Clinical Significance of High-Density Lipoprotein Cholesterol in Patients With Low Low-Density Lipoprotein Cholesterol

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Objectives
We sought to evaluate the significance of high-density lipoprotein cholesterol (HDL-C) in the context of low low-density lipoprotein cholesterol (LDL-C).

Background
Earlier studies support an inverse correlation between circulating HDL-C and coronary risk in patients with normal or elevated LDL-C.

Methods
This study involved 4,188 patients attending the Palo Alto Veterans Administration Medical Center or affiliated clinics with LDL-C levels below 60 mg/dl. Outcomes were examined 1 year after the index LDL-C date. The combined primary end point was myocardial injury or hospitalization from ischemic heart disease. The secondary end point was all-cause mortality.

Results
Mean HDL-C levels (mg/dl) by quartile (Q) were: Q1 28 mg/dl, Q2 36 mg/dl, Q3 43 mg/dl, and Q4 63 mg/dl. The rate of myocardial injury or hospitalization for ischemic heart disease showed an inverse relationship to HDL-C (adjusted odds ratios: Q1 1.59 [95% confidence interval (CI) 1.16 to 2.19], Q2 1.39 [95% CI 1.01 to 1.92], Q3 1.33 [95% CI 0.96 to 1.84], and Q4 reference) that persisted regardless of statin use or recent myocardial injury. Analyzing HDL-C as a continuous variable revealed a 10% [95% CI 3% to 17%] increase in the combined end point of myocardial injury or hospitalization for ischemic heart disease for every 10-mg/dl decrease in HDL-C. The unadjusted and adjusted incidence of all-cause mortality demonstrated a U-shaped relationship to HDL-C (adjusted odds ratios: Q1 1.13 [95% CI 0.79 to 1.62], Q2 0.97 [95% CI 0.67 to 1.40], Q3 0.74 [95% CI 0.50 to 1.09], and Q4 reference).

Conclusions
The inverse relationship between HDL-C and coronary risk persists even among patients with LDL-C below 60 mg/dl, although a U-shaped relationship is observed between HDL-C and all-cause mortality. (J Am Coll Cardiol 2008;51:49–55) © 2008 by the American College of Cardiology Foundation

As noted by the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) guidelines, low high-density lipoprotein cholesterol (HDL-C) represents a key determinant of the Framingham risk score and a common critical risk factor for ischemic heart disease (IHD) (1). Low HDL-C levels, defined as below 40 mg/dl for men and 50 mg/dl for women, remain prevalent (1–3), and numerous prospective cohort studies support a powerful inverse correlation between circulating HDL-C levels and coronary risk (4–11).

One significant limitation to those analyses, however, is that no study examined the clinical relevance of HDL-C within the context of the optional aggressive low-density lipoprotein cholesterol (LDL-C) target for higher-risk patients, below 70 mg/dl, as proposed by the 2004 update to the NCEP-ATP III (12). As such, it remains unclear whether very low LDL-C levels, now readily attainable with potent statins and combination lipid-lowering therapy, attenuate or extinguish the cardiovascular risk associated with low HDL-C. We therefore sought to quantify the cardiovascular risk associated with low HDL-C among patients with LDL-C levels below 60 mg/dl, either occurring spontaneously or achieved with lipid-lowering agents.

Methods
Population cohort. We identified male patients seen at the Palo Alto Veterans Administration (VA) Medical Center or one of 7 affiliated community clinics with fasting LDL-C
below 60 mg/dl between October 1, 1999, and September 30, 2005. For patients with more than 1 qualifying LDL-C value, we used the earliest value to determine the index date.

Comorbid conditions were defined as present at baseline if the relevant diagnostic code was recorded in any patient encounter within 5 years before the index date: IHD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 410 to 414), cerebrovascular disease (ICD-9-CM 433 to 436), peripheral arterial disease (ICD-9-CM 440 to 441), congestive heart failure (ICD-9-CM 428), diabetes mellitus (ICD-9-CM 250), hypertension (ICD-9-CM 401 to 405), malignancy (ICD-9-CM 140 to 208), chronic obstructive pulmonary disease (ICD-9-CM 490 to 496), liver disease (ICD-9-CM 570 to 571), and alcohol dependence or abuse (ICD-9-CM 303 or 305). Computerized diagnostic coding at our institution has been demonstrated to be accurate compared with chart review (13). The following laboratory abnormalities were defined as present at baseline if recorded within 12 months before the index date: troponin I (TnI) >0.07 ng/ml, creatinine >2 mg/dl, hemoglobin <10 g/dl, aspartate aminotransferase >500 IU/l, and hemoglobin A1c >7%. Use of statins, fibrates, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, or beta-blockers was defined as a prescription provided by the physician within 12 months before the index date.

**Clinical outcomes.** We selected as the combined primary end point myocardial injury (defined as TnI >0.07 ng/ml) or hospitalization with a primary diagnosis of IHD (ICD-9-CM 410 to 414) at 1 year. The secondary end point was all-cause mortality, with vital statistics obtained from the VA death records and the Social Security Death Index.

**Statistical analysis.** The patient cohort was divided into quartiles (Q1 to Q4) based on HDL-C values measured on the index date. Odds ratios for study outcomes were calculated for each quartile using multivariate logistic regression, adjusting for demographics (age, gender, race), medical history (IHD, stroke, peripheral arterial disease, heart failure, diabetes, hypertension, malignancy, chronic obstructive pulmonary disease, liver disease, alcohol use or dependence), laboratory values (LDL-C, triglycerides, TnI >0.07 ng/ml, creatinine >2 mg/dl, hemoglobin <10 g/dl, aspartate aminotransferase >500 IU/l, hemoglobin A1c >7%), and medication use (statins, fibrates, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers). Given the known association between levels of triglycerides and HDL-C values, the square of the triglycerides was added as a covariate to improve risk adjustment in multivariable analyses. Pearson chi-square analysis was used to evaluate categoric variables and analysis of variance to evaluate continuous variables. Based on earlier studies suggesting a U-shaped relationship between HDL-C and total mortality, we tested the hypothesis that adjusted odds ratios (ORs) for 1-year mortality were similar for HDL-C values above and below the midpoint of Q3 (43 mg/dl). A p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using Stata version 9.0 (StataCorp, College Station, Texas). All of the authors had full access to the data and take responsibility for its integrity. All of the authors read and agreed to the manuscript as written.

**Results**

**Baseline characteristics.** Characteristics of the cohort, categorized according to HDL-C quartile, are shown in Table 1. A total of 4,118 consecutive patients met inclusion criteria with an LDL-C below 60 mg/dl, of which 2,254 (54%) had an HDL-C below 40 mg/dl. Mean quartile HDL-C values were: Q1 28 mg/dl, Q2 36 mg/dl, Q3 43 mg/dl, and Q4 63 mg/dl. Mean LDL-C values by quartile were: Q1 47 mg/dl, Q2 49 mg/dl, Q3 50 mg/dl, and Q4 50 mg/dl. A history of IHD was noted in 35% to 46% of the cohort. Individuals in the lower HDL-C categories tended to have: higher rates of IHD, stroke, peripheral arterial disease, heart failure, diabetes, and prior myocardial injury; abnormal levels of creatinine, hemoglobin, hemoglobin A1c, and triglycerides; and greater use of fibrates, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and beta-blockers. Chronic obstructive pulmonary disease and alcohol dependence or abuse were more likely to be observed in the higher HDL-C quartiles.

**HDL-C quartile and risk of coronary events.** At 1 year, 515 patients suffered myocardial injury, 104 patients required hospital admission for IHD, and 535 patients experienced either myocardial injury or IHD hospitalization. Univariate analysis demonstrated an inverse relationship between HDL-C and the combined primary end point of myocardial injury or IHD hospitalization at 1 year (Q1 17.0%, Q2 12.7%, Q3 13.1%, Q4 10.9%; p = 0.001) (Fig. 1). The above-average absolute incidence of coronary events may be explained by the prevalence of IHD in the cohort at baseline. In multivariate-adjusted analysis, the ORs for myocardial injury or IHD admission at 1 year varied inversely to HDL-C quartile (ORs: Q1 1.59 [95% confidence interval (CI) 1.16 to 2.19], Q2 1.39 [95% CI 1.01 to 1.92], Q3 1.33 [95% CI 0.96 to 1.84], and Q4 reference) (Fig. 2). Analyzing HDL-C as a continuous variable revealed a 10% increase (95% CI 3% to 17%) in the combined primary end point of myocardial injury or IHD admission for every 10-mg/dl decrease in HDL-C. Subgroups revealed findings consistent with the primary analysis (Table 2). None of the interactions between the
subgroup variables and the primary outcome were significant (all p > 0.2). Of note, the univariate relationship between the ratio total cholesterol/HDL-C and outcomes was not statistically significant (Q1 13.9%, Q2 13.8%, Q3 13.5%, Q4 12.5%; p = 0.80). HDL-C quartile and risk of total mortality. In univariate analysis, a U-shaped relationship was observed between HDL-C and the risk of overall mortality at 1 year (Q1 9.2%, Q2 6.5%, Q3 6.3%, Q4 9.2%; p = 0.011) (Fig. 1). This relationship persisted in multivariable analysis adjusted for demographics, medical history, laboratory values, and medication use (Fig. 2). Analysis of the ORs for death from any cause using the highest HDL-C quartile as the reference quartile revealed a U-shaped curve, with the highest risk of mortality observed in the lowest and highest quartiles (ORs: Q1 1.13 [95% CI 0.79 to 1.62], Q2 0.97 [95% CI 0.67 to 1.40], Q3 0.74 [95% CI 0.50 to 1.09], and Q4 reference), similar to findings observed in prior epidemiologic studies (Fig. 3) (14–17). The ORs for total mortality for every HDL increase of 10 mg/dl was 1.09 [95% CI 0.98 to 1.20] if the HDL was above 43 mg/dl and 0.73 [95% CI 0.60 to 0.88] if the HDL was below 43 mg/dl; for difference in ORs: p = 0.001. If alcohol abuse or dependence was removed from the model, the OR for all-cause mortality in the lowest HDL-C quartile decreased compared with the highest HDL-C quartile (adjusted for alcohol: 1.13 [95% CI 0.79 to 1.62]; not adjusted for alcohol: 0.88 [95% CI 0.62 to 1.24]), suggesting the role of alcohol use as a component of the observed worsened outcomes.

Discussion

As noted by the NCEP-ATP III guidelines, low HDL-C represents a key determinant of the Framingham risk score
and a common critical risk factor for IHD (1). Isolated low HDL-C was the most frequent dyslipidemia observed in a study of men with angiographically documented premature IHD (18). A survey of 8,650 male veterans with IHD revealed an HDL-C of <40 mg/dl in 63% of the study cohort (3). In a large study of 8,545 cardiology patients in 11 European countries, HDL-C <40 mg/dl occurred in 33% of men and 40% of women despite lipid-lowering therapy and lifestyle modification (2). Approximately 45% of patients had a diagnosis of IHD, and 85% received statin therapy, achieving a mean LDL-C of 118 mg/dl. Finally, according to 2007 American Heart Association heart disease statistics, 25% of men aged 20 years and older have HDL-C values of <40 mg/dl (19).

Numerous prospective cohort studies support a powerful inverse correlation between circulating HDL-C and coronary risk among patients with normal or elevated LDL-C (4,20). According to the Framingham Heart Study, among patients aged 50 to 80 years without IHD, after a mean follow-up of 4 years, the risk of MI or IHD death decreased by 25% for every 10-mg/dl increase in HDL-C (6). After 21 years of observation, the Israeli Ischemic Heart Disease Study of men without IHD at baseline demonstrated an increased risk of IHD mortality (adjusted risk ratio 1.22 to 1.25) among subjects with HDL-C <35 mg/dl regardless of total cholesterol levels (21). In the Pravastatin Pooling Project, among IHD patients with LDL-C <125 mg/dl not on statin therapy, a 10-mg/dl increase in HDL-C was associated with a 29% decrease in the combined end point of IHD death, nonfatal myocardial infarction, or coronary revascularization after a mean follow-up of 5 years (10). More recently, low HDL-C was shown to be a key predictor of major adverse cardiac events and death (hazard ratio 2.6 to 3.3) after percutaneous coronary intervention for acute coronary syndrome (22).

Several randomized controlled trials of antidyslipidemic therapies suggest that raising HDL-C may be associated with decreased cardiovascular risk (20). The Helsinki Heart Study examined the effect of gemfibrozil on lipid parameters and cardiovascular outcomes among men without IHD and with primary dyslipidemia, defined as non–HDL-C >200 mg/dl (23). After 5 years of follow-up, treatment with gemfibrozil increased HDL-C by 11%, decreased LDL-C and triglycerides by 11% and 35%, respectively, and reduced the incidence of MI and IHD death by 34% compared with placebo. Subsequent analysis estimated that the significant reduction in IHD risk associated with a 1% increment in HDL-C (~3%) exceeded that achieved with an equivalent magnitude decrement in LDL-C (~2%) or triglycerides (0%) (24). Findings from the VA-HIT (VA HDL Intervention Trial) demonstrated that a 6% increase in HDL-C, achieved with the use of gemfibrozil, decreased IHD death and nonfatal MI by 22% after 5 years of therapy among IHD patients with an HDL-C of 160 mg/dl (mean 32 mg/dl) (7,8). Treatment with niacin has been associated with increased HDL-C and decreased mortality, as well. Before the advent of statins, the Coronary Drug Project showed that niacin therapy in men with IHD reduced the risk of MI by 26%, stroke by 24%, and the need for coronary revascularization by 67% compared with placebo after a mean 6.5 years of follow-up (25). Post-trial analysis conducted 9 years after treatment discontinuation revealed an
11% reduction in total mortality in the niacin group (26). In the HATS (HDL-Atherosclerosis Treatment Study) trial, combination niacin-simvastatin therapy administered to IHD patients with low HDL-C was associated with a 26% increase in HDL-C compared with placebo, a 60% to 90% reduction in death, myocardial infarction, stroke, or revascularization, and plaque regression by serial angiography (5). In comparison, multiple trials of statins alone achieved event reduction of only 24% to 34% and slowed but did not reverse atheroma progression (5). The most recent trial of HDL-directed therapy, the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol)-2 study, examined the effects of niacin added to background statin therapy on HDL-C and carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point (13). After 12 months of therapy, extended-release niacin increased HDL-C by 21% and decreased the rate of CIMT progression. Mean CIMT was unchanged in the niacin group compared with baseline (0.014 mm; p = 0.026) and increased significantly in the placebo group (0.044 mm; p = 0.001). Per-protocol analysis at 24 months suggested a significant regression of CIMT among niacin-treated patients compared with the placebo arm (0.041 mm; p = 0.001) (10). After controlling for changes in LDL-C and triglycerides, only differences in HDL-C were independently associated with CIMT progression. Mean CIMT was unchanged in the niacin group compared with baseline (+0.014 mm; p = 0.026) and increased significantly in the placebo group (+0.044 mm; p = 0.001). Per-protocol analysis at 24 months suggested a significant regression of CIMT among niacin-treated patients compared with the placebo arm (+0.041 mm; p = 0.001) (10). After controlling for changes in LDL-C and triglycerides, only differences in HDL-C were independently associated with CIMT progression. These consistent findings highlight both the prevalence and risk associated with low HDL-C and suggest that improved clinical outcomes may accompany increases in HDL-C.

The present study extends the clinical importance of circulating HDL-C levels to patients with very low LDL-C levels, defined as <60 mg/dl, and confirms the high prevalence of the at-risk HDL-C profile. Every 10-mg/dl decrease in HDL-C was associated with a 10% increase in the combined end point of myocardial injury or IHD admission at 1 year. Subgroup analysis of patients on statin...
therapy revealed a similar effect on the combined end point among the lowest 3 HDL-C quartiles, suggesting perhaps that statin use may attenuate the increased risk associated with low HDL-C.

Importantly, the inverse correlation between spontaneously occurring HDL-C values and cardiovascular outcomes may not be reliable in the setting of genetic or pharmacologic manipulation, despite the observations of the VA-HIT and HATS trials. Raising HDL-C, in other words, need not confer an atheroprotective benefit, as illustrated by the recent termination of the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial. Despite increasing HDL-C levels by 72%, administration of the cholesteryl ester transfer protein inhibitor torcetrapib in combination with atorvastatin was associated with a higher risk of mortality compared with atorvastatin alone (hazard ratio 1.58; 95% CI 1.14 to 2.19; p = 0.006) (27). The potential benefit of HDL-directed drugs in development, as well as the prognostic utility of HDL-C as a surrogate marker after pharmacotherapy, awaits the results of ongoing trials with “hard” clinical end points. Until then, directly addressing low HDL-C relies largely upon niacin administration and cardiac rehabilitation, which have been demonstrated to both raise HDL-C and improve outcomes (28,29).

In the present study, the risk of death from any cause, unlike IHD-related outcomes, did not fit a monotonic inverse correlation with HDL-C. Worsened outcomes were observed in not only the lowest but also the highest HDL-C quartile. Earlier epidemiologic studies conducted in the U.S., Norway, Finland, and Russia revealed a similar U-shaped relationship (Fig. 3) (14–17,30). The IHD-related mortality in those analyses consistently decreased with higher HDL-C values; however, deaths attributed to alcohol, violence, or accidents rose continuously with increasing HDL-C. One plausible hypothesis holds that, although atheroprotective, HDL-C also represents a marker for noncardiovascular conditions associated with significant morbidity and mortality, such as alcohol use. Of note, in a study of 1,962 Russian men, levels of apolipoprotein AI, the major apolipoprotein component of HDL, paralleled the degree of alcohol use across various age groups (31). In the present study, adjustment for alcohol abuse or dependence increased the OR for death from any cause in the lowest HDL-C quartile compared with the reference, supporting the role of increased alcohol use as a component of the observed worsened outcomes. Adjustment failed to account for all of the excess risk, suggesting that either underreporting of alcohol use or unknown confounding factors contributed to increased mortality in the highest HDL-C quartile.

The strengths of the present study include the stringent LDL-C inclusion criteria and the large study cohort. Eligibility required an LDL-C of <60 mg/dl, limiting analyses to patients not previously examined in epidemiologic studies or clinical trials. A recent analysis of the TNT (Treating to New Targets) study found an inverse relationship between HDL-C and cardiovascular events among patients with LDL-C <80 mg/dl (32). The present study is unique in that its LDL-C threshold of 60 mg/dl lies below the optional aggressive 70 mg/dl target for higher-risk patients proposed by the 2004 update to the NCEP-ATP III (12). The present findings therefore demonstrate that even among patients with LDL-C levels well below current guidelines, either occurring spontaneously or achieved with pharmacotherapy, low HDL-C carries prognostic significance. In addition, this study evaluated a diverse population encompassing both primary and tertiary care centers, thereby permitting generalizability of its findings beyond the clinical trial setting.

**Study limitations.** Despite our attempts to control for potential confounders, the nonexperimental design remains susceptible to bias; consequently, unmeasured variables may have confounded results. Our study used a database from a VA health care system covering much of northern California. As such, the patients were predominately male, and nonfatal events that occurred outside the system were not captured. However, the number of observed events was adequate to demonstrate a significant association between HDL-C and outcomes. Furthermore, it is unlikely that noncaptured events were systematically more or less prevalent among those with low HDL-C. Finally, we did not examine other lipoprotein parameters such as LDL particle size, apolipoprotein B, and lipoprotein (a), and, without information regarding cause of death, we were unable to provide data regarding cardiovascular or cancer mortality.

**Implications for clinical practice.** Management of patients presenting with a combined low HDL-low LDL lipid profile remains a clinical conundrum, one likely to become increasingly prevalent with the availability of safe and effective LDL-lowering strategies. In the setting of low LDL-C, no evidence has been available to support or refute additional cardiovascular risk conferred by decreased HDL-C. The present study provides such evidence, identifying an inverse relationship between HDL-C and IHD events even among patients with LDL-C <60 mg/dl that persisted after adjustment for patient comorbidities. It is unclear if statin use attenuates the increased risk associated with low HDL-C. These findings support the need for comprehensive risk assessment, including HDL-C measurement, for all patients regardless of LDL-C status and suggest vigilant risk factor modification among the low HDL population.

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