

DECEMBER 2010



# Pharmacist<sup>®</sup>

## Pharmacy Perspectives in Dyslipidemia Management

Strategies for Improving Patient Outcomes



© Steve Oh, M.S. / Phototake

This activity is supported by an educational grant from Abbott Laboratories.  
CPE online testing available at [www.practicingclinicians.com/eclinic/testing](http://www.practicingclinicians.com/eclinic/testing)

## CONTINUING EDUCATION INFORMATION

**Target Audience:** Pharmacists

**Type of Activity:** Knowledge

**Program Description:** Despite evidence supporting the early implementation of aggressive lipid-lowering therapy in patients at risk for coronary heart disease (CHD), many patients are not being screened, started on appropriate therapy, or treated to target lipid levels. With their knowledge of lipid-lowering medications, treatment indications, optimal dosing, and safety issues, pharmacists are well-positioned to manage the medical treatment of patients with dyslipidemia. Pharmacists are highly accessible at both the point of medication dispensing and the point of care. Through effective patient education and monitoring, pharmacists can also improve medication adherence and treatment success, enabling more patients to reach their treatment targets.

### FACULTY

**Joel C. Marrs, PharmD, BCPS (AQ Cardiology), CLS**  
Assistant Professor  
University of Colorado Denver School of Pharmacy  
Department of Clinical Pharmacy  
Aurora, Colorado

### ACCREDITATION



Continuing Education Alliance is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is approved for 2.0 contact hours (0.2 CEUs).

® Universal Activity Number 0270-0000-10-003-H01-P

The providers of this program have waived the processing fees.

The estimated time to complete this activity is 2 hours.

**Release date:** December 1, 2010

**Expiration date:** December 1, 2012

This activity is supported by an educational grant from Abbott Laboratories.

**Faculty Disclosure:** All faculty and planners participating in continuing education activities sponsored by Continuing Education Alliance are expected to disclose to the audience any significant support or substantial relationship(s) with providers of commercial products and/or devices discussed in this activity and/or with any commercial supporters of the activity. In addition, all faculty are expected to openly disclose any off-label, experimental, or investigational use of drugs or devices discussed in this activity. The faculty and planning committee have been advised that this activity must be free from commercial bias, and based upon all the available scientifically rigorous data from research that conforms to accepted standards of experimental design, data collection, and analysis.

**Dr Marrs** has nothing to disclose with regard to commercial interests.

The Planning Committee for this activity included Ruth Cohen, Margaret Inman, Caitlin Prinsen, and Leslie Wald of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

**Disclaimer:** The opinions or views expressed in this CPE activity do not necessarily reflect the opinions or recommendations of Continuing Education Alliance, U.S. Pharmacist, or Abbott Laboratories.

### How to Receive Credit:

Participants wishing to earn CPE credit must:

1. Read the supplement.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and evaluation form online at: [www.practicingclinicians.com/eclinic/testing](http://www.practicingclinicians.com/eclinic/testing)

After login, please enter the code: CAE74310

Successful completion of the self-assessment is required to earn CPE credit. Successful completion is defined as a cumulative score of at least 70%. A certificate of credit will be automatically generated upon successful completion of the activity.

## U.S. Pharmacist Continuing Education

**GOALS:** To educate participants on treatment goals and appropriate medications for each type of dyslipidemia, to describe opportunities for pharmacists to collaborate with a health care team in managing patients with dyslipidemia, and to present methods of improving patient adherence.

**LEARNING OBJECTIVES:** After completing this activity, participants should be better able to:

- Differentiate among medical treatment options for optimizing lipid levels in patients with dyslipidemia, based on their CHD risk level and each agent's lipid-specific effects and safety profile
- Recognize barriers to effective dyslipidemia treatment, such as suboptimal dosing, titration failure, and potentially unsafe drug interactions or combinations that should be brought to the attention of the prescribing physician
- Educate patients about dyslipidemia and the importance of adherence to their treatment regimen

*Copyright 2010 by Jobson Medical Information LLC, 100 Avenue of the Americas, New York, NY 10013-1678. No part of this publication may be reproduced or transmitted by any means, electronic or mechanical, or stored in any storage and retrieval system, without permission in writing from the publisher. U.S. PHARMACIST (ISSN 01484818; USPS No. 333-490) is published monthly by Jobson Medical Information LLC, 100 Avenue of the Americas, New York, NY 10013-1678. Periodicals postage paid at New York, NY and additional mailing offices. Acceptance of advertising in U.S. PHARMACIST does not constitute endorsement of the advertiser, its products or services. The opinions, statements, and views expressed within this publication do not necessarily reflect those of Jobson Medical Information LLC or the editors of U.S. PHARMACIST.*



# Pharmacy Perspectives in Dyslipidemia Management

## Strategies for Improving Patient Outcomes

### Introduction

Dyslipidemia is a modifiable yet highly prevalent risk factor for atherosclerotic disease and its complications, including coronary heart disease (CHD), myocardial infarction (MI), stroke, peripheral vascular disease, and cardiac death. Among adults in the United States, 16.2%, or 35.7 million people, have serum total cholesterol (TC) levels  $\geq 240$  mg/dL, and 25.3% of adults have low-density lipoprotein cholesterol (LDL-C) levels  $\geq 160$  mg/dL.<sup>1</sup> Thus, one fourth of adults in the United States are candidates for lipid-lowering therapy.<sup>2,3</sup>

Dyslipidemia management typically focuses on controlling elevated LDL-C levels based on guideline recommendations, with a secondary focus on correcting other lipid levels such as non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, and triglycerides (TGs). Despite clear evidence linking dyslipidemia to preventable cardiovascular (CV) events, a wide gap separates national treatment recommendations and real-world lipid management. Data from the National Health and Nutrition Examination Survey (NHANES) for 2003 to 2004 indicate that less than half of adults (48%) had LDL-C, HDL-C, and TG values within ranges recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines

(TABLE 1).<sup>4</sup> Lipid profiles were worse among those with risk factors for poor CV outcomes, including patients with CV disease (CVD), diabetes, or chronic kidney disease. In this group, only one third had LDL-C and non-HDL-C levels within NCEP ATP III targets, and less than 1 in 5 (17%) were at goal for LDL-C, HDL-C, and TG. Undertreatment of lipid disorders appeared to contribute to these poor trends. Among all candidates for lipid-lowering therapy, only half were being treated with medications to lower lipid values.

Even patients who achieve target LDL-C levels are at risk for adverse CV outcomes. In 2009, Sachdeva and colleagues examined data from 136,905 patients who were hospitalized with CHD, including patients with acute coronary syndromes, with stable CHD hospitalized for revascularization, or with documented CHD hospitalized for reasons other than heart failure.<sup>5</sup> Before hospital admission, only 21.1% of patients were receiving lipid-lowering medications. Many patients who present to hospitals with CHD are well within current guideline-recommended targets for LDL-C. Nearly half of the hospitalized patients in the Sachdeva study had LDL-C levels  $< 100$  mg/dL at hospital admission, and 17.6% had LDL-C levels  $< 70$  mg/dL.<sup>5</sup> These findings support the need to update current treatment guidelines to factor in the role of more aggressive lipid goals for specific patient populations and highlight the contribution of lipid risk factors other than LDL-C to assess overall CV risk.

**Joel C. Marrs, PharmD, BCPS (AQ Cardiology), CLS**

University of Colorado School of Pharmacy  
Department of Clinical Pharmacy  
Aurora, Colorado

**Table 1. NCEP ATP III Lipoprotein Targets**

TC (mg/dL)		LDL-C (mg/dL)		TGs (mg/dL)		HDL-C (mg/dL)	
Desirable	<200	Optimal	<100	Normal	<150	Low	<40
		Near optimal	100-129				
Borderline high	200-239	Borderline high	130-159	Borderline high	150-199	High	≥40
High	≥240	High	160-189	High	200-499		
		Very high	≥190	Very high	≥500		

HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; TC: total cholesterol; TGs: triglycerides.

Source: Reference 2.

## POP QUIZ | LDL-C remains the strongest marker of CV risk.

- A. True
- B. False

### Shifting Focus to New Treatment Targets

Growing evidence indicates that lipoproteins other than LDL-C play an important role in atherogenesis, atherosclerotic vascular disease, and CV morbidity and mortality. To effectively intervene in CVD, it is important to understand which lipoproteins are most clinically relevant. In the landmark INTERHEART study, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, and sedentary lifestyle accounted for more than 90% of the worldwide risk of MI.<sup>6</sup> Of these risk factors, abnormal lipid levels were most strongly linked to MI. Findings from INTERHEART reinforced the importance of targeting modifiable risk factors—particularly abnormal lipid levels—in CVD prevention. A more recent analysis of INTERHEART focused on specific lipid parameters, including plasma lipids, lipoproteins, and apolipoproteins as indices of MI risk.<sup>7</sup> The fasting apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio was a better predictor of MI risk than other candidate markers, including LDL-C/HDL-C and TC/HDL-C ( $P < .0001$ ). Overall, the ApoB/ApoA1 ratio accounted for 54% of the population-attributable risk for acute MI, whereas the LDL-C/HDL-C ratio accounted for 37% and the TC/HDL-C ratio accounted for 32%. Each increase in 1 standard deviation of the ApoB/ApoA1 ratio was associated with a 59% increase in the risk of acute MI. These findings support the incorporation of ApoB and ApoA1 into clinical practice as potential assessments of cardiac risk beyond the usual fasting lipid panel. ApoB is a reasonable assessment tool if the number of atherogenic particles is perceived to be different from the non-HDL-C concentration. In most patients the non-HDL-C value correlates well with ApoB just as the HDL-C value correlates with ApoA1.

A recent pooled analysis of the Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) and Treating to New Targets (TNT) studies

highlights the importance of non-LDL-C lipid values in assessing patient risk.<sup>8</sup> In the IDEAL and TNT studies, patients with established CHD were randomly assigned to treatment with standard dose or high-dose statin therapy. In the pooled analysis, investigators identified the lipid variables most strongly predictive of the risk of major CV events, including CV death, nonfatal MI, and fatal or nonfatal stroke. As expected, on-treatment LDL-C levels were associated with a decrease in CV risk (HR 0.90;  $P = .04$ ) in the IDEAL and TNT studies. However, elevated non-HDL-C (HR 1.31;  $P < .001$ ) and ApoB (HR 1.24;  $P < .001$ ) were stronger predictors of CV outcomes during statin treatment and both represent composite markers of atherogenic particles. Among different ratios of proatherogenic to antiatherogenic lipoproteins, the ApoB/ApoA1 ratio had the strongest relationship with future CV events (HR 1.24;  $P = .001$ ).

In several other trials, HDL-C, non-HDL-C, and ApoB abnormalities have outperformed LDL-C as predictors of CVD and adverse CV events.<sup>9,10</sup> On the strength of these data, medical societies are embracing atherosclerotic markers other than LDL-C as important targets for treatment in patients with dyslipidemia. In 2008, the American Diabetes Association (ADA) and American College of Cardiology (ACC) recommended new lipoprotein targets for patients with cardiometabolic risk factors such as diabetes, obesity, hypertension, and dyslipidemia. Specifically, the ADA/ACC recommendations advocate more aggressive treatment of patients with cardiometabolic risk to lower LDL-C, non-HDL-C, and ApoB targets (TABLE 2).<sup>11</sup>

Despite evidence supporting the early implementation of aggressive lipid-lowering therapy in patients at risk for CHD, many patients are not being screened, started on appropriate therapy, or treated to target lipid levels.<sup>12</sup> With their knowledge of lipid-lowering medications, treatment indications, optimal dosing, and safety issues, clinical pharmacists are well positioned to manage the medical treatment of dyslipidemia. Pharmacists are accessible at the point of medication dispensing and at the point of care. Through effective patient education and monitoring, pharmacists can improve medication adher-

**Table 2. ADA/ACC Treatment Recommendations for Patients With Cardiometabolic Risk Factors and Lipoprotein Abnormalities**

Risk Category	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
Highest risk patients, defined as those with: <ul style="list-style-type: none"> <li>Known CVD, or</li> <li>Diabetes plus <math>\geq 1</math> additional major CVD risk factor</li> </ul>	<70	<100	<80
High-risk patients, defined as those with: <ul style="list-style-type: none"> <li>No diabetes or known clinical CVD but <math>\geq 2</math> additional major CVD risk factors</li> <li>Diabetes but no other major CVD risk factors</li> </ul>	<100	<130	<90

ACC: American College of Cardiology; ADA: American Diabetes Association; ApoB: apolipoprotein B; CVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.  
Source: Reference 31.

ence and treatment success, enabling more patients to reach treatment goals.<sup>13</sup>

### Current Treatment Options in Dyslipidemia

In 2004, the NCEP ATP III published revised treatment recommendations that incorporated new clinical trial data supporting lower LDL-C goals for patients with dyslipidemia (TABLE 3).<sup>3</sup> The recommendations are based on risk categories as defined by risk factors and calculated 10-year risk for CHD. For example, the high-risk category includes patients with CHD or CHD risk equivalents and a 10-year risk for CHD outcomes that exceeds 20%. Effective implementation of the revised NCEP ATP III recommendations requires an understanding of key variables used to categorize patient risk:

- **CHD:** myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia
- **CHD risk equivalents:** peripheral artery disease, abdominal aortic aneurysm, carotid artery disease, diabetes, or CHD risk >20%

- **Risk factors:** cigarette smoking, hypertension (blood pressure  $\geq 140/90$  mm Hg or on antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), and age (men  $\geq 45$  years; women  $\geq 55$  years)
- **10-year risk for CHD:** estimated risk for “hard” CHD outcomes, including MI and coronary death, based on data from the Framingham Heart Study. The risk factors used to calculate 10-year risk are age, gender, cigarette smoking, TC, HDL-C, systolic blood pressure, and treatment for hypertension. Point values are calculated based on the presence of each of these risks. A risk calculator is available at <http://hp2010.nhlbi.nih.net/atpiiii/calculator.asp>

Regarding therapeutic targets, the revised NCEP ATP III guidelines suggest an LDL-C goal of <100 mg/dL in high-risk patients, with an optional LDL-C goal of <70 mg/dL for patients at very high risk. Once lipid-lowering drug therapy is required, clinicians should initiate regimens sufficient to achieve a 30% to 40% reduction in LDL-C levels with an initial focus on statin therapy.<sup>3</sup>

**Table 3. 2004 Update to NCEP ATP III Lipoprotein Targets**

Risk Category	LDL-C (mg/dL)	Non-HDL-C (mg/dL) <sup>a</sup>
Highest risk patients, defined as those with: <ul style="list-style-type: none"> <li>Known CHD or</li> <li>Risk equivalent (10-y risk &gt;20%)</li> </ul>	<100 (optional <70)	<130
Moderately high-risk patients, defined as those with: <ul style="list-style-type: none"> <li><math>\geq 2</math> Risk factors (10-y risk 10%-20%)</li> </ul>	<130 (optional <100)	<160
Moderate risk patients, defined as those with: <ul style="list-style-type: none"> <li>2 Risk factors (10-y risk &lt;10%)</li> </ul>	<130	<160
Low-risk patients, defined as those with: <ul style="list-style-type: none"> <li>0-1 Risk factor</li> </ul>	<160	<190

<sup>a</sup> Only target once LDL-C goal met and TGs >200 mg/dL  
CHD: coronary heart disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.  
Source: Reference 3.

**Table 4. Essential Lifestyle Modifications for Dyslipidemia Management**

Lifestyle Component	Recommendation
Diet considerations	
Saturated fats <sup>a</sup>	<7% of total calories
Dietary cholesterol	<200 mg/d
Plant stanols/sterols	2 g/d
Viscous (soluble) fiber	10-25 g/d
Total calories (energy)	Adjust to maintain desirable body weight/prevent weight gain
Physical activity	
Moderate exercise	Enough moderate exercise to expend ≥200 kcal/d

<sup>a</sup> *Trans* fatty acids should also be kept at a low intake.  
Source: Reference 2.

### Therapeutic Lifestyle Changes

Diet and other lifestyle modifications are the essential first steps for managing elevated cholesterol levels (TABLE 4). The NCEP ATP III guidelines recommend limiting the intake of LDL-C-raising nutrients, including saturated fats (<7% of total calories) and cholesterol (<200 mg/d). Dietary options for lowering LDL-C include plant stanols/sterols (2 g/d) and soluble fiber (10-25 g/d). Patients should also be advised to adjust their total daily caloric intake to maintain a desirable body weight and prevent weight gain. Moderate exercise, defined as enough to expend ≥200 kcal per day, is also an important lifestyle intervention for patients with dyslipidemia.<sup>2</sup>

**POP QUIZ** The most effective monotherapy for raising HDL-C is:  
**A. Statins**  
**B. Niacin**  
**C. Ezetimibe**  
**D. Omega-3 fatty acids**

### Pharmacotherapy

When lifestyle modifications alone do not achieve desired lipid goals, addition of lipid-modifying pharmacotherapy

is appropriate. Decisions regarding drug therapy should be individualized and based on expected benefits, tolerability profile, effects on quality of life, comorbid diseases, and treatment costs.<sup>2</sup> Each class of lipid-modifying drug therapy is associated with a range of expected effects on lipid profiles (TABLE 5).<sup>14-16</sup> The magnitude of therapeutic benefit is often greatest in patients who are farthest from the treatment goal.

Before initiating lipid-modifying drug therapy, baseline lipid and lipoprotein levels should be measured as a point of reference for monitoring treatment response. Other baseline laboratories such as a liver profile, uric acid, and blood glucose should be obtained in accordance with drug selection.

Baseline and follow-up evaluations are important for monitoring drug safety and determining the need for dose adjustments or other treatment modifications (TABLE 6).

### Statins

Statins are the most effective agents for reducing serum LDL-C concentrations. By competitively inhibiting HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, statins reduce cholesterol content in the liver. To compensate, there is an increase in the expression and turnover of hepatic LDL receptors, which lowers serum LDL-C levels. Hepatic LDL receptors also absorb intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) remnants, reducing the concentration of TG-rich proteins. Statins also have modest HDL-C-raising properties, which vary among individual agents.<sup>2</sup>

Depending on the agent and dose used, statins reduce LDL-C 18% to 63%, and TG 7% to 30%, and increase HDL-C 5% to 15%.<sup>14,17</sup> These effects translate to improved clinical outcomes among patients receiving statin therapy. Statins reduce risk of acute coronary syndromes, coronary procedures (e.g., percutaneous coronary interventions), and stroke when used in primary and secondary prevention.<sup>2,18-22</sup>

**Table 5. Drug Therapies and Expected Changes in Lipid Profile**

Drug Class	Serum LDL-C	Serum HDL-C	Serum TGs
Statins	↓18%-63%	↑5%-15%	↓7%-30%
Nicotinic acid	↓5%-25%	↑15%-35%	↓20%-50%
Fibric acid derivatives	↓5%-20%	↑10%-35%	↓20%-50%
Cholesterol absorption inhibitors (ezetimibe)	↓17.7%	↑1.3%	↓5.7%
Bile acid sequestrants	↓15%-30%	↑3%-5%	No effect or increase
Prescription omega-3 fatty acids	↑0%-46%	↑0%-14%	↓19%-45%

Source: References 14-16.

**Table 6. Monitoring Parameters for Lipid-Modifying Therapy**

Drug Class	Monitoring Parameters	Follow-up Schedule
Bile acid sequestrants	Indigestion, bloating, constipation, abdominal pain, flatulence, nausea	Evaluate symptoms initially and at each follow-up visit; check time of administration with other drugs
Niacin (nicotinic acid)	Flushing, itching, tingling, headache, nausea, gas, heartburn, fatigue, rash	Evaluate symptoms initially and at each follow-up visit
	Peptic ulcer	Evaluate symptoms initially, then as needed
	FBS, uric acid	Obtain an FBS and uric acid initially, 6-8 weeks after starting therapy, then annually or more frequently if indicated to monitor for hyperglycemia and hyperuricemia
	ALT and AST	Obtain an ALT/AST initially, 6-8 weeks after reaching a daily dose of 1500 mg, 6-8 weeks after reaching the maximum daily dose, then annually or more frequently if indicated
Statins	Muscle soreness, tenderness, or pain	Evaluate muscle symptoms and CK initially. Evaluate muscle symptoms at each follow-up visit. Obtain a CK when patient has muscle soreness, tenderness, or pain
	ALT, AST	Evaluate ALT/AST initially, approximately 12 weeks after starting, then annually or more frequently if indicated
Fibrates	Abdominal pain, dyspepsia, headache, drowsiness	Evaluate symptoms initially and at each follow-up visit
	Cholelithiasis	Evaluate history and symptoms initially, and then as needed

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatinine kinase; FBS: fasting blood sugar.

Source: Reference 2.

Weng and colleagues reported findings from a meta-analysis of 75 randomized trials of statin therapy.<sup>23</sup> At therapeutically equivalent doses, statins provided similar efficacy in reducing LDL-C levels. For example, daily treatment with atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 to 80 mg, or simvastatin 20 mg was associated with an LDL-C reduction of 30% to 40%. Two regimens, atorvastatin  $\geq 20$  mg/d and rosuvastatin  $\geq 5$  mg/d, reduced LDL-C levels more than 40%. At equivalent doses, different statins showed similar effects on HDL-C and TG levels, but this can vary among statins. Statin equivalent doses are determined by their LDL-C-lowering potential. These estimates of therapeutically equivalent statin doses should provide guidance for switching or tapering statin therapy in clinical practice (TABLE 7).

Statins are well tolerated. They do carry a dose-dependent risk of elevated hepatic transaminases in 0.5% to

2.0% of patients. Transaminase levels often return to normal with a reduction of statin dose or even with continuation of the same dose. Treatment discontinuation is recommended in patients in whom transaminase levels increase  $\geq 3$  times the upper limit of normal.<sup>2</sup> In 2006, the National Lipid Association Statin Safety Assessment Task Force issued guidelines for liver monitoring in patients taking statins.<sup>24</sup> The guidelines advise measuring transaminase levels before starting therapy, 12 weeks after initiating therapy, after a dose increase, and periodically thereafter (TABLE 8).

Statin therapy is associated with an increased risk of myopathy. In large clinical trials of statin therapy, myopathy tends to occur at similarly low rates in the statin and placebo groups. Myopathy is more likely to develop in older patients, patients taking multiple concomitant medications, and patients with complex medical problems. Clinically significant myopathy is characterized by

**Table 7. LDL-C Reductions Achieved by Statins at Different Doses**

LDL-C Reduction (%)	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
$\geq 40$	$\geq 20$	–	–	–	$\geq 5$	$> 40$
30-40	10	80	40/80	–	–	20
20-30	–	40	10/20	20/40	–	10
$\leq 20$	–	20	–	10	–	–

Source: Reference 23.

### Table 8. National Lipid Association 2006: Recommendations to Health Professionals Regarding the Liver and Statin Safety

1. Obtain liver transaminase levels before starting therapy
2. Measure transaminase levels 12 weeks after initiating therapy, after a dose increase, and periodically thereafter. However, routine monitoring is not supported by the available evidence and the current recommendation for monitoring needs to be reconsidered by the FDA
3. Alert patients to report symptoms of potential hepatotoxicity. Evidence for hepatotoxicity includes jaundice, hepatomegaly, increased indirect bilirubin level, and elevated prothrombin time
4. Fractionated bilirubin is a more accurate prognosticator of liver injury than isolated aminotransferase levels
5. If objective evidence of significant liver injury, the statin should be discontinued
6. If an isolated asymptomatic transaminase level is  $1-3 \times \text{ULN}$ , there is no need to discontinue the statin
7. If an isolated asymptomatic transaminase level is  $>3 \times \text{ULN}$ , repeat the test; if still elevated, other etiologies should be ruled out. Consideration should be given to continuing the statin, reducing its dose, or discontinuing it based on clinical judgment
8. Patients with chronic liver disease, nonalcoholic fatty liver disease, or nonalcoholic steatohepatitis may safely receive statin therapy

ULN: upper limit of normal.  
Source: Reference 24.

muscle aches, soreness, or weakness, and elevated creatine kinase (CK) levels ( $>10$  times the upper limit of normal). Because laboratory monitoring of CK is not indicated prior to initiating statin therapy, patients should be instructed to report signs or symptoms of myopathy, such as muscle pain or weakness or brown urine. Such symptoms should prompt measurement of a CK level (TABLE 9).<sup>24</sup> Statin therapy should be discontinued in patients with confirmed or strongly suspected myopathy.<sup>2</sup> Once myopathy is resolved, re-initiation of statin therapy should be assessed, with a focus on the risk-to-benefit ratio in an individual patient.

Absolute contraindications to statin therapy include pregnancy and active or chronic liver disease. Because of the potential risk of drug interactions, statins should be used with caution in patients who are taking cyclosporine, fibrates (particularly gemfibrozil), niacin, macrolide antibiotics, various antifungal agents, and other cytochrome P450 inhibitors.<sup>2</sup> Of note, because pravastatin and rosuvastatin are not metabolized via cytochrome P450, their interaction profiles are slightly different from those of the other statins.

#### Niacin (nicotinic acid)

Niacin (vitamin B<sub>3</sub>, nicotinic acid) alters lipid levels by reducing production of TG-rich proteins in the liver and inhibiting mobilization of fatty acids from adipose tissue. These modifications in lipoprotein metabolism can reduce LDL-C levels 5% to 25% and TG levels 20% to 50%. Niacin is also the most effective agent for increasing HDL-C levels. By reducing the transfer of cholesterol from HDL to VLDL and delaying HDL clearance, niacin can increase HDL-C levels up to 35%.<sup>2</sup>

Niacin is available in immediate-release (crystalline) and sustained-released preparations in prescription and over-the-counter (OTC) forms. Nicotinamide, another formulation of vitamin B<sub>3</sub>, does not have the lipid-lowering properties of niacin.<sup>2</sup> Some OTC niacin preparations purporting to be “flush-free” may not contain any free niacin, and therefore are ineffective in treating dyslipidemia. Daily doses of  $\geq 2$  g of sustained-release niacin can cause hepatotoxicity, which is manifest in its mildest form as asymptomatic increases in liver transaminases and in its severest form as malaise, lethargy, anorexia, and other symptoms of hepatitis. Because of this risk, daily doses of these products should not exceed 2 g, and close monitoring of liver function (at baseline, every 6-12 weeks for the first year, and every 6 months thereafter) should accompany their use. Most authorities recommend that immediate-release or extended-release dosage forms be given preference to sustained-release products to avoid this risk.<sup>25</sup> OTC formulations should be used with great caution because of differences in potency and purity.<sup>26</sup>

Treatment with niacin is associated with a range of other potential side effects. The most common is flushing, a dose-limiting adverse effect that may be intolerable for some patients. Most patients taking niacin in whom flushing develops are instructed to take aspirin 325 mg 30 to 60 minutes before the niacin dose to minimize this adverse effect. However, most patients develop a tolerance to flushing with long-term niacin use. Extended-release formulations of niacin appear to decrease the risk of flushing compared with crystalline formulations.<sup>2</sup> Niacin may cause hyperglycemia, hyperuricemia, gastrointestinal (GI) distress, and hepatotoxicity.

Absolute contraindications to niacin include chronic

### Table 9. National Lipid Association 2006: Recommendations to Health Professionals Regarding the Muscle and Statin Safety

1. Whenever muscle symptoms or an increased CK level is encountered in a patient receiving statin therapy, health professionals should attempt to rule out other etiologies, because these are most likely to explain the findings. Other common etiologies include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or phencyclidine)
2. Obtaining a pretreatment, baseline CK level may be considered in patients who are at high risk of experiencing muscle toxicity (e.g., older individuals; patients receiving combination statin plus agent known to increase myotoxicity), but this is not routinely necessary in other patients
3. It is not necessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked clinically important CK elevations are rare and usually related to physical exertion or other causes
4. Patients receiving statin therapy should be counseled about the increased risk of muscle complaints, particularly if the initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional
5. CK measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate a decision of whether to continue therapy or alter doses
6. In patients who develop intolerable muscle symptoms with or without a CK elevation and in whom other etiologies have been ruled out, the statin should be discontinued. Once asymptomatic, the same or different statin at the same or lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy
7. In patients who develop tolerable muscle complaints or are asymptomatic with a CK <10 ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy
8. In patients who develop rhabdomyolysis (CK >10,000 IU/L or CK >10 × ULN with an elevation in serum creatinine or requiring IV hydration therapy), statin therapy should be stopped. IV hydration therapy in a hospital setting should be instituted if indicated for patients experiencing rhabdomyolysis. Once recovered, the risk vs benefit of statin therapy should be carefully reconsidered

Source: Reference 24.

liver disease and severe gout. Niacin should be used with caution in patients with poorly controlled diabetes, hyperuricemia, and peptic ulcer disease. Based on its side effect profile, niacin should be titrated over weeks to months to minimize side effects.<sup>2</sup>

#### Fibrates

Fibrates have a complex mechanism of action, leading to variations in potency among members of this class. Fibrates act mainly on peroxisome proliferator-activated receptor-alpha (PPAR $\alpha$ ), a nuclear transcription factor expressed in the liver and other tissues that metabolize fatty acids. By activating PPAR $\alpha$ , fibrates decrease hepatic TG secretion, increase lipoprotein lipase activity, and enhance VLDL clearance. Together, these actions lower serum TG levels.

Fibric acid derivatives, including gemfibrozil, fenofibrate, and clofibrate, are used primarily in the management of hypertriglyceridemia and mixed dyslipidemia.<sup>2</sup> These agents have potent effects, reducing serum TG 20% to 50%. In patients with severe hypertriglyceridemia, fibrates also increase HDL-C levels 10% to 35%.<sup>2</sup> The effect of fibrates on LDL-C is more modest, with reductions of 5% to 20%, depending on the underlying

lipid abnormality.<sup>2</sup>

Despite favorable effects on atherogenic dyslipidemia (high TG and low HDL-C), the effects of fibrates on clinical outcomes are unclear. In a meta-analysis of 10 randomized trials that included 36,489 patients, fibrate treatment was associated with a trend toward increased all-cause mortality (OR, 1.07;  $P = .08$ ) and a significant increase in noncardiovascular mortality (OR 1.16;  $P = .004$ ).<sup>27</sup> In another meta-analysis of 18 trials including 45,058 patients, fibrates reduced the risk of major CV events 10% ( $P = .048$ ) and reduced the risk of coronary events 13% ( $P < .0001$ ) compared with placebo, but did not reduce the risk of stroke ( $P = .69$ ).<sup>28</sup> Fibrates had no effect on all-cause mortality (RR 1.00; CI 0.93-1.08) or CV mortality (RR 0.97; CI 0.85-1.02), but showed a trend toward increased noncardiovascular mortality compared with placebo (RR 1.10; CI 0.995-1.21). This study did not specify which fibrate was predominantly used in the trials.

Fibrates can cause dyspepsia, upper GI complaints, cholesterol gallstones, and myopathy. They should be avoided in patients with severe hepatic or renal insufficiency.<sup>2</sup> Fibrates may result in a number of drug interactions, but this varies by the agent used. Gemfibrozil may

increase plasma concentrations of commonly prescribed agents such as repaglinide, pioglitazone, rosiglitazone, and the sulfonylureas. It also interferes with the metabolism of statins (except fluvastatin). Fenofibrate and bezafibrate are safe in combination therapy with statins but add little end point benefit except possibly in patients with significant atherogenic dyslipidemia (high TG and low HDL-C levels).<sup>29,30</sup>

Fibrates displace warfarin from albumin-binding sites, enhancing the hypoprothrombinemic effects. A reduction in the warfarin dosage with frequent monitoring of prothrombin time or international normalized ratio is suggested to prevent bleeding complications.

### Ezetimibe

Ezetimibe interferes with the dietary and biliary absorption of cholesterol. Ezetimibe binds to the Niemann-Pick C1-Like 1 (NPC1L1), an important mediator of cholesterol absorption found on epithelial cells in the GI tract and on hepatocytes. In addition to directly reducing cholesterol levels, cholesterol absorption inhibitors indirectly reduce LDL-C levels by increasing hepatic LDL-C receptor expression. In one randomized, placebo-controlled study in patients with primary hypercholesterolemia, treatment with ezetimibe reduced LDL-C levels 16.9% and TG levels 5.7% and increased HDL-C 1.3%.<sup>15</sup>

Early safety signals aroused concern about ezetimibe and cancer risk, leading to a closer look at this potential adverse effect in ezetimibe clinical trials. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial found an excess of new-onset cancer in patients treated with the combination of ezetimibe and simvastatin compared with placebo.<sup>31</sup> To explore this concern, Peto and colleagues conducted a meta-analysis of data from SEAS, the Study of Heart and Renal Protection (SHARP), and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT).<sup>32</sup> The pooled data included 44,137 person-years of follow-up among patients treated with ezetimibe and simvastatin ( $n = 11,263$ ) or control, including placebo or simvastatin monotherapy ( $n = 11,227$ ). There was no evidence that combination ezetimibe and simvastatin increased the risk of new-onset cancer or the risk of cancer mortality compared with controls. Analyses with longer follow-up are needed to explore the long-term benefits and risks of ezetimibe therapy in patients with dyslipidemia.

### Bile Acid Sequestrants

Bile acid sequestrants bind to bile acids within the GI tract, preventing their reabsorption and promoting their excretion. To correct the deficit, endogenous cholesterol is diverted from the liver to produce new bile salts. Reduced hepatic cholesterol content triggers an increase in hepatic LDL receptor expression, decreasing serum LDL-C concentrations 15% to 30%.<sup>2</sup> Sequestrants have

a modest effect on HDL-C, increasing HDL-C concentrations 3% to 5%.<sup>2</sup>

In a small trial of patients with dyslipidemia and type 2 diabetes mellitus, treatment with cholestyramine reduced TC 18%, LDL-C 28%, and mean plasma glucose 13% compared with placebo. Cholestyramine also reduced urinary glucose excretion 0.22 g/d ( $P < .001$ ), suggesting improved glycemic control.<sup>33</sup> Clinical trials that evaluated the lipid- and glucose-lowering effects of colesvelam added to existing type 2 diabetes treatment regimens (metformin, sulfonylurea, or insulin) showed a consistent reduction in A1C (0.50%-0.54%) versus placebo.<sup>34</sup>

Use of bile acid sequestrants is often limited by side effects. These agents may increase TG levels in some patients.<sup>2</sup> In a trial of patients with diabetic dyslipidemia, treatment with cholestyramine increased TG levels 13.5% compared with placebo.<sup>33</sup> Given this potentially adverse effect, bile acid sequestrants are contraindicated in patients with TG levels above 400 mg/dL and in patients with familial dysbetalipoproteinemia.<sup>2</sup> Careful monitoring of TG levels is necessary when sequestrants are used in patients with baseline TG levels  $>200$  mg/dL.

Bile acid sequestrants are associated with upper and lower GI distress, including constipation, abdominal pain, bloating, fullness, nausea, and flatulence. These agents may decrease the absorption of many other medications, requiring modifications in dosing schedules.

### Omega-3 Fatty Acids

Regular consumption of fish, dietary supplementation with fish oils rich in omega-3 fatty acids, or use of prescription-strength omega-3 fatty acid can correct elevated TG levels. Specifically, omega-3 fatty acids reduce the secretion of TG-rich lipoproteins from the liver, and therefore may be particularly effective in managing patients with hypertriglyceridemia.<sup>2</sup> Treatment with prescription-strength omega-3 fatty acid has been shown to reduce TG levels up to 45% in patients with high baseline TG levels ( $\geq 500$  mg/dL).<sup>16</sup> High-dose omega-3 fatty acids (0.9 g/d eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) appear to reduce the risk of major coronary events in patients with established CHD, supporting their use in secondary prevention.<sup>35</sup> Citing limited evidence, the NCEP ATP III guidelines did not include a formal recommendation for omega-3 fatty acids in primary or secondary prevention in patients with dyslipidemia.<sup>2</sup> Since publication of these guidelines, the FDA has approved a capsule formulation of omega-3-acid ethyl esters for adults with severe hypertriglyceridemia ( $\geq 500$  mg/dL).<sup>36</sup>

Omega-3 fatty acids exert a dose-related effect on bleeding time; however, there are no documented cases of abnormal bleeding as a result of fish oil supplementation, even at

high dosages and in combination with other anticoagulant medications. High dosages of fish oil may increase LDL-C levels, but the clinical relevance of this finding remains unclear.<sup>37</sup> Other potential side effects include a fishy aftertaste (which can be minimized by freezing the capsules) and GI disturbances, both of which appear to be dose-dependent.<sup>38</sup> The US FDA advises women and children to avoid fish that may have a high level of mercury (shark, swordfish, king mackerel, and tilefish).<sup>39</sup>

**POP QUIZ**

**Which therapy would you choose for a patient with atherogenic dyslipidemia (low HDL-C and high TG levels)?**

- A. Niacin and ezetimibe**
- B. Niacin and fibrate**
- C. Bile acid sequestrant and fibrate**
- D. Niacin and fish oil**

**Combination Therapies**

Combination therapy with statins and another lipid-lowering agent, such as niacin, bile acid sequestrants, fibrates, or ezetimibe, may be more effective than statin monotherapy for reaching aggressive LDL-C targets for some patients. Moreover, although current treatment recommendations focus on LDL-C as the primary target of drug therapy, secondary targets should be the focus after the primary LDL-C goal is met. Combination lipid-modifying therapy, particularly using drugs with different mechanisms of action, can expand options for achieving treatment goals across multiple lipid parameters. Certain combinations may be particularly effective for goals beyond LDL-C alone, such as reaching a non-HDL-C target, treating severe hypertriglyceridemia, and raising HDL-C levels.<sup>2</sup>

**Statins and Niacin:** Combination statin and niacin treatment improves the lipoprotein profile in patients who require aggressive lipid-lowering therapy. The Safety and Efficacy of a Combination of Extended Release Niacin and Simvastatin Trial (SEACOAST I) compared simvastatin monotherapy with a fixed-dose combination of extended-release niacin (1000 or 2000 mg/d) and simvastatin (20 mg/d) in patients with mixed dyslipidemia.<sup>40</sup> This combination showed significant dose-related improvements in several lipid parameters compared with single-agent simvastatin treatment. This included a 25% increase in HDL-C, 38% reduction in TG, and 25% reduction of lipoprotein(a) in the group treated with niacin/simvastatin 2000/20 mg/d fixed-dose combination. The reduction in lipoprotein(a) is mediated through niacin therapy, not statin therapy. The regimen was well tolerated, with flushing in ≤60% of patients in either treatment group. Most flushing episodes were mild or moderate, and only 7.5% of patients in both dosing groups discontinued treatment due to flushing.

The statin/niacin combination appears to be more effective for reducing atherosclerotic disease than combination therapy with statin and ezetimibe. The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial compared the efficacy and safety of adding extended-release niacin versus ezetimibe to statin therapy in patients with known vascular disease or CHD risk equivalents.<sup>41</sup> After 14 months, treatment with niacin/statin led to a significant regression of atherosclerosis (measured by carotid intima-media thickness) ( $P = .003$ ) and reduced the risk of CV events (myocardial infarction, myocardial revascularization, acute coronary syndrome, and CV death) compared with ezetimibe/statin therapy (1% vs 5%;  $P = .04$ ). The study's small sample size did not allow for power to detect a difference in CV events, despite statistically significant findings. Paradoxically, although ezetimibe was associated with a greater reduction in LDL-C compared with niacin ( $-17.6$  vs  $-10.0$  mg/dL;  $P = .01$ ), ezetimibe also was associated with a significant progression of atherosclerosis as measured by increased carotid intima-media thickness ( $P < .001$ ). More than one third (36%) of patients taking niacin reported flushing, but the rate of treatment discontinuations due to adverse events was comparable in the niacin and ezetimibe groups. The finding of atherosclerotic progression with ezetimibe indicates that biologic effects of ezetimibe in combination with statin therapy are not fully understood.

**Statins and Bile Acid Sequestrants:** Combination therapy with a statin and bile acid sequestrant may be appropriate for patients with severe polygenic or familial hypercholesterolemia who cannot reach target LDL-C with statin monotherapy. In one study, adding colesevelam 3.8 g/d to treatment with atorvastatin 10 mg increased the absolute LDL-C reduction from 38% to 48%.<sup>42</sup> For some patients, treatment with a sequestrant-statin combination can reduce LDL-C levels up to 70%.<sup>2</sup>

For patients with very high LDL-C levels, combination therapy should be initiated early in the course of treatment, rather than up-titrating statin monotherapy to the maximum tolerated dose. If an efficacy plateau appears above the target level, a third lipid-lowering agent may be added. Niacin is a safe choice as a third agent to add to the statin plus bile acid sequestrant regimen.

**Statins and Fibrates:** Combination statin and fibrate therapy may be effective for patients with elevated LDL-C levels and mixed dyslipidemia. In a multicenter, double-blind study of patients with mixed dyslipidemia, the combination of fenofibric acid (ABT-335) 135 mg/d and atorvastatin 40 mg/d increased HDL-C

12.6%, decreased LDL-C 35.4%, and decreased TG 42.1% compared with baseline values.<sup>43</sup> Combination therapy also significantly improved non-HDL-C and VLDL compared with baseline. Despite early concerns about myopathy with this combination, there were no reports of rhabdomyolysis in any monotherapy or combination therapy dosing groups.

In a phase 3 trial of patients with mixed dyslipidemia, combination ABT-335 and low-dose rosuvastatin (10 mg/d) therapy significantly increased HDL-C (20.3% vs 8.5%;  $P < .001$ ) and decreased TG (47.1% vs 24.4%;  $P < .001$ ) compared with rosuvastatin monotherapy.<sup>44</sup> The ABT-335/rosuvastatin combination had a safety profile similar to that of either monotherapy, with no reports of rhabdomyolysis. In another study of patients with mixed dyslipidemia and type 2 diabetes mellitus, combination therapy with ABT-335 and atorvastatin, rosuvastatin, or simvastatin provided more favorable changes in LDL-C, non-HDL-C, ApoB, HDL-C, and TG levels than either monotherapy.<sup>45</sup>

Gemfibrozil interferes with the metabolism of statins (except fluvastatin), resulting in an increased potential for myopathy. Fenofibrate and bezafibrate are safe in combination therapy with statins but add little end point benefit except possibly in patients with significant atherogenic dyslipidemia (high TG and low HDL-C levels).<sup>29,30</sup> The lowest effective dose of both the statin and fibrate should achieve treatment goals.

**Statins and Ezetimibe:** In patients who do not achieve target LDL-C levels with statin therapy alone, combination therapy with ezetimibe and a statin may provide additional LDL-C-lowering, but its effect on CV outcomes is controversial. Treatment options for patients whose LDL-C levels were not adequately lowered with simvastatin 20 mg/d were evaluated by 2 multicenter, double-blind clinical trials.<sup>46</sup> Patients who were switched to combination therapy with 10-mg ezetimibe/20-mg simvastatin had greater improvement in lipid parameters than those who received simvastatin 40 mg/d. Within 6 weeks, 75% of patients in the ezetimibe/simvastatin group had reached a target LDL-C level of  $< 100$  mg/dL compared with 42% in the high-dose simvastatin group ( $P < .01$ ). Tolerability was comparable in both treatment arms, with a similar proportion of patients reporting drug-related adverse events in the combination therapy and high-dose monotherapy groups (9.8% vs 6.3%;  $P = .5$ ).

However, ezetimibe-based combination therapy does not appear to have definitive clinical benefits, despite improvements in lipid parameters. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, adding ezetimibe to statin therapy resulted in a 16.5% greater reduction in LDL-C ( $P < .01$ ) and a 6.6% greater reduc-

tion in TG ( $P < .01$ ) compared with statin monotherapy; but after 2 years of treatment, ezetimibe had no effect on the progression of atherosclerosis as measured by carotid intima-media thickness ( $P = .29$ ).<sup>47</sup> In addition, ezetimibe/statin therapy has yet to demonstrate CV event outcome reductions compared with other combination therapies. Ezetimibe/statin therapy was associated with progressive atherosclerotic disease in the ARBITER 6-HALTS trial. By comparison, combination statin/niacin therapy resulted in a significant regression of atherosclerosis (measured by carotid intima-media thickness) and showed a decrease in the risk of CV events relative to ezetimibe/statin therapy, but this was a small study not powered to detect a difference in events between treatment arms.<sup>41</sup>

Questions regarding the risk of incident cancer and cancer mortality with ezetimibe have been addressed by data from large randomized trials. In a meta-analysis of data from the SEAS trial, SHARP, and IMPROVE-IT, combination therapy with ezetimibe and simvastatin did not increase the risk of new-onset cancer or cancer mortality compared with control (single-agent simvastatin or placebo).<sup>32</sup>

**Statins and Omega-3 Fatty Acids:** For certain patient populations, the combined use of statins and omega-3 fatty acids may have favorable effects on lipid parameters and CV outcomes. The Japan EPA Lipid Intervention Study (JELIS) evaluated statin therapy with or without the addition of EPA 1800 mg/d in 18,645 patients with baseline TC levels of  $\geq 6.5$  mmol/L ( $\geq 225$  mg/dL).<sup>48</sup> Most patients (90%) were taking very low dose pravastatin (10 or 5 mg/d), with the remaining patients taking another statin regimen. After a mean follow-up of 4.6 years, 3.5% of patients receiving statin monotherapy reached the primary composite end point of any major coronary event, which included sudden cardiac death, fatal and nonfatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. By comparison, 2.8% of patients in the statin/EPA group reached this end point, representing a 19% relative reduction in the risk of major coronary events with the addition of EPA to statin therapy ( $P = .011$ ). Differences in on-treatment lipid parameters may account for the differences in coronary event rates in the 2 treatment groups. Although LDL-C levels decreased 25% in both treatment groups, patients in the statin/EPA group had a greater decrease in TG levels than those in the statin monotherapy group (9% vs 4%;  $P < .0001$ ).

The JELIS study authors noted that this Japanese trial may have limited clinical applicability to Western populations because background omega-3 consumption in Japan is so much greater.<sup>48</sup> Moreover, the doses of statin used in this trial were very low, despite the high baseline LDL-C levels of subjects in the control and study arms.

More recently, a US trial also showed the benefits of prescription omega-3-acid ethyl esters (P-OM3) in patients receiving statin therapy.<sup>49</sup> Bays and colleagues compared treatment with P-OM3 4 g/d or placebo in patients who were receiving escalating doses of open-label atorvastatin 10 to 40 mg/d. All patients had elevated non-HDL-C (>160 mg/dL) and TG ( $\geq$ 250 mg/dL and  $\leq$ 599 mg/dL) levels at baseline. During the 16-week treatment period, the addition of P-OM3 significantly improved non-HDL-C, TC, TG, VLDL, and HDL-C levels at every atorvastatin dose. However, treatment with P-OM3 and atorvastatin did not improve LDL-C, ApoB, or ApoA1 levels beyond statin therapy alone. Combination therapy was well tolerated, with similar discontinuation rates due to adverse events in the P-OM3 plus atorvastatin (6.5%) and atorvastatin monotherapy (4.9%) groups. Overall, these findings suggest that this combination improves some lipoprotein parameters in patients with elevated non-HDL-C and TG levels.

**Niacin and Fibrin Acid Derivatives:** Patients with atherogenic dyslipidemia benefit from combination therapy with niacin and fibrin acid derivatives. Superko and colleagues examined the effect of niacin (1500 mg/d) alone or in combination with gemfibrozil (1200 mg/d) in patients with combined hyperlipidemia.<sup>50</sup> Compared with niacin monotherapy, combination treatment provided significantly greater improvement in lipoprotein subclass distribution, including a 71% reduction in IDL, a 52% reduction in dense LDL-III, a 37% reduction in ApoB, and a 90% increase in HDL<sub>2</sub> subfraction. Combination therapy also resulted in a greater reduction in the ApoB/ApoA1 ratio compared with niacin monotherapy ( $P < .005$ ).

## POP QUIZ

**How have pharmacist-led interventions been more effective than usual care in patients with dyslipidemia? (More than one answer may be correct.)**

- A. Greater reductions in LDL-C**
- B. More patients getting to goal lipid levels**
- C. Better adherence to treatment**
- D. Greater use of formulary medications, resulting in cost savings**

### Pharmacist's Role in Optimization of Patient Care

Multidisciplinary care is emerging as an important treatment model for chronic diseases. In the management of dyslipidemia, pharmacists are well positioned to enhance patient care. Pharmacists can lead multidisciplinary care teams by addressing barriers to successful treatment such as medication nonadherence, drug interactions, and monitoring for adverse reactions. Increasing evidence

shows that pharmacists significantly improve delivery of dyslipidemia care. In several studies, pharmacist-managed clinics improved lipid management, including attainment of LDL-C goals, compared with control groups managed by primary care physicians.<sup>51-54</sup> In these studies, better patient education and more intensive lipid-lowering therapy with medication titration and monitoring were key factors in the success of the pharmacist-managed clinics.

### Pharmacist-Led Lipid Interventions

Machado and colleagues conducted a systematic review of 23 clinical trials to evaluate the relationship between pharmacist-led interventions and lipid profiles among patients with hyperlipidemia.<sup>54</sup> The studies represented diverse practice settings, including medical clinics or medical centers ( $n = 12$ ), community pharmacies ( $n = 8$ ), hospitals ( $n = 2$ ), and 1 trial of home-based care among hospital-discharged patients. Within these settings, the role of the pharmacist included patient education (78%) and medication management (74%), often independent of physician supervision. The meta-analysis included 2343 patients (824 in the pharmacist intervention group and 1519 in the control group).

Participation in pharmacist care was associated with a 22-mg/dL further reduction in TC level compared with standard care ( $P = .034$ ). Overall reductions in TC were 34.2 mg/dL in the pharmacist-intervention group ( $P < .001$  vs baseline) and 13.7 mg/dL in the control group ( $P = .186$  vs baseline). LDL-C was reduced significantly from baseline (32.6 mg/dL;  $P = .004$ ), but not significantly more than the control group (17.5 mg/dL;  $P = .109$ ). Compared with baseline levels, LDL-C levels were reduced 32.6 mg/dL in the pharmacist intervention group ( $P = .004$ ) and 15.3 mg/dL in the control group ( $P = .142$ ). Other lipid outcomes also showed trends favoring pharmacist intervention versus control, including a greater reduction in TG (21.8 mg/dL;  $P = .368$ ) and an increase in HDL-C (1.18 mg/dL;  $P = .798$ ).

### Experience at the Cleveland Veterans Affairs (VA) Medical Center

The Louis Stokes Cleveland VA Medical Center (LSCVAMC) experience illustrates the potential advantages of a dedicated, pharmacist-managed lipid clinic within a large medical center. At the LSCVAMC, pharmacist-led interventions are popular among patients with complicated dyslipidemia and other members of multidisciplinary care teams.<sup>53</sup> Through telephone interviews and face-to-face sessions with patients, pharmacists provide information on diet and exercise modification and prescribe and monitor lipid-lowering agents. Pharmacists may consult with other providers about nonformulary drug requests, drug therapy recom-

mentations, and lipid therapy management for patients who are refractory to or intolerant of formulary lipid-lowering medications.

A survey at LSCVAMC revealed that 91.4% of patients and 87.8% of providers were somewhat satisfied or strongly satisfied with care provided by the pharmacist-managed lipid clinic. The proportion of patients who reached LDL-C targets rose significantly as a result of participation in the lipid clinic from 8.6% at baseline to 68.6% after a mean of 3.2 months of clinic enrollment ( $P < .001$ ). LDL-C goals, as defined by the NCEP ATP III guidelines, were  $<100$  mg/dL for 80% of patients (those with established CVD or diabetes),  $<130$  mg/dL for 16.2% of patients (those with  $\geq 2$  CV risk factors), and  $<160$  mg/dL for 3.8% of patients (those with  $\leq 1$  risk factor). Pharmacists oversaw a mean of 2.2 drug changes and 0.58 dosage changes per patient during clinic enrollment. Furthermore, more than two thirds of patients (68.6%) required use of nonformulary medications including high-potency statins and combination therapy to achieve LDL-C targets.

Other lipid measures improved as well. After enrollment in the clinic, mean TC levels decreased 19% ( $P < .01$ ). Outcomes for TG and LDL-C stratified according to whether TG values that were elevated ( $>400$  mg/dL) at baseline also were improved. After clinic enrollment, TG levels decreased 30.8% in all patients and 52.4% in those with high baseline levels ( $P < .01$ ). In addition, LDL-C decreased 19.2% in all patients and 26.7% in those without elevated baseline TG levels ( $P < .01$ ). HDL-C levels did not change, which is often the case in patients treated with statin therapy.

### Experience at Texas VA Medical Centers

At two VA medical centers in Amarillo and Lubbock, Texas, Mazzolini and colleagues evaluated lipid outcomes among patients managed at the pharmacist-led dyslipidemia clinics ( $n = 115$ ) and patients managed with usual care in the primary care setting ( $n = 115$ ).<sup>55</sup> The study included patients with established CHD as well as those at high risk of CHD. More than half had 3 CHD risk factors. After 21.6 months of follow-up, lipid clinic patients were more likely to use lipid-lowering agents than those treated with usual care (93.9% vs 24.3%;  $P < .001$ ). More patients in the lipid clinic than patients in primary care achieved LDL-C goals (64.3% vs 15.7%;  $P < .001$ ) and TC goals (82.6% vs 40.9%;  $P < .001$ ). A similar proportion of patients managed in lipid clinics or the primary care setting achieved target levels of TG (65.2% vs 52.2%;  $P = .061$ ) and HDL-C (23.5% vs 33.0%;  $P = .0143$ ). In addition to the benefits of pharmacist-led interventions observed in this study, there are still opportunities to improve management of lipid-related risk factors.

### Experiences With Other Pharmacist-Led Programs

Weaver and colleagues evaluated the benefits of a pharmacy-led dyslipidemia intervention. Led by the Patrick Air Force Base (FL) Pharmacy Service Clinic in collaboration with community providers, the program included 310 patients with CHD, diabetes, or multiple risk factors who had been unsuccessful in attaining lipid treatment goals.<sup>56</sup> Patients had significant reductions in LDL-C levels after enrollment in the pharmacy-led lipid clinic program (baseline 148.8 mg/dL vs 110.9 mg/dL after intervention;  $P < .001$ ). Reductions in LDL-C levels were apparent in the subgroup of patients with CHD (137.7 vs 104.1 mg/dL;  $P < .001$ ) and in the subgroup of patients with multiple risk factors (157.1 vs 116.0 mg/dL;  $P < .001$ ). Before enrolling into the pharmacy-led lipid clinic program, no patient had achieved LDL-C treatment goals. After enrollment, 53.2% of patients with CHD reached LDL-C targets ( $<100$  mg/dL), and 80.1% of patients with multiple risk factors were at goal ( $<130$  mg/dL). Overall, 68.6% of patients attained LDL-C treatment targets ( $P < .001$  vs baseline).

A retrospective case-control study of 88 patients with dyslipidemia also showed the benefit of a pharmacist-led lipid clinic.<sup>52</sup> In this study, a hospital-based lipid clinic program was managed by clinical pharmacists who were responsible for ordering and interpreting lipid-related laboratory results and prescribing and monitoring lipid-lowering therapy. Compared with a group of patients managed with usual care by health care teams that did not include pharmacists, patients managed in the pharmacist-led clinic had a greater reduction in LDL-C (6.5% vs 18.5%;  $P = .049$ ). These findings favored the pharmacist-led intervention even though patients enrolled in the lipid clinic were more challenging than those managed by usual care, with a higher likelihood of having  $\geq 2$  risk factors ( $P = .046$ ) and HDL-C levels  $<40$  mg/dL ( $P = .031$ ). Investigators also observed a relationship between the number of clinic visits and the magnitude of treatment response, with differences between treatment groups emerging after 3 or more visits. In the pharmacy-led group, LDL-C changes in patients who made 1, 2, or  $\geq 3$  clinic visits were -11.4%, -23.2%, and -23.7%, respectively. By comparison, in the usual care group, 1, 2, or  $\geq 3$  office visits were associated with LDL-C changes of +11.0%, -18.0%, and -7.4% ( $P = .038$ ), respectively.

### Formulary Decision Making

Pharmacists should be prepared to make informed pharmacoeconomic choices when guiding institutions on which lipid-modifying medications to place on formulary and to manage the implications of formulary changes. For example, the most potent statins are typically the newer and more expensive agents. Organizations com-

monly switch from higher-cost agents to relatively inexpensive generic products in an attempt to reduce health care costs. With many generic statins available in the United States, and more to come in the next 2 years, pharmacists may see a surge in formulary changes.

In 2008, Miller and colleagues assessed the safety and efficacy of switching statin therapy using a therapeutic conversion program versus usual-care conversion when atorvastatin was removed from an institutional formulary.<sup>57</sup> In one group, clinical pharmacists led a therapeutic conversion program for switching 30 patients from atorvastatin to a new formulary regimen of simvastatin, rosuvastatin, or ezetimibe/simvastatin. In this group, pharmacists used a conversion algorithm designed to achieve individual patient goals for LDL-C management. In the control group, primary care providers switched atorvastatin to a new formulary regimen based on an optional equipotency conversion algorithm. Patients managed in the pharmacist-led group maintained their preconversion LDL-C levels after the switch (86.7 vs 82.3 mg/dL;  $P = .44$ ), and significantly more patients reached their LDL-C targets (80% vs 97%;  $P = .04$ ). Patients in the usual-care group had an increase in mean LDL-C level before and after the conversion (78.3 vs 85.2 mg/dL;  $P = .01$ ), and fewer patients were at LDL-C goal (90% vs 75%;  $P = .01$ ). In this study, clinical pharmacists provided clinical conversions in statin therapy after a formulary change, and this resulted in superior patient care as measured by LDL-C goal attainment rates compared with standard of care.

### Patient Screening

Given the asymptomatic nature of dyslipidemia, early screening can help identify patients who may benefit from early treatment to prevent disease progression and complications. New point-of-care testing devices and strategies simplify the screening process for patients and pharmacists.<sup>58</sup> Moreover, as novel biomarkers emerge, pharmacists will need to make decisions about the roles of biomarkers in assessing risk and guiding therapy. Findings from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that high-sensitivity C-reactive protein (hs-CRP) is a sensitive marker for CV risk and an important therapeutic target, even in apparently healthy patients without elevated LDL-C.<sup>59</sup>

Screening provides an important opportunity to interact with patients who may be at risk for CVD. Pharmacists can be instrumental in providing patient education by talking with patients and distributing educational materials on atherosclerosis, therapeutic lifestyle modifications, and drug therapy. Clinical pharmacists also can communicate regularly with primary care clinicians to coordinate screening and provide early intervention for patients with dyslipidemia.

### Addressing Barriers to Successful Treatment

Several studies have identified barriers to successful lipid management. In one study of patients with prior treatment failures, the most commonly identified barriers to attaining treatment goals included undertreatment or patient nonadherence to lipid-lowering therapy (57.3%), suboptimal dosing or failure to titrate (31.7%), suboptimal treatment selection (31.5%), and use of combination therapies with known tolerability concerns (14.1%).<sup>56</sup> Failure to titrate medications (clinical inertia) can diminish treatment success. Pharmacists can combat this problem by monitoring for treatment response, ensuring optimal dosing, and switching or intensifying treatment when efficacy has plateaued.

Adherence to lipid-lowering therapy is reported in the literature to be consistently low, with 30% to 73% of patients discontinuing statin therapy within 1 year of initiation.<sup>60</sup> Cultural factors and issues related to treatment complexity, tolerability, and increasing out-of-pocket cost can adversely affect long-term medication adherence. Patients may have different cultural expectations related to weight control, body image, exercise, and diet that increase the difficulty of implementing therapeutic lifestyle changes. Poor health literacy also may interfere with a patient's ability to take medications as prescribed.<sup>61</sup>

Poor adherence is related to specific features of certain drug regimens. In a study of 5759 patients who were initiating both antihypertensive therapy and lipid-lowering therapy, adherence became less likely as the number of prescription medications increased.<sup>62</sup> Like many patients with dyslipidemia, patients were managing multiple medical comorbidities; the mean prescription burden was 3.6 medications per patient. During the first year of follow-up, the mean proportion of days covered (PDC) for both antihypertensive and lipid-lowering therapies was 53.9%. Among patients with 0, 1, and 2 prior medications, adherence (PDC  $\geq 80\%$ ) to antihypertensive and lipid-lowering therapies was 41%, 35%, and 30%, respectively. Only 20% of patients with 10 or more prior medications were adherent to their new antihypertensive and lipid-lowering therapy regimen.

Pharmacists can address many of these common barriers to successful lipid management. Potential solutions include simplifying treatment regimens (e.g., using combination therapy with 1 pill) with sensitivity to medication costs, monitoring patients for medication adherence, flagging patients who require more intensive patient education, involving the patient's family in reaching treatment goals, and increasing follow-up with the patient's primary care physician and other members of the multidisciplinary care team.<sup>63</sup> The Federal Study of Adherence to Medications in the Elderly (FAME) trial was a multiphase investigation that included 200 community-based patients aged  $\geq 65$  years taking at

least 4 chronic medications.<sup>63</sup> The study was conducted from June 2004 to August 2006. Initially, all 200 patients entered a 2-month run-in phase that provided a baseline for medication adherence using pill counts and for blood pressure and LDL-C readings. Of these patients, 174 then entered a 6-month intervention phase that included standardized medication education, regular follow-up by pharmacists, and all medications dispensed in time-specified blister packs. Following the intervention phase, 159 patients were randomly assigned to continue the pharmacy care program or return to their usual care for an additional 6 months.

The average medication regimen consisted of 9 chronic daily medications. At the beginning of the first phase of the study, the average medication adherence was 61.2%. After 6 months of intervention, medication adherence increased to 96.9% ( $P < .001$ ) and was associated with significant improvements in systolic blood pressure (133.2 to 129.9 mm Hg;  $P = .02$ ) and LDL-C (91.7 to 86.8 mg/dL;  $P = .001$ ). Six months after randomization, the persistence of medication adherence decreased to 69.1% among patients assigned to usual care, but was sustained at 95.5% in pharmacy care ( $P < .001$ ). The pharmacy-care group had significant reductions in systolic blood pressure compared with the usual care group, but there were no significant differences between the groups in LDL-C level or reduction at the end of the study.

A 2010 meta-analysis of 11 adherence studies enrolling 6681 patients with dyslipidemia examined the benefits of pharmacist-led interventions.<sup>64</sup> Patient education, including the use of videotapes, booklets, and newsletters distributed by the pharmacist, increased adherence to lipid-lowering therapy 13% ( $P = .005$ ). Simplifying the drug regimen—e.g., reducing medication intake from 4 times daily to twice daily—improved mean medication intake 11% ( $P = .01$ ). Use of patient reminders also significantly improved medication adherence. Across various studies, regular phone reminders increased adherence to statin therapy 9% to 24% ( $P < .05$ ). Giving patients who were initiating lipid-modifying therapy a simple calendar that included medication reminders improved adherence 8% ( $P < .005$ ). Overall, providing education and reminders were the most effective strategies for improving adherence to lipid-modifying therapies.

**What advice would you give to a patient seeking “natural” remedies for his/her elevated LDL-C?**

- A. Encourage aggressive therapeutic lifestyle modifications.**
- B. Suggest a fish oil supplement.**
- C. Suggest red yeast rice.**
- D. Tell him/her that natural therapies don’t have documented efficacy.**

**Monitoring Safety and Efficacy of Nonprescription Medications**

Pharmacists may be directly involved in routine monitoring of drug safety and tolerability. In addition, pharmacists should be alert to other safety-related factors that may interfere with treatment success. In an attempt to avoid side effects associated with standard lipid-lowering therapies, some patients may be relying on nonprescription formulations that are not effective for treating dyslipidemia. For example, inositol hexanicotinate has been promoted as a form of “no-flush” or “flush-free” niacin, yet appears to have little clinical efficacy.<sup>65</sup> Flushing is a common dose-limiting side effect of immediate-release niacin that contributes to the low rates of adherence to this formulation of niacin therapy. Extended-release niacin formulations have a better tolerability profile, including a lower risk of flushing, leading to better patient acceptance and a lower discontinuation rate. However, given the concerns about flushing, even with extended-release niacin, a “flush-free” option may be attractive for some patients and providers. The “flush-free” compound inositol hexanicotinate is composed of 6 molecules of niacin covalently attached to inositol by ester bonds. There is no evidence that inositol hexanicotinate is metabolized to free niacin or that treatment with inositol hexanicotinate alters plasma lipid levels. Inositol hexanicotinate may not induce flushing, but only because niacin appears to have no bioavailability in this formulation.<sup>65</sup>

Another example comes from a Government Accountability Office (GAO) study of deceptive or questionable marketing practices and potentially dangerous advice by manufacturers of herbal dietary supplements.<sup>66</sup> The product labeling on one garlic supplement stated that “Hundreds of scientific studies have proven [this product] to be number one, working to enhance the body’s immune function, protect cells from free radical damage, and reduce cardiovascular risk factors, including issues with blood pressure, cholesterol ...”<sup>66</sup> There is no conclusive evidence supporting the efficacy of garlic in altering lipid parameters or cardiovascular outcomes.

Another dietary supplement, red yeast rice (*M. purpureus*), is not recommended for patients with hypercholesterolemia. The supplement contains naturally occurring monacolin K, the active ingredient in lovastatin. A lack of uniformity among products, possibility of contamination, and risk of severe adverse reactions (myopathy, rhabdomyolysis) pose a threat to individuals using this product.<sup>67,68</sup> Overall, red yeast rice has not been shown to be a safe alternative to statins for patients with hyperlipidemia despite its demonstrated efficacy in controlled clinical trials. Pharmacists should be aware of its popularity as a “natural” way to lower serum cholesterol and discuss the risks and benefits of this supplement with their patients. Red yeast rice has been shown to be effective in lowering cholesterol in

patients who are intolerant to statins due to myalgias.<sup>69</sup>

In its study of dietary supplements, the GAO found at least 1 potentially hazardous contaminant in 37 of the 40 herbal dietary supplements it tested. The GAO screened for specific contaminants most likely to have negative health consequences if consumed, including lead, arsenic, mercury, cadmium, and residues from organochlorine and organophosphorous pesticides.<sup>66</sup> In addition, there are numerous reports of imported herbal medications that contain unlabeled prescription ingredients.

Discussing the safety and efficacy of nonprescription products is an important component of patient education. Pharmacists should be alert to potential interactions between prescription medications and herbal preparations. “Natural” products, as well as some foods, use hepatic pathways (CYP 450 system) for metabolism and excretion and may delay or speed elimination of prescription drugs. Therefore, it is important to ask patients about all medications they are taking, including prescription medication, OTC drugs, or herbal/nutritional supplements.

## Conclusions

Clinical pharmacists have many opportunities for improving dyslipidemia management, including identifying at-risk patients who may benefit from therapy, ensuring the safe initiation of lipid-lowering treatment, monitoring patients for adherence, treatment response, and tolerability, and providing ongoing patient education. National guidelines may help health care professionals more effectively screen and categorize patients on the basis of CHD risk and therefore determine the need for and type of intervention. More aggressive approaches to lipid-lowering treatments are recommended for patients at higher risk, including those with certain comorbidities such as diabetes or chronic kidney disease. Studies have demonstrated that pharmacist-led interventions, including lipid clinics, can help patients achieve these more aggressive goals. The pharmacist is well positioned to enhance screening opportunities, assess risk, recommend and monitor therapies, and provide pharmacoeconomic guidance in formulary management. ■

### Participants wishing to earn CPE credit must:

1. Read the supplement.
2. Relate the content material to the learning objectives.
3. Complete the self-assessment questions and evaluation form online at:  
[www.practicingclinicians.com/eclinic/testing](http://www.practicingclinicians.com/eclinic/testing)

After login, please select the code: **CAE74310**

**Successful completion of the self-assessment is required to earn CPE credit. Successful completion is defined as a cumulative score of at least 70%. A certificate of credit will be automatically generated upon successful completion of the activity.**

## REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics—2010 Update: A Report From the American Heart Association. *Circulation*. 2010;121(7):e46-e215.
2. 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) final report. *Circulation*. 2002;106(25):3143-31421.
3. 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(2):227-239.
4. Ghandehari H, Kamal-Bahl S, Wong ND. Prevalence and extent of dyslipidemia and recommended lipid levels in US adults with and without cardiovascular comorbidities: the National Health and Nutrition Examination Survey 2003-2004. *Am Heart J*. 2008;156(1):112-119.
5. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. *Am Heart J*. 2009;157(1):111-117.
6. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364(9438):937-952.
7. McQueen MJ, Hawken S, Wang X, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. *Lancet*. 2008;372(9634):224-233.
8. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117(23):3002-3009.
9. Jiang R, Schulze MB, Li T, et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care*. 2004;27(8):1991-1997.
10. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation*. 2005;112(22):3375-3383.
11. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31(4):811-822.
12. Olson KL, Potts LA. Role of the pharmacist in the management of dyslipidemia. *J Pharm Pract*. 2006;19(2):94-102.
13. Chisholm-Burns MA, Kim Lee J, Spivey CA, et al. US Pharmacists' Effect as Team Members on Patient Care: Systematic Review and Meta-Analyses. *Med Care*. 2010;48(10):923-933.
14. Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. *Am J Cardiol*. 2001;88(5):504-508.
15. Dujovne CA, Ertinger MP, McNeer JE, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90(10):1092-1097.
16. Dall TL, Bays H. Addressing lipid treatment targets beyond cholesterol: a role for prescription omega-3 fatty acid therapy. *South Med J*. 2009;102(4):390-396.
17. Jones PH, Davidson MH, Stein EA, et al, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). *Am J Cardiol*. 2003;92(2):152-160.
18. Waters DD, LaRosa JC, Barter P, et al. Effects of high-dose atorvastatin on cerebrovas-

- cular events in patients with stable coronary disease in the TNT (treating to new targets) study. *J Am Coll Cardiol*. 2006;48(9):1793-1799.
19. Colhoun HM, Betteridge DJ, Durrington PN, et al. 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(9435):685-696.
  20. Collins R, Armitage J, Parish S, et al. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet*. 2003;361(9374):2005-2016.
  21. Sever PS, Dahlof B, Poulter NR, et al. ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361(9364):1149-1158.
  22. SPARCL Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355(6):549-559.
  23. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis of the therapeutic equivalence of statins. *J Clin Pharm Ther*. 2010;35(2):139-151.
  24. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. 2006;97(8A):89C-94C.
  25. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. *Arch Intern Med*. 2004;164(7):697-705.
  26. Poon IO, Chow DS, Liang D. Dissolution profiles of nonprescription extended-release niacin and inositol niacinate products. *Am J Health Syst Pharm*. 2006;63(21):2128-2134.
  27. Saha SA, Kizhakepunnur LG, Bahekar A, Arora RR. The role of fibrates in the prevention of cardiovascular disease—a pooled meta-analysis of long-term randomized placebo-controlled clinical trials. *Am Heart J*. 2007;154(5):943-953.
  28. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375(9729):1875-1884.
  29. Ginsberg HN, Elam MB, Lovato LC, et al; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1563-1574.
  30. BIP Study Group. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease. The Bezafibrate Infarction Prevention (BIP) Study. *Circulation*. 2000;102(1):21-27.
  31. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359(13):1343-1356.
  32. Peto R, Emberson J, Landray M, et al. Analyses of cancer data from three ezetimibe trials. *N Engl J Med*. 2008;359(13):1357-1366.
  33. Garg A, Grundy SM. Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. A short-term, double-blind, crossover trial. *Ann Intern Med*. 1994;121(6):416-422.
  34. Fonseca V, Handelsman Y, Staels B. Colesevelam lowers glucose and lipid levels in type 2 diabetes: the clinical evidence. *Diabetes Obes Metab*. 2010;12(5):384-392.
  35. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet*. 1999;354(9177):447-455.
  36. LOVAZA [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
  37. Harris WS. N-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr*. 1997;65(suppl 5):1645S-1654S.
  38. Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in *Circulation*. 2003;107:512]. *Circulation*. 2002;106(21):2747-2757.
  39. U.S. Food and Drug Administration. What you need to know about mercury in fish and shellfish. 2004 EPA and FDA advice for: women who might become pregnant, women who are pregnant, nursing mothers, young children. <http://www.fda.gov/food/foodsafety/product-specificinformation/seafood/foodbornepathogenscontaminants/methylmercury/ucm115662.htm>. Accessed October 6, 2010.
  40. Ballantyne CM, Davidson MH, McKenney J, et al. Comparison of the safety and efficacy of a combination tablet of niacin extended release and simvastatin vs simvastatin monotherapy in patients with increased non-HDL cholesterol (from the SEACOAST I study). *Am J Cardiol*. 2008;101(10):1428-1436.
  41. Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med*. 2009;361(22):2113-2122.
  42. Hunninghake D, Insull W Jr, Toth P, et al. Coadministration of colesvelam hydrochloride with atorvastatin lowers LDL cholesterol additively. *Atherosclerosis*. 2001;158(2):407-416.
  43. Goldberg AC, Bays HE, Ballantyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. *Am J Cardiol*. 2009;103(4):515-522.
  44. Jones PH, Davidson MH, Kashyap ML, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: a phase 3 study. *Atherosclerosis*. 2009;204(1):208-215.
  45. Jones PH, Cusi K, Davidson MH, et al. Efficacy and safety of fenofibric acid co-administered with low- or moderate-dose statin in patients with mixed dyslipidemia and type 2 diabetes mellitus: results of a pooled subgroup analysis from three randomized, controlled, double-blind trials. *Am J Cardiovasc Drugs*. 2010;10(2):73-84.
  46. Rotella C, Zaninelli A, Le Grazie C, et al. Ezetimibe/simvastatin vs simvastatin in coronary heart disease patients with or without diabetes. *Lipids Health Dis*. 2010;9:80.
  47. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med*. 2008;358(14):1431-1443.
  48. Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomized open-label, blinded endpoint analysis. *Lancet*. 2007;369(9567):1090-1098.
  49. Bays HE, McKenney J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. *Mayo Clin Proc*. 2010;85(2):122-128.
  50. Superko HR, Garrett BC, King SB 3rd, et al. Effect of combination nicotinic acid and gemfibrozil treatment on intermediate density lipoprotein, and subclasses of low density lipoprotein and high density lipoprotein in patients with combined hyperlipidemia. *Am J Cardiol*. 2009;103(3):387-392.
  51. O'Donnell DC, Chen NT, Piziak VK. Goal attainment and maintenance of serum cholesterol level in a pharmacist-coordinated lipid clinic. *Am J Health Syst Pharm*. 2001;58(4):325-330.
  52. Till LT, Voris JC, Horst JB. Assessment of clinical pharmacist management of lipid-lowering therapy in a primary care setting. *J Manag Care Pharm*. 2003;9(3):269-273.
  53. Collins C, Kramer A, O'Day ME, Low MB. Evaluation of patient and provider satisfaction with a pharmacist-managed lipid clinic in a Veterans Affairs medical center. *Am J Health Syst Pharm*. 2006;63(18):1723-1727.
  54. Machado M, Nassor N, Bajcar JM, et al. Sensitivity of patient outcomes to pharmacist interventions. Part III: systematic review and meta-analysis in hyperlipidemia management. *Ann Pharmacother*. 2008;42(9):1195-1207.
  55. Mazzolini TA, Irons BK, Schell EC, Seifert CF. Lipid levels and use of lipid-lowering drugs for patients in pharmacist-managed lipid clinics versus usual care in 2 VA Medical Centers. *J Manag Care Pharm*. 2005;11(9):763-771.
  56. Weaver JG, McManus JE, Leung T, et al. Impact of pharmacy-led dyslipidemia interventions on medication safety and therapeutic failure in patients. In: Hendriksen K, Battles JB, Marks ES, Lewin DI, eds. *Advances in Patient Safety: From Research to Implementation*. Vol 1, Research findings. Rockville, MD: Agency for Healthcare Research and Quality; February 2005. AHRQ Publication No. 05-0021-1.
  57. Miller AE, Hansen LB, Saseen JJ. Switching statin therapy using a pharmacist-managed therapeutic conversion program versus usual care conversion among indigent patients. *Pharmacotherapy*. 2008;28(5):553-561.
  58. Rodis JL, Thomas RA. Stepwise approach to developing point-of-care testing services in the community/ambulatory pharmacy setting. *J Am Pharm Assoc*. 2006;46(5):594-604.
  59. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.
  60. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. *Ann Pharmacother*. 2010;44(9):1410-1421.
  61. Kripalani S, Gatti ME, Jacobson TA. Association of age, health literacy, and medication management strategies with cardiovascular medication adherence. *Patient Educ Couns*. 2010;81(2):177-181.
  62. Benner JS, Chapman RH, Petrilla AA, et al. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Health Syst Pharm*. 2009;66(16):1471-1477.
  63. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA*. 2006;296(21):2563-2571.
  64. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev*. 2010;3: CD004371.
  65. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol*. 2007;99(6A):22C-31C.
  66. *Government Accountability Office*. Herbal dietary supplements. Examples of deceptive or questionable marketing practices and potentially dangerous advice. Publication number GAO-10-662T, 2010. <http://www.gao.gov/new.items/d10662t.pdf>. Accessed October 21, 2010.
  67. Klimek M, Wang S, Ogunkanmi A. Safety and efficacy of red yeast rice (*monascus purpureus*) as an alternative therapy for hyperlipidemia. *PT*. 2009;34(6):313-327.
  68. Gordon RY, Cooperman T, Obermeyer W, Becker DJ. Marked variability of monacolin levels in commercial red yeast rice products. Buyer beware! *Arch Intern Med*. 2010;170:1722-1727.
  69. Becker DJ, Gordon RY, Halbert SC, et al. Red yeast rice for dyslipidemia in statin-intolerant patients: a randomized trial. *Ann Intern Med*. 2009;150:820-859.

---

NOTES:

