Council for Cardiology Practice

What is new in the “2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias”

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The 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias strongly confirms the LDL-C targets and risk categories proposed in the 2019 Guidelines and better refines cardiovascular risk using SCORE2 and SCORE2-OP and “risk modifiers”, also suggesting early intervention on LDL-C in post-ACS. Statin as first choice, and other lipid lowering drugs with proven cardiovascular benefit including Ezetimibe, PCSK9i and bempedoic acid, are recommended to lower LDL-C levels and reduce the risk of CV events.

Topic(s):
Lipids
DYSLIPIDAEMIA. DEDICATED TO SCOTT GRUNDY, A PIONEER IN LIPIDOLOGY

Take-home messages

1. LDL-C targets remain the same as in the 2019 Guidelines.
2. SCORE2 and SCORE2-OP are now recommended for calculating cardiovascular risk.
3. Risk modifiers have been incorporated into the 2025 update in order to refine clinical assessment.
4. Statins are the first choice as lipid-lowering drug treatment. Non-statin therapies are recommended when patient statin tolerance thresholds are in danger of being exceeded or the LDL-C goals are not reached with statins alone.
5. Lipid-lowering therapies are advised at post-ACS index hospitalisations.
6. Statins are recommended for use in patients with HIV and patients at risk of cancer therapy-related CV toxicity.
7. Dietary supplements or vitamins are not indicated for reducing LDL-C.

Introduction

The Focused Update Guidelines on dyslipidaemia [1] complement the publication of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular (CV) risk [2], with new scientific acquisitions and alignment with the most recent ESC Guidelines on risk calculation (using Systematic COronary Risk Evaluation-2 [SCORE2] and SCORE2-Older Persons [SCORE2-OP] for apparently healthy people ≥70 years of age, instead of the SCORE algorithm for apparently healthy persons in primary prevention) [3].

The recommendation for using SCORE2 and SCORE2-OP in risk calculation

The recommended use of SCORE2 and SCORE2-OP changes the perspective of CV prevention, further supporting preventive strategies, focusing on: a) 10-year fatal and non-fatal CV disease risk in apparently healthy people <70 years and ≥70 years of age, respectively, without established atherosclerotic CV disease (ASCVD), diabetes mellitus, chronic kidney disease, genetic/rare lipid or blood pressure (BP) disorders, and b) prevention in the older adult population.

Low density lipoprotein cholesterol (LDL-C) as a major determinant of ASCVD and therapeutic target according to risk categories

A major point of this Focused Update remains the strength which identifies LDL-C and other apolipoprotein B-containing lipoproteins as the causal factor for ASCVD according to the following statements endorsed by the Focused Update:

The total burden of ASCVD is described by both CV morbidity (non-fatal myocardial infarction [MI] and non-fatal stroke) and mortality. The SCORE2 and SCORE2-OP algorithms consider the risk for MI, ischaemic stroke, or fatal atherosclerotic CV events over the next 10 years, calibrated on the national CVD mortality rates in various countries (different risk charts are used for low, moderate, high, and very high CVD risk countries), and are proposed in this Focused Update, already having been endorsed by the latest ESC Guidelines on CVD prevention [3]. Since it is estimated that the risk of total CVD events is 2–3 times higher than the risk of fatal CVD events, in this Focused Update, a 2x multiplier was used to convert previous SCORE-based thresholds into the SCORE2- or SCORE2-OP-based thresholds to define different categories of total CVD risk (for primary prevention, in apparently healthy individuals the threshold for very high risk is a calculated SCORE2 or SCORE2-OP ≥20% for a 10-year risk of fatal or non-fatal CVD; the high risk range is a SCORE2 or SCORE2-OP ≥10% and <20%; the moderate risk range is a SCORE2 or SCORE2-OP ≥2% and <10%; and low risk is defined as a SCORE2 or SCORE2-OP <2%). It is underlined that these algorithms should not be used to estimate risk among persons with existing ASCVD or among persons currently on lipid-lowering therapy; they should not be used to “re-assess” risk using lipid measurements obtained after initiating guideline-recommended lipid-lowering therapy.

To better refine the assessment of CV risk in patients without known ACVSD and without history of any of the diseases used to define the categories of “very high”, “high”, “moderate” and “low” CV risk (diabetes, chronic kidney disease, familial hypercholesterolaemia [FH]), and to refine the risk estimation based on the SCORE2 and SCORE2-OP algorithms, a few “modifier” risk factors have been incorporated into this update, in order to upgrade the level of risk in patients at moderate risk or individuals around treatment decision thresholds presenting the following listed conditions (IIa,B).

Risk modifiers

Demographic / clinical conditions

- Family history of premature CVD (men <55 years; women <60 years)
- High-risk (e.g., Southern Asian) ethnicity
- Stress symptoms and psychosocial stressors
- Social deprivation
- Obesity
- Physical inactivity
- Chronic immune-mediated / inflammatory disorder
- Major psychiatric disorders
- History of premature menopause
- Pre-eclampsia or other hypertensive disorders of pregnancy
- Human immunodeficiency virus

- Obstructive sleep apnoea syndrome

Biomarkers

- Persistently elevated high-sensitivity C-reactive protein (hs-CRP; >2 mg/L)
- Elevated Lp(a) (>50 mg/dL or > 105 nmol/L)

In addition, the presence of subclinical coronary atherosclerosis detected by imaging or increased coronary artery calcium (CAC) score by computed tomography are considered risk modifiers and should be used to improve risk classification in individuals at moderate risk (IIa,B).

Two main sections of this update which bring substantial changes with a major impact on clinical practice are the new recommendations on new low-density lipoprotein cholesterol-lowering therapies and the use of lipid-lowering combination therapies during index hospitalisation for acute coronary syndromes.

Recommendations on LDL-C-lowering therapies, including two new agents for LDL-C-lowering treatment (bempedoic acid and, specifically for patients with familial hypercholesterolaemia, evinacumab)

As a main strategy, the recommendations are to add non-statin therapies with proven cardiovascular benefit, taken alone or in combination, to lower LDL-C if LDL-C goals are not achieved with the maximum tolerated dose of a statin (approach confirmed with respect to the 2019 guidelines).

Bempedoic acid, an oral small molecule that inhibits cholesterol synthesis upstream of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase pathway, has been added to the therapeutic options to reduce LDL-C, complementing the recommendations for pharmacological LDL-C lowering with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 [PCSK9] monoclonal antibodies of the 2019 full Guidelines document (see Dr Dimitri Richter's focus on bempedoic acid in this month's edition of CardioPractice). Of note, the table showing recommendations for pharmacological low-density lipoprotein cholesterol lowering complements the analogous table in the 2019 ESC/EAS Guidelines and does not replace it.

A recommendation (Class IIa, LOE B) for the use of evinacumab has been added for patients with homozygous FH aged 5 years or older who are not meeting LDL-C goals despite receiving maximum doses of lipid-lowering therapy to lower LDL-C levels [4].

Recommendations for lipid-lowering therapy during index hospitalisation of acute coronary syndrome (ACS)

The recommendations in this Focused Update for lipid-lowering therapy during index hospitalisation of ACS represent a major change in the strategic approach to the early treatment of dyslipidaemias after an acute coronary event and are major new indications for clinical practice.

In the last few years, evidence for the need to introduce an appropriate lipid-lowering therapy soon after ACS is increasing [5,6].

The complication rates are higher soon after ACS, with the highest risk for thrombotic complications and cardiac death in the first weeks/months following hospital admission [7-11].

Recent data showed positive coronary plaque size and composition changes after acute and very intensive LDL-C reduction post ACS [12,13].

It is reasonable that lipid-lowering treatment should be started as early as possible, to affect LDL-C at the moment of maximum risk [7-11], avoiding an unnecessary delay in reaching LDL-C targets. Immediate initiation of high-intensity statin therapy and combination treatment with one or more classes of non-statin therapy with proven CV benefit is needed, with the choice of drugs based on the magnitude of LDL-C lowering required.

Two very important clinical recommendations of this Focused Update are:

- It is recommended to appropriately intensify lipid-lowering therapy during the index ACS hospitalisation for patients who were on any lipid-lowering therapy before admission. The choice should be based on the magnitude of additional LDL-C lowering needed to achieve the LDL-C goal. (I,C)
- For patients who present with ACS and were lipid-lowering therapy naive, initiating combination therapy with high-intensity statin plus ezetimibe during index hospitalisation should be considered when the LDL-C goal is not expected to be achieved with statin therapy alone. (IIa, B)

Lp(a) and Hypertrigliceridaemias as additional risk factors

To refine the risk assessment, since Lp(a) concentration is predominantly determined by genetics (and depends also on ethnicity), a recommendation (IIa, B) is to consider Lp(a) measurement at least once in each adult's lifetime. Lp(a) should be considered clinically significant above 50 mg/dL (IIa, B), levels that are included in the list of "risk-modifying" biomarkers, which means for example that high Lp(a) levels in a "moderate risk" patient place the patient in the "high risk" category.

However, despite industry targeting Lp(a), it has not yet been demonstrated whether Lp(a) reduction reduces the risk of ASCVD.

As for the treatment of hypertriglyceridaemia, a clear indication from this Update is to recommend statins as the first drug of choice to reduce CVD risk in high-risk patients, confirming the 2019 Guidelines.

For patients with severe hypertriglyceridaemia (>750 mg/dL, >8.5 mmol/L) due to familial chylomicronaemia syndrome, treatment with volanesorsen (300 mg/week), an antisense oligonucleotide targeting hepatic apolipoprotein C-III (ApoC-III) messenger RNA that lowers plasma levels of ApoC-III, triglycerides, and chylomicrons, approved by the European Medicines Agency, should be considered to lower triglyceride levels and reduce the risk of pancreatitis (IIa, B).

Although the reasons for controversial results are not clear, the update presents a new recommendation following the STRENGTH trial and REDUCE-IT trial [14,15]: in high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride level: 135–499 mg/dL or 1.52–5.63 mmol/L) despite statin treatment, high-dose icosapent ethyl (2x2 g/day) should be considered in combination with a statin (IIa, B).

However, the update underlines that statins are the first choice of treatment in hypertriglyceridaemia and that LDL-C reduction is the main objective of treatment in high-risk or very high-risk patients.

Recommendations for statin therapy in primary CV disease prevention in two specific settings: persons with human immunodeficiency virus (HIV) and patients with cancer at high or very high risk of developing cancer therapy-related cardiovascular toxicity

The Focused Update brings new indications on the basis of new evidence favouring the use of statins in HIV [16] and in patients who may develop cancer therapy-related CV toxicity [17,18], as already indicated by the 2022 ESC Guidelines on cardio-oncology [19]:

HIV: For people in primary prevention aged ≥40 years with HIV, statin therapy is recommended irrespective of estimated cardiovascular risk and LDL-C levels; the choice of statin should be based on potential drug–drug interactions (I,B).

Cancer: Statins should be considered for primary prevention in adult patients at high or very high risk of developing chemotherapy-related cardiovascular toxicity due to anthracycline-based therapy (IIa,B).

Dietary supplements or vitamins are not indicated for reducing low density lipoprotein cholesterol (LDL-C)

According to the available evidence, the Focused Update does not support the use of dietary supplements or vitamins for reducing LDL-C levels and lowering the risk of ASCVD. Recommendation: there is no indication for dietary supplements or vitamins to reduce LDL-C and lower the risk of ASCVD (III,B).

Risk calculation: the use of SCORE2/SCORE2-OP instead of the SCORE algorithm for apparently healthy persons in primary prevention. Using SCORE2/SCORE2-OP instead of SCORE used for CV risk disease calculation shows a stronger focus on: a) early prevention (the score defines the risk for both fatal and non-fatal CV events), and b) CV prevention in older adults (giving information on risk in apparently healthy subjects ≥70 years of age).

The risk scores SCORE2 and SCORE2-OP consider the risk for MI, ischaemic stroke, or fatal atherosclerotic CV event over the next 10 years, calibrated on the national CVD mortality rates in the various countries: very high risk: a calculated SCORE2 or SCORE2-OP ≥20% for 10-year risk of fatal or non-fatal CVD; high risk: SCORE2 or SCORE2-OP ≥10% and <20%; moderate risk: SCORE2 or SCORE2-OP ≥2% and <10%; low risk: SCORE2 or SCORE2-OP <2%. SCORE2-OP is recommended in apparently healthy people ≥70 years of age without established ASCVD, DM, CKD, genetic/rare lipid or BP disorders for estimation of 10-year fatal and non-fatal CVD risk.

Recommendations on LDL-C-lowering therapies include two new agents for LDL-C-lowering treatment (bempedoic acid, and evinacumab specifically for patients with homozygous familial hypercholesterolaemia)

Bempedoic acid option included in the therapeutic choices: the update recommends non-statin therapies with proven cardiovascular benefit, such as ezetimibe, or PCSK9 mAb, or bempedoic acid, taken alone or in combination, to lower LDL-C if the LDL-C goals are not achieved with the maximum tolerated dose of a statin.

Recommendations for early and intense (not a step-wise approach) lipid-lowering therapy during index hospitalisation of acute coronary syndrome

- *The choice should be based on the magnitude of additional LDL-C lowering needed to achieve the LDL-C goal, if already on treatment.*
- *For lowering therapy-naïve patients, initiating combination therapy with high-intensity statin plus ezetimibe during index hospitalisation should be considered when the LDL-C goal is not expected to be achieved with statin therapy alone*

Lp(a) and Hypertrigliceridaemias as additional risk factors

- *For patients with severe hypertriglyceridaemia (>750 mg/dL, >8.5 mmol/L) due to familial chylomicronaemia syndrome, treatment with volanesorsen (an antisense oligonucleotide targeting hepatic ApoC-III) should be considered to lower triglyceride levels and reduce the risk of pancreatitis.*
- *In high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride level 135–499 mg/dL or 1.52–5.63 mmol/L) despite statin treatment, high-dose icosapent ethyl (2x2 g/day) should be considered in combination with a statin.*

Recommendations for statin therapy in primary CV disease prevention in two specific settings, irrespective of the LDL-C levels:

Risk calculation: the use of SCORE2/SCORE2-OP instead of the SCORE algorithm for apparently healthy persons in primary prevention. Using SCORE2/SCORE2-OP instead of SCORE used for CV risk disease calculation shows a stronger focus on: a) early prevention (the score defines the risk for both fatal and non-fatal CV events), and b) CV prevention in older adults (giving information on risk in apparently healthy subjects ≥70 years of age).

- **persons with HIV infection**
- **patients with cancer at high or very high risk of developing cancer therapy-related cardiovascular toxicity**

Dietary supplements or vitamins are not indicated for reducing LDL-C and lowering the risk for ASCVD.

Despite an extensive section in the 2019 Guidelines, the available updated evidence does not support the use of dietary supplements/vitamins.

LDL-C are a major determinant of ASCVD and therapeutic target according to "risk categories"

- LDL-C as well as other apolipoprotein B (apoB)-containing lipoproteins are not only a risk factor for ASCVD, but a direct cause of ASCVD
- In clinical practice, the concentration of circulating LDL-C accumulated within the artery wall leading to overt ASCVD is estimated by measuring plasma levels of LDL-C
- Lowering LDL-C plasma levels should be the main focus for preventing atherosclerotic CV events
- The clinical benefit of lowering LDL-C depends on the achieved LDL-C reduction and intervention should be guided by the baseline levels of LDL-C and by the individual's CV risk; the "CV risk categories" are superimposed on the corresponding previous table of the 2019 guidelines, with the exception of the introduction of SCORE2 or SCORE2-OP instead of SCORE
- LDL-C treatment goals in each CV risk category have not changed from the 2019 Guidelines
- As a main strategy, non-statin therapies with proven cardiovascular benefit, taken alone or in combination, are recommended to lower LDL-C if the LDL-C goals are not achieved with the maximum tolerated dose of a statin (approach confirmed with respect to the 2019 Guidelines).

The "CV risk categories" are superimposed on the corresponding previous table of the 2019 guidelines, with the exception of the introduction of SCORE2 or SCORE2-OP instead of SCORE.

Risk modifiers (conditions that should be used to improve the risk classification in moderate risk or around the treatment thresholds) are similar to those indicated in the 2019 guidelines. Lp(a) and hypertrigliceridaemias are considered additional risk factors.

LDL-C are a major determinant of ASCVD and therapeutic target according to "risk categories"
In the update are better focused biomarkers (hs-CRP [>2 mg/L], elevated Lp(a) [>50 mg/dL or >105 nmol/L]) and subclinical atherosclerotic coronary disease; atrial fibrillation, left ventricular hypertrophy, and chronic kidney disease are not included in the updated list.
As for the treatment of hypertriglyceridaemia a clear indication from this update is to recommend statins as the first drug of choice to reduce CVD risk in high-risk patients, confirming the 2019 Guidelines.

Table 1. Indications confirmed with respect to the 2019 Guidelines on Dyslipidaemias.

hs-CRP: high-sensitivity C-reactive protein

Table 2. New indications compared to the 2019 Guidelines on Dyslipidaemias.

ApoC-III: apolipoprotein C-III; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; DM: diabetes mellitus; HIV: human immunodeficiency virus; LDL-C: low-density lipoprotein-C; PCSK9 mAb: proprotein convertase subtilisin-kexin type 9 monoclonal antibody; SCORE2: systematic coronary risk evaluation-2; SCORE2-OP: systematic coronary risk evaluation-2-older persons