

## Dyslipidemia and Cardiovascular Risk Reduction: A Review Based on the Evidence

### What We Know About Dyslipidemia

- ➔ Cardiovascular disease (CVD) is the leading cause of death in the United States
- ➔ Dyslipidemia, a leading risk factor for CVD and stroke, includes high low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), and elevated triglyceride (TG) levels
- ➔ Efforts to prevent CVD have a high priority and include risk-reduction therapy

### Learning Objectives

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

- ➔ Discuss current guidelines for the management of dyslipidemia
- ➔ Describe the results of recent clinical trials relevant to the management of dyslipidemia
- ➔ State lipid goals according to patients' level of cardiovascular risk

### Cardiovascular Disease: Why Is the Burden Still So Heavy?

Cardiovascular disease accounted for 37% of all deaths in the United States in 2003 (the latest year available), and more than 71 million American adults are believed to have some form of CVD.<sup>1</sup> The total US cost of cardiovascular and cerebrovascular diseases in 2006 was estimated at more than \$403 billion.<sup>1</sup> Efforts to prevent CVD have high priority and include the assessment of risk and risk-reduction therapy.

There is an urgent need to improve screening for and management of dyslipidemia in primary care

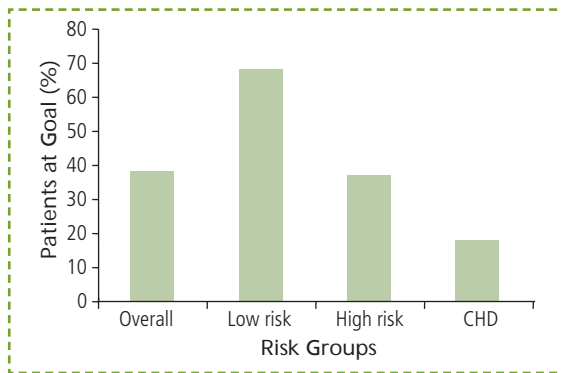
How should muscle pain complaints be handled?  
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## Dyslipidemia and Cardiovascular Risk Reduction: A Review Based on the Evidence

Dyslipidemia, a leading risk factor for CVD and stroke, includes high LDL-C, low HDL-C, and elevated TG levels. According to a survey conducted in 2003, almost half of US adults had total cholesterol levels of 200 mg/dL or higher. Nearly 40% had borderline high or higher LDL levels at or above 130 mg/dL,<sup>1</sup> while more than 20% had HDL below the desired threshold of 40 mg/dL.<sup>1</sup>

### Risk Reduction Efforts Fall Short

Failure to achieve lipid goals is a persistent problem,<sup>2</sup> although more patients appear to be using lipid-lowering medications than ever before. The Lipid Treatment Assessment Project (L-TAP) survey found that only 38% of patients diagnosed with dyslipidemia reached National Cholesterol Education Program (NCEP)–recommended targets for LDL-C, despite treatment (Figure 1).<sup>2</sup>



**Figure 1.** In the L-TAP survey, only 38% of patients with dyslipidemia treated with lipid-lowering medications reached NCEP LDL goals. The highest success rate (68%) was seen in low-risk patients. Only 37% of high-risk patients achieved goals, and the success rate was lowest among patients with coronary heart disease (18%). Pearson TA et al.<sup>2</sup>

The reasons so many patients do not reach treatment goals are complex and involve both patients and healthcare providers. Not all clinicians follow the NCEP lipid screening and intervention guidelines to the letter.<sup>3,4</sup> Many high-risk patients are not assessed as the guidelines recommend and therefore do not receive adequate treatment.<sup>3,4</sup> Even after receiving a diagnosis, counseling, and treatment recommendations, many patients do not adhere to lifestyle modifications and medication regimens for long.<sup>3</sup>

Persistence with medication is measured as the percentage of patients who continue to take their medication as prescribed over a designated period. A recent analysis of pharmacy records to determine how many patients persisted with statin therapy found that overall persistence dropped from 56% at 9 months to 35% at 12 months.<sup>5</sup> The fall-off in adherence was seen across all subgroups of patients: men, women, younger, older, and patients who did or did not pay directly for their

### NCEP ATP III Risk Interpretations for Lipid Levels

Test	Optimal	Borderline High Risk	High Risk	Very High Risk
Total cholesterol	<200	200-239	≥240	
LDL-C	<100	130-159	160-189	≥190
HDL-C	≥60	40-59	<40*	
TG	<150	150-199	200-499	≥500

\*In clinical practice, HDL-C levels <40 mg/dL in men and <50 mg/dL in women are considered high risk. Expert Panel<sup>7</sup>; ADA<sup>8</sup>; Mosca L et al.<sup>9</sup>

medications.<sup>5</sup> By the end of the study, adherence was down to 34% for men, 18% for women, 19% for patients aged younger than 65 years, and 41% for patients aged 65 years and older.<sup>5</sup>

Another measure of medication adherence is the number of gap days between prescription refills, which indicates if patients are taking medications inconsistently and missing doses. The number of gap days between prescription refills was greater for women than for men, indicating further that women were less likely than men to adhere to therapy.<sup>5</sup> These findings may reflect that patients perceive CVD risk differently. Older men, for example, may be more aware that they are at risk for heart disease and, therefore, more likely to take medications to reduce that risk.<sup>5</sup> Regrettably, most US women do not understand that heart disease is the leading cause of death for women, and instead believe breast cancer to be a greater health concern.<sup>6</sup>

It is clear that there is an urgent need for primary care clinicians to increase their efforts to follow current guidelines and improve screening for and management of dyslipidemia in their patients. As part of these efforts, clinicians also need to counsel their patients more effectively about the threat of CVD and to explain how important it is to adhere to therapeutic lifestyle changes (TLCs) and prescribed medication regimens.

## Risk Assessment Is the Critical First Step

The NCEP Adult Treatment Panel (ATP) III risk interpretations for each fasting lipid parameter are shown in Table 1.<sup>7</sup>

Levels of LDL-C between 100 and 129 mg/dL are considered to be near or above optimal, indicating a relatively low risk for CVD. Levels of HDL-C below 40 mg/dL are considered too low because they are associated with a higher risk of coronary heart disease (CHD).<sup>7</sup>

Although the NCEP ATP III guidelines do not differentiate HDL interpretation according to gender, the American Diabetes Association (ADA) and the American Heart Association (AHA) make such a distinction. Both of these organizations advise that HDL-C levels in women should be above 50 mg/dL, rather than above 40 mg/dL as in men.<sup>8,9</sup>

When a fasting lipoprotein profile has been obtained, the next step is to evaluate the main determinants of risk, as listed in Table 2. Patients at highest risk are those with a history of CHD or who have risk factors equivalent to CHD.<sup>7</sup>

### NCEP ATP III Main Determinants of Risk

- CHD or CHD risk equivalents:
  - Other clinical atherosclerotic disease (peripheral arterial disease, peripheral vascular disease, abdominal aortic aneurysm, symptomatic carotid artery disease, or stroke)
  - Diabetes
- Cigarette smoking
- Hypertension (BP  $\geq$ 140/90 mm Hg, or using antihypertensive medication)
- High LDL-C level ( $>$ 130 mg/dL)
- Low HDL-C level ( $<$ 40 mg/dL)
- Family history of premature CHD (male first-degree relative aged  $<$ 55 years or female first-degree relative aged  $<$ 65 years)
- Age (men aged  $\geq$ 45 years, women aged  $\geq$ 55 years)

BP = blood pressure.  
Expert Panel.<sup>7</sup>

In patients who do not have existing CHD or a CHD risk equivalent, the next step is to use a risk assessment tool to determine the Framingham risk score.<sup>7</sup> The Framingham score estimates the patient’s risk of developing CHD over the next 10 years. An online tool for estimating the Framingham risk is available at the NCEP Web site.<sup>10</sup> This calculator uses data from the Framingham Heart Study to estimate the 10-year risk of a “hard” CHD event (myocardial infarction [MI] or coronary death) in adults 20 years of age or older who do not have heart disease, a risk equivalent, or diabetes. Other tools, including online calculators, spreadsheet calculators, and calculator software for handheld devices, are available at the NCEP Web site,<sup>11</sup> the Mobile Lipid Clinic Web site,<sup>12</sup> and the Reynolds Risk Score Web site for calculating risk in women.<sup>13</sup>

The final step is to determine the patient’s NCEP ATP III risk category. According to the Framingham risk score and other important risk factors, the patient may be considered to be at low risk, moderate risk, moderately high risk, high risk, or very high risk of a cardiovascular (CV) event.<sup>14</sup> Each risk category is described in Table 3. The category *very high risk* has been suggested for patients who have established CVD plus 1 of the following<sup>14</sup>:

- ▶ Multiple risk factors (especially diabetes)
- ▶ A severe and poorly controlled risk factor (eg, persistent cigarette smoking)
- ▶ Multiple risk factors indicating metabolic syndrome
- ▶ Acute coronary syndrome

**NCEP ATP III Risk Categories**

Risk Category	Criteria
Low risk	0-1 risk factor
Moderate risk	≥2 risk factors; 10-year risk <10%
Moderately high risk	≥2 risk factors; 10-year risk 10%-20%
High risk	CHD or CHD risk equivalents, or ≥2 risk factors with a 10-year risk >20%
Very high risk	Established CVD plus 1 of 4 additional factors

Expert Panel<sup>7</sup>; Grundy SM et al.<sup>14</sup>

**Metabolic Syndrome in Risk Assessment**

Metabolic syndrome encompasses a cluster of abnormalities, including dyslipidemia, that increase the risk of developing CVD and diabetes. Several organizations have proposed definitions for the metabolic syndrome; the 2 most recent proposals are summarized in Table 4.<sup>15,16</sup> The AHA/National Heart, Lung, and Blood Institute (NHLBI) and International Diabetes Foundation (IDF) defini-

tions are similar and focus on abdominal or central obesity (as indicated by increased waist circumference), dyslipidemia, hypertension, and elevated blood glucose levels as central criteria.<sup>15,16</sup> The AHA/NHLBI definition requires the presence of 3 or more criteria for a diagnosis of metabolic syndrome.<sup>16</sup> The IDF definition requires the presence of central obesity (defined as waist circumference above ethnicity-specific thresholds) as an essential component, in addition to 2 or more of the factors listed.<sup>15</sup>

The metabolic syndrome is more common in older age groups. Data from 8814 men and women at least 20 years of age who participated in the Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994 were assessed to estimate the prevalence of the metabolic syndrome as defined by the NCEP ATP III.<sup>17</sup>

Prevalence overall increased from 6.7% at ages 20 to 29 years to a peak of 43.5% at ages 60 to 69 years, which can be extrapolated to mean that approximately 47 million US adults have the metabolic syndrome.<sup>17</sup> Although prevalence differed little between men and women in the different age groups, there were gender differences by ethnic group.

## NCEP Guidelines in a Nutshell

Primary care clinicians can take 3 essential steps to help their patients reap the greatest possible benefit from lipid-lowering efforts:

- ▶ Identify individuals at increased risk of CHD and CV events
- ▶ Start appropriate treatment in a timely manner
- ▶ Monitor treatment to ensure that it enables patients to achieve and maintain goals for lipid control

One of the challenges clinicians face is targeting treatment to have the greatest impact despite limitations of time and other resources. Patients who are at high risk stand to gain the greatest benefits from dyslipidemia treatment. Therefore, it is important to identify patients who have a 10-year Framingham risk score >20%, plan a treatment strategy to reach their lipid goals, and monitor their progress on treatment.

Even in patients with a 10% risk score, CVD risk is still considerable. These patients may start with TLCs, but most will need the addition of lipid-lowering medications to reach goal. Patients who are at lower levels of risk should also be informed about health conditions and risks that may develop, as well as the measures they can take to avoid CVD in the future. This information may help motivate patients to follow through and possibly prevent adverse outcomes.

**Metabolic Syndrome Definitions: AHA/NHLBI and IDF**

Components	AHA/NHLBI ≥3 Components	IDF WC + ≥2 Components
WC	≥102 cm (40") in men; ≥88 cm (35") in women	Europid ≥94 cm (37") in men; ≥80 cm (31.5") in women South Asians, Chinese, Japanese ≥90 cm (35.5") in men; ≥80 cm (31.5") in women
TG (mg/dL)	≥150*	≥150*
HDL-C (mg/dL)	<40 in men; <50 in women*	<40 in men; <50 in women*
Blood pressure (mm Hg)	Systolic ≥130 or diastolic ≥85 <sup>†</sup>	Systolic ≥130 or diastolic ≥85 <sup>†</sup>
Fasting plasma glucose (mg/dL)	≥100 <sup>‡</sup>	≥100 <sup>§</sup>

WC = waist circumference. \*Or receiving treatment for this lipid abnormality. <sup>†</sup>Or receiving treatment for hypertension. <sup>‡</sup>Or receiving treatment for elevated glucose. <sup>§</sup>Or prior diagnosis of type 2 diabetes. IDF<sup>15</sup>; Grundy SM et al.<sup>16</sup>

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The NCEP ATP III guidelines give thresholds for initiating LDL-lowering therapy that depend on the risk level, as shown in Table 5.<sup>14</sup> For low-risk patients with fewer than 2 risk factors, TLCs are advised when LDL levels are at or above 160 mg/dL; drug therapy is recommended when LDL levels reach 190 mg/dL or higher. Further, the guidelines suggest that an LDL-lowering drug is optional in low-risk patients when LDL levels are between 160 and 189 mg/dL.<sup>14</sup>

Moderate-risk patients should begin TLCs when LDL levels are at or above 130 mg/dL; drug therapy should be considered when LDL levels reach or exceed 160 mg/dL.<sup>14</sup> For patients in the moderately high-risk category, lifestyle changes and treatment with a lipid-lowering medication are recommended when the LDL levels are at or above 130 mg/dL; drug therapy is an option at LDL levels from 100 to 129 mg/dL.<sup>14</sup> For high-risk patients, NCEP guidelines advocate TLCs and drug therapy when LDL levels are at or above 100 mg/dL, and suggest that an LDL-lowering drug is an option even at LDL levels below 100 mg/dL.<sup>14</sup> In very high-risk patients, the guidelines recommend TLCs and drug therapy when LDL levels are at 70 mg/dL or above.<sup>14</sup>

NCEP ATP III LDL Thresholds for Therapy by Risk Category

Risk Category	Risk Factors	TLCs	Consider Drug Therapy
Low risk	0-1 risk factor	≥160 mg/dL	≥190 mg/dL (optional at 160-189)
Moderate risk	≥2 risk factors; 10-year risk <10%	≥130 mg/dL	≥160 mg/dL
Moderately high risk	≥2 risk factors; 10-year risk 10%-20%	≥130 mg/dL	≥130 mg/dL (optional at 100-129)
High risk*	CHD or CHD risk equivalents; 10-year risk >20%	≥100 mg/dL	≥100 mg/dL

\*Very high risk is an additional category suggested for patients with established CVD plus at least 1 of 4 additional factors (multiple major risk factors, severe and poorly controlled risk factors such as continued cigarette smoking, metabolic syndrome, or acute coronary syndrome); the recommended LDL-C goal for very high-risk patients is <70 mg/dL.  
Grundy SM et al.<sup>14</sup>

### NCEP ATP III Therapeutic Lipid Goals

The 2004 update to the NCEP ATP III guidelines was developed to include results from recent clinical trials with statins.<sup>14</sup> The 2004 guidelines suggest that drug therapy should be sufficiently intense to achieve at least a 30% to 40% reduction in LDL levels. The addition of a fibrate or nicotinic acid should also be considered as part of therapy in high-risk patients with elevated TG levels or low HDL levels. It is further recommended that any moderately high-risk or high-risk individuals with lifestyle-related risk factors should be considered candidates for TLCs, regardless of their LDL levels.<sup>14</sup>

The NCEP 2004 update recommends specific lipid treatment goals for each risk category. The guidelines recommend reducing LDL levels to <160 mg/dL in low-risk patients, <130 mg/dL in moderate- and moderately high-risk patients, and <100 mg/dL in high-risk patients.<sup>14</sup> Further, in moderately high-risk patients, an optional LDL goal of <100 mg/dL is suggested. An LDL goal of <70 mg/dL is optional in high-risk patients and is favored in very high-risk patients (Table 6).

A review by Cheng and Leiter, published in 2006, examined the results from key clinical trials of 2005 and concluded that these recent trials support an approximate LDL target of less than 77 mg/dL for all high-risk patients, rather than an LDL goal of less than 70 for only very high-risk patients.<sup>18</sup> This target requires statin therapy at a higher dose than that required to achieve an LDL goal of less than 100 mg/dL. However, the substantial clinical benefits—a decreased risk of major coronary events and/or coronary mortality—are considered to outweigh a slight increase in adverse events associated with higher-dose statins.<sup>18</sup>

A secondary lipid target of therapy in patients with elevated TG levels ( $\geq 200$  mg/dL) is non-HDL, equivalent to very low-density lipoprotein cholesterol (VLDL) plus LDL (which includes intermediate-density lipoprotein). Non-HDL is calculated as total cholesterol minus HDL.<sup>7,14</sup> The non-HDL goal is 30 mg/dL higher than the LDL target goal, as

**NCEP ATP III Therapeutic Goals for LDL**

Risk Category	Risk Factors	LDL Goal (mg/dL)	Non-HDL Goal (mg/dL)
Low risk	0-1 risk factor	<160	<190
Moderate risk	$\geq 2$ risk factors; 10-year risk <10%	<130	<160
Moderately high risk	$\geq 2$ risk factors; 10-year risk 10%-20%	<130 (optional goal <100)	<160
High risk	CHD or CHD risk equivalents; 10-year risk >20%	<100 (optional goal <70)	<130 (optional goal <100)
Very high risk	Established CVD plus 1 of 4 additional factors	<70	<100 if TG levels are high

Expert Panel<sup>7</sup>; Grundy SM et al.<sup>14</sup>

shown in Table 6. The optional non-HDL goal in very high-risk patients with high TG levels is less than 100 mg/dL.<sup>14</sup> Non-HDL was added as a secondary target of therapy due to the atherogenic potential of remnant lipoproteins in patients with elevated TGs.<sup>14</sup>

Although HDL is not a primary target of treatment, it is nonetheless an important consideration, particularly in patients with the metabolic syndrome. Once LDL levels are reduced to target levels, the focus shifts to managing the metabolic syndrome and associated lipid abnormalities.<sup>7</sup> In addition to TLCs, specific therapies for weight reduction and increasing physical activity can help modify both lipid and nonlipid risk factors associated with the metabolic syndrome.<sup>7</sup> When TGs are high, the secondary goal of therapy becomes non-HDL.<sup>7,14</sup> If TG levels are below 200 mg/dL, the focus shifts to

HDL, which is a strong independent risk factor for CHD.<sup>7</sup> Used alone or in combination with a statin, current drugs prescribed to raise HDL are fibrates and niacin (nicotinic acid).<sup>7,14</sup> Niacin is the most effective, producing a marked increase in HDL when used in combination with a statin.<sup>14</sup> However, some patients do not tolerate niacin well because of side effects, such as skin flushing and itching.<sup>19</sup>

## **Lipid Treatment Goals in Diabetes**

The ADA advocates lifestyle changes, including dietary modification and increased physical activity, for patients with type 2 diabetes and dyslipidemia.<sup>8</sup> For patients with diabetes who do not have overt CVD, the ADA recommends a primary LDL goal of less than 100 mg/dL. In addition, for those older than 40 years, statin therapy is advised to reduce LDL levels by 30% to 40%, regardless of baseline LDL levels. Individuals with overt CVD, regardless of age, should be treated with a statin to decrease LDL by 30% to 40%. An optional LDL goal of less than 70 mg/dL is suggested. The ADA further recommends maintaining TG levels below 150 mg/dL and HDL levels above 40 mg/dL in men and 50 mg/dL in women.<sup>8</sup> On the basis of recent data, it has been suggested that all patients with diabetes—even those who do not have other risk factors—should be treated with statins.<sup>18</sup>

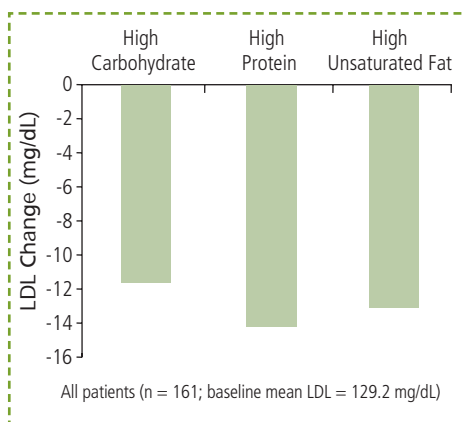
## **Therapeutic Lifestyle Changes: First Line of Therapy**

Lifestyle modification, the first line of therapy for dyslipidemia, is aimed at modifying risk factors, such as dyslipidemia, hypertension, and smoking. Healthful changes can positively and profoundly affect CV outcomes. A large observational study in men aged 40 to 75 years at baseline examined the effect of 16 years' adherence to a healthy lifestyle on the development of CHD.<sup>20</sup> The healthy lifestyle factors were (1) not smoking; (2) maintaining a healthy weight (body mass index [BMI] <25 kg/m<sup>2</sup>); (3) exercising at least 30 minutes per day; (4) moderate alcohol consumption; and (5) a healthy diet (in the top 40% of healthy diet scores). Men who were at low risk on all 5 healthy lifestyle factors had a substantially reduced risk of CHD (relative risk = 0.13) compared with men who were at low risk on no lifestyle factors and had a relative risk of 0.37 compared with all other men in the study. Furthermore, men who adopted 2 healthy lifestyle practices during study follow-up reduced their risk by 27%.<sup>20</sup> Regardless of whether medications are also used, adherence to a healthy lifestyle provides continuing benefits over time.

The AHA, recognizing the critical role of dietary and lifestyle improvements in preventing CVD, issued updated diet and lifestyle recommendations in 2006.<sup>21</sup> Specific recommendations include the following:

- ▶ Eating a healthy diet
- ▶ Maintaining a healthy body weight
- ▶ Maintaining recommended blood lipid levels
- ▶ Maintaining a normal blood pressure
- ▶ Maintaining a normal blood glucose level
- ▶ Engaging in regular physical activity
- ▶ Avoiding tobacco

Dietary changes can have substantial effects in reducing CV risk, reducing blood pressure, and improving blood lipid levels. Such changes have also been shown to significantly decrease LDL levels.<sup>22</sup> The OmniHeart randomized trial enrolled adults with prehypertension or stage 1 hypertension who were given 3 different healthful diets for 6 weeks at a time.<sup>22</sup> Each of the 3 diets was low in saturated fat (6%) and cholesterol (<150 mg/day), and contained no *trans* fat. One diet was rich in carbohydrates, similar to the Dietary Approaches to Stop Hypertension (DASH) diet. The second diet was rich in protein, with about half the protein from plant sources. The third diet was rich in unsaturated fat, primarily monounsaturated fat. The results in this study were impressive. As shown in Figure 2, all 3 diets, which were low in saturated fat, were associated with LDL decreases of 12 to 14 mg/dL.<sup>22</sup>



**Figure 2.** Effects of 3 healthful diets low in saturated fats on LDL levels. Each of the 3 diets was eaten for 6 weeks and was associated with substantial decreases in serum LDL levels (12–14 mg/dL). Appel LJ et al.<sup>22</sup>

## Lipid-Lowering Medications: Next Line of Therapy

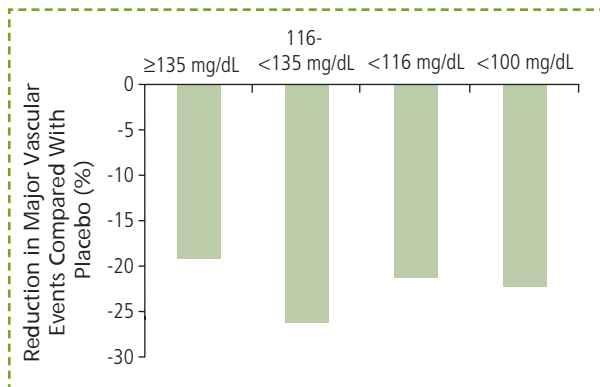
When TLCs alone are not enough to reduce LDL levels to goal, the next line of therapy is the use of lipid-lowering medications. Drug therapy should be considered an additional measure rather than a replacement for TLCs. Lifestyle modifications should be continued and reinforced throughout therapy.

### Statins

The drug of choice to reduce elevated lipid levels is a statin.<sup>19</sup> Statins are the most effective class of drugs for decreasing LDL levels; they also lower TG levels, can modestly increase HDL levels, and ultimately reduce the risk of major CV events and death.<sup>19</sup> Several recent studies have reinforced the benefits of using statins.

The Medical Research Council/British Heart Foundation (MRC/BHF) Heart Protection Study involved 20,536 high-risk adults (aged 40 to 80 years) in the United Kingdom who had existing CHD, diabetes, or other occlusive arterial disease.<sup>23</sup> Patients were treated with simvastatin 40 mg/d or placebo during a 5-year period. Results demonstrated that simvastatin decreased LDL levels by about 39 mg/dL compared with the placebo group. Patients in the simvastatin group had a significant 18% reduction in coronary death rate, a 38% reduction in the incidence of first nonfatal MI, a 27% reduction in major coronary events (nonfatal MI or coronary death), and a 25% reduction in the incidence of stroke. Further, there were similar and highly significant reductions in the risk of major vascular events in each of the subcategories of baseline LDL levels (see Figure 3), indicating that the risk reduction was not significantly influenced

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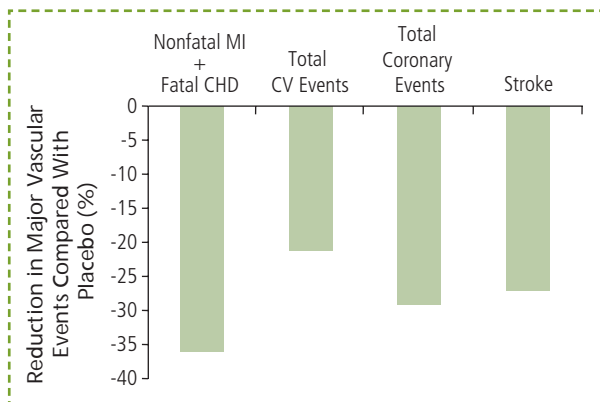
**Figure 3.**

The MRC/BHF Heart Protection Study found that simvastatin 40 mg/d for 5 years was associated with similar and highly significant reductions in the risk of major vascular events in each of the subcategories of baseline LDL levels, even in patients with baseline LDL levels  $< 100$  mg/dL. HPS Collaborative Group.<sup>23</sup>

by baseline LDL levels.<sup>23</sup> These findings support the use of statins in all high-risk patients, regardless of baseline LDL levels.

The Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA) was a multicenter, randomized, controlled, primary prevention study in Europe involving 10,305 patients with hypertension aged 40 to 79 years with at least 3 other CV risk factors.<sup>24</sup> Patients had a mean baseline LDL level of 133 mg/dL. Over the 5-year course of the study, treatment with atorvastatin 10 mg/d decreased LDL levels by 29% compared with placebo. At 5 years, atorvastatin-treated patients had a 36% lower risk of nonfatal MI and fatal CHD (Figure 4), a 21% lower risk of total CV events (including revascularization procedures), a 29% decrease in total coronary events, and a 27% reduction in stroke, all compared with placebo-treated patients.<sup>24</sup> Thus, reducing LDL levels—even in patients without dyslipidemia—can promote the primary prevention of CHD and reduce the incidence of major CV events.

The clinical benefits of intensive lowering of lipids using high-dose atorvastatin (80 mg/d) were demonstrated in 2 recent studies, each lasting nearly 5 years.<sup>25,26</sup> The Treating to New Targets (TNT) study was a prospective, randomized, multicenter study involving 10,001 patients with CHD and LDL levels below 130 mg/dL.<sup>25</sup> Patients were treated with



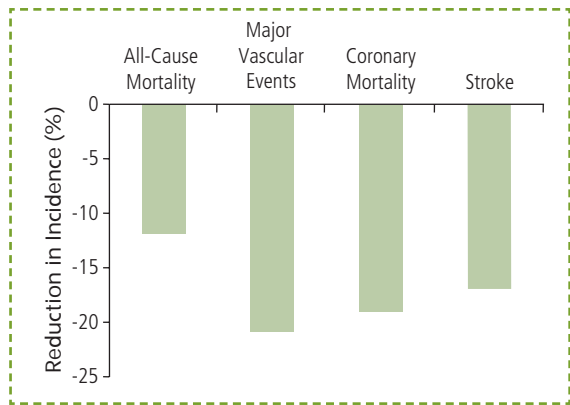
**Figure 4.**

The ASCOT-LLA study in high-risk patients with hypertension with a mean baseline LDL of 133 mg/dL showed that atorvastatin 10 mg/d over 5 years was associated with significant reductions in the risk of CV events. Sever PS et al.<sup>24</sup>

atorvastatin 10 mg or 80 mg daily. Treatment with atorvastatin 80 mg/d was associated with a significant 22% reduction in the relative risk of major CV events, which were defined as CHD death, nonfatal MI, cardiac arrest with resuscitation, or stroke.<sup>25</sup> The Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study was a prospective, randomized, multicenter study that followed 8888 patients aged 80 years or younger who had a history of acute MI.<sup>26</sup> Patients were randomized to receive either usual-dose simvastatin (20 mg/d) or high-dose atorvastatin (80 mg/d). Treatment with atorvastatin 80 mg/d was associated with significant decreases in the risk of a major CV event (including stroke), nonfatal MI, any CHD event, and any CV event, as well as a nonsignificant 11% decrease in the relative risk of coronary death, acute MI, or cardiac arrest with resuscitation.

In a meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaborators of 14 randomized trials of statins involving more than 90,000 participants, patients treated with statins for 1 year had LDL levels 14 to 68 mg/dL lower than those in patients who did not receive statins.<sup>27</sup> Results showed that each 39-mg/dL decrease in LDL was associated with a 12% decrease in all-cause mortality, a 21% reduction in major vascular events (such as MI, stroke, or coronary death), a 19% decrease in coronary mortality, and a 17% reduction in stroke (see Figure 5). These effects were significant in the first year of treatment and were even greater in subsequent years. Full adherence to statin regimens can achieve LDL reductions of  $\geq 58$  mg/dL, resulting in a 33% reduction in the incidence of major vascular events.<sup>27</sup> Statin therapy can reduce the incidence of major vascular events regardless of the patient's initial lipid levels and should be considered in all patients at high risk for major vascular events.

When initial drug treatment with a statin alone does not achieve lipid goals, therapy may be intensified by either increasing the statin dose or adding a second line of drug therapy to the statin. Lipid-lowering agents that may be used in combination with a statin include fibrates,



**Figure 5.** The CTT Collaborators' meta-analysis of 14 randomized trials showed that statin treatment for 1 year reduced all-cause mortality by 12%, major vascular events (such as MI, stroke, or coronary death) by 21%, coronary mortality by 19%, and stroke by 17% for each 39-mg/dL decrease in LDL levels. Baigent C et al.<sup>27</sup>

#### Medications That Affect Lipid Metabolism

Drug Class	Effect on LDL	Effect on HDL	Effect on TGs
Statins	↓ 18%-55%	↑ 5%-15%	↓ 7%-30%
Bile acid sequestrants	↓ 15%-30%	↑ 3%-5%	No change
Nicotinic acid	↓ 5%-25%	↑ 15%-35%	↓ 20%-50%
Fibric acids	↓ 5%-20%	↑ 10%-20%	↓ 20%-50%
Ezetimibe	↓ 18%	↑ 1%-4%	↓ 5%-10%

Expert Panel<sup>7</sup>; *Treat Guidl Med Lett*.<sup>19</sup>

niacin, ezetimibe, and bile acid sequestrants.<sup>7,14,19</sup> Table 7 summarizes the effects of the various classes of lipid-lowering medications on selected lipid parameters.<sup>7,19</sup> These medications are frequently used in combination with a statin, giving the added advantage of being able to use relatively low drug doses, thus reducing the risk of adverse effects. Further, combinations of lipid-lowering drugs may enable patients to reduce their LDL levels by 30% to 40%, thus reducing their risk of major coronary events by 30% to 40%, and enable high-risk patients to attain their LDL goal of <100 mg/dL or even <70 mg/dL.<sup>14</sup>

### **Fibrates (Fibric Acid Derivatives)**

Fibrates, such as gemfibrozil and fenofibrate, are indicated primarily to reduce TG levels. They also have modest effects in raising HDL and lowering LDL levels.<sup>7,14,19</sup>

### **Niacin (Nicotinic Acid)**

Niacin also decreases TG levels and increases HDL levels. Indeed, niacin is the most potent drug currently available for raising HDL levels. Niacin or a fibrate may be used in combination with a statin, especially when TG or HDL levels are low or when non-HDL levels are high.<sup>7,14</sup>

### **Ezetimibe**

Ezetimibe is a selective inhibitor of cholesterol absorption in the intestine, blocking the absorption of both dietary and biliary cholesterol. The effects of ezetimibe are additive with the effects of a statin on LDL and may therefore allow use of lower statin doses.<sup>14,19</sup>

### **Bile Acid Sequestrants**

Bile acid sequestrants, such as cholestyramine, colestipol, and colesevelam, are not absorbed from the gastrointestinal (GI) tract, but act to bind up bile acids in the intestinal lumen. They can reduce LDL levels and raise HDL levels, but may also further raise TGs.<sup>19</sup>

## **Timeline for Progression of Drug Therapy**

The NCEP ATP III guidelines suggest a general timeline for managing drug therapy in patients with elevated LDL levels.<sup>7</sup> If TLCs have failed to achieve treatment goals after 12 weeks, the addition of LDL-lowering drugs should be considered. Therapeutic lifestyle changes should be continuously reinforced, with drug therapy added as an adjunct.

Drug therapy typically begins with a statin at a dose that will reduce LDL levels by 30% to 40%.<sup>14</sup> After 6 weeks of drug therapy, LDL levels should be rechecked. If treatment goals are still not met, drug therapy may be intensified by either increasing the statin dose or using combination therapy (combining the statin with a second type of lipid-lowering drug). Increases in the statin dose are limited by the increasing risk of adverse effects and the so-called rule of 6's, which says that doubling the statin dose will only reduce LDL levels by an additional 6%.<sup>19</sup> Lipid levels should be checked again after about 6 weeks. If lipid goals are still not attained, consider further intensifying the drug therapy or consult with a lipid specialist. When the LDL goal has been met, consider treating other lipid risk factors and non-lipid risk factors. The patient's response to therapy should continue to be monitored every 4 to 6 months. It is not uncommon for patients to become less adherent to therapy over time. Regular monitoring can help detect and prevent the subsequent diminished response.

## CASE STUDY

### A 76-Year-Old White Woman With History of Treated Hypertension and Depression

#### Presentation

A 76-year-old white woman comes in for a routine examination. She is a nonsmoker and has a history of treated hypertension and depression. Her current medications include a calcium channel blocker (diltiazem 240 mg/d) and a selective serotonin reuptake inhibitor (SSRI; nefazodone 150 mg/d). She is uncertain about a family history of premature CHD.

#### Physical Examination

- Height: 5 ft 6 in
- Weight: 161 lb
- BMI: 26 kg/m<sup>2</sup>
- Waist circumference: 35 in
- Blood pressure: 139/82 mm Hg

#### Comment

The physical examination is unremarkable. Her BMI is in the overweight category. She has previously been diagnosed with hypertension, and her blood pressure is close to goal while taking an antihypertensive medication (diltiazem).

#### Laboratory Values

- Serum creatinine: 1.4 mg/dL
- Estimated glomerular filtration rate: 39 mL/min/1.73 m<sup>2</sup>
- Fasting plasma glucose: 94 mg/dL
- Total cholesterol: 245 mg/dL
- LDL: 156 mg/dL
- HDL: 59 mg/dL
- TGs: 148 mg/dL

#### Comment

Her creatinine is slightly elevated, and her estimated glomerular filtration rate is reduced, indicating a moderate decrease in renal function. This decrease in renal function should be considered when making therapeutic decisions, and renal function parameters should continue to be monitored. The lipid profile results indicate dyslipidemia: total cholesterol is high, LDL is borderline high, and HDL and TGs are within normal limits.

#### Clinical Decision Point

*What is your assessment of this patient's CVD risk category?*

- High
- Moderately high
- Moderate
- Lower

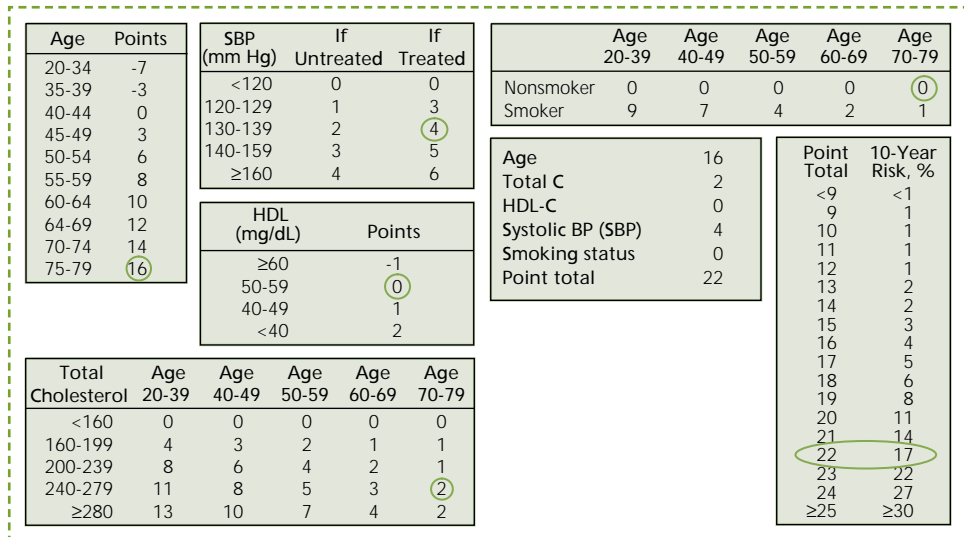
#### Comment

Using the Framingham point score to estimate this patient's 10-year risk for a "hard" CHD event (see Figure 6), she has a Framingham 10-year risk of 17%.<sup>7</sup> This score is based heavily on her age (contributing 16 points) and treated systolic blood pressure (contributing 4 points), with a smaller contribution by her total cholesterol level (2 points), adding up to a total of 22 points.

This patient has at least 2 major risk factors (age and hypertension) according to NCEP risk criteria. Since her family history of premature CHD is unknown, this is a possible third major risk factor. Thus, according to NCEP definitions, she is considered to be in a moderately high-risk category, with 2 or more risk factors and a 10-year risk between 10% and 20%.<sup>14</sup>

This patient does not have diabetes and does not meet the diagnostic criteria for the metabolic syndrome.<sup>15,16</sup> Although her waist circumference and blood pressure meet the criteria, she would need to have at least one other component to meet the most recent definitions of the metabolic syndrome.<sup>15,16</sup> Her TG level, HDL-C level, and fasting glucose all do not meet the criteria for the metabolic syndrome.

## Dyslipidemia and Cardiovascular Risk Reduction: A Review Based on the Evidence



**Figure 6. Framingham point scoring to estimate 10-year risk.** Based on point scoring for risk factors, the calculated Framingham 10-year risk for this patient is 17%. Expert Panel.<sup>7</sup>

### Therapeutic Considerations in Elderly Patients

The US population is getting older; those aged 60 years or older comprise the fastest-growing segment and are expected to account for 28% of the US population for a total of 30 million by 2050.<sup>28</sup> As patients grow older, they are more likely to have multiple chronic diseases, including CVD, cerebrovascular disease, kidney disease, diabetes, and the metabolic syndrome. Older patients also are more likely to have decreased hepatic function and decreased muscle mass. These factors can all influence screening and treatment decisions in elderly patients.

The first line of treatment for dyslipidemia remains TLCs, including dietary modification, exercise, and weight loss, if necessary. However, compliance with lifestyle modification can be difficult to achieve and sustain, particularly in elderly patients with comorbid conditions that limit physical activities. Therefore, lifestyle modification is best used in combination with drug therapy to reduce lipid levels. The NCEP guidelines for cholesterol management suggests the use of lipid-lowering medications in older patients at risk of MI.<sup>9,14</sup>

Statins are the drug of choice in the elderly, having been shown to be safe and effective, as well as reducing the risk of CVD, coronary artery disease (CAD), and stroke in this population.<sup>7,23,29-32</sup> The landmark Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was a randomized, controlled trial involving 5804 patients aged 70 to 82 years.<sup>32</sup> Pravastatin treatment over 3 years significantly reduced the risk of CHD death and nonfatal MI and resulted in a 24% decrease in mortality from coronary disease, compared with the placebo group.<sup>32</sup> This study definitively established the benefits of statin treatment in an elderly population.

Elderly patients can safely use statins provided any underlying liver or kidney problems are taken into consideration. They should also be monitored for statin-related adverse events such as myopathy or an increase in liver enzymes.<sup>29,33</sup> Although significant myopathy is uncommon, it is most frequently seen in older patients when they have comorbidities such as renal insufficiency.<sup>30</sup> Older patients taking statins should undergo regular measurement of liver and kidney function, and the lowest effective statin dose should be used.<sup>29,33</sup> Attention should be paid to any potential drug and food interactions with statins, and individual drug tolerability and patient preference should also be considered.<sup>29,33</sup>

Potential drug interactions are a particular concern in elderly patients, who are more likely to be on multiple other medications. Drug interactions with statins are frequently seen with calcium channel blockers (especially diltiazem), which inhibit certain cytochrome P450 isoenzymes.<sup>34</sup> Antidepressant medications are another class of drugs that can inhibit certain cytochrome P450 isoenzymes and interact with statins. Nefazodone, an SSRI antidepressant, is a potent inhibitor of the same P450 isoenzymes involved in the metabolism of some statins (especially atorvastatin, lovastatin, and simvastatin).<sup>34,35</sup> A number of other drugs inhibit cytochrome P450 enzymes and may thus increase plasma statin levels, necessitating a reduction in statin dosage to avoid toxicity, particularly rhabdomyolysis.<sup>19,34</sup> Consuming large quantities of grapefruit juice may also inhibit cytochrome P450 isoenzymes and thus may interfere with statin metabolism.<sup>19,34</sup> The effects of other drugs, such as warfarin, may be enhanced if used concurrently with a statin, requiring a reduction in warfarin dose.<sup>19</sup>

The woman presented in our case study represents a fairly typical elderly patient with dyslipidemia. Lifestyle modifications should be initiated first, particularly dietary modifications and increasing exercise, because her body weight is already at a healthy level. However, consideration should also be given to initiating drug therapy, because she is at moderately high risk of future CHD events.

Drug therapy must take into account the patient's decreased renal function as well as potential drug interactions with current medications (nefazodone and diltiazem). Because both of these medications have the potential to inhibit metabolism of certain statins, great care should be exercised to choose the statin least likely to be affected by interactions. Pravastatin (as used in the PROSPER trial) and rosuvastatin are not significantly metabolized by the cytochrome P450 system and would be appropriate choices. Fluvastatin is mainly metabolized by different cytochrome P450 isoenzymes and is another possible choice.<sup>19,34</sup> Given her other medications and reduced kidney function, it is important to start this patient on the lowest statin dose and then carefully titrate the dose higher if necessary. The patient's kidney and liver function should be monitored regularly.

### Other Lipid-Lowering Drugs in Elderly Patients

If moderate doses of a statin fail to decrease LDL-C levels by 30% to 40% or the patient has not reached target LDL-C levels, an additional medication, such as ezetimibe, a bile acid sequestrant, a fibrate, or niacin, may be added to the therapeutic regimen to further reduce lipid levels.<sup>14,29</sup> Ezetimibe selectively reduces absorption of cholesterol in the

intestine and may be used in conjunction with a statin to further reduce LDL-C levels.<sup>14,29</sup> Lipid-lowering agents such as fibrates and niacin also appear to be of benefit in lowering TG and LDL levels and raising HDL levels<sup>29,33</sup> as well as in reducing the risk of nonfatal MI or cardiac death, although significant reductions in overall mortality have not yet been definitively demonstrated for combination drug therapy.<sup>36</sup> There are currently few data regarding the effects of dyslipidemia treatment on overall morbidity and mortality in patients over 85 years of age. With fibrates and niacin—as with statins—consider liver and kidney function, tolerability, and potential drug interactions, and continue to monitor closely for side effects.<sup>29</sup> In particular, individual fibrates differ in their tolerability, especially with regard to GI side effects.<sup>29</sup> Fibrates can increase the effects of oral anticoagulants (such as warfarin) and oral hypoglycemic agents, and gemfibrozil inhibits the metabolism of statins, thus increasing the risk of rhabdomyolysis when gemfibrozil and a statin are used together.<sup>19</sup>

### Considerations in Women

Compared with men, the onset of CHD in women overall is delayed by 10 to 15 years. However, the presence of multiple risk factors or the metabolic syndrome can hasten the onset of CHD in women. The NCEP guidelines advocate a similar approach to primary and secondary prevention in men and women.<sup>7</sup> Statins are generally as effective and safe in women as they are in men.<sup>37</sup>

The Heart Protection Study in the United Kingdom included 15,454 men and 5082 women between 40 and 80 years of age who received either simvastatin or a placebo; results showed similar and significant decreases in the rate of major vascular events in both men and women.<sup>23</sup> The AHA Evidence-based Guidelines for Cardiovascular Disease Prevention in Women affirm the usefulness of statin therapy (along with lifestyle interventions) to reduce the risk of CVD in at-risk women with elevated levels of LDL-C.<sup>9,38</sup>

### Summary and Conclusions

Findings from recent clinical trials highlight the importance of improving patient adherence and thus improving clinical outcomes. Optimal results depend on more than just reaching lipid-level targets; adherence to lifestyle and drug interventions can help prevent MI and stroke.

Nurse practitioners and physician assistants are in an ideal position to educate patients about their individual treatment goals, foster strong patient-provider relationships, monitor patients' progress, and encourage continued adherence to measures for primary and secondary prevention of CVD.

Lipid-lowering therapy must be tailored to each patient. The level of individual CVD risk influences lipid targets, and comorbid conditions influence medication selection. Primary care clinicians must consider these patient-specific differences to improve outcomes.

Given the growing numbers of the elderly population, it is critical that primary care clinicians recognize and appropriately treat dyslipidemia in this population.

## QUESTIONS FROM SYMPOSIUM PARTICIPANTS

➔ **Q:** Should lipid testing always be done on fasting samples?

**A:** It is recommended that lipoprotein profiles should be done on fasting samples. However, LDL levels are not significantly different in the fasting versus nonfasting state. The main impact of fasting is seen in the TG levels, where fasting results in less variability.

➔ **Q:** Should levels of lipoprotein subclasses be checked routinely?

**A:** No, they need not be checked routinely. The benefit of advanced lipid testing is the ability to directly assess the more atherogenic profile associated with small, dense LDL. Most patients will have moderate TG elevations and low HDL, together with normal to slightly elevated LDL. This is a common picture in patients with the metabolic syndrome. When these numbers are reported on a routine lipid panel, small dense LDL is assumed predominant.

➔ **Q:** How should renal and hepatic function be monitored in patients on statin therapy?

**A:** Patients should have baseline renal and hepatic function measured before starting drug therapy. If the results are normal, then they should be rechecked approximately 6 weeks after treatment starts. If the baseline values are elevated, biweekly checks are advisable until the numbers stabilize or the numbers prompt dose adjustment or drug discontinuation. Statin-induced myopathy and rhabdomyolysis are more likely in patients with chronic renal insufficiency. The current guidelines reflect that statin therapy is considered safe, even in patients with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, as long as the elevations are not more than 3 times the upper limit of normal (ULN). Routine hepatic monitoring is recommended every 6 months.

➔ **Q:** Should statin therapy be avoided in patients with hepatitis C?

**A:** Hepatitis C is not an absolute contraindication to statin therapy. The decision to use statin therapy should be based on the patient's CVD risk profile. Monitoring liver function in these patients is very important. Many practitioners choose pravastatin or rosuvastatin in these patients because of a lower potential for drug-drug interactions.

➔ **Q:** How should the complaint of muscle pain be dealt with clinically?

**A:** In many patients, the cause of muscle pain is the exercise program that is recommended at the same time that the prescription is written. If a patient complains of muscle pain, a creatine kinase (CK) level should be measured. Instruct the patient to abstain from exercise for a week prior to obtaining the blood sample, because exercise is the most common cause of CK elevation. If the level is normal, the practitioner should try to allay the patient's fears. If CK level is 10 times the upper limit of normal, the drug should be discontinued immediately, as the risk of

rhabdomyolysis is high. If it is between normal and 10 times the ULN, then a clinical decision has to be made. Because drug-induced myositis is dose-dependent, one option would be to reduce the dose of the medication. Pravastatin and rosuvastatin are water-soluble statins and theoretically are less likely to cause myositis, so switching the patient to 1 of these 2 choices is another option. Continued monitoring of CK levels during therapy in these patients is advisable.

➔ **Q:** Are there significant drug-drug interactions in patients with human immunodeficiency virus (HIV) who are treated with antiretroviral (ARV) medications and statins?

**A:** Yes. Protease inhibitors can inhibit cytochrome P450 3A4, an enzyme involved in statin metabolism. Monitoring for the development of symptoms suggestive of myositis and measuring liver functions tests (LFTs) in a patient with HIV treated with protease inhibitors are important. Again, pravastatin or rosuvastatin may be optimal choices in these patients.

➔ **Q:** Does a very high HDL level modify the treatment approach in patients with high LDL?

**A:** LDL and HDL are independent risk factors for CVD. The presence of one does not negate the risk of the other. The confusion comes from the fact that high HDL is considered a “negative risk factor” in the Framingham risk calculator. Despite this, statin therapy is indicated in patients with elevated LDL levels who are considered in the moderate or higher risk categories.

➔ **Q:** Should statin therapy be discontinued once the LDL goal is attained?

**A:** No. These drugs will only lower LDL levels if taken chronically. LDL levels will return to baseline pretreatment levels about 4 weeks after discontinuation, unless significant TLCs have occurred.

➔ **Q:** Is there an LDL level for a patient on lipid-lowering therapy that is considered too low?

**A:** Not that we know of. LDL levels in a newborn are typically around 25 to 30 mg/dL, and increase with age. Cholesterol is necessary for cell-wall synthesis and is the precursor for all steroid hormones. Studies done so far have shown that it is both safe and efficacious to lower LDL to 66 mg/dL. There are no published studies that have lowered LDL further.



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