UT Southwestern Internal Medicine

Grand Rounds

April 3, 2015

Cholesterol Management Issues—2015

(Lower *is* Better)

Scott M. Grundy, MD, PhD

Professor of Internal Medicine

Conflict of Interest: This is to acknowledge that Scott M. Grundy, M.D., Ph.D., has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Grundy will not be discussing off-label uses in his presentation.

Scott M. Grundy, M.D., Ph.D.
Professor, Department of Internal Medicine
Division of Nutrition and Metabolic Diseases
Director, Center for Human Nutrition

Interests: Nutrition and metabolic diseases such as hypercholesterolemia, metabolic syndrome, and type 2 diabetes

Purpose: To examine unresolved issues in current cholesterol guidelines.

Overview: Several unresolved issues in management in patients at risk for atherosclerotic cardiovascular disease (ASCVD) need to be addressed. Critical questions are the following. Do we have enough information to set goals for cholesterol-lowering therapy? How should risk for future ASCVD be determined? How do we select patients for cholesterol-lowering drugs? At what age should drugs to reduce cholesterol levels be instituted? And what cholesterol-lowering drugs are reliable? These are the major questions to be addressed in the presentation.

Educational Objectives: To review issues of global risk assessment for ASCVD. To emphasize the need for early intervention on elevated cholesterol in higher risk individuals. To understand the selection of cholesterol-lowering drugs in persons at risk for ASCVD.

Atherosclerotic cardiovascular disease (ASCVD) remains the foremost cause of death among chronic disease. Its prevalence is increasing in many countries of the world. This increase results from aging of the population and predisposing lifestyles. Fortunately, mortality from ASCVD has been declining in most developed countries. This decline comes from improvements in preventive measures and better clinical intervention. One of the most important advances in cardiovascular field has resulted from the discovery of risk factors for ASCVD. These risk factors directly or indirectly promote development of atherosclerosis or they predispose to vascular events. The major risk factors include cigarette smoking, hypercholesterolemia, hypertension, hyperglycemia, and metabolic syndrome. The latter is an aggregation of risk factors of metabolic origin. Lifestyle factors—overnutrition and physical inactivity—contribute importantly to the major risk factors. In addition, a host of other factors, called emerging risk factors, associate with a greater risk for ASCVD. They include pro-thrombotic and pro-inflammatory states, insulin resistance, and various genetic factors. Some of the latter undoubtedly contribute to the major risk factors, but genetic influences likely affect development of atherosclerosis through ways not yet understood.

Hypercholesterolemia as a Risk Factor for ASCVD

The Cholesterol Hypothesis

The first line of evidence showing a connection between serum cholesterol levels and atherosclerosis was obtained in laboratory animals. Feeding cholesterol to various animal species results than high serum levels of cholesterol and its accumulation in the arterial wall. The latter recapitulates early stages of human atherosclerosis. Subsequently it was observed that humans with genetic forms of severe hypercholesterolemia develop premature atherosclerosis and ASCVD. Later, population surveys revealed a positive association between serum cholesterol levels and likelihood of ASCVD (1). Finally, clinical trials with cholesterol-lowering agents documented that reduction of serum cholesterol levels reduces risk for ASCVD (2,3). These findings convinced most investigators that the so-called *cholesterol hypothesis* has been proven. In other words, the relationship between cholesterol levels and ASCVD risk is bidirectional; raising cholesterol levels increases risk, whereas reducing them decreases risk.

Epidemiological Evidence

A relationship between cholesterol levels and ASCVD risk has been documented both in developing and developed countries (1). Lowest risk is observed in populations with the lowest cholesterol concentrations. Within populations, persons with the lowest cholesterol levels are at

least risk. Thus, for prevention of ASCVD in populations, "the lower, the better" for cholesterol concentrations is apparent. .

Pre-Statin Clinical Trial Evidence

Still stronger evidence for the cholesterol hypothesis comes from randomized controlled trials (RCTs) of cholesterol-lowering therapies. Earlier, several trials tested the efficacy by reducing cholesterol through diet. Results from individual dietary trials were not definitive; but meta-analysis, which combines data from all these trials, demonstrated significant risk reduction from cholesterol lowering (2). In addition, before discovery of statins, several RCTs with cholesterol-lowering drugs were performed. Some of these trials showed significant risk reduction; others gave equivocal results. But when taken together, meta-analysis again demonstrated ASCVD risk reduction (4).

Statin Clinical Trial Evidence

Finally, the most definitive support for the cholesterol hypothesis comes from RCTs with statins. A variety of statins differing in dose and potency are available. As stand-alone trials, statin therapies gave reductions in coronary heart disease (CHD), stroke, and total mortality. The strongest evidence from statin RCTs comes from meta-analysis of all the trials (3). This analysis leaves little doubt that intensive cholesterol-lowering reduces risk for ASCVD. Risk reductions range from 25-45%, depending statin and dose employed.

Cholesterol-Lowering Drugs

At present, statins are first-line cholesterol-lowering drugs. They inhibit cholesterol synthesis in the liver, which increases LDL receptors. They markedly reduce cholesterol levels. However, other cholesterol-lowering drugs are currently available or are on the horizon. Ezetimibe blocks cholesterol absorption in the intestine and also raises LDL receptor activity. A recent clinical trial called IMPROVE-IT showed that ezetimibe in combination with high-dose statins produces incremental ASCVD risk reduction (5). The results of this trial were presented at the 2014 American Heart Association scientific sessions, but they have not been published. Bile acid resins inhibit intestinal absorption of bile acids, which likewise raises hepatic LDL receptors. Bile acid resins also lower risk for ASCVD (6). Other LDL-lowering drugs include microsomal triglyceride transfer protein (MTP) inhibitors (7) and RNA antisense drugs that block synthesis of apolipoprotein B (8). Both of these drugs inhibit for secretion of atherogenic lipoproteins into the circulation. At present their use is restricted to patients with severe hypercholesterolemia. Another class of drugs inhibit cholesterol ester transfer protein (CETP); these agents lower LDL-C levels as well as raising HDL-C (9,10). They are currently being tested in RCTs. Finally, a new class of drugs inhibits a circulating protein called PCSK9; this protein blocks LDL receptors and raises LDL-C levels. Inhibition of PCSK9 markedly lowers LDL-C concentrations (11). Recent reports suggest that PCSK9 inhibitors reduce risk for ASCVD in patients with hypercholesterolemia (12,13).

Cholesterol-lowering drugs vary in their efficacy in reduction of LDL-C and atherogenic lipoproteins. Table 1 divides these drugs according to type, dose, and efficacy into three categories of intensity: low, moderate, and high**.**

Table 1. Categories of cholesterol-lowering drugs

Drug	Low-Intensity	Moderate-Intensity	High Intensity
	15-25% ↓ LDL-C	30-45%↓ LDL-C	≥45%↓ LDL-C
Lovastatin	10 mg	40 mg	
Pravastatin	10 mg	40 mg	
Simvastatin	10 mg	20 mg	
Fluvastatin	40 mg	80 mg	
Pitavastatin		2-4 mg	
Atorvastatin	5 mg	10 mg	80
Rosuvastatin		5 mg	20
Ezetimide	10 mg	10 mg + Simvastatin 10 mg	10 mg + Simvastatin 40 mg
Bile acid resin	Variable depending on agent*	Variable* + Simvastatin 10 mg	
PCSK9 inhibitor			Variable dose

* Cholestyramine 8-16 gm/day; Colestipol 10-20 gm/day; Colesevelam 3.8-4.5 gm/day

Strength of Cholesterol-ASCVD Relationship

Meta-analysis of cholesterol-lowering trials, especially statin trials, further strengthens evidence for a tight relation between degrees of reduction of serum cholesterol and ASCVD risk. There have been two types of meta-analysis. One examined the relative risk reduction accompanying a given absolute decrease in cholesterol levels. this type of analysis the Cholesterol Trialists Consortium showed that on average for every mmol/L (40 mg/dL) reduction of low-density lipoprotein cholesterol (LDL-C), risk for ASCVD is reduced by approximately 20% (3). This decrease in relative risk occurred regardless of baseline risk. Another type of meta-analysis examined the relation between change in absolute LDL-C levels and absolute risk. This analysis supports the concept that the more LDL-C is reduced the greater is the absolute decrease in risk (14). These two different types of meta-analysis underlie a fundamental difference in treatment guidelines for hypercholesterolemia. The first favors administration of a fixed dose of statins regardless of baseline cholesterol level. The second favors reducing cholesterol levels to as low as possible within the bounds of reason.

History of Guidelines for Cholesterol Management

National Cholesterol Education Program (NCEP**)**.

Among the most influential guidelines for cholesterol management have been those produced by the NECP. This program was sponsored by the National Heart, Lung and Blood Institute, and was reprehensive of many health-related organizations in the United States. Between 1987 and

2004, three major Adult Treatment Panel (ATP) reports and one update were published through NCEP. These reports identified LDL-C is the major target of cholesterol-lowering therapy. The intensity of LDL-lowering therapy was based on the aggregate knowledge derived from multiple sources and cholesterol field. Priority was given the clinical trial evidence when it was available. ATP I (1987) emphasized lifestyle therapy for primary prevention (15). Use of cholesterol-lowering drugs down played. ATP II (1993) added more emphasis on secondary prevention; this was because a large meta-analysis of cholesterol-lowering trials demonstrating CHD risk reduction with drug therapy (16). ATP III (2001) added new emphasis on high-risk primary prevention (2). At each successive ATP report, the intensity of LDL lowering therapy was increased.

NCEP: Secondary Prevention: CHD and Other Clinical Atherosclerotic Disease

The NCEP put highest priority for lipid management for patients with clinical forms of atherosclerotic disease. Most conditions included CHD, clinical carotid artery disease and peripheral arterial disease, and abdominal aortic aneurysm. ASCVD is the inclusive term for any of these conditions. The 10-year risk for future cardiovascular events in patients with established ASCVD is usually > 20%. In ATP III, the presence of ASCVD of any type warranted an LDL-C goal of < 100 mg/dL. For patients with hypertriglyceridemia, a non-HDL-C goal of < 130 mg/dL was added to take into account the atherogenicity of triglyceride-rich lipoproteins.

NCEP: Primary Prevention: Importance of Global Risk Assessment

For primary prevention, ATP III identified four levels of risk for increasing intensity of LDL-C lowering. Risk for CHD was calculated using Framingham risk scoring. Framingham risk factors included cigarette smoking, hypertension, elevated total cholesterol, low HDL-C, and advancing age. A 10 year risk $\geq$ 20% for CHD was called *high risk*. *Moderately high risk* was defined as a 10-year risk of 10-19%; at this level of risk, cholesterol-lowering drugs were considered to be cost-effective. A 10- year risk of < 10% was divided into low risk and moderate risk depending on the presence or absence of major risk factors. *Moderate risk* corresponds to a 10-year risk for CHD of approximately 5-9%. Generally speaking cholesterol-lowering drugs were not recommended for low- to- moderate risk except when LDL-C levels are very high.

ATP III Update (2004)

In 2004, ATP III underwent update and set an optional LDL-C goal of < 70 mg/dL for patients deemed to be at very high risk for future CHD events (17). This option included CHD plus other atherosclerotic conditions and/or multiple major risk factors. This progression of treatment intensity was made possible by the results of several clinical trials with statin therapy.

Disbandment of NCEP (2013)

In 2013, the National Heart Lung and Blood Institute disbanded the NCEP. This role was taken over in part by the American College of Cardiology and American Heart Association. However other organizations have also published cholesterol treatment guidelines.

European Guidelines

In parallel with NCEP guidelines have been reports on cholesterol management produced by the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) (18). These are similar in many ways to those of NCEP. There are a few exceptions. Absolute risk for informing drug therapy depends on 10-year risk for ASCVD mortality based on European epidemiologic data. The European database is named SCORE. European guidelines recognize that baseline risk for ASCVD differs between Northern and these two regions. LDL-C goals of therapy are similar but not identical to those of NCEP.

Canadian Cholesterol Guidelines

In 2013, the Canadian Cardiovascular Society issued treatment guidelines for Canada (19). These guidelines again are similar to NCEP and ESC/EAS. One difference however is a more aggressive approach to primary prevention. When drug therapy is warranted, based on absolute risk estimates, it is recommended that the LDL-C level be reduced to < 70 mg/dL.

International Atherosclerosis Society (IAS)

The IAS recently published recommendations that can be widely adapted throughout the world (20). The aim was to make these guidelines flexible enough to be compatible with national recommendations. A new feature of IAS guidelines was the introduction of lifetime risk as the marker of absolute risk to guide use of cholesterol-lowering drugs. Attempts are made to estimate lifetime risk in different populations. This approach appears to be gaining more traction among lipid experts. On the whole IAS guidelines represent a template that can be made consistent with ATP III and ECS/EAS recommendations.

American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Guidelines

In 2013, the ACC/AHA proposed a new set of guidelines for cholesterol management (21). These differ markedly from previous guidelines. They make LDL-C levels a secondary issue with no specific targets of therapy. They follow the overall guideline development strategy of ACC/AHA, which puts primary emphasis on results of randomized clinical trials (RCTs). Virtually all of such RCTs employed drug therapy. Guidelines largely restrict use of drugs to statins, because most RCT evidence comes from these agents. Indications for statin therapy are based on a new scoring algorithm created from multiple epidemiologic studies in the USA. From these studies, 10-year risk for ASCVD (CHD and stroke) has been estimated. Parameters used to calculate 10-year risk include gender, cigarette smoking, total cholesterol, HDL-C, diabetes, and age. Patients having a 10-year risk for ASCVD $\geq$ 7% are candidates for statin

therapy. When statins are used, the guidelines recommend that the highest tolerable dose be employed.

Critical Comparison of Guidelines

Decline in Emphasis on Lifestyle Intervention

Over a period of 25 years, guidelines differ in relative emphases on lifestyle intervention and cholesterol-lowering drugs. NCEP recommendations consistently placed a high priority on lifestyle modification. In earlier NCEP reports, cholesterol-lowering drugs represented an adjunct to lifestyle therapy. Without doubt, the discovery of statins and proof of their efficacy through RCTs made them an integral part of risk reduction. Earlier use was largely relegated to patients that categorically high-risk; this was because of uncertainty about long-term efficacy and safety. In the latest guidelines, statin use has been liberalized. But two critical questions have emerged. To what extent is statin use in the general population justified? Are we approaching the point where most persons in high-risk populations will sooner or later be treated with statins?

Age of Intervention: Problem of Starting Too Late

In many populations, serum cholesterol levels are relatively low throughout life. These populations have a low rate of ASCVD. Examples include people in the Far East and the Mediterranean basin. Almost certainly low cholesterol concentrations in these people can be attributed to lifestyle. The latter includes a lack of cholesterol-raising nutrients (i.e., saturated fats and dietary cholesterol) and general lack of obesity. It has been estimated from population studies that a 10% lower level of cholesterol throughout life translates into an approximate 40% decrease in risk for ASCVD by middle age (1). This finding supports earlier intervention in cholesterol-lowering.

Similar results have been reported from genetic epidemiology. Variations in several genes are known to associate with lower cholesterol levels. Foremost among these are cholesterol-lowering mutations in the protein PCSK9. Normally, circulating PCSK9 inhibits LDL receptors and raises LDL C levels. When PCSK9 is mutated, more LDL receptors remain active in removing LDL from the circulation. When populations have been examined for PCSK9 mutations, affected individuals express lower rates of ASCVD (22). Again, an approximate 10% reduction in LDL-C levels translates into a 40% lowering of ASCVD in middle age (22). These studies provide strong support early introduction of lifestyle modification to keep LDL-C levels as low as possible in the general population. Attention to minimizing cholesterol-raising nutrients out of the diet and maintaining a normal body weight should keep LDL-C about 10-15% lower than otherwise. It is not generally recognized the magnitude of the benefit that would derive from such lifestyle intervention. Unfortunately, some of the recent guidelines neglect this potential benefit.

Risk Assessment: Limitations of Risk Assessment Algorithms

Global risk assessment through risk algorithms constitutes the preferred way to inform initiation of cholesterol-lowering drugs. These algorithms derive from large population studies in which risk factors are compared to rates of ASCVD. Notable among these are the American Framingham Heart study and the European SCORE study (18). Recently, the ACC/AHA created a new algorithm based on multiple populations (including Framingham) studied in the United States (23). Of necessity algorithms must be based on previous population studies; but in fact, risk in the general population is continually changing. Growing evidence points to a decrease in population-baseline risk in many countries including the United States. For this reason, risk assessment based on previous population data tends to overestimate risk for ASCVD (24-26). This can lead to over treatment of people at lower risk. Since most individuals are not at high risk, overtreatment will greatly expand the use of drugs in the general population. Several recent reports document the problem of risk overestimation derived from prior data.

Decline in Risk Thresholds for Cholesterol-Lowering Drugs

Most guidelines place cholesterol management in the clinical setting. At the same time, recognition is given to the need for public health approach for prevention of ASCVD. Earlier guidelines stressed modification of lifestyle for cholesterol-lowering and other forms of prevention. More recently, the emphasis shifted more to earlier use of cholesterol-lowering drugs at the expanse of lifestyle intervention. Early NCEP guidelines largely restricted cholesterol-lowering drugs to patients with established CHD. Gradually, over subsequent guidelines, the risk thresholds for drug therapy reduced to high-risk (10-year risk for CHD $\geq$ 20%) and then moderately high risk patients (10-year risk for CHD 10-19%). European and Canadian guidelines have followed a similar pattern. The recent ACC/AHA guidelines focused almost exclusively on use of statins for cholesterol management. Lifestyle intervention was largely relegated to the public health sphere. Moreover, statin therapy was extended to patients deemed to be at moderate risk for ASCVD (10-year risk for CHD approximately 5-9%). This latter change greatly expands use of statin therapy in the general population.

Uncertainty about Non-Statin Drugs

Most guidelines focus on LDL-C as the primary target of treatment; and they postulate that all LDL-lowering drugs reduce risk for ASCVD in proportion to extent of LDL-C lowering. Examples of the latter include bile acid sequestrants and ezetimibe. However, the recent ACC/AHA guidelines call this assumption into question because of limited RCT-outcome trials. This caution is especially applied when non-statins drugs are added to statins. Recent RCTs suggest that this is an unnecessary precaution, but several new RCTs are underway that should provide a solid answer.

Polypill as Public Health Strategy

Because of the efficacy of statins to reduce risk for ASCVD, some investigators favor widespread use of statins in the general population as part of a public health method. It has been further proposed that consideration be given to combining other drugs with statins, e.g. blood pressure lowering drugs and aspirin—hence the name polypill approach (27). Although at first glance this may seem reasonable, it has not been accepted by the cardiovascular community. As move experience is obtained with widespread use of statins, it is possible that attempts will be made to institute the polypill approach. Indeed, the recent ACC/AHA guidelines have been a step in this direction by recommending almost universal use of statins within the clinical setting in older persons.

Differing Views on Atherogenic Lipoproteins as Target of Therapy

For many years, LDL-C was considered the primary target of cholesterol-lowering therapy. Only in recent years has it been shown that VLDL also is atherogenic. Since both LDL and VLDL similarly promote atherogenesis, the atherogenic lipoproteins should include LDL-C plus VLDL-C, or non-HDL-C. Many lipidologists now hold that non-HDL-C is a preferred target over LDL-C. A growing body of literature supports his position (20). Guidelines typically set absolute treatment goals for lipoprotein levels. These goals are adjusted for absolute risk estimates for particular patients. Recent ACC/AHA guidelines however discard lipoprotein goals and recommended treatment based exclusively on drugs used in RCTs. Essentially, these guidelines follow the approach taken by the consortium of Cholesterol Clinical Trialists (3); this approach favors recommendations that set a percentage reduction in cholesterol levels, and not absolute reductions.

Justifiable Evidence to Guide Intervention

High-Risk Conditions

ATP III introduced the concept of *CHD rise equivalents* to justify use of cholesterol-lowering drugs without the need for further risk assessment included in the list of CHD risk equivalents were non-CHD forms of ASCVD (e.g. peripheral arterial disease, carotid artery disease, abdominal aneurysm). A person with a CHD risk equivalent has roughly the same risk for future vascular events as does one with established CHD. Their identification can allow the clinician to bypass global risk assessment when making a decision about cholesterol-lowering drugs. Inclusion of all forms of clinical atherosclerotic disease into one category (ASCVD) negates the need for the concept of CHD risk equivalents; but some multiple risk factors conditions deserve the classification of *high-risk.*

Subclinical Atherosclerosis. Among the high-risk conditions for ASCVD, the most powerful is the presence of subclinical atherosclerosis (28-31). In a sense this measurement provides a summation of the effects of all of the risk factors on the development of atherosclerosis. The

most promising of the available measurements is coronary artery calcium (CAC). Recent studies show a powerful linkage between CAC measurements and ASCVD risk (28,32).

The technical term for CAC scoring is the Agatston unit. Scores of > 300 Agatston units can be considered *high-risk.* Scores of 100-299 are intermediate risk; those of 1-99 are low risk; and zero scores are *very low risk.* Of particular importance is the finding that a negative CAC correlates with very low risk of ASCVD over the next 10 years. A less powerful but still robust risk prediction is intimal medial thickness (IMT) of the carotid artery (33-35). An increased carotid IMT accompanied by a greater risk for both CHD and stroke, although stratification of risk is less well defined than for CAC.

Diabetes. ATP III identified diabetes as a CHD risk equivalent. This claim has been disputed by some investigators. Several subsequent reports support the view that diabetes is a CHD risk equivalent (36-38); others suggest that CHD patients are at higher risk than are many patients with diabetes (39,40). Nonetheless most investigators support the position that diabetes is high-risk condition. Patients with clinical diabetes are on a trajectory for increasing risk for ASCVD. Even those who do not have a 10-year risk for ASCVD equal to patients with established ASCVD will eventually achieve a high-risk status. Therefore in patients with both type 2 diabetes and type 1 diabetes should be considered potential candidates for cholesterol-lowering drugs. Clinical judgment is required as to when these drugs should be initiated; but most of those with advancing age should be considered for cholesterol-lowering drugs. For the use of drugs in patients with diabetes, the question is not if but when to initiate.

Chronic kidney disease (CKD). With advancing CKD, the risk for ASCVD rises. Nephrologists generally favor identifying CKD as a high-risk condition (41). A recent RCT demonstrated that cholesterol-lowering drugs will substantially reduce risk for ASCVD events in patients with CKD (42).

Metabolic syndrome. Epidemiological data show that patients with the metabolic syndrome have a risk for future CHD event similar to that of patients with diabetes (43-45). There is a strong overlap between metabolic syndrome and glucose intolerance (46,47); hence the majority of people with glucose intolerance are likely to have the metabolic syndrome. Most patients with this syndrome thus can be considered candidates for cholesterol-lowering drugs, especially as they advance in age or have glucose intolerance.

Major Risk Factors for ASCVD.

The major risk factors for ASCVD include, advancing age, cigarette smoking, hypertension, hypercholesterolemia. Each of these factors can be discussed briefly.

Age as a Risk Factor: Limitations for Risk Assessment

In multiple risk factor algorithms, age emerges as the most powerful risk factor. It is true that risk for ASCVD rises with aging. As a risk factor, age represents a surrogate for subclinical atherosclerosis. But to apply a fixed age in the risk algorithm will overestimate risk in individuals with little or no atherosclerosis. If the average risk imparted by age is used in a multifactorial risk algorithm, many persons will be treated with a cholesterol-lowering drug even in the absence of significant atherosclerosis. These individuals will not benefit and will have taken the drug needlessly. There is no simple solution to this dilemma. The best available approach at present is the measurement of subclinical atherosclerosis. The latter is a better indicator of a person's arterial age than is chronological age (32, 48).

Cigarette Smoking. This is a powerful risk factor for ASCVD. Smoking is particularly likely to produce premature CHD (49). Thus, patients who are unable to discontinue smoking should be given serious consideration for using a cholesterol-lowering drug. Because of the tendency for premature CHD, early intervention in heavier smokers who are cessation failures is justified. Clinical judgment is required as to the best time to introduce drug treatment. But for heavy smokers, "the earlier, the better" should be the rule.

Hypertension. Elevated blood pressure is another powerful risk factor for ASCVD. It confers a particularly high risk for stroke. Serious consideration should be given to the use of a cholesterol-lowering drug in a patient who has chronic, poorly controlled hypertension. Many hypertensive patients have either metabolic syndrome or type 2 diabetes and thereby are candidates for cholesterol-lowering drug. For a person with isolated hypertension, a mildly elevated blood pressure, or well controlled high blood pressure, measurement of subclinical atherosclerosis may be a useful adjunct for deciding whether to initiate a cholesterol-lowering drug.

Hypercholesterolemia. Cholesterol guidelines typically adjust treatment relative to estimated absolute risk of patients. Table 2 lists use categories of LDL-C and non-HDL-C as parameters to guide therapy.

Table 2. Categories of Atherogenic Lipoproteins

Category	LDL Cholesterol	Non-HDL Cholesterol
Very high	$\geq$ 190 mg/dL	$\geq$ 220 mg/dL
High	160-189 mg/dL	190-219 mg/dL
Borderline high	130-159 mg/dL	160-189 mg/dL
Borderline low	100-129 mg/dL	130-159 mg/dL
Low	70-99 mg/dL	100-129 mg/dL
Very low	< 70 mg/dL	70-99 mg/dL

However, for most patients with high cholesterol (LDL-C 160-189 mg/dL; non-HDL-C 190-219 mg/dL) or very high cholesterol (LDL-C $\geq$ 190 mg/dL; non-HDL-C $\geq$ 220 mg/dL) institution of a cholesterol-lowering drug is reasonable. Available epidemiologic data indicate that prolonged elevation of LDL-C carries a progressively higher risk for ASCVD (50).

If there is uncertainty whether to use a cholesterol-lowering drug, consideration can be given to checking for subclinical atherosclerosis. The latter may be particularly revealing in individuals with moderately high cholesterol levels. But most persons with very high cholesterol levels deserve treatment with a cholesterol-lowering drug. Use of drug therapy in a patient with borderline-high cholesterol (LDL-C 130-159 mg/dL) is more problematic. Of course, concomitant presence of high-risk conditions or a major risk factor usually will justify a cholesterol-lowering drug. When in doubt, testing for subclinical atherosclerosis can be helpful.

Other Risk Factors

Several other factors associate with ASCVD, although they have not proven to be causative. Instead, they are a marker for increased risk. Among these are a pro-inflammatory state (e.g., elevated C-reactive protein), various lipoprotein abnormalities (e.g., high triglycerides, low HDL-C, lipoprotein (a), small LDL particles), insulin resistance, and various pro-thrombotic factors. Most of these so-called *emerging risk factors* aggregate with the metabolic syndrome—an accepted higher risk condition.

Cholesterol Management Strategies

Secondary Prevention

Secondary prevention consists of intensive cholesterol-lowering therapy in patients with established ASCVD. These patients are at highest-risk for new ASCVD events. Cholesterol-lowering therapy provides the greatest reduction in risk for new events of all forms of secondary prevention. Nonetheless, aggressive treatment of all ASCVD risk factors is warranted in patients with established vascular disease.

Goals for Cholesterol-Lowering Therapies in Secondary Prevention

A simple rule for cholesterol-lowering therapy in secondary prevention is "the lower, the better". This recommendation is justified by meta-analysis of secondary prevention RCTs. Of course, there may be limitations on how low atherogenic lipoproteins can be lowered in clinical practice; for this reason, clinical judgment is required to establish the appropriate therapeutic regimen for individual patients within the framework of "the lower, the better". A reasonable goal for patients with ASCVD is an LDL-C < 70 mg/dL (non-HDL-C < 100 mg/dL), although the recent IMPROVE-IT trial showed that still further LDL-C lowering gave additional risk reduction. The field waits with interest the results of on-going trials with PCSK9 inhibitors that in combination with statins produce an even greater LDL reduction.

Role of Statins in Secondary Prevention

Statins are first-line therapy for cholesterol-lowering in secondary prevention. The general rule is that the maximum tolerable dose should be employed. The recent ACC/AHA guidelines call this maximum-intensity statin therapy. Once the maximum tolerable dose has been established for a particular patient, consideration can be given whether intensification of cholesterol-lowering therapy is warranted to achieve the goals outlined above. This can be judged by the LDL-C or non-HDL-C response to statin treatment. If the lipoprotein level fails to reach a very low range (Table 2), it may be unnecessary to add additional therapies.

Role of Non-statin Drugs in Secondary Prevention

If the reduction in atherogenic lipoproteins failed to achieve a sufficiently low level statins alone, consideration can be given to initiating the second cholesterol-lowering drug. One potential add-on drug is ezetimibe. Combining ezetimibe with maximal tolerable statin therapy produced a significant further risk reduction in patients with established ASCVD in the IMPROVE-IT trial. Recently, two reports indicate that treatment of hypercholesterolemic patients who were receiving maximal statin therapy showed incremental risk reduction when patients were treated with antibodies against PCSK9 (12,13). These studies provide additional support for the concept of "lower is better" for atherogenic lipoproteins in secondary prevention.

Triglyceride-lowering drugs

A substantial portion of patients with ASCVD have concomitant elevations in plasma triglycerides. The question has been raised with the treatment with a triglyceride lowering drug, when combined with a statin, will give additional risk reduction. RCT evidence to support their use for this purpose is limited. Nonetheless, several clinical trials demonstrate that triglyceride lowering drugs do reduce risk when used alone. Moreover, when they are used with statins in clinical trials, subgroup analysis in patients with hypertriglyceridemia suggests additional benefit (51). At present, the preferred triglyceride- lowering drug to use with statin is fenofibrate. This combination seems to be the safer than other statin-fibrate combinations.

Primary Prevention

Risk Assessment

Selection of patients for cholesterol-lowering drugs based on standard risk algorithms is problematic. These algorithms are based on population risk and are not reliably applicable for individuals. A more reliable indicator of risk is the presence of an established risk condition or risk factor (Table 3).

Table 3. Higher Risk Conditions and Major Risk Factors	
Higher Risk Conditions • Subclinical atherosclerosis • Diabetes	Major Risk Factors • Advancing age • Cigarette smoking

• Metabolic syndrome • Chronic renal disease	• Hypertension • Hypercholesterolemia

Cholesterol-Lowering Goals in Primary Prevention.

The general principle of "the lower, the better" for cholesterol levels can still be applied to primary prevention. This principle is supported by both epidemiological studies (1) and clinical trials (52). A second principle also pertains to primary prevention, namely, "the longer, the better" for low cholesterol levels (53). This latter principle follows from both population epidemiology (1) and genetic epidemiology (22). A desirable LDL-C for primary prevention is a level < 100 mg/dL. This is a reasonable goal for individuals. To the extent possible this level should be attained by lifestyle therapies. However, if a person has a higher risk condition or a major risk factor (Table 3), consideration can be given to using a cholesterol-lowering drug. It drug therapy is employed, it is reasonable to reduce the LDL-C to < 70 mg/dL. Of course, clinical judgment is required as to how aggressive to be in cholesterol-lowering therapy.

Initiation of Therapy

Lifestyle therapies. For primary prevention, there are two goals of therapy: (a) to reduce atherogenic lipoproteins to as low as possible, and (b) to start lipid lowering as early as possible. It is important to remember that keeping cholesterol levels to less than 100 mg/dL for a lifetime will virtually eliminate ASCVD in middle age (22). Table 4 summaries a lifestyle approach that will minimize serum cholesterol levels.

Table 4. Recommended lifestyle therapies to minimize cholesterol levels.	
• Dietary cholesterol	< 300 mg/day
• Saturated fatty acids	< 7% of total calories
• Trans fatty acids	< 1% of total calories
• Dietary soluble fiber	10 g/day
• Dietary plant sterols/stanols	2 g/day (optional)
• Total calorie intake	Sustain desirable body weight
• Regular physical activity	30 minutes/day

Cholesterol-lowering drugs. In persons with higher risk conditions and/or major risk factors, consideration can be given to institution of cholesterol-lowering drugs. The goal of therapy is to reduce lifetime risk for ASCVD. Atherogenic lipoproteins should be reduced to at least a low level (Table 2). Further reduction to a very low level is ideal. Some of the considerations that must be taken into account for initiation and intensification of cholesterol-lowering drugs are listed in Table 5.

Table 5. Special Considerations for Initiation of Cholesterol-Lowering Drugs in Primary Prevention
• Consider cholesterol-lowering drug therapy in persons with higher risk conditions or major risk factors (Table 3)

- In older persons (men > 45 years; women > 55 years) at higher risk (Table 3), initiate moderate-intensity drugs (Table 1) to achieve a low LDL-C (Table 2). If the patient has multiple higher risk conditions or risk factors, consider high-intensity drugs to achieve a very low LDL-C (Table 2)
- In older women who have well controlled hypertension or LDL-C 160-189 mg/dL but who are non-smokers without diabetes, measure subclinical atherosclerosis to guide the need for a cholesterol-lowering drug (CAC >100 usually justifies drug therapy)
- In younger adults (men < 45 years; women < 55 years) with high-risk conditions or major risk factors, consider starting with a low-intensity cholesterol-lowering drugs (Table 1); convert to moderate-intensity cholesterol-lowering drugs after the above age thresholds are attained. Escalate to a high-intensity drugs if needed to achieve low or very low atherogenic lipoproteins.
- In older women who have well controlled hypertension or LDL-C 160-189 mg/dL but who are non-smokers without diabetes, measure subclinical atherosclerosis to guide the need for a cholesterol-lowering drug (CAC >100 usually justifies drug therapy)
- When a drug is warranted in a higher risk patient, initiate moderate-intensity drug therapy to determine response; increase to high-intensity drug therapy if moderate intensity therapy is well tolerated and if atherogenic lipoproteins are not reduced to at least a low level (Table 2)
- In otherwise lower-risk but older persons, consider measuring subclinical atherosclerosis to determine need for a cholesterol-lowering drug (CAC >100 usually justifies drug therapy)

When statins are employed as one component of cholesterol-lowering therapy, about 10% of statin recipients will complain of a variety of side effects. These individuals come under the category of *statin-intolerant* patients. Many persons attribute non-specific symptoms to their treatments, and in these, statins may not be the cause of the complaint. Various complaints include muscle aches, joint pain, nerve pain, and cognitive symptoms. Taking a careful history will reveal which symptoms if any are most likely to be due to statins. The most consistent statin-related complain is muscle discomfort and weakness (myalgia). If the physician is convinced that a statin is to blame, several approaches to managing statin intolerance have been tried with varying degrees of success (Table 6).

Table 6. Strategies for Overcoming Statin Intolerance

- Intensify lifestyle intervention (Table 4)
- Rechallange with a lower dose of the same statins (if tolerated, increase dose to maximally tolerated dose.
- If side effects recur, try low doses of other statins.
- If all statins give side effects, try very low doses one statin
- If side effects occur, try alternate-day or twice weekly schedule of very low dose statin
- Encourage the patient to increase statin dose to maximum tolerated dose
- Consider adding Co-enzyme Q 100 mg/day (some authors report success)
- Add ezetimibe 10 mg/day
- Add bile acid resin to maximally tolerated dose

References

1. **Law MR, Wald NJ, Thompson SG**. By how much and how quickly does reduction in serum cholesterol concentration lower risk of schaemic heart disease? BMJ 1994;308:367-72.

2. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)**. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.

3. Cholesterol Treatment Trialists' (CTT) Collaborators, **Mihaylova B, EmbersonJ, Blackwell L**, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380: 581-90. Epub2012 May 17.

4. **Rossouw JE, Lewis B, Rifkind BM**. The value of lowering cholesterol after myocardial infarction. N Engl J Med 1990;323:1112-9.

5. **Califf RM, Lokhnygina Y, Cannon CP**, et al. An update on the IMProved reduction of outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. Am Heart J 2010;159: 705-9.

6. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251:351-64.

7. **Cuchel M, Bloedon LT, Szapary PO**, et al. Inhibition of microsomaltriglyceride transfer protein in familial hypercholesterolemia. N Engl J Med 2007;356:148-56.

8. **Stein EA, Dufour R, Gagne C**, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind,placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation 2012;126:2283-92. Epub 2012 Oct 11.

9. **Schwartz GG, Olsson AG, Abt M**, et al.; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;367:2089-99.

10. **Cannon CP, Shah S, Dansky HM**, et al.; Determining the Efficacy and Tolerability Investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010;363:2406-15.

11. **Lo Surdo P, Bottomley MJ, Calzetta A**, et al. Mechanistic implications for LDL receptor degradation from the PCSK9/LDLR structure at neutral pH. EMBO Rep 2011;12:1300-5.

12. **Sabatine MS, Giugliano RP, Wiviott SD**, et al.; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and Safety of

Evolocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med 2015 March 15 [Epub ahead of print]

13. **Robinson JG, Farnier M, Krempf M**, et al.; ODYSSEY LONG TERM Investigators. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med. 2015 Mar 15. [Epub ahead of print]

14. **Boekholdt SM, Hovingh GK, Mora S**, et al. Very low levels of atherogenic lipoproteins and risk of cardiovascular events; a meta-analysis of statin trials. JACC 2014;64:485-94.

15. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. **Goodman DeW S, Hulley SB, Brown WV**,et al. Arch Intern Med 1988;148:36-69.

16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (SM Grundy, Chairman). National Cholesterol Education Program: second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994;89:1333-445.

17. **Grundy SM, Cleeman JI, Merz CN**, et al.; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39. Review. Erratum in: Circulation. 2004;110:763.

18. **Catapano AL, Reiner Z, De Backer G**, et al.; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011; 217:3-46.

19. **Anderson TJ, Grégoire J, Hegele RA**, et al. 2012 update of the Canadian cardiovascular society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2013;29:151-67.

20. **Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members**. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. J Clin Lipidol. 2014;8:29-60.

21. **Stone NJ, Robinson JG, Lichtenstein AH**,et al.; American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B):2889-934.

22. **Cohen JC, Boerwinkle E, Mosley TH Jr**, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-72.

23. **Goff DC Jr, Lloyd-Jones DM, Bennett G**, et al.; American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63(25 Pt B): 2935-59.

24. **Ridker PM, Cook NR**. Statins: new American guidelines for prevention of cardiovascular disease. Lancet 2013;382:1762-5.

25. **Kavousi M, Leening MJ, Nanchen D**, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA 2014;311:1416-23.

26. **DeFilippis AP, Young R, Carrubba CJ**, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med 2015;162: 266-75.

27. **Wald NJ, Law MR**. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.

28. **Silverman MG, Blaha MJ, Krumholz HM**, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J 2014;35:2232-41.

29. **Villines TC, Taylor AJ**. Multi-ethnic study of atherosclerosis arterial age versus framingham 10-year or lifetime cardiovascular risk. Am J Cardiol 2012;110:1627-30.

30. **Ahmadi N, Hajsadeghi F, Blumenthal RS**, et al. Mortality in individuals without known coronary artery disease but with discordance between the Framingham risk score and coronary artery calcium. Am J Cardiol 2011;107:799-804.

31. **Pohle K, Ropers D, Geitner P**, et al. Analysis of coronary calcifications versus Framingham and PROCAM risk assessment in patients with a first myocardial infarction. Int J Cardiol 2006;110:231-6.

32. **Tota-Maharaj R, Blaha MJ, Blankstein R**, et al. Association of coronary artery calcium and coronary heart disease events in young and elderly participants in the multi-ethnic study of atherosclerosis: a secondary analysis of a prospective, population-based cohort. Mayo Clin Proc 2014;89:1350-9.

33. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14-22.

34. **Newman AB, Naydeck BL, Ives DG**, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. Am J Cardiol 2008; 101:186-92.

35. **Gepner AD, Young R, Delaney JA**, et al. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2015 Jan 8 [Epub ahead of print].

36. **Whiteley L, Padmanabhan S, Hole D**, et al. Should diabetes be considered a coronary heart disease risk equivalent?: Results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care 2005;28:1588-93.

37. **Juutilainen A, Lehto S, Rönnemaa T**, et al. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care 2005;28:2901-7.

38. **Carnethon MR, Biggs ML, Barzilay J**, et al. Diabetes and coronary heart disease as risk factors for mortality in older adults. Am J Med 2010;123:556.e1-9.

39. **Saely CH, Drexel H**. Is type 2 diabetes really a coronary heart disease risk equivalent? Vascul Pharmacol 2013;59:11-8.

40. **Lee C, Joseph L, Colosimo A**, et al. Mortality in diabetes compared with previous cardiovascular disease: a gender-specific meta-analysis. Diabetes Metab 2012;38:420-7.

41. **Briasoulis A, Bakris GL**. Chronic kidney disease as a coronary artery disease risk equivalent. Curr Cardiol Rep 2013;15:340.

42. **Baigent C, Landray MJ, Reith C**, et al.; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-92.

43. **Alexander CM, Landsman PB, Teutsch SM**, et al; Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210-4.

44. **Gami AS, Witt BJ, Howard DE**, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol 2007;49:403-14.

45. **Mottillo S, Filion KB, Genest J**, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. J Am Coll Cardiol 2010;56:1113-32.

46. **Grundy SM**. Metabolic syndrome: connecting and reconciling cardiovascular anddiabetes worlds. J Am Coll Cardiol 2006;47:1093-100.

47. **Alexander CM, Landsman PB, Grundy SM**. Metabolic syndrome and hyperglycemia: congruence and divergence. Am J Cardiol 2006;98:982-5.

48. **Grundy SM**. Age as a risk factor: you are as old as your arteries. Am J Cardiol 1999;83: 1455-7

49. **Khot UN, Khot MB, Bajzer CT**, et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003;290:898-904.

50. **Lloyd-Jones DM, Wilson PW, Larson MG**, et al. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. Arch Intern Med 2003;163:1966-72.

51. **Ginsberg HN**. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) Lipid trial: what we learn from subgroup analyses. Diabetes Care 2011;34 (Suppl 2):S107-8.

52. **Ridker PM, Danielson E, Fonseca FA**, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359: 2195–207.

53. **Brown MS, Goldstein JL**. Biomedicine. Lowering LDL--not only how low, but how long? Science 2006;311:1721-3.