Predicting Coronary Heart Disease Risk Using Multiple Lipid Measures*

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Principal component analysis was used to summarize variations among 7 lipid measures included in the Framingham Offspring Study (n = 2,694). An overall measure combining information from the 7 lipids was compared with conventional lipid measures in adjusted survival analyses and was found to be a superior predictor of coronary heart disease risk. ©2005 by Excerpta Medica Inc.

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Although many studies have sought independent lipid risk factors, none has evaluated how a whole suite of lipid measures (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, very LDL [VLDL] cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B) could be used together to estimate coronary heart disease risk.[1–4] Such an evaluation is possible using factor analysis, specifically principal component analysis,[5] which attempts to explain variation in the data using as few factors as possible and allows for the reduction of many variables into a single new variable. This approach using principal components will help clinicians use all available lipid information to inform patients about their future coronary heart disease risk.

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Longitudinal analysis of the public-use Framingham Offspring Study was performed using the third examination cycle (1984 to 1987) as the baseline and following the cohort through the sixth examination (1996 to 1997). Details of the design of the Framingham Offspring Study have been previously published.[6] Our cohort consisted of 2,694 patients aged ≥30 years in 1984 to 1987, with a mean follow-up of 10.6 years. Patients with coronary heart disease at baseline were excluded. Medical histories, physical examinations, and laboratory analyses performed from 1984 to 1987 were used to characterize participants. Patients who smoked cigarettes during the previous year were classified as smokers. Blood pressure measurements were taken twice and the average used in our analyses. Participants with systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or who used antihypertensive medications were classified as having hypertension. Those with fasting blood glucose >140 mg/dl or who were being treated with insulin or oral hypoglycemic agents were categorized as having diabetes. The use of antilipemic agents recorded at the third, fourth (1987 to 1990), or fifth (1991 to 1995) examination was noted and a time-dependent covariate created to describe treatment with antilipemic agents. Total plasma cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B were available for analysis in the 1984 to1987 data collection period.[7–10] Only patients who had fasted for ≥12 hours before their blood was drawn were included in our study.

Coronary heart disease was defined as the occurrence of angina pectoris, recognized and unrecognized myocardial infarction, coronary insufficiency, and coronary heart disease death. Criteria for each manifestation of coronary heart disease have been described elsewhere.[11] A panel of 3 investigators had to agree that a definite manifestation of coronary heart disease had occurred before a diagnosis was assigned.

For principal component analyses and survival analyses, we used the statistical package SAS (SAS Institute Inc., Cary, North Carolina). All survival analyses used gender, age, hypertension, diabetes, smoking status, and treatment with antilipemic agents as covariates. Because their distributions were skewed, we applied logarithmic transformations to VLDL cholesterol and triglycerides to normalize the data. Principal component analysis was used to summarize variations among 7 lipid measures: total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B. Principal component analysis creates new variables (principal components) that explain as much of the total variation in the data set as possible with the fewest number of new variables. Each principal component is a weighted linear combination of the original variables that is uncorrelated with any of the other principal components. For survival analyses, the first 3 principal components were divided into 2 classes each on the basis of whether a value was greater than or less than the median for that principal component. A new variable, called the multiple lipid measure, was created by dividing the first principal component into 3 classes (low: first and second quartile; medium: third quartile; high: fourth quartile). The multiple lipid measure was made into a 3-class variable to determine

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TABLE 1 Eigenvectors (factor loadings for standardized variables) for the First Three Principal Components

Variable	Principal Component (PC)		
	PC 1	PC 2	PC 3
Total cholesterol	0.394	0.462	−0.051
HDL cholesterol	−0.330	0.513	0.224
LDL cholesterol	0.364	0.390	−0.460
VLDL cholesterol	0.405	−0.151	0.543
Triglycerides	0.438	−0.134	0.454
Apolipoprotein A-I	−0.206	0.548	0.465
Apolipoprotein B	0.453	0.173	−0.136

TABLE 2 Survival Analyses Using Different Lipid Measures to Predict Coronary Heart Disease Risk*

Variable	Hazard Ratio	95% Confidence Interval
Multiple lipid measure		
Low	1.00	—
Medium	2.64	1.47–4.73
High	3.17	1.80–5.58
Total cholesterol (mg/dl)		
<200	1.00	—
≥200	1.82	1.12–2.95
HDL cholesterol (mg/dl)		
<40	1.81	1.20–2.73
≥40	1.00	—
LDL cholesterol (mg/dl)		
<130	1.00	—
≥130 and <160	1.33	0.83–2.14
≥160	1.64	1.02–2.66
Total cholesterol/HDL cholesterol ratio		
≤5	1.00	—
>5	2.03	1.35–3.04
Apolipoprotein B (mg/dl)		
<120	1.00	—
≥120 (4th quartile)	1.71	1.15–2.53
Apolipoprotein B/apolipoprotein A-I ratio		
<0.91	1.00	—
≥0.91 (4th quartile)	1.75	1.17–2.61

*Adjusted for gender, age, hypertension, diabetes, smoking status, and antilipemic agents.

if coronary heart disease risk increased progressively from the low to the high class.

For comparison, survival analyses were computed using total cholesterol, HDL cholesterol, the total cholesterol/HDL cholesterol ratio, apolipoprotein B, and the apolipoprotein B/apolipoprotein A-I ratio as dichotomous variables predicting coronary heart disease risk. Survival analysis using LDL cholesterol as a dichotomous variable was not significant because of the continuous nature of the relation between LDL cholesterol and coronary heart disease risk over a broad range of LDL cholesterol levels. Hence, we defined LDL cholesterol as a 3-level variable for survival analysis predicting coronary heart disease risk.

Principal component analysis of total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, apolipoprotein A-I, and apolipoprotein B produced 3 principal components that each explained >5% of the variation in the suite of lipid measures. Principal component 1 explained 49.1% of the total variation, principal component 2 explained 26.9%, and principal component 3 explained 13.6%. Eigenvectors (factor loadings for standardized variables) for these principal components are listed in Table 1. Adjusted survival analyses showed principal component 1 (as a dichotomous variable) to be a strong predictor of coronary heart disease risk (hazard ratio 2.91, 95% confidence interval 1.71 to 4.95), but not principal component 2 or principal component 3. Hence, we focused on maximizing the amount of information contained in principal component 1 and redefined it as a 3-class variable called the multiple lipid measure. Compared with the low class of the multiple lipid measure, the medium and high levels had significantly greater hazard ratios (Table 2).

Total cholesterol and HDL cholesterol are relatively good predictors of coronary heart disease risk when each is used alone (Table 2). LDL cholesterol is not as good a predictor when LDL cholesterol ≥160 mg/dl is compared with LDL cholesterol <130 mg/dl. When we used LDL cholesterol <100 mg/dl as the reference, the hazard ratio for LDL cholesterol ≥160 mg/dl increased but was no longer significant. We also tested 2 ratio measures, the total cholesterol/HDL cholesterol ratio and the apolipoprotein B/apolipoprotein A-I ratio, as a predictors of coronary heart disease risk. None of the 6 methods we used for comparison had a hazard ratio equal to that obtained using the multiple lipid measure.

Mean values for patient lipids, by multiple lipid measure class, are listed in Table 3. Class means for total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, and apolipoprotein B increase progressively as one goes from low to medium to high values of the multiple lipid measure. Similarly, class means for HDL cholesterol and apolipoprotein A-I decrease progressively as the multiple lipid measure goes from low to medium to high values. Table 4 provides more detailed information on the distribution of the cohort across multiple lipid measure–LDL cholesterol classes. Of particular interest is that patients with LDL cholesterol from 130 to 159 mg/dl can be in any of the multiple lipid measure classes. For these patients, the assessment of coronary heart disease risk is very different when the multiple lipid measure is used rather than LDL cholesterol alone.

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The National Cholesterol Education Program Adult Treatment Panel III report[12] used a hierarchy of lipid measures to make a risk assessment. However, in general, it used HDL cholesterol, LDL cholesterol, and triglycerides singly to characterize cardiovascular disease risk. VLDL cholesterol is believed to be im-

TABLE 3 Mean Lipid Measures by Classes of the Multiple Lipid Measure

Variable	Multiple Lipid Measure Class		
	Low	Medium	High
Percentage of cohort	50%	25%	25%
Coronary heart disease incidence	1.3%	5.3%	8.0%
Total cholesterol (mg/dl)*	189 ± 30	218 ± 28	252 ± 36
HDL cholesterol (mg/dl)	59 ± 14	47 ± 11	41 ± 9
LDL cholesterol (mg/dl)	113 ± 26	144 ± 26	164 ± 37
LDL cholesterol† (mg/dl)	15	26	42
Triglycerides‡ (mg/dl)	67	115	189
Apolipoprotein A-I (mg/dl)	160 ± 37	141 ± 32	132 ± 29
Apolipoprotein B (mg/dl)	80 ± 18	108 ± 19	139 ± 32

*Mean ± SD.
†SD available only for the logarithm of VLDL cholesterol.
‡SD available only for the logarithm of triglycerides.

TABLE 4 Percentage of Cohort in Each Multiple Lipid Measure–LDL Cholesterol Class

LDL Cholesterol (mg/dl)	Multiple Lipid Measure Class			
	Low	Medium	High	Total
<100	15.2%	1.2%	1.2%	17.6%
100–129	21.3%	5.5%	2.5%	29.3%
130–159	11.4%	11.8%	6.9%	30.1%
≥160	2.1%	6.5%	14.4%	23.0%
Total	50.0%	25.0%	25.0%	100%

portant because it is a measure of atherogenic remnant lipoproteins. The National Cholesterol Education Program Adult Treatment Panel III report did not make use of apolipoprotein A-I or apolipoprotein B in risk assessment.

In contrast, we used principal component analysis to define what we call the multiple lipid measure. The multiple lipid measure is a better predictor in this cohort than any of the currently used patient measures or ratios of 2 lipid measures. Patients with intermediate levels of some lipids, such as LDL cholesterol, may have questionable levels of risk. These patients could receive more accurate risk assessments using the multiple lipid measure method. This method can also identify more subjects at risk. Although only 23% of the cohort had LDL cholesterol ≥160 mg/dl, 50% had medium or high levels of the multiple lipid measure and were found to be at risk for coronary heart disease.

Like the total cholesterol/HDL cholesterol ratio or the apolipoprotein B/apolipoprotein A-I ratio, the multiple lipid measure must be calculated from the patient's lipids measured by a laboratory. At this point of exploration, the multiple lipid measure is not ready for use by clinicians. However, the data suggest that future research creating a computable risk score from multiple lipids is possible and beneficial.

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