An Evidence-Based Approach to the Use of Combination Drug Therapy for Mixed Dyslipidemia

Case Study and Commentary, Charles R. Harper, MD, and Terry A. Jacobson, MD

Dyslipidemia is one of the major modifiable risk factors for coronary heart disease (CHD), the leading cause of death among U.S. men and women. Most patients with CHD have multiple lipid abnormalities. The condition known as mixed dyslipidemia (ie, elevated LDL cholesterol and triglyceride levels combined with decreased levels of HDL cholesterol) is commonly seen in patients with diabetes and metabolic syndrome. In 2001, the Adult Treatment Panel III of the National Cholesterol Education Program (ATP III) established LDL and non-HDL cholesterol goals for patients with mixed dyslipidemia. Recently, more aggressive goals for high-risk patients were established. Treatment for these patients may require lipid-lowering drugs. Some clinicians have been reluctant to use combination therapy because of safety concerns. This article reviews the available evidence for treatment of mixed dyslipidemia.
Table 1. Updated NCEP/ATP III Guidelines for Cholesterol Management

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal, mg/dL</th>
<th>Non-HDL-C Goal, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high: CVD plus:</td>
<td>&lt; 100 (optional: &lt; 70)</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple major risk factors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly controlled risk factors*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High: CHD or CHD risk equivalent†</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Moderately high: 2 or more risk factors* and Framingham score 10%–20%</td>
<td>&lt; 130 (optional: &lt; 100)</td>
<td>&lt; 130</td>
</tr>
<tr>
<td>Moderate: 2 or more risk factors* and Framingham score &lt; 10%</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>Low: 0–1 risk factor*</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
</tr>
</tbody>
</table>


*Risk factors = hypertension, HDL-C < 40 mg/dL, cigarette smoking, age (men ≥ 45 yr)/(women ≥ 55 yr), family history (first-degree relative with CHD [male before age 55 y/female before age 65 y]), subtract risk factor for HDL ≥ 60 mg/dL.
†CHD equivalent = diabetes, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid disease, Framingham 10-year risk score > 20%.

CASE STUDY

Initial Presentation

A 46-year-old man with a history of type 2 diabetes and hypertension is referred to a cardiologist for management of suboptimal lipid levels. The referring physician is concerned because the patient’s LDL-C level is not at goal despite statin therapy and his triglyceride and HDL-C levels are not optimal.

The patient was diagnosed with type 2 diabetes and hypertension within the past 5 years; both conditions have been well controlled with medications. The patient is otherwise healthy, with no history of cardiovascular disease. His current medications include atorvastatin 40 mg/day, lisinopril 20 mg/day, glipizide 10 mg/day, and metformin 500 mg twice daily. He does not use tobacco and drinks 2 beers per month. He is a bus driver. His family history includes an 85-year-old mother with hypertension and a father who died at age 77 of a myocardial infarction (MI). He has one 50-year-old sibling who is living without medical illness.

The patient is 5′ 10″ tall and weighs 203 lb (body mass index, 29 kg/m²), with a waist circumference of 41″. Blood pressure is 128/78 mm Hg. The remainder of the physical examination is unremarkable.

Laboratory values from fasting blood tests ordered 4 weeks prior include hemoglobin A1c, 6.1%; glucose, 118 mg/dL; thyroid-stimulating hormone, 0.7 µU/mL; alanine aminotransferase, 18 U/L; aspartate aminotransferase, 23 U/L; creatinine, 0.9 mg/dL; total cholesterol, 197 mg/dL; LDL-C, 104 mg/dL; HDL-C, 32 mg/dL; and triglycerides, 305 mg/dL.

Based on the patient’s medical and dietary history and blood test results, the cardiologist rules out secondary causes of dyslipidemia (eg, poor glycemic control, renal or liver disease, hypothyroidism). She also concludes that the patient’s elevated triglyceride levels are not attributable to dietary causes (eg, high carbohydrates, alcohol abuse), drug effects (eg, thiazides, estrogen, progesterone, β blockers), or uncontrolled diabetes.

- How would this patient’s CHD risk be assessed? What are current recommended lipid levels for this patient?

Evidence from several studies, including a Finnish population-based study, reveals that patients with type 2 diabetes have a rate of first MI that is greater than or equal to nondiabetic patients who have already experienced an MI [4]. This evidence has prompted the ATP III to designate diabetes as a CHD risk equivalent (ie, carrying a risk for major coronary events equivalent to established CHD) and to thereby stipulate that diabetic patients be managed aggressively, as if they already have cardiovascular disease.

According to the revised ATP III treatment recommendations, the case patient would be classified as being at high risk for CHD based on his diagnosis of type 2 diabetes but his negative history of existing cardiovascular disease (Table 1). For patients at high risk for CHD, the ATP III recommends an LDL-C goal of less than 100 mg/dL. The case patient’s LDL-C level is currently not at goal and his triglycerides remain high. In patients with high triglycerides (ie, 200–499 mg/dL) and elevated LDL-C, attention should first be focused on achieving the ATP III goal for LDL-C. Thus, at this point, dyslipidemia treatment decisions for this patient should first focus on reaching an LDL-C of less than 100 mg/dL.
The revised ATP III treatment recommendations suggest placing moderate- to high-risk patients on a dose of statin high enough to achieve a 30% to 40% reduction in LDL-C (Table 2) [3]. Statin-induced reductions in LDL-C are dose dependent; generally, doubling the dose results in an additional 6% reduction in LDL-C. The case patient requires an additional 4% reduction in LDL-C, which could be achieved by simply doubling the dose of atorvastatin to 80 mg/day. Although the maximum recommended dose for each of the statins is generally well tolerated, increasing the dose increases the incidence of adverse events, such as transaminitis or myopathy (creatinine phosphokinase [CPK] > 10 times the upper limit of normal) [6].

A comparison of the relative efficacy of statins reveals that 10 mg/day of rosuvastatin is roughly equal to 20 to 40 mg/day of atorvastatin and 40 to 80 mg/day of simvastatin. Thus, even if the patient was switched to an equivalent dose of rosuvastatin and had the dose doubled, he would achieve only an additional 6% to 8% reduction in his LDL-C.

Another choice for this patient would be to add a second lipid-lowering drug. Bile acid sequestrants can reduce LDL-C but would be relatively contraindicated in this setting because they can markedly worsen hypertriglyceridemia. However, this would be less likely since the patient is receiving concurrent statin therapy. Ezetimibe would decrease LDL-C another 20%; however, after adding this drug, the patient would still have abnormal HDL-C and triglyceride levels and would require the addition of a third lipid-lowering drug [7]. Although a few small studies with ezetimibe and fibrates exist, the safety of concomitant use of ezetimibe and a fibrate or niacin has not been established [8].

**Treatment and Follow-up**

The cardiologist decides to try intensifying the patient’s lipid-lowering therapy by increasing his atorvastatin dose to 80 mg/day. A follow-up lipid profile and office visit are scheduled for 6 weeks later. At follow-up, the patient’s lipid levels are total cholesterol, 186 mg/dL; LDL-C, 99 mg/dL; triglycerides, 275 mg/dL; and HDL-C, 32 mg/dL.

**Once patients with mixed dyslipidemia are at ATP III goal for LDL-C, how are goals established for treatment of elevated serum triglycerides?**

- Which strategy for further LDL-C reduction would be best for this patient: increase the dose of his current statin, switch him to a more efficacious statin, or add a second lipid-lowering drug?

- What is the best drug to add to a statin when a patient has high triglyceride and low HDL-C levels and is at LDL-C goal?

Once at LDL-C goal, patients with mixed dyslipidemia require treatment focused on lowering elevated serum triglycerides. Elevated triglycerides are associated with increased CHD risk, particularly triglyceride-rich lipoproteins known as *remnant lipoproteins*. Very low-density lipoprotein cholesterol (VLDL-C) is highly correlated with remnant lipoproteins and can be combined with LDL to improve risk prediction in hypertriglyceridemic patients. The sum of VLDL-C, LDL-C, and intermediate-density lipoprotein cholesterol is known as *non-HDL cholesterol*. Non-HDL-C is simply total cholesterol minus HDL-C and is an accurate surrogate for the measurement of all the atherogenic apoprotein B–containing lipoproteins. The use of non-HDL-C as a treatment goal when triglycerides exceed 200 mg/dL is supported by a follow-up report of the Lipid Research Clinic cohort, which demonstrated a stronger correlation with coronary mortality for non-HDL-C than for LDL-C [9].

Returning to the case patient, further treatment decisions at this point should be based on his non-HDL-C, which is calculated as 154 mg/dL by subtracting his HDL-C value from his total cholesterol value (186 – 32). For such high-risk patients, the revised ATP III treatment guidelines recommend a non-HDL goal of 30 mg/dL higher than the LDL goal (Table 1). Thus, the case patient will need treatment targeted at lowering his non-HDL-C from 154 mg/dL to less than 130 mg/dL.

**Table 2. Statin Dose Required to Achieve a 30% to 40% Reduction in LDL-C Levels**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg/day</th>
<th>LDL-C Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40</td>
<td>31</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40–80</td>
<td>34</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20–40</td>
<td>35–41</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40–80</td>
<td>25–35</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5–10</td>
<td>39–45</td>
</tr>
</tbody>
</table>


Three types of agents can be considered as additive therapy for a patient with mixed dyslipidemia who is already on a statin: fibrates, niacin, and omega-3 fatty acids (fish oil).
TREATMENT OF MIXED DYSLIPIDEMIA

Table 3. Statin/Fibrate Combination Therapy: Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>Statin</th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>↑ in C_{max} (expected)</td>
<td>No effect</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>↑ in C_{max} (2-fold)</td>
<td>No effect</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>↑ in C_{max} (2-fold)</td>
<td>No effect</td>
</tr>
<tr>
<td>Rosuvasstatin</td>
<td>↑ in C_{max} (2-fold)</td>
<td>No effect</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>↑ in C_{max} (2.8-fold)</td>
<td>No effect</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>↑ in C_{max} (2- to 3-fold)</td>
<td>No effect</td>
</tr>
</tbody>
</table>

C_{max} = maximum concentration. (Adapted from Davidson MH. Combination therapy for dyslipidemia: safety and regulatory considerations. Am J Cardiol 2002;90:50K–60K. Copyright 2002, with permission from Elsevier.)

Fibrates

Fibrates have an important role in treating mixed dyslipidemia in patients with diabetes or metabolic syndrome. The 2 fibrates available in the United States are fenofibrate and gemfibrozil. When combining with a statin, fenofibrate is the preferred drug, as the risk of rhabdomyolysis is considerably lower with fenofibrate/statin than with gemfibrozil/statin because of differences in drug metabolism (Table 3) [10]. Recently, it has been shown that statins undergo significant glucuronidation when metabolized; if glucuronidation is inhibited, statin clearance is impeded and statin blood levels increase to potentially toxic levels. Gemfibrozil competes with statin drugs for certain hepatic microsomes required for glucuronidation, whereas fenofibrate uses a different set of hepatic microsomes for glucuronidation and has a minimal effect on the metabolism of statins [11]. Thus, although fibrates alone can cause myopathy and rhabdomyolysis, gemfibrozil particularly when combined with a statin, increases rhabdomyolysis risk 10- to 15-fold [12]. Current package inserts for most statins do not reflect these new data and generally state that the combination of a fibrate and a statin should be avoided unless the benefits outweigh the risks. Although fenofibrate is safer when combined with a statin, the rate of rhabdomyolysis still reflects the additive risks from each drug alone.

Efficacy Data

In patients with mixed hyperlipidemia, the fibrates have been shown to reduce LDL-C levels by 5% to 20%, to increase HDL-C by 10% to 29%, and to decrease triglycerides by 20% to 50% (Table 4). These changes are due to the activation of peroxisome proliferator activator receptor-α (PPAR-α), which in turn affects several aspects of lipid metabolism. Activation of PPAR-α has been shown to increase genetic expression of lipoprotein lipase and to suppress genetic expression of apoprotein C-III, a known inhibitor of lipoprotein lipase, thus resulting in reduced triglyceride levels [13]. The increase in HDL-C is due to an increase in apoprotein A-I and A-II production, along with up-regulation of ABC-A1 (ATP-binding cassette A1). Although gemfibrozil and fenofibrate can increase LDL-C levels in some patients, fenofibrate has been shown to decrease the number of LDL particles and to shift particle size from smaller to larger, less atherogenic particles [13]. In addition, the fibrates have been shown to reduce markers of inflammation, including high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α, and intracellular adhesion molecule [14].

Several clinical outcome trials with fibrates have been conducted. Two trials from the 1960s, the World Health Organization trial [15] and the Coronary Drug Project (CDP) [16], used clofibrate, a drug no longer used in the United States. While both of these studies demonstrated that clofibrate reduced cardiac events, concerns were raised because of a lack of total mortality benefit due to increased risk of non-CHD mortality.

More recent trials with newer fibrates have not shown any increase in non-CHD mortality. The Helsinki Heart Study (HHS) was a primary prevention trial with more than 4000 dyslipidemic men randomized to gemfibrozil 600 mg twice daily or placebo for 5 years [17]. Primary endpoints included fatal and nonfatal MI and cardiac death. No significant lipid changes were noted in the placebo group, while lipid changes for the gemfibrozil group included an 11% reduction in total and LDL-C, an 11% increase in HDL-C, and a 43% reduction in triglycerides. A 34% (P < 0.02) reduction in the incidence of CHD events was observed, and no increase in non-CHD death was noted (Table 5). In a post hoc analysis, those participants with triglyceride levels greater than 200 mg/dL and HDL-C levels less than 42 mg/dL received the greatest benefit, with a 66% reduction in events [18].

Gemfibrozil was also used in the Veterans Affairs HDL Cholesterol Intervention Trial (VA-HIT) [19]. The VA-HIT compared gemfibrozil (1200 mg/day) with placebo in 2531 patients with mixed dyslipidemia, and found a 19% reduction in the incidence of CHD events compared to placebo. These results suggest that fibrates may be beneficial for the prevention of CHD events in certain populations.

Table 4. Pharmacotherapeutic Effect on Lipoproteins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>↓15%–60%</td>
<td>↓20%–60%</td>
<td>↑3%–15%</td>
<td>↓10%–40%</td>
</tr>
<tr>
<td>Resin</td>
<td>↑20%</td>
<td>↑10%–20%</td>
<td>↑3%–5%</td>
<td>↑neutral</td>
</tr>
<tr>
<td>Niacin</td>
<td>↑25%</td>
<td>↑10%–15%</td>
<td>↑15%–35%</td>
<td>↓20%–50%</td>
</tr>
<tr>
<td>Fibrate</td>
<td>↑15%</td>
<td>↓0%–15%</td>
<td>↑6%–15%</td>
<td>↓20%–50%</td>
</tr>
<tr>
<td>Fish oil</td>
<td>↑neutral</td>
<td>↑neutral</td>
<td>↑neutral</td>
<td>↓20%–50%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>↓12%</td>
<td>↓18%</td>
<td>↑1%</td>
<td>↓8%</td>
</tr>
</tbody>
</table>

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; total C = total cholesterol; TG = triglycerides.
men with CHD and a mean LDL-C of 112 mg/dL, mean HDL-C of 32 mg/dL, and a mean triglyceride of 160 mg/dL. The primary study outcome was nonfatal MI or death from cardiac causes, and median follow-up was 5.1 years. Gemfibrozil-treated patients had a 6.3% increase in HDL-C and a 26.6% reduction in triglycerides, while LDL-C remained essentially unchanged. The absolute risk reduction was 4.4%, and the relative risk reduction was 22% (95% confidence interval, 7%–35%; \( P = 0.006 \)) (Table 5). In the subgroup analysis of this trial, most of the benefit was driven by the subset of patients with type 2 diabetes or impaired glucose tolerance. Analysis of individual endpoints reveals that patients in the diabetes subgroup had a 41% reduction in CHD death (\( P = 0.02 \)) [20].

In the Bezafibrate Infarction Prevention (BIP) study, more than 3000 patients with a prior MI or stable angina were randomized to bezafibrate 400 mg/day or placebo [21]. This study was conducted in patients with normal to mildly elevated triglycerides (mean triglyceride level, 145 mg/dL) and elevated LDL-C (mean, 148 mg/dL). There was no reduction of the combined primary endpoint of fatal or nonfatal MI and sudden death. However, post hoc analysis demonstrated a significant reduction in the combined primary endpoint for the subgroup with elevated triglycerides (> 200 mg/dL) and low HDL-C (Table 5). In another trial with bezafibrate, more than 1500 men with lower extremity arterial disease were randomized to bezafibrate 400 mg/day or placebo. Bezafibrate had no effect on the incidence of the combined primary endpoint and stroke [22].

In the Diabetes Atherosclerosis Intervention Study (DAIS), 731 patients with type 2 diabetes, normal LDL-C (mean, 130 mg/dL), low HDL-C (mean, 39 mg/dL), and high triglycerides (mean, 230 mg/dL) were randomized to fenofibrate 200 mg/day or placebo [23]. Those in the fenofibrate arm had a 6% reduction in LDL-C, a 29% reduction in triglycerides, and a 7% increase in HDL-C along with a 40% reduction in the progression rate of coronary lesions when compared with placebo. Although DAIS was not powered for hard cardiac endpoints, fenofibrate demonstrated a non-significant 23% reduction in cardiac events.

Finally, the results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were recently published [24]. This study evaluated the efficacy of fenofibrate 200 mg/day in preventing CHD events in more than 9000 patients with type 2 diabetes. Approximately 20% of the patients recruited had previous cardiovascular disease. Patients in the fenofibrate arm had a 5.8% reduction in LDL-C and a 21.9% reduction in triglycerides along with a 1.2% increase in HDL-C. There was a nonsignificant 11% reduction (\( P = 0.16 \)) in the combined primary outcome of CHD mortality and nonfatal MI. The secondary outcome of total cardiovascular disease events was significantly reduced by 11% (\( P = 0.035 \)). This reduction was driven primarily by the significant reductions in nonfatal MI (24%) and coronary revascularizations (21%). The study results were complicated by more patients starting statin therapy during the trial in the control group than the intervention group. From a safety perspective, fenofibrate was well tolerated, with 3 cases of rhabdomyolysis in the fenofibrate arm versus 1 in the placebo arm. No rhabdomyolysis was seen with combination fenofibrate/statin therapy.

In composite, the available studies suggest that fibrates are most effective in type 2 diabetics or obese metabolic syndrome patients who characteristically have high triglycerides, low HDL-C, and a predominance of small dense LDL.
patient fits into these criteria, but the case patient also required a statin to reduce LDL-C. Clinical trial evidence on combination therapy with statins and fibrates is pending the completion of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. ACCORD is a 2 × 2 multifactorial trial comparing the efficacy of 20 mg/day of simvastatin alone with 20 mg/day of simvastatin plus 160 mg/day of fenofibrate in preventing cardiovascular events; however, this trial will not be completed until 2009 [25].

Several efficacy trials have compared statin monotherapy with statin/fibrate combination therapy in terms of their effect on lipoprotein levels and particle size. One such trial is the Simvastatin plus Fenofibrate for Combined Hyperlipidemia (SAFARI) trial [26]. In this trial, more than 600 patients with combined hyperlipidemia (fasting triglycerides ≥ 150 mg/dL and ≤ 500 mg/dL, LDL-C > 130 mg/dL) were given 20 mg/day of simvastatin or combination therapy with 20 mg/day of simvastatin and 160 mg/day of fenofibrate. After 12 weeks of treatment, median triglyceride levels decreased 20.1% in the simvastatin monotherapy group compared with 43% in the combination group, for a treatment difference of 23.6% (P < 0.001). Mean non-HDL levels decreased 26.1% and 35.3%, respectively (treatment difference, 9.2%; P < 0.001), while HDL-C increased 9.7% and 18.6% (treatment difference, 8.8%; P < 0.001) in the simvastatin monotherapy versus the combination group. In addition, there was a significant increase in the large, buoyant, less atherogenic, pattern A LDL-C subclass when combination therapy was compared with simvastatin monotherapy. No clinical myopathy or drug-related serious adverse events were observed. Another trial with atorvastatin and fenofibrate yielded similar results, with greater reductions in LDL-C and triglycerides and elevation in HDL-C [27].

Niacin

Niacin is another option for the treatment of patients with mixed dyslipidemia. Immediate-release (IR) crystalline niacin has been available as a dietary supplement for several years, as have certain over-the-counter sustained-release (SR) niacin preparations requiring twice daily dosing. Only 1 extended-release (ER) niacin product is available that is approved for once daily use and requires a prescription. Combining niacin with a statin may slightly increase the risk of transaminitis and myopathy; however, the increased risk is small. Analysis of U.S. Food and Drug Administration case reports shows the combination of niacin and a statin results in no greater risk of myopathy than statin monotherapy. Rare cases of serious hepatotoxicity have been reported with the older preparations of SR niacin products; however, IR and prescription ER preparations have not been associated with serious hepatotoxicity [28].

Efficacy Data

In patients with diabetes and mixed dyslipidemia, 2 g/day of ER niacin has been shown to increase HDL-C by 20% to 25%, to decrease triglycerides by 25% to 30%, and to reduce LDL-C by 10% to 15% (Table 4) [29]. The beneficial changes in lipoproteins caused by niacin are the result of multiple mechanisms. Niacin inhibits hormone-sensitive lipase, resulting in the inhibition of free fatty acid mobilization from adipose tissue and subsequent reduced production of VLDL-C and hepatic production of apoprotein B-containing lipoproteins. Niacin inhibits diacylglycerol-2 acyl transferase, a key enzyme in the production of VLDL-C particles [30,31]. Also, unlike fibrates, which increase rates of HDL-C production, niacin inhibits the catabolism of HDL-C; thus, HDL-C is available longer in the body [32].

Combining niacin/statin therapy provides the benefit of the potent LDL-C reduction that is associated with statins in addition to potent elevation of HDL-C levels, along with further decreases in triglycerides, lipoprotein(a), and LDL-C. The efficacy of this combination has been demonstrated in several trials. In a study with the addition of 3 g/day of IR niacin and fluvastatin, LDL-C was decreased 40% from baseline, and the LDL/HDL ratio was reduced by 52% [33]. In a 52-week trial of 800 dyslipidemic patients, treatment with a combination of 2 g ER niacin and 40 mg lovastatin resulted in a 45% reduction in LDL-C, a 42% reduction in triglycerides, and a 41% increase in HDL-C [34].

In addition to niacin trials with lipoprotein outcomes, clinical trials with niacin alone and in combination have demonstrated regression of coronary atherosclerosis and reduced cardiovascular morbidity and mortality. The CDP placebo-controlled quantitative coronary angiographic trial evaluated 160 patients with low HDL-C (≤ 35 mg/dL in men and ≤ 40 mg/dL in women) and LDL-C levels at or below 145 mg/dL; participants were randomized to 1 of 4 treatments: placebo; simvastatin 10 to 20 mg day plus niacin 2 to 4 g day; antioxidant vitamins consisting of vitamin E 800 IU/day, vitamin C 1000 mg/day, beta carotene 25 mg/day, and selenium 100 µg/day; or simvastatin and niacin plus antioxidants. Baseline lipid levels averaged 31 mg/dL for HDL-C, 125 mg/dL for LDL-C, and 213 mg/dL for triglycerides. The
use of simvastatin and niacin reduced LDL-C and triglycerides by an average of 42% (P < 0.001) and 36% (P = 0.001), respectively, while increasing HDL-C by 26% (P = 0.001). The addition of antioxidants to the combination of simvastatin and niacin resulted in similar decreases in LDL-C and triglycerides but a dramatic attenuation of the HDL-C increase, resulting in a more than 18% change for simvastatin/niacin/antioxidant therapy. Compared with a mean 3.9% progression in coronary stenosis with placebo, niacin/simvastatin therapy caused a mean regression of 0.4% (P < 0.001). The composite primary endpoint of cardiac death, MI, stroke, and revascularization was reduced by 90% in the simvastatin/niacin group compared with placebo (P = 0.03).

A more recent trial, the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER-2) trial, evaluated statin/niacin therapy and the intermediate endpoint carotid intima-media thickness (CIMT) [37]. In this trial, more than 160 patients with CHD on background statin therapy were given ER niacin 1000 mg/day or placebo for 12 months. The overall difference in CIMT progression between the niacin and placebo groups was not significant (P = 0.08); however, niacin significantly reduced the rate of progression in patients without insulin resistance (post hoc analysis, P = 0.026). Although clinical trials with niacin have demonstrated significant reductions in intermediate and hard cardiac endpoints, the use of niacin is somewhat limited by poor compliance secondary to flushing and its tendency to worsen glycoemic control and exacerbate gout.

**Omega-3 Fatty Acids**

Finally, omega-3 fatty acids in the form of fish oil have been used to treat patients with hypertriglyceridemia and, in lower doses, to prevent cardiac death and sudden death. Omega-3 fatty acids are well tolerated and have an excellent safety profile with minimal drug interactions. Prescription omega-3–rich fish oil, dosed at 4 g/day, will lower triglyceride levels by 35% to 45%, depending on baseline. One concern about omega-3 fatty acids is their propensity for increasing LDL-C in patients with severe hypertriglyceridemia (levels > 500 mg/dL). In a study involving patients with triglyceride levels greater than 500 mg/dL, 4 g/day of fish oil reduced triglycerides by 45% and non-HDL-C by 14%; in addition, HDL-C levels increased by 9% and LDL-C increased by 45% (Table 4) [38]. This increase in LDL-C is similar to that seen with fibrates and is not seen in patients treated concomitantly with statins. LDL-C increases are thought to be due to the conversion of VLDL into less atherogenic, large, buoyant LDL-C (pattern A). It is important to note that although omega-3 fatty acids lower triglycerides in patients with baseline levels between 200 and 500 mg/dL, they are currently not approved for that indication pending further studies.

**Omega-3 fatty acids** are thought to lower triglycerides by multiple mechanisms, including their ability to inhibit diacyl-glycerol acetyl-transferase, their role as a natural ligand for PPAR-α, and their tendency to increase the rate of peroxisomal β-oxidation. Omega-3 fatty acids in the form of fish oil are generally well tolerated and are not metabolized via cytochrome P-450, thus making drug–drug interactions unlikely. In higher doses (3–4 g/day), patients on warfarin may have a slight increase in bleeding tendency due to the antiplatelet effect of omega-3 fatty acids [39].

There have been few clinical outcome trials using fish oil in doses large enough (ie, 2–4 g/day) to affect lipoprotein levels; however, trials have also been completed with lower-dose fish oil (1 g/day) or with dietary fish supplementation. The Diet and Reinforcement Trial (DART) showed a 29% reduction in all-cause mortality in men with CHD who were randomized to a diet higher in oily fish (mackerel 2 servings per week) [40]. The GISSI Prevenzione Trial in more than 11,000 MI patients showed that 850 mg of omega-3 fat from fish oil reduced the combined primary endpoint of death, nonfatal MI, and nonfatal stroke by 15% (P = 0.022). This risk reduction occurred with only minor nonsignificant changes in lipids [41]. The study showed a 45% risk reduction in sudden death, suggesting that low-dose omega-3 fatty acids may mediate their effect as antiarrhythmics. There are no published clinical outcome studies of omega-3 fatty acids and statins used in combination; however, multiple trials with intermediate lipid endpoints have been conducted [42,43].

**Summary of the Evidence**

In summary, there is evidence from double-blind, randomized controlled trials with hard cardiac endpoints for the use of fibrates, niacin, and omega-3 fatty acids, although the omega-3 fatty acid trials were conducted using low doses (1 g/day) that had no significant effect on lipids. Higher doses of omega-3 fatty acids (2–4 g/day) used to lower triglycerides have not been studied in a clinical outcome trials with hard cardiac endpoints. Although the trials with fibrates have shown a reduction in cardiac events, the lack of a demonstrable total mortality benefit is concerning. Finally, the niacin clinical outcome trials, although impressive, represent a relatively small number of patients when compared with the large body of evidence for statins and fibrates.

**Case Conclusion**

The cardiologist decides to add fenofibrate 145 mg/day to the patient’s statin therapy and schedules a return visit in 8 weeks. Due to the increased risk of myopathy from the statin/fibrate combination, a baseline CPK level is obtained prior to starting the fibrate, and the patient is warned to report any signs of muscle aches or weakness immediately. He returns for his follow-up visit without any...
complaints. The patient’s lipid profile reveals that his LDL-C and non-HDL-C are now at goal: his total cholesterol is 160 mg/dL, his LDL-C is 91 mg/dL, his HDL-C is 36 mg/dL, and his triglycerides are 165 mg/dL. (Table 6). His CPK, creatinine, and transaminase levels are normal.

**SUMMARY**

There are advantages and disadvantages to each of the drugs discussed, and the decision of which drug to add to a statin depends on other clinical factors in the individual patient (Table 7). In patients with diabetes, the degree of glycemic control is an important determinant. Patients with poorly controlled diabetes may be better off with a fibrate because of niacin’s tendency to worsen glycemia. Recent studies involving patients with well-controlled diabetes, including the Arterial Disease Multiple Intervention Trial (ADMIT) with IR niacin and the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) with ER niacin, have shown minor increases in hemoglobin A1c in diabetic patients treated with niacin; however, glucose levels returned to baseline 6 weeks after titration of niacin dose was completed [44,45]. In a recent post hoc analysis of the CDP, investigators found that patients with 1-hour postprandial blood glucose levels less than 140 mg/dL had a 29% reduction in nonfatal MI and a 12% reduction in all-cause mortality after 6 years, while those with 1-hour postprandial blood glucose levels greater than 220 mg/dL had a reduction in nonfatal MI and all-cause mortality of 42% and 20%, respectively [46]. This would indicate that the cardiac benefit from niacin treatment is maintained in diabetic patients despite a slight worsening in glycemic control. Niacin may be used most effectively in patients without diabetes or with well-controlled diabetes, patients with marked Lp(a) elevation, and patients with markedly reduced HDL-C levels, as niacin is the most efficacious drug at increasing HDL-C.

The fibric acid derivatives may be better choices for patients with frequent gout attacks, active peptic ulcer disease, or poorly controlled diabetes, as niacin has been shown to exacerbate these diseases. Finally, although a cardioprotective effect has been demonstrated with low doses of omega-3 fatty acids that do not affect lipids, clinical trials with doses high enough to reduce triglycerides are lacking. Therefore, omega-3 fatty acids for treatment of mixed dyslipidemia should also be considered as an option, particularly for patients who do not tolerate fibrates or niacin or who require a second or third triglyceride-lowering drug. They also should be considered a viable option if one is concerned about potential drug interactions, such as those seen with statins and fibrates.

**Table 6. Lipid Levels in Case Patient Over 14 Weeks of Intensified Lipid-Lowering Therapy**

<table>
<thead>
<tr>
<th>Visit #1</th>
<th>Visit #2</th>
<th>Visit #3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0 weeks)</td>
<td>(6 weeks)</td>
<td>(14 weeks)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Atorvastatin 40 mg/day</td>
<td>Atorvastatin 80 mg/day</td>
</tr>
<tr>
<td>Total C, mg/dL</td>
<td>197</td>
<td>186</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>104</td>
<td>99</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>305</td>
<td>275</td>
</tr>
<tr>
<td>Non-HDL, mg/dL</td>
<td>165</td>
<td>154</td>
</tr>
</tbody>
</table>

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; total C = total cholesterol.

The fabric acid derivatives may be better choices for patients with frequent gout attacks, active peptic ulcer disease, or poorly controlled diabetes, as niacin has been shown to exacerbate these diseases. Finally, although a cardioprotective effect has been demonstrated with low doses of omega-3 fatty acids that do not affect lipids, clinical trials with doses high enough to reduce triglycerides are lacking. Therefore, omega-3 fatty acids for treatment of mixed dyslipidemia should also be considered as an option, particularly for patients who do not tolerate fibrates or niacin or who require a second or third triglyceride-lowering drug. They also should be considered a viable option if one is concerned about potential drug interactions, such as those seen with statins and fibrates.

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**Author contributions:** conception and design, CRH, TAJ; analysis and interpretation of data, CRH, TAJ; drafting of the article, CRH, TAJ; critical revision of the article, CRH, TAJ.

**References**

6. Jacobson TA. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J
Table 7. Advantages and Disadvantages of Lipid-Lowering Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Advantages</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin</td>
<td>Low cost (immediate-release)</td>
<td>Worsening glycemic control</td>
</tr>
<tr>
<td></td>
<td>Clinical outcome trials (CDP, HATS)</td>
<td>Increased uric acid levels</td>
</tr>
<tr>
<td></td>
<td>Proven mortality benefit (CDP)</td>
<td>Case reports of serious hepatotoxicity with older,</td>
</tr>
<tr>
<td></td>
<td>Most efficacious drug for increasing HDL-C</td>
<td>sustained-release niacin preparations</td>
</tr>
<tr>
<td></td>
<td>Lowers Lp(a)</td>
<td>Lower patient compliance (flushing)</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Well tolerated by patients</td>
<td>Increased incidence of rhabdomyolysis when combined</td>
</tr>
<tr>
<td></td>
<td>Clinical outcome trials (HHS, VA-HIT)</td>
<td>with statins, especially gemfibrozil</td>
</tr>
<tr>
<td></td>
<td>Good safety profile (fenofibrate)</td>
<td>May increase LDL-C</td>
</tr>
<tr>
<td></td>
<td>Greatest CHD risk reduction in obese patients with</td>
<td>Lack of proven total mortality benefit</td>
</tr>
<tr>
<td></td>
<td>metabolic syndrome or diabetics</td>
<td>Use limited in renal insufficiency</td>
</tr>
<tr>
<td>Fish oil</td>
<td>Excellent safety profile</td>
<td>Lack of outcomes data when used in high doses to treat</td>
</tr>
<tr>
<td></td>
<td>Minimal side effects</td>
<td>mixed dyslipidemia</td>
</tr>
<tr>
<td></td>
<td>No cytochrome P-450 metabolism</td>
<td>Nonprescription fish oil requires 8–12 capsules to reduce triglycerides (compliance)</td>
</tr>
<tr>
<td></td>
<td>Clinical outcome trials with low doses (GISSI)</td>
<td>Possible increase in bleeding complications</td>
</tr>
</tbody>
</table>

CDP = Coronary Drug Project; CHD = coronary heart disease; GISSI = GISSI Prevenzione trial; HATS = HDL-Atherosclerosis Treatment Study; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); VA-HIT = Veterans Affairs HDL Cholesterol Intervention Trial.

24. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. FIELD Study Investigators.


CME EVALUATION: An Evidence-Based Approach to the Use of Combination Drug Therapy for Mixed Dyslipidemia

DIRECTIONS: Each of the questions below is followed by 5 possible answers. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. According to the revised NCEP/ATP III guidelines, the LDL cholesterol goal for a patient with type 2 diabetes mellitus and no evidence of clinical coronary heart disease (CHD) is
   (A) < 160 mg/dL  
   (B) < 130 mg/dL  
   (C) < 100 mg/dL  
   (D) < 70 mg/dL  
   (E) None of the above

2. In a patient with mixed dyslipidemia characterized by elevated LDL cholesterol and triglycerides but low HDL cholesterol, the secondary goal of therapy after attaining LDL goal is
   (A) Raise HDL cholesterol  
   (B) Decrease triglycerides  
   (C) Decrease ratio of total cholesterol/HDL cholesterol  
   (D) Decrease non-HDL cholesterol  
   (E) None of the above

3. The goal for non-HDL cholesterol in a patient with triglycerides above 200 mg/dL is
   (A) Less than 100 mg/dL  
   (B) Less than 70 mg/dL  
   (C) Set 30 mg/dL higher than the LDL goal  
   (D) Set 30 mg/dL lower than the triglyceride goal  
   (E) None of the above

4. Which of the following lipid-lowering therapies has the strongest clinical trial evidence in lowering CHD morbidity and mortality in diabetic patients?
   (A) Fibrates  
   (B) Ezetimibe  
   (C) Niacin  
   (D) Statins  
   (E) Omega-3 fatty acids

5. A safety issue associated with combination therapy with a statin and a fibrate in the treatment of mixed dyslipidemia is
   (A) Increased risk of glucose intolerance  
   (B) Reduction in HDL cholesterol  
   (C) Increased transaminitis  
   (D) Increased proteinuria  
   (E) Increased risk of myopathy and rhabdomyolysis
EVALUATION FORM: An Evidence-Based Approach to the Use of Combination Drug Therapy for Mixed Dyslipidemia

Participants may earn up to 1 hour of category 1 credit by reading the article named above and correctly answering at least 70% of the accompanying test questions. A certificate of credit and the correct answers will be mailed within 6 weeks of receipt of this page to those who successfully complete the test.

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2. A B C D E

3. A B C D E

4. A B C D E

5. A B C D E

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   _______________________________________________________
   _______________________________________________________
   _______________________________________________________
   _______________________________________________________
   _______________________________________________________

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   _______________________________________________________
   _______________________________________________________
   _______________________________________________________
   _______________________________________________________
   _______________________________________________________

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