Hypert triglycerideremia as a Cardiovascular Risk Factor

Melissa A. Austin, PhD, John E. Hokanson, MPH, PhD, and Karen L. Edwards, PhD

To determine the relation between plasma triglyceride levels and the risk of incident cardiovascular disease, the semiquantitative techniques of meta-analysis were applied to 17 population-based prospective studies of triglyceride and cardiovascular disease. Sixteen of these studies represented 2,445 events among 46,413 Caucasian men followed for an average period of 8.4 years, and 5 studies represented 439 events among 10,864 Caucasian women followed for an average period of 11.4 years. Univariate relative risk (RR) estimates for incident cardiovascular disease associated with a 1-mmol/L increase in triglyceride was 1.07–1.98 in men, with a summary RR of 1.32 (95% confidence interval [CI]: 1.26–1.39), indicating a 32% increase in disease risk associated with increased triglyceride. In the studies involving women, individual RR estimates for triglyceride were 1.69–2.05, with a summary RR of 1.76 (95% CI: 1.50–2.07), indicating a 76% increase in disease risk associated with increased triglyceride. After adjustment for high-density lipoprotein cholesterol and other risk factors, these risks were decreased to 14% in men and 37% in women but remained statistically significant. Three recent prospective epidemiologic studies have also shown that plasma triglyceride and low-density lipoprotein particle size predict subsequent coronary artery disease in Caucasian populations. Taken together, these studies demonstrate the importance of triglyceride levels as a risk factor for cardiovascular disease. ©1998 by Excerpta Medica, Inc.

Am J Cardiol 1998;81(4A):7B–12B

Elevated levels of plasma triglyceride have long been associated with an increased risk of cardiovascular disease. In 1959, a case-control study by Albrink and Man1 showed that fasting triglyceride levels were increased among patients with coronary artery disease compared with control subjects. The earliest prospective study of triglyceride and ischemic heart disease demonstrated an increased incidence of ischemic heart disease among men with elevated triglyceride levels at baseline compared with men with lower levels.2 However, even in this early study, the investigators speculated that the triglyceride association may not have been independent of other plasma lipid levels.

In the decades after these investigations, an extensive literature has examined the role of triglyceride as a risk factor for cardiovascular disease. In a review of these studies, Austin noted that most analyses showed a relation between triglyceride and coronary artery disease.3 However, a number of studies found that this association did not remain statistically significant after controlling for other lipid risk factors, especially high-density lipoprotein (HDL) cholesterol. In reviewing this and other evidence, the National Institutes of Health Consensus Development Panel on Triglyceride, High-Density Lipoprotein, and Coronary Heart Disease concluded that "for triglyceride, the data are mixed. Although strong associations are found in some studies, the evidence for a causal relation (with coronary artery disease) is still incomplete."4 Similarly, data from the Lipid Research Clinics (LRC) Follow-up Study demonstrated that triglyceride was related to 12-year coronary artery disease mortality in both men and women5 but this relation was not statistically significant after adjustment for covariates. Thus, the role of triglyceride as a risk factor for coronary artery disease remains to be fully elucidated.

This article will focus on the relation between triglyceride and cardiovascular disease. First, the semiquantitative techniques of meta-analysis will be applied to population-based, prospective studies of triglyceride and cardiovascular disease to estimate the strength of this association in the general population and to evaluate the effect of other risk factors, especially HDL cholesterol.6,7 Then, 3 recent prospective studies that examined both plasma triglyceride and low-density lipoprotein (LDL) particle diameter (size) will be summarized.

META-ANALYSIS OF TRIGLYCERIDE AND CARDIOVASCULAR DISEASE

Published studies were selected for the meta-analysis of triglyceride and cardiovascular disease based on several criteria.8 First, only investigations that used a prospective study design were chosen, ensuring that elevations in plasma triglyceride preceded the onset of disease. Second, only studies that used population-based samples of subjects were selected, so that relative risk (RR) estimates were as applicable as possible to the general population. Because the results from the LRC Follow-up Study5 were based on a sample enriched with hyperlipidemic subjects, the RR values for this analysis were adjusted for ascertainment (hyperlipidemic vs random sample) based on results kindly provided by Dr. M. H. Criqui (personal communication). To exclude the possibility of postprandial ef-

From the Department of Epidemiology, School of Public Health and Community Medicine, and the Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, School of Medicine, University of Washington, Seattle, Washington.

This work was supported by NIH RO1 Grant HL45913 and was performed during Dr. Austin’s tenure as an Established Investigator of the American Heart Association.

Address for reprints: Melissa A. Austin, PhD, Department of Epidemiology, Box 357236, 1959 NE Pacific Avenue, University of Washington, Seattle, Washington 98195-7236.

©1998 by Excerpta Medica, Inc.
All rights reserved.
fects, only studies that evaluated fasting triglyceride levels were included. Each study cohort was included only once in the analysis, using the publication that reported the longest follow-up period. Both fatal and nonfatal cardiovascular endpoints were included, although most studies focused on myocardial infarction or coronary artery disease death. Finally, only Caucasian subjects were included in the analysis, since few data were available on other ethnic groups.

A total of 17 studies2,5,8–24 conforming to these selection criteria were identified, including 16 studies representing 2,445 events among 46,413 men followed for an average period of 8.4 years,2,5,8–13,15–24 and 5 studies representing 439 events among 10,864 women followed for an average period of 11.4 years.5,10,14,16,18 Subjects were 15–81 years of age in all of the studies. Among men, 6 studies were from the United States, 6 from Scandinavian countries, and 1 each from France, Germany, Italy, and the United Kingdom. Among women, 3 studies were from the United States and 2 from Scandinavia.

The meta-analysis was performed separately for men and women using the techniques described by Greenland.7 Briefly, RR estimates were determined for each study by calculating $\beta$, the estimated slope, from logistic regression analysis, standardized to a 1-mmol/L increase in triglyceride. To determine the statistical significance of the association and to calculate confidence intervals (CIs), the variance of $\beta$ was next computed. The $\beta$ value for each study was then weighted by the inverse of the variance, reflecting both the sample size and follow-up period of the study. Finally, the weighted $\beta$ values were averaged and converted to the summary RR value, so that the larger the study and the longer the follow-up period, the greater the contribution to the summary RR. These procedures resulted in the univariate summary RR for the association between triglyceride and cardiovascular disease. To determine the effect of covariates on this estimate, the same procedures were used to estimate the multivariate summary RR using the 6 studies that included HDL cholesterol as a covariate.5,8,16,20,22,23 Of these studies, 4 included adjustment for age, 4 for total cholesterol, 2 for LDL cholesterol, 4 for smoking, 6 for body mass index, and 5 for blood pressure. To maximize the potential effects on the multivariate summary RR, all of these covariate adjustments were included in the analysis.

As shown in Figure 1, univariate RR estimates for cardiovascular disease associated with a 1-mmol/L increase in triglyceride was 1.07–1.98 for men, with a summary RR of 1.32 (95% CI: 1.26–1.39).2,5,8–13,15–24 This indicates a 32% increase in disease risk associated with triglyceride. Among the 5 prospective studies in women,5,10,14,16,18 individual RR estimates for triglyceride was 1.69–2.05 (Figure 1), all of which were statistically significant ($p<0.05$). The summary univariate RR was higher for women than for men, 1.76 (95% CI: 1.50–2.07), although the CI was somewhat wider because of the smaller sample size (approximately 10,800 women vs approximately 46,400 men). Thus, a 1-mmol/L increase in triglyceride was associated with a 76% increase in risk of incident cardiovascular disease in women. Because only population-based studies were included, the summary RR estimates derived from this analysis provide the best available overall estimates for a relation between triglyceride levels and cardiovascular disease.

It has long been noted that triglyceride is a more potent risk factor for cardiovascular disease in Scandinavian countries than in other countries,3 and meta-analysis allows a quantitative comparison of RR risk values in different geographic locations. Among men, RR values were 2.49, 1.25, and 1.34 for studies conducted in Scandinavia, in other European countries, and in the United States, respectively (all $p<0.05$). Among studies in women, RR values were also higher in Scandinavian countries than in the United States (2.02 vs 1.71, respectively). Thus, in both men and women, univariate RR values were indeed higher for studies conducted in Scandinavian countries compared with studies conducted elsewhere.

As expected, multivariate RR estimates with adjustment for HDL cholesterol were attenuated (Figure 2). For men, the multivariate RRs for triglyceride were 0.98–1.39, with a summary RR of 1.14 (95% CI: 1.05–1.28), which was statistically significant ($p<0.05$). For women, the summary multivariate RR was higher than that for men—1.37 (95% CI: 1.13–1.66). Thus, even after adjustment for HDL cholesterol, a statistically significant increase in the risk of incident cardiovascular disease was associated with triglyceride for both men and women. Importantly, studies conducted in Scandinavia in which univariate RR values are highest are not included in these multivariate RRs since HDL cholesterol adjustments were not reported. Thus, the multivariate RR values reported here for triglyceride are likely to be conservative. Furthermore, when an external adjustment procedure was used to evaluate the confounding effect of HDL cholesterol among those not reporting adjustment for this variable,7 the multivariate summary RR was 1.22 (95% CI: 1.15–1.29) for men and 1.44 (95% CI: 1.23–1.69) for women.

In summary, based on all of the available data from population-based prospective studies, meta-analysis has shown that increases in plasma triglyceride are associated with a significant increase in risk of incident cardiovascular disease among both men and women. In men, an increase of 1 mmol/L was associated with a 32% increase in risk of disease. A greater increase in risk (76%) was found in women. Based on data from studies that reported adjustments for HDL cholesterol and other risk factors, multivariate RR estimates were attenuated but were still statistically significant, representing a 14% increase in risk for men and a 37% increase in risk for women. Importantly, because only population-based studies were included in the analysis, these results provide the best available estimates of triglyceride risk in the general population. Therefore, triglyceride is a risk factor for cardiovascular disease, independent of HDL cholesterol.
PROSPECTIVE STUDIES OF TRIGLYCERIDE AND LOW-DENSITY LIPOPROTEIN PARTICLE SIZE

Since the completion of the meta-analysis described above, 3 new studies—the Physicians' Health Study, the Stanford Five-City Project, and the Quebec Cardiovascular Study—have examined the association of baseline plasma triglyceride levels and LDL particle size with incident coronary artery disease (Table I). Previous studies showed that triglycer-
and LDL particle size, as determined by gradient gel electrophoresis, are closely correlated risk factors that are characteristic components of the “atherogenic lipoprotein phenotype.” However, until the new studies were published, prospective epidemiologic evidence examining LDL particle size as a predictor of disease was lacking. The findings from the Physicians’ Health Study were based on a 7-year follow-up of 266 men with incident nonfatal myocardial infarction or fatal coronary artery disease. Controls were matched for age, smoking, and time of randomization. Importantly, study participants were “not specifically instructed to provide fasting specimens.” In this study, mean baseline triglyceride values were higher in patients compared with controls (2.29 mmol/L vs 1.75 mmol/L, respectively; p = 0.001).

Similarly, LDL diameter values were smaller in patients compared with controls (256 Å vs 259 Å, respectively; p < 0.001). As shown in Table I, the RR for triglyceride was 1.43 (95% CI: 1.22–1.68) for a 1.13-mmol/L increase in triglyceride (p < 0.01), and the RR for LDL particle size was 1.38 (95% CI: 1.18–1.62) for an 8-Å decrease in size (p < 0.01). Thus, both triglyceride and LDL particle size were significant predictors of future coronary artery disease in this study. However, the triglyceride association was independent of other lipids (RR = 1.33; p = 0.009), whereas the association with LDL particle size was not.

### Table I

<table>
<thead>
<tr>
<th>Study</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHS</td>
<td>2,536</td>
<td>2,969</td>
</tr>
<tr>
<td>WCGS</td>
<td>2,066</td>
<td></td>
</tr>
<tr>
<td>ROG</td>
<td>3,395</td>
<td></td>
</tr>
<tr>
<td>LRC</td>
<td>4,129</td>
<td>3,376</td>
</tr>
<tr>
<td>PROCAM</td>
<td>4,407</td>
<td></td>
</tr>
<tr>
<td>CSCHDS</td>
<td>4,860</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>22,293</td>
<td>6,345</td>
</tr>
</tbody>
</table>

**Relative Risk**

FIGURE 2. Multivariate-adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between incident cardiovascular disease and a 1-mmol/L increase in triglyceride, by gender, for those studies that adjusted for HDL cholesterol. RR values are given on the x axis on a natural logarithm scale. The x axis lists each study included in the meta-analysis, ordered by sample size, and the summary RR. An RR of 1.0 (vertical dotted line) represents no association, and CIs that do not cover 1.0 indicate RRs that are statistically significant at the p = 0.05 level. See Figure 1 for key to study abbreviations. (Adapted from J Cardiovasc Risk.) Note: In a recent report from the PROCAM study in which the follow-up period was extended to 8 years, the multivariate RR reached statistical significance.
size was not (RR = 1.09; p = 0.46). This was due at least in part to the strong inverse relation between triglyceride and LDL particle size, with an estimated Spearman correlation coefficient of −0.71 in this study.

The Stanford Five-City Study26 was based on incident cases of coronary artery disease, both fatal and nonfatal, identified through community surveillance from 1979–1992. Controls were selected based on matching criteria for age, sex, ethnicity, treatment or control city, and time of surveillance. A total of 124 case-control pairs (90 male and 34 female pairs) were identified, and the analysis was based on the case-control difference in LDL particle size (Table I). For all subjects, a highly significant case-control mean difference was found (−5.1 Å; p <0.01), demonstrating that smaller LDL particle size predicted incident coronary artery disease in this population. The difference in LDL particle size was independent of triglyceride, HDL cholesterol, smoking, systolic blood pressure, and body mass index in multivariate analyses, in contrast to the finding from the Physicians’ Health Study25 described above.

Finally, the results of the Quebec Cardiovascular Study27 were based on findings in 2,103 men, 114 of whom developed ischemic heart disease during the 5-year follow-up period. Using 103 controls matched for age, smoking, body mass index, and alcohol intake, the RR for the lowest tertile of LDL particle size was 3.6 (p <0.01; Table I), again using a nested case-control approach. Furthermore, this relation remained statistically significant after adjustment for triglyceride (RR = 3.0; p <0.05). However, in this study triglyceride was not a significant predictor after adjustment for LDL particle size.

Taken together, the data from these 3 studies unequivocally demonstrate the importance of both triglyceride and small, dense LDL particles as predictors of coronary artery disease in middle-aged Caucasian men and women.

### Table I

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
</tr>
<tr>
<td></td>
<td>Univariate</td>
</tr>
<tr>
<td>Physicians’ Health Study25</td>
<td>1.4*</td>
</tr>
<tr>
<td>Univariate</td>
<td>(100-mg/dL increase)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.3*</td>
</tr>
<tr>
<td>Quebec Cardiovascular Study27</td>
<td>1.3</td>
</tr>
<tr>
<td>Univariate</td>
<td>(−1-SD increase)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>−5.1 Å*</td>
</tr>
<tr>
<td>Stanford Five-City Study26</td>
<td>—</td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
</tr>
</tbody>
</table>

*p <0.01; †p <0.05.

CHD = coronary heart disease; LDL = low-density lipoprotein; SD = standard deviation.

### SUMMARY AND CONCLUSIONS

Meta-analysis of data from population-based prospective studies has demonstrated that increased plasma triglyceride is associated with a 32% increase in risk of cardiovascular disease in men and a 76% increase in risk of cardiovascular disease in women. After adjustment for HDL cholesterol and other risk factors, these risks were decreased to a 14% increase in men and a 37% increase in women but remained statistically significant. These results, based on more than 46,400 men and 10,800 women, show that plasma triglyceride is an independent risk factor for cardiovascular disease. More recent prospective epidemiologic studies have also shown that plasma triglyceride and LDL particle size, 2 highly interrelated risk factors, predicted subsequent coronary artery disease in 3 different Caucasian populations.

These results demonstrate the growing recognition of the importance of triglyceride as a risk factor for cardiovascular disease and the urgent need for clinical trials to determine whether lowering plasma triglyceride levels will decrease disease risk.

10. Bottonier LE, Carlson LA. Risk factors for death for males and females: a


