Beyond LDL-Cholesterol: The Role of Low HDL-Cholesterol and Elevated TG in Residual Cardiovascular Risk Remaining After Statin Therapy

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One of the most effective classes of medications for preventing cardiovascular events is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, more commonly known as statins. Statin therapy has been shown to decrease cardiovascular morbidity and mortality rates in virtually every patient population studied and will likely continue to be a mainstay of cardiovascular risk prevention for years to come. However, close examination of statin clinical trial data reveals that, even though this class of drugs has been highly effective, an unacceptably large number of patients on statins still experience cardiovascular events. For example, in the Scandinavian Simvastatin Survival Study (4S) trial, which studied patients with very high levels of low-density lipoprotein cholesterol (LDL-C and known coronary heart disease (CHD), a significant risk reduction was observed with statin treatment. A greater percentage of patients on placebo (28%) experienced a major cardiovascular event than did patients on statin therapy (19%), and the relative risk of a major cardiovascular event in the statin-treated patients was 0.66.²⁷ On the other hand, those results from 4S also indicate that, over the 5 years of the study, almost 20% of statin-treated patients still had a cardiovascular event. In several major statin trials, significant residual cardiovascular risk remained even after significant reductions in LDL-C had been achieved.²⁷⁻³² Thus, despite the decrease in cardiovascular events due to statin treatment, two-thirds of the adverse cardiovascular events still occurred, which indicates that both patient lifestyle changes and new pharmacological strategies are necessary to address cardiovascular disease.³³

Additional trials have included high-risk patients with CHD or diabetes who were treated with intensive LDL-lowering statin therapy. In 3 of these trials, as shown in Figure 1, lowering LDL-C to approximately 100 mg per dL was compared with more intensive LDL-C lowering to approximately 70 mg per dL to investigate cardiovascular event reduction even in high-risk patient populations.^{14-16,34} In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study, 4,162 patients with acute coronary syndrome (ACS) were treated with either pravastatin 40 mg or atorvastatin 80 mg. Treatment with pravastatin reduced LDL-C to 95 mg per dL, whereas treatment with high-dose atorvastatin reduced LDL-C to 62 mg per dL.¹⁴ Clinical events were reduced in the high-dose atorvastatin group versus the pravastatin group; however, over the course of the 2-year trial, 22.4% of the individuals treated with intensive statin therapy (atorvastatin 80 mg) still suffered a major cardiovascular event.¹⁴ Similar results have been observed in the Incremental Decrease

in End Points Through Aggressive Lipid Lowering (IDEAL) study and the Treating to New Targets (TNT) study. After 4.8 years in the IDEAL study, 12.0% of patients experienced a major cardiovascular event even after intensive LDL-C lowering with 80 mg per day of atorvastatin.¹⁶ In the TNT trial, after 4.9 years of follow-up, 8.7% of patients receiving 80 mg per day of atorvastatin still suffered a major cardiovascular event.¹⁵ Thus, significant residual cardiovascular risk remains in patients even after intensive statin therapy that achieves LDL-C goals <100 mg per dL.^{14-16,34}

Patients with diabetes, another high-risk population, show significant cardiovascular risk reduction when treated with statins. A meta-analysis of 14 statin trials by the Cholesterol Treatment Trialists' Collaborators examined data of major vascular events in patients with diabetes.² A reduction in LDL-C in individuals with a prior history of CHD and either with or without diabetes was associated with a significant reduction in cardiovascular events. There was a 9% proportional reduction in all-cause mortality per 1 mmol per L (39 mg per dL) reduction in LDL-C in individuals with diabetes ($P=0.02$) and a 13% reduction in those without diabetes ($P<0.001$). Moreover, there was a significant 21% reduction in major vascular events per 1 mmol per L (39 mg per dL) reduction in LDL-C in people with diabetes ($P<0.001$) and those without diabetes ($P<0.001$).² Nonetheless, in patients with diabetes treated with statin therapy, the cardiovascular event rate (i.e., residual cardiovascular risk) remained unacceptably high, and was even higher than the cardiovascular event rate of those patients without diabetes who received placebo.² It is clear, then, that residual cardiovascular risk remains in all patients treated with statins, and that the residual cardiovascular risk is particularly high in patients with diabetes treated with statins.

Cardiovascular Risk and Lipid Parameters Beyond LDL-C

Residual cardiovascular risk is undoubtedly multifactorial, and likely due to a variety of both traditional and emerging risk factors. However, recent evidence suggests the important contribution to cardiovascular risk of lipid parameters beyond LDL-C, such as high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C). For example, Genest et al. reported that although 34% of patients with premature heart disease had LDL-C levels >160 mg per dL, more than half of the patients with premature heart disease (57%) had low HDL-C levels.³⁵ Additionally, it has been reported that, in both male and female patients with premature coronary artery disease (CAD), the greatest risk factor is actually low HDL-C levels, though these

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individuals often possess high TG levels, as well.³⁶ Although this study had small sample sizes (n=87 men; n=15 women), men and women with premature CAD had LDL-C values of approximately 130 mg per dL, which is near the average LDL-C level in the United States today. Conversely, the study found that TG levels were significantly higher and HDL-C levels were significantly lower in men and women with premature CAD, compared with patients from the Framingham Offspring Study who were free of CHD at baseline.³⁶

In addition, a shift in the lipid parameters of patients with CHD has been observed. In past decades, the most frequently seen coronary care unit patient was probably a male cigarette smoker who suffered a myocardial infarction (MI) and who had an LDL-C level near 170 mg per dL. In more recent years, the profile of patients has changed; the average LDL-C level of an MI survivor today is 130 mg per dL, which is similar to the average LDL-C level in individuals without CHD. On the other hand, the average HDL-C level is much lower. According to the Third National Health and Nutrition Examination Survey, which provides a cross-sectional examination of the United States to determine lipid parameters across many different risk factors, more than one third of the adult population has low HDL-C levels.³⁷ About 35% of adult men were reported to have HDL-C levels <40 mg per dL, and about 39% of adult women were reported to have HDL-C levels <50 mg per dL.³⁷

The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines report that low HDL-C is a significant, independent risk factor for CHD. This independent relationship is maintained between HDL-C and CHD even after correction for other risk variables, such as TG levels, obesity, and diabetes.¹⁸ In general, low HDL-C is correlated with elevations of serum TG and remnant lipoproteins and is strongly and inversely associated with CHD risk.¹⁸ There are a number of different mechanisms through which HDL-C may exert its antiatherogenic effects. It has been established, for example, that various atherogenic lipoproteins, including LDL-C and very low-density lipoprotein cholesterol (VLDL-C), can deposit cholesterol in the artery wall. In vitro studies have shown that HDL-C may promote the efflux of cholesterol from foam cells in atherosclerotic lesions through reverse cholesterol transport.³⁸ There are several other mechanisms, as well, as indicated by evidence demonstrating the inhibition of atherogenesis through antioxidant and anti-inflammatory properties.^{18,38,39} In addition, HDL-C is a component in a number of other basic physiologic processes, such as antithrombotic activity, antiapoptotic activity, vasodilatory activity, and endothelial repair.^{39,40}

A meta-analysis of 4 large prospective studies, considered classic trials in the field, revealed consistent effects of HDL-C levels. In an analysis of data from the Coronary Primary Prevention Trial, the Multiple Risk Factor Intervention Trial, the Lipid Research Clinics Prevalence Mortality Follow-up Study, and the Framingham Heart Study, for every 1 mg per dL (0.026 mmol

FIGURE 1 Residual Cardiovascular Risk After Intensive Statin Therapy

^aMean or median LDL-C after treatment

In the PROVE IT-TIMI 22 study, 22.4% of patients treated with intensive statin therapy (80 mg of atorvastatin) suffered a major cardiovascular event, compared with 26.3% of patients receiving low-dose statin (40 mg of pravastatin) therapy (P=0.005).¹⁴ In the IDEAL study, 12.0% of patients experienced a major cardiovascular event after intensive LDL-C lowering with statin therapy (80 mg of atorvastatin) after 4.8 years of follow-up, compared with 13.7% of patients receiving 20 mg of simvastatin (P=0.02).¹⁶ In the TNT study, a major cardiovascular event occurred in 8.7% of patients receiving intensive statin therapy (80 mg of atorvastatin) versus 10.9% of those receiving 10 mg of atorvastatin after 4.9 years (P<0.001).¹⁵

CVD=cardiovascular disease.

per L) increase in plasma level of HDL-C, there was a decrease in CHD risk of approximately 2% in men and 3% in women independent of other risk factors, including plasma LDL-C.⁴¹ In another analysis of Framingham Heart Study data, a significant increase in the number of cardiovascular events was observed in patients with low HDL-C levels (<34 mg per dL), especially women (P<0.01).^{42,43} Importantly, as shown by data from the Framingham Health Study, as HDL-C decreases, it contributes significantly to CHD risk at all LDL-C levels. Even when LDL-C levels are optimal (<100 mg per dL), the lower the HDL-C level, the higher the risk of CHD.⁴⁴

Figure 2 shows several scenarios in patients with differing levels of LDL-C and HDL-C and the resulting risk level for each individual. Patient 3, with very low HDL-C, has a very high risk of CHD that is equivalent to the risk level of a patient with very high LDL-C (220 mg per dL) and normal HDL-C. Therefore, in individuals who have near optimal LDL-C levels (100 mg per dL), the lower the HDL-C level, the higher the risk of CHD.⁴⁴ Even when LDL-C levels are well controlled with intensive statin

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FIGURE 2 HDL-C Modifies Cardiovascular Risk

As shown in the patient scenarios on the left side of Figure 2, if all patients have near optimal levels of LDL-C (100 mg per dL), the lower the HDL-C level, the higher the risk of CHD. Also note that in a patient with an LDL-C level of 220 mg per dL and an HDL-C level of 45 mg per dL, the risk of CHD (1.2) is equivalent to that in a patient with optimal LDL-C and low HDL-C (1.2).⁴⁴

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therapy, the heightened risk of CHD conferred by low HDL-C remains. The TNT trial investigated the efficacy of high-dose statin therapy, compared with low-dose statin therapy in patients with stable CHD. Patients were randomized to receive either atorvastatin (80 mg), with a target LDL-C of 70 mg per dL, or atorvastatin (10 mg), with a target LDL-C of 100 mg per dL. Results from TNT showed that patients with lower LDL-C levels had an approximate 25% risk reduction of having a CHD event. However, as Figure 3 shows, even if individuals had low LDL-C levels, they still had a very high rate of CHD events if they also had low HDL-C levels. With higher HDL-C levels, the CHD rate decreased significantly. In particular, the TNT data revealed that, even for patients in the lowest stratum of LDL-C (≤ 70 mg per dL) after 3 months of statin treatment, there was an increased 5-year risk for major cardiovascular events if HDL-C levels also were low.⁴⁵ The risk for a major cardiovascular event differed significantly among quintiles of HDL-C levels ($P=0.03$) in which those patients in the highest HDL-C quintile (≥ 55 mg per dL) had a lower risk for major cardiovascular events than did patients in the lowest HDL-C quintile (Q1 <37 mg per dL; hazard ratio [HR] vs. Q5 = 0.61).⁴⁵

Although LDL is recognized as the most important atherogenic lipoprotein, elevations in TG levels can be considered a marker for atherogenic remnant lipoproteins. VLDL-C and other TG-rich lipoproteins are able to enter the artery wall and initiate atherosclerotic processes and aid in foam cell formation just as LDL can. Because VLDL-C is the most readily available measure

FIGURE 3 Low HDL-C Is Associated With High Cardiovascular Risk (TNT Study)

Hazard Ratio Versus Q1	0.85	0.57	0.55	0.61
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In the TNT study, patients with low LDL-C levels (≤ 70 mg per dL) after 3 months of statin treatment had an increased 5-year risk for major cardiovascular events if HDL-C levels were low. The risk for a major cardiovascular event differed significantly among quintiles of HDL-C levels (multivariate regression; $P=0.03$). Patients in the highest HDL-C quintile (≥ 55 mg per dL) had a lower risk for major cardiovascular events than did patients in the lowest quintile (<37 mg per dL). The mean LDL-C level in this group of patients ($n=2,661$, receiving statin therapy for 3 months) was 56 mg per dL; mean TG level was 126 mg per dL.⁴⁵

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CVD=cardiovascular disease.

of atherogenic remnant lipoproteins, it is often combined with LDL-C to improve cardiovascular risk prediction (i.e., VLDL-C+LDL-C=non-HDL-C). When serum TG levels are elevated, the measure called non-HDL-C better represents the concentrations of all atherogenic lipoproteins than does LDL-C.¹⁸ Non-HDL-C incorporates all atherogenic lipoproteins, including LDL-C, VLDL-C, lipoprotein(a) (Lp[a]), and intermediate-density lipoprotein cholesterol (IDL-C). Non-HDL-C, according to the NCEP ATP III guidelines, is a secondary target of therapy after LDL-C goals have been reached and when TG levels are ≥ 200 mg per dL.¹⁸

Various studies have investigated the influence of the level of one or more of the components of atherogenic dyslipidemia on cardiovascular risk. A recent meta-analysis by Sarwar et al. included 29 prospective studies (262,525 participants; 10,158 CHD cases) to investigate the association between TG and CHD risk.⁴⁶ The meta-analysis showed an adjusted odds ratio (OR) of 1.72 (95% confidence interval [CI]=1.56-1.90) in patients

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in the highest third versus those in the lowest third of TG values. A strong and statistically significant association was found between TG level and CHD risk, regardless of the duration of the follow-up, gender, fasting status, and adjustment for HDL-C, though adjusting for HDL-C attenuated the magnitude of the association between TG level and CHD risk.⁴⁶ The meta-analysis showed a strong and significant association between a high TG level and cardiovascular risk.

In the previously mentioned PROVE IT-TIMI 22 trial, intensive and normal statin therapy were compared to examine a combination of LDL-C and TG levels on cardiovascular risk in patients with ACS. Participants in the study were randomized to either atorvastatin (80 mg) or pravastatin (40 mg) within days of their cardiac event and then were followed for the next 2 years. The trial demonstrated that an LDL-C level <70 mg per dL was associated with a greater degree of CHD event reduction than was an LDL-C level <100 mg per dL. Further, the relationship between on-treatment levels of TG and LDL-C and the composite end point of CHD events (death, MI, and recurrent ACS) were assessed 30 days after initial presentation. Between the initial day 30 time point and the 2-year follow-up, significantly fewer CHD events occurred in patients who had an LDL-C level <70 mg per dL than in patients who had an LDL-C level ≥70 mg per dL (HR=0.81; $P=0.015$). Similarly, significantly fewer events occurred in patients with a TG level <150 mg per dL than in those patients with a TG level ≥150 mg per dL, as revealed through univariate analysis (HR=0.73; $P<0.001$). Even in multivariate analysis, after adjustment for age, gender, high LDL-C, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment effect, the HR associated with low on-treatment TG (<150 mg per dL) versus TG ≥150 mg per dL was 0.80 ($P=0.025$).³⁴ In univariate analysis, it appeared that for each 10 mg per dL reduction in on-treatment TG, the incidence of CHD events was reduced by 1.8% ($P<0.001$). In multivariate analysis, it also appeared that there was a significant effect of TG level on CHD event rate. After adjustment for LDL-C and other covariates, each 10 mg per dL reduction in on-treatment TG was associated with a 1.6% reduction in CHD events ($P<0.001$). Similarly, after adjustment for non-HDL-C and other covariates, each 10 mg per dL reduction in on-treatment TG was associated with a 1.4% reduction in CHD events ($P=0.01$).³⁴ On-treatment TG levels <150 mg per dL were independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG levels in patients after ACS may be an important consideration in addition to reducing LDL-C levels with statin therapy.³⁴

A Cox proportional hazards model was used to examine further the relationship between achieved LDL-C and TG at the initial day-30 time point and risk of recurrent CHD events in the PROVE IT-TIMI 22 trial, as shown in Figure 4. Compared with referent levels of LDL-C (≥70 mg per dL) and TG ≥150 mg

FIGURE 4 Triglyceride Levels and Risk of CHD Events (PROVE IT-TIMI 22)

A Cox proportional model was used to examine the relationship among low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and risk of recurrent coronary heart disease (CHD) events. Compared with LDL-C levels ≥70 mg per dL and TG levels ≥150 mg per dL (referent), lower CHD risk was observed with low on-treatment TG levels (<150 mg per dL) and LDL-C (<70 mg per dL) (hazard ratio [HR]=0.72; $P=0.017$), with a graded response for patients with LDL-C levels ≥70 mg per dL and TG levels <150 mg per dL (HR=0.85; $P=0.180$).³⁴ CHD events include death, myocardial infarction, and recurrent acute coronary syndrome (ACS); ACS patients treated with either 80 mg of atorvastatin or 40 mg of pravastatin; CHD event rate is adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment; lipid values are in mg per dL; n=4,162.

Reprinted from J Am Coll Cardiol, 2008;51(7):724-30: Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial.³⁴ (With permission from Elsevier.)

per dL), lower CHD risk was observed with low on-treatment TG (<150 mg per dL) and LDL-C (<70 mg per dL) (HR=0.72; $P=0.017$), with a graded trend observed among patients with LDL-C levels ≥70 mg per dL and TG <150 mg per dL (HR=0.85; $P=0.180$).³⁴ Patients with a TG level <150 mg per dL, even if they had LDL-C levels >70 mg per dL, experienced CHD event rates 15.0% lower than those patients who had low LDL-C but high TG. Additionally, when TG levels were <150 mg per dL, having a lower LDL-C was beneficial compared with higher LDL-C levels; however, in patients with TG levels <150 mg per dL LDL-C level did not appear to have as large an effect. The benefits conferred through reductions of LDL-C by statin therapy in the PROVE IT-TIMI 22 trial could be modulated by either having a TG level <150 mg per dL, or having a TG level >150 mg per dL. Thus, among patients receiving statin therapy after ACS, on-treatment TG level <150 mg per dL was associated with a lower risk of recurrent CHD events independent of the level of LDL-C. These data support the concept that achieving low levels of both LDL-C

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FIGURE 5 Non-HDL-C Is a Significant Predictor of CHD Risk

Data from the Framingham Heart Study revealed no association between LDL-C and the risk for incident coronary heart disease (CHD) within non-HDL-C levels. Non-HDL-C was found to be strongly associated with CHD risk within every level of LDL-C.⁵¹

Reprinted from Am J Cardiol, 2006; 98(10):1363-68: Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease.⁵¹ (With permission from Elsevier.)

and TG may be an important therapeutic strategy in patients after an ACS.³⁴

When considering lipid parameters beyond LDL-C, non-HDL-C has been gaining recognition. However, clinicians have been somewhat slow to embrace it, possibly because non-HDL-C is defined by what it is not, rather than by what it is. To address this potential difficulty, one way to think about non-HDL-C is as the total atherogenic burden, which can be quickly calculated from nonfasting lipid profiles. Mathematically, non-HDL-C is equivalent to subtracting HDL-C from total cholesterol (i.e., non-HDL-C = total cholesterol - HDL-C).

Through this calculation, all atherogenic lipoproteins, such as LDL-C, VLDL-C, IDL-C, remnant lipoproteins and particles, and Lp(a), are captured by the non-HDL-C measure. Because VLDL-C is the most readily available measure of atherogenic remnant lipoproteins, it can be combined with LDL-C to improve cardiovascular risk prediction by calculating an approximate value of non-HDL-C.¹⁸ A normal VLDL-C level is defined as the value when the TG level is <150 mg per dL, which is typically ≤30 mg per dL.¹⁸ Thus, the goal for non-HDL-C is 30 mg per dL greater than the goal for LDL-C.¹⁸ If a patient's LDL-C goal is <100 mg per dL, then the non-HDL-C goal is <130 mg per dL.

Non-HDL-C is a significant predictor of CHD risk and is highly correlated with various lipid parameters that are associated with CHD risk. Non-HDL-C is correlated with apolipoprotein

B, which is the protein portion of every atherogenic lipoprotein, and with LDL particle number and size.⁴⁷⁻⁵⁰ Data from the Framingham Heart Study were analyzed to investigate the usefulness of non-HDL-C in predicting CHD risk. In this analysis (2,693 men; 3,101 women) non-HDL-C was compared with LDL-C as a predictor of CHD risk, and VLDL-C was assessed as an independent predictor of CHD risk. After multivariate adjustment, within non-HDL-C, no association was found between LDL-C and the risk for incident CHD, as shown in Figure 5. In contrast, a strong positive and graded association between non-HDL-C and risk for CHD was observed within every level of LDL-C. These results suggest that non-HDL-C is a stronger predictor of CHD risk than is LDL-C and that VLDL-C may play a critical role in the development of CHD.⁵¹ These data also were analyzed within TG levels <200 mg per dL and ≥200 mg per dL. Overall, the association with CHD incidence was stronger for non-HDL-C within every level of LDL-C than that for LDL-C within each level of non-HDL-C, regardless of whether TG levels were <200 mg per dL or ≥200 mg per dL.⁵¹

National Guidelines for Treating Beyond LDL-C

National guidelines address the treatment of atherogenic lipid parameters beyond LDL-C, such as high TG and non-HDL-C levels and low HDL-C. According to the NCEP ATP III guidelines, elevated LDL-C is the primary therapeutic target for interventions to decrease cardiovascular risk.¹⁸ However, as discussed previously, elevated TG and low HDL-C levels also make significant contributions to increased cardiovascular risk even after LDL-C treatment goals have been reached. The NCEP ATP III guidelines indicate that an elevated non-HDL-C level in patients with hypertriglyceridemia (i.e., TG ≥200 mg per dL) imparts an increased risk for cardiovascular events even after the LDL-C goal has been reached.^{19,52} For this reason, non-HDL-C is considered to be a secondary therapeutic target (after LDL-C) that may provide additional risk reduction.⁵² A 2004 update to the NCEP ATP III guidelines emphasized the increasing evidence for the benefits of combination therapy, compared with monotherapy, by recommending the possibility of adding a fibrate or niacin to LDL-lowering therapy in high-risk patients who have elevated TG or low HDL-C levels.¹⁹

In 2007, the American Diabetes Association (ADA) and the American Heart Association (AHA) collaborated on a joint statement outlining treatment guidelines in the Primary Prevention of Cardiovascular Disease in Patients with Diabetes.⁵³ This statement combines the recommendations of both organizations where possible and also recognizes areas in which ADA and AHA recommendations differ. The joint statement, like the NCEP ATP III guidelines, recommends that LDL-C should be the primary target of lipid-lowering therapy. The ADA/AHA guidelines further recommend an LDL-C goal level <100 mg per dL in patients with diabetes.⁵³ Also, because levels of TG-rich lipoproteins, especially VLDL-C, are often elevated in patients

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with diabetes and appear to be atherogenic, they are identified as a secondary target of lipid-lowering therapy after the LDL-C goal level is achieved.⁵³

The ADA and AHA have also individually released guidelines for cardiovascular prevention that include therapies targeting multiple lipid parameters. According to the 2008 ADA guidelines, the primary goal is an LDL-C level <100 mg per dL in individuals without overt cardiovascular disease, although a lower LDL-C goal (<70 mg per dL) is an option in individuals with overt disease.⁵⁴ Additionally, the ADA recognizes serum TG concentration as a surrogate measure for atherogenic TG-rich lipoproteins and suggests a TG goal level <150 mg per dL.⁵⁴ Finally, the ADA standards suggest HDL-C goals of >40 mg per dL in men and >50 mg per dL in women.⁵⁴ The AHA suggests an alternative approach for patients who have elevated TG levels. For TG levels between 200 and 499 mg per dL, the AHA recommends that non-HDL-C should be calculated, and sets a non-HDL-C goal of <130 mg per dL.⁵³ This non-HDL-C target level is similar to that recommended by the NCEP ATP III guidelines.⁵³ Interestingly, the AHA advocates efforts to raise HDL-C levels but does not specifically designate therapeutic goals.

In addition to setting lipid goals, therapeutic recommendations have been advanced by the ADA and AHA. The 2008 ADA guidelines recommend that statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt cardiovascular disease and for diabetic patients who do not have cardiovascular disease but are older than 40 years of age and have one or more other cardiovascular risk factors.⁵⁴ One instance in which LDL-C is not the primary target of lipid-lowering therapy is in patients who have TG levels >500 mg per dL. If TG levels are >500 mg per dL, the AHA says that the greatest threat to life becomes pancreatitis; therefore, lowering TG levels to reduce the risk of pancreatitis is the primary goal. In this case, the AHA recommends that a TG-lowering therapy, such as a fibrate or niacin, is the first priority. After TG is sufficiently controlled, LDL-C and non-HDL-C levels need to be addressed through LDL-lowering therapy. Moreover, a non-HDL-C goal <130 mg per dL should be achieved in these patients, if possible.⁵³ Considering all of the lipid abnormalities, the ADA/AHA joint statement suggests that a combination of statins with fibrates or niacin may be necessary to achieve multiple lipid targets.⁵³

Similar guidelines for lipid levels and treatment recommendations were published in the 2006 AHA/American College of Cardiology Secondary Prevention Guidelines.⁵⁵ This update, related to secondary prevention for patients with known cardiovascular disease, provides target levels for TG and non-HDL-C. The guidelines recommend that if TG levels are between 200 and 499 mg per dL, the non-HDL-C goal level should be <130 mg per dL. Moreover, it is reasonable to consider reducing non-HDL-C levels to <100 mg per dL when a patient is at sufficiently high risk for cardiovascular events. The therapeutic options to reduce

non-HDL-C levels are more intensive LDL-C-lowering treatments, which will reduce LDL particle number, or the addition of niacin or a fibrate after LDL-lowering therapy has been initiated. As mentioned previously, when baseline TG levels are ≥500 mg per dL, the therapeutic intervention should be a TG-lowering treatment (i.e., a fibrate or niacin) to prevent pancreatitis before starting LDL-lowering therapy. Only after TG-lowering therapy has been initiated, and TG levels have been reduced, should efforts turn to treating LDL-C. For these patients, the non-HDL-C goal should be <130 mg per dL.⁵⁵

Again, consider the NCEP ATP III guidelines and the ADA and AHA national guidelines, all of which addressed various lipid parameters as well as therapeutic agents for achieving multiple lipid values. These national guidelines all support raising HDL-C to reduce cardiovascular risk, and they specifically mention fibrates or niacin as a therapeutic option to do so.^{18,53,54} The NCEP ATP III guidelines state: “Among lipid-lowering agents, nicotinic acid appears to be the most effective for favorably modifying all of the lipoprotein abnormalities associated with atherogenic dyslipidemia.”¹⁸ Similarly, the 2007 ADA/AHA joint scientific statement reports that “the most effective available drug for raising HDL-C levels is nicotinic acid.”^{53,56} Because there is an extensive constellation of lipid parameters that should be addressed, there is a promising future for HDL-C-raising therapies, particularly in combination with LDL-C-lowering therapies.^{57,58} The key is to increase HDL-C in a productive and nondetrimental way. Niacin safely raises HDL-C and has a completely different mechanism of action than torcetrapib, which also increases HDL-C but has been reported to also increase cardiovascular risk.⁵⁹ Niacin is the most effective currently available agent for raising HDL-C and has been in clinical use for more than 5 decades with an established safety profile.⁵⁷ Niacin can also be used safely in combination with statins and in patients with diabetes.⁵⁸

Therapeutic Options for Reducing Cardiovascular Risk

A large amount of evidence has been presented to show the efficacy of statin therapy for the reduction of both LDL-C levels and cardiovascular risk,^{2,27-32} and niacin has been investigated for its lipid-lowering effects for several decades. The first large trial that established the benefit of niacin was the Coronary Drug Project (CDP), which was a randomized, double-blind, placebo-controlled trial with a primary end point of total mortality.⁶⁰ This trial, conducted between 1966 and 1974 and published in 1975, enrolled 8,341 men with a history of prior MI to 6 treatment arms, including treatments with 5 different lipid-lowering agents. The trial's groups were: placebo, low-dose estrogen, high-dose estrogen, clofibrate, dextrothyroxine, and niacin. Both estrogen treatment groups and the dextrothyroxine group were discontinued before the scheduled completion of the study due to increased cardiovascular event rates. The clofibrate and niacin groups completed the study (follow-up ranged from 5 to 8.5 years per patient; mean 6.2 years); at the conclusion of the trial,

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the only treatment arm that showed any benefit was the niacin therapy group.⁶⁰ Total mortality tended to be lower in the niacin group (24.4%; $n=1,119$) than in the placebo group (25.4%; $n=2,789$) by the end of the study, although this difference was not statistically significant. Participants in the niacin treatment arm did have a significant reduction in the combined outcome of CHD death and nonfatal MI (15% reduction; $P<0.05$), nonfatal MI (26% reduction; $P<0.05$), and cerebrovascular events categorized as stroke or transient ischemic attack (24% reduction; $P<0.05$) during the follow-up.⁶⁰ Niacin monotherapy also provided a significant reduction in the number of patients having any cardiovascular surgery from the time of trial entry to a follow-up of 5 years (47% reduction; $P<0.05$).⁶⁰

Although the CDP demonstrated the benefits of niacin on cardiovascular risk, one of the lingering questions about niacin has been whether it promotes an increase in insulin resistance. Therefore, there has been some concern surrounding the use of niacin in patients with abnormal glucose metabolism or with diabetes. These concerns were addressed in a 2005 post-hoc analysis of CDP data that evaluated rates of nonfatal MI in patient subgroups defined by baseline fasting plasma glucose (FPG) levels.⁶¹ This additional analysis of CDP data showed that patients with diabetes appear to benefit as much, if not more, from niacin therapy than do nondiabetic patients. Compared with placebo, niacin reduced the risk of 6-year recurrent MI similarly (interactive P value is ≥ 0.05 or nonsignificant) in patients at all levels of baseline FPG.⁶¹ Individuals with a baseline FPG level <95 mg per dL had a 30% risk reduction with niacin; patients with an FPG level between 95 and 125 mg per dL showed an approximate 25% risk reduction with niacin. Perhaps most importantly, patients with FPG levels ≥ 126 mg per dL, which is the current ADA definition of diabetes, had a 57% risk reduction with niacin.^{54,61} Compared with placebo, niacin treatment tended to reduce the 6-year risk of the combined end point of CHD death or nonfatal MI similarly (interactive P value nonsignificant) in patients at all baseline FPG levels. The beneficial effect of niacin on reducing recurrent nonfatal MI and CHD events was not associated with increased baseline FPG levels, even in those patients with the highest baseline FPG levels.⁶¹ Therefore, any increase in FPG levels with niacin did not translate into any disadvantage with respect to CHD events.⁶¹

Based on the evidence that indicates the importance of lowering LDL-C and raising HDL-C as well as the efficacy of statin monotherapy or niacin monotherapy for reducing cardiovascular risk, an obvious question follows: if lowering LDL-C with statins is beneficial and raising HDL-C with niacin is also beneficial, should a combination therapy that includes both treatments be even better? Trials studying combination therapy have, in fact, shown remarkable cardiovascular risk reductions that various monotherapies—whether a statin, a high-dose statin, a fibrate, or niacin—cannot duplicate. As Figure 6 shows, significant residual cardiovascular risk remains after reducing LDL-C levels in the

major statin trials.^{27-29,32} Even with high-dose statin therapy (80 mg vs. 10 mg of atorvastatin in TNT), significant residual risk remains, even though the LDL-C level is reduced to approximately 77 mg per dL.¹⁵ As with statin monotherapy, fibrate and niacin monotherapies also are effective in reducing cardiovascular risk (Veterans Affairs HDL Cholesterol Intervention Trial [VA-HIT] and CDP); however, residual cardiovascular risk was still observed to exist in patients in those trials.^{60,62} The Familial Atherosclerosis Treatment Study (FATS) and HDL-Atherosclerosis Treatment Study (HATS) trials, although small, showed dramatic CHD event reduction with the use of combination therapies.^{63,64} In the FATS trial, a combination therapy of niacin plus a bile acid sequestrant was used, and in the HATS trial, niacin plus simvastatin was used. The striking benefits observed in both trials suggest that combination therapy may be most effective for optimally reducing CHD risk—simultaneously lowering LDL-C levels, predominantly with statins, while raising HDL-C levels yields what appears to be the most cardiovascular event reduction.^{63,64}

A meta-analysis of 23 different lipid trials investigated the cardiovascular event rate reductions associated with decreases in LDL-C levels and increases in HDL-C levels and revealed that the 2 components were statistically independent.⁶⁵ Therefore, the benefits accrued from an increase in HDL-C would be additive to those benefits conferred by a decrease in LDL-C, and the combined cardiovascular benefits would be greater than that from altering any single lipid parameter alone. The meta-analysis, in fact, demonstrated that the sum of the percent reduction in LDL-C and the percent increase in HDL-C predicts cardiovascular benefits much more effectively than either lipoprotein component alone. If this simple algorithm is proven accurate, a readily attainable 40% reduction in LDL-C and a 30% elevation in HDL-C will result in a 70% CHD risk reduction and a revolution in cardiovascular disease prevention.⁶⁵ The meta-analysis revealed a strong linear association between the composite lipoprotein variable (i.e., the sum of the HDL-C percent increase and LDL-C percent reduction, placebo adjusted) and the therapeutic reduction in the predefined primary clinical study end point rate relative to the placebo rate.⁶⁵ Importantly, combination therapy trials, including a statin-plus-resin trial and niacin-plus-statin trials, showed the largest reductions in LDL-C levels and largest increases in HDL-C levels, leading to the largest reduction in cardiovascular events. This meta-analysis supports the hypothesis that patients with vascular disease gain additive benefits from LDL-C reduction and HDL-C elevation.⁶⁵

The HATS trial enrolled 160 patients with CAD in a 3-year, double-blind, placebo-controlled study that evaluated slow-release niacin therapy. The patient population had low HDL-C levels (≤ 35 mg per dL in men or ≤ 40 mg per dL in women) and acceptable LDL-C levels (≤ 145 mg per dL). An angiogram was performed on patients at baseline and after a 2-year follow-up; the end points were angiographic evidence of a change in coronary stenosis and the occurrence of a first cardiovascular event, such

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FIGURE 6 Comparing Monotherapies With Combination Therapies

Residual cardiovascular risk remains after reducing LDL-C, even with high-dose statin therapy (80 mg of atorvastatin vs. 10 mg of atorvastatin in Treating to New Targets [TNT]). Monotherapy with fibrates or niacin is also effective in reducing cardiovascular risk, although residual cardiovascular risk remains in these patients, too. Dramatic coronary heart disease (CHD) event reduction has been observed in trials of combination therapies (niacin plus a bile acid sequestrant (BAS) or niacin plus a statin). In TNT, the control condition was 10 mg of atorvastatin; in the other trials, the control condition is placebo. In the Scandinavian Simvastatin Survival Study (4S), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), Heart Protection Study (HPS), and West of Scotland (WOS), the treatment condition is statin therapy.

The references for these data are: 4S, LIPID, HPS, WOS, TNT, Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT), Coronary Drug Project (CDP), Familial Atherosclerosis Treatment Study (FATS), and HDL-Atherosclerosis Treatment Study (HATS).^{15,27-29,32,60,63}

as death, MI, stroke, or cardiac revascularization.⁶⁴ Study participants received either active niacin plus active simvastatin or placebo niacin plus placebo simvastatin, with or without active antioxidant vitamins or placebo antioxidant vitamins. The angiographic results of the trial indicated that patients in the placebo group experienced an increase in percent stenosis, as could be expected through the natural progression of atherosclerosis. The group that received the niacin/simvastatin combination exhibited the greatest benefit. For the angiographic primary end point, which was the change in severity of the most severe stenosis in 9 proximal coronary segments, regression in stenosis was observed in patients receiving niacin/simvastatin treatment (−0.4% stenosis change) versus patients receiving placebo (+3.9% stenosis change; $P < 0.005$).⁶⁴ Interestingly, some of that benefit in stenosis regression was lost in the patients who received

antioxidant vitamins in addition to the niacin/simvastatin combination (+0.7% stenosis change), though the change was still significantly different from the placebo group ($P < 0.005$).⁶⁴ The clinical results from HATS exactly mirrored the changes observed through angiography. That is, the worst clinical results occurred in the placebo arm, the best clinical results occurred in the niacin/simvastatin combination therapy arm, and some of the benefit conferred by the niacin/simvastatin combination therapy was lost by adding antioxidant vitamins to the treatment regimen. The composite clinical end point of death from coronary causes, confirmed MI or stroke, or revascularization was reduced by 90% in patients treated with niacin/simvastatin versus placebo ($P = 0.03$).⁶⁴ Patients who also received antioxidant vitamins showed no significant change in clinical endpoints.⁶⁴ The authors concluded that the addition of niacin to simvastatin

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therapy in CAD patients with low HDL-C levels and normal LDL-C levels resulted in slight coronary atherosclerosis regression and a significant reduction (90%) in clinical coronary events over 3 years.⁶⁴ Interestingly, more in-depth analyses of the data from HATS revealed that patients receiving antioxidant vitamins in addition to niacin/simvastatin therapy had a blunted HDL-C increase.⁶⁶ Therefore, those patients did not have as large an increase in HDL-C as did those patients who received only niacin/simvastatin, which provides further evidence of the importance of HDL-C in reducing cardiovascular events and its antiatherogenic properties. Several studies have reported similar effects of antioxidant vitamins on HDL-C.^{67,68}

Although the HATS study provided noteworthy data, the study did not use a statin monotherapy group with which a niacin/statin combination therapy could be compared. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trials sought to fill this gap. These trials were based on carotid intima-medial thickness (CIMT) as the surrogate marker of atherosclerosis, which involved an examination of the thickness of the innermost lining of the carotid artery. ARBITER 2 was a double-blind, randomized, placebo-controlled study of once-daily 1,000 mg of extended-release (ER) niacin added to background statin therapy in 167 patients with known CHD and low levels of HDL-C (<45 mg per dL).⁶⁹ The background statin in the study was at the discretion of each patient's primary care physician. Thus, the 2 groups in the trial were placebo/statin and niacin ER/statin. Trial participants were then followed for 12 months, after which time the primary end point of CIMT change (in mm) was assessed. The change in CIMT during the 12 months of the trial was 0.044 mm in the placebo/statin group ($P<0.001$) and 0.014 mm in the niacin ER/statin group ($P=0.23$), though the overall difference in CIMT progression between the placebo/statin group and niacin ER/statin group was not statistically significant ($P=0.08$). Clinical cardiovascular events, defined as a composite of hospitalization for an ACS, stroke, an arterial revascularization procedure, or sudden cardiac death, occurred in 3 patients treated with niacin ER/statin combination therapy and in 7 patients treated only with a statin ($P=0.20$).⁶⁹ In both therapeutic conditions, either placebo/statin or niacin ER/statin, an increase in CIMT was observed, but the increase in CIMT tended to be greater in the placebo/statin group than in the niacin ER/statin group.

At the conclusion of the ARBITER 2 trial, the investigators continued the trial with ARBITER 3, which was a prespecified 12-month extension study of ARBITER 2 that included 130 patients who had completed the blinded 12-month end point CIMT assessment. Participants in ARBITER 3 were placed on open-label niacin ER, such that patients initially randomized to the niacin ER/statin group continued on this combination therapy and received niacin ER/statin for the entire 2-year duration of the studies. Similarly, those patients who were initially randomized to the placebo/statin group were switched to niacin ER/statin

combination therapy. In ARBITER 3 a prespecified end point was the within group changes in mean CIMT across 3 different treatment groups. The groups included patients receiving placebo/statin for 12 months ($n=61$), niacin ER/statin for 12 months ($n=78$ subjects from ARBITER 2 and 47 subjects crossing over from placebo in ARBITER 2 to niacin ER in ARBITER 3), and niacin ER/statin for 24 months ($n=57$ subjects spanning both ARBITER 2 and ARBITER 3). Among the 125 patients treated with niacin ER/statin for 12 months, there was a significant regression in CIMT (-0.027 mm; $P<0.001$ vs. placebo/statin), shown in Figure 7. Similarly, among the 57 patients treated with niacin ER/statin for 24 months, there was a significant regression in CIMT (-0.041 mm; $P<0.001$ vs. placebo/statin). Thus, when niacin ER was added to statin therapy, there was a significant regression in atherosclerosis as measured by CIMT after both 12 and 24 months of treatment.⁷⁰ In patients with diabetes or the metabolic syndrome ($n=62$), there was also a significant regression in CIMT (-0.046 mm; $P<0.001$ vs. placebo/statin) with niacin ER/statin after 12-24 months of treatment versus statin monotherapy.⁷⁰ Therefore, the ARBITER trials provide additional evidence to support the promise of long-term combination therapy in reducing cardiovascular risk. Overall, in terms of niacin/statin combination therapy safety, the National Lipid Association (NLA) Safety Task Force concluded that the 2 decades of clinical evidence since the introduction of statins do not support a general myopathic effect of niacin either alone or in combination with statins. In fact, no major clinical trial has suggested a potential drug interaction between statins and niacin, and there is no proposed theoretical mechanistic reason to expect a drug interaction.⁵⁸

When all of the evidence addressing various lipid parameters and cardiovascular risk is considered, it is clear that lipid management should not be limited to statin monotherapy. Rather, achieving multiple lipid targets and reducing cardiovascular risk should be about statins and additional therapeutic agents to further reduce cardiovascular risk by targeting lipid parameters beyond LDL-C. Current, ongoing clinical trials will augment the already substantial catalog of knowledge about atherogenic lipid species and treatments thereof. The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High TG and Impact on Global Health Outcomes (AIM-HIGH) study has enrolled approximately 3,300 men and women with vascular disease (CHD, cardiovascular disease, peripheral artery disease [PAD]) and atherogenic dyslipidemia (TG level >150 mg per dL and HDL-C level <40 mg per dL).⁷¹ A 4-year median follow-up is planned for this trial that started in September 2005. Patients enrolled in AIM-HIGH will be treated either with a combination therapy of niacin ER (2,000 mg) and simvastatin (40 mg) or simvastatin monotherapy. As a therapeutic target, the LDL-C goal level is <80 mg per dL, and the primary outcome is the first major cardiovascular event.⁷¹ The Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) has enrolled approximately 20,000 patients with preexisting ath-

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erosclerotic vascular disease (cardiovascular disease, CHD, PAD) and began in January 2007. Patients in this trial, which includes a planned 4-year follow-up, will be assigned to combination therapy with niacin ER/laropiprant (2,000 mg) and simvastatin (40 mg) or simvastatin monotherapy. Some patients may also receive ezetimibe (10 mg) to reach optimal LDL-C levels. The LDL-C target level for all groups is <77 mg per dL. The primary outcome in HPS2-THRIVE is the first major vascular event.^{72,73} The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol-HDL and LDL Treatment Strategies (ARBITER 6-HALTS) trial, which began enrolling participants in November 2006, involves approximately 400 patients with CHD or CHD equivalents who have achieved an LDL-C goal <100 mg per dL and who have a reduced HDL-C level (<50 mg per dL for men and <55 mg per dL for women). Patients on statin monotherapy will be assigned to either intensified LDL-C-lowering therapy with ezetimibe (10 mg per day) or HDL-C-raising therapy with niacin ER (≥1,000 mg per day, titrated to maximum tolerable dose up to 2,000 mg per day). The primary end point is mean CIMT change after 14 months.⁷⁴

Summary

Several lipid parameters, such as LDL-C, TG, HDL-C, and atherogenic remnant lipoproteins, are strongly associated with atherosclerosis and heightened cardiovascular risk. The primary therapeutic target is LDL-C, and lipid-lowering therapy with statins has proved to be highly beneficial for reducing cardiovascular event rates. However, a substantial amount of residual cardiovascular risk remains in patients treated with statins, even intensive statin therapy, to reduce LDL-C levels. As a result, there has been an increased focus on elevated TG levels and low HDL-C levels and their significant contributions to residual cardiovascular risk even when LDL-C levels are well controlled. In response to the increasing importance of an array of lipid parameters, several noteworthy sets of national guidelines have been published. All of the guidelines report that elevated LDL-C is the primary therapeutic target. However, these guidelines also recommend that combination therapy may be necessary to achieve multiple lipid targets, including LDL-C, non-HDL-C, HDL-C, and TG. Niacin has been demonstrated to exert beneficial effects in this regard; niacin promotes significant increases in antiatherogenic HDL-C and, consequently, reduces cardiovascular risk. Significantly, the benefits conferred by statins through the reduc-

FIGURE 7 Carotid Intima-Medial Thickness With Statin Monotherapy and Combination Therapy

In 125 patients treated with extended-release niacin (niacin ER) for 12 months, analysis of variance (ANOVA) revealed a significant regression of carotid intima-medial thickness (CIMT; -0.027 ; $P<0.001$ vs. statin monotherapy). In 57 patients treated with niacin ER for 24 months, ANOVA revealed a significant regression of CIMT (-0.041 ; $P<0.001$ vs. statin monotherapy). In patients with the metabolic syndrome (Met-S) or diabetes ($n=62$), ANOVA revealed a significant regression of CIMT (-0.046 ; $P<0.001$) in statin plus niacin ER versus statin monotherapy after 12-24 months of treatment.⁷⁰

^a $P<0.001$ versus statin monotherapy; 92.3% of patients were on simvastatin; mean dose was 36 mg per day of simvastatin, and all patients received 1,000 mg of niacin ER.

tion of LDL-C levels are additive to the benefits of raising HDL-C levels with niacin. By combining niacin with the LDL-lowering therapy of statins, several atherogenic lipid abnormalities are addressed, the progression of atherosclerosis in CHD patients is slowed, and residual cardiovascular risk is reduced. Moreover, niacin/statin combination therapy appears to be safe and may be necessary to optimally reduce cardiovascular risk in high-risk patients. The completion of several ongoing clinical outcome trials, such as AIM-HIGH, HPS2-THRIVE, and ARBITER 6-HALTS, will provide important data that should continue to expand and refine therapeutic strategies targeting dyslipidemia and cardiovascular disease.