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HOW TO manage blood cholesterol in primary and secondary prevention.

Dr Konstantinos Koskinas answers key questions on this topic

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Introduction

Low-density lipoprotein cholesterol (LDL-C) is causal of atherosclerotic cardiovascular disease, the leading cause of morbidity and mortality worldwide. Pharmacologic LDL-C lowering halts the progression of atherosclerosis and improves clinical outcomes in primary as well as secondary prevention. This article summarizes current recommendations on how to manage LDL-C levels in individuals with or without known cardiovascular disease, including recommendations on which patients should be considered for pharmacologic treatment, how low LDL-C should be lowered, and which drugs or drug combinations should be used to attain treatment goals.

Key questions

1. Why is lowering LCL-cholesterol important for cardiovascular risk reduction?

Despite major advances in understanding the pathophysiology of atherosclerosis and despite substantial progress in diagnostic and treatment modalities, atherosclerotic cardiovascular disease (ASCVD) is still the leading cause of mortality worldwide and remains a major health and economic burden to society. ASCVD is a multifactorial process regulated by a complex interplay between several risk factors including diabetes, smoking, high blood pressure and plasma levels of low-density lipoprotein cholesterol (LDL-C). The totality of evidence from preclinical investigations, genetic studies, epidemiologic cohort studies, Mendelian randomization studies, and randomized trials of LDL-C-lowering medications unequivocally supports the causal role of LDL-C in the pathogenesis of ASCVD.[1,2] These studies have consistently shown a dose-dependent, log-linear association between the absolute magnitude of exposure to LDL-C and the risk of ASCVD. Conversely, lowering plasma LDL-C reduces the risk of ASCVD events proportional to the absolute reduction in LDL-C.[2] According to meta-analyses of randomized trials of LDL-C-lowering medications, the greater the LDL-C reduction, the greater the reduction in the risk of major cardiovascular (CV) events.[3,4]

2. Which are the main LDL-C-lowering medications?

i. Statins. Statins reduce synthesis of cholesterol by hepatocytes via inhibition of the HMG-CoA reductase. The reduction in intracellular cholesterol increases the expression of LDL-receptors on hepatocytes, thereby increasing the uptake of LDL-C from the blood. The magnitude of LDL-C lowering varies among available statins and is dose-dependent. A reduction up to 45% can be achieved with potent statins at high doses.[5]

In 1994, the Scandinavian Simvastatin Survival Study (4S) showed that simvastatin reduced total mortality by 30% and major coronary events by 34% compared with placebo in 4,444 patients with coronary heart disease.[6] This landmark trial paved the road to further statin trials. A meta-analysis of 26 statin trials including more than 170,000 patients in primary as well as secondary prevention showed a 10% proportional reduction in all-cause mortality, 20% reduction in coronary artery disease death, 23% reduction in major coronary events, and 17% reduction in stroke per 1.0 mmol/L (40 mg/dL) reduction in LDL-C.[7] These results were consistent in both genders and across patient subgroups. Importantly, there was no increased risk for any non-CV cause of death in statin-treated patients. The *relative* risk reduction in relation to the magnitude of LDL-C lowering is similar in the context of primary or secondary prevention[8]; in primary-prevention subjects, however, the *absolute* risk reduction with statins is lower due to the lower baseline risk. In addition, statins have been shown to slow the progression or even enable regression of coronary atherosclerosis according to serial intravascular ultrasound studies.[9]

ii. Ezetimibe. Ezetimibe inhibits dietary cholesterol absorption in the intestine by targeting the Niemann-Pick C1-like 1 protein. In a meta-analysis of randomized controlled trials, ezetimibe monotherapy reduced LDL-C levels by about 19%.[10] The incremental reduction in LDL-C by ezetimibe when combined with statin amounts

to about 24%.[11] In the IMPROVE-IT trial including >18,000 patients with recent acute coronary syndrome, combination therapy of ezetimibe and simvastatin resulted in significant reduction in the primary study endpoint compared with simvastatin monotherapy.[11] Moreover, the addition of ezetimibe to atorvastatin resulted in greater coronary plaque regression compared with atorvastatin alone in a serial intravascular ultrasound study.[12]

iii. PCSK9 inhibitors. The proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease enzyme, reduces the expression of LDL receptors by promoting lysosomal catabolism, thereby increasing plasma LDL-C concentration. Following the observation that individuals with loss-of-function mutations of the PCSK9 have lower levels of LDL-C and lower incidence of coronary heart disease, whereas gain-of-function mutations are a cause of familial hypercholesterolemia, therapeutic strategies have been developed targeting the PCSK9.[13] Currently, two fully human monoclonal antibodies are clinically available, evolocumab and alirocumab. They result in 50-60% reductions in LDL-C levels, either as monotherapy or on top of statin, across various patient populations. According to two large outcomes trials, these medications resulted in significant reductions in cardiovascular morbidity (15% relative risk reduction) among statin-treated patients with established ASCVD.[14,15] Notably, incremental clinical benefit – without any safety signals – was observed even at very low on-treatment levels of LDL-C with these medications (substantially lower than those achieved with statins).[16]

3. Which patients should receive LDL-C-lowering medications?

According to current (2016) European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias,5 the indication for LDL-lowering drugs is determined by two factors: (i.) LDL-C levels and (ii.) total CV risk in each individual. CV risk can be quantified by means of several risk assessment tools; among these, the ESC advocates the use of the SCORE as it is derived from large, representative European cohort datasets. Based on the SCORE and/or presence of other risk conditions (e.g., diabetes or chronic kidney disease), four risk categories are defined, as summarized in the figure below.

Very high risk • Documented ASCVD: clinical or unequivocal on imaging • Diabetes with target organ damage *(such as proteinuria)* or with a major risk factor *(such as smoking, hypertension or dyslipidaemia)* • Severe chronic kidney disease *(GFR <30mL/min/1.73m²)* • SCORE ≥10%
High risk • Markedly elevated single risk factors, such as total cholesterol >8 mmol/L (e.g. in familial hypercholesterolemia) or blood pressure >180/110mmHg • Most other people with DM • Moderate chronic kidney disease *(GFR 30-59mL/min/1.73m²)* • SCORE ≥5% and <10%
Moderate risk • SCORE ≥1 and <5%
Low risk • SCORE <1%

Adapted from Catapano AL, et al. Eur Heart J 2016;37:2999-3058 (reference #5).

The figure below summarizes intervention strategies for LDL-C management as a function of total CV risk and LDL-C levels according to the 2016 ESC/EAS guidelines.[5] Lifestyle interventions (nutrition; body weight reduction if applicable; physical activity) generally represent the first-line intervention. Lipid-modifying drugs on top of lifestyle interventions are recommended for selected persons in **primary prevention** (i.e.

without known ASCVD) and for essentially all patients in **secondary prevention** (i.e. patients with known ASCVD).

	CV RISK	INTERVENTION STRATEGY	
Primary prevention	Low	LDL-C >**4.9 mmol/l**: Lifestyle intervention → Consider drug if LDL-C uncontrolled	
	Moderate	LDL-C >**2.6 mmol/l**: Lifestyle intervention → Consider drug if LDL-C uncontrolled	
	High	LDL-C **1.8 to <2.6 mmol/l**: Lifestyle intervention → Consider drug if LDL-C uncontrolled	LDL-C **≥2.6 mmol/l**: Lifestyle intervention and concomitant drug intervention
Primary or secondary prevention	Very high	LDL-C **<1.8 mmol/l** Lifestyle intervention → Consider drug if LDL-C uncontrolled	LDL-C **≥1.8 mmol/l**: Lifestyle intervention and concomitant drug intervention

Adapted from Catapano AL, et al. Eur Heart J 2016;37:2999-3058 (reference #5).

Briefly, in primary prevention, drug treatment is to be considered in individuals at low or moderate high CV risk if LDL-C levels are ≥4.9 mmol/l or ≥2.6 mmol/l, respectively, and are uncontrolled despite lifestyle interventions. For individuals at high CV risk, drug treatment is to be considered if LDL-C levels are ≥1.8 mmol/l despite lifestyle interventions, and is recommended if LDL-C levels are ≥2.6 mmol/l. For individuals in primary prevention at very high risk, drug treatment is recommended in the presence of LDL-C levels ≥1.8 mmol/l.

By definition, all patients with known ASCVD are classified in the very high risk category. Thereby, in the context of secondary prevention, drug treatment is recommended for all patients with LDL-C ≥1.8mmol/l, and is to be considered even at lower LDL-C levels.

4. How low should LDL-C levels be lowered?

Current European guidelines[5] recommend the use of treatment targets, which are dependent on each individual's total CV risk level. In other words, instead of a "one-size-fits-all" regimen that would not consider the achieved (on-treatment) LDL-C levels, this target-oriented approach advocates a tailored treatment with adjustment of drug dose (or with a combination of drugs, if applicable), aiming to reach a certain LDL-C goal in each patient. Advantages of this approach include a more specific, individualized treatment for LDL-C-lowering and CV risk reduction (also accounting for substantial inter-individual variability in treatment response to LDL-C lowering drugs); better patient–physician communication; and possibly better adherence to recommended treatment. Treatment goals are defined for each CV risk category, as summarized in the table below:

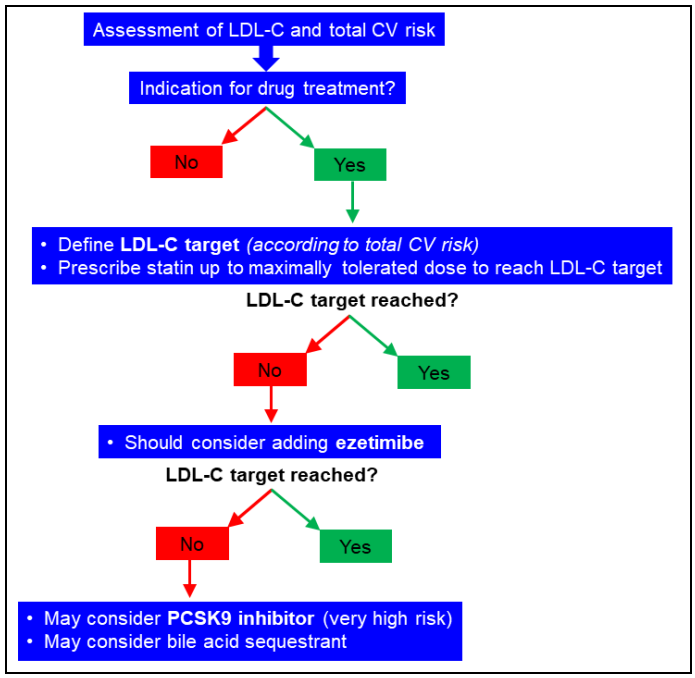
CV RISK CATEGORY	LDL-C GOAL
Very high risk	LDL-C goal **<1.8 mmol/L**, or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L
High risk	LDL-C goal **<2.6 mmol/L**, or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.2 mmol/L
Low / moderate risk	LDL-C goal **<3.0 mmol/L** should be considered

Adapted from Catapano AL, et al. Eur Heart J 2016;37:2999-3058 (reference #5).

5. How can LDL-C targets be achieved?

Statins represent the first-line treatment for LDL-C lowering, in view of the extensive evidence regarding their clinical efficacy and safety. Statins should be given up to the highest tolerable dose in order to reach the LDL-C goal for any given individual.

While recommended goals are attained with statin monotherapy in many patients, a significant proportion of high-risk or very-high risk patients require additional treatment. This can be either due to very high baseline (untreated) LDL-C levels, or because higher statin doses cannot be tolerated. In these cases, ezetimibe should be considered as second-line drug in the context of combination therapy with a statin. In case the LDL-C goal is still not reached, the addition of a bile acid sequestrant may be considered. In very high-risk patients with high LDL-C despite treatment with maximal tolerated statin plus ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor may be considered according to current ESC/EAS guidelines.[5] The proposed algorithm is summarized in the figure below.



The content of this article reflects the personal opinion of the author/s and is not necessarily the official position of the European Society of Cardiology.

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