COMMENTARY

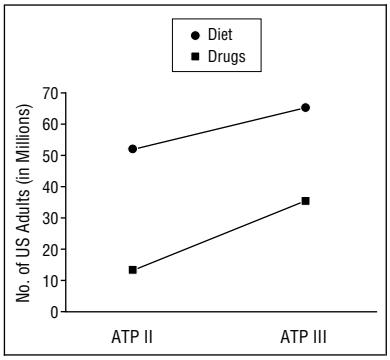
The New National Cholesterol Education Program Guidelines

Clinical Challenges for More Widespread Therapy of Lipids to Treat and Prevent Coronary Heart Disease

THE RECENTLY published National Cholesterol Education Program (NCEP) III guidelines[1] present many new clinical challenges to health care providers and their patients. These guidelines recommend stricter target lipid levels as well as a broader approach to risk assessment in an effort to reduce premature death and disability from coronary heart disease (CHD) and stroke. Many more patients, especially in primary prevention, are candidates to improve their lipid profiles under the new guidelines. It has been estimated that, as a direct result of the new NCEP III guidelines, the number of US adults eligible for lipid modification has increased from 52 million to 65 million for therapeutic lifestyle changes, including diet, and almost 3-fold, from about 13 million to 36 million, for drug therapy (**Figure**).[2] This report identifies and characterizes the untreated patients who would benefit from lipid modification and summarizes the efficacy, safety, and cost profiles of the various statins, the class of drugs with the largest and most conclusive body of evidence to support their more widespread use.[3]

GLOBAL RISK ASSESSMENT

The NCEP II guidelines[4] had asked health care providers to first consider whether the patient had experienced a prior CHD event (secondary or primary prevention) and second, to base treatment decisions primarily on levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). In contrast, the new NCEP III guidelines[1] expand the prior list of cardiovascular events to include virtually all occlusive vascular diseases of the heart (stable and unstable angina, angioplasty, or bypass) as well as the brain (ie, ischemic stroke, transient ischemic attacks, and symptomatic carotid artery stenosis) and peripheral arteries, and focus on global risk assessment rather than just lipid parameters. Global risk assessment includes quantitation of the 10-year risk of developing CHD. Such quantitation is based on the novel and important concept of a CHD risk equivalent. In the new guidelines, diabetes mellitus is elevated from a major risk factor to a CHD risk equivalent. Thus, all diabetic patients should be treated as aggressively as patients who have survived a prior occlussive event of the heart, brain, or peripheral arteries. In addition, based on this concept, a primary prevention patient with a CHD risk equivalent may have an absolute risk for developing a first event equal to or greater than that of a secondary prevention patient for developing a recurrent event. Further, primary prevention patients without a CHD risk equivalent but with multiple risk factors may also have a 10-year risk equal to or greater than that of a secondary prevention patient (ie, a survivor of a prior event) without additional risk factors. Thus, health care providers are also asked to quantitate the 10-year risk of all primary prevention patients with 2 or more risk factors using the Framingham Risk Assessment System.[5] This global risk assessment includes sex, age, TC level, smoking status, high-density lipoprotein cholesterol (HDL-C) level, and systolic blood pressure. If the absolute risk is 20% or greater, a primary prevention patient should be treated as aggressively as a patient who has experienced a previous event. The new NCEP III guidelines[1] also target primary prevention patients at high risk due to multiple metabolic risk factors or metabolic syndrome. In the United States today, metabolic syndrome is a major clinical and public health problem. The clinical problem results from the fact that the global risk of the primary prevention patient with multiple metabolic risk factors is far greater than the simple arithmetic sum of their individual risks. The public health problem results from the fact that over 25% of all US adults have metabolic syndrome. NCEP III defines metabolic syndrome as a constellation of any 3 of the 5 risk factors that include abdominal obesity (waist >101.6 cm [40 in] in men and >88.9 cm [35 in] in women), low HDL-C levels (<40 mg/dL [1.03 mmol/L] in men



United States adults eligible for therapeutic lifestyle changes, including diet and drug therapy in Adult Treatment Panel (ATP) II and ATP III (adapted from *USA Today*[2]).

Table 1. LDL-C Criteria for Goals and Initiating Therapeutic Lifestyle Changes or Drug Therapy*

Risk Group	LDL-C Goal, mg/dL	LDL-C Level, mg/dL, at Which to Consider	
		Therapeutic Lifestyle Changes	Drug Therapy
Prior CHD, CHD risk equivalent, or 10-y risk >20%	<100	>100	>130 (100-129 Optional)
10-y risk <20%			
≥2 Risk factors	<130	>130	>130 (10-y risk 10%-19%)
0-1 Risk factors	<160	>160	>190 (160-189 Optional)

*Adapted from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.[1] LDL-C indicates low-density lipoprotein cholesterol; CHD, coronary heart disease. To convert cholesterol to millimoles per liter, multiply by 0.02586.

and <50 mg/dL [1.29 mmol/L] in women), high triglyceride (TG) levels (>150 mg/dL [1.69 mmol/L]), increased blood pressure (systolic, >130 mm Hg or diastolic, >85 mm Hg), and high fasting blood glucose levels (>110 mg/dL [6.11 mmol/L]).

CRITERIA AND GOALS FOR LIPID MODIFICATION

For all patients with prior events, a CHD risk equivalent or a 10-year risk of 20% or greater, the LDL-C level goal is less than 100 mg/dL (2.58 mmol/L) (**Table 1**). For primary prevention patients with a 10-year risk of 10% to 19%, the LDL-C goal is less than 130 mg/dL (3.36 mmol/L). Finally, for those whose risk is less than 10%, the LDL-C goal is less than 160 mg/dL (4.14 mmol/L). In addition, the new NCEP guidelines also create 2 new lipid goals. First, the new guidelines raise the level of HDL-C defined as low to less than 40 mg/dL (1.03 mmol/L) (rather than 35 mg/dL [0.90 mmol/L]). Second, the new guidelines lower the level of TG defined as high to greater than 150 mg/dL (1.69 mmol/L) (rather than 200 mg/dL [2.26 mmol/L]).

SCREENING AND TREATMENT

The new guidelines recommend initial screening based on fasting TC, LDL-C, HDL-C, and TG levels. For individuals with a TG level greater than 200 mg/dL (2.26 mmol/L), health care providers are advised to treat both HDL-C and non–HDL-C levels, a new lipid parameter that is determined by combining the levels of LDL-C and very low-density lipoprotein cholesterol (VLDL-C).

THERAPEUTIC LIFESTYLE CHANGES

Unfortunately, in the United States, most individuals prefer prescription of pills to proscription of harmful lifestyles.[6,7] Therapeutic lifestyle changes, however, will confer large and usually more-than-additive benefits in terms of risk reduction.[1] In addition, the efficacy of drug therapy with statins is enhanced by beneficial therapeutic lifestyle changes, including diet. With regard to dietary changes to lower LDL-C levels, health care providers are advised to recommend saturated fat less than 7% of total calories and cholesterol less than 200 mg/d as well as plant stanols and sterols and foods with viscous (soluble) fiber to their patients. Stanols and sterols are present in certain margarine products and salad dressings. Sources of soluble fiber include legumes, cereal grains, beans, and many fruits and vegetables. Such therapeutic lifestyle changes, including diet, are likely to have beneficial effects, not just on CHD but also possibly on certain forms of cancer, especially colon and uterus, and possibly breast.

DRUG THERAPIES

While numerous drug therapies to favorably modify lipids are currently available either by prescription or over the counter, the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are recommended by the NCEP III as the first-line drug of choice for virtually all patients eligible for lipid modification by drugs.[1] NCEP III recommends that primary prevention patients whose LDL-C goal is less than 130 mg/dL (3.36 mmol/L) should have drug therapy initiated simultaneously with therapeutic lifestyle changes. Statins lower TC, LDL-C, and TG levels, and increase HDL-C levels. With regard to HDL-C levels, both major subfractions, namely 2 and 3, are protective against CHD.[8,9] Further, for the treatment of mixed dyslipidemias, statins are also the initial drug of choice. The overwhelming majority of eligible patients (>90%) will reach their NCEP goals with an LDL-C level reduction of approximately 35%.[10] In an overview, or meta-analysis, of secondary and primary prevention trials, those assigned at random to statins had 22% reduction in cholesterol levels and 30% reduction in LDL-C levels. These beneficial changes were associated with significantly reduced risks of myocardial infarction, stroke, and vascular death as well as total mortality.[3,11]

RELATIVE BENEFITS, RISKS, AND COSTS OF VARIOUS STATINS

There are currently 5 available statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin). With respect to benefits,[12] all of these drugs reduce LDL-C levels by at least 30% to 35%, but the usual starting doses of atorvastatin, fluvastatin, and simvastatin provide even larger decreases. The starting doses of atorvastatin yield the largest reduction in LDL-C levels. Higher doses will provide an even greater reduction in LDL-C levels with proportionately less increases in HDL-C levels. All statins have favorable safety pro-

Table 2. Relative Benefits, Risks, and Costs of the Most Common Initial Doses of the Various Statins Based on Average Wholesale Price per Day

Drug, mg	Benefits*			Risks		Average Wholesale Price, $
	LDL-C	HDL-C	TG	Alone	With Fibrates	
Atorvastatin, 10	≥35	≤10	≤15	Rare	Uncommon	1.97
Fluvastatin, 80	≥35	>10	>15	Rare	Rare	1.92
Lovastatin, 20	30-35	≤10	>15	Rare	Uncommon	2.64
Pravastatin, 40	30-35	≤10	>15	Rare	Rare	2.55
Simvastatin, 20	≥35	≤10	≤15	Rare	Uncommon	4.16

*Data are given as milligrams per deciliter. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglyceride. To convert cholesterol to millimoles per liter, multiply by 0.02586; to convert triglycerides to millimoles per liter, multiply by 0.01229.

files. Statin-induced liver dysfunction and myopathy are both rare. Combination therapy of statins with niacin or fibrates will yield greater elevations of HDL-C levels and lowering of TG but may increase the risk of myopathy. In this regard, cerivastatin was recently voluntarily withdrawn from the market due to deaths from rhabdomyolysis, which seemed to result primarily from an apparently idiosyncratic deleterious interaction with gemfibrozil as well as use of higher initial doses.[13] Fluvastatin and pravastatin may have a reduced potential for interactions with other drugs because of their different metabolic pathways. Unlike other statins, fluvastatin and pravastatin are not lipophilic. Further, metabolic inhibitors,[14] which include diltiazem, erythromycin, verapamil, and grapefruit juice, do not increase the concentration of fluvastatin or pravastatin. These theoretical considerations may have important clinical implications for patients requiring combination drug therapy for either lipid modification or other comorbidities such as diabetes or hypertension. They may also have important clinical and public health implications for the treatment of patients with human immunodeficiency virus infection. Both human immunodeficiency virus infection and drug therapies with protease inhibitors may contribute to extremely unfavorable lipid profiles.[15] Statin therapy is far and away the drug of choice to reduce their markedly increased risks of CHD, despite any increased risk of myopathy due to drug interactions. In a recent small randomized trial in healthy individuals given protease inhibitors, the increased concentration of statin drugs was 0% for pravastatin, 79% for atorvastatin, and 3059% for simvastatin.[16] With respect to cost of statins, based on average wholesale price per day, the published figures range from a low of $1.92 for fluvastatin to a high of $4.16 for simvastatin.[17] **Table 2** summarizes the relative benefits, risks, and costs of the most common initial doses for the various statins.

THE NEED FOR CLINICAL JUDGMENT

The new NCEP guidelines[1] are based on a totality of evidence, which is sufficient to warrant far more widespread usage of statins to treat and prevent CHD. It is also true that the NCEP III guidelines will only have an impact if they are implemented. While the guidelines allow for quantitative estimates of risks, it is equally important to consider that there is absolutely no substitute for astute clinical judgment. For example, the Framingham Risk Assessment System scores are based on a predominately white population.[5] African Americans have higher risks of CHD and stroke than their white counterparts.[18] Thus, health care providers should consider more aggressive therapies for African American patients at any given risk score. In addition, family history of premature CHD, obesity, and physical inactivity are independent risk factors[6,7] that are not included in the scores, so health care providers should also institute more aggressive therapies in patients with a given risk score who also have these risk factors.

In the previous NCEP guidelines,[4] more emphasis had been based on the ratio of LDL-C to HDL-C levels. This implied, for example, that women who tend to have high HDL-C levels did not require therapy for high LDL-C levels. In the new guidelines,[1] there is recognition of the fact that probably no level of HDL-C below 60 mg/dL (1.55 mmol/L) protects against high LDL-C levels. Conversely, there is likely to be no low level of LDL-C that protects against low HDL-C levels. Thus, there needs to be wider usage of statins in patients with high LDL-C levels despite the presence of normal or high HDL-C levels.

The new NCEP guidelines[1] also imply that patients with low LDL-C but with low HDL-C levels may be at sufficient risk to warrant lipid modification. In this context, the Airforce/Texas Coronary Atherosclerosis Prevention Study randomized primary prevention patients with normal LDL-C and low HDL-C levels to statin therapy and demonstrated cardiovascular benefits.[19]

With respect to TG levels, the new NCEP guidelines[1] recognize the emerging body of data from basic research, clinical investigations, and observational, epidemiological studies[9] to support their role as an independent coronary risk factor. In a recent randomized trial, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention trial, gemfibrozil increased HDL-C levels by 6% but decreased TG levels by 31%.[20] This trial showed a significant 22% decrease in the primary end point of fatal CHD and nonfatal myocardial infarction.

There are a number of emerging risk factors that health care providers should consider in selected subgroups of patients to better define their risk. These include a number of proinflammatory markers such

as high-sensitivity C-reactive protein,[21] as well as a proatherogenic markers such as small dense LDL-C particles.[22] In addition, a number of noninvasive assessments such as ankle-brachial index, ultrasound of carotid intimal-medial thickness, electron beam tomography of the coronary arteries, and exercise electrocardiography may help better define risk in selected subgroups of patients. For example, patients who may benefit from such assessments include primary prevention patients with normal cholesterol levels and no other risk factors for CHD but a family history of premature CHD as well as secondary prevention patients with low LDL-C levels and no other risk factors.

The clinician, however, should not let the perfect be the enemy of the possible. While there are clear research challenges, the clinical challenges are equally clear.[7]

CONCLUSIONS

The recently published NCEP guidelines[1] provide a far greater clinical challenge to health care providers to markedly increase the number of patients undergoing favorable lipid modification as a major component of their global risk assessment and management. A recent evaluation of the more restrictive previous NCEP[4] guidelines suggested that goals were being reached in only 38% of primary and 18% of secondary prevention patients.[23] The rational application of these important and timely guidelines will require both therapeutic lifestyle changes, including diet as well as drug therapy. The statin drugs have far and away the largest and most conclusive body of evidence to support their use to favorably alter lipids, including their benefit to risk and benefit to cost ratios. Their increased use in accordance with the new NCEP guidelines in secondary and primary prevention could avoid tens of thousands of premature deaths in the United States each year.

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