Coronary Artery Disease Risk in Familial Combined Hyperlipidemia and Familial Hypertriglyceridemia

A Case-Control Comparison From the National Heart, Lung, and Blood Institute Family Heart Study

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Background—Conventional wisdom suggests that a diagnosis of familial combined hyperlipidemia (FCHL) carries a substantially greater risk of premature coronary artery disease (CAD) than a diagnosis of familial hypertriglyceridemia (FHTG). However, no population-based studies have critically addressed this issue.

Methods and Results—FCHL and FHTG were diagnosed in 10.2% and 12.3% of 334 random control families and in 16.7% and 20.5% of 293 families with at least one case of premature CAD. The diagnosis of either FCHL or FHTG in an individual was associated with an odds ratio for CAD of 2.0 ($P=0.003$ and $0.002$, respectively). However, odds ratios for premature CAD associated with both lipid disorders decreased substantially and identically with further adjustment for hypertension, diabetes, and especially HDL cholesterol, triglycerides, or apolipoprotein B. Similar results were found for differences in carotid intima-medial thickness and ankle-brachial index. Metabolic syndrome was identified in 65% of FCHL and 71% of FHTG patients compared with 19% in controls without FCHL or FHTG and was associated with an odds ratio of 3.3 ($P<0.0001$). The increased prevalence of the metabolic syndrome alone could account for the elevated CAD risk associated with both FCHL and FHTG.

Conclusions—FCHL and FHTG appear more alike than dissimilar. Further, the risk of CAD in FCHL and FHTG was strongly related to features of the metabolic syndrome. These findings suggest that the hypertriglyceridemia in FHTG is not benign and may warrant a change in epidemiological, genetic, and clinical approaches to these lipid disorders. (Circulation. 2003;108:519-523.)

Key Words: coronary disease • genetics • lipoproteins • epidemiology

Conventional wisdom suggests that patients diagnosed with familial combined hyperlipidemia (FCHL) are at greater risk for coronary artery disease (CAD) than patients with familial hypertriglyceridemia (FHTG) and that these are distinct, separate syndromes. Clinicians frequently, therefore, consider hypertriglyceridemia in FHTG as benign but associated with substantial risk in FCHL. This perception appears to be based primarily on a single cross-sectional analysis of premature myocardial infarction history among families identified from lipid clinic patients.

Recently, Austin et al. conducted a prospective follow-up of CAD mortality in these same FCHL and FHTG families included together with FCHL and FHTG families ascertained from the seminal studies of Goldstein et al. Relative risks for total cardiovascular death (comparing siblings and offspring of probands versus spouse controls) were similar for FCHL and FHTG (odds ratio 1.7 for both, although the risk for FHTG was nonsignificant, presumably due to fewer cases). Interestingly, however, an increase in plasma triglycerides was associated with greater cardiovascular risk in the FHTG families compared with risk in FCHL families.

Surveys among patients selected for premature CAD have identified FCHL and FHTG as among the most common of familial lipid disorders with prevalences reported from 11% to 14% for FCHL and 5.2% to 15% for FHTG. Nevertheless, without concomitant assessment of the prevalence of FCHL and FHTG in a control population, no direct estimates of risk are possible from such surveys. Indeed, to date there have been no population-based studies providing either the prevalence of these two common lipid disorders in the general population or the
associated coronary risk. The population-based NHLBI Family Heart Study provides an opportunity to address both these questions and to examine factors associated with individual coronary risk.

## Methods

The NHLBI Family Heart Study was a multicenter, population-based study designed to identify and evaluate genetic and nongenetic determinants of CAD, preclinical atherosclerosis, and cardiovascular disease risk factors. After written informed consent was obtained, a total of 5381 subjects from 1245 families (588 general population families selected at random and 657 high CAD risk families) completed an extensive clinical examination. Blood was obtained after an overnight fast and a single plasma lipid determination was made with LDL calculated from the Friedewald equation for triglycerides under 400 and by β-quantification using ultracentrifugation for higher plasma triglycerides.

For purposes of this study, only parents, siblings, or offspring of Family Heart Study probands were considered. Premature CAD cases were defined as males with self-reported myocardial infarction, angiplasty, or coronary bypass surgery by age 55 or females with such events by age 65. These premature CAD cases were ascertained from both randomly selected families from the general population (22.6% of male and 24.8% of female cases) and a group of high-risk families (77.4% of male and 78.3% of female cases). The ages of the cases ranged from 34 to 89 years at the time of examination. Examined relatives of premature CAD cases constituted case families. Hospital records were sought for all 333 CAD cases and confirmed in 282; CAD was confirmed in 94.7%.

All analyses were performed with SAS version 8.2 for the PC (SAS Institute Inc.). Significance of univariate odds ratios were determined by the chi-square test. Odds ratios adjusted for other risk factors were determined using multiple logistic regression as implemented in PROC LOGISTIC. Analysis of variance as implemented in PROC GLM was used to compare means in three groups for continuous variables. Adjustment of hypertension and diabetes prevalences for BMI and other variables was performed with PROC GENMOD using a logistic link function and binary distribution. Potential effects of subject relatedness were tested using PROC GENMOD. As no material differences were noted, probability values obtained with PROC LOGISTIC and PROC GLM are reported.

## Results

Individual cases of premature CAD included 212 men and 121 women from 293 case families. Individual controls were 774 men and 969 women from 334 control families. Features of the families are shown in Table 1. Both FCHL (univariate OR 1.77, \(P=0.016, 95\% CI 1.11\) to 2.83) and FHTG (univariate OR 1.84, \(P=0.005, 95\% CI 1.19\) to 2.84) were more common among case families (each family treated as a single observation). Among currently on lipid-lowering medications. None of the 147 FHTG subjects reported taking lipid-lowering medications. One family with two or more LDL cholesterol levels suggestive of familial hypercholesterolemia based on previously published criteria (LDL ≥260 mg/dL in one and at least 206 mg/dL in another) was excluded from consideration of a diagnosis of FCHL or FHTG.

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families with FCHL, the distribution of phenotypes (2a = 30.1%, 2b = 12.8%, 4 = 57.1%) was not significantly different comparing case and control families.

Individual risk factors in the 333 premature CAD cases and 1743 controls are shown in Table 2. A total of 33 premature CAD cases were diagnosed with FCHL (9.91%) compared with 36 premature CAD cases (10.81%) and 111 controls with a univariate odds ratio with 100 (5.74%) among controls with a univariate odds ratio of 1.81 (P = 0.0044, 95% CI 1.20 to 2.73). Estimated premature CAD risk associated with FHTG was virtually identical, with 36 premature CAD cases (10.81%) and 111 controls (6.37%) being diagnosed with FHTG (OR = 1.94, 95% CI 1.26 to 2.99). Age of onset of CAD was not different comparing FCHL and FHTG in this population. In a further examination of individual risk, the diagnoses of FCHL or FHTG were entered initially into a multiple logistic regression equation with age and gender as the only other covariates included in the model.
TABLE 4. Elements of the Metabolic Syndrome, Common Carotid IMT (CC IMT), and Ankle-Brachial Index (ABI) in All Subjects (With or Without CAD) Having FCHL or FHTG, and in Random Controls Without FCHL or FHTG

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>FCHL</th>
<th>FHTG</th>
<th>1 vs 2</th>
<th>1 vs 3</th>
<th>2 vs 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1532)</td>
<td>(n=133)</td>
<td>(n=147)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49.6±14.7</td>
<td>52.9±14.2</td>
<td>53.9±13.8</td>
<td>0.012</td>
<td>0.0006</td>
<td>0.56</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>55.0</td>
<td>53.4</td>
<td>59.2</td>
<td>0.72</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>BMI (1364, 115, 129)*</td>
<td>27.3±5.4</td>
<td>29.5±5.3</td>
<td>29.5±5.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.98</td>
</tr>
<tr>
<td>Waist, cm (1351, 114, 129)*</td>
<td>95.9±15.3</td>
<td>101.9±15.6</td>
<td>104±14.7</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.25</td>
</tr>
<tr>
<td>Cigarette smoking (ever), %</td>
<td>34.3</td>
<td>45.1</td>
<td>40.8</td>
<td>0.013</td>
<td>0.12</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>22.9</td>
<td>44.4</td>
<td>42.9</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>5.9</td>
<td>19.5</td>
<td>23.1</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.27</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>196±37</td>
<td>247±45</td>
<td>221±36</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>117±63</td>
<td>258±168</td>
<td>298±147</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0009</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>53.0±16.1</td>
<td>43.0±12.6</td>
<td>43.2±12.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.94</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>120±34</td>
<td>153±45</td>
<td>119±34</td>
<td>&lt;0.0001</td>
<td>0.80</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ApoA1, mg/dL (374, 56, 61)</td>
<td>133±27</td>
<td>120±22</td>
<td>128±28</td>
<td>0.0012</td>
<td>0.21</td>
<td>0.11</td>
</tr>
<tr>
<td>ApoB, mg/dL (374, 56, 61)</td>
<td>103±25</td>
<td>141±29</td>
<td>122±24</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>97.6±27.1</td>
<td>113±52.8</td>
<td>111±42.8</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.59</td>
</tr>
<tr>
<td>Insulin, μU/mL</td>
<td>11.3±30.2</td>
<td>17.7±18.6</td>
<td>17.1±20.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.37</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.23±1.42</td>
<td>5.87±1.45</td>
<td>5.76±1.46</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.52</td>
</tr>
<tr>
<td>PAI-1, ng/mL (1339, 116, 131)*</td>
<td>25.3±34.0</td>
<td>47.9±47.0</td>
<td>53.6±53.2</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.74</td>
</tr>
<tr>
<td>CC IMT, mm (1238, 101, 121)*</td>
<td>0.645±0.182</td>
<td>0.724±0.209</td>
<td>0.690±0.185</td>
<td>&lt;0.0001</td>
<td>0.010</td>
<td>0.16</td>
</tr>
<tr>
<td>ABI &lt;0.9, % (1049, 98, 106)*</td>
<td>2.2</td>
<td>8.2</td>
<td>3.8</td>
<td>0.0006</td>
<td>0.34</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Shown are mean±SD. Triglycerides, insulin, and PAI-1 were log transformed for P-value testing.

*Numbers of measurements available for controls, FCHL, and FHTG, respectively, are shown in parentheses where values were missing.

Contrary to the expectation of greater risk for FCHL as compared with FHTG, we found virtually identical risks of premature CAD associated with these two common lipid disorders. Increased CAD risk in FCHL is frequently attributed to elevated production of VLDL and/or LDL. The lack of CAD risk associated with LDL cholesterol in our study and the strong and equal dependencies on triglycerides, apoB, HDL cholesterol, hypertension, and diabetes are therefore even more remarkable. Furthermore, both conditions were equally associated with virtually all elements of the metabolic syndrome. The finding of increased carotid IMT and ankle-brachial index in FCHL and FHTG patients that became nonsignificant after correction for HDL cholesterol, hypertension, and diabetes further suggests that atherosclerosis risk associated with FCHL and FHTG is transmitted primarily together with these major components of the metabolic syndrome.

Our estimates of premature CAD risk associated with FCHL and FHTG appear lower than might have been expected based on the original cross-sectional, largely descriptive Seattle studies of MI survivors and families of lipid clinic patients. However, our risk estimates are nearly identical to results based on prospective follow-up of these same families in which only a modest 70% increase in risk was observed. In the Seattle studies, the proband had to have total cholesterol or triglyceride levels above the 92.5th percentile, whereas for other relatives, a 95th percentile cutoff was used. In addition, at least one relative was required to have a 99th percentile lipid abnormality, leading to inclusion of some families with very high serum cholesterol levels. If some of these families had familial hypercholesterolemia with mixed phenotypes, as may be seen in some cases, higher coronary risks might be expected. We elected in the present study to use 90th percentile cut points and to exclude a single family with members having LDL levels suggestive of familial hypercholesterolemia. This approach has become the most commonly utilized definition of FCHL.

The prevalence of FCHL (5.7%) that we found among individuals in our randomly ascertained population is considerably higher than the 0.5% to 2% estimates for FCHL from some studies using 95th percentile lipid cutoffs. When we used 95th percentile total cholesterol and triglyceride cutoffs and required at least two different phenotypes, we found prevalences of FCHL of 4.5% and 3.27% in our cases and controls, respectively (OR for CAD 1.40, 95% CI 0.78 to 2.50; P=0.26). FHTG prevalences were 5.41% and 1.49%, respectively (OR for CAD 3.77, 95% CI 2.04 to 6.96; P<0.0001). Furthermore, when we defined FHTG using 95th percentile cutoffs, further correction for hypertension, diabetes, or LDL diminished but did not remove the risk associated with FHTG (data not shown), whereas FCHL remained nonsignificant. These findings further strengthen our observation that the elevated triglycerides in FHTG are not benign.

In contrast to the unexpectedly high rates of FCHL and FHTG in our randomly ascertained, general population, the prevalences of these lipid disorders among our premature coronary cases were similar to other series. Thus, the relatively low odds...
ratios for premature CAD risk associated with FCHL and FHTG in our study are primarily due to unexpectedly high prevalence of these lipid disorders in the CAD-free, control population.

FCHL is metabolically heterogeneous. Whereas overproduction of VLDL, with or without overproduction of LDL, appears to be the most common kinetic mechanism in FCHL probands, at least one FCHL family has been clearly documented with impaired removal of both VLDL and LDL. The few investigations comparing kinetics in families with FCHL and FHTG found increased VLDL production most commonly in both with few kinetic differences. Whereas impaired processing of VLDL makes heterozygous lipoprotein lipase deficiency an obvious candidate for FHTG, some families with FCHL appear to have this abnormality and may even show overproduction of VLDL as a result. Thus, from studies to date, kinetic mechanisms do not clearly distinguish FCHL from FHTG.

Our findings that a large percent of both FCHL and FHTG subjects also met diagnostic criteria for metabolic syndrome, and that CAD risk for both (using 90th percentile LDL and triglyceride cutoffs) was eliminated when metabolic syndrome was included in logistic models, suggests one or more shared etiological features such as increased intraabdominal fat. The persistence of differences between controls and FCHL or FHTG in our study and by others after adjustment for BMI and waist circumference is consistent with additional etiological factors.

In conclusion, FCHL and FHTG appear to be more alike than distinct in their prevalence, their metabolic profile, associated risk factors, and associated risk of premature CAD. Clinically, identification and treatment of metabolic syndrome (including all lipid abnormalities) may yield greater benefits than rigorous differential diagnosis of FCHL or FHTG because most of the associated coronary risk appears to be subsumed by features of the metabolic syndrome. These findings may warrant a change in epidemiological, genetic, and clinical approaches to FCHL and FHTG, recognizing that elevations of plasma triglycerides are not benign even when high LDL is not found in the family.

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References