Improving the Prediction of Cardiovascular Risk: Interaction Between LDL and HDL Cholesterol

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Background. The ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol (or the ratio of low-density lipoprotein [LDL] to HDL) is currently advocated to estimate the coronary risk associated with LDL and HDL cholesterol levels.
Methods. We analyzed the relation between LDL and HDL cholesterol levels to predict the risk of future coronary events. Using data from the Lipid Research Clinics Follow-up Cohort, we developed multivariate equations to predict coronary deaths among 4684 men and women followed for approximately 12 years. We used these equations to compare the predictive power of the LDL/HDL ratio with the independent effects of LDL and HDL and an LDL-HDL interaction term. We then used each model to forecast the 10-year risk of coronary death based on various lipid levels after adjustment for conventional risk factors (*eg*, blood pressure, gender, cigarette smoking).
Results. Levels of LDL and HDL and the interaction between them are all independent risk factors for coronary death. The benefits of increasing HDL are strongest among persons with high LDL. Conversely, the benefits of decreasing LDL are greatest among those with low HDL. We confirmed these observations in a published dataset showing the effects of treatment of hyperlipidemia. Predictions of benefits of treatment that were based on interaction of LDL and HDL were more accurate than predictions without interaction.
Conclusions. The LDL/HDL ratio alone may not fully capture the complex interaction between LDL and HDL and the relation of each to coronary risk.
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Key words: LDL cholesterol, HDL cholesterol, cardiovascular risk, LDL/HDL ratio.

The importance of both low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels for identification of individuals at increased risk of coronary heart disease (CHD) is now well established. Data from observational cohort studies clearly demonstrate that both lipid parameters are important independent risk factors for future coronary events.[1–6] Moreover, recent clinical trial results have also shown that changes in both LDL and HDL levels are associated with the observed reduction in coronary events after lipid therapy.[7–12] Clinical guidelines for lipid screening and treatment have recognized the importance of risk stratification based on LDL and HDL levels.[13–15] Some even recommend using the total cholesterol/HDL ratio or the LDL/HDL ratio as a simple means to identify high-risk individuals.[15] This ratio has been repeatedly shown to be a strong independent risk factor for coronary events and a substantial improvement over either LDL or HDL alone.[16–18]

Although the LDL/HDL ratio greatly simplifies cardiac risk assessment, it remains to be determined whether this simple ratio accurately captures all of the available risk information contained in LDL and HDL. For instance, individuals with an elevated LDL/HDL ratio of 5 may have a particularly low-HDL level, a high-LDL level or more modest abnormalities of both. Given a ratio of 5, it is also unclear whether depressed HDL, elevated LDL or combined abnormalities are associated with the same risk for future coronary events.

To better understand the relation between LDL and HDL cholesterol, we have used data from the Lipid Research Clinics Follow-up Cohort to describe this relation and to explore the possibility that the LDL/HDL ratio may oversimplify the quantitative importance of

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the individual lipid parameters. We demonstrate that a more complex interaction may better fit the outcomes observed among the LRC Follow-up Cohort, and we then forecast the benefits of lipid modification using the simple LDL/HDL ratio or the more complex interaction approach. Finally, we use recently published data to compare the accuracy of each model to predict the benefits of simvastatin treatment among individuals with specific lipid abnormalities.[19]

Methods

We used multivariate logistic analyses to identify independent predictors of future coronary events among individuals enrolled in the Lipid Research Clinics (LRC) Program Prevalence Follow-up Cohort. The present analysis compares a model using the ratio of LDL and HDL cholesterol with a model that uses the independent contribution of LDL and HDL cholesterol, as well as an LDL-HDL interaction term. Strictly speaking, the LDL/HDL model is the interaction of LDL with 1/HDL, with the main effects omitted, whereas the interaction model includes the main effects. For convenience, we refer to the former as the LDL/HDL model and the latter as the interaction model.

The LRC prevalence studies were conducted from 1972 to 1976 in 10 clinics in North America to determine the prevalence of dyslipoproteinemias and related factors.[20–22] A 15% random sample of participants (including those with normal and abnormal lipid values), plus selected patients with abnormal lipid values (determined primarily by sex- and age-specific threshold levels of plasma cholesterol and triglycerides), were invited to return for a second visit.[23] We did not include the selected group with abnormal lipid values in our determination of the logistic coefficients. Rather, we focused our analysis on the 15% random sample as being most representative of the full distribution of lipid values in the population.

Between 1972 and 1975, subjects invited for a second visit underwent an extensive medical examination. Study personnel then attempted to contact subjects annually during the decade from July 1977 to June 1987 to determine vital status. All fatalities were carefully classified by cause of death. A "CHD Death" was any death attributable to suspected or definite coronary heart disease.

Of the randomly selected subjects who returned for the second visit, we excluded subjects taking digitalis or antiarrhythmic and lipid-altering medications. We also removed pregnant women from our analysis, as well as subjects whose blood samples were collected within 12 hours after eating or were frozen before being analyzed. These exclusions left 4684 subjects, age 30 or older, of whom 97 eventually died of definite or suspected CHD during an average follow-up of 10 years.

To derive the 10-year logistic regression models, variables associated in univariate analyses with CHD death were entered into a forward stepwise logistic regression model. Selected variables included sex, age, current cigarette smoking, mean blood pressure (defined as 1/3 of the systolic blood pressure plus 2/3 of the diastolic blood pressure), presence of diagnosed cardiovascular disease, diabetes (use of diabetes drugs or fasting blood glucose $\geq$120 mg/dL) and the natural log of the LDL/HDL ratio. The interaction model was produced by replacing the LDL/HDL ratio of the first model with three terms: 1) the natural log of LDL-cholesterol; 2) the natural log of HDL-cholesterol; and 3) an interaction term multiplying the natural log of the LDL-cholesterol by the natural log of the HDL-cholesterol. The independent risk factors included in each of the two models are presented in Table 1.

Model Comparison

We used several methods to compare models arising from the same data. The Akaike's (AIC) and Schwarz criteria penalize models proportionally to their level of complexity, favoring less complex over more complex models. Of these two methods, the Schwarz criterion is most critical of complex models. Using either criterion, smaller values are associated with better-fitting models.

Validation

A recently published subanalysis of the Scandinavian Simvastatin Survival Study[19] (4S) provided a unique opportunity to compare the accuracy of each model to predict the benefits of lipid therapy. This study provided the necessary risk factor data for each model, for patients with isolated elevated LDL cholesterol compared with those who had the lipid triad: increased LDL plus HDL $<$1 mmol/liter (39 mg/dL) and triglycerides $>$1.80 mmol/liter (159 mg/dL). The study also provided the

TABLE 1. Odds Ratio (and 95% Wald Confidence Interval) for Risk Factors Used in the LDL/HDL and Interaction Models

Risk Factors	Model: LDL/HDL	Model: Interaction
Sex	0.45 (0.27–0.74)	0.37 (0.22–0.62)
Age	1.08 (1.06–1.10)	1.08 (1.06–1.10)
Cigarette smoking	1.91 (1.19–3.06)	1.97 (1.22–3.17)
Mean blood pressure	1.03 (1.02–1.05)	1.03 (1.02–1.05)
Diabetes	3.31 (1.83–5.97)	3.56 (1.96–6.49)
Cardiovascular disease	3.72 (2.23–6.21)	4.06 (2.41–6.82)
LDL/HDL*	5.07 (2.91–8.82)	. . .
LDL*	. . .	23.16 (7.96–67.36)
HDL*	. . .	51.54 (2.52–999.99)
LDL × HDL interaction*	. . .	0.03 (0.00–0.24)

LDL = low-density lipoprotein; HDL = high-density lipoprotein.
* Natural log transformation of LDL and HDL.

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reduction in coronary deaths with simvastatin use for each subpopulation (after 5 years of follow-up). We used the risk factor data plus the change in blood lipids to predict the outcomes in each subpopulation using the LDL/HDL and the interaction models.

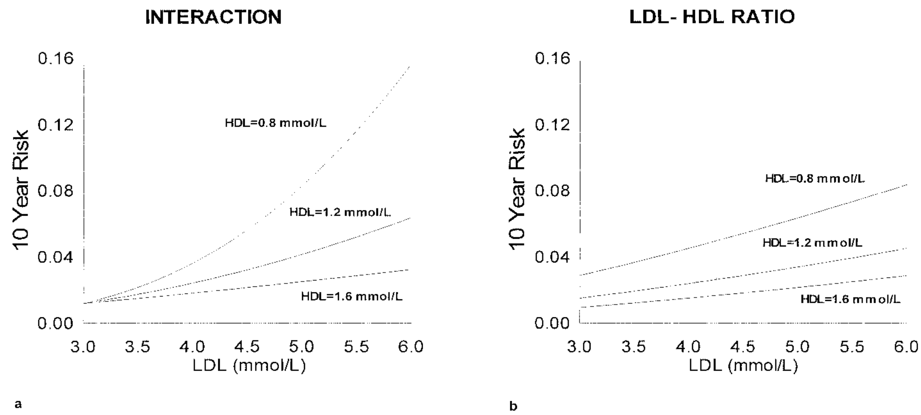

FIGURE 1. The 10-year risk of coronary death is forecasted for changes in LDL across specified HDL values. Using the complex "interaction model" (a) the benefits of reducing LDL are amplified in the presence of lower HDL levels, compared with (b) the simple "LDL/HDL ratio model."

Ten-Year Risk Predictions of the LDL/HDL and Interaction Models

We compared the forecasted 10-year risk of coronary death predicted by each of the models across various levels of LDL and HDL cholesterol for a hypothetical 55-year-old male with baseline blood pressure of 145/85 and no other coronary risk factors. We then compared the predicted benefits of lipid modification such as lowering LDL or raising HDL cholesterol levels using either model.

Results

Risk factors for coronary death found in our univariate analyses included older age, higher systolic and diastolic blood pressure, elevated total cholesterol, LDL cholesterol, depressed HDL cholesterol levels, the presence of cardiovascular disease at entry into the study, male sex, diabetes and cigarette smoking.

Two multivariate models are summarized in Table 1. The models are similar in that they both include sex, age, mean blood pressure, cigarette smoking, diabetes and cardiovascular disease. However, the first model uses only the LDL/HDL ratio to capture the risk associated with lipid abnormalities (LDL/HDL model) whereas the second incorporates three lipid terms: the LDL level, the HDL level and an interaction term between LDL and HDL (interaction model). The odds ratios for nonlipid risk factors are similar for the two models suggesting that the choice of lipid risk factors has little impact on the strong independent associations between these other factors and coronary mortality. The AIC score of 704 for the interaction model is lower than the score of 714 for the LDL/HDL model, indicating that the more complex interaction model provides a better fit of the LRC data. On the other hand, the Schwarz scores of 768 for the interaction model and 766 for the LDL/HDL model suggest that the two models are equivalent.

We used these two models to forecast the impact of modifying LDL or HDL values among 55-year-old males without known coronary disease. At a low HDL cholesterol level (0.8), reductions in LDL had a bigger effect in reducing 10-year risk of coronary death when using the interaction model (Figure 1a) compared with the ratio model (Figure 1b). As HDL levels rise, the relation between LDL and risk of coronary death becomes increasingly similar under the two models, until at a HDL level of 1.6 there is little difference between the two. This demonstrates that in the presence of low HDL cholesterol, the absolute risk associated with elevated LDL may be underestimated using the LDL/HDL ratio compared with the more complex interaction. This also implies that a simple LDL/HDL ratio underestimates the benefits associated with LDL reduction in the presence of low HDL.

Similar results are observed when focusing on HDL cholesterol. Given an elevated LDL value of 6.0, the absolute 10-year risk of coronary death is higher with the interaction model (Figure 2a) than with the ratio model (Figure 2b). As the LDL value drops, the two models become more similar. At an LDL value of 3.0, the absolute risk associated with HDL is weak for the ratio model and nearly flat for the interaction model. This suggests that HDL changes may be most beneficial among individuals with high LDL values. Moreover, the benefits of raising HDL among those with elevated LDL values may be underestimated by using a simple LDL/HDL ratio.

These conclusions are supported by the model validation on the results of the 4S study. The reported risk factors at baseline for the 4S subanalysis[19] are summarized in Table 2. (In the absence of specific diastolic blood pressure data, we assumed the average levels were those reported for the original simvastatin and placebo groups.) Among lipid triad patients, statin therapy was associated with a net difference of −38% in LDL and +7% HDL compared with

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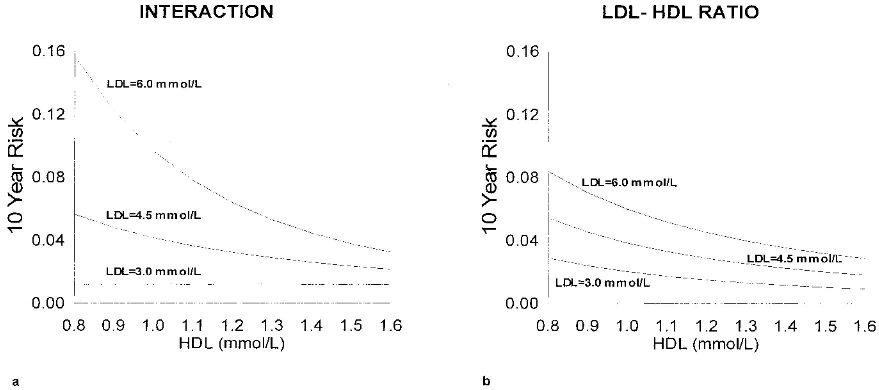

FIGURE 2. The 10-year risk of coronary death is forecasted for changes in HDL values across specified LDL values. Using the complex "interaction model" (a) the benefits of raising HDL are amplified in the presence of higher LDL values, compared with (b) the simple "LDL/HDL ratio model".

placebo. For isolated LDL patients, these net changes were −35% for LDL and +4% for HDL.

The predicted event rates and relative risk (RR) of coronary death using each model were then compared with the observed results (Table 3). In each subgroup, the interaction model more closely approximated the observed results. For instance, the interaction model predicted a benefit for statin therapy among low HDL cholesterol patients with the lipid triad (RR = 0.48) that was closer to that observed (0.34), whereas the LDL/HDL model predicted a more modest difference (0.66). Among subjects with isolated high LDL, the observed benefits of statin therapy (0.67) were more closely approximated by the interaction model (0.61) than by the LDL/HDL model (0.55).

Discussion

Barr *et al.*[24] first reported that high HDL levels were associated with a reduced risk of coronary events. This observation was largely overlooked until Castelli and coworkers[1] demonstrated more than 25 years later that LDL cholesterol and HDL cholesterol are strong independent risk factors for coronary events. This has since been confirmed in the major cohort studies[2–4] and a score of smaller prospective cohort studies.

LDL has long been recognized as the major atherogenic lipoprotein whereas HDL is believed to protect against atherosclerosis.[25] Low HDL is also associated with other atherogenic factors, termed the "metabolic syndrome." It has been proposed that, for practical purposes, the independent effects of LDL and HDL cholesterol in coronary risk can be summarized by the cholesterol/HDL ratio or the LDL/HDL ratio.[16,18] These ratios are a substantial improvement over single lipid parameters in forecasting future coronary events.[17] Moreover, the cholesterol/HDL ratio alone approximates the diagnostic discriminating ability of more complex lipid-screening guidelines.[17] If a simple ratio works so well, is there any reason to formulate a more complex strategy for incorporating LDL and HDL into global risk assessment?

The analyses presented here, using data from the Lipid Research Clinics Follow-up Cohort, demonstrate the potential usefulness of a more complex interaction. Although these analyses are restricted to fatal events (the only events available in this dataset), previous analyses of clinical trials demonstrate that fatal coronary events are strongly correlated with total coronary risk (fatal plus nonfatal events).[10–12] Although the LDL/HDL ratio is a strong risk factor for coronary deaths in this cohort, we find that LDL, HDL and an interaction between the two are all independent risk factors. We compare multivariate models using the ratio alone with models using the three lipid parameters to demonstrate the potential usefulness of the more complex assessment. Using the ratio alone, we may underestimate the long-

TABLE 2. Patient Characteristics in Subanalyses of the Scandinavian Simvastatin Survival Study (4S)[19]

	Lipid Triad		Isolated High LDL	
	Simvastatin (N = 206)	Placebo (N = 218)	Simvastatin (N = 241)	Placebo (N = 271)
Age (mean years)	57	57	59	59
Males (%)	93	93	66	66
Smokers (%)	78	78	69	69
Diabetes (%)	16	16	6	6
Total cholesterol (mean mmol/L)	6.90	6.77	6.62	6.70
LDL (mean mmol/L)	5.05	4.91	4.56	4.67
HDL (mean mmol/L)	0.86	0.85	1.65	1.62
Systolic blood pressure (mean mmHg)	137	137	140	140
Diastolic blood pressure (mean mmHg)	84	83	84	83

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TABLE 3. Prediction of Fatal Coronary Events Among 4S Participants[19] with Two Lipid Abnormalities, Comparing the LDL/HDL Model with the Interaction Model

	Lipid Triad			Isolated High LDL		
		Model Prediction			Model Prediction	
	Observed	LDL/HDL	Interaction	Observed	LDL/HDL	Interaction
Number of CHD Deaths						
Simvastatin	4.1	10.6	9.2	5.7	3.7	4.9
Placebo	12.2	16.0	19.3	8.5	6.8	8.1
Relative risk	0.34	0.66	0.48	0.67	0.55	0.61

term benefits of treating high LDL cholesterol among individuals with low HDL cholesterol and overestimate the benefits among those with high HDL values. On the other hand, the use of raising HDL cholesterol in the presence of a low LDL level may be overestimated whereas the benefits among those with a high LDL level may be underestimated. The question remains: which scenario is true?

The two models appear to fit our cohort data equally well. (It should be noted that the log of the ratio is equivalent to the difference between the logs of LDL and HDL.) However, using a ratio constrains the LDL and HDL coefficients to be in opposite directions, whereas the more complex interaction model does not. It therefore appears that, overall, a simple ratio of LDL to HDL is as accurate as the more complex interaction model. On the other hand, the potential strength of the interaction model is its ability to differentiate between individuals with extreme values of LDL or HDL, as demonstrated in Figures 1 and 2. The superior prediction of the interaction model on the 4S subanalysis supports this conclusion. To further confirm the accuracy of the more complex model predictions would require a large dataset with sufficiently high numbers of individuals with extreme values of LDL and HDL cholesterol, such that individual participant data could be used to compare the predicted events with those actually observed across the entire spectrum of LDL and HDL values observed in the population under study.

Using a single prospective dataset, the 4S study, we have been able to demonstrate that the interaction model better approximates the observed results in one clinical trial. Analysis of a number of large independent datasets will be required to demonstrate convincingly that one multivariate model is superior to the other in its ability to predict cardiovascular events.

If our observations are confirmed, more complex multivariate models could be developed that use the interaction of LDL and HDL cholesterol levels to understand better the benefits of lipid interventions and to predict more accurately the long-term cost-effectiveness of lipid therapy. Most importantly, we might also develop more accurate screening strategies to identify those individuals most likely to benefit from specific lipid interventions.

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