

## Managing Abnormal Blood Lipids

### A Collaborative Approach

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**Abstract**—Current data and guidelines recommend treating abnormal blood lipids (ABL) to goal. This is a complex process and requires involvement from various healthcare professionals with a wide range of expertise. The model of a multidisciplinary case management approach for patients with ABL is well documented and described. This collaborative approach encompasses primary and secondary prevention across the lifespan, incorporates nutritional and exercise management as a significant component, defines the importance and indications for pharmacological therapy, and emphasizes the importance of adherence. Use of this collaborative approach for the treatment of ABL ultimately will improve cardiovascular and cerebrovascular morbidity and mortality. (*Circulation*. 2005;112:3184-3209.)

**Key Words:** AHA Scientific Statements ■ lipids ■ risk factors ■ cholesterol ■ prevention

Elevated low-density lipoprotein cholesterol (LDL-C) is a major cause of coronary heart disease (CHD). The relationship between LDL-C and CHD risk is continuous over a broad range of LDL-C levels: The higher the LDL-C level, the greater the CHD risk.<sup>1</sup> Although national guidelines for cholesterol management have existed since 1988,<sup>2</sup> many individuals who are treated for elevated cholesterol have not achieved their targeted cholesterol levels. Studies<sup>3,4</sup> show that 17% to 73% of treated patients actually meet their target levels, but the people at greatest risk (patients with known CHD) rarely achieve their target levels (Figure). The Third Report of the National Choles-

terol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,<sup>5</sup> known as Adult Treatment Panel III (ATP III), called for more aggressive treatment of hypercholesterolemia. These guidelines have substantially increased the number of people who should receive lifestyle and drug treatment.<sup>6</sup> To help patients achieve the target cholesterol and triglyceride (TG) levels necessary to reduce cardiovascular risk, a multidisciplinary, collaborative approach to patient care is essential.

No one would argue that physicians are instrumental in directing the plan of care for patients with complex lipid

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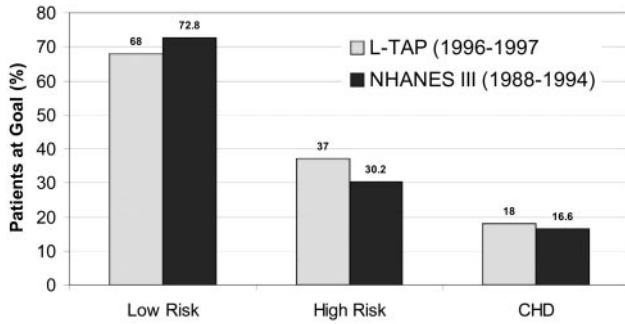
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NCEP ATP III targets not achieved in treated patients. L-TAP indicates Lipid Treatment Assessment Project; NHANES, National Health and Nutrition Examination Survey. Data derived from Jacobson et al<sup>3</sup> and Pearson et al.<sup>4</sup>

disorders; however, lipid management often requires extensive lifestyle counseling in addition to prescribed drug therapies. Because of physicians' time limitations and the expertise of other healthcare providers, patients' needs are

best met by a collaboration of physicians, nurses, dietitians, and exercise specialists, among others. Numerous studies have shown improved outcomes with a collaborative approach to CHD prevention (Table 1). In summary, the ATP III guidelines<sup>5</sup> call for a multidisciplinary method to help patients and clinicians adhere to recommendations for primary and secondary prevention of CHD. Collaborative approaches to clinical practice that facilitate aggressive drug and lifestyle treatment strategies are highly effective in assisting patients to achieve target lipid levels, initiate and sustain healthy dietary and exercise habits, reduce CHD risk, and reduce mortality.<sup>7-10</sup>

The purpose of this statement is to review the complexities of lipid management throughout the lifespan. In doing so, the role and overall importance of a multidisciplinary and collaborative approach will be discussed. With diseases of the vascular system remaining the major cause of death and morbidity in the United States and around the world, innovative approaches to care should be undertaken by all healthcare professionals.

**TABLE 1. Improved CHD Outcomes With a Collaborative Approach**

Sample	Collaborative Approach	Outcomes
1343 CHD patients <sup>7</sup>	Nurse prevention clinic vs usual care	Mortality at 4.7 y, 14.5% vs 18.9%
228 post-CABG + increased lipids <sup>8</sup>	Nurse practitioner case management vs usual care with feedback on lipids to physician	Achieved target LDL-C of <100 mg/dL 65% vs 35%
Lipid clinic patients <sup>9</sup>	Nurse managed lipid clinic vs usual care vs National Quality Assurance Program	LDL-C documented in chart: 97% vs 47% vs 44%; at goal: 71% vs 22% vs 11%; taking a lipid drug: 97% vs 51% vs 39%
417 high-risk patients with dyslipidemia <sup>10</sup>	Retrospective analysis in collaborative care clinic	Received combination therapy: 56%; monotherapy: 41%; no therapy: 2%; achieved single goal: 62% to 74%; achieved combined goals: 35%; Framingham 10-y CHD risk <1%
SCRIP <sup>29</sup> chronic CHD; 259 men, 41 women	Nurse case managers, psychologists, physicians	Improved angiographic outcomes, fewer CVD events
CHAMP, <sup>37,38</sup> n=558; 324 men, 234 women hospitalized with CHD	Physicians, nurses, nutritionists; case management vs usual care	Increased aspirin, statin, $\beta$ -blocker, and ACE inhibitor use with significant decrease in all-cause mortality at 1 y
Patients with ABL in ambulatory setting <sup>39</sup>	Multidisciplinary team vs physician in general medical clinic	Greater improvement in total cholesterol and LDL-C
300 patients with CHD evaluated by angiography <sup>29</sup>	Nurse case management vs usual care	Less CHD; significantly fewer clinic events at 4 y
585 acute MI patients <sup>30</sup>	Nurse case management vs usual care	Improved functional capacity; smoking cessation; LDL-C
1343 CHD patients <sup>45</sup>	Nurse case management vs general practice	Improved blood pressure, blood lipids, physical activity, diet
Patients at high risk for CHD <sup>33-36</sup> (Health Education and Risk Reduction Training Program [HEAR <sup>2</sup> T])	Physician directed, nurse and nutritionist case-managed	Improved LDL-C; blood pressure; physical activity; stress management; nutrition; decrease in high- and very high-risk status; increase in intermediate- and lower-risk status
Patients enrolled in cardiac rehabilitation program <sup>42</sup>	Nurse, social worker case managers added to traditional cardiac rehabilitation model	At 1 y: 77% taking lipid-lowering drugs, 78% exercising, 66% ceased smoking, increase in quality-of-life score, decrease of \$500/patient cost

ACE indicates angiotensin-converting enzyme; ABL, abnormal blood lipids.

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**TABLE 2. Primary Prevention in Children and Youth**

<b>Dietary modification</b>
Limit foods with
Saturated fats to <10% calories/d
Cholesterol to <300 mg/d
<i>trans</i> fatty acids
<b>Physical activity</b>
Increase moderate to rigorous $\geq 60$ min/d
Limit sedentary activities $\leq 2$ h/d
<b>Identification of dyslipidemia</b>
Selective screening
Family history of CHD
1 parent with blood cholesterol $\geq 240$ mg/dL
No parental history but CHD risk factors present
$\geq 1$ of the following risk factors present: high blood pressure; smoking; sedentary lifestyle; obesity; alcohol intake; use of drugs or diseases associated with dyslipidemia

Adapted from Kavey et al.<sup>19</sup>

## A Collaborative Approach for Cardiovascular Health Promotion for Children and Youth: A Population and Public Health Perspective

### Primary Prevention in Children

During the past several decades, data generated from epidemiological, clinical, and laboratory studies have provided convincing evidence that atherosclerotic-cardiovascular disease processes begin in childhood and are influenced over time by the interaction of genetic and potentially modifiable risk factors and environmental exposures.<sup>11–16</sup> On the basis of the data available in 1992, the NCEP issued the first guidelines for primary prevention of CHD beginning in childhood.<sup>17</sup> The NCEP recommendations include both an individualized/high-risk and population-based approach, with emphasis on assessment and management of elevated blood cholesterol levels in children and youth.

Both the NCEP and the American Heart Association (AHA) emphasize the population approach as the principal means for primary prevention of CHD beginning in childhood. By definition, population-based (public health) approaches are designed to shift the distribution of risk factors (ie, blood cholesterol levels) of the target population to more desirable levels. Building on the NCEP recommendations, the AHA emphasizes lifestyle modification that includes “heart-healthy” patterns of dietary intake and physical activity for the promotion of cardiovascular health and prevention of dyslipidemia and other risk factors for cardiovascular disease (CVD).<sup>18,19</sup> The AHA dietary guidelines for children and youth were recently revised.<sup>20</sup> For children 2 years old and older, emphasis is placed on the caloric and nutrient intake necessary for normal growth and developmental processes. Although some controversy exists regarding the optimal diet for cardiovascular health promotion on a population level, results from the Dietary Intervention Study in Children (DISC)<sup>21</sup> and the Turku Infant Study<sup>22</sup> demonstrate the safety and efficacy of saturated fat–restricted and cholesterol-restricted diets in children and youth. Current recommenda-

**TABLE 3. Cholesterol Levels for 2- to 19-Year-Olds**

Levels	Total Cholesterol, mg/dL	LDL-C, mg/dL
Acceptable	<170	<110
Borderline	170–199	110–129
High	$\geq 200$	$\geq 130$

Adapted from Kavey et al.<sup>19</sup>

tions targeting primary prevention in children are noted in Table 2. Given the prevalence for and trends in overweight and obesity in children and youth and the documented association between obesity and CVD risk factors, emphasis on increasing physical activity as part of weight management is an essential part of cardiovascular health promotion and risk reduction. The current AHA recommendations encourage pediatric healthcare providers to assess patterns of physical activity at every visit and to encourage physically active lifestyles for children and youth. Successful implementation of these recommendations (and the dietary recommendations) on a population level, however, will require major public health initiatives and the collaborative efforts of healthcare professionals, government agencies, schools, the food industry, and the media.

### Identifying Dyslipidemia in Children and Youth

The NCEP and the AHA recommend an individualized/high-risk approach to identifying dyslipidemia in children and youth (Table 2). A fasting lipid profile allows for a comprehensive assessment that includes measurement of total cholesterol and LDL-C, TGs, and high-density lipoprotein cholesterol (HDL-C). The AHA recommends the averaged results of 3 fasting lipid profiles as the baseline for guiding treatment modalities.

The AHA endorses the guidelines established by the NCEP in setting the following definitions for acceptable, borderline, and high total cholesterol and LDL-C levels in children and adolescents between 2 and 19 years of age (Table 3). Although these cut points are recommended to guide treatment decisions, it is important to emphasize that no long-term longitudinal studies have been conducted to determine the absolute levels in childhood and adolescence that accelerate atherosclerotic processes and predict CHD in adult life.

Lifestyle modification with an emphasis on normalization of body weight and heart-healthy patterns of dietary intake and physical activity is the cornerstone of treatment for children and youth who are identified as having dyslipidemia. This approach should be supported through school-site education and heart-healthy programs as well as through community-based activities. In the pediatric office setting or in pediatric lipid clinics, the management of dyslipidemia is best accomplished via a multidisciplinary collaborative team approach. Nurses, nurse practitioners, and dietitians experienced in the treatment of dyslipidemia in children and youth are well positioned within these settings to facilitate lifestyle modification with children and families.

The AHA recommends an “adequate” trial (ie, 6 to 12 months) of therapeutic lifestyle change before consideration of lipid-lowering medications.<sup>18,19</sup> Three general classes of lipid-lowering agents are available and have been used in the treatment of dyslipidemia in children and adolescents. These

include the bile acid sequestrants, niacin, and the HMG-CoA reductase inhibitors (statins).<sup>23</sup>

## Collaborative Approaches to Primary and Secondary Prevention of CVD in Adults

### Primary Prevention in Adults

Primary prevention of high blood cholesterol should be an important aspect of the societal approach to the promotion of cardiovascular health. Although cholesterol-lowering medications could be prescribed to people at high risk for developing high blood cholesterol, a long-term public health strategy that relies on providing medications to tens of millions of adults in the United States alone is not desirable for many reasons, including cost, inconvenience, and potential adverse effects. The approach of treating individuals at the highest risk, with selective attention to people with undesirable levels of blood cholesterol, could affect only the upper aspect of the cholesterol distribution, by reducing the cholesterol concentrations of only the people selected for individual treatment.

A growing body of evidence supports the promise of primary prevention of high blood cholesterol. Mean serum total cholesterol concentrations have declined in the United States during the past several decades.<sup>24–26</sup> A recent report demonstrated that the entire distribution of total cholesterol had shifted to lower levels in the United States during the latter half of the 20th century.<sup>27</sup> The downward shift was present at even the lower (10th and 25th) percentiles of the cholesterol distribution, at which pharmacological management can be assumed to have had virtually no impact. Thus, the downward shift in the overall distribution of cholesterol cannot be attributed solely to treatment effects but must have resulted to an important degree from population-wide behavioral and environmental influences on total cholesterol concentrations. The finding that the shift was observed among both women and men and among both blacks and whites supports the contention that population-wide behavioral and environmental influences were operating to cause this birth cohort effect.<sup>27</sup> Healthcare providers must support and advocate for continued public health approaches to improved nutrition, physical activity, and weight control.

Populations have been shown to differ in the slope of cholesterol increase with age.<sup>28</sup> In addition, the slope of the cholesterol increase with increasing age has been shown to change across birth cohorts in the United States, with more recent cohorts exhibiting a slower rate of increase in cholesterol with increasing age.<sup>27</sup> These observations indicate that the forces that influence the slope of the cholesterol increase with age may be dynamic and may therefore be modifiable through planned prevention strategies. If the rate of increase in cholesterol with increasing age could be reduced purposefully, then the expectation could be that more recent and future birth cohorts would develop clinically defined high blood cholesterol less commonly in the future. Such a strategy would equate to primary prevention of high blood cholesterol. This would enhance cardiovascular health-promotion efforts and would be most efficiently provided with a collaborative healthcare approach.

**TABLE 4. CHD Prevention in Adults: A Collaborative Approach**

Administered by nurses, health educators, and/or other healthcare providers
Adherence to recommendations of national healthcare organizations (ie, AHA, ACC, NIH)
Open and regular communication with clinical experts and medical community
Responsible for organization and collection of data for individual and clinical populations
Success depends on attention to multiple tasks
Titration of medications
Management of side effects
Use of combination therapies
Use of lower-cost medications
Behavioral interventions for lifestyle modification

### Collaborative Approaches to Secondary Prevention and Treatment in Adults: The Effect of Case Management

During the past 2 decades, our understanding of the process of atherosclerosis has improved dramatically. In addition, our understanding of the importance of multifactorial risk reduction (MFRR) has been strengthened through basic science discoveries and clinical research. Multiple clinical trials have shown that intensive programs of cardiovascular risk reduction affect the development of heart disease, including reductions in acute myocardial infarction (MI).<sup>29,30</sup>

Research has demonstrated a synergistic effect of multifactor risk reduction on both disease severity and clinical outcomes. Altering the physiology of these obstructions through MFRR improves endothelial function, decreases prothrombotic mechanisms, and can prevent plaque rupture, thus reducing the risk of acute MI and stroke. There is also great potential for stabilizing and regressing plaque after cardiovascular risk factor reduction.<sup>29</sup> Evidence is especially strong in the cholesterol arena, showing that reduction of total cholesterol, and LDL-C in particular, is effective in preventing acute MI and stroke.<sup>31,32</sup> The challenge to healthcare professionals is to implement programs that effectively identify those at highest risk and to offer cost-effective interventions. The case management model of care is an important intervention that meets this challenge. Case management provides systematic evaluation and implementation of medical treatments with regular follow-up of those at risk for a cardiac or vascular event.<sup>29,30,33–36</sup>

Case management has been well documented as a way to provide a collaborative approach to MFRR. An important study documenting the need for alternative approaches to the management of risk factors was observed in the Lipid Treatment Assessment Project (L-TAP)<sup>4</sup> (Figure). The L-TAP survey revealed that lipid management was suboptimal for all patients with and without CHD. Although 95% of investigators indicated that they were aware of the NCEP guidelines and believed they followed them, only a small proportion achieved the recommended LDL goals. Lack of achievement is likely caused by failure to titrate medications, inappropriate drug choices, limited effectiveness of some medications, intolerance to some drugs, and failure to address patient noncompliance. The results of this survey suggest that



**TABLE 5. Nutritional Factors That Affect LDL-C**

<b>Increase LDL-C</b>
Saturated and <i>trans</i> fatty acids
Dietary cholesterol
Excess body weight
<b>Decrease LDL-C</b>
Polyunsaturated fatty acids
Viscous fiber
Plant stanols/sterols
Weight loss
Isoflavone-containing soy protein (limited evidence)
Soy protein

factors other than knowledge of and attitudes toward the NCEP guidelines account for the low success rates. The L-TAP survey supports the role of a more systematic approach to the treatment of dyslipidemia.<sup>4</sup>

Case management is a collaborative clinical model that uses expert evaluation, systematic intervention, and regular follow-up (Table 4). Evidence suggests that case management results in an increase in short-term compliance, a reduction in emergency room visits, and a reduction in hospitalizations.<sup>37,38</sup>

Patients perceive that they need individualized education and counseling, as well as skills to help them set goals and resolve difficulties with lifestyle changes. They respond well to a planned approach to accessing the medical care system appropriately. The ability to help them identify and sort out symptoms supports their overall health. Finally, case management systems also help patients and family members identify appropriate community resources.

The effectiveness of a collaborative approach through case management has been well documented during the last 2 decades both in the United States and globally<sup>29,30,33–46</sup> (Table 1). Case management has been shown to be an effective approach to the management of dyslipidemia and multiple risk factors in a number of populations. In addition, this approach to managing high-risk populations has shown improved outcomes as evidenced by a reduction in morbidity and mortality rates.<sup>29,37,38</sup> Collaborative approaches that incorporate case management should be considered an ideal model for implementing MFRR in people with all forms of vascular disease such as peripheral arterial disease and cerebrovascular disease.

### Nutritional Management of Lipids

The role of the nutritionist cannot be understated. Effective nutrition education and support can improve blood lipids and body weight through the intake of heart-healthy foods and caloric restriction; improve physical activity levels; reduce insulin resistance; improve the health of people with type 2 diabetes mellitus who control their glucose; and decrease the development of type 2 diabetes. The inclusion of nutrition is key to a collaborative approach.

Dietary management of LDL-C is a major goal of CHD risk management.<sup>5</sup> In addition, drug-induced reductions in LDL-C result in a concurrent reduction in the rates of coronary disease morbidity and mortality.<sup>5</sup> There is evidence

**TABLE 6. AHA Dietary Recommendations for Achieving Desirable Blood Lipid Profile and Especially LDL-C**

Limit foods high in saturated fats
Replace saturated fats with lower-fat foods
Increase type of foods with unsaturated fat
Carefully monitor intake of food high in cholesterol
Severely limit foods containing <i>trans</i> fatty acids
Increase foods rich in viscous fiber
Increase foods containing stanol/sterol esters (special margarines, fortified orange juice, special cocoa/chocolate bars)

Adapted from Lichtenstein and Deckelbaum,<sup>62</sup> Van Horn,<sup>63</sup> and Erdman.<sup>64</sup>

from dietary studies that a marked reduction in LDL-C decreases the risk of CHD.<sup>47–53</sup> Nutritional factors that affect LDL-C levels are noted in Table 5. The principal dietary strategy for lowering LDL-C levels is to replace cholesterol-raising fatty acids (ie, saturated and *trans* fatty acids) with dietary carbohydrate and/or unsaturated fatty acids.

Many controlled clinical studies have assessed the quantitative effects of dietary changes on LDL and other lipids and lipoproteins; these have been summarized and reviewed.<sup>54,55</sup> Dietary cholesterol increases LDL-C levels.<sup>56</sup> On average, an increase of 100 mg/day of dietary cholesterol results in a 2 to 3 mg/dL increase in total serum cholesterol, of which ≈70% is in the LDL fraction.

Although there is considerable interindividual variation in response to these dietary interventions,<sup>57–59</sup> the reductions in LDL-C that may be expected with the adoption of diets that are low in saturated fat are ≈8% to 10%<sup>5,60</sup> and an additional 3% to 5% when dietary cholesterol is reduced (<200 mg/day).<sup>5</sup> Thus, implementation of a diet low in saturated fat and cholesterol would be expected to lower LDL-C by ≈11% to 15%<sup>5</sup> and possibly by as much as 20%.<sup>59,61</sup> AHA dietary recommendations for desirable lipid levels are noted in Table 6.<sup>62–64</sup>

Increasing viscous (soluble) fiber (10 to 25 g/day) and plant stanols/sterols (2 g/day) to enhance lowering of LDL-C is recommended. In addition, weight management and increased physical activity are recommended. An increase in viscous fiber of as little as 5 to 10 g/day is expected to reduce LDL-C by 3% to 5%.<sup>5</sup> Inclusion of 2 g/day of plant stanols/sterols would be expected to reduce LDL-C by 6% to 15%. A 10-lb weight loss would be expected to decrease LDL-C by 5% to 8%. In conjunction with reductions in saturated fat and cholesterol, the inclusion of the above therapeutic diet options (including weight loss) is expected to decrease LDL-C by 20% to 30%.<sup>5</sup> In addition to the therapeutic diet options of the therapeutic lifestyle change (TLC) diet, there is evidence that other dietary modifications, such as including soy protein<sup>64</sup> and nuts,<sup>65,66</sup> can lower LDL-C significantly.

Low HDL-C is an independent risk factor for coronary artery disease.<sup>5</sup> There are 2 ways by which diet may affect HDL: those caused by changes in the fatty acid composition of the diet and those that affect plasma TG levels. Because dietary fatty acids have major effects on LDL-C and HDL-C, it is necessary to evaluate these effects together to assess the potential impact of HDL change on coronary disease risk.

Thus, the ratio of LDL-C or total cholesterol to HDL-C is one benchmark for estimating the risk of CHD.<sup>67–69</sup> Increased weight is a determinant of low HDL-C levels.<sup>70</sup> Weight loss has favorable effects on HDL-C.<sup>71,72</sup> During weight loss, before weight maintenance is attained, HDL-C may decrease.<sup>71</sup> An elevated plasma TG level is an independent risk factor for CHD.<sup>73,74</sup> There are a number of underlying causes of elevated serum TGs: overweight and obesity; physical inactivity; cigarette smoking; excess alcohol consumption; high-carbohydrate diets (>60% of total energy); other diseases such as type 2 diabetes mellitus, chronic renal failure, and nephrotic syndrome; and genetic predisposition.

The principal cardiovascular significance of an elevated TG level is that it is a component of the atherogenic dyslipidemia commonly found in patients with type 2 diabetes mellitus, metabolic syndrome, and excess adiposity.<sup>75</sup> The triad of lipid abnormalities in these conditions consists of an elevated plasma TG level (> ≈150 mg/dL), reduced HDL-C level (<40 mg/dL for men; <50 mg/dL for women), and a relative excess of small, dense LDL particles that accompanies total LDL-C levels that are generally normal.<sup>76</sup> Adiposity is the principal nutrition-related influence that is found with atherogenic dyslipidemia, and ATP III recommends that treatment be focused on reducing TG levels. Consequently, for these individuals, weight loss is a primary goal as a means to lower TG levels.

Among nutrients, the major determinant of elevated TGs in atherogenic dyslipidemia is dietary carbohydrate.<sup>77</sup> In general, simple sugars and rapidly hydrolyzed starches have a greater glyceridemic effect than more complex carbohydrates and those consumed in conjunction with a higher intake of fiber. The recommended level of dietary fat is 25% to 35% of calories. Within this range, complex carbohydrates and a high-fiber diet are advised to facilitate TG lowering and to increase the levels of HDL-C and larger, more buoyant LDL particles. In addition, there is increasing evidence to support the beneficial influence of omega-3 fatty acids in the management of hypertriglyceridemia.<sup>78–82</sup>

It is evident that a growing number of diet-based treatment options can be applied selectively to individualized diet therapy for both primary and secondary prevention of coronary disease. Healthcare providers are well positioned to markedly reduce CHD risk by diet as a result of this wide array of diet-based strategies that have an impact on multiple risk factors. This is best accomplished by including the dietitian as a member of the collaborative team in the care of the patient with abnormal blood lipids.

### Impact of Physical Activity on Blood Lipids and Lipoproteins

Physical activity beneficially influences most of the atherosclerotic risk factors. The impact of regular exercise on plasma lipids and lipoproteins has been clearly defined with regard to the interactions among lipids, lipoproteins, apolipoproteins (apo), lipoprotein enzymes, and the influence of various factors such as aging, body fat distribution, dietary composition, and cigarette smoking status.<sup>83–86</sup>

The importance of physical activity, like nutrition, cannot be underestimated. Unfortunately, healthcare providers are

generally not well equipped to educate and support patients in the pursuit of a lifetime physical activity program. Providers are challenged by time constraints; by the resistance of many adults to make physical activity a part of their daily routine; and by a lack of knowledge and experience in behavioral change. A collaborative approach to the care of adults with coronary risk factors through the use of nonphysician healthcare providers such as nutritionists, nurses, and exercise physiologists can help improve patients' success in the adoption of regular physical activity. Cardiac rehabilitation programs can offer assistance to healthcare providers with exercise education and supervision when indicated—another method of enhancing a collaborative approach to risk reduction.

Exercise training studies usually observe lower plasma TG concentrations.<sup>87,88</sup> Large plasma TG reductions after exercise training are reported for previously inactive people with higher baseline concentrations,<sup>88,89</sup> although subjects with low initial TG concentrations have smaller TG reductions after exercise training.<sup>90</sup> Exercise training studies do not support an exercise-induced change in total cholesterol.<sup>88–92</sup> Rather, total cholesterol reductions are associated with body weight, percentage of body fat, and dietary fat reductions.<sup>83–86,91,92</sup>

Postprandial lipemia,<sup>93–95</sup> chylomicron, and very-low-density lipoprotein (VLDL) cholesterol are lower after aerobic exercise training<sup>83–85</sup> (Table 7). Plasma LDL-C concentrations are not lower after aerobic exercise training.<sup>88–90,92,96–98</sup> After completing 6 months of jogging (≈20 mi/week at 65% to 80% of aerobic capacity),<sup>99</sup> after 8 months of regular exercise participation,<sup>100</sup> and after 3 weeks of diet and brisk walking,<sup>101</sup> subjects exhibited greater LDL particle sizes with lower LDL-C. Cholesterol was decreased in the more-dense LDL subfractions and increased in the less-dense LDL fractions; these changes correlated with TG reductions.<sup>101</sup> Plasma lipoprotein(a) [Lp(a)], an LDL subfraction containing apo(a), is highly homologous with plasminogen and competes with plasminogen for fibrin-binding sites, inhibiting fibrinolysis.<sup>102</sup> Lp(a) does not change after regular physical activity participation.<sup>83–85,102</sup>

Exercise training longer than 12 weeks with good adherence is more likely to increase plasma HDL-C<sup>83–86,103,104</sup> in a dose-dependent manner.<sup>83–85</sup> Exercise-induced increases in HDL-C range from 4% to 22%, whereas absolute HDL-C increases are more uniform and range from 2 to 8 mg/dL. Findings show that exercise training without altered body weight and/or composition can increase HDL-C, and this is augmented by body fat loss.<sup>105</sup> HDLs can be divided into various particle sizes, with the HDL<sub>3b</sub> particle being directly related to CHD risk and the HDL<sub>2a</sub> and HDL<sub>2b</sub> particles being associated with reduced CHD risk. Exercise training is usually associated with increased HDL<sub>2b</sub> and decreased HDL<sub>3b</sub>.<sup>83–85,89,106,107</sup>

The impact of exercise training on apolipoproteins has been reviewed previously.<sup>83–85,108</sup> Increased apolipoprotein (apo) A-I levels are observed,<sup>89,90,92,107</sup> whereas apoB changes after exercise training usually parallel LDL-C changes.<sup>92</sup> ApoE levels in response to exercise appear to be mediated by many factors such as age and phenotype, with phenotype playing a strong role.<sup>83–85,108–111</sup> Exercise training

**TABLE 7. Lipid, Lipoprotein, Lipoprotein Enzymes, and Transfer Protein Changes Associated With Exercise**

	Single Exercise Session	Regular Exercise Participation
Lipid/lipoprotein		
TG	Decreases of 7% to 69%; approximate mean change 20%	Decreases of 4% to 37% Approximate mean change 24%
Cholesterol	No change*	No change†
LDL-C	No change	No change†
Small dense LDL-C particles	No change	Can increase LDL particle size usually with TG lowering
Lp(a)	No change	No change
HDL-C	Increases of 4% to 18% Approximate mean change 10%	Increases of 4% to 18% Approximate mean change 8%
Chylomicron and VLDL-C		
Lp(a)	Usually lower	Usually lower
Postprandial lipemia	Reduced	Reduced
apoA1	No change	Increased
apoB	Parallels LDL changes	Parallels LDL changes
apoE <sub>2</sub> , apoE <sub>3</sub> , apoE <sub>4</sub>	Varied response based on age, homozygote/heterozygote phenotype	Varied response based on age, homozygote/heterozygote phenotype
Enzyme		
LPL		
Activity	Delayed change ( $\geq 4$ h)	Increased
Mass	No information	Increased
HL		
Activity	No change	No change or reduced (may be reduced with weight loss)
Mass	No information	No information
LCAT		
Activity	Increased/no change	Increased/no change
Mass	No information	No information
CETP		
Activity	No change	No change/increased
Mass	Increased/decreased	Increased

HL indicates hepatic lipase; LCAT, lecithin:cholesterol acyltransferase.

\*No change unless the exercise session is prolonged (see text).<sup>88-90</sup>

†No change if body weight and diet do not change (see text).

studies provide direct evidence of a possible interactive effect between apoE polymorphism and exercise training lipoprotein/lipid change. Greater TG decreases are found in apoE<sub>2</sub> and apoE<sub>3</sub> phenotype subjects, whereas greater HDL-C increases occurred only in apoE<sub>2</sub> subjects after exercise training.<sup>112,113</sup> Although not statistically significant, increased postheparin lipoprotein lipase (LPL) activity in apoE<sub>2</sub> phenotype subjects supports exercise reductions of common CHD risk markers and the function of apoE in facilitating TG clearance.

In comparison with endurance training, less information exists to support resistance training as a modifier of plasma lipids. Studies are often contradictory, with some showing positive benefits of resistance exercise on the lipid profile<sup>114,115</sup> and others finding no benefits.<sup>116-123</sup> A decrease in body fat percentage and an increase in lean body mass after resistance training<sup>119</sup> are associated with decreased

total cholesterol and LDL-C. Both total cholesterol and LDL-C may be reduced after circuit resistance training.<sup>121</sup> In most studies, HDL-C concentrations are unresponsive to resistance training,<sup>116,122</sup> yet increases have been reported.<sup>115,124-126</sup>

The magnitude of change found for lipid and lipoprotein/lipid concentrations after a single exercise session is similar to that seen after the completion of a longitudinal exercise training program (Table 7). A measurable, beneficial effect on circulating lipids and lipoproteins/lipids may be expected after a single exercise session during which 350 kcal is expended,<sup>106</sup> whereas trained individuals may require  $\geq 800$  kcal to elicit comparable changes.<sup>127</sup> Lp(a) concentrations were not changed after short-duration exercise or longer-duration exercise sessions that required 1500 kcal of energy expenditure.<sup>128</sup> To maintain beneficial lipid and lipoprotein/lipid changes, exercise must be performed regularly.

High-intensity exercise and high-energy expenditure that causes depletion of intramuscular TG stores are needed to increase muscle LPL synthesis and release (Table 7).<sup>129</sup> Increased plasma postheparin LPL activity usually is not found until 4 to 18 hours after exercise<sup>130</sup> but is reported for endurance athletes,<sup>131</sup> and LPL activity usually is increased after exercise training.<sup>87,89,132,133</sup> Ethnic differences exist, with higher LPL values in white but not in black men after 20 weeks of endurance training.<sup>132</sup>

An inverse association exists between resting hepatic lipase activity and HDL<sub>2</sub> cholesterol, but hepatic lipase is directly related to HDL<sub>3</sub> cholesterol. In general, no changes in resting hepatic lipase activity are reported between inactive and active individuals,<sup>131</sup> and a single exercise session results in no significant hepatic lipase activity changes.<sup>127,134,135</sup> Low cholesteryl ester transfer protein (CETP) activity may provide an antiatherogenic effect by slowing hepatic HDL<sub>2</sub> catabolism and decreasing the amount of plasma cholesterol-rich particles. Cross-sectional studies report elevated plasma CETP activity in physically active people,<sup>87</sup> whereas longitudinal exercise training studies report decreased CETP activity.<sup>134,135</sup> In addition, lecithin cholesterol acyltransferase activity is increased in physically active men<sup>136</sup> but not after exercise training.<sup>87,97,132</sup>

Current data support a favorable impact for exercise training on lipid and lipoprotein profiles. Because much is known about the mechanisms responsible for changes in plasma lipid and lipoprotein modifications as a result of exercise training, a comprehensive medical management plan can be developed that optimizes pharmacological and lifestyle modifications. Scientific investigations are focusing on the molecular basis for lipid and lipoprotein change as a result of various interventions (eg, knowing a person's apoE genotype). Findings from these studies can provide a better understanding of why some people respond to exercise whereas others do not. Information about the interactive effects between regular exercise participation and pharmacological therapy is lacking.

With its favorable effect on many blood lipid abnormalities, physical activity/exercise training is a most appropriate intervention in a collaborative approach to the management of abnormal blood lipids. Activity should be undertaken at moderate to high intensity, 5 to 7 days/week, for at least 30 min/day and for  $\geq 60$  min/day by people who need to achieve weight loss. If this is done with an appropriate emphasis on nutrition and adherence, then body weight will likely be reduced and the need for medication therapy may be less in some people.

Including an assessment of an individual's physical activity patterns as part of every office visit will help to improve the recognition of its importance for both patient and provider. Developing a system for collaborating with healthcare providers who have expertise in behavior change, and exercise science for adults will support the important role of regular physical activity in regard to lipid management and overall risk reduction.

## Drug Therapy

Medical therapies for dyslipidemia are key for people at high risk for the disease and for people with known atherosclero-

**TABLE 8. New Features of ATP III<sup>136</sup>**

### Focus on multiple risk factors

Uses Framingham 10-y absolute CHD risk to identify patients for more intensive treatment (risk >20% in 10 y)

Identifies people with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes (TLC)

### Identifies people with CHD equivalents

Other forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease); diabetes; multiple risk factors that confer 10-y risk for CHD of >20%

### Modifications of lipid and lipoprotein classification

Identified LDL-C level <100 mg/dL as optimal

Raised categorical low HDL-C from <35 to <40 mg/dL

Lowered TG cut point (<150 mg/dL) to draw more attention to moderate elevations

### Modifications of ATP III for LDL-C goals<sup>137</sup>

TLC remains essential modality for LDL-C lowering

*High risk* (CHD or CHD risk equivalents): LDL-C goal remains <100 mg/dL with an optional goal <70 mg/dL

*Moderately high risk* ( $\geq 2$  risk factors; 10% to 20% 10-y risk): LDL-C goal <130 mg/dL with optional goal of <100 mg/dL; at 100 to 129 mg/dL, consider drug options

*Moderate risk* ( $\geq 2$  risk factors; 10-y risk <10%): LDL-C goal is <130 mg/dL; at  $\geq 160$  mg/dL, consider drug options

*Lower risk* (0 to 1 risk factor): LDL-C goal is <160 mg/dL; at 160 to 189 mg/dL, consider drug options

Adapted from NCEP ATP III.<sup>136</sup>

sis. A collaborative approach to medical therapies, often prescribed for a lifetime, has been shown to improve patient compliance and quality of life.<sup>29,30,33–36</sup> Millions of Americans remain at risk from dyslipidemia, in spite of safe and effective treatments.<sup>4,6</sup> Implementing a collaborative approach through the inclusion of nutritionists and nurses is key to long-term maintenance and safety of medical therapies.

Although effective drugs now exist to improve lipid profiles, no single drug is most appropriate under all circumstances. The 5 most common clinical situations in which drug therapy is needed are (1) elevated LDL-C; (2) elevated non-HDL-C in patients with high levels of TGs (200 to 500 mg/dL) despite attainment of LDL-C goals; (3) low HDL-C; (4) diabetic dyslipidemia; and (5) very high TGs and/or chylomicronemia syndrome. The appropriate treatment of these lipid abnormalities includes the use of the following classes of drugs: statins, resins, niacin, and fibrates, as well as fish oil, either singly or in combination.

An LDL-C goal of <100 mg/dL is considered optimum by ATP III.<sup>136</sup> Newer guidelines were recently published addressing clinical options for further LDL-C lowering in high-risk and very high-risk patients. This report is based on compelling new evidence from clinical trials published after ATP III was released<sup>137</sup> (Table 8).

Statins are the most potent agents for lowering LDL-C.<sup>137</sup> These agents work by competitively inhibiting the rate-limiting step of cholesterol synthesis and upregulating LDL receptors in the liver. In order of potency, they are rosuvastatin, atorvastatin, simvastatin, and then, listed alphabetically, fluvastatin, lovastatin, and pravastatin.



Patients with markedly elevated LDL-C ( $\geq 190$  mg/dL) deserve consideration for drug therapy because they are likely to have either monogenic familial hypercholesterolemia, familial defective apoB-100, or polygenic hypercholesterolemia. The drugs of choice are statins. In patients with familial hypercholesterolemia, the inherited deficiency of LDL receptors and proportionate increases in LDL-C are countered by statin therapy. To potentiate the effects of statins, drugs that are active in the gastrointestinal tract can be added. These drugs include bile acid sequestrants and cholesterol-absorption inhibitors.

Because major side effects of statins include myopathy, it appears reasonable to obtain a total creatine phosphokinase (CPK) level at baseline. Although this is not required, it may prove most useful if the patient develops muscle symptoms after starting a statin. If the baseline CPK is significantly elevated, then it is best to check for subclinical hypothyroidism or muscle disease before starting the statin.<sup>138</sup> The other major side effect of statin use is liver toxicity,<sup>137</sup> although the likelihood of liver transaminase elevations  $>3$  times the upper limit of normal is small (in stable patients usually 1% or less). Liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are obtained 6 to 12 weeks after statin therapy is initiated. Small increases in transaminases usually revert to lower values spontaneously and should not by themselves lead to the halting of statin therapy. If the ALT is  $\geq 2$  times the normal limit, then other causes of a high ALT should be investigated, such as medication use, excessive alcohol use (a clinical clue is that AST is often greater than ALT when excessive alcohol use is present), or the presence of other conditions such as gallstones or a fatty liver (consider imaging the liver and gallbladder with ultrasound if the liver transaminase elevation is symptomatic). When ALT is  $>3$  times the upper limit of normal and is confirmed on a repeat sample, statin therapy should be halted and an investigation should be undertaken to determine why this occurred.

A TG level  $\geq 150$  mg/dL is considered elevated. For patients with mildly elevated TG values (150 to 199 mg/dL), TLC may be adequate. Treatment of the disease states associated with high TGs, such as type 2 diabetes mellitus, chronic renal failure, nephritic syndrome, or hypothyroidism, may help reduce TG values toward normal. Drugs that elevate TGs, such as corticosteroid therapy, estrogen therapy, retinoid therapy, or high doses of  $\beta$ -blockers, should be stopped or substitutions should be made. TG values vary greatly, so rather than suggest a "TG target," ATP III suggested the use of non-HDL-C as a surrogate for the total of atherogenic particles (all particles carrying cholesterol except for HDL).<sup>137</sup>

Once LDL-C goals are reached, if TGs are  $\geq 200$  mg/dL, then non-HDL-C becomes a logical target for treatment. The goal levels for non-HDL-C are 30 mg/dL greater than the LDL-C goal. Statin therapy can be intensified in patients with elevated non-HDL-C. Nicotinic acid or fibric acid drugs (fibrates) are particularly useful for patients with combined elevations of cholesterol and TGs, low HDL-C, and raised non-HDL-C. For some high-risk patients, combination ther-

apy with a statin and niacin or a statin and fibrate is required to achieve both LDL-C and non-HDL-C goals.<sup>137</sup>

Low HDL-C ( $<40$  mg/dL) is considered a tertiary goal in ATP III in patients with coronary disease who have reached their LDL-C and non-HDL-C goals.<sup>137,139</sup> For all patients, behavioral changes that raise HDL-C can be recommended at the initial visit. These changes include losing excess weight, initiating regular exercise, stopping cigarette smoking, and avoiding excess carbohydrate calories in the form of sweetened foods and drinks. Because low HDL-C is a key component of the metabolic syndrome, reversal of a sedentary lifestyle and weight loss is likely to improve both HDL-C and the other parameters of this syndrome. For patients with isolated low HDL-C, HDL-C levels may not increase despite appropriate lifestyle change. Here, the goal is to lower LDL-C. For patients with CHD or CHD equivalents, drug therapy to improve HDL-C may indeed be appropriate once LDL-C and non-HDL-C goals are met. Evidence supporting medication therapy for abnormal blood lipids is noted in Table 9.<sup>140-147</sup>

In patients with high TG plus chylomicronemia syndrome,<sup>137</sup> prevention of acute pancreatitis is the primary goal. Three measures must be considered along with drug therapy if TGs are alarmingly high ( $>1000$  mg/dL) and pancreatitis is a threat: (1) introduction of an extremely low-fat diet ( $\leq 15\%$  of caloric intake); (2) removal of triggers such as high-fat meals and alcohol and drugs that greatly exacerbate hypertriglyceridemia such as oral estrogens (and tamoxifen), oral steroids, or retinoic acid; and (3) correction of disease states such as uncontrolled diabetes (this may indicate a need for insulin) and hypothyroidism. Fibrates can be effective medications for these patients.

Combination therapy with statins can be useful, but because there are few clinical trials to serve as guides, it is important to define the goals of therapy before adding another drug to statins.<sup>148</sup> Thus, to lower LDL-C to attain goal levels, a gastrointestinal-active medication such as a bile acid-binding sequestrant (the resins cholestyramine and colestipol, or colesevelam, a nonabsorbable polymer)<sup>150,151</sup> or a cholesterol-absorption inhibitor (eg, ezetimibe<sup>150</sup>) should be considered. Bile acid sequestrants are nonsystemic and hence ideal for young patients or good as a second drug<sup>137</sup> in patients who are taking statins but are still short of their goal levels for LDL-C. These drugs have been shown to reduce coronary events in primary and secondary prevention trials. To raise low levels of HDL-C, niacin should be considered.<sup>143</sup> Niacin raises blood glucose but has been shown to be effective in modifying lipid disorders in people with diabetes if glucose control is maintained.<sup>149,150</sup> For a patient with high TG levels who has the metabolic syndrome or diabetes mellitus, a fibrate such as fenofibrate or gemfibrozil can also be considered.<sup>150</sup> Caution should be exercised when combining fibrates with other cholesterol-lowering medications such as statins because of the risk of myopathy.<sup>138</sup> Indeed, when a fibrate is combined with a statin, fenofibrate is the fibrate of choice because it does not affect statin glucuronidation, as is seen with gemfibrozil.<sup>137</sup>

Bile acid sequestrants are safe drugs because they are nonabsorbable, but as expected, the major problems are

**TABLE 9. Selected Primary and Secondary Prevention Trials of Lipid Interventions**

Trial	Population	Medication	Beneficial Outcomes*
Heart Protection Study <sup>138,142,144</sup> (P, S)	High risk, diabetes, or CAD	Simvastatin	CHD events ↓ 27%, total mortality ↓ 13%
FATS <sup>140</sup> (S)	↑ ApoB; familial vascular disease	Niacin + colestipol; lovastatin + colestipol	More regression of CAD by angiography and ↓ new coronary events
WOSCOPS <sup>32</sup> (P)	↑ LDL-C	Pravastatin	Acute MI or CHD death ↓ 31%, total mortality ↓ 22%
AFCAPS-TexCAPS <sup>146</sup> (P)	↑ LDL-C, ↑ C-reactive protein	Lovastatin	↓ CHD events
HATS <sup>143</sup> (S)	Familial CHD	Simvastatin and niacin and antioxidants	Less progression of CAD by angiography and ↓ new coronary events; antioxidants reduced beneficial effects of niacin
VA HIT <sup>139,156</sup> (S)	CAD and ↓ HDL-C	Gemfibrozil	22% ↓ CHD events
Scandinavian Simvastatin Survival Study <sup>31</sup> (S)	↑ LDL-C	Simvastatin	CHD events ↓ 42%, total mortality ↓ 30%
LIPID <sup>260</sup> (S)	↑ LDL-C	Pravastatin	CHD events ↓ 24%, total mortality ↓ 13%
MIRACL <sup>261</sup> (S)	Acute coronary syndrome	Atorvastatin	↓ 16% recurrent CHD hospitalizations 16 wk posthospital discharge
CARE <sup>262</sup> (S)	↑ LDL-C	Pravastatin	CHD events ↓ 24%, total mortality ↓ 9%
Coronary Drug Project <sup>141</sup> (S); 3 arms (clofibrate, niacin, dextrothyroxine)	Men with history of MI	Niacin arm only	↓ Nonfatal MIs, no effect on total mortality, 15-y follow-up, 11% ↓ total mortality in original niacin group
Helsinki Heart Study <sup>155</sup> (P)	↑ LDL-C	Gemfibrozil	Incidence of CHD ↓ 34%
ALLHAT-LLT <sup>147</sup> (P)	↑ LDL-C	Pravastatin	↓ LDL-C 17%
DAIS <sup>145</sup> (S)	CAD + DM	Fenofibrate	Halted progression of CAD 40% by quantitative angiography
BIP <sup>157</sup> (S)	CAD	Bezafibrate	No significant end point reduction; overall trend in ↓ of primary end points

P indicates primary; S, secondary; FATS, Familial Atherosclerosis Treatment Study; WOSCOPS, West Of Scotland Coronary Prevention Study; AFCAPS-TexCAPS, Air Force Coronary/Texas Atherosclerosis Prevention Study; HATS, HDL-Atherosclerosis Treatment Study; VA HIT, Veterans Affairs High density lipoprotein cholesterol Intervention Trial study group; LIPID, Long-term Intervention with Pravastatin in Ischemic Disease; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; CARE, Cholesterol And Recurrent Events; ALLHAT-LLT, Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial-Lipid Lowering Trial; DAIS, Diabetes Atherosclerosis Intervention Study; BIP, Bezafibrate Infarction Prevention study.

\*Compared with placebo.

gastrointestinal distress and constipation. Patients should be counseled to maintain water intake. A useful clinical tactic is to use half the dose of resin with psyllium. This helps reduce constipation while it magnifies the LDL-C-lowering effects of the resin. The older resins, cholestyramine and colestipol, are more prone to interfere with the absorption of other drugs such as thyroid medication, thiazide diuretics, or warfarin.<sup>137,151</sup>

Ezetimibe is a cholesterol-absorption inhibitor.<sup>152</sup> It is absorbed, undergoes glucuronidation in the liver, and localizes in the brush border of the intestinal cell. It lowers LDL-C by ≈20%, lowers TGs, and raises HDL-C slightly. Dosing studies show that it greatly augments LDL-C lowering when it is added to statin therapy. It also lowers plant sterol absorption from the gastrointestinal tract. The clinical bene-

fits of this action are not known. It appears to be safe, although a rare hypersensitivity reaction with angioedema has been reported. The typical dose is 10 mg/day, and it can be taken at any time of the day.<sup>152</sup>

Niacin has a unique side effect profile. Patients soon recognize the flushing and itching that comes from niacin ingestion. This is observed more strongly with unmodified niacin and is less of a problem with either the extended-release or the sustained-release forms. Because the flushing is prostaglandin mediated, an aspirin tablet taken ≈1 to 2 hours before niacin ingestion can mitigate this side effect, which fortunately becomes less severe with time. All forms of niacin can raise blood sugar, uric acid, and liver enzymes and can cause upper gastrointestinal distress.<sup>139,153</sup> Contraindications to niacin include liver disease, severe gout, and peptic ulcer disease.

**TABLE 10. Supplements and Functional Foods: Lipid Effects**

Supplement/Functional Foods	Mechanism	Lipid Lowering, Average % Change	Usefulness for Lipid Management
Vitamin E	Antioxidant	No significant change in TC/LDL; lowers HDL <sub>2</sub>	May have harmful effect
Vitamin C, beta carotene	Antioxidant	No significant change in lipid profile	No clear benefit; may have harmful effect
n-3 Fatty acids (fish oils)	Inhibits VLDL synthesis	Lower TG 15% to 40%; dose 1 to 3 g/d	Useful adjunct for hypertriglyceridemia; may be useful in diabetes
Garlic	Unknown	Lowers TC/LDL ≈5%	No major role
Soy protein	may be phytoestrogen effect	Lowers TC/LDL ≈5% to 10%, nonsignificant increase in HDL; dose 25 g/d	Modest role; best used in place of high saturated fat foods
Plant sterols/stanols	Decreases dietary and biliary cholesterol absorption	Lower TC/LDL 9% to 20%, no change in HDL; dose 2 g/d	Moderate effect; may be useful adjunct
Fiber	Bile acid-binding action, decreases dietary cholesterol absorption	Lowers TC/LDL ≈5% to 15%; dose 25 to 30 g/d of dietary sources of fiber	Modest role; best used in place of high saturated fat foods

TC indicates total cholesterol.

The fibric acid drugs or fibrates have major actions on TGs because of their effects on the peroxisome proliferator activator receptor- $\alpha$ .<sup>137</sup> When used in patients with lone hypercholesterolemia, LDL-C can be lowered as much as 22%; however, most often fibric acids will be used in patients with combined hyperlipidemia, as seen in metabolic syndrome and diabetes.<sup>154</sup> In these patients, LDL-C may actually rise slightly, TGs are lowered 20% to 50%, and HDL-C is raised 10% to 20%.

Medical therapies are complex and require patient education, systematic medical follow-up, and ongoing management. A collaborative approach among nursing, nutrition, and medicine will provide improved patient compliance, greater ability to reach lipid goals, and greater safety. A major benefit of a collaborative approach to medical therapies is the improved access that patients generally have when faced with questions and/or concerns such as those regarding side effects. Support and “patient connection” can be provided through mail, telephone, fax, and the Internet. These methods can save costs by reducing emergency department visits, unnecessary physician’s office visits, and poor patient compliance.<sup>155–157</sup>

### Use of Supplements in the Management of Abnormal Blood Lipids: Do They Fit?

Billions of dollars are spent annually on dietary supplements in the United States. Given this “belief” in the value of supplements by Americans, an understanding of their efficacy and how they fit into an overall approach to the treatment of dyslipidemia is important.

The American population has embraced the use of supplements to enhance health and treat disease. Survey data show that one third to one half of the US population uses supplements.<sup>158</sup> The market for supplements has increased during the last decade, as evidenced by the expanded sections for vitamins, minerals, herbal preparations, and food supplements in pharmacies, grocery stores, and health food stores. It is estimated that spending on supplements exceeds \$17 billion annually,<sup>159</sup> and these costs represent unreimbursed health expenditures. There are many reasons why Americans use supplements to treat health problems, including lack of access to conventional medical care, desire for self-care, and

perceptions that supplements are “natural” products and thus healthier than conventional medicines. Patients rarely inform their healthcare provider about their use of supplements, and most providers have little training in or knowledge about the efficacy of supplements. This section focuses on 5 supplements that have been suggested as possible adjuncts to the treatment of abnormal blood lipids: antioxidant vitamins E and C, fish oils, garlic, soy products, and plant stanols (Table 10).

Oxidized LDL has been implicated in the process of plaque development, initiating multiple atherogenic effects.<sup>160,161</sup> Endothelial responses to oxidized LDL include increased inflammatory cells and activation of monocyte and macrophage chemotactic properties. Oxidized LDL is also thought to alter LDL receptor activity.<sup>162</sup> It has been hypothesized that a reduction in LDL oxidation would reduce plaque development and that the use of antioxidant vitamins may retard oxidation. Vitamin E is the major antioxidant incorporated into lipid particles, and in vitro studies have demonstrated that vitamin E prolongs the lag time to oxidation.<sup>163–165</sup> Despite this evidence, large-scale clinical trials examining the effect of the use of antioxidant supplements have not observed any benefit related to the primary or secondary prevention of CHD.<sup>164,166–168</sup>

Use of antioxidant vitamins for CHD prevention has continued, in part because of the notion that although there was no evidence of benefit, neither was there evidence of harm. Brown and colleagues,<sup>143</sup> however, recently found that in patients with low HDL, the lipid-lowering effects of niacin and simvastatin were blunted when antioxidant vitamins (vitamin E, vitamin C,  $\beta$ -carotene, and selenium) were added to lipid therapy. Niacin and simvastatin therapy lowered LDL-C by an average of 42% and raised HDL<sub>2</sub> cholesterol (considered cardioprotective) by 65%; the addition of antioxidant therapy showed similar LDL reductions, but HDL<sub>2</sub> levels increased only 28%. The use of antioxidants alone lowered HDL<sub>2</sub> cholesterol by 15%. Angiographic measures of stenosis also differed significantly among the groups, with the niacin and simvastatin group showing an average decrease of 0.4%. In comparison, other groups showed an increase in stenosis: niacin and simvastatin plus antioxidant therapy, 0.7%; antioxidants alone, 1.8%; and placebo, 3.9%. This

study found an adverse effect on both blood lipids and progression of stenoses. Most large, randomized clinical trials have failed to find support for the use of vitamin E in either lipid management or prevention of CHD. Although there is less evidence related to vitamin C, the work by Brown and colleagues<sup>143</sup> calls into question the use of antioxidant supplementation in the treatment of abnormal blood lipids.

The omega-3 fatty acids include  $\alpha$ -linolenic acid, found in plant sources such as flaxseed, nuts, and soy and in plant-based oils such as canola and soybean oils, and eicosapentaenoic acid and docosahexaenoic acid, found primarily in cold-water fish and fish oils. Epidemiological studies first noted a lower incidence of CAD among the Greenland Eskimos despite their consumption of a diet high in fats, particularly omega-3 fatty acids.<sup>169</sup> The proposed mechanisms to account for this cardiovascular protection include reduced plaque growth, decreased platelet aggregation, reduced blood pressure by inhibition of eicosanoid-derived vasoconstriction factors and improved endothelial function, reduced occurrence of arrhythmias, and improved lipid profiles.<sup>170</sup>

Early studies of omega-3 fatty acids observed marked lowering of VLDL and TGs of 15% to 40%, depending on the dose consumed. Total cholesterol and LDL-C results were inconsistent with decreases in LDL observed if dietary saturated fat intake was decreased.<sup>171</sup> A more recent meta-analysis that examined randomized controlled trials of omega-3 diets or supplementation and their effects on CHD end points reported average TG reductions of 20% with no significant effect on LDL-C or HDL-C.<sup>172</sup> Of note, omega-3 interventions were associated with a significant reduction in CHD mortality compared with control groups (relative risk 0.08, 95% CI 0.7 to 0.9), which suggests that the CHD benefits of omega-3 supplementation may not be entirely related to lipid effects. Hypertriglyceridemia is a common lipid abnormality among diabetic patients. Treatment with omega-3 fatty acids has been shown to lower TGs in this population by 30% without adversely affecting hemoglobin A1c levels<sup>173</sup> but with some borderline worsening of blood glucose levels.

The omega-3 fatty acids lower lipids by inhibiting the synthesis of VLDL in the liver. This results in smaller, less-dense VLDL and LDL particles<sup>169</sup> and an overall less-atherogenic lipid profile. The above actions are generally observed at doses of 3 to 4 g/day for eicosapentaenoic acid and docosahexaenoic acid, although current guidelines recommend omega-3 intake of  $\approx 1$  g/day for CHD patients or 2 fish servings per week for patients without CHD.<sup>82</sup> Although omega-3 fatty acid supplementation in doses of up to 3 g/day is considered generally safe, the reported side effects include a moderate risk of gastrointestinal upset, a low-to-moderate risk of worsening glycemia, and a very low to low risk of clinical bleeding.<sup>82</sup> Current evidence suggests that omega-3 fatty acids are safe and may benefit patients with lipid disorders that include high TGs. For patients with high TG levels ( $>500$  mg/dL), marine-derived omega-3 fatty acids at doses of 3 g/day have been shown to lower TGs by  $\approx 30\%$ .<sup>81</sup> ATP III recommends that omega-3 fatty acids be used as an adjunct to pharmacological therapy for lowering TG.<sup>5</sup> The

AHA recommends 2 to 4 g/day of eicosapentaenoic acid plus docosahexaenoic acid for patients who need to lower their TG levels given under a physician's care.<sup>82</sup> The most practical way to achieve this quantity of omega-3 fatty acids is through the use of fish oil supplements.

Multiple beneficial cardiovascular effects have been attributed to the use of garlic, including decreased blood pressure and blood lipid levels, reduced platelet aggregation, and its action as an antioxidant and anti-inflammatory agent.<sup>174–177</sup> Although a number of studies have been conducted with either garlic supplements or foods containing garlic, at present there is no clear understanding of the mechanisms of action that account for the cardioprotective effects of garlic.

In 1999, the US Food and Drug Administration reviewed the available literature and determined that an intake of 25 g/day of soy protein was associated with modest reductions in total cholesterol and LDL-C ranging from 1.5% to 4.5%.<sup>64</sup> Since that time, several additional studies examining the relationship between soy intake and lipoproteins have suggested that the magnitude of the lipid-lowering effect is related to the initial lipid level, in that the effect may exist in patients with severe hypercholesterolemia but not in those with normal lipid levels.<sup>177,178</sup> In addition, other studies have suggested that the replacement of high-saturated-fat foods with soy products may have accounted for some of the lipid effects seen in early studies.<sup>179</sup> A recent study examined the effect of soy supplementation on outcomes related to type 2 diabetes mellitus in a group of postmenopausal women and found favorable reductions in fasting insulin, total cholesterol, and LDL-C (8%, 4%, and 7%, respectively).<sup>180</sup> In total, the data suggest that soy protein has a small lipid effect, and the real benefit may be related to the use of soy as a substitute for high-saturated-fat foods.

When esterified, plant sterols form the plant stanols.<sup>181</sup> Stanols such as sitostanol and campestanol, when incorporated into the diet, consistently lower LDL-C by 9% to 20% without decreasing HDL-C.<sup>182</sup> Studies have been conducted on a variety of populations, including patients with mild hypercholesterolemia.<sup>183,184</sup> In addition, studies have demonstrated a dose-response effect with a stepwise reduction in LDL-C with increasing doses of 0.8, 1.6, 2.4, and 3.2 g of plant stanols; however, the differences in cholesterol reduction between the higher doses (2.4 and 3.2 g/day) were not statistically significant.<sup>32</sup> These data suggest that a dose of  $\approx 2$  g/day is optimum.<sup>182</sup>

The most common food products to incorporate emulsified stanols are margarines; however, European studies have evaluated emulsifying stanols in other food products, such as yogurt.<sup>185</sup> Stanols can be incorporated into low-fat products. Food products containing plant sterols and stanols are considered generally safe; however, concern related to decreased absorption of fat-soluble vitamins and long-term use of these products has been raised. There is considerable public interest in the use of supplements and dietary products to manage elevated blood lipids. Several small studies have examined the use of fiber, oat products, and nuts (almonds and walnuts) on blood lipids. Meta-analysis of studies evaluating the use of oat products suggests that lipid-lowering effects are related to dietary replacement of saturated fats.<sup>186,187</sup> Most studies



**TABLE 11. Compliance With Treatment of Abnormal Blood Lipids**

Exercise program	25% to 50% <sup>192</sup>
Long-term smoking cessation	Low <sup>193</sup>
Proper diet	<50% <sup>194</sup>
Weight management	20% of overweight individuals losing weight maintain at 1 y <sup>195</sup>
Taking medication as prescribed	0% to 100%; average of 50% <sup>196,197,199–201</sup>

report changes of  $\approx 5\%$ , with larger reductions occurring in patients with the highest initial lipid levels.

There are no available, well-tested supplements that achieve the magnitude of lipid lowering that is observed with traditional pharmaceutical therapies. With the exception of plant stanols and omega-3 fatty acids, most supplements have demonstrated only a small beneficial effect on blood lipids (Table 10). Thus, current data suggest a limited role for supplements in the treatment of abnormal blood lipids. Patient education regarding the benefits and risks of vitamins and supplements is an integral and important component in the treatment of dyslipidemia. Nutritionists are well positioned to provide information about supplements—an additional key reason for collaboration.

### Adherence Issues

In no other arena is collaboration more important than when considering adherence. Behavioral science, social science, psychology, and medicine meet at this crossroads. Through collaborative efforts, adherence to important lifesaving interventions can be positively influenced.

Adherence and compliance are interchangeable terms and are simply defined as the extent to which an individual's behavior coincides with health advice or a treatment plan. Nonadherence, considered by some a judgmental term, is used to describe a fact and may apply to the patient or the prescriber.<sup>188</sup> The focus of this section is on the patient; however, the prescribed regimen, the provider, and the system or organization in which health care is delivered, each a crucial component of the adherence equation, are also discussed.<sup>189</sup>

The efficacy of lipid-lowering therapies is well documented, but inadequate or low adherence can undermine the effectiveness of pharmacological and therapeutic lifestyle regimens.<sup>190</sup> Studies have shown repeatedly that low adherence is associated with poor outcomes, even when the treatment is a placebo,<sup>188,191</sup> which suggests that adherence confers a protective effect.

Treatment of dyslipidemia may include a special eating plan, weight reduction, smoking cessation, regular exercise, and  $\geq 1$  lipid-lowering medications. Although this therapeutic plan may represent the optimal treatment approach, it also highlights the challenge facing patients who are attempting to incorporate these changes into their lives (Table 11).<sup>192–201</sup>

There is a continually diminishing level of adherence, with at least 25% of patients in all groups discontinuing the drug by 6 months. It would not be unrealistic to think that adherence to statin therapy in the United States is lower

**TABLE 12. Factors Relating to Nonadherence**

<b>Patient related</b> <sup>207–211</sup>
Does not understand complex treatment regimen
Provider does not explain prescribed regimen
Limited staff for patient teaching
Healthcare system does not facilitate patient adherence
Provider incorrectly assumes patient adherence
Patient decides costs and risks of regimen are greater than benefit
<b>Regimen related</b> <sup>211,212</sup>
Prescribing complex regimen during 1 visit
Not offering cost-savings strategies
<b>Provider related</b> <sup>213–221</sup>
Lack of time
Absence of infrastructure
Lack of system support
Lack of reimbursement for counseling
Major focus on acute medical problems
Lack of counseling skills
<b>System related</b> <sup>30,212,213</sup>
High copayment
Frequent refill requirements
Frequent staff turnover
Established policies that do not promote treatment to goal

because Americans tend to have a higher copayment for drugs or may lack insurance that covers medications. Moreover, data show that in general, 12% of Americans do not fill their prescriptions and that 12% of those who fill the prescription never take the medication.<sup>202</sup> Some of the non-statin agents, such as the bile acid sequestrants, can be a challenge to ingest, and thus the reported nonadherence is not surprising. It is perplexing, however, that adherence is an issue for the relatively simple, once-daily statin regimen. An examination of factors associated with low adherence to lipid-lowering drug therapy revealed that the presence of side effects, the number of prescribed drugs, broken appointments, age younger than 47 years, and heavy smoking were associated with noncompliance.<sup>203</sup> Factors associated with high compliance included the patient's perception of the time the physician spent explaining and discussing the treatment plan, a belief in the efficacy of the lipid-lowering therapy, and the habit of taking the medication as part of the patient's daily routine. Cost of the medication, personal beliefs about the role of cholesterol in CHD, greater knowledge of disease and treatment, and mood and stress were not associated with adherence.<sup>203</sup>

A myriad of factors have been studied for their association with adherence in general, for example, sociodemographic traits, psychological distress, health beliefs, benefits, and barriers.<sup>204,205</sup> The relationship between several variables and adherence has been inconsistent, however.<sup>204–206</sup> The factors that are more consistently identified as related to adherence and, most important, can be addressed through interventions that are divided into 4 categories: patient-related, regimen-related, provider-related, and process-oriented or system-related factors (Table 12)<sup>207–211</sup>:

**Patient-Related Factors:** As with many patient-related factors, these situations call for an open dialogue between patient and provider that encourages the patient to examine the risks and benefits of the treatment with the guidance of the healthcare professional. The ability to maintain open communication with the patient will permit a discussion of many factors that may influence a patient's compliance and will go far in enhancing adherence.<sup>212–215</sup>

**Regimen-Related Factors:** The regimen itself has a marked impact on the patient's adherence. A regimen that is consistent with the guidelines for treatment of dyslipidemia may be overwhelming to the patient and may need to be introduced in stages (eg, start with dietary modification, then add other lifestyle changes, and finally, add pharmacotherapy). Depending on the patient's lipid values, the treatment components may need to be introduced in reverse order. If cost is a factor and the patient cannot afford lipid-lowering medication, then alternative strategies need to be tried, and dietary therapy should be emphasized. Even dietary therapy may need to be introduced gradually, with regular checkups to determine how the patient is progressing in implementing the dietary changes.

**Provider-Related Factors:** The provider plays an intricate role in the maintenance of adherence. Instructing physicians and nurses in educating and counseling patients and creating opportunities for them to practice their skills can increase their self-confidence in this area.<sup>216–223</sup> The Worcester Area Trial for Counseling in Hyperlipidemia (WATCH) evaluated the effectiveness of a training program for physicians in nutrition counseling, alone and in combination with an office support program, compared with usual care. At 12 months, the study demonstrated significant between-group differences, with those in the intervention-plus-office support group having significant reductions in fat intake, serum LDL-C levels, and body weight.<sup>224</sup> Delivery of the patient-centered intervention took 8 to 10 minutes of the clinic visit. These findings highlight the potential of professional education to enable healthcare professionals to develop their skills in behavior-change counseling and how the addition of a support system can make a significant difference in patient adherence.

**System-Related Factors:** The system drives the environment in which healthcare professionals work, whereas process-related factors affect how they deliver their care. Numerous factors related to the system can markedly affect adherence. The system can enhance adherence; for example, it can provide a tracking system that facilitates charting a patient's lipids, weight, blood pressure, or medication refills, or it can provide numerous disincentives. The policies establish the expectations: whether patients will be treated until they reach their LDL-C goal or whether referrals will be made to multidisciplinary staff for specialized services, for instance, a dietitian for weight-management counseling. Well-established, multidisciplinary systems designed to promote achievement of treatment goals by patients are in place.<sup>30,213</sup> The collective efforts of the team can address the multiple factors that influence nonadherence, can reinforce the message delivered by other members, and can increase the

probability of success in achieving and maintaining treatment adherence.<sup>212</sup>

Assessment of adherence must be incorporated into each clinical encounter. Accurate and affordable measures are lacking, however, and most have a bias toward overestimating adherence.<sup>225</sup> One reason for this measurement error is that the period being measured is usually not representative of the patient's usual behavior. Patient adherence varies in relationship to the clinical appointment, with adherence increasing immediately before and after the visit.<sup>226</sup> Thus, when patients are asked to report on their behavior, their report may be influenced by their recall of the most recent behavior, and patients may overestimate their adherence for the longer period.<sup>225</sup> A variety of methods are available to measure adherence in the clinical setting (eg, biological and electronic measures, pill counts, pharmacy refill records, self-report).<sup>227</sup>

Clinicians often rely on their own judgment of their patients' adherence; however, it has been shown that physicians overestimate their patients' adherence.<sup>208,209</sup> It is important that the clinician separate adherence from therapeutic or clinical outcome, which can be affected by numerous variables in addition to compliance<sup>225</sup>; for example, the failure of a patient to reach an LDL goal may be the result of inadequate drug dosage, individual variation in pharmacokinetic factors, daytime or seasonal variations in measurement values, or personal factors.<sup>228</sup> Conversely, goal achievement does not confirm adherence to the medication. Clinical outcomes are indirect measures of adherence, whereas patient behaviors (eg, losing weight, exercising, taking medication) are direct measures of adherence. Both direct and indirect measures have inherent advantages and disadvantages.<sup>225,229</sup> Electronic devices provide details of the patterns of adherence behavior and reveal interdose interval medication adherence, but these remain expensive and impractical for widespread clinical use. Pill counts and pharmacy refill records are useful if the patient does not hoard or share medication, and in the latter case, use only one pharmacy for refills. Direct measurement of behavior is difficult, and thus in the clinical setting there is almost total reliance on self-reported behavior.<sup>227</sup>

It has been reported<sup>209,230</sup> that asking nonresponders about their adherence would detect >50% of those with low adherence, with a specificity of 87%. Even when patients indicate that they have missed some of their medications, their estimates are usually substantially higher than the actual adherence. Given this background, although it is not the most accurate, the most practical approach is to ask patients about their behavior around taking prescribed medications or eating and exercising and start the dialogue about adherence. Taking a nonjudgmental approach and giving patients permission to report that they are not following the regimen is essential for an open discussion. Acknowledge each time how difficult it is to take medications or make lifestyle changes. An explanation of how objective data such as weight or laboratory results relate to adherence can be included in the discussion. In follow-up sessions, always ask patients about adherence. Practical indicators of inadequate adherence may also include missed appointments and lack of response to incremental

increases in dosage or treatment intensity.<sup>196</sup> When adherence is less than adequate, interventions to improve adherence need to be considered.

Similar to how factors that have an impact on adherence are categorized, strategies to remediate poor adherence or enhance adequate adherence can be divided according to the factors that they address: the patient, the regimen, the provider, or the system. The use of a combination of strategies (eg, behavioral counseling, educational approaches, supportive techniques) is recommended, as is targeting the multiple levels of adherence.<sup>189,190</sup> Beginning with the patient, the provider needs to determine not only whether the patient is ready to make a change and is confident about implementing the treatment but also whether the patient has the knowledge, skills, and resources to start the plan. Given the patient's capabilities and resources, is the regimen appropriate for the patient? Is the provider able to work within the patient's restrictions and counsel the patient about what needs to be done? Finally, can the system assist the patient and provide services needed by the patient and the provider to enhance adherence? A number of intervention strategies are available to address adherence across the multiple levels from patient to the system of care delivery. These strategies are based on several theories and models of behavioral change (eg, social cognitive theory, relapse prevention model, stages of change model) and have been tested in randomized, controlled clinical trials. Evidence supports their use in combination, in multiple settings, and by all members of the healthcare team.<sup>30,211,214,231</sup>

To realize the benefits of current therapies, improved adherence to all components of a lipid-lowering therapy must be achieved. Many strategies may appear to be complex, time-consuming, and burdensome for the clinician to implement.<sup>188</sup> A good start to addressing the problem of inadequate adherence would be to include the simplest of strategies (eg, working with the patient to address common priorities, simplifying the regimen, asking the patient about adherence, reinforcing at each visit the importance of adherence) and build on these as resources permit. The use of adherence-enhancing interventions has been shown to make a difference in the patient's clinical outcome.

### Coronary Artery Disease

It is clear that a collaborative approach to administering lifestyle changes in conjunction with a systematic approach to the use of effective lipid-lowering medications will maximize the likelihood that patients will be treated to attain well-accepted risk factor goals<sup>38</sup> and will minimize the likelihood of preventable coronary events.

Extensive clinical trial data document the effects of pharmacological lipid-lowering therapy on clinical outcomes in patients with CHD. These data include reduced rates of cardiac and overall mortality, recurrent MI, revascularization, and cerebrovascular events.<sup>31,32,148,232</sup> The studies included patients with chronic CHD, post-MI patients, coronary bypass surgery patients, and percutaneous coronary intervention patients. Although the use of pharmacological agents in this setting is fairly straightforward, lipid-lowering drugs are costly, are frequently associated with side effects and com-

pliance issues, and focus benefits only on lipid-related mechanisms of atherosclerosis. Maximization of nonpharmacological therapy for abnormal lipids, which includes modification of the quality of the diet, weight-loss interventions, and exercise programs, will serve not only to minimize dosage requirements for pharmacological lipid-lowering agents but also to provide substantial non-lipid-related preventive benefits.<sup>233–241</sup> Several structured models of collaborative approaches to abnormal blood lipids in patients with CHD have been described. These include the Stanford Coronary Risk Intervention Project (SCRIP),<sup>29</sup> the MULTIFIT program,<sup>30</sup> the Lifestyle Heart Trial,<sup>242,243</sup> the Lyon Diet Heart Study,<sup>244</sup> the Indo-Mediterranean Diet Heart Study,<sup>245</sup> and Cardiac Hospitalization Atherosclerosis Management Program (CHAMP).<sup>38</sup>

The SCRIP study tested the hypothesis that intensive multiple risk factor reduction would significantly reduce the rate of progression of atherosclerosis in the coronary arteries of men and women with CHD compared with subjects randomly assigned to the usual care of their physician.<sup>29</sup> The SCRIP approach to treating abnormal blood lipids and other coronary risk factors has been adopted in community settings with excellent reproduction of benefits and has served as a model for cardiac rehabilitation–secondary prevention programs.<sup>213,235,246–248</sup>

The MULTIFIT program was developed at 5 Kaiser Permanente Medical Centers in the San Francisco area.<sup>30</sup> The intervention is a nurse-managed, physician-directed, home-based, case-management system for coronary risk factor modification after acute MI. It has also been replicated in the clinical setting, similarly staffed by nurse-clinicians who have undergone a specific training program.<sup>249</sup>

The Lifestyle Heart Trial<sup>242,243</sup> addressed the hypothesis that comprehensive lifestyle changes (low-fat vegetarian diet, stress management training, and moderate exercise) could favorably alter the progression of coronary atherosclerosis without use of lipid-lowering drugs. Study personnel included nutritionists, nurses, and psychologists. The Lifestyle Heart Trial intervention program has been replicated successfully in the clinical setting.<sup>250</sup>

The studies of de Lorgeril et al and Singh and colleagues were primarily nutritional interventions.<sup>244,245</sup> The Lyon Diet Heart Study was a randomized secondary prevention trial that tested whether an  $\alpha$ -linolenic acid–rich Mediterranean-type diet reduced rates of recurrence after a first MI compared with a “prudent” Western diet.<sup>244</sup> Study personnel included both nutritionists and physicians. Cardiac events were reduced in the Mediterranean diet group (adjusted risk ratios 0.28 to 0.53).<sup>244</sup> The Indo-Mediterranean Diet Heart Study was similarly a randomized, controlled trial that evaluated the effectiveness of a diet rich in fruits and vegetables, high in polyunsaturates, high in dietary fiber, high in dietary antioxidants, and low in saturated fat and cholesterol.<sup>245</sup>

Finally, the process of systematically initiating the use of lipid-lowering medications, along with aspirin,  $\beta$ -blockers, and angiotensin-converting enzyme inhibitors, in patients hospitalized with an acute coronary event, in conjunction with dietary and exercise counseling, has been shown to benefit from a collaborative approach by healthcare profes-



sionals.<sup>250</sup> In the CHAMP program,<sup>38</sup> an in-hospital, nurse-case manager approach resulted in increased use of these preventive medications and was associated with improved risk factor measures such as lower LDL-C levels and a reduction in recurrent MI and mortality at 1 year.

No single study has truly sorted out the relative value of combined nutritional interventions, exercise, and lipid-lowering drugs with regard to the lowering of coronary event rates, because their effects are overlapping and confounded by nonlipid effects of lifestyle changes that affect the atherosclerotic process. These include the effects of exercise, weight loss, and nutritional modification on factors such as insulin resistance, blood pressure, and indexes of inflammation.<sup>233,234,236,239,240</sup> Collaboration provides the addition of expertise to improve lifestyle change and can synergistically improve the effects of medical therapies.

### Cerebrovascular Disease

Current understanding of the relationship between abnormal blood lipid levels, treatment of abnormal blood lipid levels, and stroke risk is incomplete and evolving. It has been a source of some confusion to clinicians and researchers that the shared association of atherosclerotic risk factors for cardiovascular and cerebrovascular disease has not extended to elevated cholesterol levels. Elevated blood cholesterol levels in general and LDL levels in particular have a well-defined relationship with risk of CHD, but a similar result has not been defined for stroke.

A meta-analysis of 45 prospective cohorts published in 1995 included 450 000 patients and 13 000 strokes over an average follow-up of 16 years. There was no association between total cholesterol level and stroke.<sup>251</sup> A meta-analysis of Asian cohorts (125 000 patients, 1800 strokes) also found no definite relationship but a trend for lower risk of ischemic stroke events and a higher risk of hemorrhagic stroke events with decreasing cholesterol levels.<sup>252</sup>

Explanations for a possible false-negative result exist. Perhaps most important is that many observational studies do not distinguish between subtypes of cerebrovascular events. Stroke is a heterogeneous disorder that includes hemorrhagic and ischemic events. Hemorrhagic stroke is unlikely to include elevated cholesterol and atherosclerosis as a pathogenic mechanism.<sup>253,254</sup>

The Multiple Risk Factor Intervention Trial (MRFIT) showed that the risk of nonhemorrhagic stroke death increased with increasing cholesterol levels in a cohort of 350 000 men.<sup>253</sup> A hospital case-control study showed that ischemic stroke of proven atherothrombotic origin was strongly associated with higher mean total cholesterol and LDL-C.<sup>255</sup> Another multicenter case-control study in France showed a strong association of increased total cholesterol and LDL-C with brain infarction that was independent of other risk factors. This association was strongest for the subsets of patients with atherothrombotic strokes, those with lacunar strokes, and patients with carotid stenosis.<sup>256</sup>

Despite the lack of a definitive association of elevated cholesterol with stroke risk, many guidelines include a recommendation for cholesterol monitoring and lowering of elevated levels because of the shared comorbidity of cerebro-

vascular disease and CHD.<sup>257</sup> In fact, the cause of subsequent mortality in patients with cerebrovascular disease over the long term is more likely to be CHD rather than cerebrovascular disease.<sup>258</sup> This may be more or less true for different subtypes of cerebrovascular disease. Patients with internal carotid artery atherosclerosis, for example, appear to have a particularly high risk of comorbid coronary disease and subsequent cardiac morbidity.<sup>259</sup>

Recent studies that have shown that cholesterol-lowering drugs may have benefits with regard to subsequent cerebrovascular and cardiovascular risk have again raised questions about the role of lipid levels and their management in stroke. Notably, these studies were initiated in patients with coronary vascular disease; however, they included stroke outcomes as predefined secondary end points.<sup>31,141,148,254,260–263</sup>

Secondary prevention studies are limited to date but so far do not show a benefit for the use of statins. It remains unclear whether lipid-lowering treatment in general and statins in particular are helpful in secondary stroke prevention because available data are limited.<sup>264</sup> It cannot be assumed that the benefit of stroke risk reduction in coronary patients extends to secondary stroke prevention. Reduction of stroke risk in these trials may relate in part to reduction of postcoronary event cerebral emboli and not to primary atherothrombotic stroke. Studies are currently under way to specifically address the benefit of statin therapy in secondary stroke prevention.<sup>265</sup>

Although other nonpharmacological interventions (diet, exercise) are effective for lowering serum lipid levels,<sup>266,267</sup> the precise relationships between these serum lipid levels and stroke risk has not been rigorously assessed in prospective trials. Observational studies have given mixed results in the association of various dietary components with stroke risk. Dietary fat intake, for example, has not been shown to affect stroke risk,<sup>268</sup> whereas fish intake has been more variably associated.<sup>269,270</sup> Cereal and whole-grain fiber consumption has also been linked to lower stroke risk.<sup>271,272</sup> Results of observational studies do not clearly allow definitive recommendations to be made; however, prospective trials of diets, particularly low-fat diets, have intrinsic challenges, and therefore their benefits may never be truly defined.<sup>267,273</sup>

Exercise and physical activity have been more consistently linked with lower stroke rates.<sup>274–276</sup> This effect appears to have a dose-response relationship, with more vigorous exercise being more clearly protective. A prospective clinical trial would likely be required to establish the level of physical activity required for preventing stroke.

Although the benefits of lipid-lowering therapies in stroke patients require further elucidation, it is important to remember that elevated lipid levels and cerebrovascular disease actually rarely occur in isolation. Comorbidity in terms of other vascular risk factors and other vascular disease is common, especially when considered over the lifetime of the patient. Just as the benefits of statins may not be limited to their lipid-lowering effects, the benefits of diet and exercise also have an effect on diabetes and hypertension and thereby reduce not only stroke risk but also the risk of coronary disease and peripheral vascular disease both in stroke and other high-risk patients. Hence, a truly collaborative effort to reduce lipid levels in stroke patients is likely to have a benefit



that extends beyond lipid lowering. Many physicians may assume that knowledge of healthy lifestyle choices and their impact on stroke risk are well known to patients; however, specific recommendations by physicians regarding exercise and diet do appear to influence patient behavior and should not be omitted.<sup>277</sup>

### Peripheral Arterial Disease

Peripheral arterial disease (PAD) is a major manifestation of systemic atherothrombosis that presents as occlusive disease in the arterial circulation to the lower extremities. The epidemiology has been well described; the disease affects ≈12% of the adult population, which increases to 20% in patients >70 years old.<sup>278</sup> In the United States, this has been extrapolated to a national prevalence of ≈8 to 10 million affected individuals. Thus, PAD represents one of the most common manifestations of systemic atherothrombosis.<sup>279–281</sup>

Numerous epidemiological studies have documented a 6-fold excess risk of cardiovascular mortality and a 3-fold excess risk of all-cause mortality.<sup>282</sup> This risk is present even in patients who have not yet had a cardiovascular event, thus emphasizing the importance of early detection and aggressive treatment of this systemic disease. Given these data, the first treatment goal is to aggressively modify cardiovascular risk factors in patients with PAD and prescribe antiplatelet therapies. An aggressive risk-reduction strategy should lead to a reduction in overall risk of cardiovascular events. Primary evidence now supports the use of statins, angiotensin-converting enzyme inhibitors, and clopidogrel in patients with PAD even without previous evidence of a cardiovascular event.<sup>148,281,283</sup> Once these systemic goals have been accomplished, recognition of the daily limitations imposed by claudication and prescription of appropriate symptomatic treatments should become the next clinical priority.

Alterations in lipid metabolism are a major risk factor for all forms of atherosclerosis. In PAD, several lipid fractions are critically important in determining the presence and progression of peripheral atherosclerosis. Independent risk factors for PAD include elevations of total cholesterol, LDL-C, TGs, and Lp(a).<sup>278,284,285</sup> For every 10 mg/dL increase in total cholesterol concentration, there is a corresponding 8% to 10% increase in the risk of PAD.<sup>278</sup> Increases in HDL-C and apoA-1 are protective against PAD.<sup>284</sup>

Initial investigations in the treatment of lipid disorders centered on surrogate markers of efficacy.<sup>286–288</sup> Until recently, there was no direct evidence of the mortality benefits of treating the PAD population with statin drugs. Thus, data from the Heart Protection Study (HPS) are an important addition to understanding the role of lowering LDL-C levels in this population.<sup>148</sup> The HPS included 6748 patients with PAD. Simvastatin at a dose of 40 mg/day was associated with a 12% reduction in total mortality, 17% reduction in vascular mortality, 24% reduction in CHD events, 27% reduction in all strokes, and 16% reduction in noncoronary revascularizations. Similar results were obtained in the PAD subgroup, whether or not they had evidence of coronary disease at baseline. Thus, the HPS demonstrated that in patients with PAD (even in the absence of a previous MI or stroke), aggressive LDL lowering was associated with a marked

reduction in cardiovascular events (MI, stroke, revascularization, and vascular death). HPS is the first large, randomized trial of statin therapy to demonstrate that aggressive lipid modification can significantly improve outcomes in the PAD population. A limitation of HPS was that the evidence in PAD was derived from a subgroup analysis, and no trial has been conducted to evaluate the PAD population exclusively. Despite these limitations, all patients with PAD should lower their LDL-C levels to <100 mg/dL. Additional recommendations are to use fibrates or niacin to modulate HDL-C and TG levels. The Arterial Disease Multiple Intervention Trial (ADMIT) demonstrated the safety and efficacy of niacin in the PAD population.<sup>153</sup> Niacin was effective for lowering TG levels and increasing HDL-C levels without causing a change in glucose metabolism.

Patients with PAD have a marked reduction in exercise performance, as evidenced by a reduction in peak oxygen uptake ≥50% when compared with age-matched healthy controls.<sup>289,290</sup> Patients with claudication have a reduced walking speed and distance, have lower physical function scores on standardized questionnaires, have shorter 6-min walk distances and speeds, and even experience alterations in balance and coordination.<sup>291,292</sup> Thus, an important treatment goal, as stated above, is to improve exercise performance, walking ability, and functional status.

Several drugs have been developed for claudication, the most effective of which is cilostazol.<sup>293</sup> More recent studies have tested the hypothesis that statins may improve endothelial function and other aspects of PAD, leading to improvement in clinical symptoms. In 2 studies,<sup>294,295</sup> patients treated with statins demonstrated a trend toward improvement in peak walking time and significant increases in claudication onset time. The treadmill findings were supported by a parallel increase in physical function.

On the basis of these studies, at least 2 randomized trials suggest that statins may improve limb function. Additional evidence was supported by assessing the relationship between statin use and limb functioning in a recently published cross-sectional study.<sup>296</sup> This study also supported the concept that statins may improve limb functioning. Thus, the weight of evidence suggests that statins may be an important modulator of symptoms and systemic risk. On the basis of this concept, several trials are under way or ongoing to examine the overall clinical benefit of statins and other lipid-modifying agents in treating symptoms of claudication.

For patients with PAD, a comprehensive approach to the management of lipid disorders involves exercise, nutrition, and medical expertise. A collaborative approach is more likely to improve patient quality of life as well as outcomes. Again, the focus must fall equally on medical therapies, surgical interventions, and prevention. Nutrition, physical activity, smoking cessation, stress management, and social support all play key roles in the care of people with complex illnesses such as peripheral vascular disease. Providing this care involves many collaborative partners with supportive medical systems.

### Conclusion

This perspective on a collaborative approach to managing abnormal blood lipids presents an organized overview of the

evidence that supports a multidisciplinary case-management approach to cardiovascular risk reduction and, particularly, abnormal blood lipids. The significance of incorporating a collaborative approach to cardiovascular risk reduction and ultimately improving cardiovascular morbidity and mortality is emphasized.

Primary prevention has demonstrated that population-wide influences on cholesterol levels shift the cholesterol distributions to lower levels and thus reduce the rate of increase of cholesterol concentration levels with aging. Behavioral and environmental influences specific to this reduction in cholesterol are best addressed by the collaboration of various healthcare professionals and public health efforts.

This collaborative approach goes beyond the traditional cardiovascular patient to address patients with PAD and

cerebrovascular disease. Data support the assertion that aggressive lipid-lowering therapy in patients with peripheral vascular disease will improve cardiovascular morbidity and mortality rates and alleviate claudication symptoms. In addition, statin therapy has been shown to reduce the incidence of stroke in patients when lipid levels were reduced.

Ideal blood lipid levels can be accomplished only by adherence to lifestyle and pharmacological regimens. This is a complex process. It can be accomplished by addressing the multilevel components of potential barriers to adherence that are related to the patient, the regimen, the provider, and the system. By elevating the importance of adherence in the collaborative approach to the management of abnormal blood lipids, we will see a more profound impact on the reduction of cardiovascular and cerebrovascular morbidity and mortality.

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