesterol interaction and have come to widely disparate conclusions. Some researchers have found that triglyceride and cholesterol levels (or cholesterol subfractions) each modified the association between the other lipid levels and CHD, though the nature of the interaction varied among the studies. Others, however, have failed to find statistical evidence for a triglyceride-cholesterol interaction at all. This lack of consistency casts further doubt on the clinical use of triglyceride measurement.

While these analyses do not support the measurement of triglyceride as a useful tool for CHD risk assessment, they do not preclude the possibility that treatment of hypertriglyceridemia may reduce the risk of CHD. Unfortunately, despite 4 decades of active investigation, the clinical value of lowering elevated triglyceride levels remains unclear. Observational studies have provided inconsistent results, particularly after statistical adjustments for important predictors of CHD, such as HDL and fasting blood glucose level. One recent meta-analysis, however, found evidence for an independent association between triglyceride levels and CHD in men and women, even after adjustment for HDL level, though the estimates did not include adjustment for fasting blood glucose level, an important potential confounder.

No clinical trial has examined treatment directed specifically at hypertriglyceridemia. Most trials that have analyzed alterations in triglyceride levels and response to cholesterol-lowering medication have not found a statistically significant association between changes in triglyceride levels and reduction in CHD risk, though others have identified such a relationship. The Helsinki Heart Study found that the benefit of treatment with gemfibrozil was precipitating pancreatitis.

Second, only a single baseline measurement of triglyceride was used. Triglyceride measurements are more imprecise than other lipid measurements and this variability may cause the assessment of triglyceride-CHD associations to be underestimated. Third, different end points were used in the data sets, though the consistency of findings across studies with diverse end points strengthens the conclusions. Finally, the enrollment criteria for the MRFIT study complicate the analysis and interpretation of observational studies with this data set, adjustments for the 3 enrollment criteria variables were made for all analyses with these data to address this problem.

CONCLUSIONS

These analyses do not confirm the results of prior studies suggesting an important role for triglyceride measurement in estimating CHD risk. In the 3 studies that included men, triglyceride measurement did not provide clinically useful information for estimating CHD risk, beyond that contained in the measurement of cholesterol subfractions alone. In the 1 study that included women participants, evidence of a triglyceride-cholesterol interaction was observed; however, these results were based on a small number of outcome events and require validation in other data sets to confirm their existence. Evidence does not support the routine measurement of serum triglyceride levels for assessing risk of CHD.

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