

CASE STUDY

A 55-Year-Old Man With LDL-C Near Goal and Multiple Risk Factors



Presentation

The patient is a 55-year-old nonsmoking white man previously diagnosed with hypertension (HTN), elevated cholesterol, and impaired fasting plasma glucose (FPG). The patient's father, who was also overweight and had type 2 diabetes mellitus (T2DM), died at age 62 from a heart attack. The patient has worked as an electrician for 30 years. He played football in high school and plays softball with friends most Sundays. Although he has tried to exercise more, he has gained weight in the past 5 years, and the solidly muscular build of his youth has given way to central obesity. His wife tries to watch his diet, but the patient admits that he has a difficult time "sticking to her rules." His primary care clinician has warned him that the combination of HTN, hyperlipidemia, and elevated FPG raises the possibility that the largely asymptomatic progression of atherosclerosis has already begun. Two years ago, he was prescribed a statin and an angiotensin receptor blocker (ARB), given dietary guidelines to help with weight loss and cholesterol reduction, and urged to join a gym and work with a trainer to start a routine he could stick to.

The patient has gained 10 lb since his last consultation, is feeling frustrated and remorseful, saying he "doesn't want to die the way his father did." He claims he is more motivated now to take better control of his health.

Physical Examination

- Height 5 ft 11 in
- Weight 285 lb
- Waist 42 in
- BMI 39.7 kg/m²
- Blood pressure 140/85 mm Hg

BMI = body mass index.

Current Medications

- Losartan 50 mg/d
- Atorvastatin 10 mg/d

Laboratory Results

- Lipid profile
 - TC 207 mg/dL
 - LDL-C 98 mg/dL
 - HDL-C 36 mg/dL
 - Non-HDL-C 171 mg/dL
 - TGs 364 mg/dL

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- FPG 121 mg/dL
- Thyroid function Within normal limits
- Serum creatinine 1.5 mg/dL
 - CrCl 59 mL/min
 - Urine microalbumin 42 mg/dL
- LFT Within normal limits

CrCl = creatinine clearance; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LFT = liver function tests; TC = total cholesterol; TGs = triglycerides.

Clinical Decision Point

Based on the patient's presentation, the immediate goal of management is:

- Weight reduction
- Lower TGs
- Reduce blood pressure
- Develop a multifactorial approach, targeting obesity, elevated lipids, and elevated serum glucose

Comment

The patient's BMI at 39.7 kg/m² places him in the category of "obese."¹ Moreover, his waist circumference (42 in)—a measure of abdominal adiposity—is more highly correlated with metabolic risk factors than an elevated BMI.² Obesity also clusters with other CVD risks, such as dyslipidemia and T2DM² and is associated with greater all-cause mortality.^{3,4} Obesity alone is considered an independent risk factor for CVD and diabetes. In addition, the patient presents a classic profile for metabolic syndrome (Table 1).

The patient's lipid profile meets the criteria for mixed dyslipidemia, which is characterized by high serum levels of TG, low levels of HDL-C, sometimes, as in this case, in the presence of LDL-C levels at or close to Adult Treatment Panel (ATP) III goal. His elevated TG levels are a marker for large quantities of the highly atherogenic small, dense LDL (sd-LDL) particles, which are now considered a more accurate measure of aberrant metabolic activity than LDL-C.^{5,6}

Although the patient's LDL-C of 98 mg/dL is close to goal, his TG level is considered high (200-499 mg/dL).² In this setting, the LDL-C underestimates the cardiovascular (CV) risk as LDL particle (LDL-P) is most likely significantly increased. Therefore, ATP III recommends calculating his non-HDL-C (non-HDL-C = TC – HDL-C) and using this lipid fraction as a secondary target for treatment. The goal value for non-HDL-C is LDL-C target + 30 mg/dL.²

Table 1. Diagnostic Criteria for Metabolic Syndrome and Case Study Profile (≥3 of 5 required for diagnosis)

Risk Factor	Defining Levels ^a	Case Study Values
Waist circumference	>40 in (men); >35 in (women)	41 in
TGs	≥150 mg/dL	364 mg/dL
HDL-C	<40 mg/dL (men); <50 mg/dL (women)	36 mg/dL
Blood pressure	≥130/≥85 mm Hg	140/85 mm Hg (taking ARB)
FPG	≥100 mg/dL	121 mg/dL

ARB = angiotensin receptor blocker.

^aGrundy SM et al. *Circulation*. 2005;112:2735-2752.

The patient presents a challenging, but not uncommon, clinical scenario that puts him at significant risk for coronary heart disease (CHD). He is being treated for HTN and hypercholesterolemia, although the former has not reached goal, and his FPG of 121 mg/dL is close to the level defining frank T2DM (126 mg/dL) established by the American Diabetes Association (ADA). The ADA considers this “pre-diabetes” glycemic state a risk factor for CVD as well as T2DM.⁷ In many patients, T2DM is not diagnosed until significant and irreversible damage has occurred, eg, retinopathy and/or peripheral neuropathy.⁸

Decision: Develop a multifactorial approach, targeting obesity, elevated lipids, and elevated glucose.

In patients with multiple risk factors for CHD, all components must be addressed; simultaneous treatment is common and generally preferred. While the patient's TC, LDL-C, and blood pressure levels are within or very close to target levels on his current medications, lifestyle modification, non-HDL-C, TG management, and his insulin resistance must also be taken into consideration.

Lifestyle modification has great potential to reduce weight, blood pressure, and CHD risk. The Lifestyle Interventions for Blood Pressure Control (PREMIER) study evaluated the effects of lifestyle changes and diet on approximately 800 subjects with and without metabolic syndrome. Lifestyle modification consisted of moderate-intensity physical activity; restriction of sodium, alcohol, and saturated fat; and the Dietary Approaches to Stop Hypertension (DASH) diet. These modifications led to considerable reductions in blood pressure in both groups, ranging from a reduction in systolic blood pressure of 9.8 mm Hg in patients with metabolic syndrome to 11.2 mm Hg in those without metabolic syndrome. Lifestyle modification also led to reductions in fasting insulin levels and improvement in insulin resistance. Importantly, participants with metabolic syndrome lost 5.0 ± 5.0 kg and those without lost 5.4 ± 6.1 kg.⁹

Residual Risk: The Importance of Non-HDL-C

Non-HDL-C is a primary research topic and target for treatment. Non-HDL-C contains all known potentially atherogenic lipid particles, including LDL, intermediate density lipoprotein (IDL), and very low-density lipoprotein cholesterol (VLDL-C) remnants. It has been hypothesized that high non-HDL-C may reflect elevated VLDL-C, TG-rich lipoprotein, or remnant lipoprotein, especially in persons with low levels of LDL-C.¹⁰ While LDL is the primary carrier of cholesterol in plasma, the remnant lipoproteins VLDL and IDL are the major transporters of TG.

The Framingham Heart Study and the Framingham Offspring Study investigated

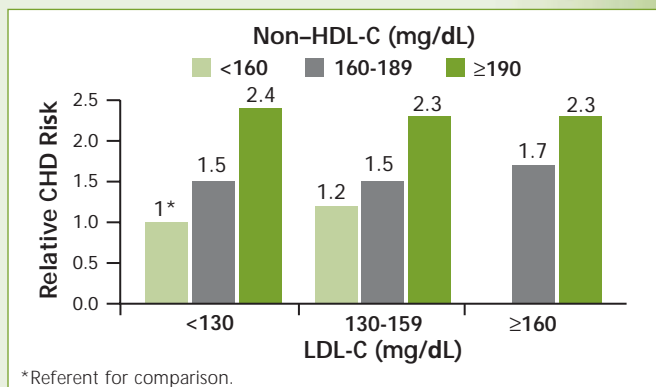


Figure 1. Risk of CHD incidence for the joint distribution of non-HDL-C and LDL-C, adjusted for age, gender, study, smoking status, systolic blood pressure, and prevalent diabetes. Liu J et al.¹⁰

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the contribution of lipid fractions other than LDL-C levels to CHD risk. This study demonstrated that LDL-P was a better predictor of future cardiac events than LDL-C.^{10,11} Analyses from the Framingham cohort found that non-HDL-C appears to be a better predictor of CHD incidence than LDL-C. The risk of CHD posed by non-HDL-C and LDL-C is shown in Figure 1.¹⁰ No appreciable increased risk is associated with LDL-C levels <130 mg/dL or 130 to 160 mg/dL. But in the presence of non-HDL-C levels >160 mg/dL, a strong positive and graded association was found regardless of the LDL-C level.¹⁰

Goals for non-HDL-C should be 30 mg/dL higher than LDL-C goals,² which would make this patient's level of 171 mg/dL a treatment target. ATP III recognizes that in patients with TG \geq 200 mg/dL, even when the LDL-C goal is met with statin therapy, additional therapy will be needed to attain the non-HDL-C goal.¹²

Role of Apolipoprotein B

Non-HDL-C is highly correlated with total apolipoprotein B (ApoB), which is a potential marker for all atherogenic lipoproteins. Total serum ApoB has been shown to be a strong predictor for severity of coronary atherosclerosis and CHD events.^{2,13} Each LDL, IDL, and VLDL particle carries a single ApoB-100 molecule; thus the total ApoB value represents the total number of potentially atherogenic proteins, whereas measurement of non-HDL-C provides the cholesterol content of these lipoproteins.¹³ In the INTERHEART study, which evaluated nearly 30,000 subjects in 52 countries, the ratio between apolipoprotein A1 (ApoA1) and ApoB was superior to any of the cholesterol ratios for estimating the risk of myocardial infarction (MI).¹⁴

The ADA and American College of Cardiology (ACC) now recommend ApoB as the test of choice to assess the adequacy of cholesterol-lowering therapy.⁷ However, measurement of ApoB is not always feasible in clinical practice. Because of the high correlation between non-HDL-C and ApoB levels, ATP III supports non-HDL-C as a reliable, practical, and inexpensive surrogate marker for total ApoB. When TGs are elevated, a significant fraction of non-HDL-C is contained in VLDL. In these patients, LDL-C may not be the only lipid risk factor. Therefore, ATP III recommends high non-HDL-C as a secondary target to reduce overall CHD risk.¹⁵

While the current statin therapy has lowered the patient's TC and LDL-C, his elevated TG levels are still of concern. ATP II would have placed this patient's TG in the "borderline high" range. The tighter categories of ATP III shift him to "high."¹⁵

Target: Hypertriglyceridemia

Elevated TG levels convey an increased risk for coronary disease in both men (14% increase) and women (37%), even after adjusting for other factors including HDL-C.¹⁶ The Prospective Cardiovascular Münster (PROCAM) study in nearly 5000 men found an increase in major coronary events with increasing serum TG levels; subjects with TG levels between 400 mg/dL and 799 mg/dL had 3 times the incidence of major coronary events per 1000 participants as did those with TG levels <200 mg/dL.¹⁷

In an analysis of TG levels using data from the Framingham cohort, CHD risk was increased at least 2-fold among individuals with TGs \geq 200 mg/dL and non-HDL-C >160 mg/dL in the presence of LDL-C levels <130 mg/dL.¹⁰ Using this model, the patient who has both elevated TGs and non-HDL-C, has a 2-fold increased risk for CHD. Table 2 (page 109) shows the correlation between non-HDL-C and LDL-C and their contribution to CHD risk in persons with elevated TGs.¹⁰

A New Profile for Aggressive Management

Increased attention is being focused on an important group of individuals at significant risk for cardiovascular disease (CVD) in spite of apparently normal or well-controlled levels of low-density lipoprotein cholesterol (LDL-C). These individuals typically have low levels of high-density lipoprotein cholesterol (HDL-C) and high levels of triglycerides (TGs),¹ a lipid profile that has emerged as a red flag for aggressive intervention.

The first Adult Treatment Panel (ATP) report of the National Cholesterol Educational Program (NCEP) established treatment goals and strategies for persons with high (≥ 160 mg/dL) or borderline high (130-159 mg/dL) LDL-C, and subsequent ATP reports have lowered these targets for certain classes of patients.^{1,2} The most recent ATP reports have focused attention on LDL-C as a primary therapeutic target for lipid management, unless triglyceride levels are >500 mg/dL. Additionally, non-HDL-C is a secondary target for treatment when the TG level is >200 mg/dL. Non-HDL-C is a surrogate indicator for a composite of atherogenic lipoprotein particles.

The complexities of cholesterol metabolism and transport pose significant challenges to the development of strategies for prevention and treatment of CVD. LDL-C levels that appear controlled may not adequately reflect the cardiometabolic risk of patients with an increased number of LDL particles (LDL-P). The number of particles is increasingly accepted as an important predictor of adverse cardiovascular (CV) outcomes and may be a potential target for treatment.

Look at the Lipoprotein Particles

LDL-P, the lipoproteins with the highest cholesterol content, transport cholesterol from the site of their synthesis (generally the liver) to tissues throughout the body. HDL particles function in the reverse by transporting cholesterol back to the liver and thus are usually cardioprotective.³ The most atherogenic lipoproteins are the small, dense LDL (sd-LDL) particles, which have biologic activity that differs from larger LDL-P. Persons with elevated TG levels tend to have a larger number of sd-LDL particles than those with TG levels at goal. It is possible, therefore, for 2 individuals with the same LDL-C values to have greatly differing numbers of LDL-P and thus different levels of atherosclerotic risk (Figure A).⁴ There is a disconnect between the LDL-C value and LDL-P when TG levels are increased with a larger number of particles transporting the cholesterol. An elevated TG level indicates the likelihood of a more atherogenic lipid profile often due to the presence of insulin resistance. This difference between LDL-C and LDL-P may be further obscured by the customary method of calculating LDL-C. In practice, LDL-C is seldom measured directly, but calculated by subtracting the HDL-C and one fifth of the TG values from the TC. This equation significantly underestimates the LDL-C value in persons with high TG levels.^{5,6}

Mixed—or atherogenic—dyslipidemia is defined as the combination of low HDL-C and high TG, whether or not the patient's LDL-C is elevated.⁷⁻⁹ Elevated TG levels and low HDL-C are included by ATP III as components of the metabolic syndrome, along with abdominal obesity, elevated blood pressure, insulin resistance with or without glucose intolerance, and a pro-inflammatory/pro-thrombotic state.¹

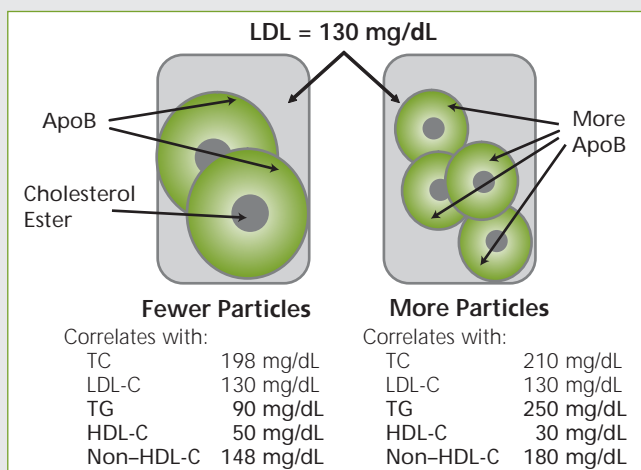


Figure A. Same LDL-C levels, different cardiovascular risk. Otvos JD et al.⁴

A New Profile for Aggressive Management

Although CV risk factors can occur individually, they more often tend to cluster (Figure B).⁵ For example, Framingham data reveal that only 1 in 5 persons with hypertension (HTN) have no other CV risk factor.¹⁰ Metabolic syndrome doubles the risk of developing atherosclerotic CVD, and in persons who do not have diabetes, it quintuples the risk of developing CVD compared with individuals who do not have this syndrome.¹¹

Thus, although guidelines including ATP III and those of the American Diabetes Association (ADA) identify controlling LDL-C as the principal goal of therapy, the other lipid fractions, HDL-C, and TGs also must be addressed to effectively lower global CVD risk.

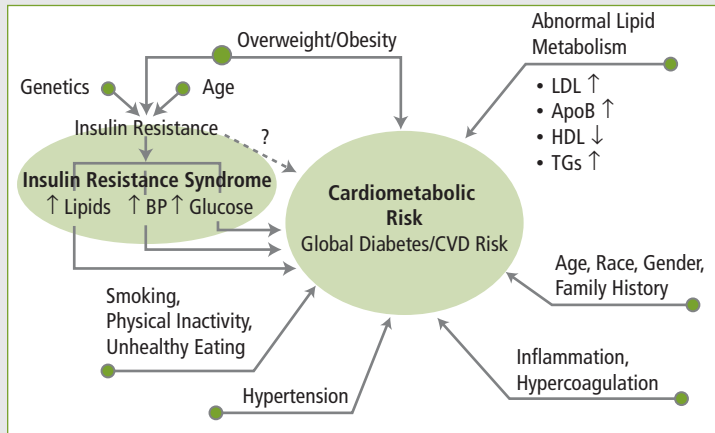


Figure B. Multiple factors contribute to cardiometabolic risk.

From Brunzell JD et al.⁵

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
2. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation*. 2002;106:2526-2529.
3. Turley SD. Dietary cholesterol and the mechanisms of cholesterol absorption. *Eur Heart J*. 1999;1 (suppl S):S29-S35.
4. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. 2002;90:22i-29i.
5. Brunzell JD, Howard BV, Davidson M, et al. Lipoprotein management in patients with cardiometabolic risk. *Diabetes Care*. 2008;31:811-821.
6. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management. *J Clin Lipidology*. 2007;1:583-592.
7. Fazio S. Management of mixed dyslipidemia in patients with or at risk for cardiovascular disease: a role for combination fibrate therapy. *Clin Ther*. 2008;30:294-306.
8. Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation*. 1997;95:1-4.
9. Grundy SM, Cleeman JI, Bairey Merz N, et al; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.
10. Kannel WB. Risk stratification in hypertension: new insights from the Framingham study. *Am J Hypertens*. 2000;13:3S-10S.
11. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation*. 2005;112:2735-2752.

Arriving at an optimum treatment strategy for this patient will require careful monitoring of the effects of treatment on all his risk factors. His elevated FPG should be further evaluated with a 2-hour oral glucose tolerance test (OGTT). The residual risk presented by his high levels of both TG and non-HDL-C is not minor and requires intervention. Combination therapy of 1 or more other lipid-lowering agents and lipid-altering strategies added to statin therapy may be warranted.

Table 2. Relative Risk^a (95% CI) of CHD Incidence Based on Non-HDL-C and LDL-C Levels in Patients With TGs \geq 200 mg/dL

Non-HDL-C, mg/dL	LDL-C (mg/dL)		
	<130	130-159	\geq 160
\geq 190	2.4 (1.55-3.73)	2.3 (1.72-3.01)	2.3 (1.90-2.69)
160-189	1.5 (1.02-2.09)	1.5 (1.23-1.85)	1.7 (1.29-2.31)
<160	1.00	1.2 (0.88-1.51)	NA

^aAdjusted for age, gender, study, smoking status, systolic blood pressure, and prevalent diabetes (at baseline). Liu J et al.¹⁰

Clinical Decision Point

What are your treatment recommendations at this time?

- Continue atorvastatin 10 mg/d
- Continue atorvastatin 10 mg/d, add long-acting niacin 250 mg/d
- Increase doses of statin to 20 mg/d
- Increase statin to 20 mg/d, add long-acting niacin

Comment

Several studies have found that there is residual CVD risk even in patients who receive intensive high-dose statin therapy and experience significant reductions in LDL-C levels.¹⁸⁻²⁰ The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study enrolled more than 4100 patients who had been hospitalized for an acute coronary event and compared the effects of standard and intensive doses of statins to prevent future cardiac events.¹⁸ Event rates of the primary end point (a composite of death from any cause, MI, documented unstable angina requiring hospitalization, revascularization, and stroke) at 2 years were 26.3% for patients who received moderate-dose therapy and 22.4% for patients who received high-dose therapy. Although this reduction in the relative risk (16%) with intensive-dose statin was statistically significant compared with standard dose, the difference in absolute risk was <4%, and the risk remained considerable.¹⁸ Since PROVE IT-TIMI 22, 2 other studies have shown that with even more aggressive treatment, residual risks for cardiac events remain substantial. These residual risks suggest that clinicians need to pay closer attention to the role of other potential risk factors (Figure 2).¹⁸⁻²⁰

According to the most recent ADA/ACC guidelines, this patient is at high risk for CHD. Although he has no known CHD or diabetes, he does have \geq 2 additional major CHD risk factors. Table 3 shows the treatment goals for patients with metabolic syndrome and lipoprotein abnormalities.⁷

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When Statins Are Not Enough

With increased focus on aggressive treatment, most patients with mixed dyslipidemia require combinations of pharmacologic agents to achieve their goals. Nicotinic acid, or niacin, appears to alter lipid levels by inhibiting hepatic lipoprotein synthesis,¹⁵ is effective for raising HDL levels, and has been used in combination with statins.²¹ Although the degree of lipid-altering efficacy varies in different studies, most have demonstrated niacin's favorable effects on lipids and lipoproteins when used

with statins.²²⁻²⁴ An open-label, randomized 12-week, multicenter study was conducted to determine whether low- to moderate-dose statin and extended-release niacin could lower LDL-C and non-HDL-C in patients with dyslipidemia.²² This combination therapy resulted in a 50% reduction in LDL-C and non-HDL-C, a 40% decrease in TGs, and about a 25% increase in HDL-C, suggesting that control of multiple lipid abnormalities can substantially decrease CHD risk.²²

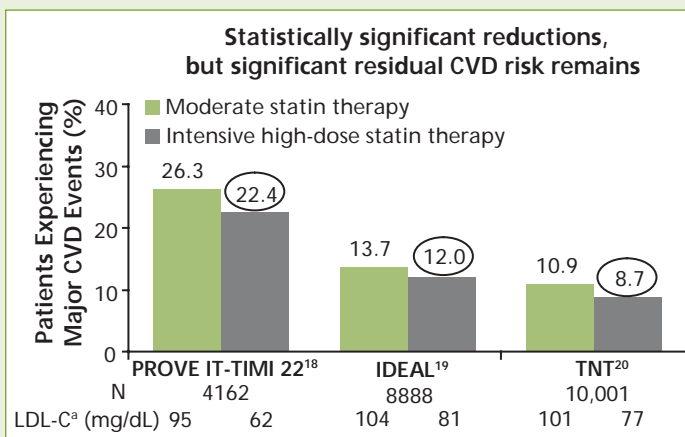


Figure 2. Residual CVD risk remains in patients treated with intensive statin therapy.

^aMean or median LDL-C after treatment.

IDEAL = Incremental Decrease in Endpoints Through Aggressive Lipid Lowering; PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22; TNT = Treating to New Targets.

Cannon CP et al¹⁸; Pedersen TR et al¹⁹; LaRosa JC et al.²⁰

Table 3. Treatment Goals for Patients With Metabolic Syndrome and Lipoprotein Abnormalities

GOALS			
	LDL-C	Non-HDL-C	ApoB
<i>Highest risk patients</i> , including those with (1) known CVD or (2) diabetes plus ≥1 additional major CVD risk factors	<70 mg/dL	<100 mg/dL	<80 mg/dL
<i>High-risk patients</i> , including those with (1) no known diabetes or known clinical CVD but ≥2 additional major CVD risk factors or (2) diabetes but no other major CVD risk factors	<100 mg/dL	<130 mg/dL	<90 mg/dL

Other major risk factors (beyond dyslipoproteinemia) include smoking, HTN, and family history of premature coronary artery disease. Brunzell JD et al.⁷

Results of the HDL Atherosclerosis Treatment Study (HATS) showed a clinical benefit in coronary artery disease in patients with low HDL-C levels treated with simvastatin plus niacin (S-N) or S-N plus antioxidants, compared with antioxidants alone or placebo.²⁵ S-N lowered cholesterol absorption markers as much as 70% ($P < .05$).²⁵

Although niacin often produces adverse effects, particularly facial flushing, a summary of rates of adverse event reports did not support the notion that these were sufficiently clinically significant to cause concern.^{26,27} However, ATP III lists a number of side effects associated with niacin, as well as an absolute contraindication in patients with chronic hepatic disease.

Decision: Increase statin dose, add long-acting niacin.

Based on the patient's laboratory results and his continued high risk for CHD, the atorvastatin dose was increased to 20 mg/d and long-acting niacin 500 mg/d was added to the regimen (titrated upward to 1000 mg/d over 4 weeks) to improve his non-HDL-C and HDL-C values.

In addition, the patient was counseled on the importance of losing weight by reducing his fat and carbohydrates and increasing physical exercise. He was referred to a nutritionist to guide and reinforce dietary and other lifestyle changes.

The results of the patient's OGTT show 2-hour plasma glucose of 155 mg/dL, suggesting he could benefit from treatment with metformin. Metformin can be considered for patients with prediabetes and at least 1 additional CV risk factor. He was started on 1000 mg/d metformin 2 months before his 3-month follow-up visit.

3-Month Follow-Up

After 3 months of combination statin/niacin treatment, the patient's lipid profile has improved, but TGs remain high; his blood pressure is slightly lower than at his initial visit. He has lost 15 lb, improving his BMI slightly, although he is still obese. His FPG has decreased slightly from the prior reading, but it is still higher than his target goal of 100 mg/dL (Table 4). In addition, his LFTs are mildly elevated from baseline.

Table 4. Physical Examination and Laboratory Results at 3- and 6-Month Follow-Up

	Visit 1	3-Month Visit		6-Month Visit	
Weight	285 lb	270 lb	↓15 lb	255 lb	↓30 lb
BMI	39.7 kg/m ²	37.7 kg/m ²	↓5%	35.6 kg/m ²	↓6%
Blood pressure	140/85 mm Hg	136/83 mm Hg		135/80 mm Hg	
TC	207 mg/dL	199 mg/dL	↓4%	189 mg/dL	↓5%
LDL-C	98 mg/dL	91 mg/dL	↓7%	86 mg/dL	↓5%
HDL-C	36 mg/dL	38 mg/dL	↑5%	41 mg/dL	↑8%
Non-HDL-C	171 mg/dL	161 mg/dL	↓6%	148 mg/dL	↓8%
TGs	364 mg/dL	300 mg/dL	↓18%	254 mg/dL	↓15%
FPG	121 mg/dL	116 mg/dL	↓4%	100 mg/dL	↓14%

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The clinician reviews these findings with the patient. The patient reports that he has experienced intolerable facial flushing since starting the new treatment regimen.

Clinical Decision Point

What change in therapy should be made at this time?

- Decrease atorvastatin to 10 mg/d
- Withdraw niacin, add fenofibrate 145 mg/d, increase atorvastatin to 40 mg/d
- None; maintain current medications and doses
- Urge more aggressive weight loss

Comment

Facial flushing reported by the patient is a frequent adverse effect of niacin treatment.² Although he is pleased with the progress he has made with his lifestyle changes, he has little interest in keeping up with his medications if they are going to cause him such distress. Although his lipid levels have improved, his TGs and non-HDL-C levels require specific targeting. Alternative therapies should be considered.

Studies have investigated the effects of fibrate treatment on primary and secondary prevention of major CHD events in patients with metabolic syndrome or dyslipidemia.^{28,29} In a subset of Helsinki Heart Study patients with CHD risk related to elevated TGs and low HDL-C levels, gemfibrozil reduced the relative risk of experiencing a cardiac event 20% over 5 years of follow-up.²⁹ In the Bezafibrate Infarction Prevention (BIP) study, patients with metabolic syndrome, most of whom had sustained an MI in the past, who took the fibric acid derivative had a 29% reduction in future risk of MI, which was a statistically significant result.²⁹ Treatment of patients with T2DM in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study produced a range of results.³⁰ Fenofibrate treatment reduced plasma TGs 29% and LDL-C 12%, effects that were apparent for the duration of the trial. HDL-C rose 5% at 4 months, but the effect was reduced to only about 2% over placebo at the end of the study. The reason for the attenuated effect is not known. Total CVD events were reduced from 13.9% to 12.5% ($P = .035$); this included a significant 21% reduction in coronary revascularization ($P = .003$) and a nonsignificant 10% reduction in stroke. Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group ($P = .18$).³⁰ Fenofibrate does not increase the risk for clinical myopathy in combination with moderate dose statins.³¹ The FIELD study also provided additional evidence of the safety of fenofibrate/statin combination therapy.³¹

Although the NCEP ATP III guidelines recommend use of fibrates in combination with statins in patients at very high risk of CHD, such as those with metabolic syndrome, clinicians may be reluctant to initiate use. Recent pharmacokinetic and mechanistic studies have demonstrated that gemfibrozil and fenofibrate have different routes of metabolism and that fenofibrate is less likely than gemfibrozil to cause harmful side effects, when used in combination with a statin.³²

Decision: Switch from niacin to fenofibrate, increase statin dose.

The clinician does not hesitate to discontinue the niacin given the patient's distress and his elevated LFTs. Fenofibrate therapy is initiated at 145 mg/d and the atorvastatin dose is increased

to 40 mg/d in pursuit of bringing the patient's lipids under better control. The patient has achieved considerable weight loss in 3 months, but is encouraged to continue his efforts with diet and lifestyle changes to further reduce his weight.

6-Month Follow-Up

At 6 months, the patient's lipid profile is improved, although his TGs remain elevated and his non-HDL-C has not decreased to goal. His FPG has decreased to 100 mg/dL and his LFTs are within normal range. He has lost an additional 15 lb, bringing his BMI down to 35.6 kg/m² (Table 4, page 111).

The patient reports that he is doing well with weight control. In addition to his weekly softball game and his gym regimen, he and his wife go dancing twice a month. He has a visit with his nutritionist every month to make sure his dietary plan is reviewed and revised according to his weight and exercise. He is especially careful about carbohydrate intake. He avoids fast foods as much as possible and has increased his exercise routine to include 5 visits to the gym weekly.

Clinical Decision Point

What changes in therapy should be made at this visit?

- Maintain fenofibrate dose, increase statin dose
- Increase fenofibrate dose, increase statin dose
- Maintain statin dose, increase fenofibrate dose
- Add prescription omega-3 fatty acids to the regimen

Comment

This patient has made good progress, but has a way to go to reach his target treatment goals, particularly for non-HDL-C and TGs. The addition of metformin to his treatment regimen, in combination with lifestyle changes, has successfully lowered his FPG <100 mg/dL and delayed or stopped his progression toward T2DM. It is important for him to demonstrate that he can lose weight gradually and maintain that weight by adopting a healthy lifestyle. It is useful to examine the probability of achieving his targets. A nationwide survey was designed to estimate the probability of target treatment goal achievement among patients with dyslipidemia.³³ This survey found that patients who had multiple CHD risk factors and dyslipidemia were less likely to achieve treatment goals. Among patients with established CHD, diabetes, or other CHD risk equivalents, <50% of patients with TGs >200 mg/dL achieved LDL-C treatment goals and most patients failed to achieve non-HDL-C goals.³³

Decision: Increase statin dose, maintain fenofibrate dose.

The patient is doing well but could do better with more aggressive treatment. Atorvastatin dose is increased to 60 mg/d and fenofibrate is maintained at 145 mg/d, which is the maximum approved dose. The patient has made good progress with behavioral adjustments and is encouraged to continue with diet and lifestyle changes.

9-Month Follow-Up

The patient continues to do well on his prescribed regimen; he has lost a total of 65 lb and his FPG is steady at 100 mg/dL. Since his first visit, his TC has been reduced 13%; LDL-C 18%; non-HDL-C 21%; and TG 40%. His HDL-C improved 25%.

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Adherence Matters

Although the patient has not reached his non-HDL-C and TG goals, he is well on his way to making major advances in reducing his CHD risks. With continued adherence to the pharmacologic and behavioral plans, it may take 6 months to a year before the full benefit from treatment becomes apparent.¹⁵

Treatment lapse is always a concern. Only about 50% of patients who are prescribed lipid-lowering therapy are still taking the medications 6 months later, and by 12 months only about 30% to 40% are adhering to the prescribed regimen.³⁴ Table 5 lists some ways that clinicians can help support and perhaps improve patient adherence.¹⁵

Table 5. Checklist to Enhance Adherence

✓ Keep the regimen simple
✓ Give the patient clear instructions
✓ Discuss adherence at every visit
✓ Follow up if patient misses appointment
✓ Use reminder tools for therapy regimens and appointments
✓ Encourage patients to engage in preventive care
✓ Reinforce and reward adherence
✓ Engage support of patient's family and friends
✓ Maintain contact
✓ Increase convenient access to care
✓ Involve patient in self-care and self-monitoring

Adapted from NCEP.¹⁵

References

1. Defining overweight and obesity. Centers for Disease Control and Prevention Web site. <http://www.cdc.gov/nccdphp/dnpa/obesity/defining.htm>. Accessed November 13, 2008.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
3. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983;67:968-977.
4. Wilcosky T, Hyde J, Anderson JJB, Bangdiwala S, Duncan B. Obesity and mortality in the Lipid Research Clinics Program Follow-Up Study. *J Clin Epidemiol*. 1990;43:743-752.
5. Nesto RW. Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. *Am J Cardiovasc Drugs*. 2005;5:379-387.
6. Peters AL. Clinical relevance of non-HDL-C in patients with diabetes. *Clin Diabetes*. 2008;26:3-7.
7. Brunzell JD, Howard BV, Davidson M, et al. Lipoprotein management in patients with cardiometabolic risk. *Diabetes Care*. 2008;31:811-821.
8. Leahy JL. Natural history of beta-cell dysfunction in NIDDM. *Diabetes Care*. 1990;13:992-1010.
9. Lien LF, Brown AJ, Ard JD, et al. Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome. *Hypertension*. 2007;50:609-616.
10. Liu J, Sempos CT, Donhue RP, et al. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol*. 2006;98:1363-1368.
11. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study—Implications for LDL management. *J Clin Lipidology*. 2007;1:583-592.
12. Grundy SM. Low-density lipoprotein, non-high-density lipoprotein, and apolipoprotein B as targets of lipid-lowering therapy. *Circulation*. 2002;106:2526-2529.
13. Andrikoula M, McDowell IF. The contribution of ApoB and ApoA1 measurements to cardiovascular risk assessment. *Diabetes Obes Metab*. 2008;10:271-278.
14. McQueen MJ, Hawken S, Wang X, et al; INTERHEART study investigators. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372:224-233.
15. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.
16. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. *Am J Cardiol*. 1998;81:7B-12B.
17. Assman G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated lipoprotein (a) are risk factors for major coronary events in middle-aged men. *Am J Cardiol*. 1996;77:1179-1184.
18. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.
19. Pedersen TJ, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437-2445.
20. La Rosa J, Grundy SM, Waters DD, et al; Treating to New Targets (TNT) investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.
21. Vega GL, Grundy SM. Lipoprotein responses to treatment with lovastatin, gemfibrozil, and nicotinic acid in normolipidemic patients with hypoalphalipoproteinemia. *Arch Intern Med*. 1994;154:73-82.
22. McKenney JM, Jones PH, Bays HE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). *Atherosclerosis*. 2007;192:432-437.
23. Guyton JR, Brown BG, Fazio S, et al. Lipid altering efficacy and safety of ezetimibe/simvastatin coadministered with extended-release niacin in patients with type IIa or type IIb hyperlipidemia. *J Am Coll Cardiol*. 2008;51:1564-1572.
24. Karas RH, Kashyap ML, Knopp RH, et al. Long-term safety and efficacy of a combination of niacin extended release and simvastatin in patients with dyslipidemia. *Am J Cardiovasc Drugs*. 2008;8:69-81.

25. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-1592.
26. Alsheikh-Ali AA, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration Adverse Event Reporting System). *Am J Cardiol*. 2007;99:379-381.
27. Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. *Am J Cardiol*. 2002;90(suppl):50K-60K.
28. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum TG and LDL-C and HDL-C concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*. 1992;85:37-45.
29. Tenenbaum A, Motro M, Fisman E, et al. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med*. 2005;165:1154-1160.
30. Keech A, Simes RS, Barter P, et al; 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;366:1849-1861.
31. Wierzbicki, AS. Fibrates after the FIELD study: some answers, more questions. *Diab Vasc Dis Res*. 2006;3:166-171.
32. Davidson MH. Statin/fibrate combination in patients with metabolic syndrome or diabetes: evaluating the risks of pharmacokinetic drug interactions. *Expert Opin Drug Saf*. 2006;5:145-156.
33. Davidson MH, Maki KC, Pearson TA, et al. Results of the National Cholesterol Education (NCEP) Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP writing group recommendations. *Am J Cardiol*. 2005;96:556-563.
34. Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust*. 1996;164:208-211.

