ABSTRACT

As a result of the National Cholesterol Education Program’s Third Adult Treatment Panel (NCEP ATP III) guidelines and subsequent developments, there is an enormous increase in the population who merit more rigorous assessment of coronary heart disease (CHD) risk, and in many cases, drug treatment. Published studies since the NCEP ATP III guidelines indicate that the optimal low-density lipoprotein (LDL) cholesterol level is below the minimum level recommended by NCEP ATP III (i.e., 100 mg/dL). Therefore, identification and aggressive treatment is even more imperative. The data also support the concept of treating the entire lipid profile (not only LDL cholesterol) in those with the highest CHD risk. Statins remain the mainstay of cholesterol therapy, but combination therapies with niacin or fibrates are generally safe and justifiable when increases in high-density lipoprotein cholesterol and decreases in triglycerides are not effectively achieved with statins alone. Because real-world patients often do not present with a solitary lipid abnormality, combination therapies will most likely become more common as practitioners become more comfortable with their safety and efficacy profiles. Ezetimibe is one of the newest agents to enter the cholesterol-lowering field. It may be useful for additional LDL lowering in those who cannot tolerate and/or do not reach LDL goals with higher doses of statins. Rosuvastatin (recently approved by the US Food and Drug Administration) and pitavastatin are the newest statins under investigation. As we struggle to incorporate the NCEP ATP III guidelines into our everyday practice, it is clear that primary care practitioners will be more aggressive in identifying and treating CHD in the general public. (Adv Stud Med. 2003;3(9A):S871-S881)

OPTIMAL TREATMENT STRATEGIES FOR PATIENTS AT RISK FOR CHD*

Benjamin J. Ansell, MD, FACP†

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The Third Adult Treatment Panel of the National Cholesterol Education Program (NCEP ATP III) has provided updated guidelines on the detection of patients at risk for coronary heart disease (CHD) and the management of high blood cholesterol. Recent strides in research have increased our understanding of the mechanisms by which cholesterol lowering can retard atherosclerosis. Our challenge now is to translate this understanding into a practical strategy for reducing patients’ likelihood of having a vascular event. There are 5 approved classes of drugs to treat dyslipidemia, with the main treatment goal to reduce the
risk of future CHD events (Table 1). Although statins are the dominant drug class, other medications also have important roles for reducing triglycerides and increasing high-density lipoprotein (HDL) cholesterol levels (niacin and fibrates) or for additional low-density lipoprotein (LDL) cholesterol reduction in conjunction with statin therapy (bile-acid sequestrants and cholesterol-absorption inhibitors).

**STATINS**

Numerous well-designed, large, placebo-controlled, randomized studies have provided strong support for the use of statins in primary and secondary prevention of CHD. Figure 1 shows the posttreatment LDL cholesterol levels and the final event rate for both treatment and placebo groups for the major statin trials. These results provided some of the basis for the NCEP ATP III goals for lowering LDL cholesterol. The ultimate message from these studies is that at any LDL level, lowering LDL offers significant benefit in the setting of other vascular risk factors. This benefit extends both to patients with (secondary prevention) and without (primary prevention) established CHD. All evidence indicates that statin therapy is superior to placebo in reducing vascular events in populations at increased risk for CHD.

Since the NCEP ATP III guidelines were published, additional information about the benefits of statins has been published. Results from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial emphasize the urgency of lowering LDL cholesterol immediately after an acute coronary event manifested as unstable angina or non–Q-wave myocardial infarction (MI). In this study, atorvastatin treatment (80 mg daily) initiated 24 to 96 hours after the onset of an acute coronary syndrome significantly reduced the risk of recurrent symptomatic myocardial ischemia with objective evidence requiring emergency rehospitalization (relative risk, 0.74; 95% confidence interval, 0.57–0.95; P = .02). Statins are also effective in treating individuals who are at increased coronary disease risk, regardless of whether they have hyperlipidemia. This includes patients with diabetes mellitus, other types of atherosclerotic vascular disease, and those with multiple risk factors. We have also learned that

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**Table 1. Approved Drug Classes for Treating Dyslipidemia**

<table>
<thead>
<tr>
<th>Class</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Inhibit cholesterol synthesis, upregulate LDL receptors, reduce VLDL, increase HDL, reduce non-HDL cholesterol</td>
</tr>
<tr>
<td>Niacin</td>
<td>Reduces VLDL production, decreases uptake of HDL</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Activate PPARα, increase lipoprotein lipase activity, decrease VLDL production</td>
</tr>
<tr>
<td>Bile-acid binding resins</td>
<td>Prevent reabsorption of bile acids, upregulate LDL receptors</td>
</tr>
<tr>
<td>Cholesterol-absorption inhibitors</td>
<td>Selectively inhibit intestinal cholesterol absorption</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein; HDL = high-density lipoprotein; PPARα = peroxisome proliferator-activated receptor alpha.

Data from Kwiterovich; Piepho; Plutzky.

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**Figure 1. LDL Lowering with Statins: Reduced CHD Events**

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LDL = low-density lipoprotein; CHD = coronary heart disease; Rx = treatment group; PL = placebo group; CARE = Cholesterol and Recurrent Events Trial; 4S = Scandinavian Simvastatin Survival Study; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease Study; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study. Adapted with permission from Illingworth DR. Management of hypercholesterolemia. Med Clin North Am. 2000;84(1):23-42.
LDL cholesterol levels of 100 mg/dL may no longer be the ultimate goal; greater improvements in CHD risk may be achieved at even lower levels. As a result of the NCEP ATP III guidelines and the developments since, there is an enormous increase in the population who should be assessed for CHD risk and, in many cases, treated with drug therapy. The post-NCEP ATP III data are discussed here.7

The Heart Protection Study (HPS) is one of the most interesting studies to be published since the NCEP ATP III guidelines. The HPS compared the safety and efficacy of simvastatin (40 mg) versus placebo as well as a combination of antioxidant vitamins (vitamin E/beta-carotene/vitamin C) versus placebo in a factorial assessment of almost 21,000 individuals at increased risk for CHD death.8,9 They were selected for clinical factors other than lipid levels that placed them at increased risk. The study began approximately 10 years before the ATP III guidelines were published, but the study population closely matched those who are now identified as having CHD risk equivalents. A criterion for inclusion in HPS was a total cholesterol level greater than 135 mg/dL, which would apply to the vast majority of people, especially those with increased risk of CHD. Thus, results from the HPS are considered to be universally applicable to the entire US adult population with coronary risk equivalents.

In the statin arm of the HPS, all patients taking a statin experienced a 24% reduction in risk of cardiovascular events compared with those taking placebo (P < .0001). By contrast, no difference from placebo was observed in the vitamin arm of the trial. Of particular interest was the broad range of risk reduction across different baseline LDL levels (Table 2). The 19% to 26% reduction in cardiovascular event rate was observed even in those with low (<100 mg/dL) levels of LDL cholesterol at baseline—lower than the optimal levels according to NCEP ATP III.5 Comparing these results to the other statin trials, the HPS data show that even some patients with LDL levels below 100 mg/dL (average, 90 mg/dL in HPS) continue to reduce their cardiovascular risk with statin therapy. Thus, patients with significant CHD risk factors but normal LDL levels will still benefit (with clinical and cost effectiveness) from statin therapy (Figure 2).10

Similarly, the recently completed Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed a 36% reduction in the cumulative incidence of nonfatal MI and fatal CHD with atorvastatin (10 mg) compared with placebo (P < .0005).11 The study was stopped early (at 3.3 years vs the original 5-year design) because of the clear benefits observed in patients taking atorvastatin. A total of 10,305 hyper-

Table 2. The Heart Protection Study: Vascular Events by Baseline LDL Cholesterol Level

<table>
<thead>
<tr>
<th>Baseline LDL (mg/dL)</th>
<th>Vascular Events, n (%)</th>
<th>Reduction in Cardiovascular Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin (n = 10,269)</td>
<td>Placebo (n = 10,267)</td>
<td></td>
</tr>
<tr>
<td>&lt;100</td>
<td>282 (17.6)</td>
<td>358 (22.2)</td>
</tr>
<tr>
<td>100–129</td>
<td>668 (19.0)</td>
<td>871 (25.7)</td>
</tr>
<tr>
<td>≥130</td>
<td>1083 (22.0)</td>
<td>1356 (27.2)</td>
</tr>
<tr>
<td>All patients</td>
<td>2033 (19.8)</td>
<td>2585 (25.2)</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein.
Data from the Heart Protection Study Collaborative Group.8

Figure 2. Primary and Secondary Prevention Trials with Statins

LDL = low-density lipoprotein; HPS = Heart Protection Study; all other study acronyms can be found in the legend for Figure 1.
Adapted with permission from Ballantyne CM. Am J Cardiol. 1998;82:Q-12Q.10
tensive patients participated in the lipid-lowering arm of ASCOT; they also had at least 3 other CHD risk factors (ie, they were very high-risk patients). These risk factors included left ventricular hypertrophy or other specified electrocardiographic abnormalities, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischemic attack, male sex, age 55 years or older, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL cholesterol of at least 6, or a family history of premature CHD. As with the HPS, the cardiovascular benefits were extended to those with baseline LDL levels of 90 mg/dL. As with other statin trials, the safety profile was favorable, with similar numbers of noncardiovascular deaths in both arms of this study. There were no significant differences in incidence of fatal cancers, serious adverse events, or liver function abnormalities.

**Other Measures of Risk**

Risk is also defined by HDL cholesterol levels. NCEP ATP III guidelines indicate that the primary target in managing a patient with low HDL cholesterol is to lower LDL levels. HDL level affects overall risk, but lowering LDL reduces that risk. This is clear from one of the landmark statin studies, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).12 The 6605 patients in this study had no clinical evidence of CHD, but had slightly elevated baseline lipid levels: total cholesterol, 221 mg/dL; LDL, 150 mg/dL; HDL, 38 mg/dL. They were also middle-aged or older (men, 45–73 years; women, 55–73 years), adding to CHD risk. Treatment with lovastatin reduced LDL levels by 25% but raised HDL levels by only 6%; yet, patients taking the statin experienced a 37% decrease in major coronary events and 40% reduction in fatal or nonfatal MIs. These results emphasize the importance of continuing LDL reduction as a treatment goal, even in patients for whom low HDL cholesterol is the more obvious risk factor. Further study is needed to determine the additional benefits of raising HDL cholesterol levels.

**Multiple Risk Factors**

Unfortunately, many patients in real-world practice settings do not fall neatly into distinct categories of risk based on abnormalities of a single lipid parameter. Studies of male patients with a previous MI show that nearly two thirds have elevated levels of total cholesterol, the vast majority have elevated LDL cholesterol levels, one third have elevated triglycerides, and nearly two thirds have low HDL cholesterol levels (Figure 3).13 Therefore, evaluation of the entire lipid profile is even more important in the real-world primary care practice.
The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) evaluated the safety and efficacy of a fibrate (gemfibrozil) in 2534 men with relatively healthy levels of LDL cholesterol (<140 mg/dL at baseline) but with elevated triglycerides and low HDL cholesterol (<40 mg/dL). The results at 1 year (although the median follow-up was 5.1 years) show no significant reductions in LDL levels (on-treatment level was 113 mg/dL), although mean LDL particle size increased. However, the mean HDL level was 6% higher, and the mean triglyceride level was 31% lower (Figure 4A); mean total cholesterol level was 4% lower in the gemfibrozil group compared with the placebo group. These effects persisted throughout the study and were essentially the same at year 5 as they were in year 1. The relative reduction in event risk over 5 years, however, was 22% in the gemfibrozil group (Figure 4B). Interestingly, although the change in triglyceride levels was most impressive, the increase in HDL cholesterol was most strongly associated with risk reduction. Extended-release gemfibrozil is not a formulation available in the United States, and fibrates have not been shown to reduce stroke in other trials.

Niacin is another therapeutic option for treating patients with low HDL cholesterol and high triglycerides. In a study comparing extended-release niacin (more easily tolerated than standard niacin preparations) with gemfibrozil in a population of patients very similar to those in the VA-HIT study, the results show significantly greater increases in HDL levels and significantly lower triglyceride levels with niacin compared with gemfibrozil (Figure 5). Benefits in reduced levels of lipoprotein(a) and fibrinogen were also observed with the niacin preparation. LDL levels were essentially unchanged with niacin.

Niacin’s mechanism of action is not as well characterized, but it appears that niacin has 2 important roles in cholesterol regulation:

- It inhibits very-low-density lipoprotein synthesis, thus decreasing triglyceride levels.
- It raises HDL levels.

Niacin may also increase LDL particle size; large particles are less able to penetrate the arterial endothelium, thus avoiding oxidation, ingestion by macrophages, and contribution to plaque formation (please see article by Keith C. Ferdinand, M D, in this issue). Thus, a combination of statin plus niacin is able to target 3 major treat-

![Figure 5. Extended-Release Niacin vs Gemfibrozil](image)

**Table 3. Mean Lipid Levels from the HDL Atherosclerosis Treatment Study (HATS)**

<table>
<thead>
<tr>
<th></th>
<th>LDL (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Quantitative Coronary Angiography</th>
<th>Cardiovascular Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>125</td>
<td>31</td>
<td>213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>116</td>
<td>34</td>
<td>196</td>
<td>+3.9 ± 5.2</td>
<td>24</td>
</tr>
<tr>
<td>Niacin plus statin†</td>
<td>75</td>
<td>40</td>
<td>126</td>
<td>-0.4 ± 3.0</td>
<td>3</td>
</tr>
<tr>
<td>Vitamins</td>
<td>112</td>
<td>33</td>
<td>238</td>
<td>+1.8 ± 4.2</td>
<td>21</td>
</tr>
<tr>
<td>Niacin/statin/vitamins</td>
<td>79</td>
<td>36</td>
<td>164</td>
<td>+0.7 ± 3.2</td>
<td>14</td>
</tr>
</tbody>
</table>

* P < .03 vs comparator drug.
HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a).

* Non-HDL level, ~175 mg/dL.
† Non-HDL level, ~108 mg/dL.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Data from Brown et al.14
ment goals: LDL, HDL, and triglycerides. There are numerous data to support statins for primary and secondary prevention of CHD, and there are also data to support secondary prevention of CHD with niacin.

A recent study tested the benefits of combination therapy (niacin plus a statin), and the results provide important insights into determining optimal treatment for the highest-risk patients. The HDL Atherosclerosis Treatment Study (HATS), using a 2 × 2 factorial design, studied several strategies to determine which was most effective in optimally reducing vascular risk. A total of 160 patients (mean age: men, 63 years; women, 70 years) were included. They had angiographically proven CHD, LDL levels of 145 mg/dL or lower, and HDL levels below 35 mg/dL in men and below 40 mg/dL in women. The study endpoints were angiographic change in the 9 highest-grade stenoses and time to first cardiovascular event (i.e., MI, cardiovascular accident, hospitalization for unstable angina). Every patient in this trial received nonpharmacologic intervention (dietary and smoking counseling, exercise training) and in addition, were randomized into one of 4 groups: 1) niacin and simvastatin; 2) antioxidant vitamins E, C, beta carotene, and selenium; 3) both niacin/simvastatin plus antioxidant vitamins; or 4) no drug therapies (i.e., nonpharmacologic intervention only).

At study entry, patients had LDL levels of 125 mg/dL, but low HDL levels (31 mg/dL) and high triglyceride levels (213 mg/dL). Mean non-HDL cholesterol was 175 mg/dL at baseline, which is higher than the NCEP ATP III goal of below 130 mg/dL.

Table 3 outlines the lipid parameters at baseline and study end for the 4 treatment groups. Those receiving the combination of statin plus niacin or statin/niacin/antioxidant vitamins achieved significantly lower LDL levels, some improvement in HDL levels, and significant lowering of triglycerides. Those receiving statin plus niacin or statin/niacin/antioxidants achieved stability in stenosis as measured by quantitative coronary angiography. The cardiovascular event rate for the statin plus niacin group was dramatically lowered compared with the other 3 treatment groups; this benefit did not extend fully to those receiving statin/niacin/antioxidant vitamins. The decrease in event rate with niacin plus statin translates to a 90% lower risk of cardiovascular events for those receiving simvastatin/niacin compared with the placebo group. The cardiovascular event risk reduction for those receiving simvastatin/niacin compared with the other 3 groups was 60%. These results
showed a substantial clinical benefit with simvastatin/niacin therapy; there was no benefit with antioxidant vitamins. Also of importance was the reduction of non-HDL levels to about 108 mg/dL (below the 130 mg/dL target established by NCEP ATP III).

Traditionally, combination therapy of statin plus niacin has been problematic because of poor tolerability. However, data suggest that adverse events in patients taking lovastatin alone and the combination lovastatin/extended-release niacin are similar.\(^\text{17,18}\) The greatest differences are seen in flushing, which has caused discontinuation in approximately 10% of study patients, but it can be attenuated by a number of different strategies, including aspirin therapy and avoidance of alcohol.\(^\text{17,18}\)

**Blocking Cholesterol Absorption**

Another mechanism to reduce blood cholesterol levels is to reduce the absorption of dietary cholesterol. A recently approved cholesterol-absorption inhibitor, ezetimibe, appears to interfere with a cholesterol transport protein at the brush border of the intestinal lumen, preventing cholesterol from being absorbed. Ezetimibe reduces LDL cholesterol levels 15% to 25%, with an average reduction in clinical studies of 18%. It has once-daily dosing and is well tolerated, with side effects similar to placebo.\(^\text{19}\)

Efficacy data from ezetimibe monotherapy show little effect on triglyceride or HDL cholesterol levels, but a reasonable effect on LDL levels (Figure 6), with decreases of up to nearly 20%.\(^\text{20}\) The safety profile is similar to placebo. When ezetimibe is given as combination therapy with a low-dose statin, the effect on LDL lowering is additive, with a 17% additional lowering of LDL levels above what is seen with a low-dose statin. In 75% of patients treated with 10 mg ezetimibe plus 10 mg simvastatin, LDL cholesterol levels were reduced by 50% within 2 weeks of starting treatment.\(^\text{21,22}\) Safety data indicate good tolerability with both monotherapy and combination therapy (Table 4).\(^\text{23}\) Ezetimibe may therefore be useful in patients who are unable to tolerate higher statin doses but need further reductions in LDL cholesterol levels. LDL lowering follows “the rule of 6”—LDL level is reduced an additional 6% with each doubling of statin dose.\(^\text{24}\) As suggested by Stein, adding 10 mg ezetimibe to 10 mg simvastatin would achieve the same LDL reductions as 3 doublings of the 10-mg statin dose (Figure 7).\(^\text{21}\) However, there is approximately 1.3% risk of significant liver function abnormalities with combination ezetimibe/statin therapy, in contrast to hepatotoxicity.

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**Table 5. Statins in Development**

<table>
<thead>
<tr>
<th>Product</th>
<th>Development Phase</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>Recently approved</td>
<td>LDL ↓ 34% to 65%</td>
</tr>
<tr>
<td></td>
<td>(August 2003)</td>
<td>HDL ↑ up to 14%</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>Phase II</td>
<td>LDL ↓ up to 38%</td>
</tr>
<tr>
<td></td>
<td>(expected launch 2005)</td>
<td>HDL ↑ 7% to 9%</td>
</tr>
<tr>
<td>Ezetimibe/simvastatin</td>
<td>Phase III</td>
<td>LDL ↓ 18% to 50%</td>
</tr>
<tr>
<td>combination</td>
<td>(expected filing 4Q 2003)</td>
<td>HDL ↑ 5% to 9%</td>
</tr>
<tr>
<td>CETP-I /atorvastatin</td>
<td>Phase II</td>
<td>LDL ↓ up to 70%</td>
</tr>
<tr>
<td>combination</td>
<td>(projected launch 2006?)</td>
<td>HDL ↑ 50%</td>
</tr>
</tbody>
</table>

LDL = low-density lipoprotein; HDL = high-density lipoprotein; CETP = cholesterol ester transfer protein.

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**Figure 7. Potential New Role for Combination Therapy for Lipid Management**

LDL = low-density lipoprotein. Reproduced with permission from Stein E. Results of phase II/III clinical trials of ezetimibe, a novel selective cholesterol absorption inhibitor. Eur Heart J Suppl. 2001;3(suppl E):E11-E16.\(^\text{21}\)
with statins alone (roughly 0.4%). It is also important to note that clinical trials demonstrate that statins are the agents that affect clinical event rates.

**New Statins/Statins in Development**

A number of new statins and statin combinations are in development. A summary is presented in Table 5. Rosuvastatin, recently approved by the US Food and Drug Administration (FDA), has been shown to lower LDL cholesterol levels up to 65% and raise HDL levels by approximately 14%—twice as much as the other statins.

Rosuvastatin (40 mg) has also been compared with niacin 2 g or combination rosuvastatin plus extended-release niacin in 2 different dosages: rosuvastatin 40 mg plus niacin 1 g, or rosuvastatin 10 mg plus niacin 2 g. Rosuvastatin alone reduced LDL and non-HDL cholesterol significantly more than niacin alone or the rosuvastatin 10 mg/niacin 2 g combination; reduction with the rosuvastatin 40 mg/niacin 1 g combination was similar to that with rosuvastatin alone. Compared with rosuvastatin alone, the rosuvastatin 10 mg/niacin 2 g combination produced significantly greater increases in HDL cholesterol and apolipoprotein A1. Only niacin alone did not offer any reduction in LDL; the combinations offered similar benefits in LDL reduction compared with rosuvastatin alone. Over 24 weeks, rosuvastatin alone was better tolerated than either niacin alone or the niacin and rosuvastatin combinations (withdrawal due to adverse events: rosuvastatin, n = 1/46; niacin, n = 10/72; rosuvastatin 40 mg/niacin 1 g, n = 7/72; rosuvastatin 10 mg/niacin 2 g, n = 13/80). The safety data for rosuvastatin compared with other statins are very similar.

The manufacturer of the ezetimibe plus simvastatin combination, as discussed above, is expected to file for FDA approval in 2003. A newer therapeutic approach inhibits cholesterol ester transfer protein (CETP), the enzyme that transfers cholesteryl ester between triglycerides and HDL. A CETP inhibitor has been shown to reduce atherosclerosis in cholesterol-fed rabbits. In early human studies, CETP inhibitors have been shown to increase HDL cholesterol levels. A combination of a CETP inhibitor and atorvastatin is in Phase II clinical trials.

**Conclusion**

Studies published since the NCEP ATP III guidelines indicate that the optimal LDL cholesterol level is...
below the minimum recommended by NCEP ATP III (100 mg/dL). Therefore, identification and aggressive treatment is even more imperative. The data also support the concept of treating the entire lipid profile (LDL, HDL, non-HDL, triglycerides, and total cholesterol) in those with the highest CHD risk. Statins remain the mainstay of cholesterol therapy, but combination therapies with niacin or fibrates may offer the added benefits of increases in HDL and decreases in triglycerides that may not be achieved with statins alone. Because many patients present with combined dyslipidemia, concomitant drug therapies will most likely become more common as practitioners become more comfortable with their safety and efficacy profiles. Ezetimibe is one of the newest agents to enter the cholesterol-lowering field. It may be useful for additional LDL lowering in those who do not tolerate higher doses of statins. Rosuvastatin and pitavastatin are the newest statins under investigation. Rosuvastatin also offers strong LDL lowering, and data suggest that it safe and effective in combination with niacin. As we strive to incorporate the NCEP ATP III guidelines into our everyday practice, it is clear that primary care practitioners will be more aggressive in identifying and treating CHD in the general public.

### Case Study

A 53-year-old woman with type 2 diabetes presents for a routine annual examination. She is a nonsmoker, mildly overweight (body mass index [BMI], 28 kg/m²; waist 33 in), and is prehypertensive according to the Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (blood pressure, 135/80 mm Hg). Her only current medication is metformin for her diabetes. Her lipid parameters are as follows:

<table>
<thead>
<tr>
<th><strong>Baseline Lipid Profile</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol</strong></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>Non-HDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
</tr>
</tbody>
</table>

According to the lipid profile, her LDL cholesterol is above target. Her low HDL and high triglycerides add to her risk. She probably has small, dense LDL cholesterol. Her non-HDL cholesterol level is also well above optimal levels, and her diabetes, even with metformin, is not well controlled.

Secondary causes of hyperlipidemia were ruled out; thyroid-stimulating hormone, urine protein, liver function testing, and creatinine levels were normal.

### Discussion

Because she has established diabetes, it is not appropriate to calculate a coronary risk score for this patient, but to treat her dyslipidemia to targets of LDL cholesterol below 100 mg/dL and non-HDL cholesterol below 130 mg/dL. Based on her lipid profile and the NCEP ATP III guidelines, it is appropriate to start both therapeutic lifestyle changes (TLC) and lipid-lowering medication (ie, statin).

### Follow-Up

After 3 months of TLC and statin therapy, the patient's blood pressure decreased slightly and she has lost weight (BMI, 27 kg/m²; waist 32 in). Her new lipid profile is as follows:

<table>
<thead>
<tr>
<th><strong>Lipid Profile at Visit 2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol</strong></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>LDL</td>
</tr>
<tr>
<td>HDL</td>
</tr>
<tr>
<td>Non-HDL</td>
</tr>
<tr>
<td>Triglycerides</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
</tr>
</tbody>
</table>

The patient's LDL cholesterol level is at goal, and her HDL cholesterol level is just slightly above the...
level at which it is considered a major risk factor. Her triglycerides continue at unhealthy levels, and she meets criteria for the metabolic syndrome (HDL <50 mg/dL, blood pressure ≥130/85 mm Hg, and fasting plasma glucose >110 mg/dL) in addition to her suboptimally controlled diabetes. Her non-HDL cholesterol has not reached target levels (<130 mg/dL).

**DISCUSSION**

There are several viable therapeutic options for this patient. TLC should be intensified. Further weight loss, omega-3 fish oil supplementation (6-9 g daily), and/or simple carbohydrate restriction are all strategies that offer potential for triglyceride lowering. One could also increase the statin dose and/or strength; this would avoid increased costs with combination drug therapy, while continuing to lower triglycerides and maintaining once-daily dosing. However, adding niacin or a fibrate (ie, fenofibrate) would also be an option for lowering triglycerides, with likely greater efficacy than an increased statin dose. Combination with ezetimibe could be considered if the patient is unable to tolerate higher doses of statin, but has less potential to lower triglycerides compared with the other agents. There are many options for this patient, and the ultimate strategy should include aggressive treatment of the entire lipid and metabolic profile.

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