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
LEARNING OBJECTIVES

After reading this issue of *CMDManagement™*, participants should be able to:

- Interpret and apply to practice as appropriate the results of recent clinical trials underscoring the management of patients with mixed dyslipidemia, namely elevated TG and low HDL-C
- Discuss the safety and efficacy of combination therapy for the treatment of lipid disorders based on recent clinical-trial results
- Determine the appropriateness of combination therapy as secondary prevention among patients with diabetic dyslipidemia
- Identify strategies to improve global risk-factor control among patients at high risk for cardiovascular disease

TARGET AUDIENCE: primary-care physicians, cardiologists, endocrinologists, and other healthcare professionals who treat patients at risk for, or with, CVD

RELEASE/END DATES: 9/7/07–9/7/08

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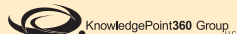
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Beyond LDL-C: Focus on HDL-C and TG— A Review of Clinical-Trial Data

Clinical-trial data have shown that reduction of LDL-C levels significantly reduces the incidence of coronary heart disease (CHD), decreases the occurrence of cardiac events, and slows atherosclerotic progression. Based on this evidence, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) identifies LDL-C as the primary target of cholesterol-lowering therapy.¹ However, a substantial number of individuals still experience cardiac events or exhibit evidence of atherosclerotic progression despite achieving significant LDL-C reduction with treatment. An inadequate response in some patients may be related to metabolic abnormalities that cannot be fully modified by LDL-C reduction. This article reviews the latest clinical-trial data related to the primary and secondary prevention of CHD via strategies that go beyond LDL-C reduction, with a focus on increasing HDL-C levels and decreasing TG levels, or both.

Trial: Japan EPA Lipid Intervention Study (JELIS)

Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.

Emerging evidence suggests that an increased intake of long-chain omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) protects against CHD mortality. JELIS was a randomized, open-label study that examined the effects of long-term EPA use on major coronary events in hypercholesterolemic patients in Japan who consumed a large amount of fish. A total of 18,645 patients with TC >253 mg/dL received 1,800 mg of EPA with statin (n=9,326) or statin only (n=9,319) over 5 years. The primary endpoint was any major coronary event, which included sudden cardiac death, fatal and nonfatal myocardial infarction (MI), and other nonfatal events such as unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At a mean follow-up of 4.6 years, the primary endpoint occurred in 262 patients (2.8%) in the EPA group and in 324 patients (3.5%) in the control group, representing a significant 19% relative reduction in major coronary events ($P=0.011$). Posttreatment LDL-C concentrations decreased 25% in both treatment groups. Among patients with a history of coronary artery disease (CAD) receiving EPA treatment, major coronary events were significantly reduced by 19% ($P=0.048$). Among patients with no history of CAD, EPA treatment reduced major coronary events by 18%, but this result was not statistically significant ($P=0.132$).

These findings suggest that EPA may be of value in reducing major coronary events when used with LDL-C-lowering therapy.

Trial: SAFARI

Grundy SM, Vega GL, Yuan Z. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia [The SAFARI Trial]. *Am J Cardiol*. 2005;95(4):462-468.

It is well-documented that patients with combined hyperlipidemia (ie, elevated TG, and LDL-C, and multiple lipoprotein abnormalities) are at increased risk for CHD. SAFARI was a randomized, double-blind, active-controlled study that evaluated the

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effectiveness and tolerability of simvastatin plus fenofibrate versus simvastatin alone for combined hyperlipidemia. Following a 6-week diet and placebo run-in period, 618 patients with combined hyperlipidemia (fasting TG ≥ 150 and ≤ 500 mg/dL, and LDL-C > 130 mg/dL) were randomized to simvastatin 20 mg (n=207) or combination simvastatin 20 mg plus fenofibrate 160 mg (n=411) for 12 weeks. From baseline to week 12, median TG levels decreased 43.0% with simvastatin plus fenofibrate and 20.1% with simvastatin monotherapy, representing a significant treatment difference of -23.6% ($P < 0.001$). Likewise, simvastatin plus fenofibrate compared with simvastatin alone produced a significantly greater decrease in mean LDL-C (31.2% vs 25.8%; treatment difference, -5.4%; $P < 0.001$) and a significantly greater increase in mean HDL-C (18.6% vs 9.7%; treatment difference, +8.8%; $P < 0.001$). There were no drug-related serious adverse events noted during the trial, and none of the subjects experienced clinical myopathy or severe liver function abnormalities.

The principal finding of this study is that combination therapy with simvastatin plus fenofibrate produces a favorable lipoprotein profile in patients with combined hyperlipidemia.

Trial: Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

Keach A, Simes RJ, Barter P, et al, for the FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366(9500):1849-1861.

A randomized controlled study, FIELD evaluated the effects of long-term fenofibrate therapy on cardiovascular events among patients with type 2 diabetes. Dyslipidemia in these patients places them at increased risk for CVD. A total of 9,795 patients with type 2 diabetes aged 50–75 years (TC 117–253 mg/dL and TC/HDL-C ratio of ≥ 4.0 or TG < 195 mg/dL) were randomized to micronized fenofibrate 200 mg (n=4,895) or to placebo (n=4,900). Among these patients, 2,131 had previous CVD, whereas 7,664 did not. The primary endpoint was coronary events (CHD death or nonfatal MI). After a median of 5 years, 5.9% (n=288) of patients on placebo and 5.2% (n=256) of patients on fenofibrate had a coronary event, representing a nonsignificant relative reduction of 11% (hazard ratio [HR] 0.89, 95% confidence interval [CI], 0.75–1.05; $P = 0.16$). Fenofibrate therapy was associated with a significant 24% reduction in nonfatal MI (HR, 0.76; 95% CI, 0.62–0.94; $P = 0.010$) and a nonsignificant increase in CHD mortality (HR, 1.19; 95% CI, 0.90–1.57; $P = 0.22$). Moreover, total CVD events were significantly reduced from 13.9% to 12.5% (HR, 0.89; 95% CI, 0.80–0.99; $P = 0.035$). Coronary revascularization decreased by 21% (HR, 0.79; 95% CI, 0.68–0.93; $P = 0.0003$). Total mortality occurred at a similar rate among the fenofibrate and placebo groups (7.3% vs 6.6%; $P = 0.18$). Also, patients treated with fenofibrate had significantly less albuminuria progression ($P = 0.002$) and significantly less retinopathy needing laser treatment (5.2% vs 3.6%; $P = 0.0003$). However, these patients also experienced a slight increase in pancreatitis (0.8% vs 0.5%; $P = 0.031$) and pulmonary embolism (1.1% vs 0.7%; $P = 0.022$).

In patients with diabetes, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events but did reduce total cardiovascular events, primarily because of fewer nonfatal MIs and revascularizations. The investigators surmised that the higher rate of statin use in the placebo group may have masked a moderately large treatment effect with fenofibrate on the primary endpoint.

Trials: Studies of Peroxisome Proliferator-Activated Receptor (PPAR- α) Agonists

Nissen SE, Nicholls SJ, Wolski K, et al. Effects of a potent and selective PPAR- α agonist in patients with atherogenic dyslipidemia or hypercholesterolemia. Two randomized controlled trials. *JAMA*. 2007;297(12):1362-1373.

Currently available fibrates are weak agonists of the PPAR- α , a ligand-activated nuclear transcription factor that modulates the expression of genes involved in lipid

and glucose metabolism. Potent and selective PPAR- α agonists have been investigated as possible treatments for dyslipidemia and hypercholesterolemia. These multicenter controlled trials assessed the effects of LY518674, a PPAR- α agonist that is approximately 10,000 times more potent than fenofibrate, in patients with dyslipidemia or hypercholesterolemia. In the atherogenic dyslipidemia study, patients with elevated TG and low HDL-C were randomized to placebo, fenofibrate (200 mg), or LY518674 (10, 25, 50, or 100 μ g) for 12 weeks. In the hypercholesterolemia study, patients with elevated LDL-C were randomized to placebo or atorvastatin (10 or 40 mg) for 4 weeks, then to placebo or to LY518674 (10 or 50 μ g) for 12 more weeks. In the dyslipidemia study, LY518674 (25 μ g) and fenofibrate increased HDL-C by 5.9 mg/dL (15.8%) and 5.5 mg/dL (14.4%), respectively (both $P < 0.001$ vs placebo; $P = 0.79$ between treatments). Greater LY518674 doses produced smaller HDL-C increases. Decreases in TGs were comparable with LY518674 and fenofibrate. LY518674 was also associated with a

dose-dependent increase in LDL-C. In the hypercholesterolemia study, LY518674 (10 or 50 μ g) increased HDL-C by 6.3 to 6.7 mg/dL (12.5%–15.0%), while decreasing LDL-C by 21.4 to 26.0 mg/dL (13.2%–15.8%) and TGs approximately 37%. Among patients with dyslipidemia, LY518674 and fenofibrate decreased TGs and increased HDL-C but also increased serum creatinine. In contrast to fenofibrate, LY518674 also increased LDL-C but did not further lower LDL-C when combined with atorvastatin. Among patients with hypercholesterolemia, LY518674 reduced TG and increased HDL-C. In the dyslipidemia study, LY518674 (at higher doses of 50 and 100 mg) and fenofibrate raised serum creatinine levels ($P < 0.001$ versus placebo).

This study confirms previous reports that fenofibrate raises creatinine levels. The clinical significance of this increase with some fibrates is unresolved.

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RADIANCE 1, ILLUSTRATE: Effects of a CETP Inhibitor on Atherosclerotic Progression

One strategy proposed in recent years to raise HDL-C levels is inhibition of cholesteryl ester transfer protein (CETP), which facilitates the transfer of cholesteryl ester from HDL-C to LDL-C and VLDL-C. CETP inhibition thus results in a higher HDL-C. One of the first CETP inhibitors to undergo clinical trials was torcetrapib, which had been shown to increase HDL-C by >50%.¹ Two recent studies examined the effects of torcetrapib on carotid intima-media thickness (CIMT), a surrogate marker for CVD endpoints.^{2,3}

Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (RADIANCE 1), assessed whether torcetrapib can reduce atherosclerotic vascular disease by increasing HDL-C levels among 850 patients with heterozygous familial hypercholesterolemia (FH), who underwent B-mode ultrasound at baseline and follow-up to measure CIMT change.

- After an atorvastatin run-in period, patients received atorvastatin or atorvastatin plus torcetrapib 60 mg for 2 years. In the atorvastatin-only group, mean HDL-C was 52.4 mg/dL and mean LDL-C was 143.2 mg/dL versus 81.5 mg/dL and 115.1 mg/dL, respectively, with torcetrapib.
- During the study, average systolic blood pressure (BP) increased by 2.8 mm Hg in the torcetrapib-atorvastatin group versus the atorvastatin-only group.
- The increase in maximum CIMT was 0.0053 mm/year in the atorvastatin-only

group and 0.0047 mm/year in the torcetrapib-atorvastatin group ($P = 0.87$).

- Annualized change in mean CIMT for the common carotid artery decreased 0.0014 mm/yr in the atorvastatin-only group versus an increase of 0.0038 mm/year in the torcetrapib-atorvastatin group ($P = 0.005$).
- Among patients with FH, torcetrapib plus atorvastatin versus atorvastatin alone did not result in further reduction of progression of atherosclerosis, and correlated with disease progression in the common carotid segment, despite an increase in HDL-C and decreases in LDL-C and TG.

The Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) trial determined the effect of torcetrapib on the progression of coronary atherosclerosis among 1,188 patients with CAD who underwent intravascular ultrasound (IVUS).

- After treatment with atorvastatin to reduce LDL-C to <100 mg/dL, patients were randomized to atorvastatin alone or atorvastatin plus torcetrapib 60 mg. At 2 years, disease progression was measured by repeat IVUS in 910 patients.
- Torcetrapib plus atorvastatin, versus atorvastatin alone, was associated with an approximate 61% relative increase in HDL-C and a 20% relative decrease in

LDL-C, achieving a LDL-C / HDL-C ratio of <1.0. However, torcetrapib was also associated with an average increase in systolic BP of 4.6 mm Hg.

- There was no significant difference in the increase in percent atheroma volume between the atorvastatin-only and torcetrapib-atorvastatin groups (0.19% vs 0.12%; $P = 0.72$).
- Torcetrapib was associated with a substantial increase in HDL-C and decrease in LDL-C, and an increase in BP. No significant decrease in atherosclerotic progression was noted.

These angiographic trials show that raising HDL-C and lowering LDL-C with the CETP inhibitor, torcetrapib, does not retard progression of coronary atherosclerosis nor promote regression. Note: A larger trial, Investigation of Lipid Level management to Understand its iMPact IN Atherosclerotic Events (ILLUMINATE), was halted in 2006 because of adverse events seen with torcetrapib.⁴ It is not known if the adverse effects of torcetrapib are class-wide. Other CETP inhibitors are currently in development.

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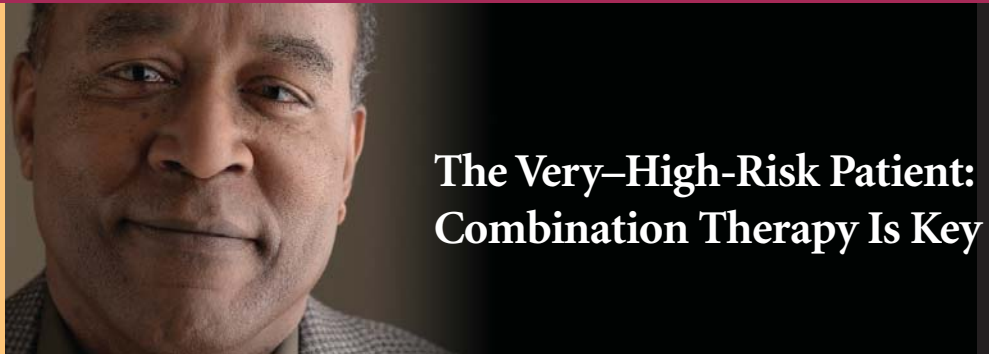
CASE STUDY

Initial Physical Exam:

- ◆ Height: 5'11"
- ◆ Weight: 220 lb
- ◆ Body mass index (BMI): 30.7 kg/m²
- ◆ Waist circumference: 40"
- ◆ Hip circumference: 44"
- ◆ Waist-to-hip ratio: 0.91
- ◆ Average sitting BP: 147/95 mm Hg (two readings, 15 min apart)
- ◆ Heart rate (HR): 76 bpm; normal sinus rhythm
- ◆ Extremities: No pedal edema; no calf tenderness
- ◆ HEENT: Normal
- ◆ Neck: Normal
- ◆ Chest and cardiac: Within normal limits
- ◆ Lungs: clear, no rales or wheezes
- ◆ Abdomen: slightly protuberant; benign; no tenderness; no masses; no organomegaly
- ◆ Neurologic: no focal motor or sensory signs; no obvious varicosities
- ◆ Pulses: easily palpable in distal extremities

Lab Findings:

- ◆ Fasting plasma glucose (FPG): 127 mg/dL
- ◆ HbA1c: 7.5%
- ◆ TC: 260 mg/dL
- ◆ TG: 350 mg/dL
- ◆ LDL-C: 160 mg/dL
- ◆ HDL-C: 30 mg/dL
- ◆ Non-HDL-C: 230 mg/dL
- ◆ Creatinine: 0.9 mg/dL
- ◆ Microalbumin: 75 mg/dL
- ◆ Aspartate aminotransferase (AST): 23 IU/L
- ◆ Alanine aminotransferase (ALT): 26 IU/L
- ◆ Thyroid-stimulating hormone (TSH): 4.5 mU/L



The Very-High-Risk Patient: Combination Therapy Is Key



The following case was provided by CCMD Education Council Member Scott M. Grundy, MD, PhD. Dr Grundy is Director of the Center for Human Nutrition and a Professor of Internal Medicine at the University of Texas Southwestern Medical Center in Dallas.

Financial disclosures: Dr Grundy has been an investigator on research grants awarded to the University of Texas Southwestern Medical Center in Dallas from Merck & Co., Inc., Abbott Laboratories, and Kos Pharmaceuticals. He has also served as a consultant for Merck & Co., Inc., Merck-Schering Plough, Kos Pharmaceuticals, Pfizer Inc, Eli Lilly & Company, Glaxo Smith Kline, Abbott Laboratories, Fournier, Bristol-Myers Squibb, Sankyo, AstraZeneca, and Sanofi-Aventis.

This case was peer reviewed by Herbert L. Muncie, Jr., MD, a Professor of Family Medicine at Louisiana State University in New Orleans, LA. Dr Muncie has indicated no relevant financial relationships.

LP is a 56-year-old African-American male who works as a retail salesman in Houston, Texas. At age 48, he was diagnosed with type 2 diabetes and, for 6 years, had been treated with oral hypoglycemic agents. Two years ago, he was switched to insulin. Last year, he experienced a non-ST-segment elevation myocardial infarction (MI). He comes to you today at the insistence of his daughter for further evaluation. (See column for physical examination and laboratory findings.)

Medical History

LP has a 20-year history of hypertension. His mother is 77 years of age and has hypertension; his father is deceased from diabetes and stroke. He has one sister, age 60, who also has diabetes. Prior to quitting smoking after his MI, he had smoked for 30 years.

Initial Visit

For the past 2 years, LP had been treated with a statin. You defer lipid-lowering therapy and opt to maximize therapeutic lifestyle changes (TLC) and control of diabetes. You refer LP to a dietician and increase his insulin dose.

Follow-Up

Two months later, LP has lost 5 pounds, and his HbA1c is 6.8%. His lipids are: TC 245 mg/dL, TG 300 mg/dL, LDL-C 150 mg/dL, HDL-C 35 mg/dL, and non-HDL-C 150 mg/dL. Because he is not to goal, you resume therapy with simvastatin 40 mg qd.

In another 2 months, LP returns, having lost 3 more pounds. His HbA1c is 6.6%, and his lipids are: TC 170 mg/dL, TG 280 mg/dL, LDL-C 80 mg/dL, HDL-C 35 mg/dL, and non-HDL-C 135 mg/dL.

Discussion

LP had not received lipid-lowering therapy from the time of his diabetes onset 8 years ago. At that time, the use of lipid-lowering for primary prevention in patients with diabetes was not widely recognized. In 2001, the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program identified diabetes as a CHD risk equivalent, meaning that patients with diabetes, particularly middle-aged persons with type 2 diabetes, have a risk for new-onset CHD roughly equivalent to that of patients with established CHD.¹ Although this has been questioned by some investigators, there is agreement that patients with diabetes are at "high risk" for future CHD.² In the Collaborative Atorvastatin Diabetes Study (CARDS), lipid-lowering treatment significantly reduced the risk for first MI in patients with diabetes.³ Secondary-prevention trials have also shown that statin therapy reduces cardiovascular events in patients with diabetes and CHD risk.⁴⁻⁶

LP clearly benefited from better control of diabetes and improvement in his lipid profile, in addition to benefits for other metabolic syndrome risk factors.⁷

LDL-C Goal

According to ATP III, the LDL-C goal in high-risk patients is <100 mg/dL.¹ A recent update to ATP III listed a lower LDL-C goal of <70 mg/dL for *very-high-risk* patients, including those with diabetes and CHD.⁸ The risk for CHD events among these patients is essentially twice that of CHD patients without diabetes.⁹ Trials have suggested incremental risk reduction from LDL-C levels in the range of 70 mg/dL in very-high-risk patients.¹⁰⁻¹³ This was also noted in meta-analyses of recent trials.¹⁴⁻¹⁵ For this reason, consideration can be given to intensifying lipid-lowering therapy to achieve even lower LDL-C levels. The patient's complete lipid profile, particularly non-HDL-C and HDL-C, must be re-examined before changing therapies.

Non-HDL-C Goal

Recently, studies have shown that non-HDL-C is a better predictor of future CHD events than LDL-C.¹⁶⁻²² Because of this, ATP III designated non-HDL-C as a secondary target of therapy after LDL-C.¹ This target is brought into play when TGs are ≥200 mg/dL. At lower TG levels, LDL-C is highly correlated with non-HDL-C levels. Even so, non-HDL-C may replace LDL-C as the primary target in all patients. In this patient, whose TG level is >200 mg/dL, non-HDL-C is clearly a secondary target of therapy. Incremental therapy in this patient should be chosen to lower non-HDL-C and LDL-C. The non-HDL-C goal is 30 mg/dL higher than the LDL-C goal, making LP's non-HDL-C goal <100 mg/dL.

HDL-C Goal

According to ATP III, HDL-C is a tertiary target of therapy.¹ A low HDL-C is <40 mg/dL in men (LP's level is 35 mg/dL). Although low HDL-C strongly associates with higher CHD risk, the mechanisms underlying this association are not well understood. Still, it is known that HDL-C is inversely associated with non-HDL-C levels; thus, part of the association between low HDL-C and CHD almost certainly is confounded by a higher

non-HDL-C. Further, low HDL-C is a marker for other metabolic syndrome risk factors and may directly accelerate atherogenesis. Before this mechanism can be proven, clinical trials need to be carried out with agents that uniquely raise HDL-C.

Therapeutic Options

Primary and secondary treatment targets for this patient with residual hypertriglyceridemia are LDL-C and non-HDL-C, respectively, with HDL-C as a tertiary target. Four options can be considered as "add-ons" to current statin therapy:

Maximizing TLC. Weight reduction combined with an appropriate exercise regimen is indicated to further improve LP's lipoprotein profile and to offer greater diabetes control; his other risk factors should also improve.

Intensifying statin therapy to further reduce LDL-C and non-HDL-C based on data from Treating to New Targets (TNT), in which increasing atorvastatin from 10 to 80 mg produced a 25% further reduction in new coronary events²³

Standard-dose statin + a second LDL-C-lowering drug. Adding ezetimibe, a cholesterol absorption inhibitor, 10 mg to standard-dose statin therapy will lower LDL-C and non-HDL-C levels nearly the same as changing to a high-dose statin.²⁴ A similar result can be attained by adding a bile-acid sequestrant (eg, colestevlam), which improves glucose control in patients with diabetes.²⁵ Bile-acid sequestrants should be avoided in patients with severe hypertriglyceridemia because of their tendency to raise TG concentrations.

Adding a fibrate for TG lowering. Fibrates can


reduce CVD risk but, at best, only about half that of statins.¹ Although there are no data showing that fibrates further reduce CVD risk with a statin, their favorable effects on lipoprotein metabolism make them an option. When combining with a statin, fenofibrate is the best option, as it is the least likely to cause severe myopathy.²⁶ Fenofibrate lowers LDL-C and non-HDL-C when combined with a statin in patients with hypertriglyceridemia.²⁷

Adding niacin to lower TG. Evidence supports a risk-reduction action of niacin, with limited evidence of benefit with statin therapy.^{28,29} Niacin can be combined with a statin in patients with diabetes for non-HDL-C reduction.³⁰ It also produces a striking rise in HDL-C levels. Although it can be used in patients with diabetes, monitoring is necessary to prevent a rise in glucose levels.♥

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ATP III: Risk Categories, LDL-C, Non-HDL-C Goals

Risk Category	LDL-C Goal	Non-HDL-C Goal
High: CHD or risk equivalent (10-yr risk >20%)	<100 mg/dL (Optional: <70)	≥100 mg/dL
Moderately-high: 2+ risk factors (10-yr risk 10%-20%)	<130 mg/dL	≥130 mg/dL
Moderate: 2+ risk factors (10-yr risk <10%)	<130 mg/dL	≥130 mg/dL
Low: 0-1 risk factor	<160 mg/dL	≥160 mg/dL

Grundy SM et al. *Circulation*. 2004;110(2):227-239.

Beyond LDL-C continued from page 3

Trial: Relationship of Statins, HDL-C, and Regression of Coronary Atherosclerosis

Nichols SJ, Tuzcu EM, Sipahi I, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA*. 2007;297(5):499-508.

This post-hoc analysis examined the relationship between statin-induced changes in LDL-C and HDL-C levels and atheroma burden. The investigators combined raw data from four prospective randomized trials performed in the United States, North America, Europe, and Australia including 1,455 patients with angiographic coronary disease. During statin therapy, mean LDL-C levels were reduced from 124.0 mg/dL to 87.5 mg/dL (23.5% decrease; $P < 0.001$), and HDL-C levels increased from 42.5 mg/dL to 45.1 mg/dL (7.5% increase; $P < 0.001$). Such changes were associated with a mean increase in percent atheroma volume from 39.7% to 40.1% (0.5% increase; $P = 0.001$) and a mean decrease in total atheroma volume of 2.4 mm³ ($P < 0.001$). The use of statin therapy in this study was accompanied by coronary atherosclerosis regression when LDL-C is substantially reduced and HDL-C is increased by >7.5%.

These findings suggest that statin benefits may be observed when patients attain a threshold LDL-C/HDL-C ratio—rather than a specific LDL-C or HDL-C value. The clinical impact of atherosclerotic regression (ie, whether it results in a reduction of clinical events) awaits further study.

Trial: Effects of Rosuvastatin and Atorvastatin on High-Density Lipoproteins

Asztalos BF, Le Maulf F, Dallal GE, et al. Comparison of the effects of high doses of rosuvastatin versus atorvastatin on the subpopulations of high-density lipoproteins. *Am J Cardiol*. 2007;99(5):681-685.

Although both atorvastatin and rosuvastatin effectively reduce LDL-C and TG, rosuvastatin is more effective in increasing HDL-C. This study compared the effects of daily high doses of rosuvastatin (40 mg) with atorvastatin (80 mg) on HDL particles during a 6-week period in 306 hyperlipidemic patients. Both atorvastatin and rosuvastatin elicited significant increases in large α -1 ($P < 0.001$) and α -2 ($P < 0.001$ for rosuvastatin; $P < 0.05$ for atorvastatin) HDLs and significant ($P < 0.001$) decreases in small pre- β -1 HDL levels. However, increases in the two large HDL particles were significantly greater with rosuvastatin than with atorvastatin (α -1, 24% vs 12%; α -2, 13% vs 4%; $P < 0.001$). Increases in α -1 and α -2 levels correlated with increases in HDL-C levels, whereas decreases in pre- β -1 levels correlated with decreases in TG levels. These authors have previously reported that increased levels of the two large HDL particles decrease the risk of CHD and protect against progression of coronary atherosclerosis (superior to HDL-C).

Statins appear to increase larger HDL particles. In short-term studies, rosuvastatin raises larger HDL particles significantly more than does atorvastatin.

Trial: Effect of Aerobic Exercise Training on HDL-C

Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol. *Arch Intern Med*. 2007;167(10):999-1008.

This meta-analysis examining the effects of exercise training on HDL-C levels includes 25 randomized controlled trials. A statistically significant but modest increase in mean HDL-C level (2.53 mg/dL; $P < 0.001$) was noted across the trials. The minimal weekly exercise volume necessary for increasing HDL-C was estimated to be 900 kcal of energy expenditure per week or 120 minutes of exercise per week. Moreover, univariate regression analysis demonstrated that every 10-minute prolongation of exercise per session was associated with an approximate increase in HDL-C of 1.4 mg/dL. No significant association between exercise frequency or intensity was found.

These results indicate that regular aerobic exercise modestly increases HDL-C, with a minimum exercise volume required for a significant increase.

Trial: TG and CHD Risk

Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease. 10,158 incident cases among 262,525 participants in 29 western prospective studies. *Circulation*. 2007;115(4):450-458.

Although several epidemiological studies have demonstrated a link between serum TG levels and CHD risk, this link is weakened after adjustment for other risk factors. This publication reports on two separate nested case-control comparisons in two different prospective, population-based cohorts (Reykjavik study and European Prospective Investigation of Cancer [EPIC]-Norfolk study), plus an updated meta-analysis of 27 additional prospective studies in general Western populations. The strength of the association was substantially attenuated after adjustment for baseline values of several established risk factors. The adjusted odds ratio (OR) for CHD was 1.76 (95% CI, 1.39–2.21) in the Reykjavik study and 1.57 (95% CI, 1.10–2.24) in the EPIC-Norfolk study in a comparison of patients in the top third with those in the bottom third of usual log-TG values. Comparable findings (adjusted OR, 1.72; 95% CI, 1.56–1.90) were noted in the meta-analysis, which involved 10,158 incident CHD cases from 262,525 participants across 29 studies.

The weakening of the association between TG and CHD risk by adjustment for other risk factors indicates that high TG is a marker for multifactorial risk. In addition, the residual independence in risk after adjustment suggests that VLDL, as well as LDL, is atherogenic. ♥



Compliments of your
healthcare professional:

Considering... The Nutrition Facts Label

A Guide to Understanding and Choosing the Right Foods for Your Heart Health

SUMMER 2007

If reading a food's nutrition label confuses you, you're probably not alone. But reading and understanding a nutrition label is easier than you may think. In fact, it's like reading the table of contents of a book: it tells you what's inside. The key is taking your time and reading carefully. The following information, which breaks down the major parts of a nutrition label, will help you to make quick, informed, and healthy decisions about the foods that you eat.

1. Serving Size

- ❖ A nutrition label always lists the *serv-ing* size, which is an amount of food. The serving size helps you to understand the amount of food you're eating.
- ❖ In this example, the serving size is *7 crackers*.
- ❖ The label also tells you the number of servings of the particular food. In this label, there are *8 servings total*.

2. The Percent Daily Value (%DV)

- ❖ This part of the label shows recommended dietary advice for all Americans. It will be the same on all nutrition labels.
- ❖ The *%DV*, which means *Percent Daily Value*, tells you if a serving of food is high or low in a nutrient. It is based on a 2,000 calorie/day diet.
- ❖ If you want to eat less of a nutrient, choose foods with a lower %DV (5%DV or less), and if you're looking to eat more of a nutrient, choose foods with a higher %DV (those with 20% or more). In this example, the *total fat (3g) in one serving is 5%DV of total fat intake*.

3. Calories

- ❖ Calories are a measure of the energy you get from food. They are important because eating more calories than your body uses can lead to weight gain.
- ❖ Calories are for *one serving*. In this example, *one serving (7 crackers) has 120 calories*.
- ❖ Another important part of this section is the number of calories that come from fat. For this number, lower is better because it's a good idea to limit fat intake. Here, *25 calories* are from fat. *A rule to follow:* no more than 30% of your calories should come from fat.

4. Nutrients

❖ Total Fat

- Your body needs fat, but eating too much fat may put you at risk for heart (*cardiovascular*) disease.
- *Total fat* is the number of fat *grams* in *one serving* of food. This example has *3g of total fat in one serving*—that's 5% of your daily amount. Fat intake should be limited to less than 56 grams per day on a 2,000-calorie diet.
- *Saturated* and *trans* fats are "bad" fats (found in many "fast foods") that can lead to heart disease. This example has *0g per serving* for both *saturated* and *trans* fats.
- *Polyunsaturated* and *monounsaturated* fats are "better" fats (found in olive oil, avocados, and most nuts) and may be healthier for your heart. This example has *1.5g of polyunsaturated fat* and *0.5g of monounsaturated fat*.

❖ Cholesterol

- The cholesterol in a serving is expressed in *milligrams*.
- Eating foods high in cholesterol can raise your risk for heart disease.
- In this example, *one serving has 0mg of cholesterol*. In a 2,000-calorie diet, limit your cholesterol to 300 mg/day.

❖ Sodium (Salt)

- This number measures the *milligrams* of salt in *one serving*.
- Eating too much sodium can lead to *hypertension*—a risk factor for heart disease and stroke. Certain people with diseases like *hypertension* or *diabetes* should limit sodium from their diets.
- In this example, *one serving has 85mg of sodium*—that's 6% of the total daily amount in a 2,000-calorie diet.

Nutrition Facts	
Serving Size:	7 Crackers (29g)
Servings Per Container:	About 8
Amount Per Serving:	
Calories:	120 Calories from Fat: 25
% Daily Value	
Total Fat 3g	5%
Saturated Fat 0g	0%
Trans Fat 0g	
Polyunsaturated Fat 1.5g	
Monounsaturated Fat 0.5g	
Cholesterol 0mg	0%
Sodium 85mg	6%
Total Carbohydrate 21g	7%
Dietary Fiber 3g	13%
Sugars 0g	
Protein 3g	
Vitamin A	0%
Vitamin C	0%
Calcium	0%
Iron	6%

*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

❖ Total Carbohydrates

- This number tells you how many *grams of carbohydrates* are in *one serving*.
- Eating too many simple carbohydrates (*sugars*) can lead to obesity or diabetes—both are risk factors for heart disease.
- In this example, *one serving has 21g of total carbohydrates*, including *3g of dietary fiber* and *0g of sugar*—that's 7% of the total daily amount in a 2,000-calorie diet.

5. Get Enough of These

- ❖ Most Americans don't get enough *dietary fiber*, *vitamin A*, *vitamin C*, *iron*, and *calcium* in their diets. Eating enough of these nutrients can help reduce your risk for certain diseases.

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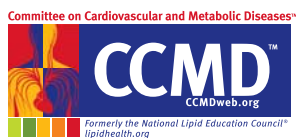
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Case Study continued from page 5

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Clinical Trials Update

The following references are relevant to the case study examining combination therapy in the very-high-risk patient:

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The following links are relevant to the feature story reviewing clinical-trial data on lipid levels.

Current Literature:

Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

http://www.ccmdweb.org/content/currentliterature/cm_litshow.asp?a=185

Usefulness of Omega-3 Fatty Acids and the Prevention of Coronary Heart Disease

http://www.ccmdweb.org/content/currentliterature/cm_litshow.asp?a=278

Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events in 9795 People With Type 2 Diabetes Mellitus (the FIELD Study): Randomised Controlled Trial

http://www.ccmdweb.org/content/currentliterature/cm_litshow.asp?a=277

Effect of Aerobic Exercise Training on Serum Levels of High-Density Lipoprotein Cholesterol: A Meta-Analysis

http://www.ccmdweb.org/content/currentliterature/cm_litshow.asp?a=380

Dynamic Slide Library:

Meta-Analysis: Effects of Aerobic Exercise on Lipids

http://www.ccmdweb.org/content/dynamic_slide_library/slide.asp?sid=482&keyword=meta%

FIELD: Fenofibrate Effect on Lipids

http://www.ccmdweb.org/content/dynamic_slide_library/middle.asp?sid=533&cid=4

Podcasts:

Impact of Dietary n-3 Fatty Acid and Statins on HDL and Total Cholesterol Levels in US Adults: An Analysis of the 1999–2002 National Health and Nutrition Examination Survey

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The following links are relevant to the case study examining combination therapy in the very-high-risk patient.

Current Literature:

Effects of Long-Term Fenofibrate Therapy on Cardiovascular Events in 9795 People With Type 2 Diabetes Mellitus (the FIELD Study): Randomised Controlled Trial

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Primary Prevention of Cardiovascular Disease With Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre Randomised Placebo-Controlled Trial

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MRC/BHF Heart Protection Study of Cholesterol-lowering With Simvastatin in 5,963 People With Diabetes: A Randomised Placebo-Controlled Trial

http://www.ccmdweb.org/content/currentliterature/cm_litshow.asp?a=25

High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction. The IDEAL Study: A Randomized Controlled Trial

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Joint Distribution of Non-HDL and LDL Cholesterol and Coronary Heart Disease Risk Prediction Among Individuals With and Without Diabetes

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Collaborative Atorvastatin Diabetes Study (CARDS): Results Summary

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IDEAL Study: Effect of Treatment on LDL-C
http://www.ccmdweb.org/content/dynamic_slide_library/middle.asp?sid=511&cid=5

Guidelines-at-a-Glance

Guide to Primary Prevention of Cardiovascular Disease in Patients With Diabetes
<http://www.ccmdweb.org/content/guidelines/guide11.asp>