

GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD CHOLESTEROL

Kenneth R. Feingold MD, Emeritus Professor of Medicine, University of California San Francisco, San Francisco, CA. Kenneth.feingold@ucsf.edu

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ABSTRACT

The LDL-C hypothesis holds that high blood LDL-C levels are a major risk factor for atherosclerosis cardiovascular disease (ASCVD) and lowering LDL-C levels will reduce the risk for ASCVD. This hypothesis is based on epidemiological evidence that both within and between populations higher LDL-C levels increase the risk for ASCVD, and conversely, randomized clinical trials (RCTs) demonstrating that lowering LDL-C levels will reduce ASCVD risk. LDL-C levels can be reduced by both lifestyle interventions and cholesterol-lowering drugs. Widely used LDL-C lowering drugs are statins, ezetimibe, bempedoic acid, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. In this chapter we discuss the information provided in the two major guidelines on how to select and treat patients to lower LDL-C levels; the 2018 AHA/ACC/Multi-Society report and the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), and representatives other European organizations guidelines from published in 2020. Additionally, we discuss the key principles that clinicians should utilize when deciding who to treat and how aggressively to treat hypercholesterolemia to lower the risk of ASCVD. Specifically, 1) the sooner one initiates LDL-C lowering therapy the greater the benefit, 2) the greater the decrease in LDL-C the greater the benefit, 3) the higher the LDL-C level the greater the benefit, and 4) the higher the absolute risk of ASCVD the greater the benefit. Following these general principles will help clinicians make informed decisions in deciding on their approach to lowering LDL-C levels and will facilitate discussions with patients on the benefits and risks of treatment. These decisions need to balance the benefits of treatment vs. the potential side effects and cost and the preferences of individual patients.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the foremost cause of death among chronic diseases. An aging population combined with an atherogenic lifestyle increases the risk of ASCVD. Even so, mortality from ASCVD has been declining in most developed countries. This decline comes from improvements in preventive measures and better clinical interventions. One of the most important advances in the cardiovascular field resulted from identifying risk factors for ASCVD. Risk factors directly or indirectly promote atherosclerosis, or they otherwise predispose to vascular events. The major risk factors are cigarette smoking, dyslipidemia, hypertension, hyperglycemia, and advancing age. Dyslipidemia consists of elevations of atherogenic lipoproteins (LDL, VLDL, Lp(a), and remnants) and low levels of HDL. Advancing age counts as a risk factor because it reflects the impact of all risk factors over the lifespan. Several other factors, called risk enhancing factors, associate with higher risk for (1). Lifestyle factors (for ASCVD example. overnutrition and physical inactivity) contribute importantly to both major and enhancing risk factors. Hereditary factors undoubtedly contribute to the identifiable risk factors; but genetic influences also

affect ASCVD risk through other ways not yet understood (2).

THE CHOLESTEROL HYPOTHESIS AND CHOLESTEROL LOWERING THERAPY

There is now indisputable evidence that elevated serum cholesterol levels increase the risk of ASCVD. The first evidence for a connection between serum cholesterol levels and atherosclerosis came from studies in laboratory animals (3). Feeding cholesterol to various animal species raises serum cholesterol and causes deposition of cholesterol in the arterial wall (3). The latter recapitulates the early stages of human atherosclerosis. Subsequently, in humans, severe hereditary hypercholesterolemia was observed to cause premature atherosclerosis and ASCVD (3). Later, population surveys uncovered a positive association between serum cholesterol levels and ASCVD (4,5). Finally, clinical trials with cholesterollowering agents documented that lowering serum cholesterol levels reduces the risk for ASCVD (6). These findings have convincing proven the *cholesterol hypothesis*. Moreover, the relationship between cholesterol levels and ASCVD risk is bidirectional; raising cholesterol levels increases risk, whereas reducing levels decreases risk (Figure 1).

Cholesterol Hypothesis



Cholesterol Level

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 the risk for ASCVD. This bidirectional relationship between cholesterol levels and ASCVD provides ample support for the cholesterol hypothesis.

Epidemiological Evidence

A relationship between cholesterol levels and ASCVD risk is observed in both developing and developed countries (4,5). Populations with the lowest cholesterol levels and LDL-C levels have the lowest rates of

ASCVD. Within populations, individuals with the

lowest serum cholesterol or LDL-C levels carry the least risk. In other words, "the lower, the better" for cholesterol levels holds, both between populations and for individuals within specific populations.

Pre-Statin Clinical Trial Evidence

Several earlier randomized controlled trials (RCTs) tested whether reducing cholesterol levels through

diet, bile acid sequestrants, or ileal exclusion operation reduced ASCVD events. A summary of the results of these trials is shown in table 1 (4).

Table 1. Summary of Pre-Statin Clinical Trials of Cholesterol-Lowering Therapy							
Intervention	No. trials	No. treated	Person- years	Mean 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 (4)

Statins and Clinical Trial Evidence

Statins were discovered in the 1970s by Endo of Japan (7). Seven statins have been approved for use in clinical practice by the FDA and they are now generic (for a detailed discussion of statins see the Endotext chapter on Cholesterol Lowering Drugs (8)). Statins inhibit HMG-CoA reductase decreasing cholesterol synthesis and increasing hepatic LDL receptors resulting in a decrease in LDL-C levels. Over the past three decades, a series of RCTs have been carried out that documents the efficacy and safety of statin therapy. In these RCTs, statin therapy has been shown to significantly reduce morbidity and mortality from ASCVD. Although individual RCTs produced significant results, the strongest evidence of benefit comes from meta-analysis. i.e., by combining data from all the trials (6).

Meta-analysis has shown that for every mmol/L (39 mg/dL) reduction in LDL-C with statin therapy there is an approximate 22% reduction in ASCVD events (6,9-12). Another report (13) showed that an almost identical relationship holds when several different kinds of LDL-lowering therapy were analyzed together. This response appears to be consistent throughout all levels of LDL-C. Individual statins vary

in their intensity of cholesterol-lowering at a given dose (1,8) (Table 2). For example, per mg per day, rosuvastatin is twice as efficacious as atorvastatin, which in turn is twice as efficacious as simvastatin. Statins are best classified according to percentage reductions in LDL-C. As shown in Table 2, moderateintensity statins reduce LDL-C by 30-49 %, whereas high-intensity statins reduce LDL-C by > 50%. Absolute reductions vary depending on baseline levels of LDL-C. For example, for a baseline LDL-C of 200 mg/dL, a 50% reduction in LDL-C equates to a 100 mg/dL (2.6 mmol/L) decline; this translates into a 59% reduction in 10-year risk for ASCVD events. In contrast, in a patient with a baseline LDL-C of 100 mg/dL, a 50% reduction in LDL-C equates to a 50 mg/dL (1.3 mmol/L) decline, which will reduce ASCVD risk by about 30%. Thus, at lower and lower levels of LDL-C, progressive reductions of LDL-C produce diminishing benefit from cholesterol-lowering therapy. This modifies the aphorism "lower is better". Whereas the statement is true, it must be kept in mind that there are diminishing benefits from intensifying cholesterollowering therapy when LDL-C levels are already very low. One needs to balance the benefits of further reducing LDL-C levels with the side effects and costs of additional therapy.

Table 2. Categories of Intensities of Statins						
Drug	Low-Intensity 20-25% ↓ LDL-C	Moderate-Intensity 30-49% ↓ LDL-C	High Intensity ≥50% ↓ LDL-C			
Lovastatin	10-20 mg	40-80 mg				
Pravastatin	10-20 mg	40-80 mg				
Simvastatin	10 mg	20-40 mg				
Fluvastatin	20-40 mg	80 mg				
Pitavastatin		1-4 mg				
Atorvastatin	5 mg	10-20 mg	40-80 mg			
Rosuvastatin		5-10 mg	20-40 mg			

Non-Statin Cholesterol-Lowering Drugs

Other agents are currently available that lower LDL-C levels. Bile acid sequestrants inhibit intestinal absorption of bile acids, which like statins raise hepatic LDL receptors (8). They are moderately efficacious for reducing LDL-C concentrations. A large RCT showed that bile acid sequestrants significantly reduce risk for CHD in patients with baseline elevations in LDL-C (14). Theoretically, bile acid sequestrants could enhance risk reduction in patients with ASCVD who are treated with statins.

Ezetimibe blocks cholesterol absorption in the intestine and also raises hepatic LDL receptor activity (8). It moderately lowers LDL-C (15-25%). The combination of statin + ezetimibe is additive for LDL-C lowering (15). A clinical trial (16) demonstrated that adding ezetimibe to moderate intensity statins in very high-risk patients with ASCVD is beneficial showing that combination reduced risk therapy of cardiovascular events more than a statin alone (16). In this trial, the higher the risk, the greater was risk reduction (17). Ezetimibe is a generic drug and relatively inexpensive.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes degradation of LDL receptors and raises LDL-C levels (8). Inhibition of PCSK9 increases the number of hepatic LDL receptors and markedly lowers LDL-C concentrations (50-60% decrease) (8,18). Studies have shown that PCSK9 inhibitors reduce risk in ASCVD patients at very high risk when combined

with statins (19,20). PCSK9 inhibitors are relatively expensive drugs.

Bempedoic acid is an adenosine triphosphate-citrate lyase (ACL) inhibitor and thereby inhibits cholesterol synthesis leading to an increase in LDL receptor activity (8,21). Bempedoic acid typically lowers LDL-C by 15-25% (8,21). A RCT has demonstrated that bempedoic acid reduces ASCVD in statin intolerant patients (22). Bempedoic acid is not generic and therefore is relatively expensive.

For additional information on cholesterol and triglyceride lowering drugs see the chapters in Endotext that address these topics (8,23).

PRIOR U.S. GUIDELINES FOR CHOLESTEROL MANAGEMENT

National Cholesterol Education Program (NCEP)

The early guidelines for cholesterol management in the United States have been those developed by the NECP. This program was sponsored by the National Heart, Lung and Blood Institute (NHLBI) and included many health-related organizations in the United States (24). Between 1987 and 2004, three major Adult Treatment Panel (ATP) reports (4,25,26) and one update were published (27) (Table 3). Over time the guidelines recommended more stringent LDL-C goals as the results of RCTs were published and added non-HDL-C levels as a goal.

Table 3. National Cholesterol Education Program's Adult Treatment Panel (ATP) Reports					
Guideline	ATP I	ATP II	ATP III	ATP III Update	
Year	1987	1994	2001	2004	
Thrust	Primary	Secondary	High-risk primary	Very high risk	
	prevention	prevention	prevention		
Drugs	Bile acid resins	Same as ATPI	Same as ATP II	Same as ATP III	
	Nicotinic acid	+Statins			
	Fibrates				
Major Targets	LDL-C; HDL-C	LDL-C; HDL-C	LDL-C;	LDL-C; Non-	
			Non-HDL-C	HDL-C	
LDL-C goal	Low risk <190	Low risk <160	Low risk <160	Low risk <160	
(mg/dL)	Moderate risk	Moderate risk	Moderate risk	Moderate risk	
	<160 High	<130 High	<130	<130	
	risk < 130	risk <100	Moderately high	Moderately high	
			risk <130	risk <130 High	
			High risk < 100	risk < 100 Very	
				high risk < 70	

Transfer of NHLBI Guidelines to American Heart Association (AHA) and the American College of Cardiology (ACC)

In 2013, NHLBI made the decision to remove treatment guidelines from its agenda. This was done even though it had almost finished writing prevention guidelines. These included guidelines for high blood cholesterol, high blood pressure, obesity, and nutrition. Late in this process, the guideline process was transferred to the American Heart Association (AHA) and American College of Cardiology (ACC). Then in 2013 the NHLBI guidelines for high blood cholesterol were modified to fit the criteria for guideline development required by AHA/ACC. The 2013 cholesterol guidelines (28) adhered closely to the Institute of Medicine (National Academy of Medicine) recommendations for evidence-based guidelines (29). These recommendations advocated priority to randomized controlled trials (RCTs) as the foundation of evidence-based medicine. The NHLBI cholesterol committee carried out an extensive review of the literature and limited recommendations based largely on RCTs. Most acceptable RCTs had utilized statin therapy in middle-aged people. Therefore, the 2013 committee did not include detailed report recommendations for younger or older adults. Recommendations were largely limited to the age range 40-75 years. High-intensity statin therapy was recommended for patients with established ASCVD. For primary prevention, risk was stratified by use of a pool cohort equation (PCE), which was derived from five large population studies in the United States (30). The PCE was an extension of the Framingham Heart Study risk equations. 10-year risk for ASCVD was based on the following risk factors: age, gender, cigarette smoking, blood pressure, total cholesterol, HDL cholesterol, and presence or absence of diabetes. Although the PCE was validated in another large study (31), it has been criticized by some investigators as being imprecise for many individuals or specific groups (32-36).

For primary prevention, an effort was made to determine what level 10-year risk is associated with efficacy of reduction of ASCVD from statin RCTs. It was determined that statins are effective for risk reduction when 10-year risk for ASCVD is \geq 7.5%. Most primary prevention trials employed moderate intensity statins, so these were recommended for most patients; but in one RCT (37), a high-intensity statin appeared to produce greater risk reduction than found with moderateintensity statins. So high-intensity statins were considered a favorable option in patients at higher 10-year risk. Notably LDL-C goals were not emphasized. It was recognized that these recommendations may not be optimal for all patients; therefore, consideration should be given to any extenuating circumstances that could modify the translation of RCTs directly into clinical care. A clinician patient risk discussion thus was advocated for all patients to consider the pros and cons of statin therapy.

There are many guidelines discussing the management of LDL-C, but the 2 major guidelines are the 2018 AHA/ACC/Multi-Society report (1) and the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), and representatives from other European organizations guidelines published in 2020 (38). In this chapter these two guidelines will be discussed.

2018 AHA/ACC/MULTI-SOCIETY REPORT

2013 cholesterol guidelines were revised by AHA/ACC in collaboration with multiple other societies concerned with preventive medicine (1). These guidelines extended those published in 2013. They expanded recommendations to include children, adolescents, young adults (20-39 years), and older patients (> 75 years). Although RCTs may be lacking in these categories, epidemiology and clinical studies indicate that high blood cholesterol is an important risk factor for future ASCVD in these age ranges. From the evidence acquired over many years related to the cholesterol hypothesis, it is reasonable to craft recommendations based on the totality of the evidence. These guidelines proposed a top 10 list of recommendations to highlight the key points. These key points will be examined.

Lifestyle Intervention

1) In all individuals emphasize a heart healthy lifestyle across the life-course.

There is widespread agreement in the cardiovascular field that lifestyle factors contribute to the risk for ASCVD. These factors include cigarette smoking, sedentary life habits, obesity, and an unhealthy eating pattern. The ACC/AHA strongly recommends that a healthy lifestyle be adopted throughout life. These recommendations are strongly supported by 2018 cholesterol guidelines. They are the foundation for cardiovascular prevention and should receive appropriate attention in clinical practice (39). For a detailed discussion of the effect of diet on lipid levels and atherosclerosis see the Endotext chapter The Effect of Diet on Cardiovascular Disease and Lipid and Lipoprotein Levels (40).

Secondary Prevention

 In patients with clinical ASCVD reduce LDL-C with high-intensity statin or maximally tolerated statins to decrease ASCVD risk. The goal of therapy is to reduce LDL-C by 50% or greater. If necessary to achieve this goal consider adding ezetimibe to moderate statin therapy.

The strongest evidence for efficacy of statin therapy is a meta-analysis of RTCs carried out in patients with established ASCVD. As previously mentioned, the best fit line comparing percent ASCVD versus LDL-C in secondary prevention studies demonstrates that for every mmol/L (39mg/dL) reduction in LDL-C the risk for ASCVD is decreased by approximately 22% (9). High intensity statins typically reduce LDL-C by 50% or more; this percentage reduction occurs regardless of baseline levels of LDL-C. This explains why the guidelines set a goal for LDL-C secondary prevention to be a \geq 50% reduction in levels. There are two options to achieve such reductions. RCTs give priority to the use of high-intensity statins. But, if high-intensity statins are not tolerated, similar LDL-C lowering can

be attained by combining a moderate-intensity statin with ezetimibe (15,16). The RACING trial, a randomized trial that compared rosuvastatin 10 mg plus ezetimibe 10 mg vs. rosuvastatin 20 mg, demonstrated a similar effect on ASCVD events (41). An approach to lowering LDL-C in patients with ASCVD is shown in Figure 2.



Figure 2. Secondary Prevention in Patients with Clinical ASCVD (1).

VERY HIGH-RISK PATIENTS WITH ASCVD

 In very high-risk patients with ASCVD first use a maximally tolerated statin +/- ezetimibe to achieve an LDL-C goal of < 70mg/dL (<1.8mMol/L). If this goal is not achieved consider adding a PCSK9 inhibitor. 2018 guidelines defined very high risk of future ASCVD events as a history of multiple ASCVD events or one major event plus multiple high-risk conditions (Table 4). This definition is based in large part on subgroup analysis of the IMPROVE-IT trial (16,17).

Table 4. Very High Risk of Future ASCVD Events (1)

Major ASCVD Events

Recent ACS (within the past 12 months)

History of MI (other than recent acute coronary syndrome event listed above)

History of ischemic stroke

Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

High Risk Conditions

Age ≥65 y

Heterozygous familial hypercholesterolemia History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) **Diabetes mellitus** Hypertension CKD (eGFR 15-59 mL/min/1.73 m²) Current smoking Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe History of congestive heart failure

ABI indicates ankle-brachial index; CKD indicates chronic kidney disease.

Recent RCTs have demonstrated that the addition of non-statins to statin therapy can enhance risk reduction. These RCTs (and their add-on drugs) were IMPROVE-IT (ezetimibe) (16), FOURIER (evolocumab) (19), and ODYSSEY OUTCOMES (alirocumab) (20). All RCTs were carried out in patients at very high-risk. For IMPROVE-IT, addition of ezetimibe to statin therapy produced an additional 6% reduction in ASCVD events. In this trial, baseline LDL-C on moderate-intensity statin alone averaged about 70 mg/dL; in spite of this low level, further LDL lowering with addition of ezetimibe enhanced risk reduction. RCTs with the two PCSK9 inhibitors (evolocumab and alirocumab) restricted recruitment to patients having LDL-C \geq 70 mg/dL on maximally tolerated statin+ ezetimibe. In these RCTs, the duration of therapy was only about 3 years. A marked additional LDL lowering was achieved. In both trials, the risk for ASCVD events was reduced by 15%.

2018 guidelines allow consideration of PCSK9 inhibitor as an add-on drug if patients are at very high risk for future ASCVD events and have an LDL-C > 70 mg/dL (or non-HDL-C > 100mg/dL) during treatment with maximally tolerated statin plus ezetimibe (Figure 3). This latter threshold LDL-C was chosen because it was a recruitment criterion for PCSK9 inhibitor therapy in reported RTCs (19,20)

An important question about the use of PCSK9 inhibitors is whether they are cost-effective. When they first became available, they were marketed at a very high cost, which was widely considered to be excessive. More recently, the cost of these drugs has declined considerably, and one can anticipate that the price will continue to decrease. An analysis of costeffectiveness has shown that at current prices in very high-risk patients PCSK9 inhibitors can be costeffective (42). Another analysis (43) of approximately 1 million patients with ASCVD in the Veterans Affairs system indicate that approximately 10% of patients will be classified as very high risk and having LDL-C > 70mg/dL while taking maximal statin therapy plus

ezetimibe. These later patients are potential candidates for PCSK9 inhibitors.



Figure 3. Secondary Prevention in Patients with Very High-Risk ASCVD (1).

Primary Prevention

SEVERE PRIMARY HYPERCHOLESTEROLEMIA

4) In patients with severe primary hypercholesterolemia (LDL-C greater than 190mg/dL (>4.9mMol/L)) without concomitant ASCVD begin high-intensity statin therapy (or moderate intensity statin + ezetimibe) to achieve an LDL-C goal of < 100mg/dL; if this goal is not achieved consider adding a PCSK9 inhibitor in selected patients at higher risk. Measurement of 10-year risk for ASCVD is not necessary. Patients with severe hypercholesterolemia are known to be at relatively high risk for developing ASCVD (44,45). In view of massive evidence that elevated LDL-C promotes atherosclerosis and predisposes to ASCVD, it stands to reason that such patients deserve intensive treatment with LDL-lowering drugs. RCTs with cholesterol-lowering drugs demonstrate benefit of statin therapy patients with in severe hypercholesterolemia (46,47). It is not necessary to calculate 10-year risk in such patients. Moreover, patients who have extreme elevations of LDL-C (e.g., heterozygous familial hypercholesterolemia) may be candidates for PCSK9 inhibitors if LDL-C cannot be

lowered sufficiently with maximal statin therapy plus ezetimibe.

PATIENTS WITH DIABETES

5) In patients with diabetes mellitus aged 40 to 75 years with an LDL-C ≥70 mg/dL (≥1.8 mmol/L), without concomitant ASCVD, begin moderate-intensity statin therapy. For older patients (≥ 50 years), consider using high-intensity statin therapy (or moderate intensity statin plus ezetimibe) to achieve a reduction in LDL-C of ≥ 50%. Measurement of 10-year risk for ASCVD is not necessary.

Middle-aged patients with diabetes have an elevated lifetime risk for ASCVD (48). The trajectory of risk is steeper in patients with diabetes than in those without. For this reason, estimation of 10-year risk for ASCVD with the pooled cohort equation (PCE) is not a reliable indicator of lifetime risk. Meta-analysis of RCTs in middle-aged patients with diabetes treated with moderate intensity statins therapy shows significant risk reduction (12). Hence, most middle-aged patients with diabetes deserve statin therapy. With progression of age and accumulation of multiple risk factors, increasing the intensity of statin therapy or adding ezetimibe seems prudent (Tables 5 and 6). It is not necessary to measure 10-year risk before initiation of statin therapy in these patients with diabetes.

 Table 5. Diabetes Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes (1)

 Long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus

 Albuminuria ≥30 mcg of albumin/mg creatinine

 eGFR <60 mL/min/1.73 m2</td>

 Retinopathy

 Neuropathy

 ABI <0.9</td>

ABI indicates ankle-brachial index.

Table 6. ASCVD Risk Enhancers (1)

Family history of premature ASCVD Persistently elevated LDL > 160mg/dl (>4.1mmol/L Chronic kidney disease* Metabolic syndrome** History of preeclampsia History of premature menopause Inflammatory disease (especially rheumatoid arthritis, psoriasis, HIV) Ethnicity (e.g., South Asian ancestry) Persistently elevated triglycerides > 175mg/dl (>2.0mmol/L) Hs-CRP > 2mg/L Lp(a) > 50mg/dl or >125nmol/L Apo B > 130mg/dl Ankle-brachial index (ABI) < 0.9

*Chronic kidney disease definition- eGFR 15–59 mL/min/1.73 m2 with or without albuminuria.

**Metabolic syndrome definition- increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis).

Other factors that can increase the risk of ASCVD include social deprivation, physical inactivity, psychosocial stress, major psychiatric disorders, obstructive sleep apnea syndrome, and metabolic associated fatty liver disease (38).

PRIMARY PREVENTION PATIENT WITHOUT OTHER FACTORS

6) Initiation of primary prevention should begin with a clinician-patient risk discussion.

This discussion is necessary to put a patient's total risk status in perspective. The risk discussion should always begin with a review of the critical importance of lifestyle intervention. This is true for all age groups. Beyond the issue of lifestyle, the discussion can further consider the potential benefit of a cholesterollowering drug, especially statin therapy. When the latter may be beneficial, the provider should next review major risk factors and estimated 10-year risk for ASCVD derived from the pooled cohort equation (PCE) risk calculator (49) (https://tools.acc.org/ASCVD-Risk-Estimator-

Plus/#!/calculate/estimate/). Estimation of lifetime risk is also useful, particularly in younger individuals who often have a low 10-year risk but a high lifetime risk. All major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated]), should be discussed. In patients 40-75 years, the 10-year risk estimate is most useful. In these patients, four categories of 10year risk for ASCVD are recognized: low risk (<5%); borderline risk (5-7.4%); intermediate risk (7.5-19.9 %), and high risk (\geq 20%). Estimates of lifetime risk for patients 20-39 years also are available (https://www.acc.org/guidelines/hubs/blood-

<u>cholesterol</u> or <u>https://qrisk.org/lifetime/index.php)</u> and should be obtained in younger individuals. Three other components of the risk discussion are: risk enhancing factors (see #8), possible measurement of coronary artery calcium (CAC) (see #9), and a review of extenuating life circumstances (issues of cost and safety considerations, as well as patient motivation and preferences). The decision to initiate statin therapy should be shared between the clinician and patient. All of these factors deserve a full discussion in view of the fact that statin therapy represents a lifetime commitment to taking a cholesterol-lowering drug.

Patients should also recognize that atherosclerosis begins early in life and progresses overtime before manifesting as clinical disease. The cumulative LDL-C levels ("LDL-C years") strongly influence the timing of clinical manifestations (figure 4). In patients with high LDL-C levels (homozygous and heterozygous familial hypercholesterolemia) ASCVD can occur early in life whereas in patients with loss of function mutations in PCSK9 and low LDL-C level have a reduced occurrence of ASCVD.



Figure 4. Relationship between cumulative LDL-C exposure, age, and the development of the clinical manifestations of ASCVD. Figure from reference (50).

patients should be appraised of Additionally, comparisons of the reduction in ASCVD events in individuals with genetic variations resulting in life-long reductions in LDL-C levels vs. individuals treated with statins to lower LDL-C later in life. Variants in the HMG-CoA reductase, NPC1L1, PCSK9, ATP citrate lyase, and LDL receptor genes result in a lifelong decrease in LDL-C and a 10mg/dL decrease in LDL-C with any of these genetic variants was associated with a 16-18% decrease in ASCVD events (51). As noted above, a 39mg/dL decrease in LDL-C in the statin trials resulted in a 22% decrease in ASCVD events. Thus, a life-long decrease in LDL-C levels results in a decrease in ASCVD events that is three to four times as great as that seen with short-term LDL-C lowering with drugs later in life suggesting that the sooner the LDL-C level is lowered the better the prevention of cardiovascular events.

7) In adults 40 to 75 years of age without diabetes and LDL-C ≥70 mg/dL (≥1.8 mmol/L), RTC's show that moderate intensity statin therapy is efficacious when 10-year risk for developing ASCVD is ≥ 7.5%. Therefore, initiating statin therapy should be considered in the risk discussion.

A 10-year risk \geq 7.5% does not mandate statin therapy but indicates that moderate-intensity statins can reduce risk by 30-40% with a minimum of side effects (52). This fact alone can justify moderate intensity statin therapy, but only if other considerations noted above (#6) are taken into account in the risk discussion. An approach to lipid lowering in primary prevention patients is shown in figure 5.



Figure 5. Approach to Primary Prevention in Patients without LDL-C >190mg/dl or Diabetes (1).

 Determine presence of risk-enhancing factors in adults 40 to 75 years of age to inform the decision regarding initiation of statin therapy.

If risk assessment based on PCE is equivocal or ambiguous, the presence of risk enhancing factors in patients at intermediate risk (10-year risk 7.5 to 19.9%), can tip the balance in favor of statin therapy. Risk enhancing factors are shown in Table 6.

9) IF A DECISION ABOUT STATIN THERAPY IS UNCERTAIN IN ADULTS 40 TO 75 YEARS OF AGE WITHOUT DIABETES MELLITUS, WITH LDL-C LEVELS ≥ 70 MG/DL, AND WITH A 10 YEAR ASCVD RISK OF ≥ 7.5% TO 19.9% (INTERMEDIATE RISK) CONSIDER MEASURING Coronary Artery Calcium (CAC).

CAC measurements are a safe and inexpensive method to assess severity of coronary atherosclerosis. CAC scores generally reflect lifetime exposure to coronary risk factors and therefore in young individuals (men < 40 years of age; women < 50 years of age) the long-term predictive value is limited because the CAC score is often 0. Studies show that CAC accumulation is a strong predictor of probability of ASCVD events (53). A CAC core of zero generally is accompanied by few if any ASCVD events over the subsequent decade. Reevaluation in 5-10 years is indicated. A CAC score of 1-100 Agatston units is associated with relatively low rates of ASCVD, both in middle-aged and older patients. In contrast, a CAC >100 Agatston units carries a risk well into the statinbenefit zone. CAC > 300-400 is equivalent to clinical ASCVD. Data such as these led to the following recommendation of 2018 guidelines for patients at intermediate risk by PCE.

a. If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, those with a strong family history of premature ASCVD, and possibly chronic inflammatory conditions such as HIV.

b. A CAC score of 1 to 99 Agatston units favors statin therapy in intermediate-risk patients \geq 55 years of age, whereas benefit in 40-54 years is marginal (note this focuses on 10-year risk and a CAC score in this range in a younger individual is predictive of an increased long-term risk (54)).

c. A CAC score ≥100 Agatston units (or ≥75th percentile), strongly favors statin therapy, unless otherwise countermanded by clinician–patient risk discussion.

Monitoring

10) Assess adherence and percentage response to LDL-C lowering medications and/or lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment and every 3-12 months as needed.

Remember that the LDL-C goal for patients with ASCVD or severe hypercholesterolemia is a \geq 50% reduction in LDL-C. For most such patients, this goal can be achieved by high-intensity statin therapy <u>+</u> ezetimibe. In ASCVD patients at very high risk, the goal is an LDL-C lowering >50% and an LDL-C < 70 mg/dL. To achieve these goals, it may be necessary to combine a PCSK9 inhibitor with maximal statin

therapy <u>+</u> ezetimibe. For statin therapy in primary prevention, the goal is a lowering of \geq 35%. This goal can be achieved in most patients with a moderate intensity statin <u>+</u> ezetimibe

2018 guidelines did not set a precise on-treatment LDL-C target of therapy, but instead, offer percent reductions as goals of therapy. Baseline levels of LDL-C can be obtained either by chart review or withholding statin therapy for about two weeks. In addition, ontreatment LDL-C can provide useful information about efficacy of treatment (Figure 6). This figure shows expected LDL-C levels for 50% or 35% reductions at different baseline levels of LDL-C. For example, in secondary prevention, an on-treatment LDL-C of <70 mg/dL can be considered adequate treatment regardless of baseline LDL-C. On-treatment levels in the range of 70-100 mg/dL are adequate if baseline-LDL C is known to be in the range of 140- 200 mg/dL; if there is uncertainty about baseline levels, reevaluation of statin adherence and reinforcement of treatment regimen is needed. For optimal treatment, on-treatment levels in this range warrant consideration of adding ezetimibe to maximal statin therapy. If on treatment LDL-C is > 100 mg/dL, the treatment regimen is probably inadequate, and intensification of therapy is needed. For primary prevention, the LDL-C goal is a reduction > 35%, and a similar scheme for evaluating efficacy of therapy can be used.

Secondary	Secondary Prevention: Goal \geq 50% \downarrow LDL-C				ntion: Goal≥3	5% ↓LDL-C
Baseline LDL	-C On-Rx LDL-C	Action		Baseline LDL-C	Predicted On-Rx LDL-C	Action
100 mg/dL 120 mg/dL 140 mg/dL	50 mg/dL 60 mg/dL 70 mg/dL	Good-to-go		100 mg/dL 120 mg/dL 140 mg/dL	65 mg/dL 80 mg/dL 90 mg/dL	Good-to-go
160 mg/dL 180 mg/dL 200 mg/dL	80 mg/dL 90 mg/dL 100 mg/dL	Reevaluate, reinforce, and consider ezetimibe		160 mg/dL 180 mg/dL 200 mg/dL	105 mg/dL 115 mg/dL 130 mg/dL	Reevaluate, reinforce, and consider ezetimibe
≥ 200 mg/dL	. ≥ 100 mg/dL	Probably insufficient treatment		≥ 200 mg/dL	≥ 130 mg/dL	Probably insufficient treatment

Figure 6. Predicted on-treatment LDL-C compared to baseline LDL-C and suggested actions for each category of on-treatment LDL-C in secondary and primary prevention.

Other Issues

OTHER AGE GROUPS

2018 guidelines offered suggestions for management of high blood cholesterol in children, adolescents, young adults (20-39 years), and elderly patients > 75 years. There is no strong RCT evidence to underline cholesterol management in these populations. Instead, treatment suggestions depend largely on epidemiologic data. Lifestyle intervention is a primary method for cholesterol treatment in these age groups. However, under certain circumstances LDL-lowering drugs may be indicated. This is particularly the case for patients with familial hypercholesterolemia or similar forms of very high LDL-C. In young adults, particularly those with other risk factors, LDL lowering drug therapy (statin or ezetimibe) may be reasonable when LDL-C levels are in the range of 160-189 mg/dL or if the lifetime risk is high. Older adults who have concomitant risk factors are potential candidates for initiation of stating or continuation of existing statin

therapy. In all cases, clinical estimation of risk status is critical in a decision to initiate statins.

For details on the approach to treating hypercholesterolemia in older adults see the Endotext chapter entitled "Management of Dyslipidemia in the Elderly" (55). For details on the approach to treating hypercholesterolemia children and adolescence see the Endotext section on Pediatric Lipidology.

STATIN NON-ADHERENCE

In spite of proven benefit of statin therapy in high-risk patients, there is a relatively high prevalence of nonadherence to the prescribed drug (56). Some studies suggest that up to 50% of patients discontinue use of prescribed statins over the long run (57-60). This finding creates a major challenge to the health care system for prevention of ASCVD. Table 7 lists several factors that may contribute to a high prevalence of nonadherence.

Table 7. Factors Associated with Statin Nonadherence
Healthcare system factors
Accompanying medical care costs
Lack of medical oversight and follow-up (provider therapeutic inertia)
Provider concern for side effects
Patient factors
Uncertainty of benefit
Lack of health consciousness
Lack of motivation
Lack of perceived benefit
Perceived side effects
Nocebo effects
Myalgias
Myopathy
"Brain fog"
Misattributed symptoms or syndromes (arthritis, spondylosis, neuropathy, insomnia,
mental confusion and memory loss, fibromyalgia, gastrointestinal symptoms, liver
dysfunction, cataract; cancer).

When a decision is made to initiate statin therapy, the presumption is that statins are a lifetime treatment. Their use is similar to other medications, such as antihypertensive drugs, which are expected to be taken for the rest of one's life. Such treatments imply indefinite participation in the healthcare system. This means regular ongoing visits to a prescribing clinic. Even for those with medical insurance there are usually co-pays for the visit, not to mention the cost of transportation to and from the clinic. All of these cost-related issues can be an impediment to long-term statin usage. Provider therapeutic inertia (56) can result from lack of provider education, excessive workload, and concerns about statin side effects.

From the patient's point of view, common issues are lack of understanding of the potential benefits of therapy and lack of health consciousness and motivation. A related problem is the expectation of side effects because of preconditioning by information received from the news media, package inserts, Internet, family, and friends. This expectation can discourage individuals from continuation of statin therapy (nocebo effect) (61). The most common symptoms attributed to statin therapy are muscle pain and tenderness (myalgias) (8). A complaint of statin intolerance is registered in about 5-15% of patients. If myalgias attributed to statins are due to actual pathological changes, the character of the changes is yet to be determined. In almost all cases, serum creatine kinase (CK) levels are not increased. Still, in rare cases, especially when blood levels of statins are raised, severe myopathy (rhabdomyolysis) can occur. This proves that statins can be myotoxic. Table 8 lists conditions associated with statin-induced severe myopathy (62,63). In most such cases, severe myopathy is reversible. If the cause can be identified and eliminated, a statin can be cautiously reinstituted. Alternatively, a non-statin LDL-lowering drug (e.g., ezetimibe, bempedoic acid, or PCSK9 inhibitor) can be substituted for the offending statin (8,64). For a detailed discussion of statin side effects and the management of patients with statin intolerance see the Endotext chapter on cholesterol lowering drugs (8).

Table 8. Factors Associated with Statin - Induced Rhabdomyolysis					
Advanced age (>80 y)					
Small body frame and fragility					
Female sex					
Asian ethnicity					
Pre-existing neuromuscular condition					
Known history of myopathy or family history of myopathy syndrome					
Pre-existing liver disease, kidney disease, hypothyroidism					
Certain rare genetic polymorphisms					
High-dose statin					
Postoperative periods					
Excessive alcohol intake					
Drug interactions (gemfibrozil, antipsychotics, amiodarone, verapamil, cyclosporine, macrolide					
antibiotics, azole antifungals, protease inhibitors)					

EUROPEAN GUIDELINES FOR CHOLESTEROL MANAGEMENT

The most influential of European guidelines for management of cholesterol and dyslipidemia are

those developed by the European Society of Cardiology (ESC), the European Atherosclerosis Society (EAS), and representatives from other European organizations (65). A task force appointed by these organizations have published an update on dyslipidemia management (38). The recommendations of this report resemble in many ways those of the 2018 AHA/ACC guidelines (1). But notable differences can be identified for specific recommendations. A review of these differences may help to identify gaps in knowledge needed to format best recommendations. In the following, recommendations proposed by AHA/ACC and by ESC/EAS will be compared. These comparisons should illuminate areas of uncertainty where more information is needed for definitive recommendations. At the same time, it is important to emphasize that in many critical areas the two sets of guidelines are in strong agreement. These will be noted first.

Agreement Between AHA/ACC and ESC/EAS Guidelines

There is agreement that elevated LDL-C is the major atherogenic lipoprotein and that LDL-C is the primary target of treatment. Likewise, both guidelines agree that the intensity of LDL-C lowering therapy should depend on absolute risk to patients. In other words, patients who have the highest risk should receive the most intensive cholesterol reduction. Both guidelines emphasize therapeutic lifestyle intervention as the foundation of risk reduction, both for elevated cholesterol and for other risk factors. The highest risk patients are those with ASCVD and are potential candidates for combined drug therapy for LDL-C lowering. For primary prevention, the intensity of treatment depends on absolute risk as determined by population-based algorithms. For drug therapy, statins are first-line treatment, but in highest risk

patients, consideration can be given to adding nonstatin drugs (e.g., ezetimibe and PCSK9 inhibitors). Beyond population-based algorithms for primary prevention, measurement of other dyslipidemia markers, or other higher risk conditions can be used as risk- enhancing factors to modify intensity of lipidlowering therapy.

Differences Between AHA/ACC and ESC/EAS Guidelines

DEFINITION OF VERY HIGH RISK

This definition is important because it sets the stage for considering intensive LDL-C lowering and the use of combined drug therapy for LDL-C lowering. AHA/ACC defines very high risk as a history of multiple ASCVD events or of one event + multiple high-risk conditions. This limits the definition of very high risk to the highest risk patients among those with ASCVD. In contrast, ESC/EAS considers all patients with clinical ASCVD or ASCVD on imaging as very high risk. Additionally, ESC/EAS allows extension of the definition to highest risk patients in primary prevention, that is, to patients with multiple risk factors and/or subclinical atherosclerosis (table 9). Overall, more patients will be identified as being at very high risk by ESC/EAS guidelines. This could enlarge the usage of PCSK9 inhibitors. AHA/ACC limits the use of PCSK9 inhibitors to patients at highest risk, because of their high cost. One recent study (43) showed that only about 10% of patients with established ASCVD will be eligible for PCSK9 inhibitors by AHA/ACC recommendations.

Table	9. ESC/EAS Cardiovascular Risk Categories
Very H	ligh-Risk
\triangleright	ASCVD, either clinical or unequivocal on imaging
\triangleright	DM with target organ damage or at least three major risk factors or T1DM of long
	duration (>20 years)
\triangleright	Severe CKD (eGFR <30 mL/min/1.73 m2)
\succ	A calculated SCORE >10% for 10-year risk of fatal CVD.
\triangleright	FH with ASCVD or with another major risk factor
High-	Risk
\triangleright	Markedly elevated single risk factors, in particular Total Cholesterol >8 mmol/L
	(>310mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP >180/110 mmHg.
\triangleright	Patients with FH without other major risk factors.
\triangleright	Patients with DM without target organ damage, with DM duration > 10 years or another
	additional risk factor.
\succ	Moderate CKD (eGFR 30-59 mL/min/1.73 m2).
\succ	A calculated SCORE >5% and <10% for 10-year risk of fatal CVD.
Mode	rate Risk
\triangleright	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without
	other risk factors.
\succ	Calculated SCORE >1 % and <5% for 10-year risk of fatal CVD*.
Low R	lisk
\triangleright	Calculated SCORE <1% for 10-year risk of fatal CVD

SCORE= Systematic Coronary Risk Estimation. * Total CVD event risk is approximately three times higher than the risk of fatal CVD.

GOALS FOR LDL-C

In 2013, the AHA/ACC eliminated specific numerical goals for LDL-C in both primary and secondary prevention. Recommendations for LDL-C lowering therapy were based exclusively on RCTs of statin therapy. These recommendations have been criticized for lacking a means to evaluate the efficacy of statin therapy. In 2018, AHA/ACC identified 2 goals for LDL-C lowering, namely, \geq 50% LDL-C reduction in secondary prevention and \geq 35% reduction in primary prevention. These values are based on the expected reductions achieved by high-intensity statins for secondary prevention and by moderate-intensity statins for primary prevention. Again, no numerical targets are identified. The only exception was the recognition of an LDL-C threshold goal of 1.8 mmol/L

(70 mg/dL) for consideration of PCSK9 inhibitors in very high-risk patients on maximal statin therapy + ezetimibe.

ESC/EAS supports the 50% reduction of LDL-C in high-risk patients but also includes a goal of <1.8 mmol/L (70 mg/dL) (table 10). This goal applies to all high-risk patients, whether in primary or secondary prevention. For very high-risk patients, the goal is an LDL-C of < 1.4 mmol/L (55 mg/dL). For moderate-risk patients in primary prevention, the goal is LDL-C <2.6 mmol/L (100 mg/dL). The guideline task force presumably believed that having defined LDL-C goals facilitates cholesterol-lowering therapy in clinical practice. Additionally, following the ESC/EAS LDL-C goals will most likely result in lower LDL-C levels in many patients.

Table 10. ESC/EAS LDL Cholesterol Goals					
Very High Risk	LDL-C reduction of >50% from baseline and an LDL-C goal of <1.4 mmol/L (<55				
	mg/dL) is recommended				
High Risk	LDL-C reduction of >50% from baseline and an LDL-C goal of <1.8 mmol/L (<70				
	mg/dL) is recommended				
Moderate Risk	LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered				
Low Risk	LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.				

In patients with ASCVD who experience a second vascular event within 2 years while on maximally tolerated statin therapy an LDL-C goal of < 1mMol/L (40mg/dL) may be considered.

In addition, the ESC/EAS also provided goals for non-HDL-C and apolipoprotein B (table 11).

Table 11. ESC/EAS Goals of Therapy					
	Non-HDL-C Apo B				
Very High Risk	<85mg/d;	<65mg/dL			
High Risk	<100mg/dL	<80mg/dL			
Moderate Risk	<130mg/dL	<100mg/dL			

Figure 7 provides an overview of the ESC/EAS recommended treatment based on risk and baseline LDL-C levels.

	Total CV risk	Untreated LDL-C levels						
	(SCORE) %	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)	
Primary prevention	<1, low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention	
	Class*/Levelb	VC	I/C	I/C	VC	IIa/A	IIa/A	
	≥1 to <5, or moderate risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention	
	Class ^a /Level ^b	VC	I/C	IIa/A	Ila/A	Ila/A	Ila/A	
	≥5 to <10, or high-risk (see Table 4)	Lifestyle advice	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	
	Class ^a /Level ^b	Ila/A	IIa/A	Ila/A	I/A	I/A	I/A	
	≥10, or at very-high risk due to a risk condi- tion (see Table 4)	Lifestyle advice	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	
	Class*/Levelb	IIa/B	IIa/A	I/A	I/A	I/A	I/A	
Secondary prevention	Very-high-risk	Lifestyle inter- vention, con- sider adding drug if uncontrolled	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and con- comitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	Lifestyle inter- vention and concomitant drug intervention	
	Class*/Levelb	Ila/A	I/A	I/A	VA	VA	I/A	

Figure 7. ESC/EAS treatment recommendations based on risk and baseline LDL-C levels.

RISK ESTIMATION FOR PRIMARY PREVENTION

AHA/ACC employed a pooled cohort equation (PCE) developed from five large population groups in the USA to estimate 10-year risk (and lifetime risk) for ASCVD events. ESC/EAS for several years has employed a SCORE algorithm based on risk for ASCVD **mortality** in European populations. Both PCE and SCORE are used to define "statin eligibility" for primary prevention. A study suggests that more people are "eligible" for statin therapy using PCE compared to SCORE (66). If this finding can be confirmed, it suggests that ESC/EAS guidelines are less aggressive for reducing LDL-C in lower risk individuals (compared to AHA/ACC guidelines). In contrast, ESC/EAS appears to be more aggressive in

use of non-statins for LDL lowering in higher risk patients than is AHA/ACC.

RISK ENHANCING FACTORS

AHA/ACC proposed that several risk enhancing factors favor the decision to use statin therapy in patients at intermediate risk. The European guidelines provide a similar list of factors that should be considered in determining risk and modifying the SCORE result. Notable among risk enhancing factors were apolipoprotein B (apoB) and lipoprotein (a) (Lp[a]).

SUBCLINICAL ATHEROSCLEROSIS

AHA/ACC propose that CAC measurement can assist in deciding whether to use statin therapy in patients at intermediate risk. AHA/ACC in particular noted that the absence of CAC justifies delaying statin therapy. No other modalities of measurement of subclinical atherosclerosis were advocated by AHA/ACC. In contrast, ESC/EAS supported use of both CAC and carotid or femoral plaque burden on ultrasonography to determine risk. These guidelines suggest that the finding of substantial subclinical atherosclerosis in any arterial bed elevates a patient's risk to the category of established ASCVD and can justify adding non-statin therapy to statins in such patients.

GUIDELINE SPECIFICITY

AHA/ACC guidelines place great emphasis on data from RCTs to justify its recommendations. However, RTC's related to specific questions typically are limited in number. AHA/ACC recommendations are highly codified and kept to a minimum. ESC/EAS in contrast bases its recommendations both on clinical trials and other types of evidence. It explores available evidence in greater detail, and many of its recommendations are more nuanced. This approach to guideline development has its advantages and disadvantages. For example, it gives the reader a broader base of information to assist in clinical decisions. On the other hand, many of its recommendations are made outside of an RCT-evidence base. Without doubt, cholesterol management in all age and gender groups with various risk factor profiles is complex. The ESC/EAS attempts to provide a rationale for management of this complexity. The AHA/ACC, on the other hand, simplifies management as much as possible; it is written specifically for the general practitioner, and leaves the complexities of management to a lipid specialist. ESC/EAS delves into the complexities in more detail so that its recommendations are applicable to both the general practitioner and specialist.

IMPORTANT CHANGES SINCE THESE GUIDELINES WERE PUBLISHED Risk Calculators

PREVENT RISK CACULATOR

In the US there is a new risk calculator called PREVENT (67). The PREVENT risk calculator is based on a much larger and more contemporary sample than the pooled cohort equation (PCE) risk calculator (68). Prevent is based on data from more than 6 million individuals from 46 datasets, including both population research studies and health system electronic medical records. In contrast, PCE was derived from approximately 25,000 individuals from 5 research datasets.

There are several notable differences between the PREVENT and PCE risk calculators.

1) PREVENT calculates risk in patients age 30-79 whereas PCE calculates risk in patients age 40-75. 2) The PCE calculator uses age, gender, white or African American, total cholesterol, HDL-C, systolic BP, whether on treatment for BP, whether diabetic, and whether smoker as the variables to calculate risk. PREVENT uses age, gender, total cholesterol, HDL-C, systolic BP, BMI, eGFR, whether on BP or lipid lowering medications (i.e., statins), whether diabetic, and whether a current smoker to calculate risk. In addition, PREVENT allows for the use of optional variables, HbA1c, urine albumin/creatinine ratio, and Zip Code (for estimating social deprivation index) for further personalization of risk assessment. Note that PREVENT does not use race or ethnicity but does include variables related to glucose metabolism, renal disease, and obesity and can be used in patients taking statins .

3) The main result for the PCE calculator is the 10-year risk of cardiovascular disease. The main result of the PREVENT calculator is both the 10-year and 30-year risk (if <60 years of age) of cardiovascular disease, ASCVD only, and heart failure only.

It should be noted that fewer patients will be identified as eligible for statin therapy using the PREVENT calculator compared to the PCE calculator. A study found that 18.8% of patients eligible for statin therapy using the PCE calculator would not be identified using the PREVENT calculator (69). Another study found that using the PREVENT calculator would reclassify approximately half of US adults to lower risk categories compared to the PCE calculator (70). Additionally, studies have shown that the mean estimated 10-year ASCVD risk is approximately 50% lower with the PREVENT calculator compared to the PCE calculator (71,72).

The current recommendations for treatment were based on the PCE risk estimates and thus, there are concerns that using the PREVENT calculator may result in not treating as many patients. New AHA/ACC guidelines are being developed, and it is possible that the new recommendations will be adjusted to compensate for the differences in the risk calculated using the PCE and PREVENT calculators. Some experts recommend using the PCE calculator when deciding on treatment if one is following the current AHA/ACC guidelines.

SCORE2 RISK CALCULATOR

The SCORE risk calculator was developed in 2003 to determine the 10-year cardiovascular mortality in healthy individuals (73). In 2021 SCORE was replaced by SCORE2, which updated the risk prediction algorithms and in instead of determining cardiovascular mortality determines cardiovascular disease which includes cardiovascular mortality and non-fatal myocardial function and stroke endpoints (74). The prediction model in SCORE2 was based on 45 cohorts with 677,684 individuals from 13 countries. In addition, SCORE2-OP estimates cardiovascular risk in individuals greater than 70 years of age or older and SCORE2-Diabetes estimates cardiovascular risk with type 2 diabetes in patients (75,76)(https://www.escardio.org/Education/ESC-

<u>Prevention-of-CVD-Programme/Risk-</u> assessment/esc-cvd-risk-calculation-app)

The variables used in SCORE2 to calculate risk are age (40-69), sex, smoking, systolic BP, total cholesterol, HDL-C, and whether they live in a low, moderate, high, or very high-risk region (see below). SCORE2 provides an estimate of the 10-year risk of cardiovascular disease. Low-risk countries: Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the United Kingdom (UK). Moderate-risk countries: Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden. High-risk countries: Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey. Very high-risk countries: Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine, and Uzbekistan.

In individuals 70 years of age or older one should use the SCORE2-OP calculator and for individuals with type 2 diabetes one should use the SCORE2-Diabetes calculator. SCORE2-OP uses the same variables as SCORE2, but SCORE2-Diabetes includes HbA1c, age at diagnosis of diabetes, and eGFR. Both provide an estimate of the 10-year risk of cardiovascular disease.

In conjunction with the development of SCORE2 the European Society of Cardiology developed guidelines for healthy individuals (77). The conversion of 10-year risk to CVD risk categories for healthy individuals is shown in Table 12 and LDL-C goals for these CVD risk categories are shown in table 13. Note that the use of very high risk and high risk is not equivalent to the use of these terms in the ESC/EAS lipid guidelines discussed above.

Table 12. Cardiovascular Disease Risk Categories Based on SCORE2 and SCORE2-OP in Healthy Individuals						
	<50 years	50–69	≥70 years			
		years				
Low-to-moderate CVD risk: risk factor treatment	<2.5%	<5%	<7.5%			
generally not recommended						
High CVD risk: risk factor treatment should be	2.5 to <7.5%	5 to <10%	7.5 to <15%			
considered						
Very high CVD risk: risk factor treatment	≥7.5%	≥10%	≥15%			
generally recommended						

Table 13. LDL-C Goal Less Than 100mg/dL							
Age	Low-to-moderate CVD risk	High CVD risk	Very high CVD risk				
< 50	Usually not indicated	Consider	Recommended				
50-69	Usually not indicated	Consider	Recommended				
>70	Usually not indicated	Consider	Recommended				

In all age groups, consideration of risk modifiers, lifetime CVD risk, treatment benefit, comorbidities, frailty, and patient preferences may further guide treatment decisions.

KEY PRINCIPLES

There are certain key principles that clinicians should utilize when deciding who to treat and how aggressively to treat hypercholesterolemia. Understanding these principles will allow clinicians to help their patients decide on the best approach to LDL-C lowering.

The Sooner the Better

It is widely recognized that atherosclerosis begins early in life and slowly progresses ultimately resulting in clinical manifestations later in life (78). Several studies have demonstrated the presence of atherosclerosis in young individuals (79-83). The extent of the atherosclerotic lesions correlates positively with total cholesterol and LDL-C and negatively with HDL-C levels (79,80,83-90). These studies clearly demonstrate that atherosclerosis begins early in life with the prevalence increasing with age and the extent and onset of lesions is influenced by total cholesterol and LDL-C levels. Moreover, an increased total cholesterol early in life also predicted an increased risk of developing cardiovascular disease later in life (91-93).

Genetic studies have further illustrated the key role of exposure to total cholesterol and LDL-C in determining the time when clinical manifestations of ASCVD occur. In patients with homozygous familial hypercholesterolemia (FH), LDL-C are markedly elevated, and cardiovascular events can occur early in life. Greater than 50% of untreated patients with homozygous FH develop clinically significant ASCVD by the age of 30 and cardiovascular events can occur before age 10 in some patients (45). In patients with heterozygous FH LDL-C levels are elevated but not to the levels seen with homozygous FH and cardiovascular events occur later in life but still at a relatively younger age. Untreated males with heterozygous FH have a 50% risk for a fatal or nonfatal myocardial infarction by 50 years of age whereas untreated females have a 30% chance by age 60 (45). Conversely, individuals with genetic variants in PCSK9, HMG-CoA reductase, LDL receptor, NPC1L1, or ATP citrate lyase that lead to a decrease in LDL-C levels have а reduced risk of developing cardiovascular events (50,51). The relationship between genetic disorders that alter LDL-C levels and the time to develop clinical cardiovascular events is illustrated in figure 4. The figure clearly illustrates that

the age when one clinically manifests ASCVD depends on the level of LDL-C. With very high LDL-C levels clinical events occur early in life and with low LDL-C levels events will occur at an older age leading to the concept of LDL years.

Of major importance is that the reduction in ASCVD events is much greater in individuals with lifelong decreases in LDL-C compared to the reductions in ASCVD events seen with statin treatment (Table 14). A lifelong 10mg/dL decrease in LDL-C due to polymorphisms in genes that affect LDL-C is associated with a 16-18% decrease in ASCVD events (51). In contrast, a decrease in LDL-C of 39mg/dL over 4-5 years with statin therapy results in only a 22% decrease in ASCVD events (6,9). Thus, a life-long decrease in LDL-C levels results in a decrease in cardiovascular events that is three to four times as great as that seen with short-term LDL-C lowering with drugs. Figure 8 illustrates the benefits of early treatment in reducing LDL-C years and delaying the development of ASCVD.

Table 14. Effect of Reduction in LDL-C by Genetic Variants on the Risk of ASCVD			
Gene	Odds ratio for ASCVD events per 10mg/dL decrease in LDL-C		
	(95% CI)		
ATP citrate lyase	0.82 (0.78–0.87)		
HMG CoA reductase	0.84 (0.82–0.87)		
NPC1L1	0.84 (0.79–0.89)		
PCSK9	0.83 (0.80–0.87)		
LDL receptor	0.83 (0.80–0.87)		

Statin treatment decreases ASCVD by approximately 22% per 39mg/dL decrease in LDL-C.



Figure 8. The effect of early lowering of LDL-C on the development of ASCVD.

In addition to calculating the 10-year risk of ASCVD events it is important to calculate either the lifetime or 30-year risk. This is particularly important in younger

individuals where the 10-year risk of ASCVD events may be relatively low, but the long-term risk may be high. In the discussion of therapy with patients they need to be aware of their long-term risk and the potential advantages of early treatment.

Lowering LDL-C levels by lifestyle changes early in life will have long-term benefits. Additionally, in selected individuals initiating drug therapy sooner rather than latter will reduce ASCVD events later in life.

The Lower the Better

A variety of different types of studies have clearly demonstrated that more robust lowering of LDL-C results in an increased decrease in ASCVD events.

- Statin trials have demonstrated that ASCVD events are decreased even in patients with low LDL-C levels (10). In patients with an LDL-C less than 70mg/dL, statin treatment resulted in a 37% decrease in ASCVD events despite the patients having a low LDL-C.
- Intensive statin therapy results in a greater decrease in LDL-C levels compared to moderate statin therapy. Moreover, intensive therapy also results in a greater decrease in ASCVD events (10).
- Adding ezetimibe to statin therapy resulted in a lower LDL-C than statin therapy alone and furthermore decreased ASCVD events (16).
- Adding a PCSK9 inhibitor to statin therapy decreases LDL-C levels and results in a greater reduction in ASCVD events than statins alone (19,20).

Taken together these studies clearly demonstrate that the lower the LDL-C level the greater the decrease in ASCVD events. However, there may be a threshold where further lowering of LDL-C does not result in further benefits. In the ODYSSEY trial using the PCSK9 inhibitor alirocumab, the decrease in ASCVD events was similar in patients with an LDL-C less than 25mg/dL and those with an LDL-C between 25-50mg/dL (94). Future studies are required to define if there is a threshold where further LDL-C lowering is not beneficial.

Clinicians need to balance the benefits of more aggressively lowering LDL-C levels with the risks and costs of high dose or additional drug therapy. Both statins and ezetimibe are generic drugs and very inexpensive. Thus, in many patients the use of the combination of a statin (either high intensity or moderate intensity) and ezetimibe will maximize the decrease in LDL-C and more effectively reduce ASCVD events, with minimal risk and at low cost. In contrast, PCSK9 inhibitors and bempedoic acid are relatively expensive and clinicians will need to balance the benefits and the increased costs.

The Higher the LDL-C the Greater the Benefit

The percent decrease in LDL-C levels that occurs with statin treatment or the use of other LDL-C lowering drugs is similar regardless of the baseline LDL-C level. However, the absolute decrease in LDL-C will be greater if the starting LDL-C is higher. As discussed earlier. the Cholesterol Treatment Trialists demonstrated that the relative risk reduction in cardiovascular events per 39mg/dL (1mmol/L) decrease in LDL-C is similar in patients with a low or high baseline LDL-C level. Thus, as shown in table 15 the treatment of patients with high baseline LDL-C levels will result in greater decreases in ASCVD events. A meta-analysis of 34 trials with 270,288 individuals found that LDL-C lowering was associated with a progressively greater relative risk reduction in ASCVD events in patients with increased baseline LDL-C levels (95).

Table 15. The Higher the Baseline LDL-C the Greater the Reduction in ASCVD			
Baseline LDL-C 80mg/dL	Baseline LDL-C 160mg/dL		
Atorvastatin 80mg reduces LDL-C by 50% to	Atorvastatin 80mg reduces LDL-C by 50% to		
40mg/dl (40mg/dL decrease)	80mg/dl (80mg/dL decrease)		
A 40mg/dL decrease in LDL-C will result in	An 80mg/dL decrease in LDL-C will result in		
an approximate 22% decrease in ASCVD	an approximate 44% decrease in ASCVD		
events	events		

The Greater the Risk of ASCVD the Greater the Benefit

Analysis by the Cholesterol Treatment Trialists found that the relative risk reduction was similar regardless of the underlying ASCVD risk (9). However, the absolute risk reduction was much greater in patients with a high risk of ASCVD (table 16) (9). Additionally, studies have shown that in patients with a high polygenic risk score for ASCVD events statin therapy reduces ASCVD events to a greater extent again indicating the higher the risk the greater the benefit of lowering LDL-C (96,97).

Table 16. Risk of Cardiovascular Events in High and Low Risk Patients			
5-year event	Relative Risk (CI) per 39mg/dL reduction in	Absolute Decrease in Events	
risk	LDL-C	per Annum*	
<10%	0.68 (0.62-0.74)	0.3%	
10-20%	0.79 (0.75-0.84)	0.5%	
20-30%	0.81 (0.78-0.85	1.1%	
>30%	0.79 (0.75-0.83	2.2%	

*Percent of patients on placebo having an event minus percent of patients on statin therapy having an event. Data from Cholesterol Treatment Trialists (9).

In the IMPROVE-IT trial lowering LDL-C with ezetimibe and the ODYSSEY and FOURIER trials using PCSK9 inhibitors a greater reduction in ASCVD

events was observed in high risk patients (see reference (98) for discussion of these studies). Table 17 provides a list of indicators of high risk.

Table 17. High Risk Indicators for ASCVD Events Diabetes Atherosclerosis in multiple sites (peripheral arterial disease, cerebral vascular disease, coronary arteries) History of prior coronary artery bypass graft surgery Acute coronary syndrome Multiple MIs Recent ASCVD events Genetic lipid disorders High polygenic risk score

Following these general principles will help clinicians make informed decisions in deciding on their approach to lowering LDL-C levels and will facilitate discussions with patients on the benefits and risks of treatment. For an in-depth discussion of these key principles see the following references (98,99).

SUMMARY

Advances in the drug therapy of elevated cholesterol levels offer great potential for reducing both new-onset ASCVD and recurrent ASCVD events in those with established disease. This benefit can be enhanced by judicious use of lifestyle intervention. But among drugs, statins are first-line therapy. They are generally safe and inexpensive. They have been shown to reduce ASCVD events in both secondary and primary prevention. Ezetimibe has about half the LDL-lowering efficacy of statins; it too is generally safe and is a relatively inexpensive genetic drug. Ezetimibe can be used as an add-on drug to moderate intensity statins, especially for those who do not tolerate a highintensity statin or in combination with high intensity statins to markedly decrease LDL-C levels. PCSK9 inhibitors are powerful LDL-lowering drugs, and they appear to be safe. The major drawback is cost. If the cost of these inhibitors can be reduced, they too have

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the potential for wide usage, especially in patients who are "statin intolerant". Bempedoic acid has been shown to reduce ASCVD events in statin intolerant patients and in combination with ezetimibe can result in significant decreases in LDL-C levels. A major challenge for use of cholesterol-lowering drugs is the problem of long-term non-adherence.

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