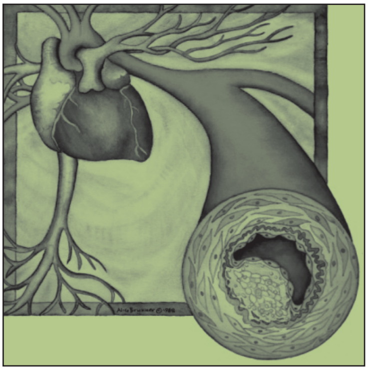


Dyslipidemia:
When Statins Alone Fail

What We Know About Dyslipidemia

- Elevated TGs and low HDL-C contribute to residual cardiovascular risk in patients on statin therapy to lower LDL-C
- Niacin is effective for reducing cardiovascular risk and slows atherosclerosis progression when added to statin therapy in patients with coronary heart disease
- Fibrate monotherapy can reduce cardiovascular risk in patients with metabolic syndrome or diabetes
- Combinations of statins plus fibrate or niacin correct atherogenic lipid abnormalities and appear to be safe

Learning Objectives

After completing this activity, participants should be better able to:

- Identify patients who would benefit from combination therapy for dyslipidemia based on results of recent clinical trials
- Develop optimal treatment strategies for lowering LDL-C and raising HDL-C levels in patients with mixed dyslipidemia
- Educate patients on the benefits and long-term safety data associated with combination drug therapy for dyslipidemia

Statin therapy alone is beneficial but does not eliminate CVD risk

How do you explain the importance of elevated TGs to patients? **See page 14**

Statin Therapy for Dyslipidemia: Residual Risk

The use of statins to reduce levels of low-density lipoprotein cholesterol (LDL-C) is a proven strategy in reducing cardiovascular disease (CVD) risk. However, many patients who have achieved LDL-C goals have residual CVD risk due in part to other facets of the lipid profile, such as low levels of high-density lipoprotein cholesterol (HDL-C) or elevated triglycerides (TGs). The metabolic syndrome, a combination of 3 or more factors including dyslipidemia, hypertension, abdominal obesity, and hyperglycemia, is a strong predictor of progression to diabetes, which itself is a coronary heart disease (CHD) risk equivalent.

Several approaches to CVD risk factor management have been developed in the context of available evidence from controlled clinical trials. These approaches include intensified statin therapy as well as combinations of statins with fenofibrate, omega-3 fatty acids, or extended-release niacin. To examine the impact of these treatment options in the context of clinical care, a case study examining the management of a patient with mixed dyslipidemia and type 2 diabetes is presented (see page 12).

Collective CV Risk: Metabolic Syndrome, Type 2 Diabetes

Metabolic syndrome, a condition characterized by abdominal obesity and atherogenic dyslipidemia with or without hypertension and hyperglycemia (Table 1),[1] represents a clustering of metabolic factors that appear to promote CVD. Individuals with metabolic syndrome usually have some degree of insulin resistance, regardless of fasting glucose levels.[1] Type 2 diabetes is considered a CHD equivalent,[1] and the metabolic syndrome is considered an independent risk factor for CVD. However, recent results from the large Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and British Regional Heart studies demonstrated that metabolic syndrome was not associated with a significantly increased risk of CVD, but remained strongly associated with the development of type 2 diabetes.[2]

According to the 2004 update of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, individuals with the metabolic syndrome plus established CVD are considered at very high risk for cardiovascular (CV) events. This also applies to individuals who have CVD plus multiple other risk factors (in particular diabetes), acute coronary syndrome, or other poorly controlled risk factors, such as smoking. LDL-C goals for patients in the high and very high risk categories are <100 mg/dL and <70 mg/dL, respectively. Lipid-lowering therapy for patients at moderate or high risk should be of sufficient intensity to achieve at least a 30% to 40% reduction from baseline LDL-C levels.[3] For patients with type 2 diabetes, the American Diabetes Association (ADA) recommends lipid cut points of <100 mg/dL for LDL-C, >40 mg/dL for HDL-C (>50 mg/dL for women), and <150 mg/dL for TG.[4]

TABLE 1

American Heart Association/National Heart, Lung, and Blood Institute Criteria for Diagnosis of Metabolic Syndrome[a]

Risk Factor	Defining Level	
	Women	Men
Waist[b]	>88 cm (>35 in)	>102 cm (>40 in)
TGs[c]	≥150 mg/dL	
HDL-C[c]	<50 mg/dL	<40 mg/dL
Blood pressure[c]	≥130/≥85 mm Hg	
Fasting glucose[c]	≥100 mg/dL	

[a]Diagnosis is established by the presence of ≥3 risk factors; [b]Lower cutpoints (≥90 cm in men and ≥80 cm in women) for Asian Americans; [c]On drug treatment for elevated TG or glucose levels, hypertension, or reduced HDL-C levels.
Adapted from Grundy SM et al.[1]

Intensifying Statin Therapy: A Sound Approach?

The rationale for intensifying statin therapy is to further lower LDL-C levels. Recent intensive vs less intensive statin trials suggest incremental relative risk benefit from lower LDL-C levels; however the absolute risk reduction is attenuated at progressively lower LDL-C levels.

All randomized statin trials demonstrate that residual CVD risk persists in actively treated subjects compared with those on placebo.[5-10] In these trials, the CV event rates range from 5.5% to 19.4% in treated patients over 5 years (Figure 1).[5,9] Subsequent trials of intensive statin therapy show residual CVD risk of up to 12% in patients with stable CHD[11,12] and 22.4% in the setting of acute coronary syndromes.[13] Clearly, statin therapy alone does not eliminate a patient's CVD risk.

Diabetes places a patient at increased risk for CVD. Patients with diabetes who are treated with statins have higher subsequent CV event rates than untreated nondiabetic patients (Table 2).[6,7,14-17] The Heart Protection Study (HPS) analysis of patients with diabetes showed that statin therapy reduced CVD risk by 22% compared with placebo, but the residual CVD event rate in the statin treatment group was 20.2% over 5 years.[14] In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin resulted in a 32% reduction in risk, but 8% of those patients treated with statins had CV events over 5 years.[18] Clearly, other approaches aimed at lowering atherogenic lipid abnormalities must be considered.

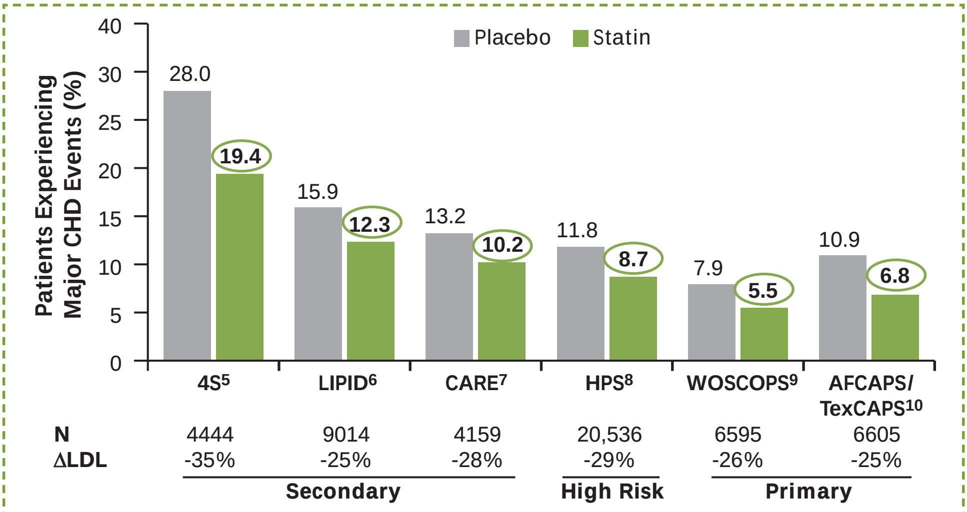


Figure 1. Lowering LDL-C levels reduces, but does not eliminate, CVD risk. Residual CVD risk in 6 clinical trials of statin therapy is shown. Despite significant decreases in LDL-C, patients continued to be at substantial risk for CVD events.

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cardiac Angiography in Renally Impaired Patients; LIPID = Long-Term Intervention with Pravastatin in Ischemic Disease; 4S = Scandinavian Simvastatin Survival Study; WOSCOPS = West Of Scotland Coronary Prevention Study. Scandinavian Simvastatin Survival Study Group[5]; Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group[6]; Sacks FM et al[7]; Heart Protection Study Collaborative Group[8]; Shepherd J et al[9]; Downs JR et al.[10]

TABLE 2

Patients With Diabetes: Particularly High Residual CVD Risk After Statins

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[a14] (CHD patients)	19.8%	25.7%	33.4%	37.8%
CARE[b7]	19.4%	24.6%	28.7%	36.8%
LIPID[c6]	11.7%	15.2%	19.2%	22.8%
PROSPER[d15]	13.1%	16.0%	23.1%	18.4%
ASCOT-LLA[c16]	4.9%	8.7%	9.6%	11.4%
TNT[e17]	7.8%	9.7%	13.8%	17.9%

[a]CHD death, nonfatal MI, stroke, revascularizations; [b]CHD death, nonfatal MI, CABG, PTCA; [c]CHD death and nonfatal MI; [d]CHD death, nonfatal MI, stroke; [e]CHD death, nonfatal MI, resuscitated cardiac arrest, stroke (80-mg vs 10-mg atorvastatin).

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; TNT = Treating to New Targets.

LIPID Study Group[6]; Sacks FM et al[7]; HPS Collaborative Group[14]; Shepherd J et al[15]; Sever PS et al[16]; Shepherd J et al.[17]

Zeroing in on Residual Risk: The Role of Atherogenic Dyslipidemia

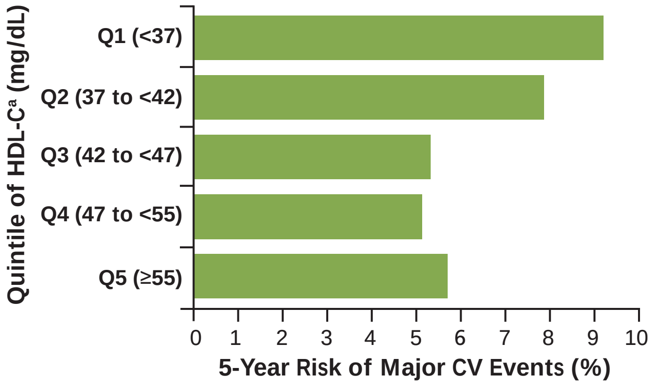
The lipid profile that characterizes metabolic syndrome and is also prevalent in diabetes contributes to residual CVD risk. "Atherogenic dyslipidemia" consists of elevated TGs, with low levels of HDL-C, with or without high levels of LDL-C. These patients also have proportionally more small, dense LDL-C and fewer large HDL-C particles.[19,20] This profile becomes more pronounced as glycemic control in patients with diabetes progressively erodes.[20]

Triglycerides

Produced by the liver and derived from both dietary sources and adipose tissue stores, TGs are carried by very low-density lipoproteins (VLDLs) and chylomicrons.[21] In observational studies, high TG levels were shown to be a risk factor for CHD[21] such that individuals with TG levels in the top tertile of values were at higher risk for CHD than individuals in the bottom tertile, with similar risks in men and women (odds ratio: 1.72; 95% CI: 1.56-1.90).[22] This risk is somewhat lower when adjusted for HDL-C levels.[22] Elevated TG levels appear to confer significant increased CHD risk independent of LDL-C and HDL-C levels[23] and the risk remains significant in patients treated with statins.[24]

Non–HDL-C

High levels of non–HDL-C, a term used to describe cholesterol carried in LDL-C as well as VLDL and other atherogenic lipoproteins that contain apolipoprotein B-100,[25] predict CVD risk independent of LDL-C levels.[26] In individuals with high TG levels, non–HDL-C is a stronger predictor of CV mortality than LDL-C alone.[27] NCEP ATP III recommends



No. of Events	No. of Patients	Hazard Ratio (95% CI) vs Q1
57	473	Referent
50	525	0.85 (0.57-1.25)
34	550	0.57 (0.36-0.88)
34	569	0.55 (0.35-0.86)
35	544	0.61 (0.38-0.97)

Figure 2. Low levels of HDL-C predict CVD risk even when LDL-C levels are well controlled. In these data from the TNT study, subjects with HDL-C levels ≤42 mg/dL were at increased risk for major CV events, despite all subjects' LDL-C levels being <70 mg/dL; n = 2661. [a]Treatment level (3 months). Barter P et al.[29]

non–HDL-C levels as a secondary therapeutic target after LDL-C for individuals with TG levels ≥200 mg/dL, with a goal of <130 mg/dL for those at high risk.[25] Although not all laboratories report a separate value for non–HDL-C, it can be calculated in the office by subtracting HDL-C from the total cholesterol value. The goal for non–HDL-C is the patient's LDL-C goal plus 30 mg/dL.[27]

HDL-C

HDL-C is inversely related to CHD risk. In many patients, low HDL-C levels occur with high TG levels. HDL-C may play a protective role through its promotion of reverse cholesterol transport and its antioxidant and anti-inflammatory properties.[21] It is estimated from observational studies that a 1-mg/dL increase in HDL-C confers a decrease in CHD risk of 2% in men and 3% in women.[28] The risk associated with low HDL-C levels is independent of LDL-C and remains even for patients treated to LDL-C levels <70 mg/dL (Figure 2).[29] Statin treatment to lower LDL-C has a modest effect (+ 5%-10%) on HDL-C levels.[8,24]

Choosing the Right Combination Therapy

NCEP ATP III states that elevated non–HDL-C is a target for intervention, and that elevated TG and/or low HDL-C levels are reasonable targets for treatment.[21] The addition of a fibrate or niacin to LDL-lowering therapy is appropriate for high-risk patients with elevated TG or low HDL-C levels.[3] First-line therapy should be therapeutic lifestyle changes (TLC),[30] but patients at higher risk should be considered for pharmacologic therapies that specifically benefit TG and HDL-C, such as fibrates and niacin.[21]

TLC	
Glycemic control	
Statin therapy to achieve LDL-C <100 mg/dL (<70 mg/dL with CHD)	
TG ≥500 mg/dL	Fibrate Omega-3 fatty acids
TG ≥150-500 mg/dL	Fibrate (with slightly low or normal HDL-C) Niacin (with very low HDL-C)
TG <150 mg/dL and Low HDL-C	Niacin

Figure 3. ADA recommendations: lipid management in well controlled diabetes or metabolic syndrome (A1C <7%; HDL-C <40 mg/dL in men, <50 mg/dL in women). American Diabetes Association.[4,19]

Rationale for Fibrate Therapy

Combination fibrate/statin therapy can achieve the goals of lowering LDL-C and raising HDL-C, while positively modifying non–HDL-C levels.[21] In clinical trials, fibrates reduced TG levels 30% to 50% and increased HDL-C levels 5% to 15%, while lowering LDL-C levels ≤20%. Fibrates also modify the LDL-C particle size from smaller to larger, less dense particles.[27] For patients with diabetes, fibrates are recommended by the American Diabetes Association as secondary therapy after TLC for raising HDL-C and lowering TG levels. In addition, fibrates in conjunction with glycemic control and a statin are recommended for treatment of combined hyperlipidemia.[4,19] Recommendations for patients with well controlled diabetes (eg, A1C <7.0%) or metabolic syndrome are shown in Figure 3.

Fibrate Therapy: Evidence From Clinical Trials

Several clinical trials have established the efficacy of fibrate monotherapy in primary[31,32] and secondary[33,34] prevention of CVD in patients with diabetes or metabolic syndrome (Table 3). The results from these studies showed significant reductions in CVD rates.

In the Veterans Affairs HDL Intervention Trial (VA-HIT), men with CHD, HDL-C ≤40 mg/dL, and LDL-C ≤140 mg/dL randomly received gemfibrozil or placebo. Treatment with gemfibrozil resulted in a 24% reduction in the composite end point of CHD death, stroke, or MI at an average follow-up of 5.1 years. Importantly, gemfibrozil had a greater treatment effect on most individual end points for the subgroup of patients with diabetes (Figure 4).[34]

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study examined patients with type 2 diabetes who were not on statin therapy at study entry. These individuals were randomly assigned to receive fenofibrate or placebo and were followed for 5 years. In the overall population, fenofibrate treatment resulted in a nonsignificant 11% decrease in the rate of composite coronary events, and significant reductions in the secondary end points of nonfatal MI, total CVD events, and revascularization, (24%, 11%, and 21%), respectively. In a subgroup analysis of the subjects with no history of CVD, a highly significant 19% relative risk reduction in total CVD events was

TABLE 3

Outcomes in Clinical Trials With Fibrates for Treatment of Patients With Diabetes or Metabolic Syndrome

Trial	N	Major CVD Event Rate		RRR	*P*
		Control	Drug		
Primary Prevention					
HHS[a31]	292	13.0%	3.9%	71%	<.005
FIELD[b32]	7664	10.8%	8.9%	19%	.004
Secondary Prevention					
BIP[c33]	1470	18.4%	14.1%	25%	.03
VA-HIT[d34]	769	29.4%	21.2%	32%	.004

[a]Patients with TG >204 mg/dL and an LDL:HDL >5 (may or may not have had diabetes or metabolic syndrome); [b]Patients with diabetes and no prior CVD; [c]Patients with metabolic syndrome; [d]Patients with diabetes.
BIP = Bezafibrate Infarction Prevention; HHS = Helsinki Heart Study.
Manninen V et al[31]; Keech A et al[32]; Tenenbaum A et al[33]; Rubins HB et al.[34]

achieved with fenofibrate (*P* = .004). Lipid response to fenofibrate resulted in reductions of 11% in TC, 12% in LDL-C, and 29% in TG, and increased HDL-C by 5% after 4 months of treatment.[32]

Fenofibrate is also being assessed in the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which is examining lipid-modifying strategies as 1 of 3 interventions for CVD risk reduction in 5518 patients with type 2 diabetes. Subjects were randomly assigned to receive a statin with either fenofibrate or placebo[35] and results are expected in 2010.

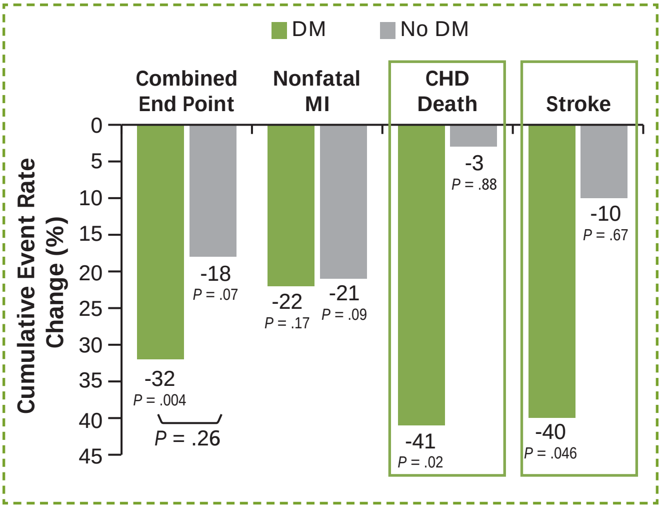


Figure 4. CVD risk reduction in the VA-HIT study: comparison of patients with and without diabetes. The VA-HIT diabetic subgroup analysis compared the effects of gemfibrozil (1200 mg/d) on CVD outcomes in patients with diagnosed diabetes (n = 627), undiagnosed diabetes (n = 142), impaired fasting glucose (n = 323), or normal individuals (n = 1425). On most end points, patients with diabetes had more powerful responses to gemfibrozil therapy. *P* values vs placebo. DM = diabetes mellitus. Rubins HB et al.[34]

Safety of Fibrate/Statin Combination Therapy

Fibrate monotherapy is rarely associated with myopathy. However, there have been concerns of an additive effect when fibrates are combined with statins.[36] There may be safety differences between the fibrates when combined with statins. In a study of cases of rhabdomyolysis reported to the US Food and Drug Administration (FDA), the incidence occurred 15 times more often with gemfibrozil than with fenofibrate (8.6 vs 0.58 per 1 million prescriptions, respectively).[37] It has been shown that gemfibrozil can increase statin blood levels by interfering with their catabolism in the liver.[36] Fenofibrate does not affect the pharmacokinetics of statins and may therefore be safer to use in combination,[36] although it is generally recommended to avoid combinations with high-dose statins.

Rationale for Using Omega-3 Fatty Acids

Omega-3 fatty acids, which include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), regulate lipid metabolism partly by decreasing hepatic TG synthesis at doses of 3 to 4 g/d.[38] Omega-3 fatty acids are available as dietary supplements, however, 10 to 15 capsules per day may be needed to achieve the recommended dose of 4000 mg.[39] An FDA-approved prescription formulation is available to treat patients with TG levels >500 mg/dL at a dose of 4 capsules per day.[40]

Expected Lipid Response With Omega-3 Fatty Acids

A prospective, randomized, double-blind study assigned subjects with severe hypertriglyceridemia (500-2000 mg/dL) to receive omega-3 fatty acids 4 g/d (n = 22) or placebo (n = 20) for 16 weeks. Omega-3 fatty acids produced a 32% decrease in VLDL

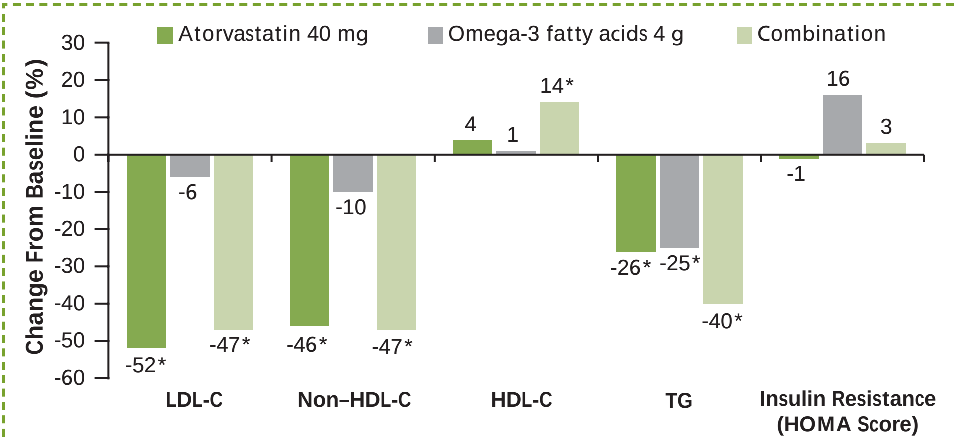


Figure 5. Percentage change from baseline in lipid measures after 6 weeks of omega-3 fatty acid/statin combination therapy in insulin-resistant obese men with dyslipidemia. In a double-blind, placebo-controlled trial, the independent and combined lipid effects of treatment with atorvastatin (40 mg) and/or omega-3 fatty acids (4 g/d) were studied in 48 men with dyslipidemia. Statin monotherapy and combination therapy produced significant improvements in lipid measures compared with placebo. Omega-3 fatty acid therapy significantly reduced TG, but had no significant effect on other lipid measures. N = 48; **P* <.05 vs placebo. HOMA = homeostasis model assessment. Chan DC et al.[38]

(*P* = .001), a 45% decrease in TGs (*P* <.0001), and a 13% increase in HDL-C (*P* = .004). However, LDL-C increased by 32% (*P* = .0014).[39]

The effect of combined omega-3 fatty acids and a statin on lipid profiles was studied in a group of insulin-resistant obese men. Subjects received atorvastatin alone, omega-3 fatty acid alone, a combination of the 2, or placebo for 6 weeks. Patients taking the combination therapy achieved significant improvement in lipid measures (Figure 5). Omega-3 monotherapy did not increase LDL-C levels, and there were no significant changes in insulin resistance in any of the study groups.[38]

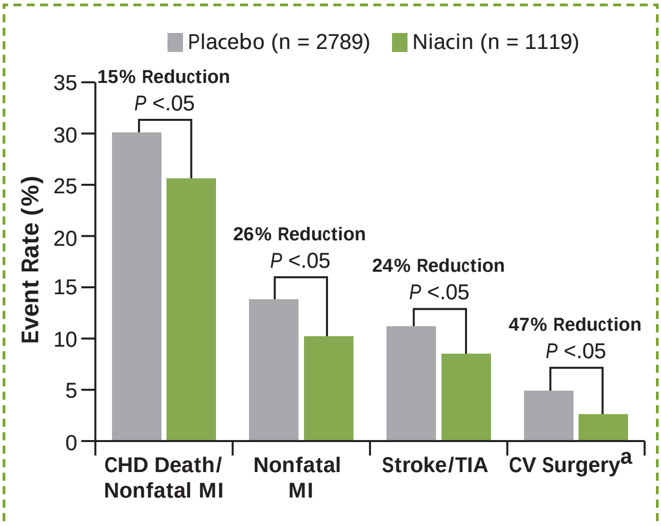


Figure 6. Effects of niacin therapy on macrovascular outcomes after 6.2 years of follow-up in the CDP study. There were 2789 patients in the placebo group and 1119 patients in the niacin group. At this follow-up point, niacin provided a significant reduction in the combined outcome of CHD death and nonfatal MI, nonfatal MI, and cerebrovascular events. Niacin also provided a significant reduction in the number of patients having any CV surgery from trial entry to a follow-up of 5 years. [a]5-year incidence. TIA = transient ischemic attack. CDP Research Group.[43]

The use of omega-3 acid ethyl esters as secondary prevention in a group of patients with recent MI was evaluated in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) Prevenzione-99 open-label study.[41] Patients who had an MI within 3 months of study entry were randomly assigned to receive omega-3 acid ethyl esters (850-882 mg/d; n = 2836) or no supplemental therapy (n = 2828) while all received recommended post-MI care. Participants were followed for 3.5 years. Supplementation with omega-3 acid ethyl esters produced a 15% relative risk reduction in the study's primary end point of all-cause death/nonfatal MI/nonfatal stroke (12.3% vs 14.6%; *P* = .023) and a 20% relative risk reduction in the secondary end point of CVD death/nonfatal MI/nonfatal stroke (9.2% vs 11.4%; *P* = .008).[41] All-cause mortality was significantly lower after only 3 months of treatment and CVD mortality was significantly reduced after 6 to 8 months.[42] This study prompted the American Heart Association (AHA) to recommend use of omega-3 fatty acids (EPA + DHA) 1000 mg/d in all patients after MI.

In these studies, gastrointestinal disturbances were the most frequently reported adverse effect of omega-3 therapy.[39,41]

Benefits of Niacin

Niacin positively affects lipid profiles by decreasing LDL-C, TG, and lipoprotein(a) levels and increasing lipoprotein particle size. Importantly, it is the most effective drug for raising HDL-C levels.[4] As previously mentioned, the addition of niacin to LDL-C–lowering therapy is appropriate for patients at high risk with elevated TG or low HDL-C levels.[3] In patients in the Coronary Drug Project (CDP) treated with niacin and followed for more than 6.2 years, there was a significant reduction in macrovascular end points (Figure 6).[43]

Evidence From Clinical Trials With Extended-Release Niacin

In patients enrolled in the CDP study, niacin therapy achieved sustained reduction of 10% in TC and 26% in TG over 5 years.[43,44] In combination with statins or statin/ezetimibe, niacin resulted in greater improvements in lipid profiles than statin therapy alone[45] or the statin/ezetimibe combination.[46] Several recent clinical trials illustrate the impact of different niacin/statin combinations on lipid levels (Table 4).[47] In the Comparative Effects on Lipid Levels (COMPELL) study, niacin/statin combinations also lowered levels of lipoprotein(a).[45]

Niacin was shown to reduce CVD risk in the CDP study of lipid-modifying therapies, which enrolled men aged 30 to 64. Although no mortality benefit was seen at the initial 5-year analysis,[43] niacin therapy compared with placebo resulted in reduced all-cause and CHD mortality at 15 years.[44] Both all-cause mortality (hazard ratio [HR] 0.84; *P* <.005) and CHD mortality (HR 0.86, *P* <.05) were significantly lower in the niacin group compared with the placebo group. Benefits of niacin were independent of baseline fasting plasma glucose (FPG) and were most pronounced in the group with FPG ≥126 mg/dL at baseline. In a post hoc analysis, these patients achieved a 57% reduction in the rate of nonfatal MI and a 24% reduction in CHD mortality at 6-year follow-up.[44] Several studies are examining the effect of extended-release niacin on clinical outcomes in patients with

TABLE 4

Percentage Change From Baseline in Lipid Values From Clinical Trials With Niacin ER/Statin Combination Therapy

	LDL-C	Non–HDL-C	HDL-C	TG
COMPELL[45]				
Atorvastatin 40 mg/niacin ER 2 g	-56%	-55%	+22%	-47%
COMPELL[45]				
Rosuvastatin 20 mg/niacin ER 1 g	-51%	-49%	+24%	-40%
OCEANS[47]				
Simvastatin 40 mg/niacin ER 2 g	-25.0%	-27.3%	+23.9%	-35.9%
Guyton[46]				
Simvastatin 10 mg/ezetimibe 10 mg/niacin ER 2 g	-58.5%	-55.6%	+30.2%	-42.5%

OCEANS = An Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients With Dyslipidemia.
McKenney JM et al[45]; Guyton JR et al[46]; Karas RH et al.[47]

well-controlled LDL-C on statins and low HDL-C (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes [AIM-HIGH]), or in combination with a prostaglandin-D receptor inhibitor in patients with low HDL-C, to determine if treatment can lead to a reduction in vascular events (HPS2 Treatment of HDL to Reduce the Incidence of Vascular Events [HPS2-THRIVE]).[48]

Safety of Niacin/Statin Combination Therapy

Niacin monotherapy appears to be safe and is well tolerated at moderate doses. In clinical trials, discontinuations due to adverse events are most commonly related to flushing and cutaneous effects.[45] As a result, patients given niacin should be educated about the potential of flushing and how to manage it. While there have been concerns about an increased risk of myopathy in combination with statins, a comparison of adverse event reports to the FDA from 1999 to 2005 found no increased risk with niacin extended release (ER)/lovastatin combination therapy compared with lovastatin or niacin ER monotherapy.[49] Niacin therapy can increase plasma glucose levels, which is a significant concern for patients with diabetes. A systematic review concluded that at doses ≤2.5 g/d, niacin is associated with minor increases in FPG (4%-5%) that are easily managed by adjusting diabetes therapy. This small increase is outweighed by niacin's beneficial effect on lipid profiles.[50]

Role of Fixed-Dose Combinations: Adherence to Long-term Therapies

Many patients at risk for CHD take multiple medications, and adherence to therapy is an ongoing clinical challenge. Among the many factors that contribute to poor adherence is the requirement for multiple drugs to achieve goals in CV risk reduction, which can increase the potential for side effects and increase costs. The pharmaceutical industry has responded to this challenge by developing a number of fixed-dose combination pills. Combinations of a statin with ezetimibe, amlodipine, or niacin ER are available, and additional combinations with fenofibrate or glucose-lowering agents are in clinical development. Fixed-dose combination pills to treat diabetes have been shown to improve adherence by 13% compared with 2-pill regimens.[51] The disadvantage of fixed-dose combinations is limited dose flexibility; however, treatment is simplified for patients who tolerate combined medications, which can improve adherence.

PCE Takeaways

- Individuals with atherogenic dyslipidemia are at high risk for CVD irrespective of LDL-C
- Lowering LDL-C remains the primary target of therapy
- With TG >200 mg/dL, non–HDL-C is the secondary target (non–HDL-C goal 30 mg/dL higher than the LDL-C goal)
- Addition of a fibrate or niacin is recommended for patients on statin therapy with high non–HDL-C but LDL-C lower than target
- Fibrates appear to reduce CVD risk in metabolic syndrome and diabetes by modifying non–HDL-C, HDL-C, and TG levels
- Niacin is the most effective agent for increasing HDL-C and has beneficial effects on other lipids
- Fibrates or niacin combined with statins have additive effects on lipid abnormalities and appear safe at moderate doses

CASE STUDY

A 65-Year-Old White Man With a History of Coronary Artery Bypass Graft Surgery

Presentation

The patient is a 65-year-old white man with a history of coronary artery bypass graft (CABG) surgery 1 year prior to presentation. At his last visit (6 months ago), his FPG was elevated (118 mg/dL) and he was counseled to begin a regimen of TLC, including weight loss and increased exercise. His current medications include ramipril 10 mg once daily for hypertension, atorvastatin 20 mg once daily, and a daily multivitamin.

Physical Examination

- Blood pressure: appears to be well controlled
- Body mass index: 32 kg/m^2
- Height: 6 ft
- Waist: 40.6 in
- Weight: 236 lb

Laboratory Results

The following are within the desired range:

- LDL-C: 80 mg/dL
- Total cholesterol (TC): 173 mg/dL

The following are outside recommended limits:

- HDL-C: 38 mg/dL
- Non–HDL-C: 135 mg/dL
- TG: 280 mg/dL

TG and HDL-C levels have deteriorated in the past 6 months; TG has increased by 30 mg/dL and HDL-C decreased by 10 mg/dL. His FPG is 138 mg/dL, a 20-mg/dL increase since his last visit, suggesting that he may have diabetes despite TLC.

Clinical Decision Point

What is this patient's CHD risk category?

- Very high
- High
- Moderately high
- Moderate
- Low

Comment

Based on laboratory results and physical examination, the patient fits the criteria for metabolic syndrome,[1] and his FPG is consistent with a diagnosis of type 2 diabetes as set by the American Diabetes Association (≥126 mg/dL) (Table 5).[4] According to the 2004 NCEP ATP III update, this patient falls into the "very high" risk category for CVD.

Given the patient's newly diagnosed type 2 diabetes, he is placed on an oral glucose-lowering agent. Diagnoses of type 2 diabetes and metabolic syndrome are not mutually exclusive—individuals can have both.

Clinical Decision Point

What would be your next step in managing his dyslipidemia?

- Intensify statin therapy by doubling the dose of atorvastatin to 40 mg/d
- Maintain statin dose at 20 mg/d and add a fibrate
- Maintain statin dose at 20 mg/d and add omega-3 acid ethyl esters (3-4 g/d)
- Maintain statin dose at 20 mg/d and add niacin ER (1000 mg/d)

The following treatment options are not sequential choices; potential advantages and drawbacks of each option for this patient are discussed.

Table 5. Metabolic Syndrome Criteria

Risk Factor	Defining Level		Case
	Women	Men	
Waist[a]	>88 cm (>35 in)	>102 cm (>40 in)	103 cm (40.6 in)
TGs[b]	≥150 mg/dL		280 mg/dL
HDL-C[b]	<50 mg/dL	<40 mg/dL	38 mg/dL
Blood pressure[b]	≥130/≥85 mm Hg		Controlled on ACEI
Fasting glucose[b]	≥100 mg/dL		138 mg/dL

[a]Lower cutpoints (≥90 cm in men and ≥80 cm in women) for Asian Americans; [b]or drug treatment for elevated TG or glucose levels, hypertension, or reduced HDL-C levels.
Grundy SM et al.[1]

Option 1: Increase the Statin

Comment

Increasing statin dose is not an adequate way to manage the atherogenic lipid profile characteristic of metabolic syndrome and diabetes because it has little or no effect on the other lipid components (triglycerides, non–HDL-C, and HDL-C) that contribute to CVD risk.

Option 2: Add a Fibrate

Comment

The patient is counseled to reinforce TLC, and fenofibrate 145 mg/d is added to his current statin regimen.

At 3 months, his lipid profile and glucose levels have improved (Table 6). He reports no musculoskeletal adverse effects and has no renal or hepatic effects.

NCEP ATP III recognized that patients with elevated TG and low HDL-C have significant residual CVD risk that requires intervention, even when LDL-C levels are well controlled. The NCEP ATP III recommendation was to add a fibrate or niacin to existing statin therapy. Results of several clinical trials support the efficacy of fibrates for primary or secondary prevention to reduce the major CVD event rate in patients with diabetes or metabolic syndrome,[31-34] but do not provide strong evidence for benefit as secondary prevention in patients without diabetes.[34] The potential for statin and fibrate combinations to increase myopathy should be considered; fenofibrate is a preferred choice in combination with statins.

Option 3: Add Omega-3 Acid Ethyl Esters

Comment

Supplementing statin therapy with omega-3 fatty acids can produce significant reductions in TG, but has a little effect on raising HDL-C. Results of the GISSI-Prevenzione study suggest omega-3 acid ethyl esters are an effective adjunct to standard post-MI care for secondary prevention at 1000 mg/d, which will have little effect on TG levels. Omega-3 acid ethyl esters are indicated for patients with very high TG levels (>500 mg) at 4000 mg/d, which can result in significant TG reductions but little change in HDL-C and a possible increase in LDL-C.

Option 4: Add Niacin

Comment

The patient is counseled to reinforce TLC and is prescribed niacin ER (1000 mg at bedtime) along with his current statin (atorvastatin 20 mg). At his 3-month follow-up visit, his lipid profile has improved. He mentions no musculoskeletal adverse effects, and there are no renal or hepatic lab abnormalities. A comparison of baseline and 3-month findings is shown in Table 7.

For patients with diabetes, niacin ER is recommended (after TLC) for raising HDL-C and lowering TG, along with glycemic control and a statin for treatment of combined hyperlipidemia.[4,19] Clinicians should be alert for minor increases in FPG, and proactively manage flushing effects through education.

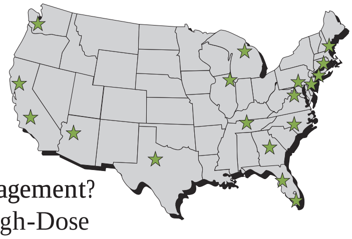
Table 6. 3-Month Follow-up Laboratory Results: Fibrate/Statin Combination

Lipid Profile	Visit 1	Visit 2 (3-month follow-up)
TC (mg/dL)	173	141 (19% reduction)
LDL-C (mg/dL)	80	69 (14% reduction)
Non–HDL-C (mg/dL)	136	97 (29% reduction)
HDL-C (mg/dL)	38	44 (16% increase)
TG (mg/dL)	280	140 (50% reduction)
Glucose Level	**Visit 1**	**Visit 2 (3-month follow-up)**
FPG (mg/dL)	138	95 (31% reduction)

Table 7. 3-Month Follow-up Laboratory Results: Niacin ER/Statin Combination

Lipid Profile	Visit 1	Visit 2 (3-month follow-up)
TC (mg/dL)	173	164 (5% reduction)
LDL-C (mg/dL)	80	72 (10% reduction)
Non–HDL-C (mg/dL)	136	118 (13% reduction)
HDL-C (mg/dL)	38	46 (21% increase)
TG (mg/dL)	280	180 (36% reduction)
Glucose Level	**Visit 1**	**Visit 2 (3-month follow-up)**
FPG (mg/dL)	138	120 (13% reduction)

Questions From Symposium Participants



Q: Since the outcome of the ENHANCE trial, what role should ezetimibe play in lipid management?

A: The Effect of Combination Ezetimibe and High-Dose Simvastatin versus Simvastatin Alone on the Atherosclerotic Process in Patients With Heterozygous Familial Hypercholesterolemia (ENHANCE) trial looked at simvastatin 80 mg compared with simvastatin/ezetimibe (80/10 mg) in a group of patients with heterozygous familial hypercholesterolemia.[52] These patients had very high baseline LDL-C levels (>300 mg/dL) and were being treated or had previously been treated with statins. The investigators found no additional benefit of the combination in terms of disease progression measured by carotid intima media thickness (IMT). Based on this study, the current recommendation is to titrate the statin to full dose and reserve ezetimibe for patients who don't respond.

Q: How do you explain the importance of elevated TGs to patients?

A: One approach is to characterize lipids as a delivery and cleanup system. Each type of lipid is carried in particles, which are generated in the liver. The body needs TGs and cholesterol for cell membranes and other functions. TGs and cholesterol are processed by the liver and then delivered by VLDL to the tissues. When the right amount is delivered, everything is okay. When too much is delivered, these particles start to accumulate in the blood. HDL is there to clean up the leftovers. Dyslipidemia results when this system is out of balance. Usually patients with high TG levels are overweight/obese. This presents an opportunity to talk with them about visceral obesity and explain how fat cells around the abdomen are releasing fat into the system and overwhelming it. This extra fat goes to the liver, where 1 of 3 things happens: the fat is metabolized for energy, released as VLDL/TG, or stored with the result that fatty liver develops. Elevated TG levels indicate the system is out of balance and the patient has to lose weight and change lifestyle, including being more active.

Q: Is there a preferred statin for combination therapy?

A: Statins vary in potency; newer statins are more efficacious. Patients may respond better to one statin than another. Fibrates can be combined safely with any of the statins, with a caveat that they should not be combined with high-dose statins to minimize the risk of myopathy from the combination, and fenofibrate should be chosen. Gemfibrozil in combination should be avoided for this reason.

Q: Can LDL-C ever be too low?

A: Our bodies can synthesize cholesterol and therefore make new LDL-C every day. Because our body needs cholesterol to replace the cells we lose every day and for hormonal function, the body will make enough cholesterol to not require it in our diet. Patients can be treated intentionally to an LDL-C level of 50 mg/dL with no ill effects. This has been studied carefully in randomized statin trials and results have shown that low LDL-C does not lead to any kind of problem.

Q: If a patient had a CV event, should the goal be to drive the LDL-C level down by another 30% to 40%, regardless of the baseline LDL-C level?

A: Yes. When statin therapy is implemented, the guidelines state to achieve not only a LDL-C goal but to also lower LDL-C by at least 30% to 40%. The HPS showed that when high-risk patients were treated with a statin, it dramatically reduced the risk of a recurrent event regardless of baseline LDL-C. If a patient with low LDL-C on treatment continues to have events, it is helpful to check lipoprotein(a) levels. For patients with high lipoprotein(a), adding niacin while further reducing LDL-C may be beneficial.

Q: Is statin therapy needed for a patient with diabetes who has an HDL-C of 90 mg/dL and total cholesterol of 210 mg/dL?

A: Absolutely. This patient's non–HDL-C (TC – HDL) is 120 mg/dL, and according to guidelines, the reasonable non–HDL-C goal for a patient with diabetes is 30 mg/dL above their LDL-C goal, which would make it 100 mg/dL. Thus, this patient is not at goal. It is wrong to assume that because the HDL-C is high, the patient's lipid profile is acceptable. This patient has an elevated LDL particle concentration and elevated HDL-C may or may not be cardioprotective. It does not eliminate the risk associated with too many LDL particles floating around. This patient should be on a statin.

Q: What is the relationship between apo-B and non–HDL-C?

A: The total cholesterol measurement includes all the cholesterol that is carried in lipoproteins. The atherogenic particles contain apo-B, and HDL contains apo-A. Therefore, the simplest way to think about it is that apo-B and non–HDL-C levels measure the same thing. That is why the non–HDL-C equation is total cholesterol minus HDL-C.

Q: What is the role of C-reactive protein?

A: One problem with C-reactive protein (CRP) as a cardiac marker is that it is not very specific, so anyone with allergy, arthritis, or any inflammation is going to have a high CRP level. For more specificity, lipoprotein-associated phospholipase A2 (LP PLA2) is another biomarker. This is an inflammatory biomarker unique to the endothelium and is not influenced by systemic inflammation. CRP testing as a cardiac marker is not necessary for a patient who is being treated with a statin, niacin, or fibrate because these treatments lower CRP. CRP should be used for risk stratification in patients with a Framingham risk score between 10% and 20%. The CRP tests must be done 1 week apart and the 2 values must be averaged together, which most patients find inconvenient.

Q: What are the components of omega-3 fatty acids and what is their relevance?

A: The 2 active components of fish oil are EPA and DHA. The EPA concentration should be higher than the DHA. The total amount of EPA/DHA should be at least 500 mg, which is the amount commonly claimed for over-the-counter products. However, there are differences among brands of omega-3 fatty acids. When several omega-3 fatty acid preparations were analyzed, some did not contain the labeled amounts of EPA and DHA and others contained mercury, although at negligible levels.[53,54] That is the frustrating part of using alternative therapies. Available by prescription only, a pharmaceutical grade omega-3 acid ethyl ester is regulated by the FDA and is safe. EPA and DHA in sufficient amounts are very effective in reducing hepatic TG production, and can lower plasma TG by up to 45%.

Q: Does extended-release niacin cause less flushing or must aspirin be added to decrease the flushing?

A: Treating patients with niacin ER can be a challenge. Niacin ER is formulated with a polymer coating that is on and throughout the pill. Patients who take over-the-counter immediate-release niacin have to take it 3 times a day, and about 60% to 70% are going to have hot flashes and flushing. Over-the-counter "no flushing" niacin is actually nicotinamide, not niacin. There is no free active nicotinic acid, therefore no flushing, but there also is no niacin, therefore no lipid benefit. Aspirin (325 mg) helps block the prostaglandin-mediated reaction that occurs when niacin is used, which is what causes the hot flashes and flushing, and normally lasts 20 to 30 minutes. Although flushing is a nuisance, niacin is an effective treatment. Patients should be encouraged to learn to manage this side effect, which will diminish with time. Let them know that the longer they take niacin ER, the fewer side effects they will have.

Q: Is there an age at which statin therapy can be discontinued?

A: Age is not so much the issue as the individual needs of the patient. Older, functioning patients who are at risk for CVD should continue statins indefinitely.

Q: What should be done for a patient on a statin who has an elevated creatine kinase (CK) or creatine phosphokinase level but no symptoms of myalgia?

A: If CK is significantly high (eg, >1000 IU), statin treatment must be discontinued. If the CK level comes down after discontinuation, the causal relationship is clear. Statin-related myalgia is not uncommon (10%). When it happens, one approach is to try switching statins, as patients tolerate statins differently, or use the lowest dose possible, and consider every-other-day dosing. There are other causes of elevated CK. For example, patients might have a primary muscle disorder that wasn't diagnosed prior to starting statin therapy. Too often, patients self-diagnose exercise or work-related muscle aches and cramps as statin-related myalgia and want to stop treatment. The first step is to make sure that any complaints of muscle pain are indeed related to the statin, not other causes.

Q: Is it safe for patients with hepatitis to take statins?

A: That is a difficult question. In a patient with active hepatitis B or C and dyslipidemia, a bile acid sequestrant might be used. For patients with hepatitis in remission, a cautious approach to statin use is advised. Liver enzymes are affected by fatty liver as well as hepatitis, so it is good to evaluate the underlying cause. If possible, it is prudent to treat for dyslipidemia and monitor the liver function tests for changes because these patients are at higher risk for CV events.

Q: What over-the-counter products are recommended for lipid lowering?

A: Over-the-counter products, including niacin, red yeast rice, and omega-3 supplements, are acceptable for persons in the low-risk category. However, for patients with diabetes or a previous CV event, it is more appropriate to use medicines that have been shown to produce beneficial outcomes. Because clinicians are familiar with these medicines, they know what to expect and can achieve the right result for the particular high-risk patient. With niacin, it is important to note that over-the-counter sustained-release niacin is less safe in terms of hepatic effects than prescription products.

It is up to the clinician to explain to patients why untested or unregulated products are not a good choice. If patients are educated properly and provided with the information, it helps them understand why they are using a specific treatment and that increases compliance.

"With this new drug, cholesterol forms *outside* of the body, where it can't clog the arteries."

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