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Hyperlipidemia: How low can you go?

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Hyperlipidemia: How low can you go?

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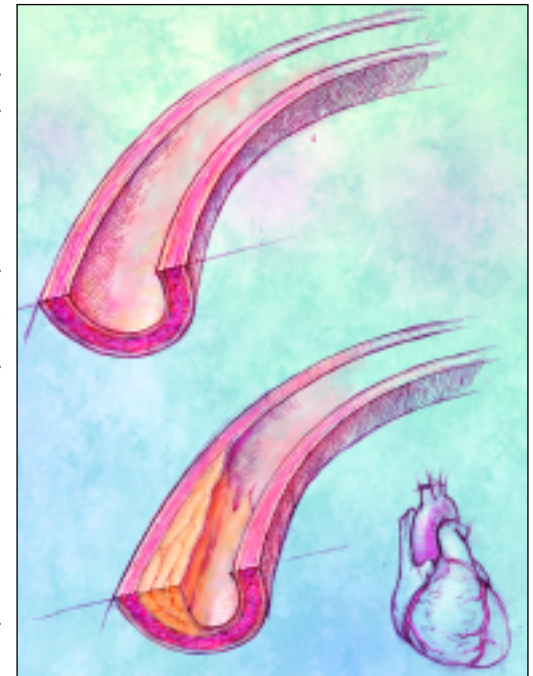
Antilipemic therapy has become a cornerstone in the treatment and prevention of coronary heart disease (CHD). Pharmacist-run hyperlipidemia clinics have become an integral part of managing patients with abnormal lipid profiles. However, new data are accumulating that influence the treatment of these patients. In order to ensure adequate treatment of these individuals, it is important to remain current with this information. What follows is a summary of the latest findings.

Impact of CHD and occurrence of hyperlipidemia

CHD remains the No. 1 cause of death in the United States. Approximately one million individuals have either a new or recurrent CHD-related event annually, and of these, 40% are fatal. Despite these statistics, control of hyperlipidemia remains sub-optimal. Analysis of the latest National Health & Nutrition Examination Survey (NHANES 1999-2000) demonstrates that decreases in total cholesterol (TC) concentrations in adults 20 years old or older are slowing. Compared with a TC decrease of 8 mg/dl

in the time periods of 1976-1980 and 1988-1994, TC decreases in 1988-1994 and 1999-2000 were 1.7 mg/dl.

Only 69.5% of patients in NHANES had their total cholesterol measured. Of these, 50.5% had a TC of 200 mg/dl or more. Of the patients with elevated cholesterol, 35% were aware of their condition, 12% were receiving treatment, and 5.4% had a TC of less than 200 mg/dl.



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GOAL

To understand the implications of the most recent findings on lipid-lowering therapy as they apply to safe and effective treatment of patients

CREDIT

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES

Upon completion of this article, the pharmacist should be able to:

- ✓ Determine appropriate lipid-lowering goals based upon risk stratification
- ✓ Understand the most recent clinical findings and apply them to goals for lipid-lowering therapy
- ✓ Select appropriate antilipemic therapy based on an individual patient's baseline lipid profile, lipid-lowering goals, and risk for adverse drug reactions
- ✓ Compare and contrast antilipemic agents with respect to efficacy and side effects
- ✓ Monitor antilipemic therapy appropriately in light of the most recent research findings and recommendations

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

The recent evidence underscores the need for improved control, and these statistics demonstrate ample opportunity to intervene.

Summary of NCEP-ATP III

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, & Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) continues to emphasize low-density lipoprotein (LDL) cholesterol as the primary treatment goal.

While continuing focus on individuals with existing CHD, additional emphasis highlights primary risk reduction in individuals with a high risk for developing CHD. ATP III considers these individuals to have CHD risk equivalents and sets goals equivalent to those of CHD patients (see Table 1). Diabetes has been elevated from a risk factor to a CHD risk equivalent due to the high 10-year CHD-related event incidence and the high rate of associated mortality. Risk assessment in patients without CHD or risk equivalents involves two steps. The first step is to assess an individual patient's risk factors. If multiple (two or more) risk factors exist, Framingham risk scoring is used to calculate 10-year risk for developing CHD (available at www.nhlbi.nih.gov/about/framingham/riskabs.htm).

The risk score is based on data gathered from the Framingham Heart Study, which included a predominantly Caucasian population in Massachusetts. The Framingham risk score assigns points in a step-wise fashion using the following risk factors (in order of consideration): age, either LDL or total cholesterol concentration, high-density lipoprotein (HDL), blood pressure, diabetes, smoking status, and presence of diabetes. The higher the score, the greater the risk of CHD in the next 10 years. If the risk is more than 20%, the patient is considered to have CHD equivalency. For patients without CHD or CHD equivalents, the number of risk factors and the 10-year risk determine the LDL goal.

ATP III introduces non-HDL cholesterol—LDL + very-low-density lipoprotein (VLDL)—as a secondary goal after LDL is controlled. It reserves low HDL as a tertiary goal due to a lack of evidence demonstrating benefit from increasing HDL. To reach goals, ATP III emphasizes therapeutic lifestyle changes (TLC) as the cornerstone of therapy. These include reduced intake of saturated and trans fatty acids, increased physical activity, and weight control. The panel recommends these modifications regardless of LDL goal and as a measure to decrease population risk for CHD. As with previous ATP guidelines, initiation of medication with TLC is dependent upon risk stratification and baseline LDL.

Life after NCEP ATP III

ATP III was released in 2001; five landmark trials and prospective epidemiological studies released since then address issues that were unanswered at that time. Taken together, these data suggest that current LDL goals are inadequate to reduce the incidence of CHD. Indeed, the ATP III emphasis on an LDL of less than 100 was meant to be a threshold for benefit, not the goal of maximum benefit.

Only one of these trials, the Antihypertensive & Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) failed to demonstrate a significant decrease in CHD in patients with hyperlipidemia, hypertension, and at least one additional risk factor. This may be because the lipid arm of the trial was unblinded, and patients were permitted to cross between the placebo and antilipemic treatment arms. In contrast, the lipid-lowering arm of the Anglo-Scandinavian

Table 1
CHD risk equivalents

- Clinical atherosclerotic disease: peripheral arterial disease, aortic abdominal aneurysm, symptomatic carotid artery disease
- Diabetes mellitus
- Multiple risk factors conferring a Framingham 10-year risk >20%:
 - Cigarette smoking
 - Hypertension (blood pressure \geq 140/90 mmHG or on antihypertensive medications)
 - Low HDL cholesterol (<40 mg/dl)
 - Family history of premature CHD in a first-degree relative (male <55 years; female <65 years)
 - Age (men \geq 45 years; women \geq 55 years)

Cardiac Outcomes Trial (ASCOT) demonstrated such a significant decrease in non-fatal myocardial infarction (MI) and fatal CHD in the treatment group that the trial was halted early. Patients had hypertension and three additional CHD risk factors, and average follow-up was 3.3 years (vs. the originally planned five years). The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) extended the beneficial effects of statins on cardiovascular disease (CVD) to older (70-82) patients.

The final two trials challenge the current LDL goals in high-risk patients. The Pravastatin or Atorvastatin Evaluation and Infection-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) randomized patients who had acute coronary syndrome to receive either “standard” LDL-lowering therapy (pravastatin 40 mg daily) or intensive therapy (atorvastatin 80 mg daily). After two years of therapy, patients in the intensive therapy group had a significantly lower incidence of a composite coronary endpoint (death from all causes, MI, documented unstable angina requiring rehospitalization, revascularization, and stroke). Standard therapy reduced LDL to 92 mg/dl, whereas intensive therapy lowered LDL to 62 mg/dl. Although the results suggested that intensive LDL reduction decreases the risk for coronary events, patients with lower baseline LDLs (<125 mg/dl) had more modest reductions and did not have significantly fewer coronary events.

The Heart Protection Study (HPS) randomized patients with coronary disease, other occlusive arterial disease, or diabetes to receive either 40 mg of simvastatin daily or placebo. After five years of follow-up, all-cause mortality, major vascular events, coronary-

Table 2
Modified NCEP-ATP III goals

	Goal	Start medication
Primary goal: LDL	LDL goal (mg/dl)	LDL (mg/dl)
High risk (CHD or equivalent)	<100; optional <70	≥100 (consider if <100)
Moderately high risk (≥2 risk factors; 10-year risk 10%-20%)	<130; optional <100	≥130 (consider if 100-129)
Moderate risk (≥2 risk factors; 10-year risk <10%)	<130	≥160
Lower risk (0-1 risk factors; 10-year risk <10%)	<160	≥190
Secondary goal: non-HDL cholesterol (LDL + TG/5)	30 mg/dl above LDL goal	
Tertiary goal: HDL	>40 mg/dl	Not known

Adapted from Grundy et al. *J Am Coll Cardiol* 2004;44:720

related deaths, nonfatal MI + coronary-related death, and nonfatal and fatal stroke were significantly reduced in the treatment group. The results were similar regardless of CHD, arterial disease or diabetes, gender, or age. The benefit appeared to extend over the range of baseline LDL and was comparable in groups with LDLs of ≥ 135 mg/dl, <116 mg/dl, and <100 mg/dl. Not all the study data are available yet, so the exact significance of these results is not yet known.

Implications of recent findings

The results of post-ATP III trials led the NCEP Coordinating

Committee to release a statement in 2004 suggesting updates to the ATP III guidelines (see Table 2). This statement was endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association (AHA). When taken together with prospective epidemiologic data, the recent findings demonstrate a positive correlation between LDL and risk for CHD.

The relationship appears to be logarithmic rather than linear; risk rises steeply with LDL. This means that patients with the identical risk factors for CHD (or absolute risk) will experience the same absolute benefit per mg/dl LDL lowering relative to their baseline LDL. This benefit amounts to a 1% reduction in CHD risk for every 1 mg/dl LDL lowering obtained. This also means that patients who start with a low baseline LDL have a lower risk for CHD and receive more modest effects from LDL reduction. For example, if a patient has a baseline LDL of 160, his relative risk of CHD is approximately 2.5 that of the general population. If the patient's LDL is lowered 50%, to 80 mg/dl, the risk is also lowered by 50%, to 1.25. On the other hand, if a patient starts with an LDL of 100 mg/dl, the risk is closer to 1.7. Lowering the LDL 50%, to 50 mg/dl, lowers the risk to 1.0, a reduction of 0.7.

When ATP III was released, it was unknown whether the benefit of LDL-lowering extended below 100 mg/dl, and whether the benefits outweighed the risks. Both HPS and PROVE-IT suggest, but do not definitively prove, that the reduction of CHD does extend below current LDL goals for patients in the moderately high to high-risk categories. It is currently unknown what the "basement" LDL goal for this benefit is. Ongoing trials should shed more light on this issue. As a result of recent data, the panel suggests an optional LDL goal of <70 mg/dl in patients with CHD or CHD equivalent, particularly if they also have acute coronary syndrome. In patients with two or more risk factors and a 10-year risk score of 10%-20%, the suggested LDL goal is <100 mg/dl (see Table 2).

Diabetes mellitus and LDL goals

As many as 80% of patients with diabetes will develop or die of macrovascular complications, including CHD. It was for this reason that diabetes was elevated from a risk factor for developing CHD to a CHD risk equivalent. A meta-analysis of the data available for large-scale clinical trials indicates that the number (of patients) needed to treat (NNT) for prevention of CHD-related events in patients with preexisting CHD (secondary prevention) is 13.8 over an average of 4.9 years. Primary prevention, although not as robust, yields an NNT of 34.5 over 4.3 years.

Even with this knowledge, the optimal LDL goal for patients with diabetes is nebulous. Patients with diabetes and CHD derived the most benefit from statin therapy in HPS. An LDL <70 mg/dl is a reasonable option in these patients. Patients without CHD but who had diabetes and a baseline LDL <116 mg/dl derived only marginal benefit from intensive statin therapy. The NCEP update panel recommended clinical judgment when initiating medication at an LDL of <100 mg/dl in this population.

A statement released by the American College of Physicians supports the LDL goal of <100 mg/dl in both primary and secondary prevention. It recommended statins as first-line therapy in diabetes, because this class of medications has the most evidence of benefit. It also recommended that at least moderate doses of statins be used. For primary prevention, it recommended doses of atorvastatin (Lipitor) 20 mg/day, lovastatin 40 mg/day, pravastatin 40 mg/day, or simvastatin 40 mg/day. For secondary prevention, the college recommended statin doses used in clinical trials: fluvastatin (Lescol) 80 mg/day, lovastatin 40-80 mg/day, pravastatin 40 mg/day, or sim-

Table 3

Comparison of statins

Agent	Equivalent dose	Hydrophilic?	CYP metabolism
Rosuvastatin (Crestor)	5 mg/day	Yes	2C9
Atorvastatin	10 mg/day	No	3A4
Simvastatin	20 mg/day	No	3A4
Lovastatin	40 mg/day	No	3A4
Pravastatin	40 mg/day	Yes	—
Fluvastatin	80 mg/day	No	2C9

vastatin 20-40 mg/daily.

Meeting LDL goals

The newly suggested goals may be a challenge to meet, particularly with statin monotherapy in patients with dramatically elevated baseline LDLs. Table 3 lists the doses of the currently available statins needed to achieve a dose reduction of 30% to 40%. Each additional dose increase of an individual agent decreases LDL by approximately an additional 6%.

Even high-dose statins rarely achieve the >50% reduction needed in these patients. Treatment may, therefore, involve combination therapy.

Implementation of TLC is an integral part of the therapeutic plan in patients who need dramatic LDL reduction. The benefits of the AHA Step I and II diets were previously documented. New data suggest benefits of dietary soluble fiber (found in oats, barley, psyllium, eggplant, and okra) and plant stanols and sterols (see Table 4). In patients placed on an AHA Step II diet, the addition of a dietary portfolio (including per 1,000 kcal/day: 1 gm plant sterols, 9.8 gm soluble fiber, 21.4 gm soy protein, and 14 gm whole almonds) was superior to placebo and comparable to lovastatin 20 mg daily. Both resulted in an approximate 30% LDL reduction.

Although not associated with LDL reduction, exercise involving endurance training (aerobic activity) is associated with reduction in triglycerides (TG) and an increase in HDL. In addition, physical activity changes the LDL profile from the more atherogenic small, dense LDLs to less-dense forms. Moderate- to high-intensity activity is recommended for 30-60 minutes daily on five to seven days of the week. While exercise itself does not lower LDL, weight loss can. As little as 10 lb. of weight reduction can have a dramatic effect on both LDL and TG.

Table 4
Antilipemic agent comparison

	TC	LDL	HDL	TG
TLC				
AHA low-saturated-fat diet		-8%-10%		
Dietary cholesterol <200 mg/day		-3%-5%		
5-10 gm/day viscous (soluble) fiber		-3%-5%		
2 gm/day plant stanols or sterols		-6%-15%		
10-lb. weight loss		-5%-8%		
Exercise		no effect	+4%-22%	
SINGLE AGENTS				
Gemfibrozil 600 mg b.i.d.	-10%	no effect	+10%-15%	-20%-50%
Fenofibrate 145 mg	-18.7%	-20.6%	+11.0	-28.9%
Ezetimibe 10 mg	-12%	-18%	+8%	+1%
Niacin				
1,000 mg	-3	-5	+18	-21
1,500 mg	-8	-12	+20	-13
2,000 mg	-10	-14	+22	-28
Colesevelam				
3.8 gm	-7	-15	+3	+10
4.5 gm	-10	-18	+3	+9
ADJUNCTIVE TO STATIN THERAPY				
Colestipol/cholestyramine	-10%	-10%	+12%	+12%
Colesevelam	-10%	-10%	+3%	-1%
Ezetimibe	-17%	-25%	+2%-3%	-14%
Niacin	-10%	-15%-25%	+25%	-30%
Adapted from White CM et al. <i>PSAP V</i> . 2004. ACCP: Kansas City.				

If TLC alone or a TLC/statin combination is inadequate to meet LDL goals, combination medication may be needed. The lipid-lowering capabilities of nonstatin medications are presented in Table 4. Combination therapy can be specifically tailored to fit individual lipid abnormalities. If LDL is the specific target, a bile acid sequestrant (e.g., cholestyramine, colestipol, or colesevelam [Welchol]) or a cholesterol-absorption inhibitor (ezetimibe [Zetia]) may be appropriate. The dyslipidemia commonly associated with diabetes involves elevated TG, TC, and non-HDL cholesterol accompanied by low HDL. This dyslipidemia may respond better to a statin-niacin or statin-fibrate combination. Although niacin use is associated with glucose elevations, it has been effective in patients whose glucose control is monitored. To avoid the myopathy associated with the statin-fibrate combination, fenofibrate should be used instead of gemfibrozil.

Side effects associated with statin therapy

Although statins are the single most potent agents for lowering LDL, they also raise concerns for side effects. Both hepatotoxicity and myopathy have received much attention. Case reports have also highlighted concern over additional side effects such as neuropathy. The National Lipid Association (NLA) Statin Safety Task Force recently released recommendations regarding these side effects and suggested guidelines for monitoring patients.

Hepatotoxicity: Statin-related asymptomatic elevations in the liver enzymes aspartate aminotransferase (AST) or alanine aminotransferase (ALT) are dose-related, but unrelated to the degree of LDL reduction. The incidence of elevation more than three times the upper limit of normal (ULN) in patients receiving statins is <1% in low to moderate doses and approximately 2% to 3% in high doses. It also appears to be transient in 70% of cases, even if the dose of statin is continued. Despite these elevations, serious liver dysfunction and liver failure have never been definitively tied to statin therapy. The inci-

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dence, approximately one case in one million, does not differ from that seen in the general population. Because prescribing information for marketed statins has not changed, recommendations for monitoring liver function tests (LFTs) are based more on medical-legal issues than supporting clinical data. Current recommendations include LFT monitoring at baseline, 12 weeks, after a dose increase, and periodically thereafter. If results of LFTs are found to be more than three times ULN, the test should be repeated. If the results are still elevated, other causes should be ruled out before reducing the statin dose or discontinuing it.

Myopathy: Muscle symptomatology, or myopathy, is the most frequent and most important side effect associated with statin therapy. It encompasses a constellation of disorders, including symptomatic myopathy (muscle pain, weakness, or cramps), creatine kinase (CK) elevations without symptoms (asymptomatic myopathy), and rhabdomyolysis (change in renal function with CK elevation). Rhabdomyolysis is further classified into mild (CK elevations <10 times ULN), moderate (≥ 10 but <50 times ULN, regardless of renal function) and marked (≥ 50 times

Table 5
Factors for nonadherence and predictors for improved adherence

Decreases adherence	Improves adherence
Time from therapy initiation (decreased persistence)	Rapid attainment of goal LDL Follow-up tests Follow-up visits
Medication cost	Use formulary agents Utilize generics Pill-splitting
Fear of adverse effects outweighs perceived benefits	Motivational interviewing –open-ended questions –respect patient health beliefs –tailor education to patient –actively involve patient in treatment plan Increase provider access between appointments Regular follow-up Determine temporal relationship
Patient experiences adverse effect	Determine severity Rule out other causes Education re: benefits versus risks Drug discontinuation/retrial Switch to different agent

ULN).

Although statin-induced myopathy does not appear related to the degree of lipid-lowering, myopathy has been reported, albeit rarely, with niacin, fibrates, and ezetimibe monotherapy. Indeed, analysis of the multicenter, intensive lipid-lowering trials such as HPS and PROVE-IT fails to reveal an increased incidence of myopathy. Incidence in statin therapy does appear to be dose related and is influenced by blood concentrations and CYP metabolism status. Risk factors include age >70 years, impaired renal function (creatinine clearance <20 ml/min), female gender, small body frame or frailty, untreated hypothyroidism, and sedative hypnotic/alcohol abuse.

Although data are currently lacking, a relationship has been suggested between statin-induced myopathy and the following: surgery, diabetic proteinuria, baseline CK concentrations, acute illness or infection, during vigorous exercise, or certain ethnic/racial groups (such as Asians). Caution should still be exercised under these conditions until more concrete data are available.

Drug interactions can also increase the risk for myopathy. Lovastatin, atorvastatin, and simvastatin are all metabolized by 3A4,

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and concomitant therapy with CYP 3A4 inhibitors increases the risk of myopathy. The simvastatin and lovastatin package inserts advise against concomitant administration of the 3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, protease inhibitors, nefazodone, or more than one quart grapefruit juice/day. If one of these inhibitors must be given, the manufacturers recommend suspending simvastatin or lovastatin therapy, particularly if dosed at the higher end of the therapeutic range. If given with cyclosporine, danazol, gemfibrozil, or > 1 gm niacin/day, the maximum daily doses of simvastatin and lovastatin should not exceed 10 mg or 20 mg, respectively. Gemfibrozil, but possibly not fenofibrate, appears to interfere with the metabolism of simvastatin and atorvastatin, possibly causing the formation of an unstable glucuronide. Thus, combination with fibrate therapy should be done with extreme caution. The maximum daily doses of simvastatin and lovastatin should not exceed 20 mg or 40 mg, respectively, if given with amiodarone or verapamil.

The exact etiology of myopathy is not currently understood. It is thought to be tied to intramuscular statin concentrations. While the relationship of blood levels to myopathy suggests support of this theory, actual intramuscular statin concentration data are lacking. A switch to a more hydrophilic statin (see Table 3) is not an unreasonable option, but myopathy has been reported with all statins. The point at which statins block cholesterol synthesis also inhibits the production of numerous other substances necessary for normal cellular function.

One of these substances is ubiquinone (coenzyme Q10, or CoQ10). CoQ10 is needed for energy production and cell stability. Diet is a poor source of CoQ10, so biosynthesis is the main means of production. Current data are unclear as to the relationship between statins and intracellular CoQ10 concentrations. Serum and intramuscular CoQ10 levels do not correlate. Intramuscular CoQ10 levels are not decreased by low statin doses in nonmyopathic patients, but 80-mg doses of both simvastatin and atorvastatin decreased both intramuscular CoQ10 lev-

els and mitochondrial volume (where most CoQ10 is synthesized). Studies also demonstrated that patients with myopathy have decreased intramuscular CoQ10 levels. These patients appear to have decreased symptoms with CoQ10 supplementation, but the data are preliminary. Thus, routine CoQ10 supplementation isn't recommended at this time, although it is not unreasonable, so long as a patient chooses a reliable product with good quality control.

Currently, it is not recommended to routinely monitor CK levels. It is reasonable to obtain a pretreatment level, particularly in high-risk patients. Counsel patients on muscle symptoms. If myopathy develops, other causes should be ruled out before discontinuing the statin, unless lab work suggests rhabdomyolysis. In patients with a CK <10 times ULN and no evidence of change in renal function, the statin can be continued. If the patient has intolerable muscle symptoms, the statin should be discontinued until the patient is asymptomatic, and then a retrial attempted. If the patient has recurrent symptoms, a trial of an alternate statin should be attempted. If the patient has symptoms with multiple agents, another lipid-lowering agent should be used.

Other side effects

Although case reports of decreased renal function and renal failure have been reported with statin therapy without rhabdomyolysis, current clinical data fail to establish causality. The incidence appears no different from that of the general population. It is not recommended to routinely monitor serum creatinine or for proteinuria. If a patient develops renal dysfunction during statin therapy, there is no need to discontinue the statin. Chronic kidney disease does not contraindicate statin use, but these patients may need to be more closely monitored for myopathy.

Peripheral neuropathy has been reported in patients taking statins. The incidence appears very rare, with an odds ratio of 1.8 by meta-analysis. If a patient develops neuropathy while on a statin, other causes should be ruled out before the statin is discontinued. Therapy with

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another statin should be considered if causality occurs.

Adherence to antilipemic medication

Clinical data from the West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated that patients taking >75% of their prescribed statin had a mortality reduction one-third greater than that of those taking <75%. An additional clinical trial in more than 5,500 patients demonstrated a lower risk of MI in patients who were >80% compliant with their statin. Adherence studies suggest a much lower rate of continuation therapy. Although patients taking statins are more likely to continue taking their medication than those on nonstatins, adherence is still below therapeutic rates. Examination of claims data in both New Jersey and Quebec in the early 1990s demonstrated a one-year statin adherence rate of 64.3%, well below the threshold for benefit. None of the patients in this study paid anything out of pocket for their medication.

In patients with coronary artery disease (CAD), only 41% took their statins regularly. Discontinuation rates increase over time and are predictably influenced by insurance coverage. In one study, the 12-month discontinuation rate was 39%, increasing to 57% at 18 months. Patients who had an annual \$1,000 medication benefit maximum were more likely than those with full coverage to discontinue therapy, although the 21-month discontinuation rate in the latter was still 60%. In a 36-month study, the percentages of patients taking >80% of their statin doses were 59%, 40%, 34%, and 21% at three, six, 12, and 36 months, respectively. Adherence varied inversely with the degree of LDL control obtained within the first three months, with patients achieving the most LDL-lowering being 1.15-1.26 times more likely to continue therapy. The decrease in adherence over time has significant repercussions on the benefits of statin therapy, which can take two to five years to have a significant effect on CHD-related events.

The length of statin therapy influences the economic impact. Long-

term data are lacking, but one-year data fail to demonstrate any medical cost savings. Thus, persistence of statin therapy must continue for multiple years to realize any cost savings. Assuming a 100% adherence rate and LDL goal achievement, projected cost savings could range from approximately \$30,000 to \$260,000 per life year saved (LYS) for primary prevention and \$1,200 to \$40,000 for secondary prevention, depending upon patient age and gender. These data suggest that patient nonadherence with therapy contributes significantly to the failure to impact population lipid profiles as demonstrated by NHANES.

Impact of pharmacists on outcomes

If data suggest the extent of patient nonadherence, they also suggest ways to improve the success of antilipemic therapy. Patients with manifestations of CHD who are adherent with antilipemic therapy within the first three months are more likely to continue taking medication over the long term. Patients who have regular physician visits and follow-up lab work are also more likely to be adherent. Rapid achievement of LDL goals (within the first three months) may also improve adherence. Statin therapy is also associated with lower discontinuation rates than other therapies. Cost of therapy and insurance coverage will also impact therapy.

The current hyperlipidemia picture is ripe with opportunities for pharmacist intervention. Because lovastatin, pravastatin, and simvastatin are all available as generics, the simple education of physicians and patients may go a long way toward cost savings, particularly in elderly patients on Medicare Part D plans. Tablet-splitting has also been shown to be neutral in effect on the lipid profile and can be used as a further saving for cash-paying patients. Refill reminders, courtesy calls, and three-month fills (when possible) may also improve patient success.

The real potential for pharmacist impact is in collaborative practice. In its recommendations, ATP III suggests state-of-the-art multidisciplinary

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nary approaches to achieve LDL goals. Among its options is collaborative care with pharmacists. It also recommends electing a physician office advocate to help deliver or prompt care. Pharmacists can become that advocate through collaborative practice agreements. Several studies have documented benefits from incorporating pharmacists into the treatment of hyperlipidemia. In one study, clinical pharmacists practicing under a collaborative prescriptive protocol achieved a 5% to 22% greater reduction in LDL than did usual care. The magnitude of LDL reduction was directly related to the number of clinical pharmacy visits, but not usual office visits.

In a larger patient population, clinical pharmacists operating under physician-approved plans were able to attain a goal LDL <100 mg/dl in 72% (versus 18% of controls) of patients with CHD in 6.5 months. At 18 months after discontinuation of the services, the mean LDL in the treatment group remained stable at 95 mg/dl (versus 111 mg/dl in controls).

Pharmacists can also transcend the office and become community champions for ensuring that patients at risk achieve optimal lipid-lowering. Several studies have documented pharmacist ability to improve patient compliance with antilipemic therapy. In one study, pharmacists identified a 35.5% rate of nonadherence in their patient population. They were able to improve nonpharmacologic therapy adherence in 48.3% of these cases and medication adherence in 21.6%, bringing the adherence rate within the range of therapeutic benefit.

In the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP), the impact of the community pharmacist on patient out-

comes was so dramatic that the study was halted early. Patients in the study had CHD or CHD risk equivalents and were randomized to receive usual care or intervention by a clinical pharmacist. The patients in the intervention group had a significant increase in cholesterol risk management, as evidenced by an increase in prescriptions for antilipemic medication initiation or dose adjustments and significantly more fasting lipid profiles. An extension of this study, SCRIP-plus, improved patient adherence to >80%.

Table 5 offers some suggestions for improving patient adherence based upon the presenting reason for nonadherence. Many of these methods have demonstrated effectiveness in clinical trials.

Conclusions

Meeting the current LDL goals can be a challenge for the busy clinician. Because lipid-lowering is fraught with drug interaction-driven adverse effects and pharmacodynamic nuances, pharmacist expertise can only augment effective therapy. The benefit of pharmacist inclusion as a member of a patient's lipid control team has already been documented. This role should continue to be crucial as ongoing clinical trials clarify the extent of optimal lipid control.

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White CM, McBride BF, Kalus JS. Dyslipidemias. In: *Pharmacotherapy Self Assessment Program (PSAP)*, 5th edition. 2004. American College of Clinical Pharmacy (ACCP): Kansas City. pp. 165-190.

References are available upon request.

TEST QUESTIONS

Mark the most appropriate answer. The answer form follows the test questions.

1. According to ATP III, the LDL goal for a patient with diabetes is:
a. <190 mg/dl c. <130 mg/dl
b. <160 mg/dl d. <100 mg/dl
2. After determining the presence of CHD or CHD equivalents, which of the following is no longer considered a factor for risk stratification?
a. Diabetes
b. Hypertension
c. HDL
d. Family history of premature heart disease
3. Which of the following is the primary goal of ATP III?
a. Lower non-HDL cholesterol c. Lower LDL
b. Lower total cholesterol d. Increased HDL
4. Which of the following studies influenced the change in LDL goal in high-risk patients?
a. ALLHAT c. ASCOT
b. HPS d. PROSPER
5. According to recent findings, each 1% reduction in LDL leads to how much reduction in CHD risk?
a. 1% c. 5%
b. 2% d. 10%
6. Which of the following conditions should receive the highest priority for an LDL goal <70 mg/dl?
a. Peripheral vascular disease
b. Diabetes mellitus
c. A smoker with hypertension and an HDL of 30 mg/dl
d. Acute coronary syndrome
7. Which of the following is *not* a source of soluble fiber?
a. Wheat bran c. Eggplant
b. Barley d. Psyllium
8. Which of the following has no effect on LDL?
a. A low-fat diet c. Plant stanols
b. Aerobic exercise d. A 10-lb. weight loss
9. Which of the following statins is most potent on a milligram-for-milligram basis?
a. Pravastatin c. Rosuvastatin
b. Lovastatin d. Simvastatin
10. Which of the following agents would be the best adjunct to add to a statin in a patient with diabetic-type dyslipidemia?
a. Niacin c. Colestipol
b. Gemfibrozil d. Ezetimibe
11. A patient following TLC and taking 80 mg of simvastatin daily has a fasting lipid profile that includes LDL 112 mg/dl, HDL 70 mg/dl, and non-HDL 133 mg/dl. His goal is an LDL <100 mg/dl. Which of the following agents would be the best adjunct?
a. Niacin c. Ezetimibe
b. Gemfibrozil d. Fenofibrate
12. According to the ATP III, which of the following is the cornerstone of antilipemic therapy?
a. A statin c. Soluble fiber
b. Fenofibrate d. TLC

TEST QUESTIONS

- 13.** Which of the following is a serious side effect of statins?
- a. Liver failure
 - b. Neuropathy
 - c. Rhabdomyolysis
 - d. Muscle soreness
- 14.** According to clinical evidence, how often should LFTs be monitored?
- a. No routine monitoring is necessary
 - b. Every three months
 - c. At baseline and annually
 - d. At every dose increase
- 15.** According to current guidelines, when should a statin be discontinued?
- a. If LFTs are more than three times ULN
 - b. If LFTs are more than three times ULN on two occasions
 - c. If the patient has other known causes of hepatotoxicity
 - d. Only after other causes have been ruled out
- 16.** If a patient presents with mild muscle pain after lifting weights and has a CK three times the ULN, which of the following is appropriate?
- a. Stop the statin and switch to a nonstatin antilipemic
 - b. Request that the physician refer the patient for a workup
 - c. Supplement with CoQ10
 - d. Continue the statin at the current dose
- 17.** Which of the following statins is hydrophilic?
- a. Simvastatin
 - b. Pravastatin
 - c. Atorvastatin
 - d. Simvastatin
- 18.** Which of the following statements regarding CoQ10 and statins is true?
- a. CoQ10 reverses myopathy.
 - b. The main source of CoQ10 is dietary.
 - c. Simvastatin 80 mg/daily has reduced intramuscular CoQ10.
 - d. Oral CoQ10 can be recommended to treat myopathy.
- 19.** Which of the following contraindicates simvastatin therapy?
- a. Chronic liver disease
 - b. Ketoconazole
 - c. Marathon running
 - d. Renal insufficiency
- 20.** Which of the following lab tests is reasonable to monitor in an asymptomatic patient?
- a. LFT
 - c. Lipid profile

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ANSWER FORM

Hyperlipidemia: How low can you go?

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Test questions start on preceding page

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