

















# 2025 Focused Update of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias

Developed by the task force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

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**Patient Forum**

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## Keywords

Guidelines • Dyslipidaemia • Lipid-lowering drugs • Low-density lipoproteins • Lipoprotein(a) • Hypertriglyceridaemia • Cardiovascular risk • Familial hypercholesterolaemia • Acute coronary syndromes

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## Abbreviations and acronyms

ACS	Acute coronary syndromes
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ApoC-III	Apolipoprotein C-III
ART	Antiretroviral therapy
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AVS	Aortic valve stenosis
CAC	Coronary artery calcium
CI	Confidence interval
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease

DHA	Docosahexaenoic acid
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
FCS	Familial chylomicronaemia syndrome
FDA	US Food and Drug Administration
FH	Familial hypercholesterolaemia
HDL	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HR	Hazard ratio
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein(a)
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event(s)
MI	Myocardial infarction
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PPAR	Peroxisome proliferator-activated receptor
PUFA	n-3 polyunsaturated fatty acid
PWH	People with HIV
SCORE2	Systematic Coronary Risk Evaluation 2
SCORE2-OP	Systematic Coronary Risk Evaluation 2-Older Persons
TC	Total cholesterol
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal

## 1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. The European Society of Cardiology (ESC) Guidelines are intended for use by health professionals but do not override their individual responsibility to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with the patient or the patient's caregiver where appropriate and/or necessary aiming at shared care decisions. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription and to respect the ethical rules of their profession.

The ESC Guidelines represent the official position of the ESC on a given topic. Guideline topics are selected for updating after annual expert review of new evidence conducted by the ESC Clinical Practice Guidelines (CPG) Committee. ESC Policies and Procedures for formulating and issuing the ESC Guidelines can be found on the ESC website (<https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines>).

Interim Focused Updates are created when the publication of new evidence could influence clinical practice before the next full update of a Guideline is published. This Focused Update provides new and revised recommendations for the 2019 ESC/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias. View the full 2019 ESC/EAS Guidelines here: <https://doi.org/10.1093/eurheartj/ehz455>. This Task Force was selected by the ESC and EAS to include professionals involved with the medical care of patients with this pathology as well as methodologists.

Guidelines Task Forces perform a critical review and evaluation of the published literature on diagnostic and therapeutic approaches including assessment of the risk–benefit ratio. Recommendations are based on major randomized trials and relevant systematic reviews and meta-analyses, when available. Systematic literature searches are conducted in cases of controversy or uncertainty to ensure that all key studies were considered. For recommendations related to diagnosis and prognosis, additional types of evidence are included, such as diagnostic accuracy studies and studies focused on the

development and validation of prognostic models. The strength of each recommendation and the level of evidence supporting it are weighed and scored according to predefined criteria as outlined in [Tables 1](#) and [2](#). Patient-Reported Outcome Measures (PROMs) and Patient-Reported Experience Measures (PREMs) are also evaluated when available as the basis for recommendations and/or discussion in these Guidelines.

Evidence tables summarizing key information from relevant studies are generated to facilitate the formulation of recommendations, to

**Table 1** Classes of recommendations

	Definition	Wording to use	
Classes of recommendations	<b>Class I</b>	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
	<b>Class II</b>	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
	Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
	Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
	<b>Class III</b>	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

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**Table 2** Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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enhance comprehension of recommendations after publication, and to reinforce transparency in the Guidelines development process. The tables are published in their own section of the Focused Update and reference specific recommendation tables.

After an iterative process of deliberations, a first Task Force vote on all recommendations is conducted prior to the initiation of rounds of review. A second Task Force vote on all recommendations is conducted after the final round of review and revision. For each vote, the Task Force follows ESC voting procedures and all recommendations require at least 75% agreement among voting members to be approved. Voting restrictions may be applied based on declarations of interests.

The writing and reviewing panels provide declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest are reviewed according to the ESC declaration of interest rules which can be found on the ESC website (<http://www.escardio.org/doi>) and are compiled in a report published in a supplementary document with the Guidelines. Funding for the development of this ESC/EAS Focused Update was derived entirely from the ESC and EAS with no involvement of the healthcare industry.

The ESC CPG Committee supervises and co-ordinates the preparation of new Guidelines and Focused Updates and approves their publication. In addition to review by the ESC CPG Committee, this ESC/EAS Focused Update underwent multiple rounds of peer review on a dedicated online review platform. The review was conducted by topic experts, including members from ESC National Cardiac Societies and from relevant ESC Subspecialty Communities. The Focused Update Task Force considered all review comments and was required to respond to all those classified as major. After appropriate revisions, the Task Force and the ESC CPG Committee members and the EAS Executive Committee approved the final document for publication in the *European Heart Journal* and in *Atherosclerosis*.

Unless otherwise stated, the Focused Update content refers to sex, understood as the biological condition of being male or female, defined by genes, hormones and sexual organs. Off-label use of medication may be presented in this Focused Update if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition. However, decisions on off-label use must be made by the responsible health professional giving special consideration to ethical rules concerning healthcare, the specific situation of the patient, patient consent, and country-specific health regulations.

## 2. Introduction

Since the publication of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular (CV) risk,<sup>1</sup> there have been several randomized controlled trials that might change patient management ahead of the next scheduled full dyslipidaemia Guidelines. This 2025 Focused Update addresses changes in recommendations for the treatment of dyslipidaemias based on new evidence published up until 31 March 2025. All major randomized controlled clinical trials and meta-analyses published after the publication of the 2019 ESC/EAS Guidelines were presented and discussed in detail before a consensus was reached about any possible classes of recommendations (see [Table 1](#)) and levels of evidence (see [Table 2](#)) to be assigned; these were then voted upon for inclusion by all Task Force members. Members with declared conflicts of interests in specific topics were asked to abstain from voting on those topics.

The Task Force considered and discussed the following new studies, trials, and any meta-analyses: Systematic Coronary Risk Evaluation 2 (SCORE2)

and Systematic Coronary Risk Evaluation 2-Older Persons (SCORE2-OP) for estimation of 10 year CV risk;<sup>2,3</sup> CLEAR Outcomes [Cholesterol Lowering via Bempedoic Acid, an ACL (adenosine triphosphate-citrate lyase)-Inhibiting Regimen];<sup>4</sup> ELIPSE HoFH (Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia);<sup>5</sup> APPROACH (Reduction of Triglyceride Levels in Familial Chylomicronemia Syndrome);<sup>6</sup> REPRIEVE (Pitavastatin to Prevent Cardiovascular Disease in HIV Infection);<sup>7</sup> STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia);<sup>8</sup> STOP-CA (Atorvastatin for Anthracycline-Associated Cardiac Dysfunction);<sup>9</sup> SPORT (Supplements, Placebo, or Rosuvastatin Study);<sup>10</sup> and OMEMI (Omega-3 Fatty acids in Elderly with Myocardial Infarction).<sup>11</sup> Beside these trials, the Task Force also considered and discussed: combination therapy with high-dose statin plus ezetimibe and intensification of lipid-lowering therapy during the index hospitalization for patients presenting with acute coronary syndromes (ACS), as well as new data on lipoprotein(a) [Lp(a)] as a risk modifier.

Only results that would lead to new or changed Class I/IIa or Class III recommendations were selected for inclusion in Recommendation Tables. All new recommendations included in this Focused Update are additive to the recommendations of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias, and all changed recommendations substitute those of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias.

After due deliberation, the Task Force decided to update recommendations for the following sections of the 2019 ESC/EAS Guidelines for the management of dyslipidaemias:

- Recommendations for CV risk estimation, with implementation of the new SCORE2 and SCORE2-OP risk prediction algorithms.
- Recommendations on low-density lipoprotein cholesterol (LDL-C)-lowering therapies, including two new agents for LDL-C-lowering treatment (bempedoic acid and evinacumab specifically for patients with homozygous familial hypercholesterolaemia)(FH).
- Recommendations for lipid-lowering therapy during index hospitalization of ACS.
- Recommendations on Lp(a).
- Recommendations for drug treatment in patients with hypertriglyceridaemia.
- Recommendations for statin therapy in primary CV disease (CVD) prevention for people with human immunodeficiency virus (HIV) infection.
- Recommendations for statin therapy for patients with cancer at high or very high chemotherapy-related CV toxicity risk.
- Recommendations for dietary supplements.

## 3. Estimation of total cardiovascular risk and implications for dyslipidaemia management

Atherosclerosis is caused by the progressive deposition of LDL-C and other apolipoprotein-B (ApoB)-containing lipoproteins within the artery wall, which triggers a cascade of inflammatory reactions leading to the formation and progression of atherosclerotic plaque. As more atherogenic lipoproteins become accumulated within the arterial wall over time, the atherosclerotic plaque gradually enlarges and the risk of having an acute atherosclerotic CV event increases. LDL-C is not only a risk factor for atherosclerotic CV disease (ASCVD), but like other ApoB-containing lipoproteins is a direct cause of ASCVD;<sup>12</sup>

therefore, lowering plasma LDL-C levels should be the main focus for preventing atherosclerotic CV events.

In clinical practice, the concentration of circulating LDL-C that can become trapped within the artery wall is estimated by measuring plasma levels of LDL-C, which represent the total amount of cholesterol carried by low-density lipoproteins. The objective of estimating a person's risk of having an atherosclerotic CV event is to identify individuals at elevated risk who may benefit from interventions to lower LDL-C and other modifiable causes of ASCVD. The clinical benefit of lowering LDL-C depends on the achieved LDL-C reduction; therefore, individuals with higher CV risk require more intense LDL-C lowering to achieve the same absolute level of residual CV risk while on treatment as compared with individuals with lower risk. For example, assuming an average 20% proportional (relative) reduction in risk per each mmol/L lower LDL-C,<sup>13</sup> lowering LDL-C by 1 mmol/L (38.67 mg/dL) would reduce the risk of a person with a 20% absolute risk of having an acute atherosclerotic CV event to 16% (i.e. a 20% relative but 4% absolute risk reduction), whereas it would reduce the risk of a person with a 10% absolute risk to 8% (a 20% relative but 2% absolute risk reduction). This Focused Update continues to endorse the concept supported in the 2019 ESC/EAS Guidelines<sup>1</sup> that a person's estimated absolute risk of having an acute CV event should be used to guide the intensity of LDL-C lowering. We also acknowledge that the CV risk reduction achievable by a similar magnitude of lowering atherogenic lipid levels appears to be greater at younger ages.<sup>14,15</sup>

Numerous randomized trials have demonstrated that lowering LDL-C reduces the risk of both fatal and non-fatal myocardial infarctions (MI) and ischaemic strokes<sup>13</sup> as well as ischaemic events in

peripheral arterial territories.<sup>16</sup> Therefore, because CVD morbidity (non-fatal MI and non-fatal stroke) combined with CVD mortality better reflects the total burden of ASCVD, and in line with the current 2021 ESC Guidelines on CVD prevention,<sup>17</sup> this Focused Update endorses the use of risk scores such as SCORE2 and SCORE2-OP (instead of the SCORE algorithm) for estimation of the risk of experiencing an MI, ischaemic stroke, or fatal atherosclerotic CV event over the next 10 years in persons without known CVD aged between 40 and 89 years (*Recommendation Table 1*).

While calculation of the SCORE was based on each person's total cholesterol level, non-high-density lipoprotein (HDL)-cholesterol (which is calculated as total cholesterol minus HDL-C) is used as an input in the SCORE2 and SCORE2-OP risk algorithms. Moreover, while the SCORE algorithm assessed the 10 year risk of fatal CVD in persons aged up to 70 years, the SCORE2/SCORE2-OP algorithms (accessible at <http://www.heartscore.org>) can estimate 10 year risk for both fatal and non-fatal CV events also for apparently healthy people aged  $\geq 70$  years (up to 89 years). SCORE2 and SCORE2-OP are calibrated to four clusters of countries (low, moderate, high, and very high CVD risk) based on national CVD mortality rates;<sup>2,3</sup> details and risk charts for these country clusters are in the 2021 ESC Guidelines on CVD prevention.<sup>17</sup>

*Table 3* presents the updated definitions for very high, high, moderate, and low CVD risk, using the SCORE2/SCORE2-OP instead of the SCORE algorithm for apparently healthy persons (primary prevention). This table is intended to replace *Table 4* of the 2019 ESC/EAS Guidelines.<sup>1</sup> As a general concept, it is estimated that the risk of total CVD events is 2–3 times higher than the risk of fatal CVD events, although this may

**Table 3 Cardiovascular risk categories**

<b>Very high risk</b>	<p>People with any of the following:</p> <ul style="list-style-type: none"> <li>Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque<sup>a</sup> on coronary angiography or CT scan or on carotid or femoral ultrasound or markedly elevated CAC score by CT<sup>b</sup></li> <li>DM with target organ damage,<sup>c</sup> or at least three major risk factors, or early onset of T1DM of long duration (&gt;20 years)</li> <li>Severe CKD (eGFR &lt;30 mL/min/1.73 m<sup>2</sup>)</li> <li>A calculated SCORE2 or SCORE2-OP <math>\geq 20\%</math> for 10 year risk of fatal or non-fatal CVD</li> <li>FH with ASCVD or with another major risk factor</li> </ul>
<b>High risk</b>	<p>People with any of the following:</p> <ul style="list-style-type: none"> <li>Markedly elevated single risk factors, in particular TC &gt;8 mmol/L (&gt;310 mg/dL), LDL-C &gt;4.9 mmol/L (&gt;190 mg/dL), or BP <math>\geq 180/110</math> mmHg</li> <li>Patients with FH without other major risk factors</li> <li>Patients with DM without target organ damage,<sup>c</sup> with DM duration <math>\geq 10</math> years or another additional risk factor</li> <li>Moderate CKD (eGFR 30–59 mL/min/1.73 m<sup>2</sup>)</li> <li>A calculated SCORE2 or SCORE2-OP <math>\geq 10\%</math> and &lt;20% for 10 year risk of fatal or non-fatal CVD</li> </ul>
<b>Moderate risk</b>	<p>People with any of the following:</p> <ul style="list-style-type: none"> <li>Young patients (T1DM &lt;35 years; T2DM &lt;50 years) with DM duration &lt;10 years, without other risk factors</li> <li>Calculated SCORE2 or SCORE2-OP <math>\geq 2\%</math> and &lt;10% for 10 year risk of fatal or non-fatal CVD</li> </ul>
<b>Low risk</b>	<ul style="list-style-type: none"> <li>Calculated SCORE2 or SCORE2-OP &lt;2% for 10 year risk of fatal or non-fatal CVD</li> </ul>

ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndromes; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAC, coronary artery calcium; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol; TIA, transient ischaemic attack.

<sup>a</sup>Typically defined by >50% stenosis.

<sup>b</sup>e.g. CAC score >300.

<sup>c</sup>Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

**Table 4** Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

Total CV risk	Untreated LDL-C levels					
	<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) <sup>a</sup>
<b>Low</b>	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle modification, consider adding drug if uncontrolled	N/A <sup>a</sup>
<b>Moderate</b>	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle modification, consider adding drug if uncontrolled	Lifestyle modification, consider adding drug if uncontrolled	N/A <sup>a</sup>
<b>High</b>	Lifestyle advice	Lifestyle advice	Lifestyle modification, consider adding drug if uncontrolled	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
<b>Very high: primary prevention</b>	Lifestyle modification, consider adding drug	Lifestyle modification, consider adding drug	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention
<b>Very high: secondary prevention</b>	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention	Lifestyle modification and concomitant drug intervention

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; N/A, not applicable.

<sup>a</sup>In individuals with untreated LDL-C levels ≥4.9 mmol/L, total CV risk is already at least high (Table 3).

vary considerably according to age and sex. In this Focused Update, a 2× multiplier was used to convert previous SCORE-based thresholds<sup>17</sup> into the SCORE2- or SCORE2-OP-based thresholds to define different categories of total CVD risk. Notably, this Task Force continues to emphasize that risk is a continuum and cut-off points that are used in any CVD risk model to define different levels of risk are, in part, arbitrary and based on the risk levels at which benefit is evident in clinical trials. Therefore, the SCORE2- and SCORE2-OP-based thresholds presented in this document (Table 3) reflect this concept.

Because existing population-based CVD risk models are relatively crude tools for individual risk prediction,<sup>18</sup> attention to additional characteristics that are known to increase CV risk is reasonable in order to refine risk assessment, as already discussed in the 2021 ESC Prevention Guidelines.<sup>17</sup> This is particularly relevant for persons around treatment decision thresholds (Recommendation Table 1). Clinical conditions and selected biomarkers that can be considered as risk modifiers are summarized in Box 1. Their presence may support reclassifying an individual to a higher risk category than would be calculated by the SCORE2 or SCORE2-OP algorithm, and may thereby guide decisions about LDL-C goals and lipid-lowering interventions.

This Focused Update endorses the Class IIa recommendation of the 2019 ESC/EAS Guidelines<sup>1</sup> that arterial (carotid and/or femoral) plaque burden should be considered as a risk modifier in individuals at low or

### Box 1 Risk modifiers for consideration beyond the risk estimation based on the SCORE2 and SCORE2-OP algorithms

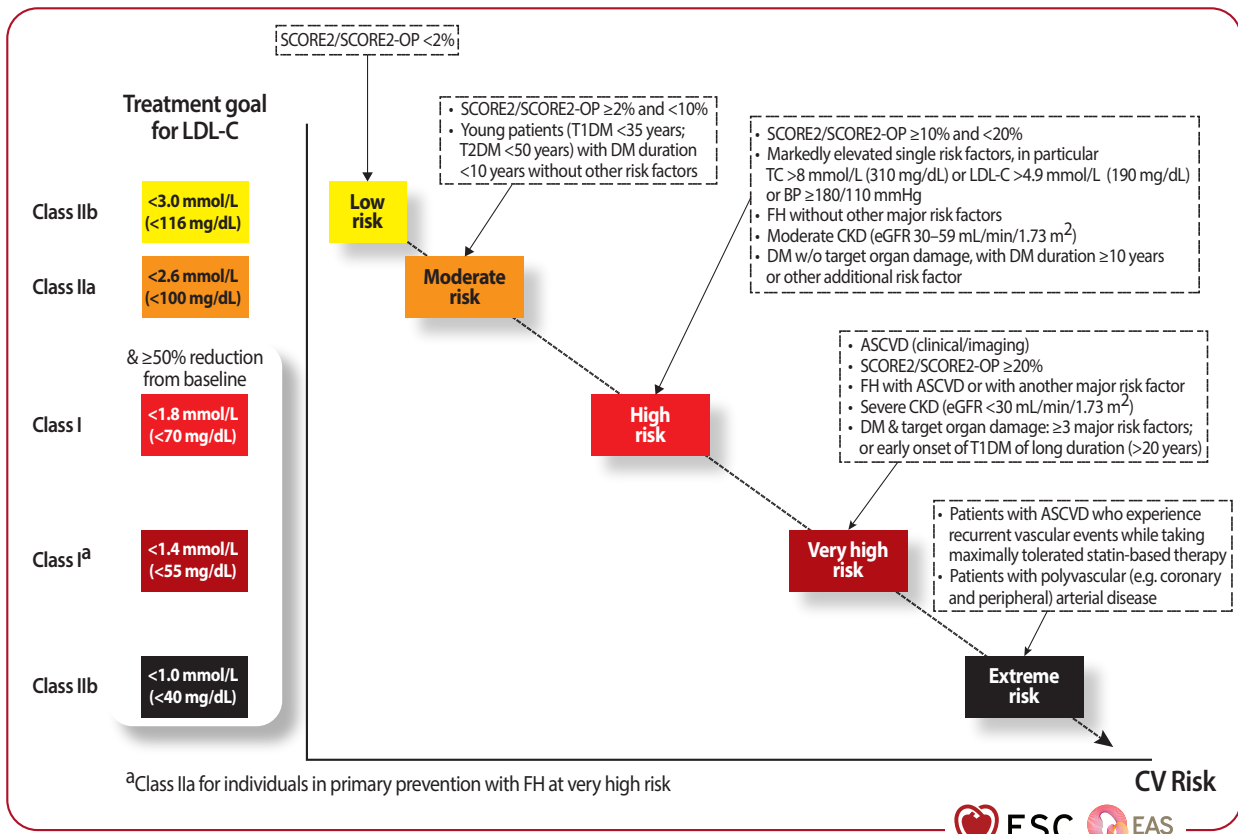
#### Demographic/clinical conditions

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

#### Biomarkers

- Persistently elevated hs-CRP (>2 mg/L)
- Elevated Lp(a) [>50 mg/dL (>105 nmol/L)].

CVD, cardiovascular disease; hs-CRP, high sensitivity C-reactive protein; Lp(a), lipoprotein(a).



**Figure 1** Treatment goals for low-density lipoprotein cholesterol across categories of total cardiovascular risk. ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons; T1DM, type 1 DM; T2DM, type 2 DM; TC, total cholesterol.

moderate risk. Recent studies have provided important new evidence regarding the clinical risk associated with subclinical atherosclerosis documented on coronary or peripheral arterial imaging in persons without clinical ASCVD.<sup>19</sup> While there are no randomized trials showing that the use of coronary artery calcium (CAC) to classify CV risk and guide therapeutic management improves CV outcomes, nevertheless consideration of CAC improves both discrimination and reclassification.<sup>20</sup> An elevated CAC score has been associated in a graded fashion with a higher risk of adverse CV events in persons without clinical ASCVD (primary prevention),<sup>21–23</sup> at markedly elevated CAC values (e.g. CAC score >300), the risk was similar or even higher than the risk of patients with known clinical ASCVD (secondary prevention).<sup>24,25</sup> Conversely, a CAC score of zero has been associated with a lower risk of ASCVD events and mortality in persons at low to moderate estimated CV risk.<sup>26</sup> Consideration of CAC improves the accuracy of predicted CVD risk by means of the SCORE2 algorithm.<sup>27</sup> While the presence of significant (typically, obstructive) plaque on invasive or computed tomography (CT)-based coronary angiography was defined as a feature of very high CV risk in the 2019 ESC/EAS Guidelines,<sup>1</sup> the presence of less advanced coronary atherosclerosis with non-obstructive plaques was more recently shown to be associated with an increased risk of subsequent MI.<sup>28</sup> Against this background, while coronary imaging or CAC measurement are not indicated as broad screening tests for the purpose of CV risk estimation, this Focused Update includes

a new recommendation that the presence of subclinical atherosclerosis by imaging or increased CAC score, if measured, should be considered as risk modifiers in individuals at moderate risk or individuals around treatment decision thresholds (*Recommendation Table 1*). It should be noted, however, that statin therapy may lead to a decrease in lipid-rich plaque and an increase in calcification, indicating plaque stabilization,<sup>29,30</sup> therefore, CAC score should be interpreted with caution in statin-treated patients.

For patients with type 2 diabetes mellitus (T2DM) without ASCVD, the 2023 ESC Guidelines for CVD management in patients with diabetes recommend the use of the SCORE2-Diabetes algorithm to estimate 10 year CVD risk.<sup>31,32</sup>

It is important to note that the LDL-C treatment goals (*Figure 1*) and therapeutic guidance (*Table 4*) for persons in each risk category have not changed from the 2019 ESC/EAS Guidelines.<sup>1</sup> The intensity of the recommended LDL-C lowering continues to be determined by a person's level of risk. Previous studies indicated potential underestimation of CV risk based on the SCORE2 and SCORE2-OP,<sup>18</sup> and under-treatment with lipid-lowering therapy in primary prevention if statins were to be recommended only for persons at very high risk.<sup>33</sup> Importantly, however, as outlined in the 2019 ESC/EAS Guidelines,<sup>1</sup> the recommendation to initiate pharmacological LDL-C-lowering therapy in primary prevention is not restricted to persons at very high risk, but depends on both the estimated CV risk and the baseline (untreated) LDL-C levels (*Table 4*). This concept was previously illustrated in

Table 5 of the 2019 ESC/EAS Guidelines, and is now described (without changes vs the 2019 ESC/EAS Guidelines) in [Recommendation Table 1](#).

We further emphasize that the SCORE2 and SCORE2-OP risk-estimating algorithms were derived from cohorts of participants without clinical ASCVD who were not receiving lipid-lowering therapy. As a result, these algorithms should not be used to estimate risk among persons with existing ASCVD or among persons currently on lipid-lowering therapy, and they should not be used to 're-assess' risk using lipid measurements obtained after initiating Guideline-recommended lipid-lowering therapy.

Finally, this Task Force emphasizes that atherosclerosis is a chronic progressive disease that begins early in life and slowly progresses over time, and the cumulative exposure to higher LDL-C levels at younger ages is associated with a higher ASCVD risk later in life.<sup>34</sup> Conversely, exposure to lower levels of atherogenic lipids at younger ages has the potential to reduce the lifetime risk of developing CVD<sup>35</sup> and mitigate further progression of subclinical atherosclerosis.<sup>15</sup> The discrepancy between our understanding of the biology of how atherosclerosis develops and the practical consequences of informing treatment decisions based on 10 year risk underscores the need to develop a new generation of risk- and benefit-estimating algorithms. These algorithms should: (i) accurately estimate the lifetime risk of having an acute CV event for all individuals regardless of age, and (ii) provide personalized guidance on the optimal timing and intensity of LDL-C lowering needed by each person to reduce their remaining lifetime risk of developing an atherosclerotic CV event.

## 4. New low-density lipoprotein cholesterol-lowering therapies

Bempedoic acid is an oral small molecule that inhibits cholesterol synthesis by inhibiting the action of ATP-citrate lyase, a cytosolic enzyme upstream of the 3-hydroxy-3-methylglutaryl-coenzyme A reductase pathway.<sup>40</sup> Bempedoic acid is a prodrug and the activating enzyme (very long-chain acyl-CoA synthetase-1) is not expressed in skeletal muscle.<sup>41</sup> Treatment with bempedoic acid has muscle-related adverse events similar to placebo.<sup>40,42</sup> Bempedoic acid (single dose available, 180 mg/day) reduces LDL-C levels by approximately 23% as monotherapy, approximately 18% when given on a background of statin therapy,<sup>40,42</sup> and by 38% when given in a fixed-dose combination with ezetimibe.<sup>43,44</sup> Treatment with bempedoic acid decreased C-reactive protein and did not result in increased haemoglobin A1c levels in patients with normoglycaemia or pre-diabetes.<sup>45</sup> Mendelian randomization studies have demonstrated that a genetic variant mimicking the effect of ATP-citrate lyase inhibition and lowering plasma LDL-C levels by the same mechanism of action is associated with similar reductions in the risk of CVD as statins and other non-statin lipid-lowering drugs with proven benefit per unit decrease in LDL-C levels.<sup>46</sup>

The CLEAR Outcomes study was a randomized, double-blind, placebo-controlled study that aimed to determine bempedoic acid's potential for CV risk reduction in statin-intolerant patients at high risk of developing major adverse CV events (MACE) during a median

### Recommendation Table 1 — Recommendations for cardiovascular risk estimation in persons without known cardiovascular disease (see also [Supplementary data online, Evidence Table 1](#))

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
SCORE2 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. <sup>2 c</sup>	I	B
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. <sup>3 c</sup>	I	B
Presence of subclinical coronary atherosclerosis by imaging or increased CAC score by CT should be considered as risk modifiers in individuals at moderate risk or individuals around treatment decision thresholds to improve risk classification. <sup>24,27,28,36 d</sup>	IIa	B
Risk modifiers <sup>e</sup> should be considered in individuals at moderate risk or individuals around treatment decision thresholds to improve risk classification. <sup>17,27,37 f</sup>	IIa	B
In primary prevention, <sup>g</sup> pharmacological LDL-C-lowering therapy is recommended in persons: <ul style="list-style-type: none"> <li>• at very high risk and LDL-C ≥1.8 mmol/L (70 mg/dL), or</li> <li>• at high risk and LDL-C ≥2.6 mmol/L (100 mg/dL)</li> </ul> despite optimization of non-pharmacological measures, to lower CVD risk. <sup>1,13,38,39</sup>	I	A
In primary prevention, <sup>g</sup> pharmacological LDL-C-lowering therapy should be considered in persons: <ul style="list-style-type: none"> <li>• at very high risk and LDL-C ≥1.4 mmol/L (55 mg/dL) but &lt;1.8 mmol/L (70 mg/dL), or</li> <li>• at high risk and LDL-C ≥1.8 mmol/L (70 mg/dL) but &lt;2.6 mmol/L (100 mg/dL), or</li> <li>• at moderate risk and LDL-C ≥2.6 mmol/L (100 mg/dL) but &lt;4.9 mmol/L (190 mg/dL), or</li> <li>• at low risk and LDL-C ≥3.0 mmol/L (116 mg/dL) but &lt;4.9 mmol/L (190 mg/dL)</li> </ul> despite optimization of non-pharmacological measures, to lower CVD risk. <sup>1,13,38,39</sup>	IIa	A

ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; SCORE2, Systematic Coronary Risk Evaluation 2; SCORE2-OP, Systematic Coronary Risk Evaluation 2-Older Persons

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

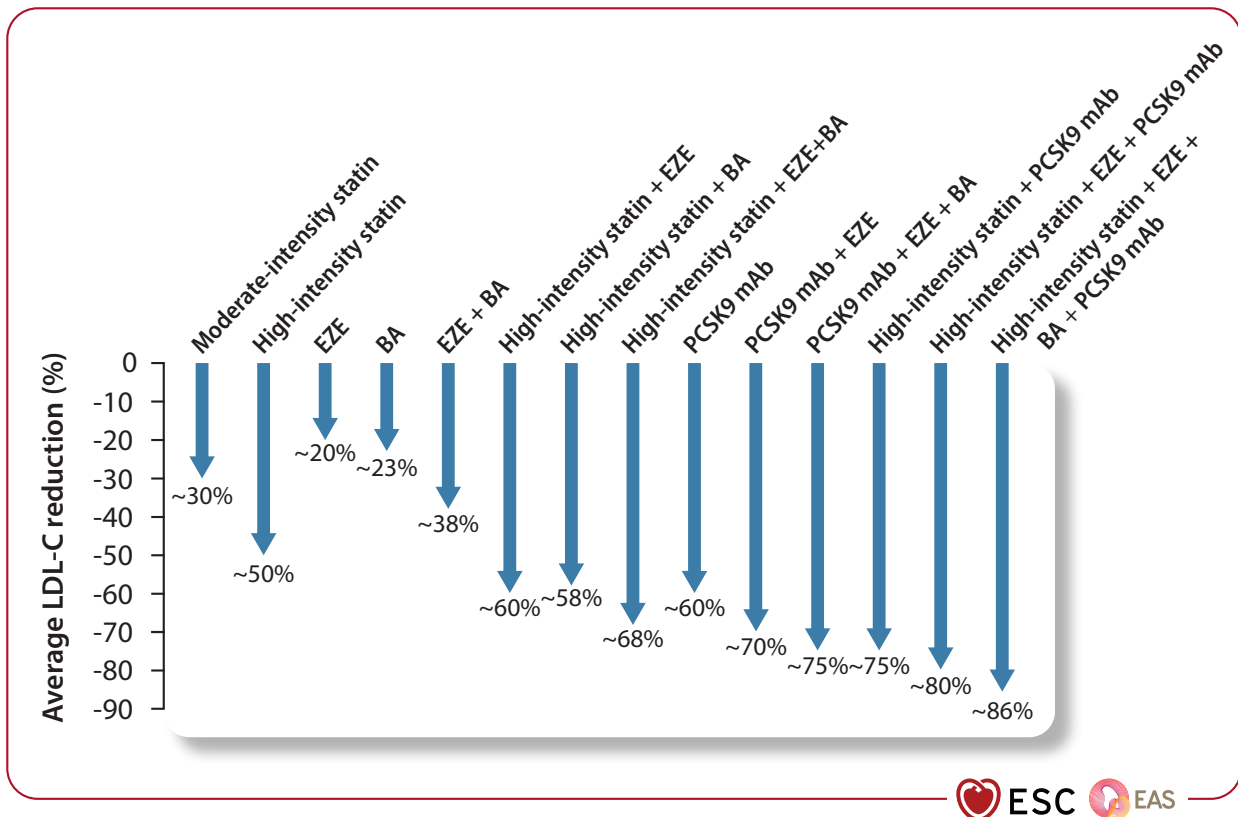
<sup>c</sup>Revised recommendation replacing the respective recommendation based on SCORE in the 2019 ESC/EAS Guidelines.

<sup>d</sup>Revised recommendation replacing the recommendation on CAC score for CV risk assessment in the 2019 ESC/EAS Guidelines.

<sup>e</sup>Listed in [Box 1](#).

<sup>f</sup>New recommendation.

<sup>g</sup>Persons without known clinical atherosclerotic cardiovascular disease.



**Figure 2** Average reduction in low-density lipoprotein cholesterol levels with different pharmacological therapies with proven cardiovascular benefits. BA, bempedoic acid; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; PCSK9 mAb, proprotein convertase subtilisin/kexin type 9 monoclonal antibody.

of 40.6 month follow-up.<sup>4</sup> A total of 13 970 patients were randomized, with approximately 70% in secondary prevention and 30% in primary prevention. Patients taking a small dose of a statin (daily dose of atorvastatin <10 mg or equivalent) were allowed and constituted 23% of the trial population. The time-averaged difference in LDL-C between the bempedoic acid and placebo arms was 0.57 mmol/L (22 mg/dL). Treatment with bempedoic acid reduced the rate of MACE, defined as a composite of death from CV causes, MI, stroke, or coronary revascularization, by 13% [hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.79–0.96;  $P = .004$ ]. There was no apparent effect on CV death (HR, 1.04; 95% CI, 0.88–1.24). Cardiovascular risk reduction with bempedoic acid is similar to that achieved with statins for a given absolute magnitude of LDL-C lowering.<sup>47</sup> The rate of myalgia was similar in the two arms. Treatment with bempedoic acid increased the risk of having elevations in hepatic enzymes [ $>2\times$  upper limit of normal (ULN) for either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), 4.5% vs 3.0%], renal impairment (11.5% vs 8.6%), hyperuricaemia (10.9% vs 5.6%), gout (3.1% vs 2.1%), cholelithiasis (2.2% vs 1.2%), increased platelet count (7.2% vs 0.8%), and decreased haematocrit levels (2.3% vs 0.1%). Because bempedoic acid leads to a small and reversible increase in uric acid, caution is required in patients with a history of gout, even though gout does not constitute an absolute contraindication to bempedoic acid.

New recommendations for the use of bempedoic acid for LDL-C lowering [complementing the recommendations for pharmacological LDL-C lowering with statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) of the 2019 ESC/EAS Guidelines<sup>1</sup>] are shown in [Recommendation Table 2](#).

*Figure 2* summarizes the average percentage reduction in LDL-C levels with different pharmacological therapies, alone or in combination. It should be kept in mind that there is considerable inter-individual variability in the LDL-C-lowering response to any given lipid-lowering drug or combination, which necessitates monitoring of the treatment effects after initiation or adaptation of any LDL-C-lowering therapy. As outlined in the 2019 ESC/EAS Guidelines,<sup>1</sup> LDL-C levels should be measured 4 to 6 weeks after initiation or intensification of lipid-lowering therapy.

Inclisiran, a small interfering ribonucleic acid (RNA) molecule that inhibits the synthesis of PCSK9, may represent an alternative approach to PCSK9 mAbs (alirocumab and evolocumab). Inclisiran has been shown in phase III trials to lower LDL-C levels by approximately 50%.<sup>48</sup> Two CV outcome trials with inclisiran [ $>16\,000$  patients with CVD (NCT03705234) and 17 000 patients with established ASCVD (NCT05030428)] are currently ongoing and expected to report their primary outcomes in 2026 and 2027, respectively.

In patients with homozygous FH, in whom statins and PCSK9 inhibitors have little efficacy and may not suffice to adequately lower LDL-C levels,<sup>49</sup> evinacumab, an mAb against ANGPTL3 (angiopoietin-like 3), has shown potential benefits with a reduction of LDL-C close to 50%.<sup>5,50,51</sup>

Patients who are unable to take statins because of adverse effects represent a challenge in clinical practice. In such cases, the addition of a non-statin lipid-modifying agent to a maximally tolerated statin is a valuable therapeutic option.<sup>1</sup> New evidence supporting the reduction in the risk of ASCVD events with ezetimibe in the absence of statin therapy (although not necessarily due to statin intolerance) in older persons

aged  $\geq 75$  years without history of coronary artery disease was provided in the randomized, open-label EWTOPIA 75 (Ezetimibe Lipid-Lowering Trial on Prevention of Atherosclerotic Cardiovascular Disease in 75 or Older).<sup>52</sup> As a general concept, this Task Force recommends to add non-statin therapies with proven cardiovascular benefit, such as ezetimibe, a 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; the choice should be based on the magnitude of additional LDL-C lowering needed, patient preference, treatment availability, and cost.

**Recommendation Table 2 — Recommendations for pharmacological low-density lipoprotein cholesterol lowering (see also Supplementary data online, Evidence Table 2)**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Non-statin therapies with proven cardiovascular benefit, <sup>c</sup> taken alone or in combination, are recommended for patients who are unable to take statin therapy to lower LDL-C levels and reduce the risk of CV events. The choice should be based on the magnitude of additional LDL-C lowering needed. <sup>4,53,54</sup>	I	A
Bempedoic acid is recommended in patients who are unable to take statin therapy to achieve the LDL-C goal. <sup>4</sup>	I	B
The addition of bempedoic acid to the maximally tolerated dose of statin with or without ezetimibe should be considered in patients at high or very high risk in order to achieve the LDL-C goal. <sup>42,55</sup>	IIa	C
Evinacumab should be considered in patients with homozygous familial hypercholesterolaemia aged 5 years or older who are not at LDL-C goal despite receiving maximum doses of lipid-lowering therapy to lower LDL-C levels. <sup>5,50,51</sup>	IIa	B

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CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

This table complements the table of recommendations for pharmacological low-density lipoprotein cholesterol lowering in the 2019 ESC/EAS Guidelines and does not replace it.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Ezetimibe, PCSK9 monoclonal antibodies, bempedoic acid.

## 5. Combination of lipid-lowering therapies during index hospitalization for acute coronary syndromes

A clear association between intensive lipid-lowering therapies and better outcomes in patients after ACS was demonstrated two decades ago,<sup>56,57</sup> supporting 'the lower the better' principle for LDL-C reduction in this clinical setting. Lipid-lowering therapy is one of the pillars of the management of these patients, both in the early post-ACS setting<sup>58</sup> and in the chronic, stabilized period after an ACS.<sup>59</sup> Patients experiencing ACS are at particularly elevated risk of recurrent CV events, especially within the first year after hospital discharge.<sup>60</sup> Observational

data show a 10% cumulative incidence of a second MI, a stroke, or CV death within the first 100 days after experiencing an MI,<sup>61</sup> reaching 33% at 5 years.<sup>62</sup> Even in an ideal post-ACS scenario, it can take up to 12 weeks for patients to receive optimal LDL-C-lowering therapy following the current stepwise approach that was recommended in the 2019 ESC/EAS Guidelines.<sup>1</sup> This early post-ACS period corresponds to the most vulnerable phase after a major coronary event. Observational data show that Guideline-directed, intensive lipid-lowering therapy is infrequently prescribed, with few dose adjustments performed after hospital discharge,<sup>63</sup> and that the majority of patients do not achieve their goals.<sup>17,64,65</sup> The reasons for this are multifactorial and may include prescription inertia (prescription of lower-intensity statin), sub-optimal patient adherence related to side effects of lipid-lowering therapies or reluctance to being treated with statins,<sup>59</sup> and delays or losses to follow-up after discharge from index hospitalization.

The IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study showed that the addition of ezetimibe to statin therapy (simvastatin 40 mg) within <10 days (median 5 days) after an ACS event resulted in incremental lowering of LDL-C levels and a modest but significant reduction of adverse CV events.<sup>66</sup> Small studies have recently demonstrated that very intensive LDL-C-lowering treatment initiated in the acute phase after ACS is safe, feasible, and effective in getting more patients to recommended LDL-C goals.<sup>67–69</sup> In addition, recent data from the HUYGENS<sup>70</sup> (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) and PACMAN-AMI<sup>71</sup> (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) trials reported improvements in coronary plaque size and composition in response to acute and very intensive LDL-C reduction in the vulnerable post-ACS population. A continuous reduction in CV adverse events has been described even when LDL-C reduction exceeded current Guideline-recommended treatment goals.<sup>72–74</sup> Recent data from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) Registry reported the lowest risk of CV events in those patients who achieved early and sustained LDL-C lowering to recommended goals after MI. A stepwise approach for LDL-C lowering after MI might therefore result in delayed goal attainment as compared with early intensification of treatment.<sup>75,76</sup> These data support 'the sooner, the lower, the better' as a therapeutic strategy for LDL-C lowering in patients with ACS.<sup>58</sup>

As the extent of LDL-C reduction in response to pharmacological interventions is predictable based on baseline LDL-C levels, it is reasonable to assume that a significant proportion of ACS patients will not achieve their target goal with high-intensity statin treatment alone, prescribed at discharge.<sup>77</sup> Therefore, and in line with the current 2023 ESC Guidelines for the management of patients with ACS,<sup>58</sup> this Task Force proposes a strategy of early, intensive LDL-C lowering to be considered in all patients with ACS, with immediate initiation of statin therapy and combination treatment with one or more classes of non-statin therapy with proven CV benefit as needed, depending on each patient's lipid-lowering therapy prior to the ACS event. The choice of drug for combination therapy should be based on the magnitude of additional LDL-C lowering required. Several drugs and drug combinations with various efficacies and onsets of action are available to enable such a 'strike early and strong' approach (Figure 2). Recommendation Table 3 includes two new recommendations for this clinical setting, for patients who present either with or without pre-existing lipid-lowering therapy at the time of the ACS event. Beyond the treatment in the acute ACS phase, LDL-C should be checked 4 to 6 weeks after initiation or intensification of lipid-lowering therapy,

and lifelong treatment to lower LDL-C levels to recommended targets is strongly recommended.<sup>1</sup>

Several ongoing clinical trials, such as EVOLVE-MI (EVOlocumab Very Early After Myocardial Infarction; NCT05284747) and AMUNDSEN-real [Evolocumab or normal strategies to reach LDL objectives in acute myocardial infarction upbound to PCI (percutaneous coronary intervention); EUDRACT:20210–005738–0], are investigating the potential benefit of introducing evolocumab at the time of the ACS event. The results of these trials are expected in 2026–2027.

**Recommendation Table 3 — Recommendations for lipid-lowering therapy in patients with acute coronary syndromes (see also Supplementary data online, Evidence Table 3)**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Intensification of lipid-lowering therapy during the index ACS hospitalization is recommended for patients who were on any lipid-lowering therapy before admission in order to further lower LDL-C levels.	I	C
Initiating combination therapy with high-intensity statin plus ezetimibe during index hospitalization for ACS should be considered in patients who were treatment-naïve and are not expected to achieve the LDL-C goal with statin therapy alone. <sup>66</sup>	IIa	B

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This table complements the ESC 2019 ESC/EAS Guidelines table and does not replace it. ACS, acute coronary syndromes; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 6. Lipoprotein(a)

Epidemiologic and genetic studies strongly support a likely causal and direct continuous association between high plasma levels of Lp(a) and higher risk of ASCVD and aortic valve stenosis (AVS).<sup>78</sup> Emerging data are suggesting that high Lp(a) may confer a higher risk of ASCVD and AVS per particle or cholesterol content than LDL-C.<sup>37,79–84</sup> The mechanisms by which Lp(a) and LDL lead to these increased risks therefore likely differ.<sup>78</sup> Based on studies from the United Kingdom, Denmark, and the United States of America, the highest risks were for MI and AVS, less in peripheral artery disease and heart failure, and the lowest risks were for ischaemic stroke and CV and all-cause mortality.<sup>37,78,79,85–90</sup> Risk from high Lp(a) increases slightly at levels of 30 mg/dL (62 nmol/L) to 50 mg/dL (105 nmol/L) and becomes clinically relevant above 50 mg/dL (105 nmol/L), with higher levels associated with a greater increase in CV risk. Lp(a) concentration is predominantly determined by genetics (>90%), more than any other lipoprotein, and levels vary with ethnicity.<sup>83</sup> There is an incremental increase in risk caused by higher Lp(a) levels, and if Lp(a) level is not considered, risk might be substantially underestimated (Figure 3).<sup>78</sup> Lp(a) measurement should be considered at least once in every adult's lifetime,<sup>1</sup> either at the first lipid profile or at the next one if lipid profiles have previously been performed. Screening is particularly relevant in younger patients with FH or premature ASCVD and no other identifiable risk factors, or a family history of premature ASCVD or high Lp(a) levels, or in individuals at moderate risk or around treatment decision thresholds to improve risk classification. Lp(a) levels may increase

after menopause and a second measurement is reasonable, particularly if the pre-menopausal levels were borderline.<sup>78,91</sup> For Lp(a) measurement, there is substantial variability among different assays, in part relating to apo(a) structure and variability in Kringle-IV repeats, potentially under- or overestimating Lp(a) levels. Although measurement in molar units (nmol/L) is preferred, mass units (mg/dL) can be used for clinical purposes.

Although Lp(a) has not yet been shown to improve risk prediction on top of currently recommended scores (SCORE2, SCORE2-OP), another study testing whether elevated Lp(a) could improve MI risk prediction beyond conventional risk factors showed that Lp(a) concentrations >47 mg/dL reclassified 23% of first MI events correctly, while no events were reclassified incorrectly, in a cohort of 8720 individuals.<sup>84</sup>

Whether lowering Lp(a) reduces the risk of ASCVD and AVS progression has yet to be shown; the extent of Lp(a) lowering required for clinical benefit is also not known. In the absence of specific Lp(a)-lowering therapies, early risk factor management and more intensive LDL-C lowering is reasonable, considering both absolute CV risk and Lp(a) levels.<sup>78</sup> An online Lp(a) risk and benefit algorithm is available at [http://www.eas-society.org/LPA\\_risk\\_and\\_benefit\\_algorithm](http://www.eas-society.org/LPA_risk_and_benefit_algorithm). Although small studies have suggested that statins may have a slight Lp(a) increasing effect, individual-level data on participants in seven randomized, placebo-controlled, statin outcome trials found that statins had no effect on Lp(a) concentrations.<sup>92</sup> Therefore, clinical decision-making should be influenced by the degree of Lp(a) elevation and the patient's other risk factors, and patients with high levels of Lp(a) should be strongly encouraged to take or continue to take high-intensity statins if their risk is sufficiently high.<sup>93</sup>

Currently, there are specific Lp(a)-lowering medications being tested in randomized clinical trials. The injectable RNA (either antisense oligonucleotide or small interfering RNA)-based therapies that target apolipoprotein(a) production in the hepatocyte lower Lp(a) concentration by 80%–98%.<sup>94–97</sup> An oral small molecule inhibitor and a small interfering RNA that can lower Lp(a) significantly are currently under investigation.<sup>98–100</sup>

**Recommendation Table 4** includes a new recommendation reflecting the increase in CV risk across the spectrum of elevated Lp(a) levels.<sup>1</sup> It is reasonable to consider elevated Lp(a) levels >50 mg/dL (≥105 nmol/L) (affecting at least 20% of the population)<sup>83</sup> in order to refine CV risk estimation across the spectrum of CV risk; moreover, this cut-off level should be considered as a risk modifier to potentially reclassify the CV risk category specifically in individuals at moderate risk or individuals close to treatment decision thresholds (see **Box 1** and **Recommendation Table 1**).

**Recommendation Table 4 — Recommendations for measurement of lipoprotein(a) (see also Supplementary data online, Evidence Table 4)**

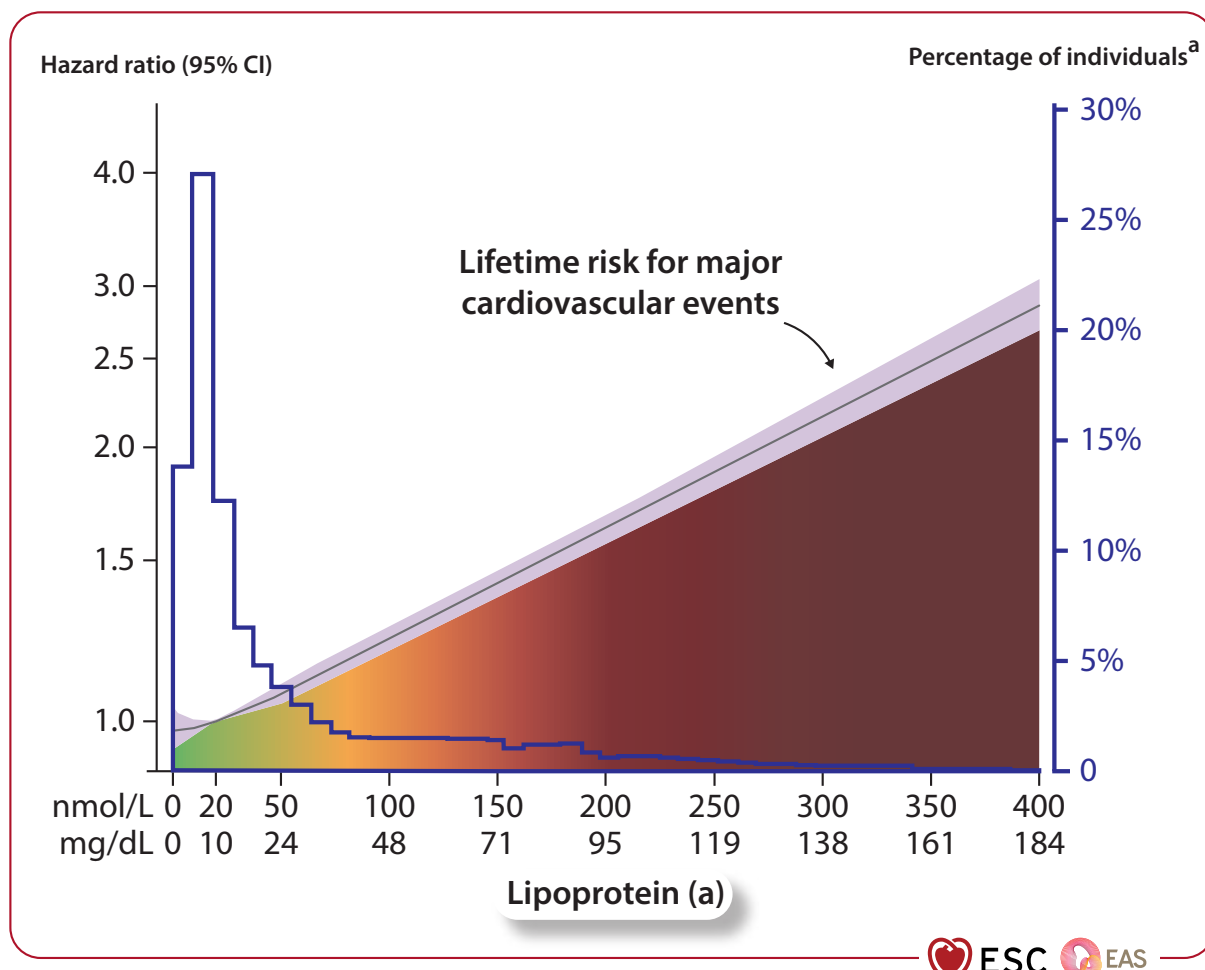
Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Lp(a) levels above 50 mg/dL (105 nmol/L) should be considered in all adults as a CV risk-enhancing factor, with higher Lp(a) levels associated with a greater increase in risk. <sup>37,101</sup>	IIa	B

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CV, cardiovascular; Lp(a), lipoprotein(a).

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.



**Figure 3** Association between Lp(a) levels and lifetime risk of major cardiovascular events. CI, confidence interval; Lp(a), lipoprotein (a). The risk of major CV events starts to slightly increase in individuals with Lp(a) levels  $>62$  nmol/L (30 mg/dL), and the increase in risk becomes more pronounced in individuals with Lp(a) levels  $\geq 105$  nmol/L (50 mg/dL). The grey lines indicate the smoothed adjusted hazard ratio and 95% confidence interval (left y-axis) for lifetime risk for major CV events for a given Lp(a) concentration relative to the median Lp(a) in the population (data from the United Kingdom Biobank, sub-analysis including 415 274 white individuals).<sup>78</sup> <sup>a</sup>The blue line shows the frequency distribution of Lp(a) levels, with respective percentages indicated in the right y-axis (data from the United Kingdom Biobank including 443 180 individuals without prior atherosclerotic CVD).<sup>37</sup>

## 7. Hypertriglyceridaemia

Triglyceride levels are associated with CV risk independent of LDL-C levels.<sup>102–104</sup> With respect to pharmacological treatment of hypertriglyceridaemia, this Task Force continues to recommend statins as the first drug of choice to reduce CVD risk in high-risk patients.<sup>1</sup>

Currently available fibrates (gemfibrozil, fenofibrate, bezafibrate) have moderate triglyceride-lowering effects.<sup>105–107</sup> Fenofibrate and bezafibrate lead to small decreases in LDL-C, but have not reduced MACE (MI, ischaemic stroke, CV mortality) or total mortality in patients treated with statins. A reduction in non-fatal MI was only seen in subgroup analyses of patients with atherogenic dyslipidaemia (low HDL-C and high triglycerides) in these trials.<sup>105,106</sup> In a pre-specified subgroup analysis of the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, fenofibrate was associated with a lower risk of lower-limb amputations, likely not mediated by lipid-related mechanisms.<sup>108</sup> The PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides IN PatiENts With DiabeTes) trial

recently showed that the selective peroxisome proliferator-activated receptor (PPAR- $\alpha$ ) modulator pemafibrate<sup>109</sup> did not reduce the risk of MACE in 10 497 patients with T2DM, mild-to-moderate hypertriglyceridaemia and low HDL-C levels; notably, pemafibrate increased ApoB and LDL-C levels in that trial. Overall, in contrast to the robust evidence of ASCVD risk reduction with LDL-C lowering therapies, the efficacy of triglyceride lowering with fibrates in reducing ASCVD risk has not been established. This Focused Update supports the Class IIb recommendations of the 2019 ESC/EAS Guidelines for the use of fenofibrate or bezafibrate.<sup>1</sup> Fibrates are not indicated to lower serum cholesterol or LDL-C levels.<sup>110</sup>

Regarding n-3 polyunsaturated fatty acids (PUFAs), the STRENGTH trial was published following the publication of the 2019 ESC/EAS Guidelines.<sup>1</sup> The trial failed to demonstrate benefit of a combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) preparation in 13 078 patients (70% with diabetes; 56% with established ASCVD) in lowering MACE (composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization).<sup>8</sup>

Reasons for the discordant results of the negative STRENGTH trial vs those of the positive REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial),<sup>111</sup> which were published 2 years earlier, may be related to differences in the study populations, active treatment compounds (mixture of EPA and DHA vs high-dose icosapent ethyl, i.e. a highly purified EPA ethyl ester, respectively), or placebo formulation (corn oil vs mineral oil-containing placebo, respectively).<sup>112–114</sup> Proposed mechanisms of action of how EPA specifically reduces cardiovascular risk are the distinct effects on lipid oxidation, inflammation, membrane structure/organization, cholesterol domain formation, and endothelial function.<sup>115,116</sup> In view of the newer evidence from the STRENGTH trial, this Focused Update revised the respective recommendation for PUFAs by explicitly stating that high-dose icosapent ethyl (as in the REDUCE-IT trial) should be considered for high-risk or very high-risk patients with elevated triglyceride levels (fasting triglyceride level 135–499 mg/dL [1.52–5.63 mmol/L]) despite statin therapy to lower CVD events (*Recommendation Table 5*).

Volanesorsen is an antisense oligonucleotide targeting hepatic apolipoprotein C-III (ApoC-III) messenger RNA that lowers plasma levels of ApoC-III, triglycerides, and chylomicrons. In a phase III, double-blind, randomized 52 week trial including 66 patients with familial chylomicronaemia syndrome (FCS) and markedly elevated triglyceride levels (mean baseline levels 2209 mg/dL [24.96 mmol/L]), volanesorsen was shown to lower triglyceride levels by 77% within 3 months; levels <750 mg/dL (<8.48 mmol/L) were achieved in 77% of volanesorsen-treated patients. Common adverse events include thrombocytopenia requiring frequent monitoring and injection-site reactions in 60% of the patients treated with volanesorsen.<sup>6</sup> A meta-analysis of individual patient data from three randomized controlled trials including patients with triglyceride levels >500 mg/dL (>5.65 mmol/L) ( $n = 207$ ) showed a significant reduction in the risk of acute pancreatitis during a median follow-up of 8.1 months.<sup>117</sup> Volanesorsen has been approved by the European Medicines Agency (EMA) [but not by the US Food and Drug Administration (FDA)] as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis in whom response to diet and triglyceride-lowering therapy has been inadequate. This drug should be considered for patients with severe hypertriglyceridaemia due to FCS (new recommendation in *Recommendation Table 5*).

Currently, new triglyceride-lowering medications are being tested in randomized clinical trials. Injectable RNA-based therapies (either antisense oligonucleotide or small interfering RNA) targeting ApoC-III can lower triglyceride concentrations by up to 80% depending on the dose, interval, specific agent, and patient population.<sup>118–121</sup>

## 8. Primary prevention in people with human immunodeficiency virus infection

People with HIV (PWH) have a two-fold increased risk of ASCVD compared with the general population.<sup>17,122</sup> Underlying mechanisms include chronic inflammation, immune activation, dyslipidaemia caused by antiretroviral therapy (ART), and traditional CV risk factors.<sup>123</sup> Cardiovascular risk is often underestimated in PWH using conventional risk prediction tools.<sup>124</sup> In the 2019 ESC/EAS Guidelines,<sup>1</sup> the recommendation was that lipid-lowering therapy (mostly statins) should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high-risk patients (Class IIa, Level C). The recently published REPRIEVE trial justifies an update in the recommendation for statins in PWH. REPRIEVE was a multicentre, randomized, double-blind, placebo-controlled trial that enrolled 7769 participants in primary prevention with HIV, aged 40 to 75 years with low-to-moderate ASCVD risk receiving ART.<sup>7</sup> Patients were randomized to pitavastatin 4 mg once daily or placebo. The primary endpoint was MACE, a composite of CV death, MI, hospitalization for unstable angina, stroke, transient ischaemic attack, peripheral arterial ischaemia, revascularization, or death from an undetermined cause. The trial was stopped prematurely for efficacy after a median follow-up of 5.1 years, and showed a 35% lower incidence of MACE in the pitavastatin vs the placebo group (HR, 0.65; 95% CI, 0.48–0.90;  $P = .002$ ). Efficacy was similar for men and women—an important finding as women have a higher risk of HIV-associated ASCVD.<sup>125</sup> Of note, rates of muscle-related symptoms and new-onset diabetes were higher in PWH treated with pitavastatin (2.4% vs 1.3% and 5.3% vs 4.0%, respectively). The 5 year number needed to treat to prevent one MACE was 106. In the REPRIEVE trial, pitavastatin 4 mg daily did not interact with antiretroviral drugs; as co-administration of certain statins and specific antiretroviral drugs may result in significant drug interactions, the choice of statin should be based on potential drug interactions.<sup>126</sup> The new recommendation in this Focused Update for statin therapy in PWH aged  $\geq 40$  years in primary prevention is included in *Recommendation Table 6*.

Although outcome trials of other lipid-lowering therapies have not been performed in PWH, data on LDL-C reduction and tolerability are available for ezetimibe and PCSK9 mAbs.

Ezetimibe as monotherapy or in combination with statin therapy reduces LDL-C levels in PWH receiving ART to a similar extent as in people without HIV and is well tolerated, although available studies are small.<sup>127–129</sup> Regarding PCSK9 inhibitors, a randomized, double-blind trial including 464 PWH receiving ART (35.6% with documented ASCVD) showed that evolocumab reduced LDL-C levels by 56.9%

### Recommendation Table 5 — Recommendations for drug treatment of patients with hypertriglyceridaemia (see also Supplementary data online, Evidence Table 5)

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
High-dose icosapent ethyl (2 × 2 g/day) should be considered in combination with a statin 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) to reduce the risk of cardiovascular events. <sup>8,111</sup>	IIa	B
Volanesorsen (300 mg/week) should be considered in patients with severe hypertriglyceridaemia (>750 mg/dL or >8.5 mmol/L) due to familial chylomicronaemia syndrome, to lower triglyceride levels and reduce the risk of pancreatitis. <sup>6,117</sup>	IIa	B

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

compared with placebo and was well tolerated.<sup>130</sup> As yet no data are available for the efficacy and safety of bempedoic acid or icosapent ethyl in PWH.

**Recommendation Table 6 — Recommendations for statin therapy in primary prevention for people with human immunodeficiency virus infection (see also Supplementary data online, Evidence Table 6)**

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Statin therapy is recommended for people in primary prevention aged $\geq 40$ years with HIV, irrespective of estimated cardiovascular risk and LDL-C levels, to reduce the risk of cardiovascular events; the choice of statin should be based on potential drug interactions. <sup>7</sup>	<b>I</b>	<b>B</b>

HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 9. Patients with cancer at high or very high chemotherapy-related cardiovascular toxicity risk

Anthracycline-based chemotherapy is a key component of several chemotherapy regimens for many types of cancer (e.g. breast cancer or lymphoma). Its use is associated with the development of heart failure in up to 20% of patients within 5 years, depending on the accumulated dose received.<sup>131</sup>

Recently, four randomized trials assessed the cardioprotective role of statins in patients with cancer receiving anthracycline-based therapy.<sup>9,132–134</sup> The STOP-CA trial was a multicentre, double-blind, randomized controlled trial comparing atorvastatin 40 mg daily against placebo in 300 patients with lymphoma. The primary endpoint, defined as the proportion of patients with  $\geq 10\%$  absolute decline in left ventricular ejection fraction (LVEF) to a final LVEF value  $< 55\%$  at 12 months, occurred more frequently in the placebo compared with the atorvastatin group (22% vs 9%, respectively;  $P = .002$ ).<sup>9</sup> Three smaller trials yielded mixed results<sup>132–134</sup> (see [supplementary data](#) online), which may be explained by differences in patient populations, CV risk, sample sizes, outcomes, or follow-up duration. Although the evidence supporting the use of statins as cardioprotective treatment for anthracycline-induced cardiotoxicity is not unequivocal, this Focused Update supports the Class IIa recommendation introduced in the 2022 ESC cardio-oncology Guidelines<sup>135</sup> for statin treatment in patients at high or very high risk of developing cancer therapy-related CV toxicity (new [recommendation in Recommendation Table 7](#)). This was based on the net positive results of the largest of these trials (STOP-CA) and two meta-analyses of available randomized trials (including unblinded trials),<sup>136,137</sup> in combination with the overall safety of statins without reported increase in hepatotoxicity or myopathy in this setting.<sup>9,132–134</sup>

The effects of non-statin lipid-lowering therapies on LVEF or other cardiovascular outcomes in patients receiving cancer therapy have not been tested.

**Recommendation Table 7 — Recommendations for statin therapy in patients receiving cancer therapy (see also Supplementary data online, Evidence Table 7)**

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Statin should be considered in adult patients at high or very high risk of developing chemotherapy-related cardiovascular toxicity <sup>c</sup> to reduce the risk of anthracycline-induced cardiac dysfunction. <sup>9,132–134</sup>	<b>IIa</b>	<b>B</b>

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

<sup>c</sup>Baseline cardiovascular toxicity risk stratification discussed in detail in the 2022 ESC Guidelines on cardio-oncology.<sup>135</sup>

## 10. Dietary supplements

The role of healthy dietary habits in lowering atherogenic lipid levels and reducing CV risk is discussed in detail in the 2019 ESC/EAS Guidelines.<sup>1</sup> A healthy diet is generally defined as a dietary pattern low in saturated fat, with a focus on wholegrain products, vegetables, fruit, and fish.<sup>1</sup> With respect to dietary supplements, however, there has not been compelling evidence that these can reduce CV risk. For red yeast rice preparations, although a clinically relevant hypocholesterolaemic effect has been reported with selected (purified, high-dose) preparations, convincing evidence of a clinical benefit resulting from this treatment is missing. Similarly, there has not been evidence that supplementation with PUFAs can lower LDL-C levels or reduce the risk of CV events—with the exception of high-dose, purified icosapent ethyl used in the context of hypertriglyceridaemia. Along the same lines, the recently published OMEMI trial that tested PUFA (DHA + EPA) in elderly patients (age 70–82 years) without elevated triglycerides with recent (2–8 weeks) acute MI did not show a reduction in clinical events compared with placebo.<sup>11</sup> The recent SPORT trial was a single-centre, randomized, single-blind study in persons without history of ASCVD and an increased 10 year risk of ASCVD. Participants ( $n = 199$ ) were randomized to rosuvastatin 5 mg daily, placebo, fish oil, cinnamon, garlic, turmeric, plant sterols, or red yeast rice. At 28 days, LDL-C reduction (the study's primary endpoint) was greater with rosuvastatin than with all supplements or placebo, and none of the dietary supplements led to a significant LDL-C reduction compared with placebo.<sup>10</sup> Phytosterols reduce cholesterol absorption in the intestinal lumen and increase cholesterol excretion, and at doses of up to 2 grams per day they can reduce LDL-C levels by approximately 10% without reported adverse events. There are no studies showing benefit of phytosterols on CV outcomes.<sup>138</sup> In June 2022, the European Parliament and the Council prohibited the marketing of food supplements containing  $\geq 3$  mg/day of monacolins from red yeast rice. Concretely, this corresponds to a ban on monacolins from red yeast rice at a daily dose of  $\geq 3$  mg/day, while lower doses of these supplements are under restrictions (warnings) and European Union scrutiny.<sup>139</sup>

Based on the totality of available evidence and in view of the new trials published after 2019,<sup>10,11</sup> this Focused Update does not support the use of dietary supplements or vitamins without documented safety and significant LDL-C-lowering efficacy for lowering the risk of ASCVD (new recommendation in [Recommendation Table 8](#)).

**Recommendation Table 8 — Recommendations for dietary supplements (see also Supplementary data online, Evidence Table 8)**

Recommendation	Class <sup>a</sup>	Level <sup>b</sup>
Dietary supplements or vitamins without documented safety and significant LDL-C-lowering efficacy are not recommended to lower the risk of ASCVD. <sup>10,11</sup>	III	B

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ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.

## 11. Evidence tables

Evidence tables are available at *European Heart Journal* online.

## 12. Data availability statement

No new data were generated or analysed in support of this research.

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## 14. Appendix

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