Cardiovascular Disease Mortality in Familial Forms of Hypertriglyceridemia: A 20-Year Prospective Study

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Background—Familial combined hyperlipidemia (FCHL) and familial hypertriglyceridemia (FHTG) are 2 of the most common familial forms of hyperlipidemia. There is a paucity of prospective data concerning the risk of cardiovascular disease (CVD) in such families. The purposes of this study were to estimate 20-year total and CVD mortality risk among relatives in these families and to evaluate plasma triglyceride as a predictor of death.

Methods and Results—The study was based on lipid and medical history data from 101 families ascertained in 2 studies conducted in the early 1970s. Vital status and cause of death was determined during 1993 to 1997 for 685 family members, including first-degree relatives of the probands and spouse control subjects. Compared with spouse control subjects, 20-year CVD mortality risk was increased among siblings and offspring in FCHL (relative risk 1.7, \( P = 0.02 \)) after adjustment for baseline covariates. In FHTG families, the relative risk was also 1.7 but was not statistically significant (\( P = 0.39 \)). Baseline triglyceride was associated with increased CVD mortality risk independent of total cholesterol among relatives in FHTG families (relative risk 2.7, \( P = 0.02 \)) but not in FCHL families (relative risk 1.5, \( P = 0.16 \)) after adjustment for baseline covariates.

Conclusions—This prospective study establishes that relatives in FCHL families are at increased risk for CVD mortality and illustrates the need for effective prevention strategies in this group. Baseline triglyceride level predicted subsequent CVD mortality among relatives in FHTG families, adding to the growing evidence for the importance of hypertriglyceridemia as a risk factor for CVD. (Circulation. 2000;101:2777-2782.)

Key Words: cardiovascular diseases ■ follow-up studies ■ hyperlipoproteinemia ■ lipids ■ mortality

The familial forms of hypertriglyceridemia, familial combined hyperlipidemia (FCHL) and familial “monogenic” hypertriglyceridemia (FHTG), are 2 common forms of familial hyperlipidemia among families with coronary heart disease (CHD).1-4 These well-established clinical disorders of lipid and lipoproteins were first characterized at the University of Washington in the early 1970s. The characteristics and estimated frequencies of these familial disorders were described2,5,6 on the basis of families of myocardial infarction survivors and families of hypertriglyceridemic patients without clinical CHD. Similar studies were performed in Finland during the same time period.7

There is a paucity of information about the long-term risk of cardiovascular disease (CVD) in the familial forms of hypertriglyceridemia. Cross-sectional data from the Seattle studies consistently demonstrated an increased prevalence of CHD among relatives of probands in families with FCHL.1,2 However, for FHTG, increased familial risk was found among families ascertained through myocardial infarction survivors3 but not among families ascertained through probands free of coronary artery disease.1 The incidence of CVD in these familial disorders has never been evaluated.

The common feature of FCHL and FHTG is elevated plasma triglyceride levels in relatives. Although the importance of elevated plasma cholesterol as a risk factor for CHD is indisputable,8,9 the role of triglyceride has been controversial for >3 decades10,11 and has been referred to as the “forgotten risk factor.”12 However, accumulating epidemiologic evidence1,3,14 strongly suggests that elevated triglyceride is associated with increased risk of CVD independent of HDL cholesterol. Recent findings from the Copenhagen Male Study revealed that increasing baseline triglyceride was associated with higher incidence of ischemic heart disease during an 8-year follow-up within each tertile of HDL.

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cholesterol.\textsuperscript{15} The association between triglyceride levels and risk of CVD has never been studied prospectively in the familial forms of hypertriglyceridemia.

The purpose of this study was to evaluate 20-year total mortality and cardiovascular mortality risk in families with FCHL and FHTG on the basis of 101 families originally studied in the early 1970s. Two questions were addressed: (1) is there increased risk for total mortality and for CVD mortality among first-degree relatives of probands in FCHL and FHTG families compared with spouse control subjects, and (2) does baseline triglyceride predict subsequent cardiovascular mortality among relatives in hypertriglyceridemic families?

**Methods**

**Family Ascertainment**

This analysis is based on 2 baseline family studies, both conducted at the University of Washington in the early 1970s. Baseline study \textsuperscript{1,2} identified families with FCHL or FHTG ascertained through probands who were myocardial infarction survivors; baseline study \textsuperscript{2} ascertained families through probands with hypertriglyceridemia but with no clinical evidence of coronary disease. Twenty-year follow-up on 101 families from baseline studies 1 and 2 are reported here. Of these, 62\% were classified as FCHL and 38\% were classified as FHTG at baseline.

Eligible family members for the mortality follow-up study were first-degree relatives of probands (parents, siblings, and offspring) and spouses of probands, siblings, and offspring, \textasciitilde18 years of age, who participated in 1 of the 2 baseline studies. This totaled 718 family members, including 435 first-degree relatives of probands and 283 spouse control subjects (Table 1).

**Baseline Data**

Family pedigrees were available from the baseline studies.\textsuperscript{1,2} Lipid determinations were based on fasting blood samples. In the early 1970s, total cholesterol was measured by AutoAnalyzer II method N-24a, and triglyceride level was determined by a semiautomated method modified from the procedures of Carlson.\textsuperscript{16,17} also with the use of the AutoAnalyzer. The triglyceride assay has been replaced with new methodology,\textsuperscript{18} and a comparison of the methods demonstrated a linear relation between the 2 sets of triglyceride values (Brunzell, unpublished data). This relation was used to convert the baseline triglyceride values to be comparable with current methodology. At baseline, study subjects completed a medical history questionnaire, including birth date, sex, smoking status, and self-reported diabetes, hypertension, and prior myocardial infarction.

**Follow-Up Procedures, Vital Status, and Cause-of-Death Classification**

Study subjects were designated “confirmed alive” at follow-up if they agreed to participate in the study by completing a personal medical history form and/or providing a blood sample or if they personally declined participation. Living subjects not contacted in person were categorized as “reported alive” on the basis of information supplied by family members. Deceased study subjects were designated “confirmed dead” on the basis of death certificates. If a copy of the death certificate could not be obtained, subjects were designated “reported dead” on the basis of information from family members. Vital status could not be determined for 29 (4\%) study subjects, and these were excluded. For the total mortality analysis, confirmed and reported deceased categories were combined, as were the confirmed living and reported living categories.

A modified version of the Cardiovascular Health Study protocol was used for cause-of-death classification.\textsuperscript{19} All medical records were prescreened by a research assistant and were blinded to the deceased subject’s lipid levels, presence or absence of hyperlipidemia diagnosis, family history of hyperlipidemia, and to all baseline study data and family relationship (relative of proband or unrelated spouse). Cause of death was classified for each deceased study subject by the study physician (M.J.M.), based on all available medical records. Cardiovascular death was defined as fatal myocardial infarction, CHD, atherosclerotic cerebral vascular accident (stroke), or peripheral vascular disease (aortic aneurysm, revascularization procedures). These categories were combined as CVD death, and deaths not attributed to CVD were combined as non-CVD deaths. Nineteen subjects whose deaths were not confirmed by death certificate were excluded from the CVD mortality analysis.

All study participants provided written informed consent at the time they were enrolled in the baseline studies in the early 1970s. For the follow-up study, the University of Washington Institutional Review Board approved the methods used to contact living family members and to obtain records on deceased subjects.\textsuperscript{20}

**Statistical Analysis**

The mortality analyses were performed with the use of Cox regression for censored survival data based on person-years of follow-up.\textsuperscript{21,22} The time variable was the subject’s age, so that each subject entered the follow-up analysis at the age he or she was ascertained to be in the early 1970s. Age at follow-up, defined as age at death for deceased subjects and age at study participation, refusal, or date reported living for living subjects, was the end point age for the analysis. With the use of this approach, all reported relative risks are adjusted for age. Since the survival ages of members of the same family may be correlated as the result of genetic or environmental similarities, modified standard error estimators that account for correlations between members of the same kindred were used.\textsuperscript{23}

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**TABLE 1. Baseline Characteristics of First-Degree Relatives and Spouse Control Subjects**

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>% Women</th>
<th>Mean Age±SD</th>
<th>Triglycerides, mg/dL</th>
<th>Total Cholesterol, mg/dL</th>
<th>Prior Myocardial Infarction</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Current Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial combined hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives of probands</td>
<td>287</td>
<td>52.3</td>
<td>46.4±15.7</td>
<td>202±281</td>
<td>246±62</td>
<td>8.7</td>
<td>6.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Spouse control subjects</td>
<td>195</td>
<td>58.5</td>
<td>47.4±11.4</td>
<td>134±111</td>
<td>225±43</td>
<td>7.3</td>
<td>3.1</td>
<td>16.2</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-degree relatives of probands</td>
<td>148</td>
<td>52.7</td>
<td>45.6±17.8</td>
<td>211±275</td>
<td>216±41</td>
<td>2.0</td>
<td>6.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Spouse control subjects</td>
<td>88</td>
<td>63.6</td>
<td>48.0±12.7</td>
<td>138±102</td>
<td>224±48</td>
<td>2.3</td>
<td>4.7</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*Fifteen subjects (5 relatives and 10 spouses) were missing lipid data at baseline. \textsuperscript{†}Twenty-one subjects (9 relatives and 12 spouses) missing baseline medical history data.
relative risks were also adjusted for covariates with the use of data from the baseline medical history questionnaire. For covariates in which the assumption of proportional hazards was not met, stratification adjustment was used.

Twenty-one study subjects were missing baseline medical history data, and these subjects were excluded from the survival analysis. Fifteen study subjects were missing baseline triglyceride and cholesterol determinations and were excluded from analyses that include these variables. Because the frequency distribution of triglyceride was skewed, a natural log transformation was used, and relative risks for a 1-unit increase in log triglyceride are reported.

Results

Baseline Data
Baseline characteristics of the 718 eligible study subjects are shown in Table 1. Among the first-degree relatives of probands, approximately half of the study subjects were women, whereas the proportions of female spouses were somewhat higher. Among the first-degree relatives, overall average ages varied from 46 to 48 years. By definition, mean baseline triglyceride levels were higher among relatives than spouse control subjects in the FCHL families and in the FHTG families (Table 1). Also, as expected, total plasma cholesterol levels were higher among relatives in FCHL families compared with both spouse control subjects and with relatives in FHTG families. Prior myocardial infarction at baseline was less frequent among both relatives and spouses in FHTG families compared with FCHL families. The prevalence of self-reported diabetes was higher among first-degree relatives in both types of families compared with spouse control subjects.

20-Year Mortality Among Relatives in FCHL and FHTG Families
In the FCHL families, 36% of siblings and offspring of probands were dead at follow-up compared with 29% of spouse control subjects in the same generations. On the basis of on the Cox regression model, a 40% increase in total mortality risk was seen among siblings and offspring compared with spouse control subjects, adjusting for sex, baseline study, and diabetes, hypertension, smoking, and prior myocardial infarction at baseline (Table 2). Among the FHTG families, the proportion of deceased siblings and offspring at follow-up was slightly lower than for spouse control subjects, and the relative risk for total mortality did not differ statistically from 1.0 ($P = 0.67$).

Siblings and offspring in FCHL families were at a 70% increased risk of CVD mortality compared with spouse control subjects (relative risk 1.7, 95% CI 1.1 to 2.7, $P = 0.02$), adjusting for sex, baseline study, and diabetes, hypertension, smoking, and prior myocardial infarction at baseline. Among FHTG families, the relative risk was also 1.7 but was not statistically significant (95% CI 0.50 to 5.9, $P = 0.39$), possibly because of the smaller sample size.

Triglyceride as a Risk Factor for CVD Mortality
Baseline triglyceride was a significant predictor of subsequent CVD mortality among families in this study. As shown in Figure 1, a positive association was seen between increasing baseline levels of triglyceride and age-standardized CVD mortality rate for relatives in all families. Adjusting for age,
sex, baseline study, baseline covariates, and type of family, a 1–natural log unit increase in triglyceride resulted in a statistically significant relative risk of 1.9 (P = 0.001) for cardiovascular death among first-degree relatives of probands (Table 3). This relative risk was reduced to 1.7 after adjusting for total cholesterol at baseline but remained statistically significant (P = 0.009). There was strong evidence that the relative risk for cholesterol varied with attained age, ranging from 2.9 at age 20 years to 0.96 at age 80 years, with adjustment for baseline covariates.

Since there were 17 family members with fasting triglyceride values >500 mg/dL, the analysis was repeated excluding these study subjects. The magnitude of the associations remained similar, although probability values were larger. Furthermore, in a sensitivity analysis, the results were only altered by the most extreme and implausible assumptions about eligible study subjects whose vital status or cause of death could not be determined.25

The relation between triglyceride and age-standardized rates for CVD mortality appeared to be different for relatives in FHTG families and FCHL families (Figure 2). After adjustment for baseline cholesterol levels, the association of baseline triglyceride and CVD mortality remained statistically significant for FHTG relatives but not for FCHL relatives. Deaths among FCHL relatives occurred over a wide age range, including premature deaths, whereas none of the CVD deaths were premature for FHTG relatives. There was little evidence for differences among study subjects from the 2 baseline studies (data not shown).

**Discussion**

This 20-year, prospective study of hypertriglyceridemic families demonstrated that first-degree relatives of probands in families with FCHL were at a statistically significant (70%) increased risk of CVD mortality compared with spouse control subjects. Because FCHL is one of the most common forms of hyperlipidemia among families with CHD, identifying FCHL families and implementing effective risk factor intervention strategies could have an important impact on CVD prevention. A similar but nonsignificant increased risk of cardiovascular mortality was seen among relatives in FHTG families. A larger sample of families or longer follow-up time will be needed to resolve this equivocal result for FHTG. Sample sizes also precluded determining whether the results differed for the 2 baseline studies.

Among FCHL families, the relative risk estimates reported here may be conservative if an autosomal dominant mode of inheritance is operating, as was proposed in baseline study 1.2 Under such a genetic model, only approximately half of the first-degree relatives of probands would be expected to carry a proposed disease susceptibility allele, reducing the apparent risk among all relatives combined in comparison with control subjects. Relative risk estimates also could be conservative if spouses in these families are at increased risk of CVD as the result of assortative mating of lifestyle and risk factors,26 although the sex differential inherent in using spouse control subjects could introduce other biases.

**TABLE 3. Baseline Triglyceride as Predictor of 20-Year Cardiovascular Disease Mortality Among First-Degree Relatives of Probands**

<table>
<thead>
<tr>
<th>Sample Size†</th>
<th>No. Died of CVD</th>
<th>Person-Years</th>
<th>Triglyceride Relative Risk* (95% CI)</th>
<th>Triglyceride Adjusted for Total Cholesterol‡ Relative Risk$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All families</td>
<td>401</td>
<td>66</td>
<td>7960</td>
<td>1.9§, P = 0.001 (1.3, 2.8)</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>264</td>
<td>45</td>
<td>5244</td>
<td>1.7, P = 0.06 (0.99, 3.0)</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>137</td>
<td>21</td>
<td>2716</td>
<td>2.9, P &lt; 0.001 (1.7, 5.2)</td>
</tr>
</tbody>
</table>

*Per 1–natural log unit increase; Cox regression analysis with adjustment by stratification for smoking and with adjustment for age, sex, baseline study, diabetes, hypertension, and prior myocardial infarction at baseline.

†Includes parents, siblings, and offspring. Excludes 4 relatives missing baseline triglyceride values.

‡By stratification.

§Further adjusted by stratification for family type.
The original classifications that defined familial hyperlipidemias in the 2 baseline studies were used in this analysis. Since that time, FCHL has been characterized by an overproduction of apolipoprotein B and has been associated with small, dense LDL.27–30 Both of these lipid disorders are risk factors for CHD31–35 and may underlie at least a portion of the increased familial risk of CVD mortality. Individuals with FHTG have been found to have increased hepatic triglyceride synthesis with secretion of triglyceride-rich lipoproteins.27,30 The increased triglyceride synthesis is associated with hepatic colic acid synthesis,36,37 possibly secondary to a partial block in intestinal bile acid absorption. Like bile acid–binding resins, this proposed block also may increase triglyceride synthesis. Although the association of baseline triglyceride and CVD mortality among relatives from FHTG families in this study was statistically significant and independent of total cholesterol (relative risk 2.7, \( P = 0.02 \)), how these metabolic processes might alter risk for CVD remains to be determined.

The genetic differences between FCHL and FHTG are not fully understood. Although no studies to date have investigated the molecular basis of FHTG, 2 recent reports based on families ascertained in Finland and in the Netherlands have suggested the existence of novel genes for FCHL on human chromosomes 138 and 11,39 respectively. Other studies have proposed that the clustering of lipid abnormalities in FCHL may be related to the insulin resistance syndrome and that mutations in the lipoprotein lipase gene and the hormone-sensitive lipase gene may be involved in FCHL.40–43 Baseline plasma triglyceride levels predicted subsequent CVD mortality among all relatives in these hypertriglyceridemic families (relative risk 1.9 for a 1-log unit increase in triglyceride [mg/dL]), and this result remained statistically significant after adjustment for total cholesterol. These relative risks are similar to those reported from population-based studies, including the Lipid Research Clinics Follow-up Study,44 the Physicians’ Health Study,31 and a meta-analysis of population-based, prospective epidemiological studies.13 Furthermore, the results presented here resemble 5-year mortality data recently reported from the Benzaflibrate Infarction Prevention Registry, in which the 4th and 5th quintiles of triglyceride were associated with increased risk of CHD mortality among both men and women.45 Because HDL cholesterol and apolipoprotein measurements were not available at the time of the baseline Seattle studies, the findings reported here must be interpreted cautiously. Even so, clinical trials are needed to determine if lowering triglyceride levels with the use of statins and/or fibrates, especially among patients with combined hyperlipidemia,46,47 will reduce subsequent risk of CVD.

In conclusion, this prospective study establishes that relatives in FCHL families are at increased risk for CVD mortality and illustrates the need for effective prevention strategies in this group. Baseline triglyceride levels predicted subsequent CVD mortality among relatives in FHTG families, adding to the growing evidence for the importance of hypertriglyceridemia as a risk factor for CVD.

**Acknowledgments**

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**References**


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