Evaluating the Incremental Benefits of Raising High-Density Lipoprotein Cholesterol Levels During Lipid Therapy After Adjustment for the Reductions in Other Blood Lipid Levels

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Background: The role of high-density lipoprotein cholesterol (HDL-C) as a therapeutic target to prevent cardiovascular (CV) events remains unclear. We examined data from the Framingham Offspring Study from 1975 through 2003 to determine whether increases in HDL-C levels after lipid therapy was started were independently associated with a reduction in CV events.

Methods: Using Cox proportional-hazards regression, we evaluated the risk of a CV event associated with changes in blood lipid levels among individuals who started lipid therapy. The independent effect of HDL-C levels on future CV risk (average follow-up, 8 years) was estimated after adjustment for changes in low-density lipoprotein cholesterol, plasma triglycerides, and pretreatment blood lipid levels. Potential confounders (eg, smoking status, weight, and the use of β-blockers) were then added to the model. Interactions between blood lipid levels were also explored.

Results: The change in HDL-C level was a strong independent risk factor for CV events (hazard ratio, 0.79 per 5-mg/dL increase; 95% confidence interval, 0.67-0.93) after adjustment for the other lipid changes associated with treatment. This relationship remained stable across a wide range of patient subgroups and did not appear to be associated with a specific drug class. An important interaction was observed: the lower the pretreatment low-density lipoprotein cholesterol level, the greater the impact of raising the HDL-C.

Conclusions: Raising HDL-C levels with commonly used lipid medications appears to be an important determinant of the benefits associated with lipid therapy. These results support the further evaluation of therapies to raise HDL-C levels to prevent CV events.

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THE RELATIONSHIP BETWEEN the concentration of high-density lipoprotein cholesterol (HDL-C) and the risk of cardiovascular (CV) events has been assessed in several population studies, where it has been found that, for every 1-mg/dL increase (to convert to millimoles per liter, multiply by 0.0259) in HDL-C level, there is a 2% to 3% decrease in the risk of future events.[1] This inverse relationship between HDL-C levels and CV events is independent of low-density lipoprotein cholesterol (LDL-C) levels and remains apparent even when levels of LDL-C have been reduced by aggressive statin treatment to below 70 mg/dL.[2]

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In support of the human epidemiologic observations, numerous studies in animal models have shown that interventions to raise HDL-C levels inhibit the development of atherosclerosis.[3-6] Furthermore, HDL-C has several known functions with the potential to protect against the development of atherosclerosis and its sequelae.[7-9] These include promoting the efflux of cholesterol from cells in the artery wall, promotion of endothelial function, and repair and inhibition of thrombosis.[7,8] High-density lipoprotein cholesterol also stimulates endothelial nitric oxide production and has antioxidant[8] and anti-inflammatory activities.[9] Evidence from human intervention studies suggests that increasing the level of HDL-C is associated with a reduction in atheroma progression as measured in coronary[10,11] and carotid[12] arteries. Thus, there is a compelling case for considering interventions to raise HDL-C levels as a strategy to reduce CV risk.

In contrast to the consistent trial data showing the cardioprotective effects of reducing LDL-C levels with statins, the evidence that raising HDL-C levels trans-

lates into a reduction in CV events is at best circumstantial and remains controversial. Indeed, enthusiasm for therapy to raise HDL-C levels has been somewhat dampened by the recent results of treating humans with the cholesteryl ester transfer protein inhibitor torcetrapib. Despite increasing HDL-C levels by more than 60% in these human studies, treatment with torcetrapib had no apparent effect on atherosclerosis and was associated with an increase in major CV events and total mortality.[13-16] Whether the adverse effects of torcetrapib were related to the inhibition of cholesteryl ester transfer protein, to the associated increase in HDL-C levels, or to an off-target effect of the drug is currently being tested in studies with other cholesteryl ester transfer protein inhibitors that do not share the known off-target effects of torcetrapib.

Despite the adverse results with torcetrapib, numerous epidemiologic and clinical trial studies support the proposition that therapies to raise HDL-C levels have the potential to reduce CV events.[10,11,17,18] On the other hand, in a recently published meta-regression analysis of lipid therapy trials, Briel and coworkers[19] concluded that increasing HDL-C levels did not appear to be associated with a reduction in CV events. To further address this issue, we have analyzed data from individuals treated with lipid-modifying therapy in the Framingham Offspring Study and have tested the hypothesis that a change in the concentration of HDL-C is an inverse and independent predictor of future CV events.

METHODS

STUDY DESIGN

We analyzed public domain data from the Framingham Offspring Study from 1975 through 2003. We focused only on those individuals who started lipid therapy between visits 2 and 6. This strategy provided plasma lipid levels for each individual before therapy was started and at 1 or more follow-up visits. For this report, a CV event included the development of angina pectoris, coronary insufficiency, myocardial infarction, coronary death, transient ischemic attack, and fatal or nonfatal thrombotic stroke as previously defined by the Framingham investigators. Detailed descriptions of the examination procedures and CV events have been reported previously.[20,21]

MULTIVARIABLE MODELS TO EVALUATE THE IMPACT OF CHANGES IN HDL-C LEVELS

The change in HDL-C levels after lipid-modifying therapy was calculated for each individual. For individuals with multiple visits while receiving therapy, the average of all available lipid measurements was used to estimate levels during treatment. Similar estimates were also completed for the change in LDL-C and plasma triglyceride levels. After dividing the cohort into quartiles of change in HDL-C levels, we produced Kaplan-Meier curves for each subgroup. Trends across changes in HDL-C level quartiles were assessed using the log-rank χ^2 test for trend.

Exploratory univariate analyses compared changes in other covariates across quartiles of change in HDL-C levels to identify potential confounders. Cox proportional-hazards regressions were used to estimate the association between HDL-C levels and CV events after adjustment for baseline lipid levels and changes following treatment. A second model then adjusted for baseline levels and changes in LDL-C levels. In a third model, additional potential confounders were added to model 2. Potential confounders that might be associated with changes in HDL-C levels and CV events were selected by inspecting the variables in **Table 1** (eg, plasma triglyceride levels and use of β-blockers) or on the basis of previously published studies (eg, smoking status, change in blood pressure, age, sex, and prevalent diabetes mellitus or CV disease). Finally, we evaluated possible interactions between levels of HDL-C and other blood lipids.

RESULTS

Patients included in this analysis (n=454) started lipid-modifying therapy between the second and sixth examination cycles. The type of lipid drug was unknown for 95 patients. Among the remaining 359 patients, 344 (96%) patients were taking 1 drug only, including statins (72%), fibrates (17%), resins (4%), or niacin (7%), and 15 patients (4%) were taking more than 1 drug.

When stratified by the change in HDL-C levels (Table 1), factors associated with larger increases in HDL-C levels included smaller changes in LDL-C levels, larger changes in plasma triglyceride levels, and less frequent use of β-blockers.

During an average follow-up period of 8 (SD, 4) years, 79 individuals experienced a CV event, including 5 coronary deaths, 24 myocardial infarctions, 29 cases of angina or coronary insufficiency, 1 stroke death, 11 thrombotic strokes, and 9 transient ischemic attacks. When we stratified individuals into quartiles of HDL-C change, a significant (log-rank χ^2 test for trend, $P=.006$) inverse relationship was observed between changes in HDL-C levels and CV event–free survival (**Figure 1**). After adjustment for the pretreatment HDL-C levels, age, and sex, the decreased hazard ratio (HR) for cardiovascular events (**Table 2**) associated with a 5-mg/dL rise in HDL-C level was 0.80 (95% confidence interval [CI], 0.69-0.94) (model 1). Further adjustment for pretreatment LDL-C levels and changes in LDL-C levels (model 2) did not substantially change the HR (0.79; 95% CI, 0.68-0.93). The HR remained stable after the addition of potential confounders such as plasma triglyceride levels, changes in plasma triglyceride levels, the use of β-blockers, prevalent CV disease or diabetes mellitus when lipid therapy was started, and changes in body mass index, systolic blood pressure, or smoking status (0.79; 95% CI, 0.67-0.93) (model 3).

The impact of changes in HDL-C level appeared to be remarkably stable across a wide range of subpopulations, as demonstrated in **Figure 2**. Overall, a 1% increase in HDL-C level was associated with a 2% drop in CV risk. An important interaction was also observed between the pretreatment levels in LDL-C and changes in HDL-C levels. Stratifying by tertiles of LDL-C levels prior to treatment, the lower the LDL-C, the greater was the risk reduction associated with the increase in HDL-C (**Figure 3**). This significant interaction ($P<.05$) was also present after adjustment for all the covariates in model 2 (Table 2), when pretreatment levels of LDL-C and HDL-C and changes in LDL-C levels

Table 1. Patient Characteristics Stratified by the Change in HDL-C Level

	Quartiles (Median) Change in HDL-C Level, mg/dL			
	–37.0 to –3.0 (–6) (n=117)	–2.7 to +2.3 (0) (n=108)	+2.5 to +7.0 (5) (n=121)	+7.5 to +35.0 (11) (n=108)
Age, y[a]	60.5 (7.5)	61.1 (8.4)	60.9 (8.4)	60.1 (8.5)
Female sex, %	42	33	40	46
Untreated HDL-C level, mg/dL[a]	48 (13)	40 (10)	39 (10)	40 (11)
Average[b] treated HDL-C level, mg/dL[a]	41 (11)	40 (10)	44 (10)	53 (13)
Untreated LDL-C level, mg/dL[a]	171 (37)	160 (33)	160 (43)	160 (43)[c]
Average[b] treated LDL-C level, mg/dL[a]	126 (35)	122 (30)	125 (34)	127 (38)
Change in LDL-C level, mg/dL[a]	–45 (41)	–38 (31)	–35 (38)	–34 (40)[c]
% Change in LDL-C level[a]	–24 (22)	–22 (18)	–19 (24)	–18 (27)[c]
Untreated triglyceride level, mg/dL[a]	209 (201)	212 (133)	273 (267)	293 (363)[d]
Change in triglyceride level, mg/dL[a]	–23 (190)	–28 (91)	–94 (233)	–144 (355)[e]
Systolic blood pressure[a]	134 (20)	133 (20)	130 (20)	133 (20)
Change in systolic blood pressure[a]	–0.0 (17.7)	–2.7 (19.4)	–1.4 (17.5)	1.5 (19.1)
BMI[a]	28.8 (4.6)	29.2 (4.2)	28.4 (4.0)	28.1 (4.2)
Change in BMI[a]	0.8 (2.0)	0.2 (1.8)	0.3 (1.7)	0.4 (2.2)
Comorbidities or treatments, %				
Diabetes	15	18	15	19
Current smoker	15	16	12	17
Quit smoking after lipid therapy started	35	40	40	37
Prevalent CV disease	33	32	29	38
Lipid medications, %				
Unknown	26	20	18	23
Statins only	54	59	56	57
Resins only	4	3	3	3
Niacin only	4	7	7	4
Fibrates only	11	11	17	13
1 Medication	74	76	81	72
≥2 Medications	1	5	2	7
Antihypertensive medications, %				
β-Blockers	38	44	30	22[d]
Calcium channel blockers	22	26	26	27
Renin angiotensin	19	20	17	22
Diuretics	16	13	16	13

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.

[a] Data are given as mean (SD).

[b] Refers to the average value of all available posttreatment visits.

[c] $P<.05$.

[d] $P<.01$.

[e] $P<.001$.

were included in the model as continuous variables. The resulting HR for a 5-mg/dL increase in HDL-C level can be calculated using the following equation:

$$\mathrm{HR} = \mathrm{Exp}[5 \times \beta\mathrm{HDL\text{-}C} + 5 \times (\beta\mathrm{HDL\text{-}C} \times \mathrm{LDL\text{-}C}) \times \mathrm{LDL\text{-}C}],$$

where Exp indicates exponential, βHDL-C is the estimated β coefficient for changes in HDL-C level, LDL-C is the pretreatment LDL-C level, and βHDL-C × LDL-C is the interaction between changes in HDL-C and pretreatment LDL-C levels. The β coefficient for the interaction was 0.00074 (95% CI, 0.00002-0.0014).

COMMENT

It is well established that HDL-C level is an inverse predictor of CV risk. Whether interventions that increase HDL-C levels reduce the risk of future events is less certain. In this analysis of individuals starting pharmacotherapy for dyslipidemia, there was an inverse relationship between changes in HDL-C levels and CV events. Despite a limited number of CV events to analyze, the greater the increase in HDL-C level, the lower the CV risk—an observation that persisted after adjustment for changes in levels of LDL-C and plasma triglycerides and other potential confounders such as changes in smoking habits or body weight. We found that a 1% increase in HDL-C level was associated with a 2% reduction in CV risk, remarkably consistent with the epidemiologic data from prospective cohort studies of individuals not receiving lipid therapy.[1]

As with any therapeutic intervention, analyses of data from a randomized clinical trial based on a clear a priori hypothesis remain the only way to prove causality. In the absence of such data, concerns regarding residual confounding cannot be dismissed. Accordingly, there re-

mains the possibility that changes in factors associated with HDL-C levels and CV events might explain the results observed herein. Although we adjusted for changes in LDL-C and plasma triglyceride levels, as well as a variety of other factors, additional unforeseen confounders remain a concern.

Despite the obvious shortcomings of this analysis, these data provide some of the strongest evidence currently available to support the hypothesis that raising HDL-C levels is associated with a reduction in CV risk. Unlike data from highly selected subjects enrolled in a clinical trial, the data from this study are more representative of individuals treated in a community setting, albeit an extensively studied one. The subjects in the present analyses included those who, at the time they started lipid therapy, had known CV disease and/or diabetes mellitus, or neither condition. Treatment was initiated at a time when therapeutic guidelines in the United States primarily targeted LDL-C levels. Hence, the changes in HDL-C levels were unlikely to be the focus of treatment or to bias the assignment of clinical outcomes.

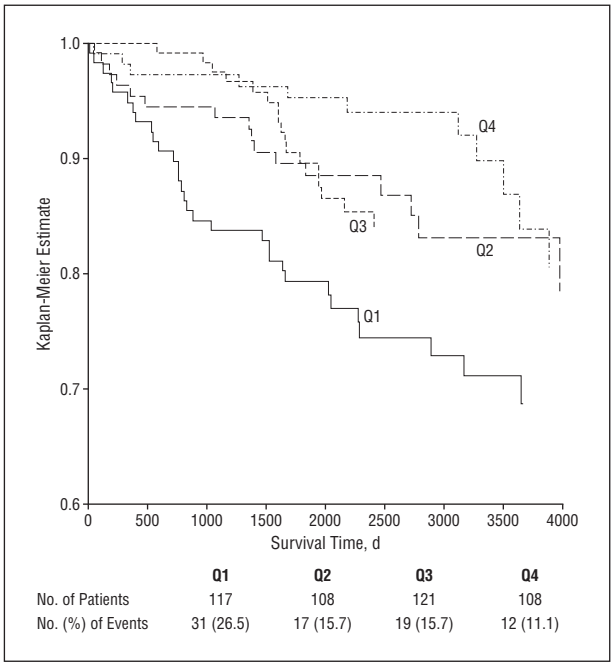

Figure 1. Kaplan-Meier survival estimates of time free from a cardiovascular event by quartiles (Qs) of change in high-density lipoprotein cholesterol level. Q1 indicates a change of –37.0 to –3.0 mg/dL; Q2, –2.7 to +2.3 mg/dL; Q3, +2.5 to +7.0 mg/dL; and Q4, +7.5 to +35.0. To convert cholesterol to millimoles per liter, multiply by 0.0259.

The conclusion that raising HDL-C levels is associated with lower CV risk appears to be robust across a wide spectrum of patients and does not appear to be uniquely associated with a specific class of drugs, as demonstrated in Figure 2. The broad range of treated patients and drug therapies resulted in a wide range of lipid responses, providing the necessary heterogeneity to demonstrate the association between HDL-C level changes and CV events. Similar levels of heterogeneity are largely lacking in clinical trials testing 1 specific therapy in a relatively homogeneous group of patients. Meta-regression analyses of clinical trials are also often restricted by limited heterogeneity based on the average results reported for each study rather than individual patient data. This may explain the negative results obtained by Briel et al[19] when the results of 108 randomized trials were combined. In the Framingham data set, strong heterogeneity is reflected by the wide variation in observed HDL-C level changes ranging from –37 mg/dL to +35 mg/dL or median values of –6 mg/dL in the lowest quartile to +11 mg/dL in the highest.

The heterogeneity in LDL-C values before treatment was initiated also was useful for identifying an important interaction between baseline LDL-C levels and changes in HDL-C levels. This finding suggests that raising HDL-C levels may be particularly beneficial among individuals with mixed dyslipidemia compared with those

Table 2. Results of a Cox Proportional Hazards Model Evaluating the Impact of Increases in HDL-C Level on CV Events[a]

	HR (95% CI)		
	Model 1[b]	Model 2[c]	Model 3[d]
Increase in HDL-C level, per 5 mg/dL	0.80 (0.69-0.94)	0.79 (0.68-0.93)	0.79 (0.67-0.93)
Decrease in LDL-C level, per 10 mg/dL		0.95 (0.88-1.02)	0.91 (0.85-0.98)
Untreated HDL-C level, per 5 mg/dL	0.94 (0.85-1.04)	0.93 (0.84-1.04)	1.01 (0.89-1.14)
Untreated LDL-C level, per 10 mg/dL		0.98 (0.91-1.05)	0.92 (0.86-0.99)
Decrease in triglyceride level, per 10 mg/dL			1.02 (1.00-1.04)
Untreated triglyceride level, per 10 mg/dL			1.02 (0.99-1.04)
β-Blocker use			1.16 (0.70-1.92)
Age in years			1.02 (0.98-1.05)
Cigarette smoking			1.23 (0.64-2.34)
Diabetes mellitus			1.09 (0.60-2.01)
Female sex			0.55 (0.31-0.99)
Prevalent CV disease			2.67 (1.57-4.55)
Systolic blood pressure, per mm Hg			1.00 (0.99-1.02)
BMI, per index unit			0.95 (0.89-1.01)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

[a] Increasingly complex models adjust for baseline blood lipid levels, changes in blood lipid levels, and other potential confounders.

[b] Adjusted for untreated HDL-C levels.

[c] Adjusted for model 1 and LDL-C levels.

[d] Adjusted for model 2 and other covariates.

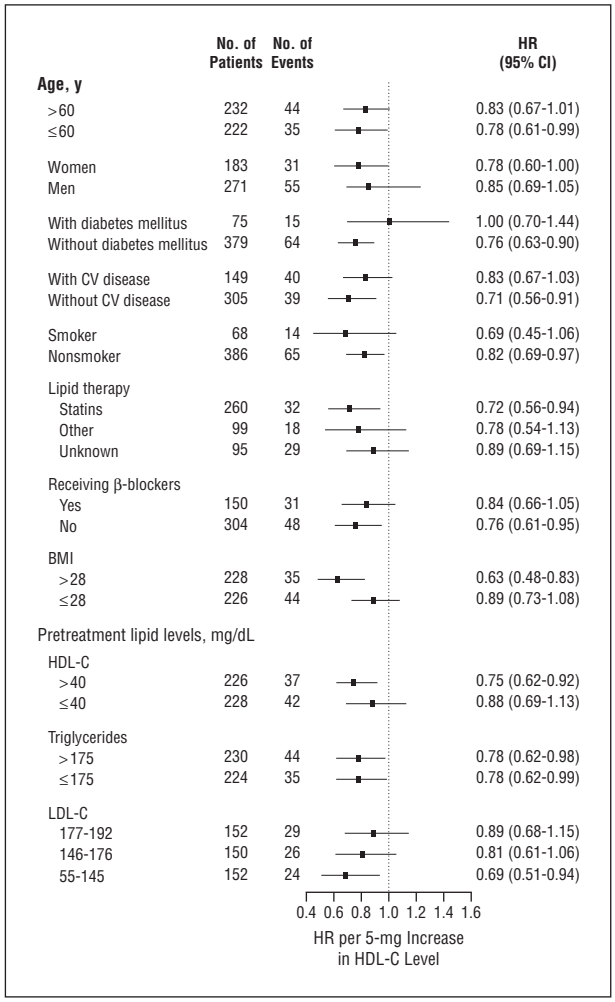

Figure 2. Hazard ratios (HRs) associated with raising high-density lipoprotein cholesterol (HDL-C) level 5 mg/dL among specific subgroups of individuals. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; CV, cardiovascular; and LDL-C, low-density lipoprotein cholesterol. To convert cholesterol to millimoles per liter, multiply by 0.0259.

with isolated elevations in LDL-C levels. This is consistent with the findings of a secondary analysis of the Scandinavian Simvastatin Study by Ballantyne et al,[22] which demonstrated that individuals with the lipid triad (high LDL-C, low HDL-C, and high triglyceride levels) received significantly greater benefits from statin therapy than did individuals with isolated high LDL-C levels. This was despite similar reductions in LDL-C levels. Similarly, a post hoc analysis of the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering Study[23] identified that pretreatment HDL-C levels were significantly associated with clinical outcomes but only among those individuals with LDL-C levels below the median for participants in the study. Among those with LDL-C levels above the median, there was no significant relationship between HDL-C levels and ischemic events.

Clinical trial data also support the Framingham Offspring Study results presented herein. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 2 Study,[24] the addition of extended-release niacin to statin therapy slowed the progression

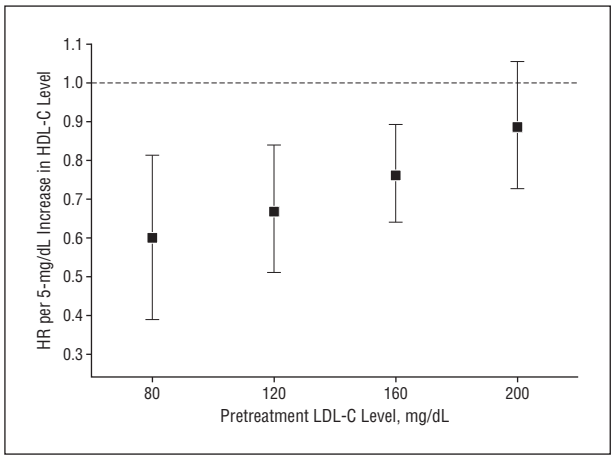

Figure 3. Hazard ratios (HRs) associated with changes in high-density lipoprotein cholesterol (HDL-C) level. The model was adjusted for the pretreatment levels of low-density lipoprotein cholesterol (LDL-C) and HDL-C, the change in LDL-C level, and the interaction between the change in HDL-C level and pretreatment LDL-C levels. The interaction results in greater risk reduction associated with a 5-mg/dL increase in HDL-C level among individuals with lower LDL-C levels. To convert cholesterol to millimoles per liter, multiply by 0.0259.

of atherosclerosis among individuals with known coronary heart disease. Unfortunately, in that study, there were not enough cardiovascular events observed to confirm a benefit on clinical outcomes. Detailed analyses of clinical outcomes in several lipid therapy trials have also demonstrated that raising HDL-C levels was associated with clinical benefits. These studies include the National Heart, Lung, and Blood Institute Type II Coronary Intervention Study,[25] the Lipid Research Clinics Coronary Primary Prevention Trial,[26] the Helsinki Heart Study,[27] the HDL-Atherosclerosis Treatment Study,[28] the Scandinavian Simvastatin Survival Study,[29] and the Veterans Affairs High-Density Lipoprotein Intervention Trial.[30] Increases in HDL-C levels (5%-26%) were independently associated with a reduction in CV events observed in each trial. Finally, recent post hoc analyses of 1 of the failed torcetrapib trials showed an inverse relationship between changes in HDL-C levels and the percentage of atheroma volume among patients receiving torcetrapib therapy.[31]

In conclusion, although the benefits of raising HDL-C levels remain to be confirmed in randomized clinical trials, it appears that the modest changes in HDL-C levels resulting from treatment with commonly used lipid drugs are associated with a reduction in CV risk independent of the effects on other lipid measures. Among individuals receiving lipid therapy to lower LDL-C levels, raising HDL-C levels should be evaluated further as a secondary goal of treatment.

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sign: Grover and Joseph. *Acquisition of data:* Grover and Kaouache. *Analysis and interpretation of data:* Grover, Kaouache, Joseph, Barter, and Davignon. *Drafting of the manuscript:* Grover and Davignon. *Critical revision of the manuscript for important intellectual content:* Grover, Kaouache, Joseph, and Barter. *Statistical analysis:* Grover, Kaouache, and Joseph. *Obtained funding:* Grover. *Administrative, technical, and material support:* Grover and Davignon. *Study supervision:* Grover.

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