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A Critical Appraisal of Dyslipidemia Therapy

Author: **Michael E. McIvor, MD**, Medical Director of Foundation Research, St. Petersburg Heart Center, St. Petersburg, Fla.

Editor's Note—*First clinicians treated total blood cholesterol (TC) levels to lower our patients' risk of suffering a cardiovascular event. Then we modified our therapeutic target and treated low-density lipoprotein (LDL) cholesterol levels rather than TC, realizing that not all lipoproteins were atherogenic, and in fact that high-density lipoprotein (HDL) cholesterol was cardioprotective. More recently, there has been the realization that even LDL cholesterol can have different levels of atherogenicity, and we have begun to measure LDL subpopulations. This advanced lipid profiling is done in the belief that small, dense LDL particles penetrate the arterial wall more efficiently, are more oxidizable, and therefore are more atherogenic than larger LDL particles. We are also beginning to appreciate the important role of hypertriglyceridemia and low HDL cholesterol levels in the global risk a patient faces for suffering a cardiovascular event. This expanded spectrum of therapeutic targets pushes clinicians to the increased use of combination therapy in order to more aggressively lower our patients' total cardiovascular risk with a customized treatment regimen. A number of nonpharmacologic and pharmacologic therapies are now available to address these various therapeutic targets, many of which have now been documented in large, randomized, prospective clinical trials to lower patient mortality and morbidity.*

At the same time, many lipid-lowering therapies are expensive and carry a small but definite risk of side effects. Consequently, national guidelines urge the stratification of patients by their global risk of future clinical events so that we can be more aggressive with high-risk patients and less aggressive with low-risk patients. The stratification scheme has become ever more precise, but in so doing, the stratification algorithms have become complex enough to be impractical for busy clinicians. Handheld computers and Internet sites that calculate a patient's risk are helpful aids, but a simple approach to dyslipidemia that customizes therapy to a patient's individual needs remains a desirable but elusive goal.

This review offers one such simple approach. Based on a patient's lipoprotein abnormality, the algorithm described below begins with achievable, practical therapeutic lifestyle changes and then adds pharmacologic agents in stepwise fashion to address abnormalities of LDL cholesterol, triglycerides, and HDL cholesterol. While the approach is aggressive, it is not based on driving lipid levels to extremely low levels. While some of the lipid targets appear less stringent than conventional wisdom would suggest (eg, accepting an LDL cholesterol target of 130 mg/dL), the approach below is in compliance with the spirit and letter of national guidelines.

Introduction

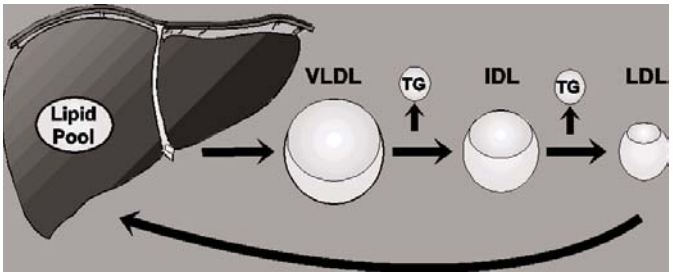
Hyperlipidemia has long been recognized as increasing a patient's risk for the development of atherosclerosis and subsequent cardiovascular events. Effective therapies have been developed to reduce this risk, yet the process of customization of a therapeutic regimen in a given patient remains controver-

sial. Some patients have elevated cholesterol levels. Others have hypertriglyceridemia. Some have both abnormalities. It is not surprising, then, that a "one size fits all" approach to the treatment of dyslipidemia fails to meet the needs of our patients. A review of the rationale for various treatment targets and the strategies to reach those targets may be helpful in understanding how to best treat our patients one at a time.

Lipoproteins, Not Lipids

Dietary fat and dietary cholesterol contribute to blood lipid levels, but the lipid story really begins in the liver, where de novo cholesterol and triglyceride (TG) synthesis by the hepatocyte supplies most of the liver's lipid pool. As lipids are hydrophobic, they must become more soluble before they can travel through the aqueous medium of the blood to reach the peripheral tissue where the cholesterol is used for the creation and maintenance of cell membranes, for energy storage, etc. The lipids become more soluble wrapped in protein. In particular, some TG- and cholesterol-rich lipoproteins contain the apoprotein B-100. These transport particles deliver lipids to adipocytes and other targets, and then the depleted particles return to the liver to recycle their lipid and protein remnants into new lipoproteins. Lipids can also be packaged into lipoproteins in the intestine. These chylomicrons contain B-48 rather the B-100. Other lipoproteins, such as high-density lipoproteins (HDL), contain mostly protein (especially the proteins apo AI and apo AII, rather than B-100) and contain little, if any, lipid when they leave the hepatocyte. These HDL particles can gather cholesterol from the periphery and transport the lipid back to the liver, a process known as reverse cholesterol transport (*see Figure 1*).

Figure 1. Panel A



Hepatocytes create pools of triglyceride and cholesterol, which are then packaged into lipoproteins such as the triglyceride-rich very low-density lipoproteins (VLDL). As the triglyceride cargo of the VLDL particle is unloaded into adipocytes, intermediate density lipoproteins (IDL) and ultimately low density lipoproteins (LDL) result. VLDL, IDL, and LDL particles all contain one apo B-100 molecule to make the lipid soluble in blood. Once depleted of their lipid contents, these "B lipoproteins" return to the liver for recycling.

Traditionally, lipoproteins are separated by centrifugation. TG-rich particles are more buoyant, and protein-rich particles are more dense. TG-rich particles emerging fresh from synthesis in the liver are known as very low-density lipoproteins (VLDL). After removal of some of the TG, the particles are less buoyant and become intermediate density lipoproteins (IDL). The main cholesterol transport lipoprotein is low-density lipoprotein (LDL). VLDL, IDL, and LDL all contain apo B-100. High concentrations of these types of particles are atherogenic (*see Figure 2*). On the other hand, HDL is involved in reverse cholesterol transport, as well as in antioxidant and anti-inflammatory functions. HDL is cardioprotective. In view of the different functions of these lipoproteins, we can no longer treat total cholesterol levels. If total cholesterol is elevated, but this cholesterol is largely contained in HDL particles, treatment might not be warranted. Of the particles synthesized by the liver, it is only elevated levels of the atherogenic lipoproteins, which contain apo B-100, that are the proper focus in dyslipidemic patients. In other words, risk is imparted by all non-HDL cholesterol, not total cholesterol.

On a routine lab slip, we do not find HDL or LDL measurements. We find instead a measurement or calculation of HDL or LDL *cholesterol* levels. This can lead to some incorrect conclusions. For example, LDL has as its main function the transport of cholesterol. Not surprisingly, LDL cholesterol (LDL-C) levels are higher than HDL cholesterol (HDL-C) levels. One might conclude that LDL is a more important lipoprotein because there is more LDL-C. However, the concentration of LDL and HDL are usually equal (approximately 500 mg/dL) even when LDL-C is 140 mg/dL and HDL-C is 40 mg/dL. That is, the lipoproteins are mostly protein, and the cholesterol is just the cargo that these particles carry. An LDL truck has a large cargo space for cholesterol; an HDL cargo truck has a small cargo space for cholesterol. The trucks are about the same mass, but the capacities of their cholesterol cargo spaces

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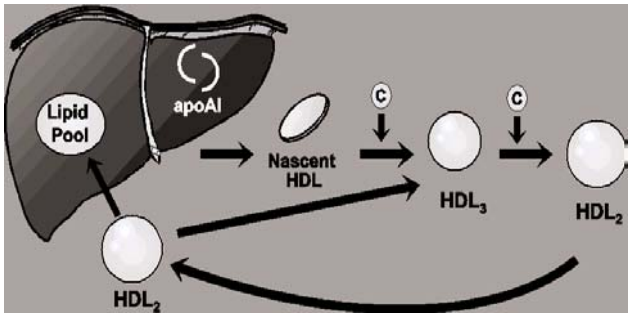
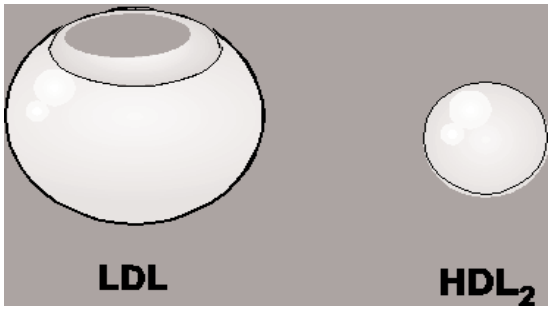
Figure 1. Panel B



Hepatocytes also produce apo AI protein. Two crescent-shaped apo AI molecules form a ring, insert themselves into the cell membrane of the hepatocyte, and tear a piece of the membrane away to form a disc, the nascent form of high-density lipoprotein (HDL). This HDL can then gather cholesterol from the periphery to form a sphere. The subpopulation of larger, cholesterol-rich HDL particles is known as HDL_2. HDL_2 then returns to the liver to deliver its cholesterol load to the hepatocyte for recycling, a process known as reverse cholesterol transport. The new lipid-depleted particle is known as HDL_3.

Figure 3.



LDL particles carry most of the cholesterol being transported from the liver to the periphery. The main purpose of LDL particles is to transport cholesterol. HDL does carry some cholesterol back to the liver (reverse cholesterol transport), but it has other functions (eg, anti-oxidant and anti-inflammatory functions), as well. HDL particles are smaller than LDL particles, and there is less cholesterol per particle in HDL. However, in a typical patient, there are 10 times more HDL particles than all the VLDL, IDL, and LDL particles combined. It is important, then, not to underestimate HDL's importance simply because a lab slip indicates a lower level of HDL cholesterol (HDL-C) than LDL cholesterol (LDL-C).

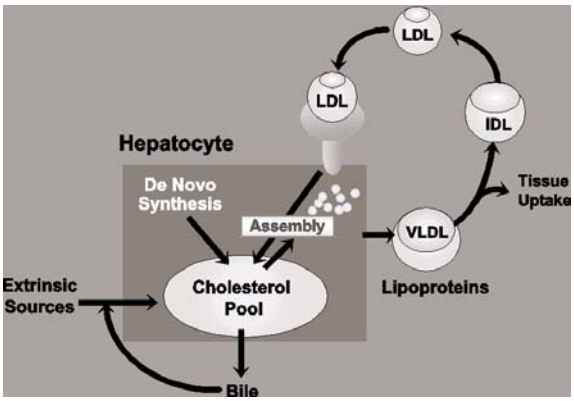
are very different (*see Figure 3*). On the lab slip, we are only looking at the amount of cargo that these transport particles are carrying, not the size of the transport particle itself.

It is important not to let the differences in cholesterol cargo capacity of LDL and HDL lead us to view HDL as less important than LDL. First, as already discussed, the role of these 2 types of particles is very different. Secondly, there are actually more HDL particles than LDL particles. In fact, in normal patients there are roughly 10 times more HDL particles than all the VLDL, IDL, and LDL particles *combined*. Many of the HDL particles are "off road" trucks, having left the bloodstream to migrate through the tissues to perform anti-oxidant and anti-inflammatory functions. LDL is certainly important, and lowering LDL-C is an important clinical objective. However, the oft-overlooked HDL particle is also important, perhaps equally important compared to LDL.

Likewise, many clinicians are surprised to learn that IDL, not LDL, is the most atherogenic particle. If this is so, then why is IDL-C not to be found on the lab slip? Under normal circumstances, IDL is a short-lived particle, quickly giving up its triglyceride cargo to become LDL. Normally, then, IDL-C is included in the calculated LDL-C levels. In diabetic dyslipidemia and type III hyperlipoproteinemia, however, IDL becomes more important. The treatment of elevated IDL can differ from therapy for elevated LDL-C, so again incorrect interpretations of lab values can hinder our attempts to optimize the therapy of our patients.

Over the last decade, it has become apparent that even within a lipoprotein class there are subpopulations of particle size and density. LDL particles can be relatively larger and more buoyant, or smaller and denser. In virtually all studies of this issue, small, dense LDL is argued to be more atherogenic. For example, in the Quebec Cardiovascular Study, patients with a predominantly small, dense LDL phenotype (LDL phenotype pattern B) had 3 times the cardiovascular risk compared to patients with identical LDL-C levels but larger, more buoyant

Figure 2.



Hepatocytes create intracellular lipid pools from dietary sources of fat and carbohydrate, as well as from de novo synthesis. These lipids are assembled into lipoprotein transport particles (VLDL, IDL, and LDL), which deliver the lipid to the peripheral tissue. The LDL particles then return to the hepatocyte and bind to LDL and scavenger receptors, so that the components of the remnant lipoproteins can be recycled.

LDL particles (LDL phenotype pattern A).[1]

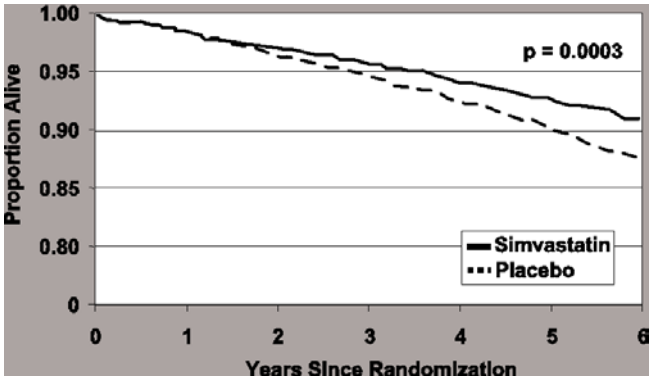
If we take a "one size fits all" approach to dyslipidemia therapy, there may be some unintended consequences. If a patient has atherogenic small LDL particles, it makes sense that we would want to increase LDL particle size to create less mischievous particles. However, if the LDL particle size increases, it is because we are filling up the cargo capacity of the depleted small LDL particle with cholesterol. Therapies that increase LDL particle size (such as fibrates and thiazolidine-diones) will increase LDL-C levels (because there is now more cholesterol in the larger LDL particles) while actually lowering cardiovascular risk (because larger LDL particles are less atherogenic). If we were focused only on LDL-C levels with a "one size fits all" mentality, we would unfortunately back away from therapies that target small LDL particles, when these are the very therapies that some patients need.

Has it become too complex for the nonspecialist to treat dyslipidemic patients? Our national guidelines have certainly grown in complexity. Once, patients were grouped by counting the number of major risk factors (smoking, diabetes, hypertension, family history of premature atherosclerosis, low HDL-C). The current National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines urge ever more precise risk stratification of patients to assure that those at the highest risk receive the most aggressive therapy.[2] This is laudable, but clinicians now need to enter patient data into an algorithm to calculate a patient's 10-year risk of suffering a clinical event, a process complex enough to require a handheld computing device or a PC. More than 200 independent risk factors for coronary heart disease have been identified.[3] How should these emerging risk factors (eg, hyperhomocysteinemia, inflammatory cytokines, high sensitivity C reactive protein, plasminogen activator inhibitor-1, etc) be addressed in treating patients? As our appreciation of the complexity of the atherosclerosis disease process increases, there is a dizzying array of factors to consider in our patients. A case can be made for a simpler, more practical approach that still meets the spirit and the letter of our national guidelines for dyslipidemia therapy and is customizable to individual patient needs. Fortunately, such a simple, practical approach exists, as is described below.

LDL Cholesterol: The Primary Target

LDL-C is well established as a major risk factor for the development of atherosclerosis.[2] Further, therapies that lower LDL-C reduce the incidence of myocardial infarction, stroke, and death (*see Figure 4*). While therapeutic lifestyle changes (TLCs) are the bedrock of therapy, in the absence of weight loss, dietary manipulations and exercise have only a modest (~10%) effect on LDL-C. The major breakthrough in the treatment of LDL-C was the development of HMG CoA reductase inhibitors, or statins.[4-9] To this we can now add LDL-lowering agents that limit dietary cholesterol absorption, bile acid sequestrants, niacin, and fenofibrate (but not the fibrate gemfibrozil), which has a neutral effect on LDL-C. With our current armamentarium, we can achieve an acceptable LDL-C level in most patients. The question is, what LDL-C level should we desire?

Figure 4. Panel A



Beginning with the landmark 4S trial (panel A), HMG CoA reductase inhibitors have been proven to reduce the risk of death, myocardial infarction, and stroke in dyslipidemic patients. These findings have been repeatedly confirmed in large, prospective, placebo-controlled, randomized clinical trials such as the CARE (panel B), West of Scotland (panel C), LIPID (panel D), AFCAPS/TexCAPS (panel E), and most recently ASCOT (panel F) trials. For both patients with dyslipidemia but no previous cardiovascular event[4,5] and for those dyslipidemic patients with established clinical CHD[6-9] statin therapy is the bedrock of therapy.

Figure 4. Panel B

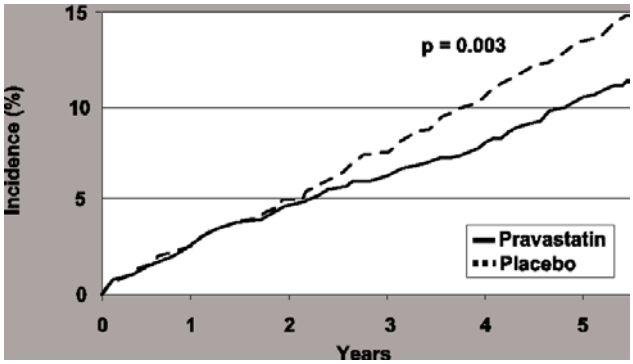


Figure 4. Panel C

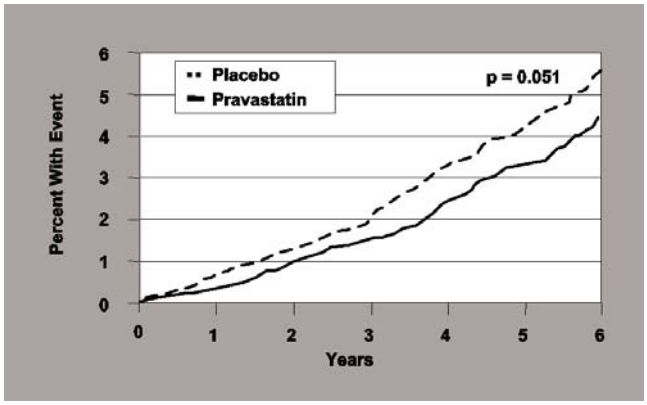


Figure 4. Panel D

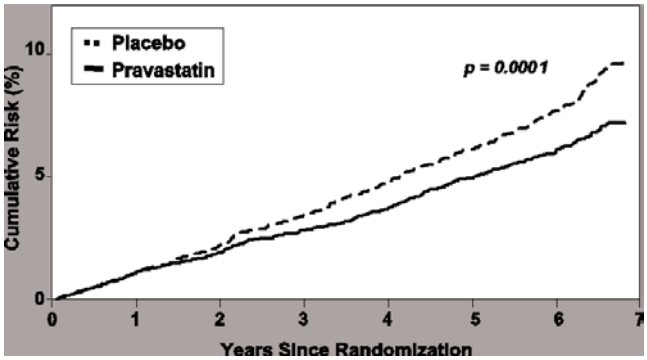


Figure 4. Panel E

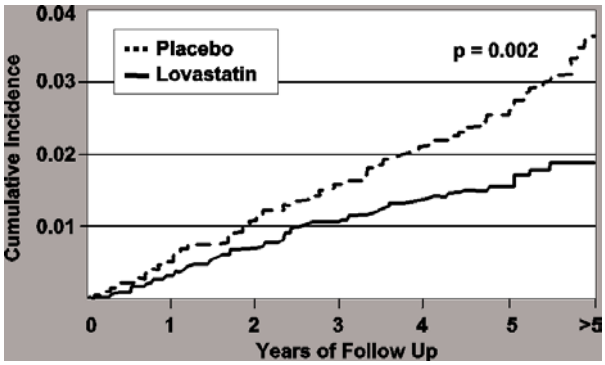
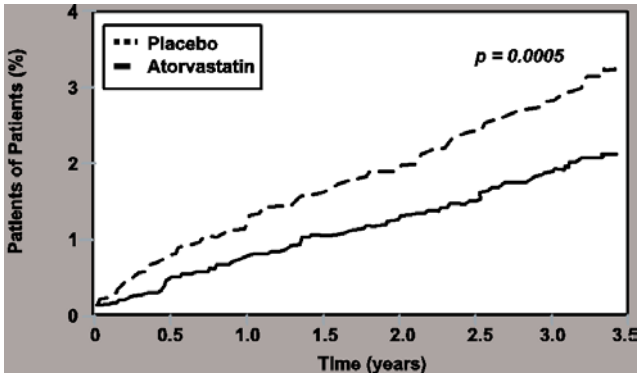


Figure 4. Panel F



Opinion 1: LDL-C is Everything, and Lower is Better

We are born with an LDL-C of 50 mg/dL, and physiologically anything over 70 mg/dL is unnecessary. At a level of 100 mg/dL, hepatic LDL receptors are maximally upregulated. LDL-C at all levels can be oxidized and thereby be rendered atherogenic. Although the major statin trials reduced LDL-C levels with a fixed dose of statin and did not titrate therapy to a target LDL-C level, it is logical that treating to an LDL-C level of 130 mg/dL is reasonable, that 100 mg/dL is optimal, and that at 70 mg/dL maximal benefit is obtained. These levels are achievable with statin monotherapy, or with combinations of cholesterol absorption inhibitors, bile acid sequestrants, niacin, fenofibrate, and statins.

However, while this approach is logical, we should remember that there is no clinical trial support for the hypothesis that aggressive lowering of LDL-C is the best approach to the dyslipidemic patient. This is an attractive paradigm since this is a simple approach. It is an obtainable objective for most patients, although side effects and costs increase as higher doses of aggressive therapy are used. The TNT trial with atorvastatin[10] and the SAGE[11] and PROVE IT[12] trials comparing atorvastatin to pravastatin will shed some light on whether titrating therapy to a specific LDL-C level is warranted.

Opinion 2: After Reaching an LDL-C of 130 mg/dL, the Benefits of LDL-C Lowering are Marginal

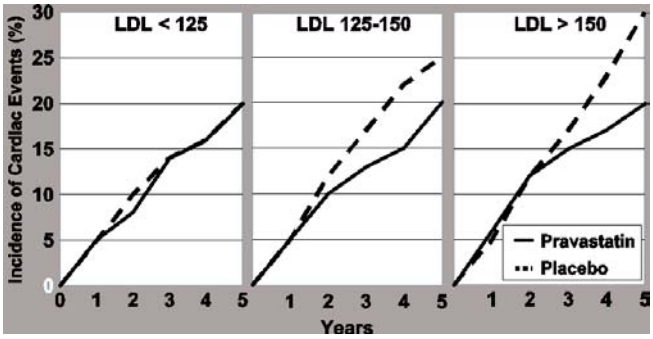
In the CARE study of pravastatin in postmyocardial infarction patients with average LDL-C levels, a reduction in clinical events was seen.[5] However, patients entering the trial with an LDL-C ≤ 125 mg/dL had no benefit. In the more recent ALLHAT trial, patients in the usual care group lowered their LDL-C to 130 mg/dL during the study. Lowering LDL-C to 100 mg/dL with pravastatin in ALLHAT yielded no further clinical benefit compared to the usual care group.[13] The West of Scotland (WOSCOPS) trial showed that lowering LDL-C more than 20% provided no further reduction in cardiac risk,[14] a finding confirmed in the Pravastatin Pooling Project of more than 20,000 patients.[15] In the AVERT trial, the benefit of lowering LDL-C with atorvastatin in patients with an LDL-C below 130 mg/dL was marginal (*see Figure 5*).[16]

Once LDL-C has been reduced below 130 mg/dL, many clinicians believe that abnormalities of the rest of the lipid profile become a more important consideration. For example, in the VA HIT trial, patients with atherosclerosis and an LDL-C of 115 mg/dL were treated with the fibrate gemfibrozil. LDL-C was not lowered by gemfibrozil, but TG decreased 27% and HDL-C rose 8.6%. These lipid changes were associated with a significant reduction in mortality.[17](*See Figure 7*.)

Opinion 3: There is a 'Statin Effect, Beyond Which Combination Therapy Must be Used to Achieve Further Benefit'

In a posthoc analysis of the 4S trial of simvastatin, patients were divided into quartiles according to their baseline LDL-C. No matter what the baseline LDL-C, patients enjoyed the same clinical benefit—namely, approximately a 25% reduction in risk.[18] In the AFCAPS/TEXCAPS trial of lovastatin, clinical benefit again had little relation to achieved levels of LDL-C. Baseline risk correlated to baseline LDL-C, but treatment with a statin lowered all patients to a new, common level of risk.[19] The more recent Heart Protection Study of simvastatin also showed the same 24% reduction in risk for all patients, regardless of baseline LDL-C levels.[20] The much smaller HATS study suggests that to achieve greater benefit in our patients, combination therapy can be used. In HATS, adding niacin to simvastatin reduced events 70% compared to simvastatin monotherapy.[21](*See Figure 6*.) Unfortunate-

Figure 5. Panel A



In the CARE trial, one-third of patients were treated to an LDL-C level below 125 mg/dL (panel A). In the ALLHAT trial, patients in the "usual care" group lowered their LDL-C level below 130 mg/dL, while the group treated with pravastatin achieved an LDL-C near 100 mg/dL (panel B). Both the CARE (panel A) and ALLHAT (panel C) trials suggest that lowering LDL-C below 130 mg/dL with a statin would be expected to produce little, if any, benefit. For patients with no previous CHD, the WOSCOPS study showed that lowering LDL-C more than 20% produced no additional benefit (panel D). The AVERT study used the highest dose of our most potent statin, and showed only a marginal benefit despite driving LDL-C levels below 100 mg/dL (panel E). These data suggest that after LDL-C has been lowered below 130 mg/dL with a statin, combination therapy with a fibrate or niacin might be required to achieve more event reduction.

Figure 5. Panel B

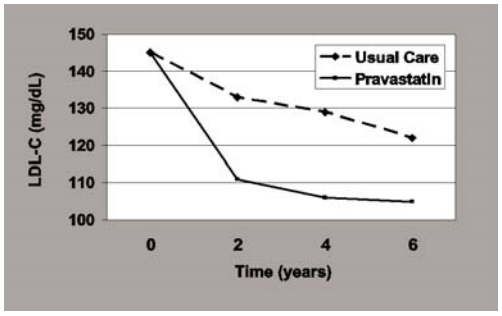


Figure 5. Panel C

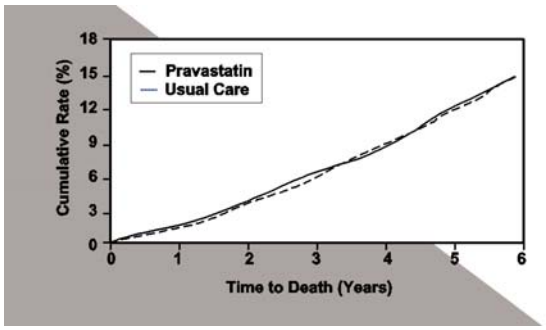


Figure 5. Panel D

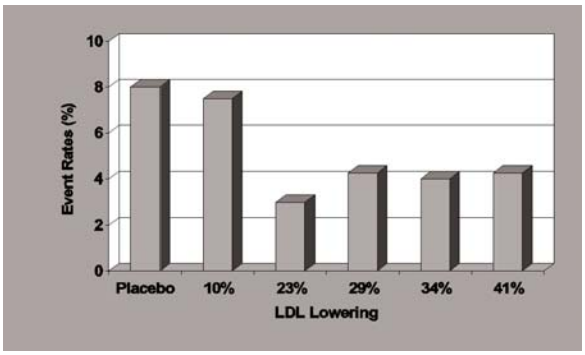
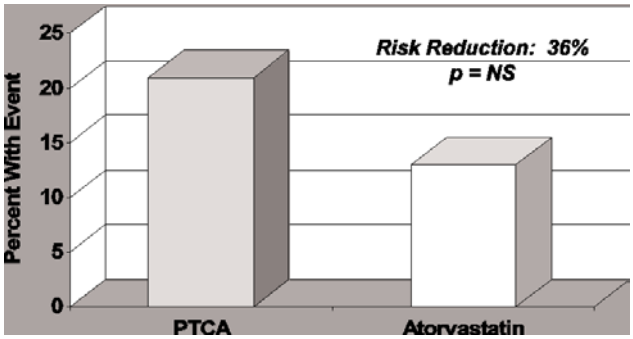


Figure 5. Panel E

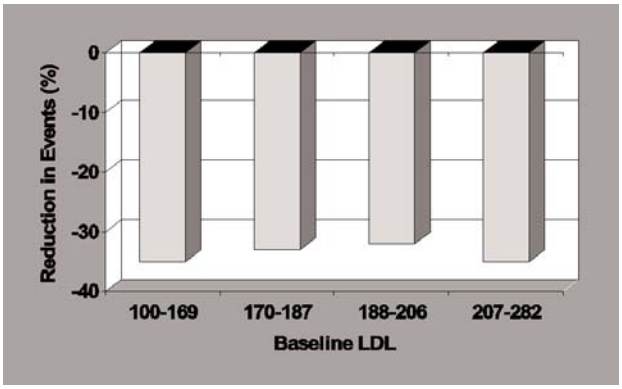


ly, the large trial of combination therapy was the Lipids in Diabetes Study (LDS), which compared the combination of cerivastatin with fenofibrate with each agent used as monotherapy in diabetic patients. LDS was discontinued when cerivastatin was removed from the market.[22]

Recommendation

For patients with an LDL-C above 130 mg/dL, pharmacologic therapy (beginning with a statin) is indicated. The NCEP ATP III guidelines suggest that for patients who have a baseline LDL-C below 130 mg/dL, or for those who achieve an LDL-C level below 130 mg/dL on therapy, that there are 3 options. First, in patients whose only lipid abnormality is an elevated LDL-C, one can push on to lower LDL-C levels (eg, an "optimal" LDL-C of 100 or even 70 mg/dL). Alternatively, one can re-emphasize TLCs. This is especially true for obese, sedentary patients with the metabolic syndrome or type II diabetes. Finally, one can consider combining statins with fibrates or niacin to address TG and HDL-C abnormalities, as well as LDL-C. All of the large, randomized trials to date have used a fixed dose of lipid-lowering agents. There is no trial that lowered patients to specified lipid target levels. In other words, in the absence of clinical trial support for an evidence-based medicine approach for LDL-C targets, clinicians should customize therapy to the individual needs of the patient before them. For most patients, a prudent approach would be to use a statin to lower LDL-C to ≤ 130 mg/dL and then to use niacin or fibrate therapy to achieve HDL-C and TG

Figure 6. Panel A



A posthoc analysis of the 4S study (panel A), and the Pravastatin Pooling Project meta-analysis (panel B) suggest a "statin effect." The AFCAPS/TexCAPS trial also showed that in patients with different baseline LDL-C levels (and consequently different baseline risk for cardiovascular events), lovastatin brought all patients to a common risk level (panel C). On treatment LDL-C levels did not correlate with risk of an event in AFCAPS/TexCAPS. Statins appear to produce a 25% reduction in risk despite age, gender, diabetes status, baseline LDL-C, or the magnitude of LDL-C reduction. The HATS study holds out the new paradigm that to achieve benefit beyond statin therapy, combination therapy (in this case statin + niacin) should be employed. In HATS, combination therapy significantly reduced events compared to statin monotherapy (panel D).

Figure 6. Panel B

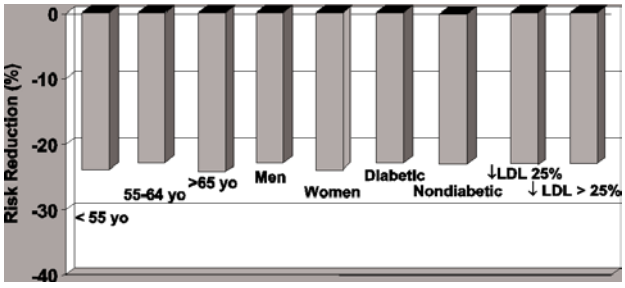


Figure 6. Panel C

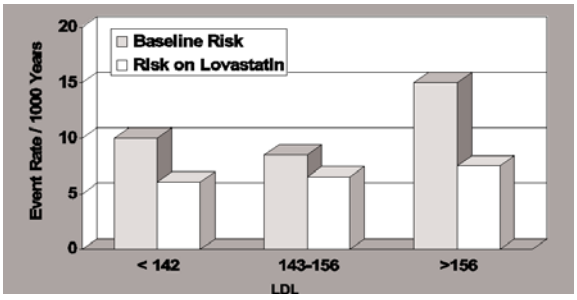
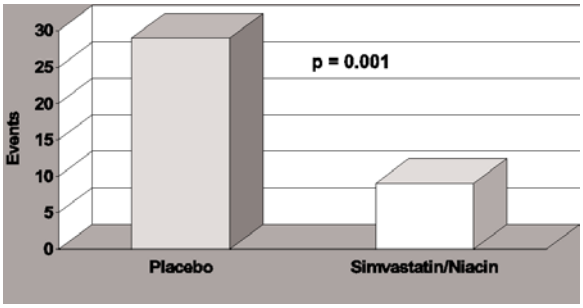


Figure 6. Panel D



targets. Fenofibrate (unlike gemfibrozil) is a PPARa agonist that also inhibits HMG CoA reductase, so like niacin will lower LDL-C, as well as TG. Combination therapy with these agents (on background of statin therapy) will likely result in an achieved LDL-C of 100 mg/dL or lower, while simultaneously addressing a broader spectrum of cardiovascular risk factors.

Special Forms of LDL

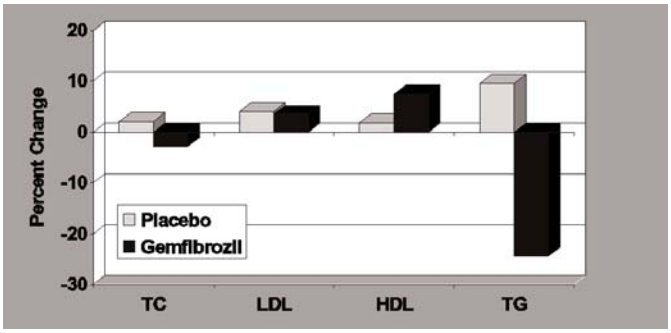
Lipoprotein (a), or Lp(a), deserves a special mention. This genetically derived type of LDL consists of an LDL particle wrapped in the protein apo (a). Apo (a) resembles plasminogen in its structure, so competes with plasminogen. Consequently, Lp(a) impairs fibrinolysis. Lp(a) is highly oxidizable and is more atherogenic than LDL, although the atherogenicity of Lp(a) is relatively less in African-American patients than in other subgroups. Statins do not lower Lp(a) levels; in fact, in most studies statins raise Lp(a) slightly. Lp(a) screening should be considered in patients whose LDL-C levels are resistant to statin therapy and in patients with a strong family history of premature atherosclerosis. Lp(a) levels can rise in the presence of hyperglycemia and can be increased by fish oil therapy. Treatment options for Lp(a) elevations include estrogen, niacin, and fenofibrate.

LDL exists in a variety of subpopulations, ranging from large, buoyant LDL particles to smaller, denser LDL particles. As discussed above, the small, dense LDL (sdLDL) is thought to be more atherogenic since it is prevalent in patients at high risk, such as patients with the metabolic syndrome or diabetes. While therapy targeting sdLDL has not been studied in a large clinical end point trial, treating sdLDL does slow progression of atherosclerosis. Statins generally have not been effective in shifting LDL subpopulations toward larger particle size, though they do lower total LDL levels. If large LDL particles predominate, then statins lower large LDL. If most of the LDL is in small, dense LDL particles, then statins lower small dense LDL. Statins do not shift LDL phenotype, however. A possible exception is atorvastatin, which in small studies increased LDL particle size.[23-24] Fibrates and niacin more effectively treat sdLDL.

HDL Cholesterol: The Frustrating Target

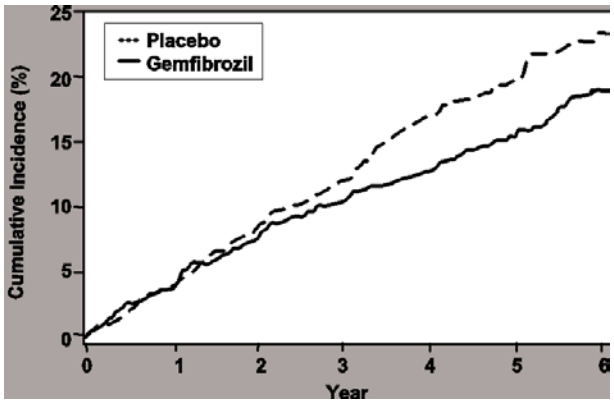
There is little controversy that HDL-C is an important lipoprotein. As discussed above, HDL-C has roles as an anti-inflammatory agent, as an anti-oxidant, and in reverse cholesterol transport. As with LDL, there are different HDL subpopulations. There is some controversy about the effects of the vari-

Figure 7. Panel A



The VA HDL Intervention Trial (VA HIT) used the fibrate gemfibrozil rather than statin therapy for patients who had suffered a myocardial infarction but who had a "normal" LDL-C (average, 111 mg/dL). Gemfibrozil had no effect on LDL-C but raised HDL-C and lowered triglycerides (panel A). This therapy resulted in a mortality benefit (panel B), especially in hyperinsulinemic (insulin-resistant) patients.

Figure 7. Panel B



ous HDL subpopulations. HDL particles can be large and lipid-rich (HDL_2) or smaller and lipid-poor (HDL_3). It is thought that the larger HDL_2 particles, which contain more cholesterol, reflect a more robust reverse cholesterol transport, so are more anti-atherogenic. However, the smaller HDL particles play a more important role in the antioxidant and anti-inflammatory functions of HDL. A careful reading of the available population studies suggests that all HDL is cardioprotective, ie, the most cardioprotective HDL species in a given population is the HDL that is most common in that population.[25-28] This is probably because the different forms of HDL are continually converting from one into the other as they gain or lose lipid. From a clinical standpoint, then, the more HDL-C the better, no matter what its form.

HDL-C is a frustrating clinical target because our current tools have limited effectiveness. Truly antiatherogenic levels of HDL-C are 75-85 mg/dL. It is unlikely that we can reach such a goal in a patient whose baseline HDL-C is 25 mg/dL. Increasing dietary fat intake, aerobic exercise, moderate alcohol consumption, and smoking cessation all raise HDL-C. Pharmacologically, high-dose statins lower HDL-C, while lower levels of HMG CoA reductase inhibition modestly raise HDL-C. One study comparing atorvastatin to simvastatin showed that, at doses producing identical LDL-C reduction, simvastatin raised HDL-C and apo AI levels, while atorvastatin lowered them.[29]

As discussed previously, gemfibrozil raised HDL-C in the VA HIT study to produce a statistically significant clinical benefit.[17] (*See Figure 7.*) Fenofibrate raises HDL-C even more effectively. Fibrates, as PPARa agonists, increase the production of apo AI and apo AII and therefore HDL particle production. Fibrates also increase the efficiency of cholesterol removal from HDL in the liver. Classically, niacin was the drug of choice for HDL-C and remains perhaps the most potent of the available agents for this purpose. It, too, increases the efficiency of lipid removal from HDL returning to the liver. The limitation of niacin is that many patients with low HDL-C are insulin resistant, and niacin increases insulin resistance. Fibrates, on the other hand, increase insulin sensitivity. Most of the benefit in the VA HIT study was in the hyperinsulinemic (insulin-resistant) patient.

Recommendation

NCEP ATP II recommended an HDL -C target of 35 mg/dL. The current ATP III recommendations have raised this to 40 mg/dL. No matter what the goal, our current therapies have limited potency. One can conclude that the real goal is to raise HDL-C as much as we can for our patients.

Triglycerides: The Forgotten Target

Triglyceride levels vary inversely with HDL-C levels in most patients. It has therefore been difficult to tease out whether hypertriglyceridemia is an independent risk factor, or is simply a marker for patients with low levels of HDL-C. Consequently, in the past, triglycerides were only a treatment target if TG levels were high enough to threaten pancreatitis. However, in the Helsinki Heart Study, patients with modest hypertriglyceridemia and low HDL-C had a nearly 4-fold increased risk for cardiac events, and gemfibrozil therapy reduced risk by 70%.[30] It is generally accepted today that hypertriglyceridemia is a risk factor both directly and through the effects of TG on HDL, LDL particle size, and hypercoagulability.

Hypertriglyceridemia is directly linked to the production of small, dense LDL particles (LDL phenotype pattern B). Through cholesterol ester transfer protein (CETP), TG can be transferred from TG-rich lipoproteins to LDL and HDL, which in turn transfer cholesterol to VLDL and IDL. When TG-rich LDL gives up its TG to peripheral tissue, small, dense lipid-depleted LDL particles result. Modest TG elevations (≥ 200 mg/dL) are usually associated with smaller LDL particles. Framingham showed that triglycerides increase risk, especially in women.[31] In the Paris Prospective Study, elevated TG increased risk regardless of cholesterol level.[32] Often, TG levels must be pushed below 100 mg/dL before a patient "converts" to LDL phenotype pattern A.

HDL is created from VLDL particles as they give up their lipid load to the periphery. As the large lipoprotein shrinks, the "excess" membrane becomes an HDL particle. Thus, when TG levels are increased, HDL-C levels are low. As TG levels fall,

more HDL particles are created, and HDL-C levels rise. TG also increase plasma viscosity, raise fibrinogen, raise plasminogen activator inhibitor 1 (PAI-1, the "anti-tPA molecule) levels, and activate clotting factors of the coagulation cascade. Either directly or indirectly, then, TG are a legitimate treatment target.

While resins raise TG levels, statins, fibrates, and niacin all lower TG. Fish oil (omega-3 fatty acids) is also effective in lowering TG. Unlike hypercholesterolemia, TG levels can respond dramatically to TLCs. Weight loss, aerobic exercise, and limiting dietary carbohydrates (especially simple sugars such as alcohol, fruit juices, soft drinks, etc) can reduce TG levels to normal. A common cause of iatrogenic hypertriglyceridemia is hormone replacement therapy with estrogen. If LDL-C, HDL-C, and TG are all elevated, hypothyroidism should be excluded.

Recommendation

NCEP ATP III lowered the recommended therapeutic target for TG from 200 to 150 mg/dL, reflecting a growing appreciation for the importance of TG. The Baltimore COLTS study suggests that a target of 100 mg/dL is optimal.[33] This would require combination therapy in nearly all patients. A reasonable approach in 2003 is that TG should be lowered to ≤ 200 mg/dL in all patients with TLCs, fish oil, statins, fibrates, and/or niacin. For TG between 100 and 200 mg/dL, the consequences of the TG should be considered. TG lowering may be desirable as an indirect means of raising HDL-C. Lowering TG could also shift a patient's LDL phenotype to larger, more buoyant, less atherogenic particles. If a patient has low HDL-C or if advanced lipid testing reveals a small, dense LDL phenotype, intensifying therapy to lower TG below 100 mg/dL with combination therapy is rational. Because combination therapy increases the incidence of side effects, monitoring of renal, hepatic, and muscle function is more important in this setting.

Therapeutic Lifestyle Changes: Lose 10% of Body Weight, with a Diet to Match the Form of Dyslipidemia

While a "prudent diet" and a "prudent lifestyle" have long been recognized as ingredients for a healthy life, such therapeutic interventions were viewed as unrealistic for patients of the First World. There is growing evidence that these therapies are both the safest and most potent therapies that we can recommend to our patients. For example, while pharmacologic therapies such as metformin, ramipril, and pravastatin have been shown to prevent the onset of diabetes, therapeutic lifestyle changes (TLCs) were shown to be even more effective.[34]

TLCs work in many of the same ways as pharmacologic agents. For example, fibrates activate the gene for lipoprotein lipase (LPL) production. LPL transfers triglycerides from VLDL and IDL into adipose tissue, lowering blood triglyceride levels. As VLDL and IDL become smaller lipoproteins, HDL particles are generated. Thirty minutes of daily aerobic exercise also activates LPL, driving triglyceride levels down and raising HDL-C levels. The NCEP ATP III guidelines suggest daily activity that would burn 200 kCal/d. As a guide to walking intensity, the American Heart Association recommends the "sing test." If, during activity, the patient can still sing, then he or she should pick up the pace a bit. If, on the other hand, the patient is too breathless to talk during the activity, then the pace is too vigorous.

Dietary therapy is also a major component of TLCs. Our efforts in this arena have gradually become more focused. LDL-C-raising nutrients are saturated fats, trans-fatty acids, and dietary cholesterol. A simple assessment of dietary cholesterol and saturated fats is obtained with the CAGE assessment of a patient's dietary habits:

C-Cheese/dairy fats (milk/cream/ice cream/yogurt)
A-Animal fats (meats/fried foods)
G-Got it away from home (eating out/buying meals for home consumption)
E-Extra-high fat foods (candy/cookies/pastries/pies)

Trans-fatty acids, such as are found in butter, stick margarine, and shortening, are particularly atherogenic, (raising LDL-C levels, and lowering HDL-C) and are therefore to be avoided. Dietary cholesterol, while atherogenic, has much less impact on blood lipid levels. It should be remembered, however, that most dietary manipulations have little (~10-15% lowering) effect on LDL-C levels.

On the other hand, triglyceride levels are very responsive to TLCs. Carbohydrate intake and carbohydrate tolerance are closely related to triglyceride levels. Restricting dietary carbohydrates, especially simple sugars, can dramatically affect triglyceride levels as discussed above. Tight control of hyperglycemia in diabetics can also lower triglyceride levels substantially. Not surprisingly, patients with the metabolic syndrome or overt type II diabetes mellitus can respond well to diets with relaxed restrictions on fat and protein (eg, the "Sugar Busters," "Atkins," or "Protein Power" diets). These diets increase carbohydrate restrictions. On the other hand, patients with normal carbohydrate tolerance do well with a fat-restricted diet as a part of their prevention program (eg, an "Ornish"-type diet). The authors of guidelines have been hesitant to endorse different diets for different patient groups, preferring instead to recommend a TLC diet of 60% carbohydrate, < 7% saturated fat, and less than 200 mg dietary cholesterol for all patients. It appears that virtually any diet that results in a 10% loss of body weight will likely result in clinical benefit.

An increase in dietary fiber is now widely encouraged from a number of perspectives. Insoluble fiber is the fiber that gives form and stiffness to vegetables (making carrots firm, for example). More helpful in treating dyslipidemia is soluble fiber, eg, the viscous component of fruits and vegetables. Citrus fruits and beans are good sources of soluble fiber. Other plant components discussed in NCEP ATP III include plant sterols (and the hydrogenated stanols), which are found in soybeans and pine trees. These plant components lower LDL-C levels. Soy protein also has a small LDL-C-lowering effect.

The question of dietary supplements is often raised for dyslipidemic patients. A multivitamin and folic acid are recommended for all patients, including dyslipidemic patients. Antioxidants have not been shown to be helpful, although many clinicians still use them in high-risk patients. Fish oil capsules, on the other hand, may be helpful. One gram of omega-3 fatty acids (generally found in 2 or 3 fish oil capsules) has been shown to significantly reduce mortality even in patients already taking ACE inhibitors, statins, beta-blockers, and antiplatelet agents.[35] Higher doses of fish oils can significantly reduce triglycerides.

The unhealthiest aspect of the US lifestyle is not what percentage of our calories come from fat. In fact, NCEP ATP III no longer has a target level for total dietary fat. The main dietary problem facing Americans is not what kinds of foods that they eat. The main problem we face is that most Americans are overweight or obese. A major insight of the NIH obesity guidelines is that it is unrealistic to continue to hold out the achievement of ideal body weight as the main therapeutic objective in obese Americans.[36] Significant health benefits will accrue if patients can lose 10% of their body weight. This is a realistic, achievable, short-term goal. It really doesn't matter how patients achieve this goal, although extreme diets rarely produce long-term weight loss. Virtually every obese patient can lose 10% of his or her body weight. This should be the focus of a dietary TLC. Chronically, one can then consider the dietary modifications suggested above. Clinicians can begin, however, by advocating a 10% weight loss by a means of the patient's choice.

The Art of Combination Therapy

All dyslipidemic patients require combination therapy to achieve therapeutic lipid targets. At the very least, pharmacologic therapy is combined with TLCs. We now recognize that a large percentage of our patients also require multiple pharmacologic agents to achieve our ever more aggressive lipid targets. Half of American men with CHD have the metabolic syndrome, which can include glucose intolerance or frank diabetes. Addressing the low HDL-C and hypertriglyceridemia of these patients usually requires niacin or fibrates to be added to baseline statin therapy. A lovastatin/niacin combination in a single tablet is now available. No significant rise in myopathy occurs with this combination, but a small increase in hepatotoxicity merits monitoring of liver function.

Because niacin increases insulin resistance,[37] some clinicians will prefer adding insulin-sensitizing fibrates to statin therapy in patients with the metabolic syndrome. Recently, however, cerivastatin was removed from the marketplace, due in part to adverse outcomes (particularly myopathy) in patients who used this statin in combination with gemfibrozil. Other statins, particularly water-soluble statins such as pravastatin or fluvastatin, seem to have less interaction. Likewise, fenofibrate may have less interaction with statins. This is due to the metabolic pathways used by lipid agents in the liver, in particular glucuronization. Statins are metabolized primarily by UGT 1A1 and 1A3. Fenofibrate primarily is metabolized by UGT 1A9 and 2B7. Since they go through different UGT metabolic pathways, fenofibrate-statin interactions are uncommon. Gemfibrozil, on the other hand, is widely metabolized through glucuronization pathways and shares the UGT 1A1 and 1A3 pathways with statins. Gemfibrozil-statin interactions, then, are more common.[38]

Three strategies are of value when combining statins and fibrates. First, if it is apparent that combination therapy will be desirable from the outset in a patient with combined dyslipidemia (eg, a patient with an LDL-C of 175 mg/dL and TG of 350 mg/dL), the fibrate can be started first, bringing the TG under control, and perhaps lowering LDL-C as well if fenofibrate is selected. With this approach, a lower dose of statin may be sufficient to meet LDL-C goals. If the statin is initial therapy, the statin dose may be increased over time, trying to address all lipid targets with statin monotherapy. Adding a fibrate to maximum dose statin will increase the risk of myopathy.

This introduces the second strategy. For patients already on a statin, the statin dose should be halved before adding a fibrate. Finally, as a third strategy, consideration should be given to use of a water-soluble statin in combination therapy, as these statins penetrate muscle poorly. That being said, it should be noted that the lipid-soluble atorvastatin has been used successfully with fenofibrate to achieve lipid targets in a small diabetic population without complication.[39]

Combination therapy with bile acid sequestrants was problematic in the past because the nonspecific binding of resins interfered with the pharmacokinetics of other drugs. The more specific binding of colesevelam reduces this problem. In addition to being useful adjuncts that lower the required dose of statins or other drugs in a given patient, nonsystemic lipid-lowering agents such as colesevelam and ezetimibe are attractive for adolescent patients and women of child-bearing potential.

Summary: An Integrated Approach to Dyslipidemia

As the treatment options in antiatherosclerotic therapy become more varied, they also become more complex, bordering on being too complex to be practical for busy clinicians to implement. At the same time, it is clear that we should customize therapy to the individual needs of our patients, such as those with the metabolic syndrome. Fortunately, there is a simple treatment algorithm for dyslipidemia that conforms to the national guidelines, provides aggressive treatment, and is in keeping with the state of the art of our knowledge of the role of lipids in atherosclerosis.

Step 1: TLCs

Most Americans are overweight or obese. Losing 10% of ideal body weight by a method of the patient's choice and exercising 30 minutes per day are achievable goals. The most successful patients will exercise for an hour a day. This level of exercise is optimal, but this represents a significant effort beyond the level of commitment of most patients.

Step 2: Use a Statin to Lower LDL-C < 130 mg/dL

The Heart Protection Study provides evidence that all patients with dyslipidemia benefit from statin therapy, regardless of their baseline LDL-C. However, 4S, WOSCOPS, LIPID, the Pravastatin Pooling Project, and AFCAPS/TexCAPS all argue against titrating LDL-C to a given level. In 4S, CARE, and ALLHAT, no significant further benefit was seen once LDL-C fell below 130 mg/dL. It seems clear that we should lower LDL-C below 130 mg/dL in virtually all patients with a statin. Once this modest LDL-C target is achieved, attention should shift to TG and HDL-C.

Step 3: Lower TG Below 150 mg/dL with Fish Oil, a Fibrate, or Niacin

Targeting TG not only alleviates the hypercoagulable state induced by hypertriglyceridemia, but also shifts the LDL phenotype toward larger more buoyant particles and raises HDL-C

levels. While TLCs can normalize TG levels, most patients will need pharmacologic therapy as well. Fibrates are particularly useful here. Once TG are ≤ 150 mg/dL, advanced lipid testing can be used to determine which patients should be even more aggressively treated. If a patient has an LDL phenotype pattern B, the appropriate TG target may be 100 mg/dL or lower.

Step 4: Raise HDL-C Above 40 mg/dL with a Fibrate or Niacin

This is the most difficult lipid goal. Niacin and fenofibrate are the most effective pharmacologic weapons in our armamentarium to raise HDL-C, but the effects of smoking cessation, weight loss, and exercise should not be overlooked.

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CME Questions

13. Large, prospective, randomized trials that substantiate an LDL-C goal of 100 mg/dL include:
    a. 4S.
    b. LIPID.
    c. WOSCOPS.
    d. AFCAPS/TexCAPS.
    e. None of the above

14. Hypertriglyceridemia is associated with all of the following *except*:
    a. small, dense LDL particles.
    b. low levels of HDL-C.
    c. increased cardiovascular risk.
    d. a prothrombotic state (elevated fibrinogen and PAI-1 levels).
    e. lower high sensitivity C reactive protein (hsCRP) levels.

15. Lipoprotein (a) can be lowered by:
    a. statins.
    b. fenofibrate.
    c. fish oil.
    d. niacin.
    e. a and c
    f. b and d
    g. None of the above

16. Current guidelines set a body weight target of:
    a. achievement of ideal body weight.
    b. achievement of 120% of ideal body weight.
    c. loss of 10% of body weight.
    d. return to the patient's weight at age 25.
    e. sustained weight loss of 5 lbs/y.

17. The safest and most effective therapy for dyslipidemia are:
    a. therapeutic lifestyle changes (TLCs).
    b. statins.
    c. fibrates.
    d. niacin.
    e. resins.

18. Effective strategies for combination therapy include:
    a. adding fibrate or niacin first, then adding a statin in mixed dyslipidemia.
    b. using a water soluble statin.
    c. cutting the dose of the statin in half when initiating a fibrate.
    d. choosing fenofibrate over gemfibrozil when using a fibrate with a statin.
    e. All of the above

Answers: 13.(e); 14.(e); 15.(f); 16.(c); 17.(a); 18.(e)

In Future Issues:

The Skinny on Best-Seller Diets—John La Puma, MD, FACP