RISK ASSESSMENT AND GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD CHOLESTEROL

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ABSTRACT

The cholesterol hypothesis holds that high blood cholesterol is a major risk factor for atherosclerosis cardiovascular disease (ASCVD) and lowering cholesterol levels will reduce risk for ASCVD. This hypothesis is based on epidemiological evidence that both within and between populations higher cholesterol levels raise the risk for ASCVD; and conversely, randomized clinical trials (RCTs) show that lowering cholesterol levels will reduce risk. Cholesterol in the circulation is embedded in lipoproteins. The major atherogenic lipoproteins are low density lipoproteins (LDL) and very low density lipoproteins (VLDL). Together they constitute non-high density lipoproteins (non-HDL). Clinically these lipoproteins are identified by their cholesterol (C) content, i.e. LDL-C, VLDL-C, and non-HDL-C. Atherogenic lipoproteins can be reduced by both lifestyle intervention and cholesterol-lowering drugs. The efficacy of lifestyle intervention is best demonstrated in epidemiological studies, whereas efficacy of drugs is revealed through RCTs. Currently available cholesterol-lowering drugs are statins, ezetimibe, bile acid sequestrants, niacin, and fibrates. The latter two generally are reserved for patients with hypertriglyceridemia; here they can be combined with statins that together lower non-HDL-C. Highest priority to cholesterol-lowering therapy goes to patients with established ASCVD (secondary prevention). RCTs in such patients show that “lower is better” for cholesterol reduction. The greatest risk reductions are achieved by reducing LDL-C concentrations to < 70 mg/dL. For primary prevention, priority in use of cholesterol-lowering drugs goes to patients with higher risk conditions (subclinical atherosclerosis, diabetes, metabolic syndrome, and chronic kidney disease) or major risk factors (cigarette smoking, hypertension, and hypercholesterolemia). If doubt exists whether to use cholesterol-lowering drugs in patients with these conditions/factors, measurement of subclinical atherosclerosis can be helpful for clinical decision. A reasonable LDL-C goal for primary prevention is an LDL-C in the range of 70-99 mg/dL. Both population epidemiology and genetic epidemiology show that low serum cholesterol throughout life will minimize lifetime risk of ASCVD. For this reason, cholesterol-lowering intervention should be carried out as early as possible, preferably by lifestyle change. If cholesterol concentrations are high in younger adults, it may be judicious to introduce cholesterol-lowering drugs. For complete coverage of this area and all of Endocrinology, visit www.endotext.org.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the foremost cause of death among chronic diseases. Its prevalence is increasing in many countries of the world. This increase results from aging of the population and adoption of predisposing lifestyles. Yet, 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 the cardiovascular field resulted from the discovery of risk factors for ASCVD. Risk factors directly or indirectly promote 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. A host of other factors, called emerging risk factors, associate with higher risk for ASCVD. These consist of pro-thrombotic and pro-inflammatory states, insulin resistance, and various genetic factors. Hereditary factors undoubtedly contribute to the major risk factors; but genetic influences likely affect ASCVD risk through other ways not understood.

HYPERCHOLESTEROLEMIA AS A RISK FACTOR FOR ASCVD

The Cholesterol Hypothesis

The first evidence for a connection between serum cholesterol levels and atherosclerosis came from laboratory animals. Feeding cholesterol to various animal species raises serum levels of cholesterol and results in the accumulation of cholesterol in the arterial wall. The latter recapitulates early stages of human atherosclerosis. Subsequently, severe hypercholesterolemia was observed to cause premature atherosclerosis and ASCVD. Later, population surveys uncovered a positive association between serum cholesterol levels and likelihood of development of ASCVD (1). Finally, clinical trials with cholesterol-lowering agents documented that lowering of serum cholesterol levels reduces the risk for ASCVD (2,3). These findings have convinced most investigators that the *cholesterol hypothesis* is proven. In other words, the relationship between cholesterol levels and ASCVD risk is bidirectional; raising cholesterol levels increases risk, whereas reducing levels decreases risk (Figure 1).

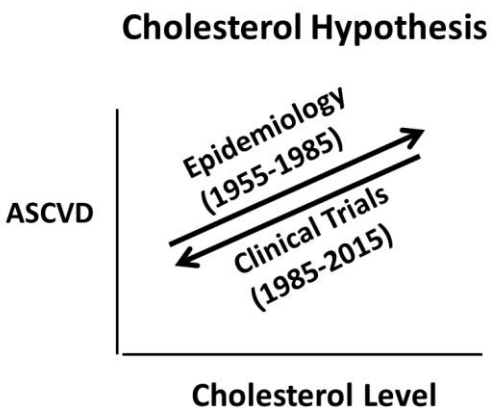

Figure 1. The cholesterol hypothesis. Between the years 1955 and 1985, many epidemiologic studies showed a positive relation between cholesterol levels and atherosclerotic cardiovascular disease (ASCVD) events. Over the next 30 years, a host of randomized controlled clinical trials have demonstrated that lowering cholesterol levels will reduce risk for ASCVD. This bidirectional relationship between cholesterol levels and ASCVD provides ample support for proof of the cholesterol hypothesis.

Figure 1

Epidemiological Evidence

A relationship between cholesterol levels and ASCVD risk holds in in both developing and developed countries (1). Populations with the lowest cholesterol levels have the lowest risk for ASCVD. Within populations, individuals with the lowest serum cholesterol carry the least risk. In other words, “the lower, the better” for cholesterol levels holds, both between populations and for individuals within populations.

Pre-Statin Clinical Trial Evidence

Another line of evidence supporting the cholesterol hypothesis comes from randomized controlled trials (RCTs) of cholesterol-lowering therapies. Several earlier RCTs tested the efficacy by reducing cholesterol through diet, bile acid sequestrants, or ileal exclusion operation (Table 1) (2). Taken alone, results from some of the smaller trials were not definitive; but meta-analysis, which combines data from all RCTs, demonstrated significant risk reduction due to cholesterol lowering. In addition, before discovery of statins, several secondary-prevention RCTs were performed with various cholesterol-lowering drugs. Although some of these trials showed significant risk reduction, others gave equivocal results. But when taken together, meta-analysis again demonstrated ASCVD risk reduction from cholesterol reduction (4).

Table 1. Summary of Results of Pre-Statin Clinical Trials of Cholesterol-Lowering Therapy						
				Mean		

Intervention	No. trials	No. treated	Person-years	cholesterol reduction (%)	CHD incidence (% change)	CHD Mortality (% change)
Surgery	1	421	4,084	22	-43	-30
Sequestrants	3	1,992	14,491	9	-21	-32
Diet	6	1,200	6,356	11	-24	-21

This table is derived from National Cholesterol Education Program Adult Treatment Panel III (2)

Statin Clinical Trial Evidence

Finally, the most definitive support for the cholesterol hypothesis comes from RCTs with statins. Several statins differing in dose and potency are available. As stand-alone trials, statin therapy produced significant reductions in coronary heart disease (CHD), stroke, and total mortality. But the strongest evidence from statin RCTs comes from meta-analysis, i.e., combining data from all the trials (3). Meta-analysis leaves little doubt that intensive cholesterol-lowering reduces risk for ASCVD. Risk reductions range from 25-45%, depending on statin and dose employed.

Currently available cholesterol-lowering drugs or those under study are listed in Table 2.

Table 2. Cholesterol Lowering Drugs

Drug Class	Mechanism of Action	Effects on Plasma Lipids	LDL-C lowering	Side effects
Statins	Inhibit HMG CoA reductase Raise LDL receptor activity	Reduce LDL and VLDL Minimal effect on HDL	30-55% depending on dose	Myalgia Cognitive dysfunction

				Raises plasma glucose
Bile acid sequestrants	Impairs reabsorption of bile acids Raise LDL receptor activity	Reduces LDL Raises VLDL Minimal effect on HDL	15-25%, depending on dose	Constipation GI distress Raise Triglycerides
Ezetimibe	Impairs absorption of cholesterol Raises LDL receptor activity	Reduces LDL Reduces VLDL Minimal effect on HDL	15-25%	Rare
Niacin	Reduces hepatic secretion of VLDL	Reduces VLDL Reduces LDL Raises HDL	5-20%	Flushing, rash, raise plasma glucose, hepatic dysfunction, others
Fibrates	Reduces secretion of VLDL Enhances degradation of VLDL	Reduces VLDL (lowers TG 25-35%) Small effect on LDL Raises HDL	5-15%	Myopathy (in combination with statins) Gallstones Uncommonly various others
MTP inhibitors	Reduces hepatic secretion of VLDL	Reduces VLDL and LDL	50+%	Fatty liver
Mipomersen (RNA antisense)	Reduces hepatic secretion of VLDL	Reduces VLDL and LDL	50+%	Fatty liver
CETP inhibitors	Blocks transfer of cholesterol from HDL to VLDL&LDL	Raises HDL Lowers LDL	20-30%	Under study

PCSK9 inhibitors	Blocks effects of PCSK9 to destroy LDL receptors	Lowers LDL	45-60%	Under study

First-line cholesterol-lowering drugs at present are statins. They inhibit cholesterol synthesis in the liver, which increase LDL receptors. In this way they markedly lower cholesterol levels. Beyond statins, other cholesterol-lowering drugs are currently available or loom on the horizon. Bile acid sequestrants inhibit intestinal absorption of bile acids, which likewise raises hepatic LDL receptors. They are moderately efficacious for reducing LDL-C concentrations. A large RCT showed that bile acid sequestrants significantly reduce risk for CHD (5). Ezetimibe blocks cholesterol absorption in the intestine and also raises LDL receptor activity. It moderately lowers LDL-C. A recent clinical trial (6) tested whether adding ezetimibe to high-dose statins enhances risk reduction for ASCVD. The results of this trial were positive; combination therapy reduced risk more than a statin alone. Results were presented at the 2014 American Heart Association scientific sessions, but they have not yet been published.

Niacin and fibrates, which are primarily triglyceride-lowering drugs, have been used for many years. They modestly reduce cholesterol levels as well. Their effects on ASCVD risk vary. Niacin used alone appears to attenuate risk, but apparently not when used in combination with high-intensity statin (7). Like niacin, fibrates moderately reduce risk for CHD when used alone in patients with hypertriglyceridemia; risk reduction is less in those who do not have elevated triglycerides (8). When fibrates are used in combination with statins, risk for severe myopathy is greater than for statins alone. Fenofibrate is the preferred fibrate in combination with statins because it carries the lowest risk of myopathy (9).

Other LDL-lowering drugs include microsomal triglyceride transfer protein (MTP) inhibitors (10) and RNA antisense drugs that block hepatic synthesis of apolipoprotein B (11). Both of these drugs inhibit secretion of atherogenic lipoproteins into the circulation. At present their use is restricted to patients with severe hypercholesterolemia. Another class of drugs inhibits cholesterol ester transfer protein (CETP); these agents lower LDL-C levels as well as raising HDL-C (12,13). They are currently being tested in RCTs. Finally, a new class of drugs inhibits a circulating protein called proprotein convertase subtilisin/kexin type 9 (PCSK9); this protein promotes degradation of LDL receptors and raises LDL-C levels. Inhibition of PCSK9 markedly lowers LDL-C concentrations (14). Recent reports suggest that PCSK9 inhibitors reduce risk for ASCVD in patients with hypercholesterolemia (15,16).
As shown in Table 3, cholesterol-lowering drugs vary in their efficacy for reduction of LDL-C. This table divides commonly used drugs into three categories of intensity for LDL-lowering: low, moderate, and high.

Table 3. Categories of Intensities of Cholesterol-lowering Drugs[a]

Drug	Low-Intensity	Moderate-Intensity	High Intensity
	20-25% ↓ 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 (or other moderate-intensity statin)
Bile acid sequestrant	Variable	Variable + Simvastatin 10 mg	

[a] Categories for moderate and high intensity statins derived from ACC/AHA guidelines (25)

Cholesterol-ASCVD Relationship: Two Types of Meta-Analysis

Meta-analysis of cholesterol-lowering trials, especially statin trials, further strengthens evidence for a tight relation between reduction of serum cholesterol and decreased ASCVD risk. There have been two types of meta-analysis (Figure 2). One examined the relative risk reduction accompanying a given absolute decrease in cholesterol levels. Here the Cholesterol Trialists Consortium showed that on average for every mmol/L (40 mg/dL) reduction of LDL-C the risk for ASCVD is reduced by approximately 20% (3). This relative-risk reduction risk occurs regardless of baseline risk. In sum, meta-analysis of statin RCTs indicate that for every 1% lowering of LDL-C the risk for ASCVD over the next 5-10 years is reduced by 1%. Thus, if LDL-C falls by 50%, the corresponding risk reduction should be 50%.

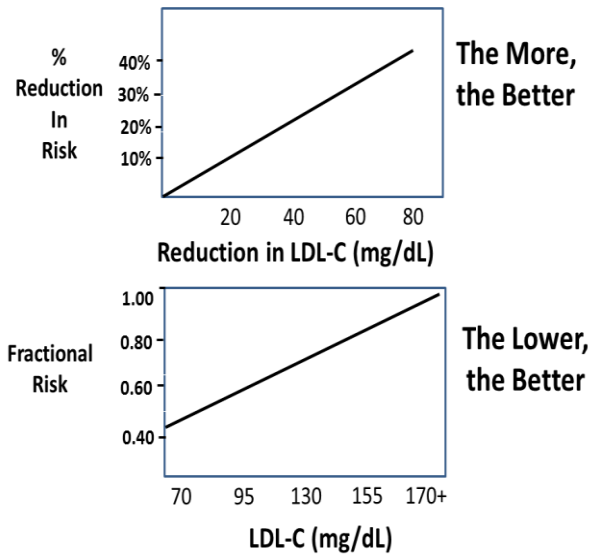

Figure 2. Meta-analysis approaches to find the relation between ASCVD risk and LDL cholesterol (LDL-C) levels. The above graph summarizes the approach taken by a consortium of cholesterol clinical trialists (3). This approach compares the percent change in risk with the change in LDL-C concentrations. It shows that the more LDL-C is reduced the greater will be the reduction in ASCVD risk. An alternate approach to meta-analysis has been published by another group of clinical trialists (17). This analysis is summarized in the lower graph. It compares LDL-C levels in cholesterol-lowering trials to fractional risk for ASCVD. At lower concentrations of LDL-C fractional risk is reduced. This indicates that lower is better for LDL-C levels for risk reduction..

Figure 2.

Another type of meta-analysis examined the relation between change in absolute LDL-C levels and absolute risk. With this analysis, as LDL-C concentrations fall to lower and lower levels, risk for ASCVD progressively declines (17). Risk continues to decline even to levels as low as 50 mg/dL.

These two different types of meta-analysis underlie a fundamental difference in the structure of cholesterol-treatment guidelines. 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 feasible limits.

HISTORY OF GUIDELINES FOR CHOLESTEROL MANAGEMENT

National Cholesterol Education Program (NCEP)

Among the most influential guidelines for cholesterol management have been those of the NECP. This program was sponsored by the National Heart, Lung and Blood Institute and included many health-related organizations in the United States. Between 1987 and 2004, three major Adult Treatment Panel (ATP) reports and one update were published (Table 4).

Table 4. National Cholesterol Education Program's Adult Treatment Panel (ATP) Reports

Guideline	ATP I	ATP II	ATP III	ATP III Update

Year	1987	1992	2001	2004
Thrust	Primary prevention	Secondary prevention	High-risk primary prevention	Very high risk
Drugs	Bile acid resins Nicotinic acid Fibrates	Same as ATP I Statins	Same as ATP II	Same as ATP III
Major Targets	LDL-C; HDL-C	LDL-C; HDL-C	LDL-C; Non-HDL-C	LDL-C; Non-HDL-C
LDL-C goal (mg/dL)	Low risk <190 Moderate risk <160 High risk < 130	Low risk <160 Moderate risk <130 High risk =100	Low risk: <160 Moderate risk <130 Moderately high risk <130 High risk < 100	Low risk <160 Moderate risk <130 Moderately high risk <130 High risk < 100 Very high risk < 70

ATP reports identified LDL-C as the major target of cholesterol-lowering therapy. The intensity of LDL-lowering therapy was based on aggregate knowledge from multiple sources in the cholesterol field. Priority was given the clinical trial evidence when available. ATP I (1987) emphasized lifestyle therapy for primary prevention (18). Use of cholesterol-lowering drugs was down-played in ATP I. ATP II (1993) placed more emphasis on secondary prevention; this was because a large meta-analysis of RCTs using cholesterol-lowering drugs confirmed CHD risk reduction (19). ATP III (2001) added more 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 cholesterol management for patients with clinical forms of atherosclerotic disease. The latter included CHD, clinical carotid artery disease and peripheral arterial disease, and abdominal aortic aneurysm. ASCVD is the inclusive term for 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 high-risk patients with hypertriglyceridemia, a non-HDL-C goal of < 130 mg/dL was added.

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. Different LDL-C goals were set for different levels of risk (Table 4). 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 ≥ 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 moderate risk and low 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 individuals except when LDL-C levels are high.

ATP III Update (2004)

In 2004, ATP III underwent an 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 (20). 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

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 (ACC/AHA). In addition, other international organizations have published cholesterol treatment guidelines. These are compared with the prior guidelines in Table 5. The major national and international guidelines can be considered briefly.

Table 5. Comparison of Cholesterol Guidelines

Guideline	ATP III	Canadian	European	IAS	ACC/AHA
LDL-C goal (mg/dL)	Low risk: < 160 Intermediate Risk < 130 High risk: <100	Low risk Intermediate and high risk: < 77 (or 50%	Moderate risk: < 115 High risk: <100	Primary prevention: < 100 mg/dL Secondary Prevention:	None

	Very high risk: <70	lowering)	Very high risk <70	<70	
Non-HDL-C goal (mg/dL)	(with high TG) 30 mg/dL higher than LDL-C goal	Alternate target	30 mg/dL higher than LDL-C goal	30 mg/dL higher than LDL-C goal	None
Risk Assessment	Modified Framingahm	Modified Framingham	SCORE	Framingham adjusted for population	5-population risk tool
End points	Hard CHD events	CHD events	CHD mortality	CHD	ASCVD events
Risk projection	10-year	10-year	10-year	Long-term (to age 80)	10-year
Drug treatment threshold	≥ 10% 10-year risk	≥ 10% 10-year risk			≥ 7.5% 10-year risk
First-line drug therapy	Statins (dose adjusted to LDL-C goal)	Statins	Statins	Statins	Statins (high-intensity preferred)
Second-line drugs	Bile acid resins Nicotinic acid Fibrates Ezetimibe	Bile acid resins Nicotinic acid Fibrates Ezetimibe	Bile acid resins Nicotinic acid Fibrates Ezetimibe	Bile acid resins Nicotinic acid Fibrates Ezetimibe	Discouraged
Metabolic Syndrome	Emphasized: denotes higher risk for ASCVD	Recognized as higher risk condition	Emphasized: denotes higher risk for ASCVD	Emphasized: denotes higher risk for ASCVD	Ignored
Lifestyle	Backbone of	Backbone of	Backbone of	Backbone of	Component of ASCVD

intervention	therapy	therapy	therapy	therapy	prevention
Detection	Test all adults ≥ 20 years	adult men ≥ 40 years and women ≥ 50 years of age or post-menopausal	Not specified	Test all adults ≥ 20 years	Test adults ≥ 40 years
Categorial high-risk conditions	CHD CHD risk equivalents Diabetes	Diabetes CKD	Known CVD Diabetes CKD Very high risk factors 10-year SCORE ≥ 10%	CHD CHD risk equivalents Diabetes	Not specified
Risk Amplifiers	Emerging risk factors (esp. high CAC)	Emerging risk factors (esp. high CRP;)	Emerging risk factors (esp. family Hx; early CKD; high CIMT central obesity)	Emerging risk factors	None
Absolute LDL-C drug threshold for drug Rx	≥ 190 mg/dL	≥ 193 mg/dL		≥ 190 mg/dL	≥ 190 mg/dL

European Guidelines

In parallel with NCEP, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines have published guidelines on cholesterol management (21). These are similar in many ways to NCEP, but with a few differences. Estimates of absolute risk for informing drug therapy depend on 10-year risk for ASCVD mortality; these estimates are based on European epidemiologic data. The European database is named SCORE. European guidelines recognize that baseline risk for ASCVD differs between Northern and Southern regions of Europe; risk estimates therefore are adjusted for these two regions. LDL-C goals of

therapy expressed as mmol/L instead of mg/dL, and thus are similar but not identical to those of NCEP.

Canadian Guidelines

In 2013, the Canadian Cardiovascular Society issued treatment guidelines for Canada (22). 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 by absolute risk estimates, it is recommended that the LDL-C level be reduced to < 70 mg/dL.

International Atherosclerosis Society (IAS) and National Lipid Association (NLA)

The IAS recently published recommendations that can be widely adapted throughout the world (23). 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. The IAS report has been modified and updated by the National Lipid Association (24). The latter is similar to IAS in that it favors use of non-HDL-C as the primary lipid target of therapy, and it emphasizes lifetime risk for making decisions about cholesterol-lowering therapy.

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 (25). 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). Most cholesterol-lowering RCTs have employed drug therapy. ACC/AHA guidelines essentially restricted their analyses to trials using statins, because most RCT evidence comes from these drugs. 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) is estimated. Parameters used to calculate 10-year risk include gender, age, cigarette smoking, total cholesterol, HDL-C, systolic blood pressure, and diabetes. Patients having a 10-year risk for ASCVD $\geq$ 7.5% are considered candidates for statin therapy. When drugs are used, it is recommended that the highest tolerable dose of statins be employed.

CRITICAL COMPARISON OF GUIDELINES

Criteria for Guideline Development

Earlier guidelines were based largely on epidemiological evidence, bolstered by animal studies and genetic forms of hyperlipidemia. This evidence showed that higher cholesterol levels imposed greater risk for ASCVD (Figure 1). A logical conclusion from this evidence was that prudence favors achieving a lower cholesterol level. Confidence in this conclusion was increased as more clinical trials demonstrated reduction in ASCVD risk through cholesterol-lowering therapies. The expansion of RCT data now gives complete confidence in the value of cholesterol reduction for prevention of ASCVD. Separately some clinical trialists have promoted the concept that all recommendations to reduce medical risk must be based on RCTs. Unfortunately, there are many more important questions about clinical management than can be answered by RCTs. Recent ACC/AHA guidelines have attempted to base recommendation almost exclusively on RCTs. But this attempt leaves many issues to health-care providers for their clinical judgment. They deprive the provider of expert opinion based on a broad review of the literature by persons experienced in the field. Over the years, there has been an evolution of guidelines developed by national and international experts. The ACC/AHA guidelines introduced an entirely new paradigm of “evidence-based” guidelines. The current document will take up where other guidelines leave off and will attempt to consolidate the sum of the acquired knowledge from different disciplines that have addressed the “cholesterol problem”.

Decline in Emphasis on Lifestyle Intervention

Over a period of 25 years, guidelines differ in relative emphases on lifestyle intervention and cholesterol-lowering drugs (Table 5). 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 and safety through RCTs make them more attractive for risk reduction. Earlier use of drug therapy was largely relegated to patients that were categorically high-risk; this was because of uncertainty about long-term efficacy and safety of drug treatment. With each successive revision of guidelines, use of cholesterol-lowering drugs has been liberalized and intensified. Accordingly, less emphasis is put on lifestyle intervention.

Age of Intervention: 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 (26,27). Low cholesterol concentrations in these people derive largely from lifestyle. Eating habits include low intakes of cholesterol-raising nutrients (i.e., saturated fats and dietary cholesterol) and a general paucity of obesity. Comparing these populations with

higher risk societies imply that a 10% lower level of cholesterol translates into at least a 30% decrease in risk for ASCVD by middle age (1). Population studies thus support an earlier intervention to attain cholesterol-lowering. Genetic epidemiology gives a similar result. Several gene variants associate with lower cholesterol levels. Most notable are cholesterol-lowering mutations in the protein PCSK9. Normally, circulating PCSK9 promotes degradation of LDL receptors and thereby raises LDL C levels (28). When PCSK9 is mutated, more LDL receptors remain active and LDL-C concentrations fall. Individuals with PCSK9 mutations in turn express much lower rates of ASCVD (29). Other cholesterol-lowering mutations give a similar outcome (30). Together they indicate that for every 1% lower LDL-C level throughout life the incidence of ASCVD is $\geq$ 3% lower (29). These studies provide strong support for early introduction of lifestyle modification to keep LDL-C levels as low as possible. Attention to keeping cholesterol-raising nutrients out of the diet and maintaining a normal body weight will keep LDL-C at least 10-15% lower than otherwise. It is not generally recognized how much benefit can derive from lifestyle modification. Unfortunately, some of the recent guidelines neglect this potential benefit.

Risk Assessment: Limitations of Global Risk Algorithms

Global risk assessment through risk algorithms constitutes an accepted 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 (21). Recently, the ACC/AHA introduced a new algorithm based on multiple populations (including Framingham) that were studied in the United States (31). Of necessity algorithms must be based on previously studied populations; but in developed nations, risk for CHD and stroke have been progressively declining. Indeed, 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 (32-34). Using out-dated risk-assessment tools can result in unnecessary drug therapy in many individuals who are in fact at lower risk. Table 6 shows differences in population risk in other populations compared to that obtained in the USA from the Framingham Heart Study.

Table 6 Framingham Heart Study Recalibration Coefficients for Coronary Heart Disease in Different Populations (United States = 1.00)

Reference	Cohort	Men	Women	Combined
Eichler et al. (83)	Italy			0.37
	Scotland			0.91
	Germany			0.43
	France			0.41
	UK			0.76

	Ireland			0.76
	Australia			0.90
	New Zealand			1.15
Murrugat et al. (84)	North East Spain			0.37
Marques-Vidal et al. (85)	Switzerland	0.48	0.44	
Brindle et al. (86)	Britain	0.57		
Chow et al. (87)	Rural India	1.0	0.8	
	Urban India	1.81	1.54	
Asia Pacific Cohort Studies Collaboration (88)	"Asian" (enriched in Korean)	1.02	0.96	
Liu et al. (89)	China	0.36		
D'Agostino et al. (90)	Japanese American	0.50		
D'Agostino et al (90)	Native American	0.80	0.70	

Declining Risk Thresholds for Cholesterol-Lowering Drugs

Most guidelines put cholesterol management under clinician oversight. At the same time, the population strategy for prevention of ASCVD must remain a high priority for public health. This strategy involves primarily lifestyle modification. In clinical guidelines, lifestyle modification generally is stressed to complement the public health approach. More recently, however, emphasis has shifted to use of cholesterol-lowering drugs, and lifestyle intervention receives lower priority. Earlier NCEP guidelines restricted cholesterol-lowering drugs largely to patients with established CHD. Later, drug therapy in primary prevention was restricted to high-risk persons (10-year risk for CHD $\geq$ 20%) and still later to moderately high risk individuals (10-year risk for CHD 10-19%). European and Canadian guidelines have followed a similar pattern, i.e. to progressively lower risk thresholds for starting drugs. The recent ACC/AHA cholesterol guidelines have followed suit, but have lowered the threshold for drugs even more. Statin therapy is extended to individuals calculated to be at only moderate risk for ASCVD, i.e., a 10-year risk threshold for ASCVD of 7.5%. This value translates into a 10-year risk threshold for CHD of approximately 5%. This cut-point for initiation of cholesterol-lowering drugs is half that recommended in ATP III. The ACC/AHA threshold greatly expands use of drug therapy in the general population.

Uncertainties About Non-Statin Drugs

Most current and previous guidelines identified LDL-C as the primary target of cholesterol-lowering therapy. They are based on the assumption that all LDL-lowering drugs reduce risk for ASCVD in proportion to extent of LDL-C lowering. No inherent distinctions are made among different cholesterol-lowering drugs, e.g. statins, bile acid sequestrants, and ezetimibe. Recent ACC/AHA guidelines however call this assumption into question because of limited RCT-outcome trials with bile acid sequestrants and ezetimibe. This caution was especially applicable when non-statins drugs are added to statins. The recent IMPROVE-IT trial (6) and those with PCSK9 inhibitors (15,16) suggest this to be an unnecessary precaution; additional risk reduction occurred with two types of combined drug therapy.

Polypill as a 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 strategy. 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 (35). 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, recent ACC/AHA guidelines are a step in this direction; they recommend almost universal use of statins in older persons. This approach however is to be carried out in the clinical setting. Whether statins are destined to become a public health measure for the whole population remains to be seen (36).

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 confirmed that VLDL is also atherogenic. Since both LDL and VLDL similarly promote atherogenesis, the atherogenic lipoproteins should include LDL-C plus VLDL-C, or non-HDL-C (37,38). Many lipidologists now hold that non-HDL-C is the preferred target over LDL-C. A growing body of literature supports this position (23). A useful classification of LDL-C and non-HDL-C levels is shown in Table 7. This classification extends categories proposed in ATP III guidelines. 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; they recommend treatment based exclusively on drugs used in RCTs. These guidelines essentially follow the approach taken by the consortium of Cholesterol Clinical Trialists (3); this approach favors recommendations that aim for a percentage reduction in cholesterol levels--not absolute reductions.

Table 7. Categories of LDL Cholesterol and Non-HDL Cholesterol

Category	LDL Cholesterol	Non-HDL Cholesterol
Very high	≥ 190 mg/dL	≥ 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

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 future ASCVD events. Of all forms of secondary prevention, cholesterol-lowering therapy provides the greatest reduction in risk for new events. Nonetheless, aggressive treatment of all ASCVD risk factors is warranted for patients with established vascular disease.

Goals for Cholesterol-Lowering Therapies

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 limits on how much lowering of atherogenic lipoproteins can be achieved; for this reason, clinical judgment is required to establish the appropriate therapeutic regimen for a given patient within the “the lower, the better” framework. A reasonable goal for most patients with ASCVD is a very low level of atherogenic lipoproteins, i.e., an LDL-C < 70 mg/dL and/or non-HDL-C < 100 mg/dL. The recent IMPROVE-IT trial showed that lowering LDL-C to well below 70 mg/dL enhances risk reduction. The field waits with interest the results of on-going trials with PCSK9 inhibitors, which in combination with statins produces an even greater LDL reduction.

To maximize reduction of atherogenic lipoproteins in secondary prevention, lifestyle change is an important first step. This step should not be ignored because it can further reduce atherogenic lipoproteins even when drug therapy is employed. Table 8 summaries a lifestyle approach that will minimize serum cholesterol levels.

Table 8. 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	2 g/day (optional)
• Total calorie intake	Sustain desirable body weight
• Regular physical activity	30 minutes/day

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 high-intensity statin therapy (Table 3). This is reasonable for the majority of patients. Once the maximum tolerable dose has been established for a particular patient, consideration can be given whether still more cholesterol lowering is warranted to attain the lowest possible LDL-C level. This can be judged by the LDL-C or non-HDL-C response to statin treatment. If the LDL-C (and non-HDL-C) falls to the very low range with statins alone (Table 7), it may be unnecessary to add other therapies.

Role of Non-Statin Drugs in Secondary Prevention

If the reduction in atherogenic lipoproteins fails to achieve a sufficiently low level with statins alone, a second cholesterol-lowering drug can be considered. One possible add-on drug is ezetimibe. In the IMPROVE-IT trial, combining ezetimibe with maximal tolerable statin enhanced risk reduction in patients with established ASCVD. Two recent reports (15. 16) indicated that adding a PCSK9-inhibitor to maximal statin therapy in hypercholesterolemic patients gave more risk reduction. These several studies provide strong support for “lower is better” in secondary prevention.

Triglyceride-Lowering Drugs

Some patients with ASCVD have concomitant elevations in plasma triglycerides. An important question is whether treatment with a triglyceride- lowering drug, when combined with a statin, will additionally reduce risk. RCT evidence to support this combined drug regimen is limited. Several monotherapy trials have demonstrated that triglyceride-lowering drugs significantly decrease ASCVD risk. Moreover, when they are used with statins in clinical trials, subgroup analysis in patients with hypertriglyceridemia suggests additional benefit (39). If the decision is made to combine a fibrate with a statin, the preferred agent is fenofibrate; this is because risk for severe myopathy is very low (9).

Statin Intolerance

A proportion of patients taking statins claim intolerance (40,41). Muscle pain and weakness (myalgias) are the usual complaint. Severe myopathy is rare; but when it occurs, it can cause myoglobinuria and acute renal failure. The frequency of statin-induced myalgia is unclear but appears to range from 5 to 15% (42). Other side effects of statins may include cognitive dysfunction and rise in plasma glucose. In some patients, glucose levels rise to the diabetes range. Clinical intolerance can be defined as failure to tolerate 2 or more statins.

A reasonable goal for patients with statin intolerance is to achieve at least a 30% reduction in LDL-C levels. A general approach to attain this goal is given in Table 9. If a patient discontinues a statin because of putative intolerance, the first step is to challenge with the same statin. If myalgia recurs, an alternative statin can be tried. Fluvastatin appears to be the best tolerated of all the statins when used at standard doses (42,43). Some investigators report success with rousavastatin given 1-3 times per week (44-46). Once the limits of statin therapy are attained, consideration can be given to other LDL-lowering therapies. Maximal dietary therapy with 2 g/day of plant stanols/sterols can add significantly to LDL-C lowering (47). Adding ezetimibe usually yields another 15-20% LDL-C reduction. Other add-on agents to consider are bile acid sequestrants, niacin, and fenofibrate. Several reports demonstrate enhanced efficacy of multiple non-statin drugs (48-50). With combinations of lifestyle therapies, low dose statins, and non-statin drugs it should be possible to achieve a >30% reduction of LDL-C in most statin-intolerant patients.

Table 9. Suggestions for Attaining LDL Cholesterol Goal in Patients with Statin Intolerance	
Definition of statin intolerance	Failure to tolerate 2 or more statins at moderate-intensity or high intensity doses; confirm intolerance by challenge with same and/or alternate statin
Goal of therapy	Lower LDL-C by $\geq$ 30%
Therapeutic strategy	Employ multiple modalities in combination
Therapeutic modalities:	Employ a mix of the following therapies to achieve goal of therapy: Fluvastatin 20-80 mg/day Low dose rosuvastatin 1-3 times weekly Maximal dietary therapy with 2 g/day of plant

	stanols/sterols Ezetimibe 10 mg/day Bile acid sequestrants: dose dependent on agent employed Fenofibrate 130-200 mg/day Niacin 2+ g/day

Primary Prevention

Risk Assessment for Primary Prevention

For primary prevention, selection of patients for cholesterol-lowering drugs using standard risk algorithms is problematic. These algorithms are based on average population risk and are not necessarily reliable for individuals. A more reliable indicator of lifetime risk is the presence of higher risk conditions or major risk factors. Table 10 lists these conditions/factors and gives their approximate prevalence in the US population. Each will be discussed briefly relative to their indications for cholesterol-lowering drugs.

Table 10. Higher Risk Conditions and Major Risk Factors

Higher Risk Conditions	No. $x10^{6a}$	Major Risk Factors	No. $x10^{6}$
Subclinical atherosclerosis CAC > 100 Agatston units		Advancing age	
Diabetes	29.1	Cigarette smoking	42.1
Metabolic syndrome	77-86	Hypertension	70
Chronic kidney disease	20	Hypercholesterolemia	31
[a] Approximate prevalence in USA in millions			

Higher Risk Conditions

Subclinical Atherosclerosis. Among the higher risk conditions for ASCVD, the most powerful predictor is the presence of subclinical atherosclerosis (51-54). In a word, the atherosclerotic burden represents the cumulative effect of all risk factors driving atherogenesis. The most

promising measurement of subclinical atherosclerosis is coronary artery calcium (CAC). Recent studies show a powerful linkage between CAC measurements and ASCVD risk (51,55).

The Agatston score is the most commonly used measurement of CAC. Scores of > 300 Agatston units can be considered *high-risk.* Scores of 100-299 are *moderate-risk*; those of 1-99 are *borderline-risk*; and zero scores are *very low risk.* The predictive power of CAC appears to be largely independent of age (Figure 3). Of particular note is that a zero CAC associates with very low risk of ASCVD over the next 10 years (51,55). A less powerful but still robust risk prediction is intimal medial thickness (IMT) of the carotid artery (56-58). 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.

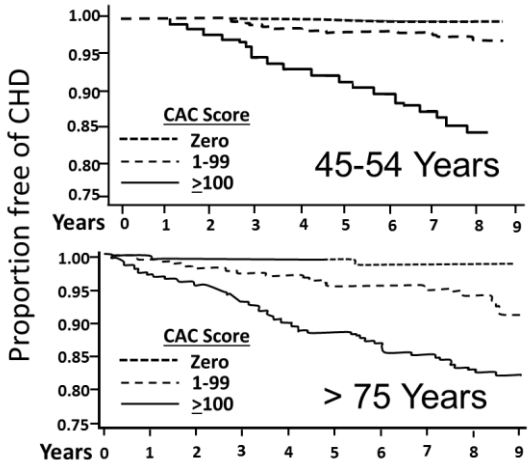

Figure 3. Portion of MESA population free of coronary heart disease (CHD) compared to baseline coronary artery calcium (CAC) score in Agatston units in two age groups: 45-54 years and > 75 years. The figure shows that the higher CAC scores associate with a smaller proportion of the population free of CHD. There were virtually no CHD events in those with zero CAC. In the 45-54 age group with CAC 1-99 units, event rates were lower than in the corresponding group >75 years. Figure modified from Tota-Maharaj et al (55).

Figure 4 compares the ACC/AHA algorithm for determining the risk threshold for cholesterol-lowering drugs and the use of CAC scores. ACC/AHA guidelines recommend use of drug therapy in most older persons, whereas many fewer will be candidates for cholesterol-lowering drugs with CAC scoring.

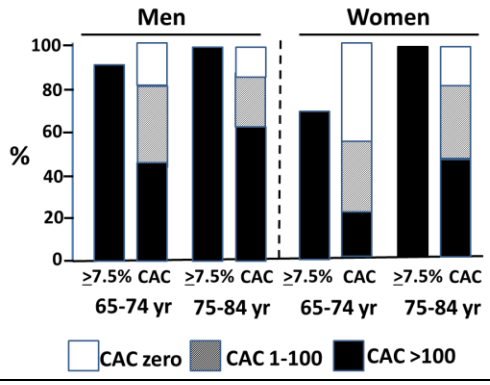

Figure 4. Comparison of the portion of the older populations (men and women) eligible for cholesterol-lowering drugs by ACC/AHA guidelines (10-year risk for ASCVD ≥ 7.5%) (31) and by coronary artery calcium (CAC) (CAC score >100 Agatston units) (91). The discrepancy is greater for women than for men.

Diabetes. Because of the high prevalence of obesity in the US population, there likewise is a high prevalence of type 2 diabetes. At present approximately 29.1 million persons in the USA have diabetes (59); ATP III identified diabetes as a CHD risk equivalent. Several subsequent reports support the claim that diabetes carries a risk for future vascular events similar to that of patients with established ASCVD (60-62); others suggest that patients with cardiovascular disease are at higher risk on average than are many patients with diabetes (63,64). Most investigators nonetheless agree that diabetes represents a high-risk condition. Patients with clinical diabetes are on a trajectory for increasing risk for ASCVD. Even when they do not have a 10-year risk for ASCVD equal to patients with established ASCVD, they eventually will fall into the high-risk category. This is true for both type 2 diabetes and type 1 diabetes; thus most patients with diabetes can 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 strong candidates for cholesterol-lowering drugs. For patients with diabetes, the question is not if but when to initiate cholesterol-lowering drugs.

Chronic kidney disease (CKD). The Centers for Disease control estimates that more than 10% of adults in the United States—more than 20 million people—have chronic kidney disease (CKD) (65). Among these, about 44% have diabetes and 28% are hypertensive.. With advancing CKD, the risk for ASCVD rises. Nephrologists generally favor identifying CKD (Stages III-V) as a high-risk condition (66). A recent RCT demonstrated that cholesterol-lowering drugs will substantially reduce risk for ASCVD events in patients with CKD (67).

Metabolic syndrome. An international consensus definition of metabolic syndrome is summarized in Table 11 (68). The total number of adults in the US with metabolic syndrome ranges from 77 to 86 million (69). Approximately one-third of these people have type 2 diabetes (69-71). Epidemiological data show that patients with the metabolic syndrome have a risk for future CHD events similar to that of patients with diabetes (72). The metabolic syndrome essentially doubles ASCVD risk (73,74). Most patients with this syndrome thus can be considered candidates for cholesterol-lowering drugs, especially when they advance in age or develop diabetes.

Table 11. Criteria for Clinical Diagnosis of the Metabolic Syndrome

Measure	Categorical Cut Points
Elevated Waist Circumference[a]	$\geq$ 102 cm in males $\geq$ 88 cm in females
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator[b])	$\geq$ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an	< 40 mg/dL (1.0 mmol/L) in males < 50 mg/dL (1.3 mmol/L) in females

alternate indicator[b])	
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator	Systolic ≥ 130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose[c] (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dl

HDL-C indicates high-density lipoprotein cholesterol.
[a]Waist circumference cutpoints for the USA according to ATP III criteria. Cutpoints for other populations are listed in the parent document (68)
[b]The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presume high triglycerides.
[c]Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the current criteria (68)

Major Risk Factors for ASCVD

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

Age as a risk factor: *Limitations in 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 applying a fixed age in the risk algorithm overestimates 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 (55,75).*

When considering lifetime risk, other risk conditions/factors take priority over age as an indicator of need for cholesterol-lowering drugs. If none of these are present, measurement of subclinical atherosclerosis is a preferred determinant of risk status.

Cigarette Smoking. This is a powerful risk factor for ASCVD. Smokers are particularly susceptible to premature CHD (76). Approximately 42.1 million Americans currently smoke (77). Persons who cannot discontinue smoking are good candidates for a cholesterol-lowering drug. This is particularly so for heavier smokers. Because of the tendency for premature CHD, early intervention in heavier, persistent smokers seems justified. Clinical judgment is required as to the best time to introduce drug treatment. But for heavier smokers, "the earlier, the better" for cholesterol lowering should be the rule.

Hypertension. Elevated blood pressure is another powerful risk factor for ASCVD. It confers a particularly high risk for stroke; but it is also is a strong risk factor for CHD. Approximately 70 million Americans have hypertension (78). Serious consideration should be given to the use of a cholesterol-lowering drug in a patient who has or has had chronic, poorly controlled hypertension. Many hypertensive patients have either metabolic syndrome or type 2 diabetes and thereby are candidates for cholesterol-lowering drug through this route. For a hypertensive patient without no other risk factors, measurement of subclinical atherosclerosis is a useful tool for deciding whether to initiate a cholesterol-lowering drug.

Hypercholesterolemia. Cholesterol guidelines typically adjust treatment relative to estimated absolute risk of patients. However, about 30 million Americans have categorical hypercholesterolemia (high or very high LDL-C (LDL-C > 160 mg/dL) (79). For most patients who have persistent hypercholesterolemia by these criteria, cholesterol lowering with drug therapy is reasonable. Available epidemiologic data indicate that a lifelong elevation of LDL-C carries a progressively higher risk for ASCVD (80). If uncertainty exists whether to use a cholesterol-lowering drug, consideration can be given to checking for subclinical atherosclerosis. For example, in hypercholesterolemic, post-menopausal women without other risk factors, advancing subclinical atherosclerosis by CAC justifies a cholesterol-lowering drug. If the CAC score is zero or borderline, drug therapy will not be needed. How to treat borderline LDL-C levels will be discussed later.

Other Risk Factors. Several other factors predict ASCVD, although they have not proven to be causative. 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 associate with metabolic syndrome or type 2 diabetes. Thus the decision to use cholesterol-lowering drugs usually will depend on these latter higher risk conditions.

Cholesterol-Lowering Goals in Primary Prevention

The general principle of "the lower, the better" for cholesterol levels can be applied to primary prevention as well as secondary prevention. This principle is supported by both epidemiological studies (1) and clinical trials (81). A second principle also pertains to primary prevention, namely, "the earlier, the better" for low cholesterol levels. This latter principle follows from both population epidemiology (1) and genetic epidemiology (29,82). For primary prevention, a

reasonable goal is to reduce cholesterol levels to a low range (LDL-C 70-99 mg/dL or non-HDL-C 100-129 mg/dL).

Initiation of Therapy

Lifestyle intervention. There are two goals of lifestyle intervention: (a) to reduce atherogenic lipoproteins to as low as possible, and (b) to start lipid lowering as early as possible. The ingredients of lifestyle intervention are listed in Table 8. It is important to remember that keeping cholesterol levels to less than 100 mg/dL for a lifetime will virtually eliminate ASCVD, at least through middle age (29).

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 (LDL-C and non-HDL-C) should be reduced to at least the low range (Table 7). Further reduction to a very low range is optional (22).

Some of the factors that must be taken into account for initiation and intensification of cholesterol-lowering drugs are listed in Table 12. When statins are employed, some patients will be intolerant of them. Options for cholesterol-lowering interventions in statin-intolerant patients are shown in Table 9.

Table 12, Considerations for Cholesterol-Lowering Therapy in Primary Prevention.

- Desirable LDL-C/non-HDL-C levels in primary prevention: LDL-C 70-99 mg/dL and non-HDL-C 100-129 mg/dL. (Table 7). Still lower levels are an option in patients at higher risk (Table 10).
- Consider cholesterol-lowering drug therapy in persons at higher risk status (higher risk conditions or major risk factors) (Table 10).
- If drugs warranted, initiate moderate-intensity drug therapy to achieve low levels of atherogenic lipoproteins (Table 3); if necessary to achieve low levels, escalate to high-intensity drug therapy (Table 3).
- If no higher risk conditions/factors are present, focus attention on LDL-C (and non-HDL-C).
  - If LDL-C is $\geq$ 190 mg/dL (non-HDL-C $\geq$ 220 mg/dL), cholesterol-lowering drug(s) are warranted.
  - If LDL-C is 160-189 mg/dL (non-HDL-C 190-219 mg/dL), consider cholesterol-lowering drug(s). In older women who have LDL-C 160-189 mg/dL, but who have well-controlled blood pressure, no smoking, and no diabetes, consider measuring subclinical atherosclerosis (see Figure 4). If CAC > 100 Agatston units, consider use of cholesterol-lowering drug(s).
  - If LDL-C is 130-159 mg/dL, initiate maximal lifestyle therapies; and if needed to achieve an LDL-C < 100 mg/dL, consider low-intensity cholesterol-lowering drug(s).
  - If LDL-C is 100-129 mg/dL, maximize dietary therapy. Low-intensity cholesterol-lowering drug(s) are an option, but may not be indicated in an otherwise low-risk person.
  - If LDL-C is below 100 mg/dL, maximize dietary therapy. Consider cholesterol-lowering drugs only when higher risk conditions/factors are present (Table 10).

- If uncertainty exists whether to employ a cholesterol-lowering drug, consider measuring subclinical atherosclerosis to determine need for drug (CAC >100 usually justifies drug therapy; if CAC score is 1-99, some authorities favor drug therapy; others do not. If CAC score is zero, drugs can be withheld.

Monitoring for Adherence and Response to Therapy

When therapies for cholesterol lowering are introduced, periodic monitoring for responses is appropriate. Timing of measurements depends on frequency of visits to the physician. Typically measurements are made about three times the first year, and if response is adequate, measurements can be made once or twice a year depending on the patient's clinical status.

SUMMARY

Population epidemiology, genetic epidemiology, and randomized controlled trials all demonstrate that lower is better for atherogenic lipoproteins (LDL-C and non-HDL-C) for prevention of ASCVD. To achieve the lowest feasible levels for these lipoproteins, a combination of lifestyle intervention and cholesterol-lowering drugs is often required. Recent research confirms that keeping cholesterol levels low throughout life amplifies risk reduction. For secondary prevention, we are largely limited to "the lower the better" approach; here an LDL-C level of < 70 mg/dL is a reasonable goal. For primary prevention, special attention must be given to persons with higher risk conditions or major risk factors. Cholesterol-lowering drugs should be considered in this situation; in most cases, setting an LDL-C goal in the range of 70-99 mg/dL is reasonable. In primary prevention, "the earlier the better" concept for cholesterol-lowering should guide management. Since long-term RCTs may not be feasible, we must rely on population epidemiology and genetic epidemiology to justify cholesterol-lowering intervention well before individuals achieve a higher risk status.

In the absence of higher risk conditions/factors, the primary focus should be on reducing atherogenic lipoproteins. In many cases sufficient cholesterol lowering can be attained with lifestyle changes alone; but judicious use of cholesterol-lowering agents may be helpful in those with higher cholesterol levels. Fortunately, there is an expanding list of effective drugs for cholesterol-lowering. At present, statins are the mainstay of cholesterol management; but both older and newer agents can be usefully employed in many patients. They can be used either in combination with statins or by replacing statins in individuals who are statin intolerant.

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