

Managing Hyperlipidemia: An Evidence-Based Approach

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Summary

To best manage patients with hyperlipidemia, clinicians need to use an evidence-based approach. Based on the evidence, statins are the medications of choice for most patients who need lipid lowering therapy. The presence of various risk factors will determine the appropriate LDL goal for a particular patient. Some patients can benefit from aggressive lipid lowering.

Key Points

- Lifestyle changes are an important part of hyperlipidemia treatment.
- Statins are the drug of choice for most patients with elevated LDL.
- Side effects with statins are uncommon, but they do occur more frequently at higher doses.
- It is optimal to have an LDL goal of less than 70 in high-risk patients and less than 100 in moderately high-risk patients.
- Diabetic patients, those with acute coronary syndrome, and those with multiple or uncontrolled risk factors are at high risk for cardiovascular events and should be treated aggressively.

AGGRESSIVELY TREATING HYPERLIPIDEMIA is an area where the biggest differences have been made in cardiovascular disease in the last few years. Lipids play a significant role in the atherosclerotic process.^{1,2} Low density lipoprotein (LDL) particles become located within the intima of the artery at areas of hemodynamic stress. The LDL particles undergo oxidative modification, which leads to uptake by the endothelial cells and expression of inflammatory markers, which increases the likelihood of thrombus formation. Inflammation induces the plaque to be unstable. When unstable plaque ruptures, a thrombus forms.

High-density lipoprotein (HDL) cholesterol has the opposite effect. It has anti-atherogenic properties and reverses cholesterol transports, helps in endothelial dysfunction, and reduces thrombosis. High HDL cholesterol is a good thing, and when risk factors are evaluated, providers can actually subtract a cardiac risk factor if the patient has high HDL cholesterol.

Treatment is not started based on one lipid measurement. Two lipid measurements at least two weeks apart and baseline tests to rule out secondary causes and to monitor liver function are needed.

Secondary causes of hyperlipidemias need to be ruled out and treated if present (Exhibit 2). Diabetes

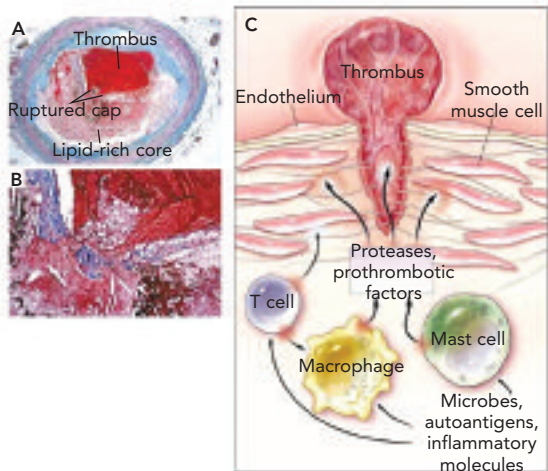
is a major secondary cause, especially of hypertriglyceridemia and low HDL. With hypothyroidism, treating the thyroid disease may revert the lipids back to normal. Medications also can be a factor in elevated lipids. As an example, thiazides and beta-blockers can worsen lipid control.

The National Cholesterol Education Program (NCEP) guidelines are used in the United States to manage lipids disorders.³ The most recent update to these guidelines was published in 2004.⁴ According to these guidelines, patients are stratified based on cardiac risk factors and coronary heart disease equivalents into low risk, moderate risk, moderately high and high risk categories (Exhibit 3).^{3,4} Each category has individual goals.

People at low risk for developing heart disease are the easiest to manage. One is considered low risk if he or she has zero to one risk factor in addition to a lipid disorder. The goal LDL is less than 160 mg/dL. If the LDL is > 160 mg/dL, the patient is started on therapeutic lifestyle changes. Because lifestyle changes are unlikely to produce a sufficient decline, medication is started if the LDL is greater than 190 mg/dL.

Patients are considered to be at moderate risk for developing heart disease if they have two or more

Exhibit 1: Atherosclerotic in the Human Artery



risk factors in addition to a lipid issue. Their goal LDL is less than 130 mg/dL. Therapeutic lifestyle changes are started if LDL is greater than 130 and medication if greater than 160 mg/dL.

The next group is patients at moderately high risk. These are people with two plus risk factors, and an estimated risk of developing heart disease in the next 10 years of 10 to 20 percent. Their goal LDL is 130 mg/dL. By the recent guideline updates, it is an option to treat these patients more aggressively to an LDL goal of less than 100.⁴ Patients with moderately high risk and multiple risk factors or severe risk factors that are uncontrolled would benefit from more aggressive treatment.

The highest risk group already has coronary disease or one of its equivalents or two plus risk factors and an estimated ten year risk of greater than 20 percent. The goal LDL for this group in general is an LDL less than 100, but there is the therapeutic option of treating them more aggressively to less than 70. Medications should be started in these patients if the LDL is greater than 100. If they are within the 70 to 100 range, it also is an option to start them on treatment then. Certain patients within this highest risk group should be treated most aggressively. Patients who have acute coronary syndrome (ACS) are at the highest risk of having a cardiovascular event in the near future. Patients with multiple risk factors or severe poorly controlled risk factors also benefit from aggressive treatment.

The risk of coronary heart disease is log linear associated with LDL cholesterol. For every 1 percent reduction in LDL, there is a relative risk reduction of 1 percent. Trials show that this occurs even at LDLs of less than 100. The updated guidelines recommend now that not only should patients get to their goal LDL, they should have a 30 to 40 percent reduction

Exhibit 2: Secondary Causes

1. DM
2. Hypothyroidism
3. Obstructive liver disease
4. Chronic renal failure, nephrotics syndrome
5. Medications: progestins, estrogen, androgens, corticosteroids, thiazides, beta-blockers, protease inhibitors, isotretinoin, alcohol and tobacco

from their baseline lipids. This is achievable with standard doses of the statins.

When treating patients with lipid disorders, LDL cholesterol is the number one goal by the guidelines. Once LDL is controlled, non-HDL cholesterol can be addressed. Non-HDL cholesterol is total cholesterol minus HDL. The patient's non-HDL goal is their LDL goal plus 30.

Therapeutic lifestyle changes (TLC) are important in controlling lipids. All patients that are above goal cholesterol or even those with just multiple risk factors should be begun on TLC.

In general, the patient should consume less than 25 to 30 percent of the calories from fat. Saturated fat intake should be reduced and dietary cholesterol should be less than 200 milligrams a day. Patient can reduce their lipids by reducing fat intake, increasing fiber to 20 to 30 grams a day, adding plant stanols and sterols in their diet, losing weight, and exercising aerobically at least 30 minutes the majority of days of the week. Patients with maximal TLC can lower their LDL by 25 to 30 percent, which can get some patients to their goal.

For a lot of patients, medications will be necessary to achieve goal lipid values. The statins work by partially inhibiting HMG-CoA reductase, which is the rate-limiting step in cholesterol synthesis. They lower LDL by 20 to 60 percent and increase HDL relatively modestly (5 to 15 percent), and lower triglycerides. These medications reduce coronary events, cardiac deaths, and the need for cardiovascular procedures. It is unknown if the LDL lowering effect of statins provides the mortality benefit or if it is the other effects of these agents. They have anti-inflammatory effects, enhance fibrinolysis, and reduce platelet function. The statins are the only lipid lowering class that has been shown to improve total mortality in primary and

secondary prevention. This is why statins are the drug of choice in patients with elevated LDL.

Although the agent of choice, they do have some adverse effects. Overall, statins are usually very well tolerated. The one-year discontinuation rate secondary to adverse effects is about 15 percent. This is much better than for the other classes of lipid lowering agents.

One of the biggest concerns with statins is myositis or muscle inflammation. Myalgias (muscle aches) occur in about 2 to 10 percent of patients, and in trials this was fairly similar to placebo.

Myositis is rare. It is seen in less than 0.5 of patients and the worst case of this, rhabdomyolysis with acute renal failure, is seen in less than 0.1 percent of patients. Rhabdomyolysis occurs most frequently in patients that are taking a statin combined with an interacting medication.

Elevated liver function tests are the other major concern. With medium dose statins, the rate is probably about 1 percent of patients, and in high dose statins about 3 percent. How often liver function tests should be checked is a matter of debate. Several recommendations have been published that state that the typical patient does not need laboratory liver function monitoring. Most clinicians will still check in patients on the highest doses of statins.

Niacin lowers LDL, increases HDL, and decreases triglycerides. It raises HDL the most of any of the lipid lowering agents. Niacin is probably most useful in patients with combined hyperlipidemia and a low HDL. It can be very effective when used in combination with a statin. A combination product of a statin and

niacin is available (Advicor®). Because it is an older medication, the outcomes based data is not as good as that with statins. There are trials that show reduced coronary events, possible reduced total mortality in secondary prevention, and possibly reduced progression of carotid disease when niacin is added to a statin.

Unfortunately, there can be a lot of adverse effects. In general, niacin has a 46 percent discontinuation rate for adverse effects. The biggest reason patients do not tolerate niacin is flushing. Special formulations, slow dose adjustments, and aspirin can be used to reduce the flushing. Hepatotoxicity has been reported. It is especially important for people not to take over-the-counter niacin preparations because the long acting over-the-counter preparations have been associated with higher rates of hepatotoxicity.

The fibric acid derivatives, gemfibrozil (Lopid®) and fenofibrate (Tricor®), are another class of lipid lowering agents. They work as ligands for peroxisome proliferator-activated receptors, which are similar to the mechanism of action of thiazolidinedione anti-diabetic agents. Although these agents can reduce LDL, in some patients they actually increase LDL. They also lower HDL and are the best for lowering triglycerides. Again, there is limited outcomes data with this class. Some trials show reduced coronary events, but no improvement in overall mortality. One recent trial in diabetics, discussed later, showed a non-significant trend for increased cardiovascular mortality in diabetics, but they may reduce progression of insulin resistance. This class is most useful in patients with hypertriglyceridemia and low HDL. About 36 percent of patients will

Exhibit 3

Risk	LGL Goal	Consider Drug
High: CAD or equivalent 2+ risk factors with 10 year risk of >20%	<100 <70 (optional)	>100 <100 (optional)
Moderately High: 2+ risk factors with 10 year risk of 10-20%	<130 <100 (optional)	>130 100-129 (optional)
Moderate: 2+ risk factors 10 year risk of <10%	<130	>160
Low: 0-1 risk factor	<160	>190

• Goal is not only to get to optimal LDL but for a reduction of LDL by 30-40% from baseline.

discontinue fibrates for adverse effects. Dyspepsia, gallstones, and myopathy, especially when gemfibrozil is used in combination with statins, can occur.

Bile acids sequestrants interrupt bile acid reabsorption, which requires bile acid synthesis from cholesterol stored in the body. They lower LDL about 15 to 30 percent and modestly increase HDL. In some patients, they can increase triglycerides. About 41 percent of patients will discontinue bile acid sequestrants because of GI upset, constipation, and gas. Because these agents can affect the absorption of other medications, they have to be separated from the patient's other medications. Because they are not systemic agents, they are the drug of choice in children and women of childbearing age.

The newest agent is ezetimibe (Zetia®), which impairs cholesterol absorption. As monotherapy, it reduces LDL by about 10 to 17 percent, modestly reduces triglycerides, but has a minimal effect on HDL. When added to a statin, ezetimibe reduces cholesterol by 20 to 27 percent and it may reduce the dose of statin needed. One of the more interesting trials found that atorvastatin 10 mg plus ezetimibe 10 mg had the same LDL reduction as atorvastatin 80 mg, the maximum dose. The combination also lowered C reactive protein (CRP) to a greater extent than atorvastatin alone. Unfortunately, there are no outcomes based trials published with ezetimibe.

With monotherapy, ezetimibe is well tolerated. In combination with statins, the risk of elevated liver function tests is modestly increased. Uses for this agent include addition to a statin in patients who do not get to goal LDL on statin monotherapy or as part of an initial combination regimen in a patient with very high LDL.

The omega-3 polyunsaturated fatty acids inhibit triglycerides synthesis and augment triglyceride clearance. They lower triglycerides by about 45 percent and increase HDL by about 13 percent. The major issue with omega-3 agents is a lack of outcomes based data. Additionally, they can increase LDL and cause dyspepsia, nausea, and may increase bleeding time.

For certain scenarios, one lipid-lowering agent will be preferred over the others. In the case of a patient with elevated LDL, statins are the drug of choice for primary and secondary prevention. Combination therapy is considered in patients who do not get to their goal on maximum statins, but there are no good evidence based trials in this group. Many clinicians will add ezetimibe or a bile acid sequesterant to statin therapy. In patients who do not tolerate a statin, a lower risk statin such as pravastatin or fluvastatin can be tried. For patients who do not tolerate any statin, various combinations of the other classes will have to be tried.

For patients with recent ACS, treatment choices

can be based on data from two landmark trials.^{5,6} In the MIRACL trial, atorvastatin 80 mg, started within 24 to 96 hours of the onset of ACS, reduced death, myocardial infarction (MI) and cardiac arrest by 16 percent. In the PROVE IT trial, 4,000 patients with acute coronary syndrome were randomized to maximum dose of atorvastatin (80 mg) versus standard dose of pravastatin (40 mg). At the end of the trial, the mean LDL was 62 mg/dL in the atorvastatin group versus 95 mg/dL. There was a 16 percent risk reduction for death, MI, and revascularization with atorvastatin (22.4 percent vs. 26.3 percent). There was a higher rate of elevated liver function tests greater than three times normal with atorvastatin (3.3 percent vs. 1.1 percent). The maximum dose atorvastatin group lowered CRP more and reduced the size of the plaques on endovascular ultrasound more.

An LDL goal of less than 70 mg/dL should be considered for any patient with ACS. Clinicians should consider starting statins in all patients with ACS regardless of their lipid level. These should be within the first 48 hours and based on the discussed trials, some clinicians would use atorvastatin in the maximum dosage.

For patients with stable coronary artery disease (CAD), the best evidence comes from the largest trial in lipids—the Heart Protection Study.⁷ Twenty thousand patients with coronary disease, peripheral vascular disease, history of cerebral vascular accidents, or diabetes were randomized to simvastatin 40 mg versus placebo or antioxidant vitamins regardless of their lipid status. This study found an impressive reduction in mortality of 13 percent and cardiovascular mortality by 18 percent in the simvastatin group. There also was a 25 percent reduction in the first cardiovascular event rate, major vascular events, and revascularization for the simvastatin group. The most exciting thing from this trial was a finding of a similar reduction in risk in all groups regardless of starting LDL.

The TNT trial was another large trial in stable CAD.⁸ In this trial, 10,000 patients with stable CAD and LDLs less than 130 were randomized to the starting dose of atorvastatin versus maximum of atorvastatin. The outcome was an impressive reduction of major cardiovascular events, death from coronary disease, MI, cardiac arrests and CVA in the maximum dose atorvastatin group. About 30 patients would have to be treated aggressively with atorvastatin to prevent one event over five years. However, mortality between the two groups in this trial was the same.

The IDEAL trial included almost 9,000 patients with a history of MI randomized to the highest dose of atorvastatin versus the starting dose of simvastatin.⁹ This study found no difference in the combined inputs of cardiovascular death, non-fatal MI or cardiac

arrest and no difference in the mortality. It did find a reduction in secondary endpoints of cardiovascular events in non-fatal MI with atorvastatin. The aggressively treated group had almost twice the discontinuation rate of the less aggressively treated group.

In the ASTEROID trial, 507 patients were treated with the maximum dose of rosuvastatin, 40 mg/day.¹⁰ Using ultrasound, this study found that atherosclerosis plaques shrank. There were some problems with this trial through; there was no comparison group, the study did not measure vessels with greater than 50 percent stenosis, and no correlation with clinical outcomes was done.

Overall, patients with stable coronary disease should have an LDL goal of less than 100 and less than 70 is an option. High dose statins appear to be safe but are not as well tolerated. Serious events are very rare and usually reversible. Additionally, more studies with clinical outcomes are needed.

Patients with diabetes are at very high risk for heart disease. In a diabetes subgroup analysis of the Heart Protection Study, there was an impressive reduction of first events rate by 25 percent with simvastatin 40 mg/day, even in patients with an LDL of less than 116.⁷ Additionally, there was a 33 percent reduction in events and a low risk of myopathy in this group. The CARDS trial studied 2838 patients with Type II diabetes that did not have CAD and had just one of the following risk factors: retinopathy, albuminuria, smoking, or hypertension.¹¹ About 70 to 82 percent of Type II diabetes patients will meet this criterion. Atorvastatin 10 mg daily was compared with placebo. Acute coronary syndrome was reduced by 36 percent, revascularization by 31 percent, and cerebrovascular accident (CVA) by 48 percent. There was a reduction in all cause mortality by about 27 percent. Based on this study, 27 diabetic patients would have to be treated for four years with atorvastatin 10 mg/day to prevent one event.

The German Diabetes and Dialysis Study published in 2005 is one of the few trials in diabetic patients on dialysis.¹² These patients were usually excluded from the other statin trials. The subjects had LDL of 80 to 190 and were randomized to atorvastatin 20 mg/day versus placebo. The on treatment LDL was 72 mg/dL versus 102 mg/dL in the placebo group. No statistical difference in the composite of death from cardiac causes, nonfatal MI, and CVA, although this was one of the highest risk groups ever studied (8.2 percent annual MI or death rate). There are many reasons hypothesized for the results of this trial, but one of the reasons probably is that patients on dialysis have such a malignant form of coronary artery disease that they may not get benefit from statins. Regardless of the results of this trial, patients

on dialysis are usually still treated with statins.

In the Field Trial, 9,795 patients with Type II diabetes who were not on a statin were randomized to fenofibrate versus placebo.¹³ In the fenofibrate group, there was a non-significant reduction in first MI or cardiovascular deaths and total cardiovascular events were reduced by 11 percent, mostly by reduction in non-fatal MI and reduced coronary revascularization. Most concerning was a non-significant increase in cardiovascular deaths.

Diabetes is a cardiovascular risk equivalent under the NCEP lipid treatment guidelines. The goal LDL is less than 100, but clinicians should strongly consider a goal less than 70 in patients with multiple risk factors. Some clinicians consider all patients with diabetes to be at such high risk that they should be treated to less than 70. All diabetic patients with coronary artery disease should be on statins regardless of their lipid levels and all diabetic patients with hypertension, retinopathy, microalbuminuria, or smoking should probably be on statins too. It is unclear whether diabetics with normal lipids and no other risk factors should be treated. Diabetic patients on dialysis may not necessarily get benefits from statins and fibrates because there is no convincing evidence that they reduce mortality or cardiovascular events in this population.

There is some data on treating lipids in patients with cerebrovascular disease. The SPARCL Trial was in 4000 patients with CVA or TIA in the previous one to six months.¹⁴ They were randomized to atorvastatin 80 mg or placebo. The mean LDL at the end of the trial was 73 mg/dL for the atorvastatin group and 129 mg/dL in the placebo group. More patients in the placebo group had a CVA during the study (13.1 percent vs. 11.2 percent). A higher number of hemorrhagic strokes occurred in the atorvastatin group (55 vs. 33). The researchers included patients with intracranial bleeds as strokes. The effect of the statin on blood clotting may be the reason for the higher rate of hemorrhagic strokes. Fewer patients died in the atorvastatin group (216 vs. 211). The number needed to treat with atorvastatin to prevent one CVA was 46. Twenty-nine people would have to be treated to prevent one cardiovascular event and 32 to prevent revascularization.

In relation to cerebrovascular disease, in a sub-analysis of the TNT Trial, the number needed to treat with atorvastatin 80 mg to prevent a cerebrovascular event was 89, to prevent a CVA was 131.¹⁵ The most useful cerebrovascular finding from this study was that there was no increased risk of intracranial bleed.

A CVA or TIA should be considered a coronary equivalent when deciding at what level to treat a particular patient. Lipid lowering therapy should be started in the hospital. There may be more benefit in preventing

cerebrovascular events by aggressive dosing, but the number needed to treat is high. Statins should be avoided in people that have had hemorrhagic strokes.

Another common problem seen clinically is low HDL. The first step for increasing HDL is lifestyle modifications.¹⁶ Exercise increases HDL about 3 to 9 percent, but the increase is related to the frequency and intensity of the exercise. Smoking cessation will increase HDL by about 4 mg/dL. Weight loss is another effective way to increase HDL but the degree of increase is related to the number of pounds lost and kept off. In the acute phase of weight loss, HDL may actually go down, but long-term, HDL increases by about .35 mg/dL per kilogram lost. Modest alcohol intake (30 gm [1 fluid oz] of ETOH per day) raises HDL 4 mg/dL. A diet rich in n-3 polyunsaturated fatty acids from oils, nuts, cold-water fish, and shellfish also will modestly increase HDL. Regrettably, there are no good outcomes based trials that show raising HDL has long-term benefits. Clinicians should consider treating low HDL in patients that are high risk for cardiovascular disease. The NCEP guidelines recommend targeting LDL levels first and then addressing HDL. In general, statins are used to raise HDL in patients who also have a high LDL. Of the various statins, rosuvastatin is the most effective for raising HDL. For patients who also have high triglycerides, a fibrate should be considered. For isolated low HDL, niacin is an appropriate choice.

Elevated triglycerides are an independent predictor of cardiovascular disease.¹⁷ Although there are various inherited disorders that can cause hypertriglyceridemia, obesity, poorly controlled diabetes, medications, and excessive alcohol intake are common contributors in the U.S. population. Hyperthyroidism and end stage renal disease are two other secondary causes of elevated triglycerides. Treatment begins with lifestyle modifications of reduced saturated fat and fructose intake. Weight loss can result in a 22 percent reduction. Exercise and alcohol restriction are very important for triglyceride reduction. In diabetics, strict glycemic control is important. Some diabetics can control their triglycerides with glycemic control alone. This is another group for which there is not good outcomes based data. In general, fibrates or niacin are started for triglycerides greater than 500 mg/dL to prevent pancreatitis. For the 250 to 499 group, it is an individual decision. For patients with both an LDL and TG elevation, a statin can be used. Combination therapy may be needed with a statin and a fibrate or niacin. Patients with coronary artery disease, CAD equivalent, multiple risk factors, metabolic syndrome or patients with a strong family history of heart disease should be treated more aggressively.

Conclusion

Total lifestyle changes are an important part of treatment and are not futile. Because of the data, statins are the drug of choice. The adverse effects with statins are uncommon, but they do occur more frequently at higher doses. The latest lipid treatment guidelines recommend an optional LDL goal of less than 70 in high-risk patients and LDL of less than 100 in moderately high-risk patients. Diabetic patients, those with acute coronary syndrome, and those with multiple or uncontrolled risk factors are at high risk for cardiovascular events and should be treated aggressively. **JMCM**

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References

1. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med*. 2005;352:29-38.
2. Mallika V, Goswami B, Rajappa M. Atherosclerosis pathophysiology and the role of novel risk factors: a clinicobiochemical perspective. *Angiology*. 2007;58:513-522.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.
4. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.
5. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL Study: a randomized trial. *J Am Med Assoc*. 2001;285:1711-1718.
6. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495-1504.
7. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002;360:7-22.
8. Deedwania P, Barter P, Carmena R, et al. Reduction of low-density lipoprotein cholesterol in patients with coronary heart disease and metabolic syndrome: analysis of the Treating to New Targets study. *Lancet*. 2006;368:919-928.
9. Pedersen TR, Faergeman O, et al. High-dose atorvastatin vs. usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437-2445.
10. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556-1565.
11. HM, Betteridge DJ, Durrington PN, et al, on behalf of the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.
12. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing dialysis. *N Engl J Med*. 2005;353:238-248.
13. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005;366:1849-1861.
14. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPAR-CL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:459-559.
15. Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovascular events in patients with stable coronary disease in the TNT (treating to new targets) study. *J Am Coll Cardiol*. 2006;48:1793-1799.
16. Ashen MD, Blumenthal RS. Clinical practice. Low HDL cholesterol levels. *N Engl J Med*. 2005;353:1252-1260.
17. Tirosh A, Rudich A, Schochat T, et al. Changes in Triglyceride Levels and Risk for Coronary Heart Disease in Young Men. *Ann Intern Med*. 2007;147:377-385.