# 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias

## Lipid modification to reduce cardiovascular risk

**External Review Round 3 – February 2019**

**Document to review:**

Please note that all tables and figures noted as "supplementary" will be taken out of the final document and placed in a web addendum prior to final publication.

**Deadline to submit your review comments: ……~~4 April~~ 2019**

Please only submit your comments on the WORD comment form and make sure you list the page and line number for each of your comments.

Thank you.

**FRONT PAGE TO BE FINALIZED UPON PUBLICATION**

# Table of contents

# Abbreviations and acronyms

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| ABI | ankle-brachial index |
| ACCELERATE | Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes |
| ACCORD | Action to Control Cardiovascular Risk in Diabetes |
| ACS | acute coronary syndromes |
| AIM-HIGH | Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes |
| ALT | alanine aminotransferase |
| ANGPTL3 | angiopoietin-like protein 3 |
| Apo | apolipoprotein |
| ART | antiretroviral treatment |
| ASCEND | A Study of Cardiovascular Events iN Diabetes |
| ASCOT-LLA | Anglo-Scandinavian Cardiac Outcomes Trial – Lipid-Lowering Arm |
| ASCVD | atherosclerotic cardiovascular disease |
| ASSIGN | CV risk estimation model from the Scottish Intercollegiate Guidelines Network |
| AURORA | A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events |
| BIOSTAT-CHF | BIOlogy Study to TAilored Treatment in Chronic Heart Failure |
| BIP | Bezafibrate Infarction Prevention |
| BMI | body mass index |
| BP | blood pressure |
| CABG | coronary artery bypass graft surgery |
| CAC | coronary artery calcium |
| CAD | coronary artery disease |
| CANTOS | Canakinumab Antiinflammatory Thrombosis Outcome Study |
| CETP | cholesteryl ester transfer protein |
| CHD | coronary heart disease |
| CI | confidence interval |
| CIID | chronic immune-mediated inflammatory diseases |
| CIRT | Cardiovascular Inflammation Reduction Trial |
| CK | creatine kinase |
| CKD | chronic kidney disease |
| CORONA | Controlled Rosuvastatin Multinational Trial in Heart Failure |
| COM-B | Capability, Opportunity and Motivation |
| CPG | Committee for Practice Guidelines |
| CRP | C-reactive protein |
| CT | computed tomography |
| CTT | Cholesterol Treatment Trialists |
| CV | cardiovascular |
| CVD | cardiovascular disease |
| CYP | cytochrome P450 |
| 4D | Die Deutsche Diabetes Dialyse Studie |

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| dal-OUTCOMES | Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome |
| DASH | Dietary Approaches to Stop Hypertension |
| DGAT-2 | diacylglycerol acyltransferase-2 |
| DHA | docosahexaenoic acid |
| DLCN | Dutch Lipid Clinic Network |
| DM | diabetes mellitus |
| EAPC | European Association of Preventive Cardiology |
| EAS | European Atherosclerosis Society |
| eGFR | estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| EPA | eicosapentaenoic acid |
| ER | extended release |
| ERBP | European Renal Best Practice |
| ESC | European Society of Cardiology |
| ESRD | end-stage renal disease |
| EVOLVE | EpanoVa fOr Lowering Very high triglyceridEs |
| FACE-BD | Fondamental Advanced Centers of Expertise in Bipolar Disorders |
| FATS | Familial Atherosclerosis Treatment Study |
| FCH | familial combined hyperlipidaemia |
| FDC | fixed dose combination |
| FH | familial hypercholesterolaemia |
| FIELD | Fenofibrate Intervention and Event Lowering in Diabetes |
| FOCUS | Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention |
| FOURIER | Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GISSI | Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico |
| GP | general practitioner |
| HAART | highly active antiretroviral treatment |
| HATS | HDL-Atherosclerosis Treatment Study |
| HbA1c | glycated haemoglobin |
| HeFH | heterozygous familial hypercholesterolaemia |
| HDL | high-density lipoprotein |
| HDL-C | high-density lipoprotein cholesterol |
| HF | heart failure |
| HHS | Helsinki Heart Study |
| HIV | human immunodeficiency virus |
| HMG-CoA | hydroxymethylglutaryl-coenzyme A |
| HPS2-THRIVE | Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events |
| HoFH | homozygous familial hypercholesterolaemia |
| HTG | hypertriglyceridaemia |

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| HR | hazard ratio |
| hsCRP | high-sensitivity C-reactive protein |
| ICD | International Classification of Diseases |
| IDEAL | Incremental Decrease In End-points Through Aggressive Lipid-lowering |
| IDL | intermediate-density lipoproteins |
| IL | interleukin |
| ILLUMINATE | Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events |
| IPD | individual participant data |
| IMPROVE-IT | Improved Reduction of Outcomes: Vytorin Efficacy International Trial |
| KDIGO | Kidney Disease: Developing Global Guidelines Organization |
| LAL | lysosomal acid lipase |
| LCAT | lecithin cholesterol acyltransferase |
| LDL | low-density lipoprotein |
| LDL-C | low-density lipoprotein cholesterol |
| LDLR | low-density lipoprotein receptor |
| LEAD | lower extremities arterial disease |
| LEADER | Lower Extremity Arterial Disease Event Reduction |
| LPL | lipoprotein lipase |
| Lp(a) | lipoprotein (a) |
| mAb | monoclonal antibody |
| mAbs | monoclonal antibodies |
| MACE | major adverse cardiovascular events |
| MESA | Multi-Ethnic Study of Atherosclerosis |
| MetS | metabolic syndrome |
| MI | myocardial infarction |
| MTP | microsomal triglyceride transfer protein |
| MUFA | monounsaturated fatty acid |
| NAFLD | non-alcoholic fatty liver disease |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NNT | number needed to treat |
| NPC1L1 | Niemann-Pick C1-like protein 1 |
| NSTE-ACS | non-ST elevation acute coronary syndrome |
| ODYSSEYOutcomes | Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab |
| PAD | peripheral arterial disease |
| PCI | percutaneous coronary intervention |
| PCSK9 | proprotein convertase subtilisin/kexin type 9 |
| PPAR-α | peroxisome proliferator-activated receptor-α |
| PRECISE-IVUS | Plaque REgression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by IntraVascular UltraSound |
| PREDIMED | Prevención con Dieta Mediterránea |
| PROCAM | Prospective Cardiovascular Munster Study |

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| PROMINENT | Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN PatiENts With DiabeTes |
| PUFA | polyunsaturated fatty acid |
| RA | rheumatoid arthritis |
| RAAS | renin–angiotensin–aldosterone system |
| RCT | randomized controlled trial |
| REDUCE-IT | Reduction of Cardiovascular Events with EPA-Intervention Trial |
| REVEAL | Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification |
| RR | relative risk |
| RYR | red yeast rice |
| SAMS | statin-associated muscle symptoms |
| SBP | systolic blood pressure |
| SCORE | Systemic Coronary Risk Estimation |
| SEAS | Simvastatin and Ezetimibe in Aortic Stenosis |
| SECURE-PCI | Statins Evaluation in Coronary Procedures and Revascularization |
| SFA | saturated fatty acid |
| SHARP | Study of Heart and Renal Protection |
| SLE | systemic lupus erythematosus |
| SMI | severe mental illness |
| SPARCL | Stroke Prevention by Aggressive Reduction in Cholesterol Levels |
| STEMI | ST-elevation myocardial infarction |
| STRENGTH | Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia |
| TC | total cholesterol |
| T2DM | type 2 diabetes mellitus |
| TG | triglycerides |
| TIA | transient ischaemic attack |
| TIMI | Thrombolysis In Myocardial Infarction |
| TNF | tumour necrosis factor |
| TRL | triglyceride-rich lipoprotein |
| ULN | upper limit of normal |
| UMPIRE | Use of a Multidrug Pill In Reducing Cardiovascular Events |
| VA-HIT | Veterans Affairs High Density Lipoprotein Intervention Trial |
| VLDL | very low-density lipoprotein |
| WHO | World Health Organization |

# 1. Preamble *(to possibly be updated prior to publication by ESC staff)*

Guidelines summarize and evaluate all available evidence on a particular issue at the time of the writing process, with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition, taking into account the impact on outcome as well as the risk-benefit ratio of particular diagnostic or therapeutic means. Guidelines and recommendations should help health professionals to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC) and by the European Atherosclerosis Society (EAS), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from the European Association of Preventive Cardiology (EAPC) and the EAS, to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management (including diagnosis, treatment, prevention and rehabilitation) of a given condition according to ESC Committee for Practice Guidelines (CPG) policy and approved by the EAS. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk-benefit ratio. Estimates of expected health outcomes for larger populations were included, where data exist. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts

of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EAS and updated. The Task Force received its entire financial support from the ESC and EAS without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new Guidelines produced by task forces, expert groups or consensus panels. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts, and in this case by EAS-appointed experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG and EAS for publication in the *European Heart Journal* and in *Atherosclerosis*. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC and EAS Guidelines covers not only integration of the most recent research, but also the creation of educational tools and implementation programmes for the recommendations. To implement the guidelines, condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, tablets, *etc*) are produced. These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available on the ESC website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

**Table 1 Classes of recommendations**

| Classes of recommendations | Definition | Suggested wording to use |
|---|---|---|
| Class I | Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective. | Is recommended/is indicated |
| Class II | 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 |
| Class III | Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful. | Is not recommended |



**Table 2 Levels of evidence**

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| 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. |



Health professionals are encouraged to take the ESC and EAS Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC and EAS Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's

responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

## 2. Introduction

The previous ESC/EAS lipid guidelines were published in August 2016.[1] The emergence of a substantial body of evidence in the last few years required a new up to date guideline.

New evidence confirms that the key-initiating event in atherogenesis is the retention of low-density lipoprotein cholesterol (LDL-C) and other cholesterol-rich apoB-containing lipoproteins within the arterial wall.[2] Several recent placebo-controlled clinical studies have shown that the addition of either ezetimibe or anti-PCSK9 monoclonal antibodies to statin therapy provide a further reduction in atherosclerotic cardiovascular disease (ASCVD) risk which is directly and positively correlated with the incrementally achieved absolute LDL-C reduction. Furthermore, these clinical trials clearly indicate that the lower the achieved LDL-C values, the lower the risk of future CV events, with no lower limit for LDL-C values, or "J"-curve effect. In addition, studies of the clinical safety of these very low achieved LDL-C values have proven reassuring, albeit monitoring for longer periods is required. For raising HDL-C, recent studies have indicated that the currently available therapies do not reduce the risk of ASCVD. Finally, human Mendelian randomization studies have demonstrated the critical role of LDL-C and other cholesterol-rich apoB-containing lipoproteins in atherosclerotic plaque formation and related subsequent CV events. Thus, there is no longer an "LDL-C hypothesis", but established facts that increased LDL-C values are causally related to ASCVD, and that lowering LDL particles and other apoB-containing lipoproteins as much as possible reduces CV events.

In order to be aligned with these new findings, the ESC/EAS Task Force members of these guidelines have proposed new LDL-C goals, as well as a revised CV risk stratification, especially relevant to high-risk and very high-risk patients.

These novel ESC/EAS guidelines on lipids provide important new advice on patient management, which should help towards enabling more clinicians to efficiently and safely reduce CV risk through lipid modification.

## 2.1 What is new in the 2019 Guidelines?

**Figure 1 New Recommendations, New and Revised Concepts**

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| **New recommendations** |
| **Cardiovascular imaging for assessment of ASCVD risk**<br>Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate-risk. |
| **Cardiovascular imaging for assessment of ASCVD risk**<br>CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate-risk. |
| **Lipid analyses for CVD risk estimation**<br>Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (64.2 mmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia. |
| **Treatment of dyslipidaemias in diabetes**<br>In patients with T2DM at VERY HIGH-risk, an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (55mg/dL) is recommended.<br>In patients with T2DM at HIGH-risk an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (< 70 mg/dL) is recommended.<br>Statins are recommended in patients with T1DM who are at HIGH or VERY HIGH-risk. |
| **Treatment of dyslipidaemias in diabetes**<br>Intensification of statin therapy should be considered before the introduction of combination therapy.<br>If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered. |
| **Treatment of dyslipidaemias in diabetes**<br>Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception. |
| **Drug treatments of patients with hypertriglyceridaemia**<br>In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135-499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statin. |
| **Treatment of dyslipidaemias in older people**<br>Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged up to 75. |
| **Treatment of dyslipidaemias in older people**<br>Initiation of statin treatment for primary prevention in older people aged over 75 may be considered. |
| **Lipid-lowering therapy in patients with ACS**<br>For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered. |
| **Changes in recommendations** |
| **Upgrades** |

| 2016 | 2019 |
|---|---|
| **Lipid analyses for CVD risk estimation**<br>ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG. | **Lipid analyses for CVD risk estimation**<br>ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis and management, and may be preferred over non HDL-C in people with high TG, diabetes, obesity or very low LDL-C. |
| **Pharmacological LDL-C lowering**<br>If the LDL goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered. | **Pharmacological LDL-C lowering**<br>If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. |
| **Pharmacological LDL-C lowering**<br>In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered. | **Pharmacological LDL-C lowering**<br>For secondary prevention, patients at very high-risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.<br><br>For very high risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. |
| **Drug treatments of hypertriglyceridaemia**<br>Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia. | **Drug treatments of hypertriglyceridaemia**<br>Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (200 mg/dL). |
| **Treatment of patients with heterozygous FH**<br>Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations. | **Treatment of patients with heterozygous FH**<br>For FH patients who are at very high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended. |
| **Treatment of patients with heterozygous FH**<br>Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance. | **Treatment of patients with heterozygous FH**<br>Treatment with a PCSK9 inhibitor is recommended in very high risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe. |

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| **Treatment of dyslipidaemias in older adults**<br>Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects. | **Treatment of dyslipidaemias in older people**<br>It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals. |
| **Lipid-lowering therapy in patients with ACS**<br>If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated. | **Lipid-lowering therapy in patients with ACS**<br>If the LDL-C goal is not achieved after 4-6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended. |

| **Recommendation grading** | | |
|---|---|---|
| **Class I** | **Class IIa** | **Class IIb** |

**New sections**

- A new section is focused on the utility of non-invasive CV imaging for classification of total CVD risk, with implications for recommended lipid modifying therapies.
- More data are provided on the biology and physiology of lipids and lipoproteins, and on their role in the pathophysiology. Emerging evidence from observational studies, RCT, and genetic (Mendelian randomization) studies unequivocally showing a causal effect of LDL-C in the development of ASCVD is discussed, and newer evidence regarding the effects of TGs and HDL on ASCVD risk is presented.
- New sections describe novel lipid-modifying medications as well as emerging approaches for lowering LDL-C, TGs and Lp(a).
- A new section discusses the inflammation-related risk in very high-risk patients and the potential role of inflammation as a therapeutic target to lower ASCVD risk.

- **New/revised concepts**

**More intensive reduction of LDL ~~cholesterol~~ C across CV risk categories**

- For very ~~high~~ high-risk patients in secondary prevention or with FH and another major risk factor (such as smoking or hypertension)~~,~~ an LDL-C reduction of at least 50% from baseline~~d~~ and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended.
  - For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) whilst taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered.
- For patients at high risk, an LDL-C reduction of at least 50% from baseline~~d~~ and an LDL-C goal of <1.8 mmol/L (70 mg/dL) are recommended.
- For individuals at moderate risk, an LDL-C goal of <2.6 mmol/L (100 mg/dL) should be considered.
- For individuals at low risk, an LDL-C goal of <~~of~~ 3.0 mmol/L (115 mg/dL) may be considered.

The rationale for the revised, lower LDL-C goals across CV risk categories ~~are~~ is discussed, based on a critical synthesis of available evidence from lipid-modifying interventions resulting in reductions in CV risk.

**Pharmacological LDL-C lowering strategies**

The section on pharmacological strategies to lower LDL-C emphasizes the concept that the absolute LDL-C reduction

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| (determined by pre-treatment LDL-C levels and the LDL-lowering efficacy of the medications) dictates the relative risk reduction, which in turn – depending on the baseline CV risk – defines the associated absolute CV risk reduction in individual patients. |
| **Risk classification in patients with FH**<br>Patients with FH and ASCVD or another major risk factor are classified as very high risk, and those without known ASCVD and without other risk factors as high-risk. Recommended treatment goals are defined accordingly. |
| **Adverse effects of statins**<br>The distinction between formal statin myopathy vs. so-called statin-associated muscle symptoms is emphasized, and the discordance in reported frequency of symptoms in RCTs vs. observational studies are critically discussed on the basis of new relevant evidence. |
| **PCSK9 inhibitors**<br>New outcome study data of PCSK9 inhibitors are presented, and updated recommendations for their clinical use are provided. |
| **Cost-effectiveness**<br>The issue of cost-effectiveness of lipid-modifying interventions is updated in view of changes in the availability of generic products for statins and ezetimibe, and of PCSK9 inhibitors. |

ACS = acute coronary syndrome; ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; CV = cardiovascular; CVD = cardiovascular disease; CT = computed tomography; FH = familial hypercholesterolaemia; HDL=high-density lipoprotein; LDL-C = low-density lipoproteins cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus; TG = triglycerides.

# 3. What is cardiovascular disease prevention?

## 3.1 Definition and rationale

Cardiovascular disease (CVD), of which atherosclerotic CVD (ASCVD) is the major component, is responsible for >4 million deaths in Europe each year. It kills more women (2.2 million) than men (1.8 million), although cardiovascular (CV) deaths before the age of 65 years are more common in men (490 000 vs. 193 000).[3] Prevention is defined as a coordinated set of actions, either at the population or individual level, aimed at eradicating, eliminating or minimizing the impact of CV diseases and their related disabilities. More patients are surviving their first CVD event and are at high risk of recurrences. In addition, the prevalence of some risk factors, notably diabetes and obesity, is increasing. The importance of ASCVD prevention remains undisputed and should be delivered at the general population by promoting healthy lifestyle behaviour,[4] and at the individual level by tackling unhealthy lifestyles and by reducing increased levels of causal CV risk factors such as lipid or blood pressure (BP) levels.

## 3.2 Development of the Joint Task Force guidelines for the management of dyslipidaemias

The present guidelines represent an evidence-based consensus of the European Task Force including the ESC and the EAS.

By appraising the current evidence and identifying remaining knowledge gaps in managing dyslipidaemias, the Task Force formulated recommendations to guide action in clinical practice to prevent ASCVD by modifying lipid plasma levels.

This document has been developed for healthcare professionals to facilitate informed communication with individuals about their CV risk and the benefits of adopting and sustaining a healthy lifestyle and of early modification of their lipid-related CV risk. In addition, the guidelines provide tools for healthcare professionals to promote up-to-date intervention strategies and integrate these strategies into national or regional prevention frameworks and to translate them into locally delivered healthcare services, in line with the recommendations of the World Health Organization (WHO) *Global Status Report on Noncommunicable Diseases 2010*.[5]

A lifetime approach to CV risk should be considered.[1] This implies that apart from improving lifestyle habits and reducing risk factor levels in patients with established ASCVD and in those at increased risk of developing ASCVD, people of all ages should be encouraged to adopt or sustain a healthy lifestyle.

# 4. Total cardiovascular risk

## 4.1 Total cardiovascular risk estimation

CV risk in the context of these guidelines means the likelihood of a person developing an atherosclerotic CV event over a defined period of time. Total CVD risk expresses the combined effect of a number of risk factors on this risk estimate. In this guideline we address the lipid-related contribution to total CV risk and how to manage it at the clinical level.

### 4.1.1 Rationale for assessing total cardiovascular disease risk

All current guidelines on the prevention of ASCVD in clinical practice recommend the assessment of total CVD risk. Prevention of ASCVD in a given person should relate to his or her total CV risk: the higher the risk, the more intense the action should be.

Many risk assessment systems are available and have been comprehensively reviewed (*Supplementary table 1*). Most guidelines use one of these risk assessment systems.[6-8]

**Supplementary table 1 Total cardiovascular disease risk assessment systems**

| System | Risk | Variables | Ref |
|---|---|---|---|
| Framingham models | 10-year risk of CHD events | Gender, age, TC, HDL-C, SBP, smoking status, diabetes, hypertensive treatment | S1 |
| Systemic Coronary Risk Estimation (SCORE) | 10-year risk of CVD mortality | Gender, age, TC or TC/HDL-C ratio, SBP, smoking status | S2 |
| ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network) | 10-year risk of first CVD event | Gender, age, TC, HDL-C, SBP, smoking – number of cigarettes, diabetes, area based index of deprivation, family history | S3 |
| QRISK2 | 10-year risk of first CVD event | Gender, age, TC to HDL-C ratio, SBP, smoking status, diabetes, area based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity, rheumatoid arthritis, CKD stages 4-5, AF | S4 |
| Prospective Cardiovascular Munster Study (PROCAM) | Two separate scores calculate 10-year risk of major coronary events and cerebral ischaemic events | Age, gender, LDL-C, HDL-C, diabetes, smoking, SBP | S5 |
| Reynolds Risk Score | 10-year risk of incident myocardial infarction, stroke, coronary revascularization or CV death | Gender, age, SBP, smoking, hsCRP, TC, HDL-C, family history of premature MI (parent age <60 years), HbA1c if diabetic | S6,S7 |

| | | | |
|---|---|---|---|
| CUORE | 10-year risk of first CVD event | Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment | S8 |
| Pooled Cohort equations | 10-year risk of CVD event | Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment, race | S9 |
| Globorisk | 10-year risk of CVD mortality | Age, gender, smoking, SBP, diabetes, TC | S10 |

AF = atrial fibrillation; BMI = body mass index; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, SBP = systolic blood pressure; TC = total cholesterol.

Ideally, risk charts should be based on country-specific cohort data. These are not available for most countries. The SCORE (Systemic Coronary Risk Estimation) system can be recalibrated for use in different populations by adjustment for secular changes in CVD mortality and risk factor prevalences. Calibrated country-specific versions are available for many European countries and can be found at http://www.heartscore.org. These are now being updated to provide recalibrated, contemporaneous country-specific charts for all European countries. Other risk estimation systems using both fatal and non-fatal events can also be recalibrated, but the process is easier and scientifically more robust for mortality than for total events. The European Guidelines on CVD prevention in clinical practice (version 2012[9] and 2016[10]) recommend use of the SCORE system because it is based on large, representative European cohort datasets and because it is relatively straightforward to recalibrate for individual countries.

Persons with documented ASCVD, type 1 or type 2 diabetes, very high levels of individual risk factors, or chronic kidney disease (CKD) are generally at very high or high total CV risk. No risk estimation models are needed for such persons; they all need active management of all risk factors. For other, apparently healthy people, the use of a risk estimation system such as SCORE which estimates the 10-year cumulative risk of a first fatal atherosclerotic event is recommended to estimate total CV risk, since many people have several risk factors that, in combination, may result in high levels of total CV risk.

Risk estimates have been produced as charts for high- and low-risk regions in Europe (*Figures 2* and *3*),[11] All International Classification of Diseases (ICD) codes that are related to deaths from vascular origin caused by atherosclerosis are included. The

reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that non-fatal events are dependent on definition, developments in diagnostic tests and methods of ascertainment, all of which can vary, resulting in very variable multipliers to convert fatal to total events. In addition, total event charts, in contrast to those based on mortality, are more difficult to recalibrate to suit different populations. That said, work is in progress to produce regional total event charts.

The SCORE data indicate that the total CVD event risk is about three times higher than the risk of fatal CVD for men, so that a SCORE risk of 5% translates into a CVD risk of ~15% of total (fatal + non-fatal) CVD end points; the multiplier is higher in women and lower in older people.

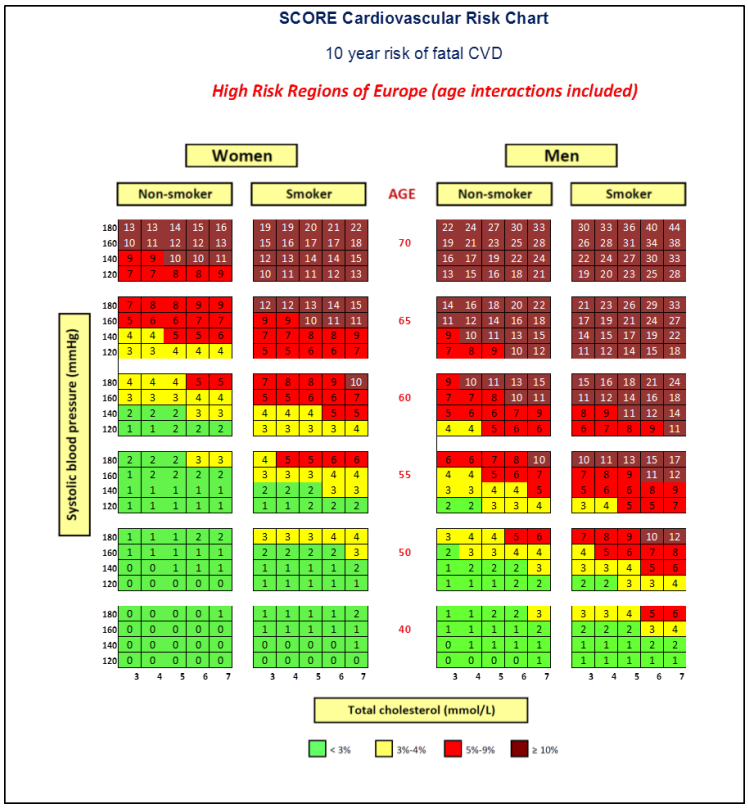



**Figure 2 SCORE chart for European populations at high CVD risk.** Ten-year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk

factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes (type 1 and 2), chronic kidney disease, familial hypercholesterolaemia or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice. Cholesterol: 1 mmol= 38.67 mg/dL

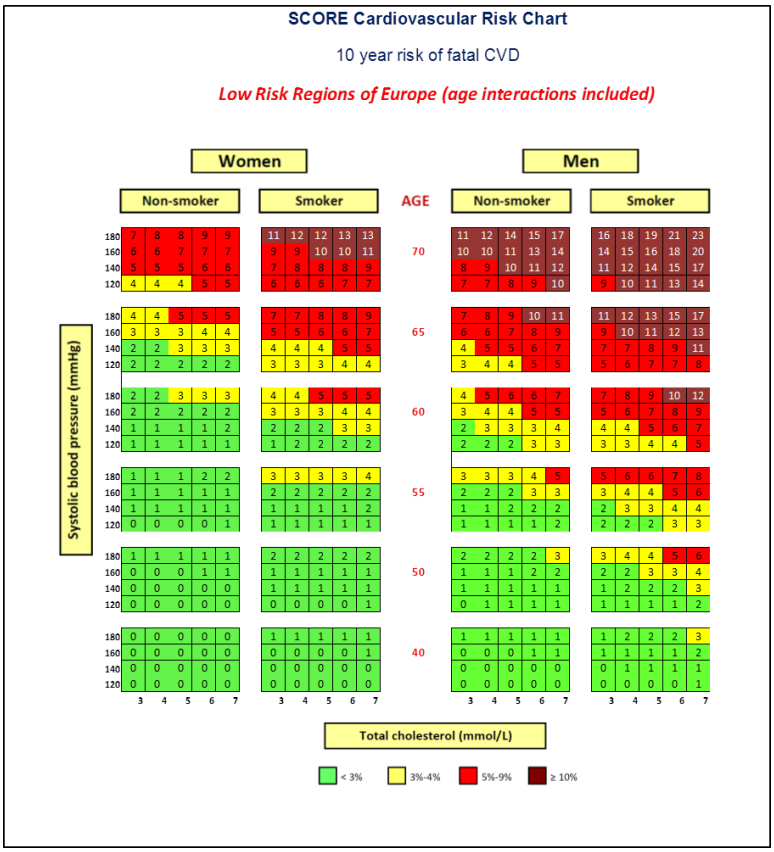
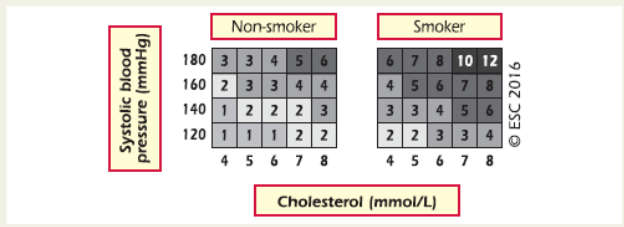



**Figure 3 SCORE chart for European populations at low CVD risk.** Ten-year risk of fatal cardiovascular disease (CVD) in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes (type 1 and 2), chronic kidney disease, familial hypercholesterolaemia, or very high levels of individual risk factors because such people are already at high-risk and need intensive risk factor advice. Cholesterol: 1 mmol= 38.67 mg/dL

Clinicians often ask for thresholds to trigger certain interventions. This is problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated. This is true for all continuous risk factors such as plasma cholesterol or systolic blood pressure (SBP). Therefore, the goals that are proposed in this document reflect this concept.

A particular problem relates to young people with high levels of risk factors; a low absolute risk may conceal a very-high relative risk requiring at least intensive lifestyle advice. To motivate young people (i.e. below 40) not to delay changing their unhealthy lifestyle, an estimate of their relative risk − illustrating that lifestyle changes can reduce relative risk substantially − may be helpful (*Supplementary figure 1*).




**Supplementary figure 1 Chart for estimating the relative risk for 10-year cardiovascular mortality in young people.** Please note that this chart shows RELATIVE not absolute risk. The risks are RELATIVE to 1 in the bottom left. Thus, a person in the top right hand box has a relative risk that is 12 times higher than a person in the bottom left. Cholesterol: 1 mmol= 38.67 mg/dL

Another approach to this problem is to use cardiovascular risk age. The risk age of a person with several CV risk factors is the age of a person with the same level of risk but with ideal levels of risk factors. Thus a high-risk 40-year-old would have a risk age ≥65 years. Risk age can be estimated visually by looking at the SCORE chart (as illustrated in (*Supplementary figure 2*). In this chart, the risk age of a person with risk factors is defined as the age at which a person with ideal risk factor levels would reach the same risk level. Ideal risk factors are non-smoking, total cholesterol (TC) ≤4 mmol/L (155 mg/dL) and SBP ≤120 mmHg. Risk age is also automatically calculated as part of the latest revision of HeartScore (http://www.HeartScore.org).

Risk age has been shown to be independent of the CV end point used,[6, 8] can be used in any population regardless of baseline risk or secular changes in mortality, and therefore avoids the need for recalibration.

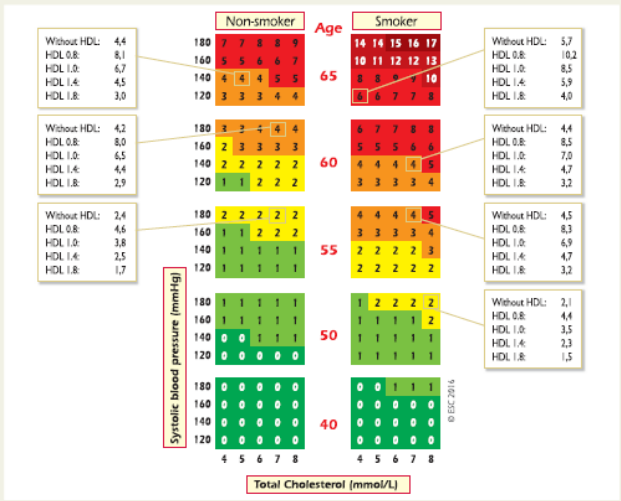
Lifetime risk is another approach to illustrate the impact of risk factors that may be useful in younger people.[12] The greater the burden of risk factors, the higher the lifetime-risk. This approach produces higher risk figures for younger people because of their longer exposure times. It is therefore more useful as a way of illustrating risk than as a guide to treatment because therapeutic trials have been based on a fixed follow-up period and not on lifetime risk.


**Supplementary figure 2 Illustration of the risk age concept**

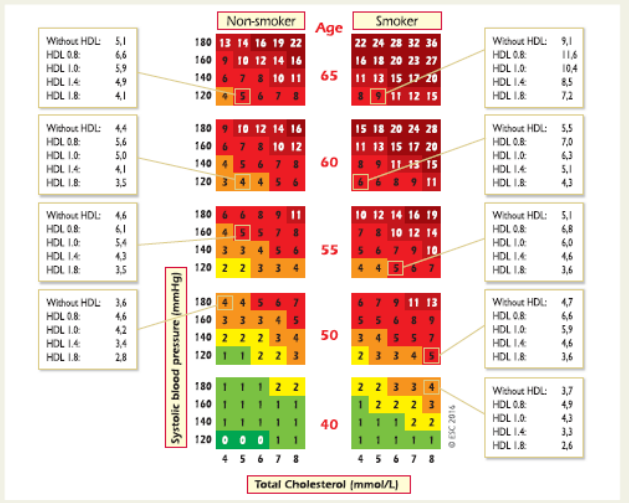
Another problem relates to old people. In some age categories the majority of people, especially male, will have estimated 10-year cumulative CV death risks exceeding the 5-10% level, based on age only, even when other CV risk factor levels are relatively low. Therefore, before initiating treatment in the elderly, clinicians should

evaluate patients carefully. The relative strength of risk factors varies with age and that SCORE overestimates risk in older people (that is, those older than 65).[13] These guidelines include illustrative charts for such people. While older people benefit from smoking cessation and control of hypertension and hyperlipidaemia (see *Section 9.3*), clinical judgement is required to avoid side effects from overmedication.

The additional impact of high-density lipoprotein cholesterol (HDL-C) on risk estimation is illustrated in *Supplementary Figures 3* and *4*; HDL-C cholesterol can be used to increase the accuracy of the risk evaluation. In these charts, HDL-C is used categorically. The electronic version of SCORE, HeartScore (http://www.heartscore.org), has been modified to take HDL-C into consideration as a continuous variable. Clinicians should be aware that at extremely high values (above approx. 90 mg/dL) of HDL-C there appears to be an increased risk of ASCVD, so at such levels HDL-C cannot be used as a risk predictor.




**Supplementary figure 3 Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk**




**Supplementary figure 4 Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk**

### 4.1.2 How to use the risk estimation charts

Using the low-risk or the high-risk SCORE charts will depend on the CVD mortality experience in each country. While any cut-off point is arbitrary and open to debate, in these guidelines the cut-off point for calling a country 'low CVD risk' is based on WHO data derived from the Global Burden of Disease Study.

Countries were categorized as low-risk if their age-adjusted 2016 CVD mortality rate was <150/100 000 (for men and women together) (http://www.who.int/healthinfo/global_burden_disease/estimates/en/). Countries with a CVD mortality rate of 150/100 000 or more are considered to be at high-risk.

*Boxes 1* to *5* summarise the main points regarding the risk estimations charts and their use.

**Box 1 How to use the risk estimation charts**

| |
|---|
| To estimate a person's 10-year risk of cardiovascular disease (CVD) death, find the table for his/her gender, smoking status, and age. Within the table find the cell nearest to the person's blood pressure (BP) and total cholesterol (TC). Risk estimates will need to be adjusted upwards as the person approaches the next age category. |
| Risk is initially assessed on the level of TC and systolic BP before treatment, if known. The longer the treatment and the more effective it is, the greater the reduction in risk, but in general it will not be more |

| |
|---|
| than about one-third of the baseline risk. For example, for a person on antihypertensive drug treatment in whom the pre-treatment BP is not known, if the total cardiovascular (CV) SCORE risk is 6%, then the pre-treatment total CV risk may have been 9%. |
| Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk. |
| The charts may be used to give some indication of the effects of reducing risk factors, given that there is apparently a time lag before the risk reduces. In general, people who stop smoking halve their cumulative risk over a relatively short period of time. |

**Box 2 Risk estimation charts for different countries**

| |
|---|
| The **low-risk charts** should be considered for use in Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Israel, Luxembourg, Netherlands, Norway, Malta, Portugal, Slovenia, Spain, Sweden, Switzerland and United Kingdom. |
| The **high-risk charts** should be considered for use in Albania, Algeria, Armenia, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Poland, Romania, Serbia, Slovakia, Tunisia and Turkey. |
| Some countries have a CVD mortality rate more than 350/100,000, and the **high-risk chart may underestimate risk**. These are Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Macedonia, Republic of Moldova, Russian Federation, Syria, Tajikistan, Turkmenistan, Ukraine and Uzbekistan. |

See http://apps.who.int/gho/data/node.home

**Box 3 Qualifiers**

| |
|---|
| The charts can assist in risk assessment and management but must be interpreted in light of the clinician's knowledge and experience and of the patient's pre-test likelihood of CVD. |
| Risk will be overestimated in countries with a decreasing CVD mortality, and underestimated in countries in which mortality is increasing. This is dealt with by recalibration (www.heartscore.org). |
| Risk estimates are lower in women than in men. However, risk is only deferred in women; the risk of a 60-year-old woman is similar to that of a 50-year-old man. Ultimately more women die from CVD than men. |
| Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low. The relative risk chart (Supplementary *figure* 1) and the estimated risk age (Supplementary *figure 2*) may be helpful in identifying and counselling such persons. |

**Box 4 Factors modifying SCORE risks**

| |
|---|
| Social deprivation – the origin of many of the causes of CVD. |
| Obesity and central obesity as measured by the body mass index and waist circumference, respectively. |
| Physical inactivity. |
| Psychosocial stress including vital exhaustion. |
| Family history of premature CVD (men: <55 years; women: <60 years). |

| |
|---|
| Chronic immune-mediated inflammatory disorder. |
| Major psychiatric disorders. |
| Treatment for human immunodeficiency virus (HIV) infection. |
| Atrial fibrillation. |
| Left ventricular hypertrophy. |
| Chronic kidney disease. |
| Obstructive sleep apnoea syndrome. |
| Non-alcoholic fatty liver disease. |

Social deprivation and psychosocial stress set the scene for increased risk.[14] For those at moderate risk, other factors, including metabolic factors such as increased apolipoprotein B (apoB), lipoprotein(a) (Lp(a)), triglycerides (TGs) or C-reactive protein (CRP), the presence of albuminuria, the presence of atherosclerotic plaque in the carotid or femoral arteries, or the coronary artery calcium (CAC) score, may improve risk classification. Many other biomarkers are also associated with increased CVD risk, although few of these have been shown to be associated with appreciable reclassification. Total CV risk will also be higher than indicated in the SCORE charts in asymptomatic persons with abnormal markers of subclinical atherosclerotic vascular damage. Re-classification is of value in people at moderate CV risk by using markers such as coronary artery calcium (CAC) score >100 Agatston units, ankle-brachial index (ABI) <0.9 or >1.40, carotid-femoral pulse wave velocity >10 m/s or the presence of plaques at carotid or femoral ultrasonography. In studies comparing these markers, CAC had the best reclassification ability.[15-17]

Some factors such as a high HDL-C (up to 2.1-2.3 mmol/L, 80-90 mg/dL),[18] or a family history of longevity, can also be associated with lower risk.

**Box 5 Risk estimation: key messages**

| |
|---|
| In apparently healthy persons, CVD risk is most frequently the result of multiple, interacting risk factors. This is the basis for total CV risk estimation and management. |
| Risk factor screening including the lipid profile should be considered in men >40 years old and in women >50 years of age or post-menopausal. |
| A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under- and over-treatment. |

| |
|---|
| Certain individuals declare themselves to be at high- or very-high CVD risk without needing risk scoring and require immediate attention to all risk factors. This is true for patients with documented CVD, diabetes, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, CAC >100, or extreme Lp(a) elevation. |
| All risk estimation systems are relatively crude and require attention to qualifying statements. |
| Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org). |
| The total risk approach allows flexibility – if optimal control cannot be achieved with one risk factor, trying harder with the other factors can still reduce risk. |

## 4.2 Risk levels

A total CV risk estimate is part of a continuum. The cut-off points that are used to define high-risk are in part arbitrary and in part based on the risk levels at which benefit is evident in clinical trials. In clinical practice, consideration should be given to practical issues in relation to the local healthcare systems. Not only should those at high-risk be identified and managed, but those at moderate-risk should also receive professional advice regarding lifestyle changes; in some cases drug therapy will be needed to reduce atherosclerotic risk.

Low-risk people should be given advice to help them maintain this status. Thus the intensity of preventive actions should be tailored to the patient's total CV risk. The strongest driver of total CV risk is age, which can be considered as 'exposure time' to risk factors.

For these reasons, the Task Force suggests the following categories of risk and LDL-C goals, based on the best available evidence and in an ideal setting with unlimited resources. These categories represent a counsel of perfection but these ideals are for guidance only and practical decision-making must be based on what is appropriate to the local situation.

With these considerations, we propose the following levels of total CV risk (*Table 3*).

**Table 3 Cardiovascular risk categories**

| | |
|---|---|
| **Very high-risk** | People with any of the following:<br>Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, |

| | |
|---|---|
| | coronary revascularisation (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 on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.<br>DM with target organ damage*, ≥3 major risk factors or early onset of T1DM of long duration (>20 years)<br>Severe CKD (eGFR <30 mL/min/1.73 $m^2$).<br>A calculated SCORE ≥10% for 10-year risk of fatal CVD.<br>~~Familial Hypercholesterolaemia (~~FH~~)~~ with ASCVD or with another major risk factor.<br>~~FH.~~ |
| **High-risk** | People with:<br>Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL), LDL-C >4.9 mmol/L (190 mg/dL), or BP ≥180/110 mmHg.<br>Patients with FH without other major risk factors<br>~~LDL-C >4.9 mmol/L (190 mg/dL) or with FH~~Patients with DM without target organ damage*, with DM duration ≥ 10 years or other additional risk factor<br>Moderate CKD (eGFR 30–59 mL/min/1.73 $m^2$).<br>A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD. |
| **Moderate-risk** | Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors<br>Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD. |
| **Low-risk** | Calculated SCORE <1% for 10-year risk of fatal CVD. |

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated GFR; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack;
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

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### 4.2.1 Role of non-invasive cardiovascular imaging techniques on the assessment of total cardiovascular disease risk

Non-invasive imaging techniques can detect the presence, estimate the extent and evaluate the clinical consequences of atherosclerotic vascular damage. Detection of

coronary artery calcification with non-contrast computed tomography (CT) gives a good estimate of the atherosclerotic burden and is strongly associated with CV events.[19] A recent meta-analysis from the US Preventive Services Task Force summarised the available evidence on the value of non-traditional risk factors for risk prediction, and found that, although there are no randomized trials showing that the use of CAC reduces health outcomes, nevertheless it improves both discrimination and re-classification.[20] Assessment of carotid or femoral plaque burden with ultrasound has also been demonstrated to be predictive of CV events, comparable to CAC,[21-24] while the measurement of the carotid intima-media thickness is inferior to CAC score and carotid plaque detection.[17, 25, 26]

In asymptomatic patients at low and moderate-risk who would be eligible for statin therapy (*see Table 4*), assessment of ASCVD with imaging may have an impact on the medical treatment, both from the physician's and the patient's point of view. Data from the MESA study showed that 41-57% of individuals who would be eligible for statin therapy had a CAC score=0 and the rate of atherosclerotic CVD events in the 10-year follow-up was low (1.5-4.9%).[27] In contrast, the rates of atherosclerotic CVD and coronary heart disease (CHD) events in individuals with a CAC score > 100 Agatston were 18.9 and 12.7 per 1000 person-years, respectively.[19] Compared with a strategy of treating all, the use of CAC score to guide long-term statin therapy has been shown to be cost-effective.[28] Note that CAC score is often very low in patients younger than 45 years of age with severe FH, including HoFH, and has a low specificity in this population. Assessment of coronary luminal stenosis over 50% and plaque composition with coronary CT angiography also provides incremental prognostic value over traditional risk stratification models.[29] In asymptomatic individuals with moderate-risk, therefore, the presence of a CAC score >100 Agatston and carotid or femoral plaque burden on ultrasonography may reclassify them to a higher risk category. Therefore, the use of methods to detect these markers should be of interest in that group (*see Recommendations table below*).[15-17] Overall, CAC score assessment with CT may be considered in individuals at low or moderate-risk in whom the respective LDL-C goal is not achieved with lifestyle intervention alone and pharmacological therapy is an option (see *Table 4*). The use of imaging techniques to determine the presence and extent of atherosclerotic

vascular damage in low-risk individuals not being considered for statin therapy is not justified due to low prognostic yield and the associated costs and radiation hazards when measuring CAC score, particularly among low-risk women.[30] Of note, CAC score is increased following statin treatment; therefore, the results of CAC score in those patients should be interpreted with caution in statin-treated patients.

**Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease**

| Recommendations | Class[a] | Level of evidence[b] |
|---|---|---|
| Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate-risk.[30, 31] | IIa | B |
| CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate-risk.[15-17, 25, 27] | IIb | B |

CAC = coronary artery calcium; CT = computed tomography; CV = cardiovascular.
[a]Class of recommendation.
[b]Level of evidence.

### 4.2.2 Risk-based intervention strategies

*Table 4* presents suggested intervention strategies as a function of total CV risk and LDL-C level. This graded approach is based on evidence from multiple meta-analyses and individual randomized controlled trials (RCTs), which show a consistent and graded absolute reduction in ASCVD risk in response to reductions in TC and LDL-C levels (*see Recommendations table below*).[32-42] These data are consistent in showing that, since the relative risk reduction is proportional to the absolute reduction in LDL-C, and the absolute reduction in LDL-C resulting from a particular drug regimen depends only on baseline LDL-C, at any given level of baseline risk the higher the initial LDL-C level the greater the absolute reduction in risk. Advice on individual drug treatments is given in *Chapter 8*.

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

| Total CV risk (SCORE) % | Untreated LDL-C levels | | | | | |
|---|---|---|---|---|---|---|
| | <1.4 mmol/L | 1.4 to <1.8 mmol/L | 1.8 to <2.6 mmol/L | 2.6 to <3.0 mmol/L | 3.0 to <4.9 mmol/L | ≥4.9 mmol/L |

| | | (55 mg/dL) | (55 to <70 mg/dL) | (70 to <100 mg/dL) | (100 to <115 mg/dL) | (115 to <190 mg/dL) | (≥190 mg/dL) |
|---|---|---|---|---|---|---|---|
| **Primary prevention** | **<1 low-risk** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle intervention, consider adding drug if uncontrolled** | **Lifestyle intervention and concomitant drug intervention** |
| | **Class[a]/Level[b]** | I/C | I/C | I/C | I/C | IIa/A | IIa/A |
| | **≥1 to <5 moderate-risk** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle intervention, consider drug if uncontrolled** | **Lifestyle intervention, consider adding drug if uncontrolled** | **Lifestyle intervention and concomitant drug intervention** |
| | **Class[a]/Level[b]** | I/C | I/C | IIa/A | IIa/A | IIa/A | IIa/A |
| | **≥5 to <10, or high-risk** | **Lifestyle advice** | **Lifestyle advice** | **Lifestyle intervention, consider adding drug if uncontrolled** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** |
| | **Class[a]/Level[b]** | IIa/A | IIa/A | IIa/A | I/A | I/A | I/A |
| | **≥10, or at very high-risk due to a risk condition (eg, FHeg, FH with another major risk factor, diabetes mellitus or chronic kidney disease)** | **Lifestyle advice** | **Lifestyle intervention, consider adding drug** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** |
| | **Class[a]/Level[b]** | IIa/B | I/A | I/A | I/A | I/A | I/A |
| **Secondary prevention** | **Very high-risk** | **Lifestyle intervention, consider adding drug** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** | **Lifestyle intervention and concomitant drug intervention** |
| | **Class[a]/Level[b]** | IIa/A | I/A | I/A | I/A | I/A | I/A |

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.

**Recommendations for cardiovascular disease risk estimation**

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| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia. | I | C |
| High-risk and very high-risk individuals may be identified on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, familial hypercholesterolaemia or a high SCORE risk and are a priority for advice and management of all risk factors. | I | C |
| Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM. | III | C |

CVD = cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; SCORE = Systemic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.

# 5. Lipids and lipoproteins

## 5.1 Biological role of lipids and lipoproteins

Lipoproteins in plasma transport lipids to tissues for energy utilization, lipid deposition, steroid hormone production and bile acid formation. Lipoproteins consist of esterified and unesterified cholesterol, TGs, and phospholipids and protein components named apolipoproteins that act as structural components, ligands for cellular receptor binding, and enzyme activators or inhibitors.

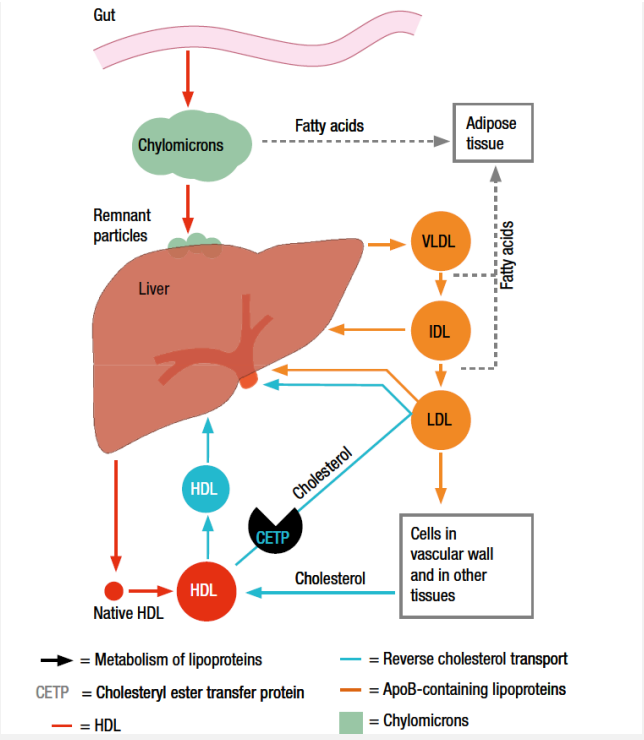
There are six major lipoproteins in blood: chylomicrons; very low-density lipoprotein (VLDL); intermediate-density lipoprotein (IDL); low-density lipoprotein (LDL); lipoprotein(a) (Lp(a)); and high-density lipoprotein (HDL) (*Table 5 and Supplementary figure 5*).

**Table 5 Physical and chemical characteristics of human plasma lipoproteins**

| | Density (g/mL) | Diameter (nm) | TG (%) | Cholesteryl esters (%) | PL (%) | Cholesterol (%) | Apolipoproteins | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Major | Others |
| Chylomicrons | <0.95 | 80–100 | 90–95 | 2–4 | 2–6 | 1 | apoB-48 | apoA-I, A- |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | II, A-IV, A-V |
| VLDL | 0.95–1.006 | 30–80 | 50–65 | 8–14 | 12–16 | 4–7 | apoB-100 | apoA-I, C-II, C-III, E, A-V |
| IDL | 1.006–1.019 | 25–30 | 25–40 | 20–35 | 16–24 | 7–11 | apoB-100 | apoC-II, C-III, E |
| LDL | 1.019–1.063 | 20–25 | 4–6 | 34–35 | 22–26 | 6–15 | apoB-100 | |
| HDL | 1.063–1.210 | 8–13 | 7 | 10–20 | 255 | 5 | apoA-I | apoA-II, C-III, E, M |
| Lp(a) | 1.006–1.125 | 25–30 | 4–8 | 35–46 | 17–24 | 6–9 | apo(a) | apoB-100 |

apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PL = phospholipids; TG = triglycerides; VLDL = very low-density lipoprotein;




**Supplementary figure 5 Lipoprotein transport and metabolism.** Most cholesterol is synthesized in the liver where it is packaged together with triglycerides (TGs) into lipoproteins containing one molecule of apolipoprotein B (apoB) or utilized for bile acid synthesis. The apoB-containing lipoproteins are secreted into the plasma as TGs-rich very low-density lipoproteins

(TRL) and are hydrolysed to liberate TGs for energy storage and consumption to become smaller, denser TRL remnants. These remnant particles can be taken up by the liver, but most are progressively hydrolysed to become low-density lipoproteins (LDL). Most of the LDL particles are taken up by the liver hepatocytes for further metabolism and secretion in the bile. Some LDL is also taken up by peripheral cells as a source of cholesterol. Apolipoprotein A1 (apoA1) containing high-density lipoprotein (HDL) particles transport excess cholesterol from the peripheral cells back to the liver in a process referred to as reverse cholesterol transport. The HDL particles can either transport cholesterol directly back to the liver, or interact with cholesterol ester transfer protein (CETP) to exchange cholesterol for TGs with TG-rich apoB-containing lipoproteins. The transferred cholesterol can then be taken back to the liver carried either by TG-rich lipoproteins or by LDL particles. TGs are a major source of energy for biological processes and are stored predominantly in adipose tissue. TGs are transported from the liver to muscle cells for energy consumption and to adipose cells for energy storage by TG-rich VLDL particles and their remnants. Dietary fat in the form of TGs is digested in the gut and then converted back into TGs in enterocytes where it is combined with cholesterol and a truncated form of apoB (apoB48) to produce TGs-rich chylomicrons. These particles are much larger and contain much more TGs than VLDL particles. Under most conditions, VLDL particles and their remnants represent < 10%, and chylomicrons represent <1%, of the total concentration of circulating apoB-containing lipoproteins, even in the immediate postprandial state.

## 5.2 Role of lipids and lipoproteins in the pathophysiology of atherosclerosis

All apoB-containing lipoproteins less than approximately 70 nm in diameter, including smaller TG-rich lipoproteins and their remnant particles, can cross the endothelial barrier, especially in the presence of endothelial dysfunction, where they can become trapped after interaction with extracellular structures such as proteoglycans.[43] ApoB-containing lipoproteins retained in the arterial wall provoke a complex, process that leads to lipid deposition and the initiation of an atheroma.[44]

Continued exposure to apoB-containing lipoproteins leads to additional particles being retained over time in the artery wall and to the growth and progression of atherosclerotic plaques. On average, people with higher concentrations of plasma apoB-containing lipoproteins will retain more particles and accumulate lipids faster, resulting in more rapid growth and progression of atherosclerotic plaques.

Because atherosclerotic plaques grow over time as additional apoB-containing lipoprotein particles are retained, the size of the total atherosclerotic plaque burden is likely to be determined by both the concentration of circulating LDL-C and other apoB-containing lipoproteins and by the total duration of exposure to these lipoproteins.

Therefore, a person's total atherosclerotic plaque burden is likely to be proportional to their cumulative exposure to these lipoproteins.[45]

Eventually the increase of the atherosclerotic plaque burden along with changes in the composition of the plaque reaches a critical point at which disruption of a plaque can result, with the formation of an overlying thrombus that acutely obstructs blood flow resulting in unstable angina, myocardial infarction (MI) or death. The risk of experiencing an acute ASCVD event therefore rises rapidly as more apoB-containing lipoproteins become retained and the atherosclerotic plaque burden increases. This provides the rationale for encouraging a healthy lifestyle to maintain low levels of apoB-containing lipoproteins throughout life to slow the progression of atherosclerosis, and also explains the motivation to recommend treatment to lower LDL-C and other apoB-containing lipoproteins for both the primary prevention of ASCVD and the secondary prevention of recurrent CV events.[45]

## 5.3 Evidence for the causal effects of lipids and lipoproteins on the risk of atherosclerotic cardiovascular disease

### 5.3.1 Low-density lipoprotein and risk of atherosclerosis

Plasma LDL-C is a measure of the cholesterol mass carried by LDL particles, by far the most numerous of the apoB-containing lipoproteins, and is an estimate the concentration of circulating LDL. Numerous epidemiologic studies, Mendelian randomization studies, and RCTs have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of ASCVD.[35, 46-51] The remarkable consistency among these studies, in addition to biological and experimental evidence, provides compelling evidence that LDL-C is causally associated with the risk of ASCVD, and that lowering LDL-C reduces the risk of ASCVD proportional to the absolute achieved reduction in LDL-C.[2, 52]

Furthermore, Mendelian randomization studies have demonstrated that long-term exposure to lower LDL-C levels is associated with a much lower risk of CV events as compared to shorter term exposure to lower LDL-C (as achieved, for example, in randomized trials).[49, 53] These data provide strong support for the concept that LDL particles have both a causal and cumulative effect on the risk of ASCVD. Therefore, the

effect of LDL-C on the risk of ASCVD appears to be determined by both the absolute magnitude and the total duration of exposure to LDL-C.[2]

The clinical benefit of lowering LDL-C is determined by the reduction in circulating LDL particles as estimated by apoB, which is usually mirrored by reduction of cholesterol carried by those particles.[2, 54, 55] Therefore, the clinical benefit of therapies that lower LDL-C by reducing LDL particle mass will be proportional to the absolute reduction in LDL-C, because – on average – the reduction in LDL-C and LDL particles will be concordant.[35, 51, 56, 57] By contrast, the clinical benefit of therapies that lower LDL-C by a mechanism that may modify dramatically their composition may not be proportional to the observed absolute reduction in LDL-C, but instead would be expected to be proportional to the absolute change in LDL particle concentration as measured by reduction in apoB.[2, 55]

**5.3.2 Triglyceride-rich lipoproteins and risk of atherosclerosis**

TG-rich VLDL particles and their remnants carry most of the circulating TGs. Therefore, the plasma TG concentration reflects the concentration of circulating apoB-containing TG-rich lipoproteins.

Elevated plasma TG levels are associated with an increasing risk of ASCVD, but this association becomes null after adjusting for non-HDL-C, an estimate of the total concentration of all apoB-containing lipoproteins.[46] Similarly, lowering TG with fibrates reduces the risk of CV events by the same amount as LDL-C lowering therapies when measured per unit change in non-HDL-C,[51] suggesting that the effect of plasma TGs on ASCVD is mediated by changes in the concentration of TG-rich lipoproteins as estimated by non-HDL-C.

Also Mendelian randomization studies suggest that the association between plasma TGs and the risk of CHD may be causal; this evidence must be interpreted with caution, however, because nearly all variants associated with TGs are also associated with HDL-C, LDL-C or Lp(a).[58-61] A recent Mendelian randomization study demonstrated that TG lowering lipoprotein lipase (LPL) variants and LDL-C lowering LDL receptor variants had the same effect on the risk of ASCVD per unit change in apoB, suggesting that all apoB-containing lipoproteins have the same effect on the risk of

CHD.[62] Together, these studies strongly suggest that the causal effect of TG-rich lipoproteins and their remnants on the risk of ASCVD is determined by the circulating concentration of apoB-containing particles rather than by the TG content itself.

### 5.3.3 High-density lipoprotein and risk of atherosclerosis

The inverse association between plasma HDL-C and the risk of ASCVD is among the most consistent and reproducible associations in observational epidemiology.[46, 63] By contrast, Mendelian randomization studies do not provide compelling evidence that HDL-C is causally associated with the risk of ASCVD.[50, 64, 65] However, this evidence must be interpreted with caution because most genetic variants associated with HDL-C are also associated with directionally opposite changes in TGs, LDL-C or both, thus making estimates of the effect of HDL-C on the risk of ASCVD very difficult using the Mendelian randomization study design. Furthermore there is no evidence from randomized trials that therapeutically increasing plasma HDL-C reduces the risk of cardiovascular events.[54, 55, 66-68] In the dal-OUTCOMES trial, treatment with the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib increased HDL-C without any effect on LDL-C or apoB, but did not reduce the risk of major CV events.[66] Similarly, in the ACCLERATE and REVEAL trials, treatment with CETP inhibitors more than doubled HDL-C levels but did not appear to reduce the risk of ASCVD events beyond that expected from the modest reductions in apoB levels.[2, 54, 55] Furthermore, several randomized trials have shown that directly infused HDL mimetics increase plasma HDL-C concentration, but do not reduce the progression of atherosclerosis as measured by intravascular ultrasound.[69, 70]

Therefore, there is currently no randomized trial or genetic evidence to suggest that raising plasma HDL-C is likely to reduce the risk of ASCVD events. Whether therapies that alter the function of HDL particles will reduce the risk of ASCVD is unknown.

### 5.3.4 Lipoprotein(a) and risk of atherosclerosis

Lp(a) is an LDL particle with an apolipoprotein(a) moiety covalently bound to its apoB component.[71] It is <70 nm in diameter and can freely flux across the endothelial barrier where it can become, similarly to LDL, retained within the arterial wall and thus may

increase the risk of ASCVD. Pro-atherogenic effects of Lp(a) have also been attributed to pro-coagulant effects and pro-inflammatory effects most likely related to the oxidized phospholipid load carried by Lp(a).[72]

Higher plasma Lp(a) concentrations are associated with an increased risk of ASCVD, but it appears to be a much weaker risk factor for most people than LDL-C.[73, 74] By contrast, Mendelian randomization studies have consistently demonstrated that lifelong exposure to higher Lp(a) levels is strongly and causally associated with an increased risk of ASCVD.[75, 76] Whilst randomized trials evaluating therapies that lower Lp(a) by 20-30% (including niacin and CETP inhibitors) have not provided evidence that lowering Lp(a) reduces the risk of ASCVD beyond that which would be expected from the observed reduction in apoB-containing lipoproteins, recent data with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have suggested a possible role for Lp(a) lowering in reducing CV risk.[77]

This conflicting evidence appears to have been reconciled by a recent Mendelian randomization study that showed that the causal effect of Lp(a) on the risk of ASCVD is proportional to the absolute change in plasma Lp(a) levels. Importantly, this study also suggested that people with extremely high Lp(a) levels >180 mg/dL (64.2 mmol/L) may have an increased lifetime risk of ASCVD similar to people with heterozygous familial hypercholesterolaemia (HeFH). Because up to 90% of Lp(a) levels is inherited, extremely elevated Lp(a) may represent a new inherited lipid disorder that is associated with extremely high lifetime risk of ASCVD and is two-fold more prevalent than HeFH.[78] However, this study[78] and another based on the THRIVE trial[79] have shown that large absolute changes in Lp(a) may be needed to produce a clinically meaningful reduction in the risk of ASCVD events.

## 5.4 Laboratory measurement of lipids and lipoproteins

Measurement of lipids and lipoproteins is used to estimate the risk of ASCVD and guide therapeutic decision-making. Quantification of plasma lipids can be performed in whole plasma and quantification of lipoproteins can be determined by their protein component. Operationally, lipoproteins are classified based on their hydrated density (*see Table 5*).

### 5.4.1 Lipoprotein measurement

Given the central causal role of apoB-containing lipoproteins in the initiation and progression of atherosclerosis, it would be ideal to directly measure the circulating concentration of atherogenic apoB-containing lipoproteins to both estimate risk and guide treatment decisions. Because all apoB-containing lipoproteins, including VLDL, TG-rich remnant particles and LDL, contain a single apoB molecule, quantitation of apoB directly estimates the number of atherogenic particles in plasma.

Standardized, automated, accurate and inexpensive methods to measure apoB are available. Fasting is not required because even in the postprandial state, apoB48-containing chylomicrons typically represent <1% of the total concentration of circulating apoB-containing lipoproteins. Furthermore, the analytical performance of apoB measurements is superior to the measurement or calculation of LDL-C and non-HDL-C.[80]

**5.4.2 Lipid measurements**

In clinical practice, the concentration of plasma lipoproteins is not usually measured directly but instead is estimated by measuring their cholesterol content. Total cholesterol in humans is distributed primarily among three major lipoprotein classes: VLDL, LDL, and HDL. Smaller amounts of cholesterol are also contained in two minor lipoprotein classes: IDL and Lp(a). A standard serum lipid profile measures the concentration of TC and HDL-C as well as TG. With these values, the LDL-C concentration can be estimated.

Plasma LDL-C can be measured directly using enzymatic techniques or preparative ultracentrifugation, but in clinical medicine it is most often calculated using the Friedewald formula:

LDL-C = TC − HDL-C − (TG/2.2) in mmol/L

or

LDL-C = TC − HDL-C − (TG/5) in mg/dL

Although convenient, the Friedewald calculated value of LDL-C has several well-established limitations:

- Methodological errors may accumulate since the formula necessitates three separate analyses of TC, TGs and HDL-C.

- A constant cholesterol/TG ratio in VLDL is assumed. With high TG values (>4.5 mmol/L or >400 mg/dL), the formula cannot be used. This should especially be considered in non-fasting samples.

To overcome the problems associated with calculated LDL-C, direct enzymatic methods for measuring LDL-C have been developed. These methods are commercially available as ready to use for automatic analysis. The definition of LDL-C by the Friedewald equation and by direct measurement is the same: non-HDL-C – VLDL-C, representing the sum of the cholesterol carried by the biochemically defined LDL, IDL and Lp(a) subfractions.

For the general population, calculated LDL-C and direct LDL-C show very strong correlations.[81-84] However, calculated LDL-C has been found to underestimate LDL-C at concentrations of TG in the range of 2 mmol/L (177 mg/dL) or above.[82, 83] Equally, at very low levels of LDL-C, calculated LDL-C may be misleading, especially in the presence of high TG.[82, 85-87] To avoid some of the problems with the Friedewald formula, a number of modifications for calculation of LDL-C have been suggested, but it remains to be proven that these modifications are superior to Friedewald's formula for estimation of CV risk.[82, 86-88] It is important to note that direct LDL-C measurements also have limitations, including systematic bias and inaccuracy in patients with dyslipidaemia, especially for high TG.[89-91]

As an alternative calculated LDL-C, non-HDL-C can be calculated as TC – HDL-C and is a measure of the TC carried by all atherogenic apoB-containing lipoproteins including TG-rich particles in VLDL and their remnants.[92]

Several methods for determination of Lp(a) are available. The complex molecular structure of Lp(a) and the variation in size of apo(a) has been a challenge in the development of analytical methods for Lp(a). Available methods are, to a varying degree, influenced by the apo(a) isoform.[93] Furthermore the concentration of Lp(a) is reported as either molar concentration (nmol/L) or as mass (mg/dL) by the various assays, and conversion between molar and mass concentrations has been found to be both size and concentration dependent.[93-95] Therefore, standardization between assays is needed to establish a reliable and reproducible method to quantify Lp(a) mass or particle number.[94]

### 5.4.3 Fasting or non-fasting?

Traditionally, blood sampling for lipid analyses has been recommended in the fasting state. Recent systematic studies comparing fasting and non-fasting samples suggest that the difference is small for most lipid parameters.[86, 96-102] Non-fasting sampling has been used in large population-based studies.[92] In most studies, non-fasting samples display a higher TG level of about 0.3 mmol/L (27 mg/dL).[92, 103] On average and for most individuals, this increment will be of no clinical significance. Indeed, a number of international guidelines recommend non-fasting sampling.[92, 104, 105]

For general risk screening, non-fasting samples seem to have at least the same prognostic value as fasting.[106] The practical advantages with non-fasting, including better patient acceptability, outweigh the potential imprecision in some patients, although the determination of some key analytes, such as fasting glucose, may be compromised. Furthermore, even if non-fasting can be used in most cases, in patients with the metabolic syndrome, diabetes or hypertriglyceridaemia (HTG), calculated LDL-C should be interpreted with caution.

## 5.5 Recommendations for measuring lipids and lipoproteins to estimate risk of atherosclerotic cardiovascular disease

Measurement of plasma TC is needed to calculate risk using SCORE, while including plasma HDL-C level can improve risk estimation using the online SCORE calculator. Therefore, both TC and HDL-C should be measured to estimate a person's risk of ASCVD using SCORE, or one of the other risk calculators (almost all of which also include measurements of TC and HDL-C).

Plasma LDL-C should be measured to estimate the risk of ASCVD that can be modified with LDL-C lowering therapies, and to assess for the presence of markedly elevated LDL-C levels that may suggest a lifetime high risk of ASCVD due to lifelong cumulative exposure to high levels of atherogenic lipoproteins, such as in familial hypercholesterolaemia (FH). Plasma LDL-C can be either calculated or measured directly.

Plasma TG should be assessed to identify people who may have a greater modifiable risk of ASCVD than is reflected by LDL-C, due to the presence of an

increased concentration of atherogenic apoB-containing TG-rich lipoproteins and their remnants; and to identify people in whom calculated and directly measured LDL-C may underestimate the risk of ASCVD by underestimating either the concentration of circulating LDL particles or the cholesterol content carried by those particles, such as those with very low levels of LDL. This may be especially relevant in patients with diabetes or the metabolic syndrome.

In general, LDL-C, non-HDL-C and apoB concentrations are very highly correlated. As a result, under most circumstances, they provide very similar information about ASCVD risk.[46, 107-110] However, under certain circumstances – including among people with elevated TG, diabetes, obesity or very low achieved LDL-C levels – the calculated or directly measured LDL-C level may underestimate both the total concentration of cholesterol carried by LDL and, more importantly, underestimate the total concentration of apoB-containing lipoproteins, thus underestimating the risk of ASCVD. In up to 20% of patients there may be discordance between measured LDL-C and apoB levels.[86, 111]

Considering the potential inaccuracy of LDL-C in dyslipidaemia, and among patients with diabetes or high TG, or in patients with very low LDL-C, measurement of both apoB and non-HDL-C is recommended as part of the routine lipid analysis for risk evaluation in patients with elevated plasma TG. Because apoB provides an accurate estimate of the total concentration of atherogenic particles under all circumstances, it is the preferred measurement to further refine the estimate of ASCVD risk that is modifiable by lipid lowering therapy.

Measurement of Lp(a) should be considered at least once in each person's lifetime, if available, to identify people who have inherited an extremely elevated level of Lp(a) ≥180 mg/dL (64.2 mmol/L) and therefore have a very high lifetime risk of ASCVD that is approximately equivalent to the risk associated with HeFH. In addition, this strategy can identify people with less extreme Lp(a) elevations who may be at a higher risk of ASCVD, which is not reflected by the SCORE system or by other lipid or lipoprotein measurements. Measurement of Lp(a) has been shown to provide a clinically significant improved risk reclassification under certain conditions and therefore should be

considered in patients who have an estimated 10-year risk of ASCVD that is close to the threshold between high and moderate risk.[112-114]

Recommendations for measuring lipids and lipoproteins to estimate the risk of ASCVD are summarized in the table below.

**Recommendations for lipid analyses for cardiovascular disease risk estimation**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| TC is to be used for the estimation of total CV risk by means of the SCORE system. | I | C |
| HDL-C analysis is recommended to further refine risk estimation using the online SCORE system. | I | C |
| LDL-C analysis is recommended as the primary lipid analysis for screening, diagnosis and management. | I | C |
| TG analysis is recommended as a part of the routine lipid analysis. | I | C |
| Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or very low LDL-C. | I | C |
| ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis and management, and may be preferred over non HDL-C in people with high TG, diabetes, obesity or very low LDL-C. | I | C |
| Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (64.2 mmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia. | IIa | C |
| Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk. | IIa | C |

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systemic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.

# 6. Treatment targets and goals

In the 2016 EAS/ESC guidelines for the management of dyslipidaemias[1, 115] and other major guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk

in adults,[41, 116] the importance of LDL-C lowering to prevent ASCVD is strongly emphasized. The European Task Force felt that limiting the current knowledge on CV prevention only to results from RCTs reduces the exploitation of the potential that is available for prevention of ASCVD. It is the concordance of the conclusions from many different approaches (from basic science, clinical observations, genetics, epidemiology, RCTs, *etc*) that contributes to the understanding of the causes of ASCVD and to the potential of prevention. The Task Force is aware of the limitations of some of the sources of evidence and accepts that RCTs have not examined different LDL-C goals systematically, but felt that it was appropriate to look at the totality of the evidence. Particular consideration was given to results from meta-analyses confirming the dose-dependent reduction in ASCVD with LDL-C lowering agents; the greater the absolute LDL-C reduction, the greater the CV risk reduction.[36, 37, 51, 117] The benefits related to LDL-C reduction are not specific for statin therapy.[34] No level of LDL-C below which benefit ceases or harm occurs has been defined.

There is considerable individual variability in the LDL-C response to dietary and drug treatments,[32] which is traditionally taken to support a tailored approach to management. Total CV risk reduction should be individualized, and this can be more specific if goals are defined. The use of goals can also aid patient–doctor communication. It is judged that a goal approach may facilitate adherence to treatment, although this consensus opinion has not been fully tested. For all these reasons, the European Task Force retains a goal approach to lipid management, and treatment goals are tailored to the total CV risk level. There is also evidence suggesting that lowering LDL-C beyond the goals that were set in the previous EAS/ESC guidelines is associated with fewer ASCVD events.[35, 118, 119] Therefore, it seems appropriate to reduce LDL-C to as low as possible, at least in patients at very-high CV risk, and for this reason a minimum 50% reduction is suggested for LDL reduction, together with reaching the tailored goal.

The lipid goals are part of a comprehensive CV risk reduction strategy, summarized in *Table 6*. The rationales for the non-lipid targets are given in the 2016 ESC Joint Prevention guidelines.[10]

**Table 6 Treatment targets and goals for cardiovascular disease prevention**

| | |
|---|---|
| **Smoking** | No exposure to tobacco in any form. |
| **Diet** | Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish. |
| **Physical activity** | 3.5-7 hours moderately vigorous physical activity per week or 30–60 min most days. |
| **Body weight** | BMI 20-25 kg/m$^2$, waist circumference <94 cm (men) and <80 cm (women). |
| **Blood pressure** | <140/90 mmHg[a] |
| **LDL-C** | **Very high-risk in primary or secondary prevention**<br>A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (55 mg/dL).<br>No current statin use: this is likely to require high-intensity LDL-lowering therapy.<br>Current LDL-lowering treatment: an increased treatment intensity is required.<br>**High-risk:** A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (70 mg/dL).<br>**Moderate-risk:**<br>A goal of <2.6 mmol/L (100 mg/dL).<br>**Low-risk:**<br>A goal of <3.0 mmol/L (115 mg/dL) |
| **Non-HDL-C** | Non-HDL-C secondary goals are <2.2, 2.6 and 3.4 mmol/L (85, 100 and 130 mg/dL) for very high-, high- and moderate-risk people, respectively. |
| **Apolipoprotein B** | ApoB secondary goals are <65, 80 and 100 mg/dL for very high-, high- and moderate-risk people, respectively. |
| **Triglycerides** | No goal but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. |
| **Diabetes** | HbA1c: <7% (<53 mmol/mol). |

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated. .[120]

[b]The term 'baseline' refers to the LDL-C level in a subject not taking any lipid lowering medication, or to the extrapolated baseline value for those who are on current treatment.

The targeted approach to lipid management is primarily aimed at reducing atherosclerotic risk by lowering LDL-C substantially to levels that have been achieved in recent large-scale trials of PCSK-9 inhibitors. Therefore, for patients at a very high CV risk, whether in secondary prevention or (rarely) in primary prevention an LDL-C

reduction of at least 50% from baseline and an LDL-C goal <1.4 mmol/L (55 mg/dL) are recommended. For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) whilst taking maximally tolerated statin-based therapy, an LDL-C goal <1.0 mmol/L (40 mg/dL) may be considered.[121, 122] For people at high CV risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal <1.8 mmol/L (70 mg/dL) are recommended. In patients at moderate CV risk an LDL-C goal <2.6 mmol/L (100 mg/dL) should be considered, while for low-risk individuals the goal is <3.0 mmol/L (115 mg/dL) may be considered (see *Recommendations table below* and *Supplementary table 2*).

**Recommendations for treatment goals for low-density lipoprotein cholesterol**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In secondary prevention patients at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended.[34-36, 121, 122] | I | A |
| In primary prevention, for individuals at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended.[34-36, 121, 122] | I | C |
| For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) whilst taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered.[121, 122] | IIb | B |
| In patients at HIGH-risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (70 mg/dL) are recommended.[35, 36] | I | A |
| In individuals at MODERATE-risk[c], an LDL-C goal of <2.6 mmol/L (100 mg/dL) should be considered.[35] | IIa | A |
| In individuals at LOW-risk[c] an LDL-C goal <of 3.0 mmol/L (115 mg/dL) may be considered.[35] | IIb | A |

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]For definitions see Table 3.

[d]The term 'baseline' refers to the LDL-C level in a subject not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

**Supplementary table 2 low-density lipoprotein cholesterol achievable as a function of the starting value and the desired % reduction**

| Starting LDL-C, mmol/L (mg/dL) | LDL-C goals, mmol/L (mg/dL) |
|---|---|
| | 50% |
| 6.2 (240) | <3.1 (120) |
| 5.9 (230) | <3.0 (115) |
| 5.7 (220) | <2.8 (110) |
| 5.4 (210) | <2.7 (105) |
| 5.2 (200) | <2.6 (100) |
| 4.9 (190) | <2.5 (95) |
| 4.7 (180) | <2.3 (90) |
| 4.4 (170) | <2.2 (85) |
| 4.1 (160) | <2.1 (80) |
| 3.9 (150) | <1.9 (75) |
| 3.6 (140) | <1.8 (70) |
| 3.4 (130) | <1.7 (65) |
| 3.1 (120) | <1.6 (60) |
| 2.8 (110) | <1.4 (55) |
| 2.6 (100) | <1.3 (50) |
| 2.3 (90) | <1.2 (45) |
| 2.1 (80) | <1.0 (40) |
| 1.8 (70) | <0.9 (35) |

LDL-C = low-density lipoprotein cholesterol.

Secondary goals have also been defined by inference for non-HDL-C and for apoB; they receive a moderate grading, as they have not been extensively studied in RCTs. The specific goal for non-HDL-C should be 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C goal; adjusting lipid-lowering therapy in accordance with these secondary goals may be considered after having achieved an LDL-C goal in patients at very high CV risk, although the clinical advantages of this approach with respect to

outcomes remain to be addressed. When secondary targets are used the recommendations are:

– non-HDL-C <2.2 mmol/L (85 mg/dL), <2.6 mmol/L (100 mg/dL) and <3.4 mmol/L (130 mg/dL) in people at very high-, high- and moderate-CV risk, respectively.[123-125]

– apoB <65 mg/dL, <80 mg/dL and <100 mg/dL in very high-, high- and moderate-total CV risk, respectively.[123, 125, 126]

To date, no specific goals for HDL-C or TG levels have been determined in clinical trials, although increases in HDL-C predict atherosclerosis regression and low HDL-C is associated with excess events and mortality in coronary artery disease (CAD) patients, even at low LDL. Clinicians should use clinical judgment when considering further treatment intensification in patients at high or very high total CV risk.

# 7. Lifestyle modifications to improve the plasma lipid profile

The pivotal role of nutrition in the prevention of ASCVD has been extensively reviewed.[127-131] Dietary factors influence the development of CVD either directly or through their action on traditional risk factors, such as plasma lipids, BP or glucose levels.

Convincing evidence of the causal association between diet and ASCVD risk is, nevertheless, available indirectly from randomized 'metabolic ward' studies showing that a high saturated fat intake causes increased LDL-C concentrations, and from cohort studies, genetic epidemiological studies, and randomized trials showing that higher LDL cholesterol causes ASCVD.

The lack of concordance between studies is due both to methodological problems, (particularly inadequate sample size or short study duration) and to the difficulty of evaluating the impact of a single dietary factor independently of any other changes in the diet.[132] In fact, as foods are mixtures of different nutrients and other components, it is not appropriate to attribute the health effects of a food only to one of its components. Moreover, if the energy intake must be kept constant, eating less of one macronutrient

implies necessarily eating more of others. The quality of the replacement (for instance, unsaturated fat vs. highly refined grains) can influence the effect observed, significantly modifying the impact on health of the nutrient replaced. These limitations suggest caution in interpreting the results of RCTs or even meta-analyses of RCTs in relation to the effect of a single dietary change on ASCVD.[132]

To overcome, at least in part, these problems, in recent years nutrition research has focused on the relationship between ASCVD on the one hand, and foods and dietary patterns – rather than single nutrients – on the other. Consistent evidence from epidemiological studies indicates that higher consumption of fruit, non-starchy vegetables, nuts, legumes, fish, vegetable oils, yogurt, whole grains, along with a lower intake of red and processed meats, foods higher in refined carbohydrates and salt is associated with a lower incidence of CV events.[133] Moreover, it indicates that the replacement of animal fats, including dairy fat, with vegetable sources of fats and polyunsaturated fatty acids (PUFAs) may decrease the risk of CVD.[134]

Dietary patterns that have been more extensively evaluated are the Dietary Approaches to Stop Hypertension (DASH) diet – particularly in relation to BP control – and the Mediterranean diet; both have proven to be effective in reducing CV risk factors and, possibly, to contribute to ASCVD prevention.[135] The most relevant difference between the Mediterranean and the DASH diet is the emphasis of the former on extra virgin olive oil. The Mediterranean diet is associated with a reduced incidence of CV and other non-communicable diseases in epidemiological studies[136, 137] and has been proven in RCTs to be effective in reducing CV events in primary and secondary prevention.[138, 139] In particular, the PREDIMED trial indicated that participants allocated to a Mediterranean type of diet supplemented with extra-virgin olive oil or nuts had a significantly lower (around 30%) incidence of major CV events, as compared to those who were on a low fat diet.[140]

In summary, despite the results of PREDIMED and a few other intervention studies with ASCVD end points that support a healthy lifestyle for ASCVD prevention, RCTs cannot represent the sole grounds on which dietary recommendations should rely. They also need to be based on the combination of large observational cohort studies and

relatively short-term randomized trials having intermediate-risk factors (such as blood lipids) as outcomes.

*Table 7* summarizes the currently available evidence on the influence of lifestyle changes and functional foods on lipoproteins, indicating the magnitude of the effects and the levels of evidence in relation to the impact on the specific lipoprotein class; for the reasons outlined above, the level of evidence is not based on RCTs with ASCVD end points. Moreover, within a guideline on the management of dyslipidaemias, information on the potential for improving the plasma lipoprotein profile by dietary means is clinically relevant, even in the absence of a clear demonstration of CV benefits.

**Table 7 Impact of specific lifestyle changes on lipid levels**

| | Magnitude of the effect | Level of evidence | Ref |
|---|---|---|---|
| **Lifestyle interventions to reduce TC and LDL-C levels** | | | |
| Avoid dietary trans fat | ++ | **A** | 131, 141 |
| Reduce dietary saturated fat | ++ | **A** | 131, 142 |
| Increase dietary fibre | ++ | **A** | 143, 144 |
| Use functional foods enriched with phytosterols | ++ | **A** | 145, 146 |
| Use red yeast rice nutraceuticals | ++ | **A** | 147-149 |
| Reduce excessive body weight | ++ | **A** | 150, 151 |
| Reduce dietary cholesterol | + | **B** | 152, 153 |
| Increase habitual physical activity | + | **B** | 154 |
| **Lifestyle interventions to reduce TG-rich lipoprotein levels** | | | |
| Reduce excessive body weight | + | **A** | 150, 151 |
| Reduce alcohol intake | +++ | **A** | 155, 156 |

| | | | |
|---|---|---|---|
| Increase habitual physical activity | ++ | **A** | 154, 157 |
| Reduce total amount of dietary carbohydrate | ++ | **A** | 150, 158 |
| Use supplements of n-3 polyunsaturated fat | ++ | **A** | 159, 160 |
| Reduce intake of mono- and disaccharides | ++ | **B** | 161, 162 |
| Replace saturated fat with mono- or polyunsaturated fat | + | **B** | 131, 139 |
| **Lifestyle interventions to increase HDL-C levels** | | | |
| Avoid dietary trans fat | ++ | **A** | 131, 163 |
| Increase habitual physical activity | +++ | **A** | 154, 164 |
| Reduce excessive body weight | ++ | **A** | 150, 151 |
| Reduce dietary carbohydrates and replace them with unsaturated fat | ++ | **A** | 150, 165 |
| Modest consumption in those who take alcohol may be continued | ++ | **B** | 156 |
| Quit smoking | + | **B** | 166 |

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.
The magnitude of the effect (+++ = more than 10%, ++ = between 5% and 10%, + = less than 5%, – = not effective) and the level of evidence refer to the impact of each dietary modification on plasma levels of a specific lipoprotein class.

## 7.1 The influence of lifestyle on total cholesterol and low-density lipoprotein cholesterol levels

Saturated fatty acids (SFAs) are the dietary factor with the greatest impact on LDL-C levels (0.02-0.04 mmol/L or 0.8-1.6 mg/dL of LDL-C increase for every additional 1% energy coming from saturated fat).[167] Quantitatively, dietary trans fatty acids have a similar elevating effect on LDL-C to that of SFAs; however, while SFAs increase HDL-C levels, trans fats decrease them.[139] Trans unsaturated fatty acids can be found in limited amounts (usually <5% of total fat) in dairy products and in meats from ruminants. 'Partially hydrogenated fatty acids' of industrial origin represent the major source of trans

fatty acids in the diet; the average consumption of trans fatty acids ranges from 0.2% to 6.5% of the total energy intake in different populations.[168] Unsaturated fat-rich oils from safflower, sunflower, rapeseed, flaxseed, corn, olives or soybean reduced LDL-C (-0.42 to -0.20 mmol/L) when used in substitution of SFA-rich food like butter or lard.[169] The effects of carbohydrate consumption on LDL-C are described in *section 7.4.3*.

Body weight reduction also influences TC and LDL-C, but the magnitude of the effect is small: in obese people, a decrease in LDL-C concentration of 0.2 mmol/L (8 mg/dL) is observed for every 10 kg of weight loss.[150, 170] The reduction of LDL-C levels induced by regular physical exercise is even smaller.[154, 171] The benefits of weight reduction and physical exercise on the CV risk profile likely impact on other risk factors, especially hypertension and diabetes.

*Table 8* summarizes the possible choices of food to lower TC and LDL-C. Given the cultural diversity of the European populations, they should be translated into practical behaviours, considering local habits and socio-economic factors.

**Table 8 Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile**

| | To be preferred | To be used with moderation | To be chosen occasionally in limited amounts |
|---|---|---|---|
| Cereals | Whole grains | Refined bread, rice and pasta, biscuits, corn flakes | Pastries, muffins, pies, croissants |
| Vegetables | Raw and cooked vegetables | Potatoes | Vegetables prepared in butter or cream |
| Legumes | Lentils, beans, fava beans, peas, chickpeas, soybean | | |
| Fruit | Fresh or frozen fruit | Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice | |
| Sweets and sweeteners | Non-caloric sweeteners | Sucrose, honey, chocolate, candies | Cakes, ice creams, fructose, soft drinks |
| Meat and fish | Lean and oily fish, poultry without | Lean cuts of beef, lamb, pork or veal, | Sausages, salami, bacon, spare ribs, hot dogs, organ meats |

| | | | |
|---|---|---|---|
| | skin | seafood, shellfish | |
| Dairy food and eggs | Skim milk and yogurt | Low-fat milk, low-fat cheese and other milk products, eggs | Regular cheese, cream, whole milk and yogurt |
| Cooking fat and dressings | Vinegar, mustard, fat-free dressings | Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup | Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat |
| Nuts/seeds | | All, unsalted (except coconut) | Coconut |
| Cooking procedures | Grilling, boiling, steaming | Stir-frying, roasting | Frying |

## 7.2 The influence of lifestyle on triglyceride levels

Weight reduction improves insulin sensitivity and decreases TG levels. Regular physical exercise reduces plasma TG levels over and above the effect of weight reduction.[154, 171, 172] Alcohol intake has a major impact on TG levels, particularly in individuals with HTG.[156, 173] The detrimental effects of a high carbohydrate diet on TGs occur mainly when refined carbohydrate-rich foods are consumed, while they are much less prominent if the diet is based largely on fibre-rich, low glycaemic index foods. This applies particularly to people with diabetes or with metabolic syndrome (MetS).[174, 175] Habitual consumption of significant amounts (>10% energy) of dietary fructose contributes to TG elevation, particularly in people with HTG or abdominal obesity. These effects are dose dependent; with a habitual fructose consumption between 15-20% of the total energy intake, plasma TG increases as much as 30-40%. Sucrose, a disaccharide-containing glucose and fructose, represents an important source of fructose in the diet.[162, 176, 177]

## 7.3 The influence of lifestyle on high-density lipoprotein cholesterol levels

Weight reduction increases HDL-C levels: a 0.01 mmol/L (0.4 mg/dL) increase is observed for every kilogram decrease in body weight when weight reduction has stabilized. Aerobic physical activity, such as 25-30 km of risk walking per week (or any equivalent activity), may increase HDL-C levels by 0.08-0.15 mmol/L (3.1-6 mg/dL).[172]

Smoking cessation may also contribute to HDL-C elevation, provided that weight gain is prevented.[166]

## 7.4 Lifestyle recommendations to improve the plasma lipid profile

LDL-C lowering represents the primary target for reducing CV risk and therefore it deserves special emphasis in the evaluation of lifestyle measures The diet recommended to the general population, and particularly to people at increased CV risk, may also be able to modify plasma TG and HDL-C levels (*Table 8*). This section focuses on dietary and other lifestyle factors that may be implemented to improve the overall lipoprotein profile.

### 7.4.1 Body weight and physical activity

Since overweight, obesity and, in particular, abdominal adiposity often contribute to dyslipidaemia, caloric intake should be reduced, and energy expenditure increased in those with excessive weight and/or abdominal adiposity.

Body weight reduction, even if modest (5-10% of basal body weight), improves lipid abnormalities and favourably affects the other CV risk factors often present in dyslipidaemic individuals.[151] While the beneficial effect of weight reduction on metabolic and surrogate markers has been demonstrated, the benefit of weight loss on mortality and CV outcome is less clear.[178]

Weight reduction can be achieved by decreasing the consumption of energy-dense foods, inducing a caloric deficit of 300-500 kcal/day. The intervention should combine diet and exercise; this approach also leads to the greatest improvement in physical performance and quality of life and mitigates reductions in muscle and bone mass, particularly in older people.[179] It is always appropriate to advise people with dyslipidaemia to engage in regular physical exercise of moderate intensity for at least 30 min/day even if they are not overweight.[171]

### 7.4.2 Dietary fat

Avoiding any consumption of trans fat is a key measure of the dietary prevention of CVD. The trans fatty acids produced in the partial hydrogenation of vegetable oils

account for 80% of total intake. Thanks to efforts made in different parts of the world, the intake of trans fatty acids has decreased substantially over the past 10-15 years.

As for saturated fat, its consumption should be <10% of the total caloric intake and should be further reduced (<7% of energy) in the presence of hypercholesterolaemia. For most individuals, a wide range of total fat intakes is acceptable and will depend upon individual preferences and characteristics. However, fat intakes that exceed 35-40% of calories are generally associated with increased intakes of both saturated fat and calories. Conversely, a low intake of fats and oils increases the risk of inadequate intakes of vitamin E and of essential fatty acids, and may contribute a reduction of HDL-C.[167]

Fat intake should predominantly come from sources of MUFAs and both n-6 and n-3 PUFAs. Not enough data are available to make a recommendation regarding the optimal n-3:n-6 fatty acid ratio.[180, 181] The cholesterol intake in the diet should be reduced (< 300 mg/day), particularly in people with high plasma cholesterol levels.

### 7.4.3 Dietary carbohydrate and fibre

Dietary carbohydrate has a 'neutral' effect on LDL-C, although their excessive consumption is represented by untoward effects on plasma TGs and HDL-C levels.[167] Dietary fibre (particularly of the soluble type), which is present in legumes, fruits, vegetables and wholegrain cereals (oats, barley), has a hypocholesterolaemic effect and represents a good dietary substitute for saturated fat to maximize the effects of the diet on LDL-C levels and to minimize the untoward effects of a high carbohydrate diet on other lipoproteins.[143, 182]

Carbohydrate intake should range between 45-55% of total energy intake, since both higher and lower percentages of carbohydrate diets are associated with increased mortality.[183, 184] A fat-modified diet that provides 25-40 g of total dietary fibre, including at least 7-13 g of soluble fibre, is well tolerated, effective and recommended for plasma lipid control; conversely, there is no justification for the recommendation of very low carbohydrate diets.[185]

Intake of added sugar should not exceed 10% of total energy (in addition to the amount present in natural foods such as fruits and dairy products); more restrictive advice concerning sugars may be useful for those needing to lose weight or with high plasma TG

values, MetS or diabetes. Soft drinks should be used with moderation by the general population and should be drastically limited in those individuals with elevated TG values or visceral adiposity.[161, 162, 177] The Prospective Urban Rural Epidemiology (PURE) study was a large, epidemiological cohort study of 135 335 individuals enrolled in 18 countries with food frequency questionnaires recorded. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke.[184] However, a metanalysis of epidemiological studies including also PURE showed a U-shaped relationship between carbohydrate intake and mortality: diets associated with the highest mortality rate had carbohydrate intakes above 70% and below 40% of energy, with minimal-risk observed when carbohydrate intake was between 45% and 55% of the total energy intake.[183]

#### 7.4.4 Alcohol

Moderate alcohol consumption [up to 10 g/day (1 unit) for men and women] is acceptable for those who drink alcoholic beverages, if TG levels are not elevated.[186, 187]

#### 7.4.5 Smoking

Smoking cessation has clear benefits on the overall CV risk, and specifically on HDL-C.[166]

## 7.5 Dietary supplements and functional foods for the treatment of dyslipidaemias

Nutritional evaluation of functional foods includes not only the search for clinical evidence of beneficial effects relevant to improved health or reduction of disease risk, but also the demonstration of good tolerability. Overall, the available evidence on functional foods so far identified in this field is incomplete; the major gap is the absence of diet-based intervention trials of enough duration to be relevant for the natural history of dyslipidaemia and CVD.

#### 7.5.1 Phytosterols

The principal phytosterols are sitosterol, campesterol and stigmasterol; they occur naturally in vegetable oils and in smaller amounts in vegetables, fresh fruits, nuts, grains and legumes. The dietary intake of plant sterols ranges between an average of 250 mg/day in Northern Europe to ~500 mg/day in Mediterranean countries. Phytosterols compete with cholesterol for intestinal absorption, thereby modulating TC levels.

The daily consumption of 2 g of phytosterols can effectively lower TC and LDL-C by 7-10% in humans (with a certain degree of heterogeneity among individuals), while it has little or no effect on HDL-C and TG levels.[146] However no studies have been performed yet on the subsequent effect on CVD. Based on LDL-C lowering and the absence of adverse signals, functional foods with plant sterols/stanols (at least 2 g/day with the main meal) may be considered: (i) in individuals with high cholesterol levels at intermediate or low global CV risk who do not qualify for pharmacotherapy; (ii) as an adjunct to pharmacological therapy in high- and very high-risk patients who fail to achieve LDL-C goals on statins or could not be treated with statins; and (iii) in adults and children (>6 years) with familial hypercholesterolaemia, in line with current guidance.[145]

### 7.5.2 Monacolin and red yeast rice

Red yeast rice (RYR) is a source of fermented pigment that has been used in China as a food colorant and flavour enhancer for centuries. Hypocholesterolaemic effects of RYR are related to a statin-like mechanism – inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase – of monacolins, which represent the bioactive ingredient. Different commercial preparations of RYR have different concentrations of monacolins and lower TC and LDL-C to a variable extent, but the consumer is not able to make that distinction.[147, 188] Moreover, the long-term safety of the regular consumption of these products is not fully documented and with some preparations safety issues owing the possible presence of contaminants have been raised. Side effects like those observed with statins have also been reported.

In the only available RCT in patients with ASCVD, a partially purified extract of RYR reduced recurrent events by 45%.[149] A clinically relevant hypocholesterolaemic effect (up to a 20% reduction) has been observed with RYR preparations providing a daily dose of 5-10 mg monacolin K.[148] Nutraceuticals containing purified RYR may be

considered in people with elevated plasma cholesterol concentrations who do not qualify for treatment with statins in view of their global CV risk. However, there is a clear need for better regulation of RYR supplements. Information regarding the precise composition of these products, of the quantities of their components and of their purity should be implemented.[188]

### 7.5.3 Dietary fibre

Available evidence consistently demonstrates a TC- and LDL-C-lowering effect of β-glucan, a viscous fibre from oat and barley. Foods enriched with these fibres or supplements are well tolerated, effective and recommended for LDL-C lowering.[189] However, the dosage to achieve a clinically relevant reduction in levels of LDL-C of 3-5% varies from 3 g to 10 g per day according to the specific type of fibre.[190]

### 7.5.4 Soy

The cholesterol lowering effect of soy is generally attributed to its isoflavone and phytoestrogen content that decreases progressively with the increasing degree of soybean processing. Soy protein has also been indicated as being able to induce a modest LDL-C-lowering effect when replacing animal protein foods. However, this was not confirmed when changes in other dietary components were taken into account.[190, 191]

### 7.5.5 Policosanol and berberine

Policosanol is a natural mixture of long chain aliphatic alcohols extracted primarily from sugarcane wax.[192] Studies show that policosanol from sugarcane, rice or wheat germ has no significant effect on LDL-C, HDL-C, TG, apoB, Lp(a), homocysteine, high-sensitivity C-reactive protein (hsCRP), fibrinogen or blood coagulation factors.[193]

As for berberine, a recent meta-analysis has evaluated its effects on plasma lipids in humans.[194] The comparative evaluation of berberine and lifestyle intervention or placebo indicated that in the berberine group, LDL-C and plasma TG levels were more effectively reduced than in the control group. However, due to the lack of high-quality randomized clinical trials, the efficacy of berberine for treating dyslipidaemia needs to be further validated. Moreover, bioavailability of the different berberine preparations is a matter of debate.[190]

### 7.5.6 n-3 unsaturated fatty acids

Observational evidence indicates that consumption of fish (at least twice a week) and vegetable foods rich in n-3 fatty acids (α-linoleic acid is present in walnuts, some vegetables and some seed oils) is associated with a lower risk of CV death and stroke but has no major effects on plasma lipoprotein metabolism.[181, 195] Pharmacological doses of long-chain n-3 fatty acids (2-3 g/day) reduce TG levels by up to 30% and the postprandial lipaemic response, but a higher dosage may increase LDL-C. α-linolenic acid is less effective on TG levels.[159, 196] Pharmacological doses of long-chain n-3 fatty acids (2-3 g/day) reduce TG levels by up to 30%; alfa-linolenic acid is less effective on TG levels. Recently, a significantly lower risk of ischaemic events, including cardiovascular death, was observed in patients with elevated triglyceride levels despite the use of statins, treated with 2 g of icosapent ethyl twice daily.[197]

## Supplementary appendix. Other features of a healthy diet contributing to cardiovascular disease prevention

The results of the PREDIMED trial, in addition to a large body of evidence from large longitudinal studies, are clearly in support of a diet inspired by the traditional Mediterranean diet as an effective approach to the lifestyle prevention of CVDs[S11,S12] This type of diet is characterized by the regular consumption of extra-virgin olive oil, fruits, nuts, vegetables and cereals; a moderate intake of fish and poultry; and a low intake of dairy products, red meat, processed meats and sweets[S13] Dietary choices inspired by this model should be recommended for both primary and secondary prevention of CVD.

Furthermore the consumption of large amounts of fruits and vegetables of different types provides a sufficient amount and variety of minerals, vitamins and antioxidants, particularly polyphenols. New evidence is accumulating on the possible beneficial effects of these compounds – which are also present in olive oil, red wine, coffee, tea and cocoa – on subclinical inflammation and endothelial function, as well as their beneficial influence on plasma TGs at fasting and particularly in the postprandial period.

In relation to salt intake, the overall recommendation is to reduce sodium intake to approximately 2.0 g/day (equivalent of approximately 5.0 g salt/day), although recent data from the PURE Study support a higher threshold.[S14] This can be achieved not only by reducing the amount of salt used for food seasoning, but especially by reducing the consumption of foods preserved by the addition of salt; this recommendation should be more stringent in people with hypertension or MetS.[S15-S17] This recommendation is prompted by the evidence for a causal association between sodium intake and BP and by data showing that salt restriction has relevant BP lowering effects.

*Box S1* lists lifestyle measures and healthy food choices for managing total CV risk. All individuals should be advised on lifestyles associated with a lower CVD risk. High-risk people, in particular those with dyslipidaemia, should receive specialist dietary advice, if feasible.

**Box S1 Summary of lifestyle measures and healthy food choices for managing total cardiovascular risk**

| |
|---|
| Dietary recommendations should always take into account local food habits; however, interest in healthy food choices from other cultures should be promoted. |
| A wide variety of foods should be eaten. Energy intake should be adjusted to prevent overweight and obesity. |
| Consumption of fruits, vegetables, legumes, nuts, wholegrain cereal foods and fish (especially oily) should be encouraged. |
| Foods rich in trans fatty acids should be avoided totally; foods rich in saturated fatty acids (SFAs) (tropical oils, fatty or processed meat, sweets, cream, butter, regular cheese) should be replaced with the above foods and with monounsaturated fat (extra virgin olive oil) and polyunsaturated fat (non-tropical vegetable oils) in order to keep SFA intake <10 % (<7% in the presence of high plasma cholesterol values). |
| Salt intake should be reduced to <5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt. |
| For those who drink alcoholic beverages, moderation should be advised (<10 g/day for women and for men) and patients with hypertriglyceridaemia should abstain. |
| The intake of beverages and foods with added sugars, particularly soft drinks, should be discouraged, especially for persons who are overweight, have hypertriglyceridaemia, metabolic syndrome or diabetes. |
| Physical activity should be encouraged, aiming at regular physical exercise for at least 30 min/day every day. |
| Use of and exposure to tobacco products should be avoided. |

# 8. Drugs for treatment of dyslipidaemias

## 8.1 Statins

### 8.1.1 Mechanism of action

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting the enzyme HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. The reduction in intracellular cholesterol promotes increased LDL receptor (LDLR) expression at the surface of the hepatocytes which in turn results in increased uptake of LDL from the blood and a decreased plasma concentration of LDL- and other apoB-containing lipoproteins, including TG-rich particles.

### 8.1.2 Effects on lipids

*6.1.2.1 Low-density lipoprotein cholesterol*

The degree of LDL-C reduction is dose dependent and varies between the different statins. A high-intensity regimen is defined as the dose of a statin that on average reduces LDL-C by ≥50%; moderate-intensity therapy is defined as the dose expected to reduce LDL-C by 30-50%. Notably, there is considerable interindividual variation in LDL-C reduction with the same dose of drug.[32] Poor response to statin treatment in clinical studies is to some extent caused by poor compliance, but it may also be explained by a genetic background.[198, 199] Interindividual variations in statin response warrant monitoring of response on initiation of therapy.

Among patients who cannot tolerate the recommended intensity of statin because of adverse effects or those who do not reach their goal, the addition of a non-statin lipid-modifying agent to a maximally tolerated statin is recommended.[200, 201]

*8.1.2.2 Triglycerides*

Statins usually reduce TG levels by 10-20% from baseline values.[202] More potent statins (atorvastatin, rosuvastatin, pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TGs (HTG), in whom the absolute risk, and therefore the absolute risk reduction, is larger.

The mechanism of the TG lowering effect has not been fully elucidated, but it seems to be partly independent of the LDLR pathway. It may involve upregulation of VLDL uptake by hepatocytes, as well as a reduction in the production rate of VLDLs; these effects seem to be dependent on pre-treatment VLDL concentrations.[203]

*8.1.2.3 High-density lipoprotein cholesterol*

In a meta-analysis[204] elevations in HDL-C varied with dose among the respective statins; such elevations ranged from 1-10%. However, given the marked statin-mediated decrement in atherogenic apoB-containing lipoproteins, the extent to which the very modest effect on HDL-C levels might contribute to the overall observed reductions in CV risk consistently observed in statin intervention trials cannot reliably be disentangled.

*8.1.2.4 Lipoprotein(a)*

Statins only marginally affect Lp(a) plasma levels. Previous studies have reported either no effect or an increase in Lp(a) levels after statin treatment.[205, 206]. The mechanisms by which statins raise oxidized phospholipids on Lp(a) require further investigation.

*8.1.2.5 Other effects of statins*

Although the reduction of LDL-C is the major effect of statins, a number of other, potentially important effects have been suggested (pleiotropic effects of statins).[207, 208] Among such effects that are potentially relevant for the prevention of CVD are anti-inflammatory and anti-oxidant effects of statin treatment. These effects have been shown *in vitro* and in experimental systems, but their clinical relevance remains unproven.[19, 209]

**8.1.3 Effect on cardiovascular morbidity and mortality**

A large number of meta-analyses have been performed to analyse the effects of statins in populations and in subgroups.[35-37, 39, 52, 210-217] In the CTT meta-analysis of individual participant data (IPD) from >170 000 participants in 26 RCTs of a statin vs. control or a more vs. less intensive statin regimen,[35] for each 1 mmol/L reduction in LDL-C, statin/more statin reduced major vascular events (MI, CAD death, any stroke or coronary revascularization) by approximately 22%, major coronary events by 23%, CAD death by 20%, total stroke by 17%, and total mortality by 10% over 5 years. The proportional

effects (per mmol/L reduction in LDL-C) on major vascular events were similar in all subgroups examined, so the absolute risk reduction was proportional to the absolute baseline risk. The relative benefits were half as large in the first year as compared to subsequent years. There was no increased risk for any non-CV cause of death, including cancer, in those allocated statins. The absolute benefit from statin treatment is lower in people in primary prevention, who are typically at lower risk.[37, 39, 215, 218] In the CTT meta-analysis of treatment in people with low-risk of vascular disease,[37] the relative risk reduction in major vascular events per mmol/L reduction in LDL-C was at least as large in low-risk individuals (i.e. in primary prevention). In those without a history of vascular disease, statin therapy reduced the risk of all-cause mortality by 9%. Similar results were reported in a Cochrane review in 2013.[216] The WOSCOPS data were recently reanalysed and demonstrated that even people without DM and 10-year predicted ASCVD risk of <7.5% benefit from statin treatment. There was also a legacy effect with a mortality benefit of 18% in all cause death over 20 years.[219] Statins are effective for the prevention of ASCVD in the elderly, including those aged >75.[220] Statins are not effective in a few specific groups, notably those with heart failure or patients receiving haemodialysis.[217, 221-225]

Current available evidence from meta-analyses suggests that the clinical benefit of statin treatment is largely a class effect, driven by the absolute LDL-C reduction; therefore the type of statin used should reflect the treatment goals in a given patient.

The following scheme may be proposed.

- Evaluate the total CV risk of the subject.
- Determine the treatment goals (depending on current risk).
- Involve the patient with decisions on CV risk management.
- Choose a statin regimen and, where necessary, additional treatments (ezetimibe, PCSK9 inhibitors) that can meet the treatment goals (percent and absolute value).
- Response to statin treatment is variable, therefore up-titration of the statin dose may be required before starting additional LDL-lowering treatments.

These are general criteria for the choice of drug. Factors such as the clinical condition of the subject, concomitant medications, drug tolerability, local treatment tradition and drug cost will play major roles in determining the final choice of drug and dose.

Furthermore, the effects of statins on a number of other clinical conditions have been evaluated. For cancer, a meta-analysis of IPD from randomized trials has shown that statins do not have any significant effect on cancer, at least over a period of about 5 years.[226] Other conditions, such as dementia,[227] hepatic steatosis,[228] venous thromboembolism,[229] atrial fibrillation[230, 231] and polycystic ovary syndrome[232] have also been studied, and no effect of statins on these conditions has been reliably demonstrated.

The suggested effect on Alzheimer's disease was recently reviewed in a Cochrane analysis reporting no conclusive effect from statins.[233] Furthermore, neurocognitive functions were extensively investigated in the EBBINGHAUS study[234] and no effect was observed among patients on a statin regimen, or on the combined regimen PCSK9 monoclonal antibody (mAb) and statin, over 2 years.

### 8.1.4 Adverse effects and interactions of statins

Statins differ in their absorption, bioavailability, plasma protein binding, excretion and lipophilicity. Evening administration is usually recommended. Lovastatin and simvastatin are prodrugs, whereas the other available statins are administered in their active form. Their bioavailability is relatively low, owing a first pass effect in the liver, and many statins undergo significant hepatic metabolism via cytochrome P450 isoenzymes (CYPs), except pravastatin, rosuvastatin and pitavastatin. These enzymes are expressed mainly in the liver and gut wall. Although statins are generally very well tolerated, statins do have some specific adverse effects on muscle, glucose haemostasis and haemorrhagic stroke. However, there is also widespread misinformation about potential adverse effects, as reviewed recently.[235, 236]

*Muscle*. Myopathy is the most clinically relevant adverse effect of statins. Among the risk factors for myopathy, the interaction with concomitant drug therapy should especially be considered (see below). Rhabdomyolysis is the most severe form of statin-induced muscle damage, characterized by severe muscular pain, muscle necrosis and myoglobinuria potentially leading to renal failure and death. In rhabdomyolysis, creatine

kinase (CK) levels are elevated at least 10 times and often up to 40 times the upper limit of normal (ULN).[237] The frequency of rhabdomyolysis has been estimated to represent 1-3 cases/100 000 patient-years.[238] Patients taking statin therapy frequently report muscle symptoms (so-called 'statin-associated muscle symptoms' [SAMS]), and in non-randomized, observational, studies statins are associated with muscular pain and tenderness (myalgia) without CK elevation or major functional loss, with the reported frequency of SAMS in such studies varying between 10-15% among statin-treated individuals.[239-241] However, in part because individuals in observational studies are not blind to the treatment they are receiving, such studies are unreliable when used to assess the adverse effects of statins.[236] By contrast, in blinded randomized trials of statin vs. placebo there is no or only a slightly increased frequency of muscle symptoms in statin-allocated groups.[242, 243] The ASCOT-LLA study addressed this issue by comparing the incidence of four different adverse events, including muscle-related symptoms, during both the blinded, placebo-controlled trial and its open-label extension study.[241] They concluded that a nocebo effect (i.e. one caused by negative expectations) may partly explain the higher frequency of SAMS in observational studies as compared to trials. Suggested practical management of muscular symptoms is shown in *Supplementary figure 6*.[201, 237, 244] Several studies have shown a considerable LDL-C lowering effect of alternative dosing such as every other day or twice a week with atorvastatin or rosuvastatin.[14, 245] Although no clinical end point trials are available, this strategy should be considered in high-risk patients in whom statin treatment with daily doses is not possible.

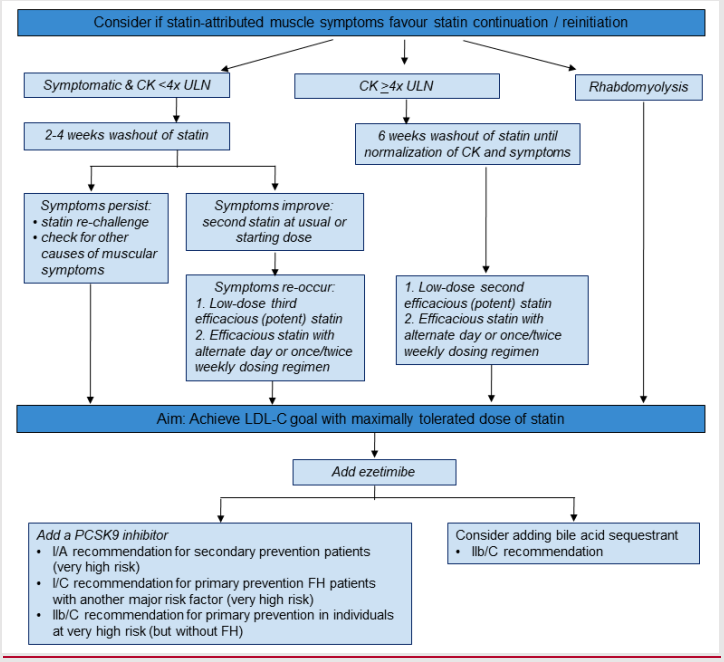
*Liver*. The activity of alanine aminotransferase (ALT) in plasma is commonly used to assess hepatocellular damage. Mild elevation of ALT occurs in 0.5-2.0% of patients on statin treatment, more commonly with potent statins or high doses. The common definition of clinically relevant ALT elevation has been an increase of three times the ULN on two consecutive occasions. Mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function. Progression to liver failure is exceedingly rare, therefore routine monitoring of ALT during statin treatment is no longer recommended.[246] Patients with mild ALT elevation due to steatosis have been

studied during statin treatment and there is no indication that statins cause any worsening of liver disease.[247-249]

*Diabetes*. Patients on statin treatment have been shown to exhibit an increased risk of dysglycaemia and development of type 2 diabetes. Several studies have shown that this is a consistent, dose-related effect.[235] A minor, not clinically relevant elevation of glycated haemoglobin (HbA1c) has also been observed. The number needed to cause one case of diabetes was estimated at 255 over 4 years of statin treatment.[250] However, the risk is higher with the more potent statins in high doses,[251] and also higher in the elderly and in the presence of other risk factors for diabetes such as overweight or insulin resistance.[252] Overall, the absolute reduction in the risk of CVD in high-risk patients clearly outweighs the possible adverse effects of a small increase in the incidence of diabetes.[236] This effect is probably related to the mechanism of action of the statins, as Mendelian randomization studies have confirmed the increased risk of diabetes in individuals with HMG CoA reductase polymorphisms that reduce cholesterol synthesis.[253]

*Haemorrhagic stroke:* In observational studies, TC is negatively associated with haemorrhagic stroke, and in the CTT meta-analysis, there was a 21% (95% CI 5%-41%; p=0.01) relative increase in haemorrhagic stroke.[254, 255] Other meta-analyses, however, have yielded conflicting findings, and there is a need for further exploration of the risk of haemorrhagic stroke in particular types of patients. Note, however, that the overall benefit on other stroke subtypes greatly outweighs this small (and uncertain) hazard.[35, 37]

*Kidney*. There is no clear evidence that statins have a clinically significant beneficial or adverse effect on renal function.[256] An increased frequency of proteinuria has been reported for all statins, but has been analysed in more detail for rosuvastatin. With a dose of 80 mg, a frequency of 12% was reported. With the approved doses up to 40 mg, the frequency is much lower and in line with the frequency for other statins. The proteinuria induced by statins is of tubular origin, usually transitory, and is believed to be due to reduced tubular reabsorption and not to glomerular dysfunction.[257, 258] In clinical trials the frequency of proteinuria is in general low and in most cases is not higher than for placebo.[259]




**Supplementary figure 6 Algorithm for treatment of muscular symptoms during statin treatment**

*8.1.4.1 Interactions*

A number of important drug interactions with statins have been described that may increase the risk of adverse effects. Inhibitors and inducers of enzymatic pathways involved in statin metabolism are summarized in *Table 9*. All currently available statins, except pravastatin, rosuvastatin and pitavastatin, undergo major hepatic metabolism via the CYPs. These isoenzymes are mainly expressed in the liver and intestine. Pravastatin does not undergo metabolism through the CYP system, but is metabolized by sulfation and conjugation. CYP3A4 isoenzymes are the most abundant, but other isoenzymes such as CYP2C8, CYP2C9, CYP2C19 and CYP2D6 are frequently involved in the metabolism of statins. Thus other pharmacological substrates of these CYPs may interfere with statin metabolism. Conversely, statin therapy may interfere with the catabolism of other drugs that are metabolized by the same enzymatic system.

**Table 9 Drugs potentially interacting with statins metabolized by CYP3A4 leading to increased risk of myopathy and rhabdomyolysis**

| Anti-infective agents | Calcium antagonists | Other |
|---|---|---|
| Itraconazole | Verapamil | Ciclosporin |
| Ketoconazole | Diltiazem | Danazol |
| Posaconazole | Amlodipine | Amiodarone |
| Erythromycin | | Ranolazine |
| Clarithromycin | | Grapefruit juice |
| Telithromycin | | Nefazodone |
| HIV protease inhibitors | | Gemfibrozil |

Adapted from Egan and Colman[260] and Wiklund *et al*.[261]

Combination of statins with gemfibrozil enhances the risk of myopathy, and its association with statins must be avoided. There is no or very little increased risk for myopathy when combining statins with other fibrates such as fenofibrate, bezafibrate or ciprofibrate.[262, 263]

## 8.2 Cholesterol absorption inhibitors

### 8.2.1 Mechanism of action

Ezetimibe inhibits intestinal uptake of dietary and biliary cholesterol at the level of the brush border of the intestine (by interaction with the Niemann-Pick C1-like protein 1 [NPC1L1]) without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption, ezetimibe reduces the amount of cholesterol delivered to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDLR expression, which in turn leads to increased clearance of LDL from the blood.

### 8.2.2 Effects on lipids

In clinical studies, ezetimibe in monotherapy at 10 mg/day reduces LDL-C in hypercholesterolaemic patients by 15-22% with a relatively high interindividual variation.[264] A meta-analysis of randomized placebo controlled trials that included over 2700 people showed an 18.5% reduction in LDL-C as compared to placebo.[265] In

addition, there was a significant 3% increase in HDL-C, a significant 8% reduction in TGs, and a 13% reduction in TC with ezetimibe as compared to placebo.

Ezetimibe added to ongoing statin therapy reduces LDL-C levels by an additional 21-27% compared with placebo in patients with hypercholesterolaemia with or without established CHD. In statin-naïve patients, ezetimibe and statin combination therapy provided up to 15% significantly greater reductions in LDL-C when compared with the same statins and doses in monotherapy. In other studies, this combination also provided significantly improved reductions in LDL-C levels when compared with doubling of the statin dose (13-20%) and after switching from statin monotherapy to ezetimibe and statin combination therapy (11-15%).[266]

Co-administration of ezetimibe and bile acid sequestrants (colesevelam, colestipol or cholestyramine) resulted in an additional reduction of LDL-C levels by 10-20% when compared with the stable bile acid sequestrant regimen alone.[267] Co-administration of ezetimibe with PCSK9 inhibitors also resulted in an additional effect. [268]

**8.2.3 Effect on cardiovascular morbidity and mortality**

The efficacy of ezetimibe in association with simvastatin has been addressed in people with aortic stenosis in the SEAS[269] and in patients with CKD in the SHARP trial.[275] In both the SEAS and SHARP trials, a reduction in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.[269, 270]

In IMPROVE-IT ezetimibe was added to simvastatin (40 mg) in patients after acute coronary syndrome (ACS).[34] A total of 18 144 patients were randomized to statin or statin plus ezetimibe and 5314 patients over 7 years experienced a CV event; 170 fewer events (32.7% vs. 34.7%) were recorded in the group taking simvastatin plus ezetimibe ($P = 0.016$). The average LDL-C during the study was 1.8 mmol/L (70 mg/dL) in the simvastatin group and 1.4 mmol/L (55 mg/dL) in patients taking ezetimibe plus simvastatin. Also, ischaemic stroke was reduced by 21% in this trial ($P = 0.008$). There was no evidence of harm caused by ezetimibe or the further LDL-C reduction. In this group of patients already treated with statins to reach goals, the absolute CV benefit from added ezetimibe was small, although significant and in line with the CTT expectations.[271] The study therefore supports the proposition that LDL-C lowering by means other than

statins is beneficial and is safe. The beneficial effect of ezetimibe is also supported by genetic studies of mutations in NPC1L1; naturally occurring mutations that inactivate the protein were found to be associated with reduced plasma LDL-C and reduced risk for CAD.[56, 272, 273]

Taken together with other studies,[274] IMPROVE-IT supports the proposal that ezetimibe should be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose, or in case a statin cannot be prescribed.[275, 276]

#### 8.2.4 Adverse effects and interactions

Ezetimibe is rapidly absorbed and extensively metabolized to pharmacologically active ezetimibe glucuronide. The recommended dose of ezetimibe of 10 mg/day can be administered in the morning or evening irrespective of food intake. There are no clinically significant effects of age, sex or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe renal insufficiency. Life-threatening liver failure with ezetimibe as monotherapy or in combination with statins is extremely rare. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated creatinine kinase levels beyond what is noted with treatment with statin alone.[264]

### 8.3 Bile acid sequestrants

#### 8.3.1 Mechanism of action

Bile acids are synthesized in the liver from cholesterol and are released into the intestinal lumen, but most of the bile acid is returned to the liver from the terminal ileum via active absorption. The two older bile acid sequestrants, cholestyramine and colestipol, are both bile acid-binding exchange resins. The synthetic drug colesevelam is also available in some countries. As bile acid sequestrants are not systemically absorbed or altered by digestive enzymes, the beneficial clinical effects are indirect. By binding the bile acids, the drugs prevent the reabsorption of both drug and cholesterol into the blood and thereby remove a large portion of the bile acids from the enterohepatic circulation. The liver, depleted of bile, synthesizes more from hepatic cholesterol, therefore increasing the

hepatic demand for cholesterol and increasing LDLR expression, which results in a decrease of circulating LDL.

### 8.3.2 Effects on lipids

At the top daily dose of 24 g of cholestyramine, 20 g of colestipol or 4.5 g of colesevelam, a reduction in LDL-C of 18-25% has been observed. No major effect on HDL-C has been reported, while TGs may increase in some predisposed patients.[277] Colesevelam can also reduce glucose levels in hyperglycaemic patients.[278]

### 8.3.3 Effect on cardiovascular morbidity and mortality

In clinical trials, bile acid sequestrants have contributed greatly to the demonstration of the efficacy of LDL-C lowering in reducing CV events in hypercholesterolaemic people, with a benefit proportional to the degree of LDL-C lowering. Of note, these studies were performed before many of the modern treatment options were available.[279-281]

### 8.3.4 Adverse effects and interactions

Gastrointestinal (GI) adverse effects (most commonly flatulence, constipation, dyspepsia and nausea) are often present with these drugs, even at low doses, which limits their practical use. These adverse effects can be attenuated by beginning treatment at low doses and ingesting ample fluid with the drug. The dose should be increased gradually. Reduced absorption of fat-soluble vitamins has been reported. Furthermore, these drugs may increase circulating TG levels in certain patients.

Bile acid sequestrants have major drug interactions with several commonly prescribed drugs and must therefore be administered either 4 hours before or 1 hour after other drugs. Colesevelam is better tolerated and has fewer interactions with other drugs and can be taken together with statins and several other drugs.[282]

## 8.4 PCSK9 inhibitors

### 8.4.1 Mechanism of action

Recently a new class of drugs, PCSK9 inhibitors, has become available that targets a protein (PCSK9) involved in the control of the LDLR.[283] Elevated levels/functions of this protein in plasma reduce LDLR expression by promoting, upon binding, LDLR

lysosomal catabolism and a subsequent increase in plasma LDL concentrations, while lower levels/functions of PCSK9 are related to lower plasma LDL- levels.[284] Therapeutic strategies have been developed mainly using monoclonal antibodies (mAbs); the mechanism of action relates to the reduction of plasma levels of PCSK9, which in turn is not available to bind the LDLR. Since this interaction triggers the intracellular degradation of the LDLR, lower levels of circulating PCSK9 will result in a higher expression of LDLRs at the cell surface and therefore in a reduction of circulating LDL-C levels.[284] Currently, the only approved PCSK9 inhibitors are two fully human mAbs, alirocumab and evolocumab. Statin treatment increases circulating PCSK9 serum levels,[285] and thus the best effect for these mAbs has been demonstrated in combination with statin.

### 8.4.2 Effects on lipids

*8.4.2.1 Low-density lipoprotein cholesterol*

In clinical trials, alirocumab and evolocumab, either alone or in combination with statins and/or other lipid-lowering therapies, have been shown to significantly reduce LDL-C levels on average by 60%, depending on dose. The efficacy appears to be largely independent of any background therapy. In combination with high-intensity or maximally tolerated statins, alirocumab and evolocumab reduced LDL-C by 46-73% more than placebo and by 30% more than ezetimibe. In patients to whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C when administered in combination with ezetimibe.[286] Both alirocumab and evolocumab have been shown to effectively lower LDL-C levels also in patients who are at high CV risk, including those with diabetes.[287] Given the mechanism of action, these drugs are effective at reducing LDL-C in all patients with the capability of expressing LDLR in the liver. Therefore, this pharmacological approach is effective in the vast majority of patients, including those with heterozygous FH and, albeit to a lower level, those with homozygous FH with residual LDLR expression. Receptor-deficient homozygous FH respond poorly to the therapy.[288]

*8.4.2.2 Triglycerides and high-density lipoprotein cholesterol*

These highly efficacious LDL-lowering agents also lower TG levels and increase those of HDL-C and apoAI as a function of the dosing regimen. In phase 2 trials, evolocumab lowered TG levels by up to 26% and raised HDL-C and apoAI by 9% and 4% respectively; similar findings have been reported for alirocumab.[289, 290] However, the TG effect must be reconfirmed in populations with higher starting plasma TG levels.

*8.4.2.3 Lipoprotein(a)*

In contrast to statins, inhibiting PCSK9 with mAbs also reduces Lp(a) plasma levels. Pooled results of phase 2 trials showed that treatment led to an Lp(a) reduction of about 30-40%.[291, 292] While recent investigations have attempted to unravel the mechanism, this remains unclear. It appears, however, to be distinct from that of statins, which also enhance LDLR function but do not lower circulating Lp(a) levels in humans. The relative contribution of this effect on the reduction of risk remains to be addressed in appropriately designed studies.

**8.4.3 Effect on cardiovascular morbidity and mortality**

Early preliminary data from phase 3 trials suggested a reduction of CV events in line with the LDL-C reduction achieved.[289, 293, 294]

Recently two major studies were completed: the FOURIER and ODYSSEY Outcomes trials.[121, 122] The design of the trials was similar as per the settings of secondary prevention and background therapy; however, the population enrolled had stable CHD, PAD or stroke; or a recent (median 2.6 months) ACS, respectively. The relative benefit ranged from 15-20% reductions in the risk of the primary endpoints. Both studies had relatively short follow-up periods, and the evidence from statin trials indicates that the clinical benefits of LDL-lowering may only emerge after about a year,[52] so these trials may have underestimated the potential impact of longer-term treatment.[122, 293]

In the FOURIER trial,[121] 27 564 patients with atherosclerotic CVD and LDL-C levels of 1.8 mmol/L (70 mg/dL) or higher who were receiving statin therapy were randomly assigned to receive evolocumab or placebo. Allocation to evolocumab reduced median LDL-C from 2.38 mmol/L [92mg/dL] at baseline to a mean of 0.78 mmol/L [30 mg/dL] at 48 weeks. After a median follow-up of 2.2 years, evolocumab treatment significantly reduced the risk of the primary end point (composite of CV death, MI,

stroke, hospitalization for unstable angina, or coronary revascularization) by 15% (HR 0.85, 95% CI 0.79 to 0.92). An analysis of the time to benefit also showed that there was a lower benefit in the first year than in subsequent years, consistent with the effects of statins observed within the CTT meta-analysis.[271] In FOURIER, allocation to evolocumab did not reduce the risk of cardiovascular mortality (HR 1.05, 95% CI 0.88-1.25) or all-cause mortality.

The ODYSSEY Outcomes trial randomized 18 924 patients after hospitalization for acute MI or unstable angina, treated with statins, and with LDL-C ≥1.8 mmol/L [70 mg/dL], non-HDL cholesterol ≥ 2.6 mmol/L [100 mg/dL], or apolipoprotein B ≥80 mg/dL, to receive injections of alirocumab or matching placebo. Allocation to alirocumab reduced the mean baseline LDL-C from 2.38 mmol/L [92mg/dL] to 1.24 mmol/L [48mg/dL] at 12 months. There was a 15% relative reduction in the primary outcome (composite of CHD death, non-fatal MI, ischaemic stroke or unstable angina requiring hospitalization) (HR 0.85, 95% CI 0.78 to 0.93) after a median follow-up of 2.8 years.[122] Although there was a significant reduction in all-cause mortality in ODYSSEY, this was an exploratory outcome and was not supported by a significant effect on cardiovascular death.

### 8.4.4 Adverse effects and interactions

Anti-PCSK9 mAbs are injected subcutaneously, every other week or once a month, at different doses depending on the agent used. The potential for interaction with orally absorbed drugs is absent, as they will not interfere with pharmacokinetics or pharmacodynamics. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms.[295] In some studies, an increase of patient-reported neurocognitive effects was described.[296] However the EBBINGHAUS trial,[234] which was specifically designed to detect neurocognitive function changes, was reassuring, as were the safety reports in both the FOURIER and ODYSSEY trials. Mendelian randomization studies have also suggested that PCSK9 inhibition may favour the onset of diabetes with an LDL-C related effect as apparently occurs for statins.[297] To date no signal has emerged from RCTs.[298-300] Although large long-term trials of PCSK9-inhibitors are needed to rule out these and other potential side-effects of inhibition of PCSK9,[301] 7-year data from the

IMPROVE-IT study have shown that prolonged low LDL-C concentrations are not associated with any clear adverse effects.[302]

A potential problem of long-term antibody treatment is the occurrence of autoantibodies. Evolocumab and alirocumab are fully human antibodies and, therefore, theoretically less likely to induce autoantibodies. To date, only a very few cases of anti-drug antibodies have been reported, and no reduction of LDL-C lowering has been observed, but long-term use needs to be monitored. Indeed, the development programme for a third PCSK9 inhibitor, bococizumab, a humanized antibody, was discontinued because of the rise of neutralising antibodies, which resulted in an attenuation of the LDL-C lowering over time, as well as a higher rate of injection site reactions.[303] However, although PCSK9 inhibitors are very effective drugs that can reduce LDL-C and cardiovascular events on top of statin and/or ezetimibe treatment, considering the cost of the treatments and the limited data on long term safety, these drugs are likely to be considered cost-effective only in those at very high risk of ASCVD, and their use may not be possible in some countries with limited health care resources.

## 8.5 Lomitapide

The microsomal TG transfer protein (MTP) transfers TGs and phospholipids from the endoplasmic reticulum to apoB, as a necessary step in the formation of VLDL. MTP inhibition thus prevents the formation of VLDL in the liver and of chylomicrons in the intestine.

Lomitapide is an MTP inhibitor designed for once-a-day oral treatment of homozygous FH. In an open-label, single-arm titration study evaluating lomitapide as adjunct therapy to statins, with or without apheresis and a low-fat diet,[304] LDL-C was reduced by 50% from baseline at 26 weeks and by 44% at 56 weeks. Lomitapide was also shown to decrease the frequency of apheresis in HoFH patients. It should be noted that the drug's effect on CV outcomes has not yet been determined. However, on the basis of the average reduction of 40-50% in LDL-C levels, a significant reduction in CV morbidity and mortality may be hypothesized in patients with HoFH treated with lomitapide.

As a consequence of its mechanism of action, lomitapide has been shown to be associated with increased aminotransferase levels which most likely reflects the increased fat in the liver, as well as poor GI tolerability.[304, 305] The GI side effects were the most frequent reasons preventing a further increase in the dose of lomitapide in clinical trials.[304] However, it has been noted that the frequency and intensity of GI side effects generally decrease with time. Therefore, prescription of lomitapide requires careful patient education and liver function monitoring during therapy.

## 8.6 Mipomersen

Mipomersen is an antisense oligonucleotide able to bind the messenger RNA (mRNA) of apoB-100, which triggers the selective degradation of mRNA molecules. After subcutaneous injection, the oligonucleotide is preferentially transported to the liver, where it binds to the specific mRNA, preventing translation of apoB protein and, consequently, reducing the production of atherogenic lipids and lipoproteins, including LDL and Lp(a).[306] An adjunct to lipid-lowering medications and diet, mipomersen is indicated to reduce LDL-C in patients with HoFH. Mipomersen is currently approved only by the FDA, and is not available in Europe.

Reactions at the injection site are the most common adverse effects observed in patients treated with mipomersen.[307] However, the main concerns regarding mipomersen safety are related to liver toxicity. Mipomersen may lead to the development of steatosis. Treated patients showed a higher increase of liver fat from baseline compared with patients randomized to placebo.[306] The efficacy and safety of long-term mipomersen treatment are currently under evaluation in patients with severe HeFH and in statin-'intolerant' patients.

## 8.7 Fibrates

### 8.7.1 Mechanism of action

Fibrates are agonists of peroxisome proliferator-activated receptor-α (PPAR-α), acting via transcription factors regulating, among other things, various steps in lipid and lipoprotein metabolism. As a consequence, fibrates have good efficacy in lowering

fasting TG levels as well as post-prandial TGs and TG-rich lipoprotein (TRL) remnant particles.

### 8.7.2 Effects on lipids

The clinical impact on the lipid profile varies among members of the fibrate class, but it is estimated to reach 50% reduction in the TG level, up to 20% reduction in the LDL-C level (but a paradoxical small LDL-C increase may be observed with high TG levels), and an increase in HDL-C up to 20%. The magnitude of effect is highly dependent on the baseline lipids levels.[308] Both the HDL-raising and TG-lowering effects of fibrates were markedly less (~5% and ~20%, respectively) in the long-term intervention trials in people with type 2 diabetes but without elevated levels of TG.[309, 310]

### 8.7.3 Effect on cardiovascular morbidity and mortality

The clinical effects of fibrates are primarily illustrated by six RCTs: HHS, VA-HIT, BIP, LEADER, FIELD, and ACCORD; in the latter trial, fenofibrate was added to statin therapy.[310-315] In CV outcome trials of fibrates, the risk reduction appeared to be proportional to the degree of non-HDL-C lowering.[51]

Although the HHS reported a significant reduction in CVD outcomes with gemfibrozil, neither the FIELD nor the ACCORD studies involving fenofibrate showed a reduction in total CVD outcomes. The LEADER trial included male participants with lower-extremity arterial disease and failed to show that bezafibrate could lead to a clinically important reduction in CVD combined end point. Decreases in the rates of non-fatal MI were reported, although often as a result of post hoc analyses. The effect was most evident in people with elevated TG/low HDL-C levels. However, the data on other outcome parameters have remained equivocal. Only one study, ACCORD, has analysed the effect of a fibrate as an add-on treatment to a statin. No overall benefit was reported in two recent meta-analyses.[316, 317] Results from other meta-analyses suggest reduced major CVD events in patients with high TGs and low HDL-C in fibrate-treated patients, but no decrease in CVD or total mortality.[318-320] Thus the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Recently a new selective PPAR-α modulator (pemafibrate) is reported to have marked efficacy in reducing TRLs.[321] PROMINENT[322] is an ongoing CVD outcome trial designed to evaluate the efficacy of

pemafibrate in some 10 000 high-risk diabetic patients with high TG and low HDL-C. Overall, the potential CV benefit of fibrates requires further confirmation.

### 8.7.4 Adverse effects and interactions

Fibrates are generally well tolerated with mild adverse effects, GI disturbances being reported in <5% of patients and skin rashes in 2%.[323] In general, myopathy, liver enzyme elevations and cholelithiasis represent the most well known adverse effects associated with fibrate therapy.[323] The risk of myopathy has been reported to be 5.5-fold greater with fibrate monotherapy (mainly with gemfibrozil) as compared to a statin and it varies with different fibrates and statins used in combination. This is explained by the pharmacological interaction between metabolism of different fibrates and pathways of glucuronidation of statins. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to marked increase in plasma concentrations of statins.[324] As fenofibrate does not share the same pharmacokinetic pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy.[323]

As a class, fibrates have been reported to raise both serum creatinine and homocysteine in both short-term and long-term studies. The increase of serum creatinine by fibrate therapy seems to be fully reversible when the drug is stopped. Data from meta-analyses suggest that a reduction of calculated glomerular filtration rate (GFR) does not reflect any adverse effects on kidney function.[319] Fibrates are associated with a slightly increased of pancreatitis.[325] The increase in homocysteine by fibrates has been considered to be relatively neutral with respect to CVD risk. However, fibrate-induced increase in homocysteine may blunt elevation in both HDL-C and apoA1, and this effect may contribute to the smaller than estimated benefits of fenofibrate in CV outcome parameters.[326]

## 8.8 n-3 fatty acids

### 8.8.1 Mechanism of action

n-3 (or omega-3) fatty acids (eicosapentaenoic acid [EPA] and DHA) are used at pharmacological doses to lower TGs. n-3 fatty acids (2-4 g/day) affect serum lipids and lipoproteins, in particular VLDL concentration. The underlying mechanism is poorly

understood, although it may be related, at least in part, to their ability to interact with PPARs and to a decreased secretion of apoB.

### 8.8.2 Effects on lipids

n-3 fatty acids reduce TGs, but their effects on other lipoproteins are trivial. More detailed data on clinical outcomes are needed to justify the use of prescription n-3 fatty acids.[327] The recommended doses of total EPA and DHA to lower TGs have varied between 2-4 g/day. Three recent studies in people with high TGs using EPA reported a significant reduction in serum TG levels of up to 45% in a dose-dependent manner.[328-330] The efficacy of omega-3 fatty acids to lower serum TGs has also been reported in meta-analyses.[160] Recently, EVOLVE II confirmed the efficacy of omega-3 fatty acids to lower serum TGs.[331]

### 8.8.3 Effect on cardiovascular morbidity and mortality

A Cochrane meta-analysis including 112 059 people from 79 trials reported no overall effect of omega-3 polyunsaturated fatty acids on total mortality (relative risk [RR] 0.98, 95% CI 0.90 to 1.03) or CV events (RR 0.99, 95% Cl 0.94 to 1.04), with only a suggestion that omega-3 fatty acids reduced CHD events (RR 0.93, 95% Cl 0.88 to 0.97).[332] Recently, the ASCEND trial,[333] that randomly assigned 15 480 patients with diabetes but without atherosclerotic CV disease to n-3 fatty acids or placebo, showed no significant difference in the risk of serious vascular events after a mean follow-up of 7.4 years (RR 1.00, 95% Cl 0.91 to 1.09).

The data remain inconclusive and the clinical efficacy of omega-3 fatty acids appears to be related to non-lipid effects.[334, 335] Moreover, the studies with omega-3 fatty acids suffer from the dose used (1 g/day) which does not affect plasma lipids to a large extent, as the dose requested to decrease plasma TGs exceeds 2 g/day. REDUCE-IT[336] aimed to evaluate the potential benefits of omega-3 oil EPA on ASCVD outcomes in people with elevated serum TGs; the trial enrolled about 8000 patients under statin therapy, with LDL-C between 1.0-2.6 mmol/L (41-100 mg/dL) and various CV risk factors, including persistent elevated TGs between 1.7-5.6 mmol/L (150-499 mg/dL) and either established ASCVD or diabetes mellitus and at least one other CV risk factor. Use of high doses (2g twice daily) of EPA as compared to placebo (mineral oil) resulted in an

approximately 25% relative risk reduction ($P < 0.001$) in major adverse CV events. Another randomized placebo-controlled trial, STRENGTH, which aims to determine whether reduction of TRLs and remnants in statin treated patients will provide additional ASCVD risk reduction, is ongoing. The VITAL trial, which reported recently, was a 2 x 2 factorial design study in which healthy participants were randomized in a 1:1 fashion to either vitamin D3 (at a dose of 2000 IU per day) and n–3 fatty acids (1 g per day as a fish-oil capsule containing 840 mg of n–3 fatty acids, including 460 mg of EPA and 380 mg of DHA). It showed that supplementation with either n–3 fatty acid at a dose of 1 g/day or vitamin D3 at a dose of 2000 IU/day was not effective for primary prevention of CV or cancer events among healthy middle-aged men and women over 5 years of follow-up.[337]

#### 8.8.4 Safety and interactions

The administration of n-3 fatty acids appears to be safe and devoid of clinically significant interactions. The most common side effect was GI disturbance. The antithrombotic effects may increase the propensity for bleeding, especially when given in addition to aspirin/clopidogrel. Recently the data from one study associated the risk of prostate cancer with high dietary intake of n-3 PUFAs.[338]

## 8.9 Nicotinic acid

Nicotinic acid has key action sites in both liver and adipose tissue. In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 (DGAT-2), resulting in decreased secretion of VLDL particles, which is also reflected in reductions in plasma levels of both IDL and LDL particles.[339] Nicotinic acid raises HDL-C and apoA1 primarily by stimulating apoA1 production in the liver.[339] Two large randomized trials with nicotinic acid – one with extended-release niacin[67] and one with niacin plus laropiprant[68] – showed no beneficial effect and an increased frequency of serious adverse effects. No medication containing nicotinic acid is currently approved in Europe.

## 8.10 Cholesteryl ester transfer protein inhibitors

To date, the pharmacological approach that leads to the greatest elevations in HDL-C levels has been direct inhibition of CETP by small molecule inhibitors, which may induce

an increase in HDL-C by ≥100% on a dose-dependent basis. Torcetrapib was studied in the ILLUMINATE trial, which was stopped early due to increased mortality.[340] Dalcetrapib raises HDL-C by 30-40% with no appreciable effect on LDL-C, offering specific insight into pure HDL-C raising. However, dalcetrapib failed to show any benefit in ACS patients in the dal-OUTCOMES trial. Evacetrapib, which raises HDL-C by 130% and lowers LDL-C by 37%, was studied in the ACCELERATE trial, which was terminated due to futility. Recently, anacetrapib, which raises HDL-C and apoAI (by +104% and +36%, respectively) and lowers LDL-C and apoB (by -17% and -18%, respectively), was studied in the REVEAL trial. Anacetrapib reduced major coronary events by 9% over a median of 4.1 years.[55] The magnitude of the relative risk reduction appeared to be consistent with the magnitude of LDL-C or non-HDL-C lowering.[341] Due to the accumulation of anacetrapib in the body, this drug has not been submitted for regulatory approval.

## 8.11 Future perspectives

### 8.11.1 New approaches to reduce low-density lipoprotein cholesterol

An alternative approach targeting PCSK9 consists of RNA interference. In a phase 1 and 2 trial, inclisiran showed a reduction of LDL-C up to 50%, in a dose-dependent way. Reductions in PCSK9 and LDL-C levels were maintained up to 6 months.[342, 343] No specific serious adverse events were observed. It remains to evaluate the effects of the inhibition of PCSK9 in the liver, as with inclisiran, or only plasma PCSK9, as with antibodies. A phase 3 trial, ORION-4, is ongoing.

Bempedoic acid is a novel first-in class, oral small molecule that inhibits cholesterol synthesis by inhibiting action of ATP citrate lyase (ACL), a cytosolic enzyme upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.[344] It has been tested so far in diabetic patients, and patients with or without statin 'intolerance'. In monotherapy, bempedoic acid reduces LDL-C by approximately 30%, and up to 50% in combination with ezetimibe. Bempedoic acid is currently being tested in phase 3 trials and some trials have been completed.[345, 346]

### 8.11.2 New approaches to reduce triglyceride-rich lipoproteins and their remnants

As genetic studies indicate that angiopoietin-like protein 3 (ANGPTL3)-deficiency protects against atherosclerotic disease and that this relationship is causal,[347] an ANGPTL3-antibody (evinacumab) is being developed. Evinacumab has been shown to decrease TGs, LDL-C, and Lp(a) in HoFH patients.[348] Another approach that is currently being investigated is the inhibition of ANGPTL3 production by antisense oligonucleotides.[349] IONIS-ANGPTL3-LRx, an antisense oligonucleotide (ASO) targeting ANGPTL3, another critical protein in the clearance of TRLs, reduces plasma TGs by up to 85%. Thus the future may yield tools to improve TRLs clearance that will be reflected in the atherogenic load of the remnant particles.

The rapid development of gene-silencing technology has allowed proteins (apo CIII) critical in the regulation of TRLs clearance processes to be targeted. A second generation antisense oligonucleotide targeting apo CIII messenger RNA has been developed.[350] Two phase III trials evaluated the safety and efficacy of volanesorsen in patients with elevated TG levels.[351, 352] Volanesorsen reduced plasma TGs by about 70% and apo CIII by 80-90%. So far the reports are encouraging for efficacy while safety has raised some concerns and is under evaluation.[353, 354]

### 8.11.3 New approaches to increase high-density lipoprotein cholesterol

Although genetic studies suggest that low HDL-C is not a cause of ASCVD, casting doubt on the possibilities of future treatment options for raising HDL-C with attenuation of CVD, major developments in the search for efficacious agents to raise HDL-C and apoA1 with concomitant benefit on atherosclerosis and CV events are on the horizon. On the one hand, interest is focused on apoA1 mimetic peptides and recombinant forms of HDL possessing potential for in vivo HDL particle remodelling and enhanced cardioprotective activity.[355] On the other, agents which enhance catabolism of TG-rich lipoproteins, such as the antisense oligonucleotide to apoCIII, and which lead to a concomitant reduction in TGs (~70%) and a marked elevation in HDL-C (~40%) in hypertriglyceridemia, are under development.[356] Importantly, however, we currently lack understanding of the relationship between the modality of raising HDL/apoAI and a possible anti-atherogenic function of HDL particles.

### 8.11.4 New approaches to reduce lipoprotein(a) levels

Another approach under study is the selective decrease of Lp(a) concentration. RNA-based therapies are now being evaluated in clinical settings. Results from studies of an anti-sense oligonucleotide in patients with normal Lp(a) values as well as in patients with elevated Lp(a) concentrations showed a reduction of more than 90%.[357] These approaches are currently being evaluated in phase 2-3 studies and an outcome trial is planned to study whether Lp(a) reduction translates into risk reduction.

## 8.12 Strategies to control plasma cholesterol

**Recommendations for pharmacological LDL-C lowering**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended to prescribe a high intensity statin up to the highest tolerated dose to reach the goals set for the specific level of risk.[33, 35, 39] | I | A |
| If the goals[c] are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.[34, 121] | I | B |
| For primary prevention~~,~~ patients at very high-risk, but without FH, ~~or with FH,~~ if the LDL-C goal is not achieved on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered. | IIb | C |
| For secondary prevention, patients at very high-risk not achieving their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.[121, 122] | I | A |
| For very high-risk FH patients (that is, with ASCVD or with another major risk factor) who do ~~For patients with FH, either in primary or secondary prevention,~~ not achieve~~ing~~ their goal[c] on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. | I | C |
| If a statin-based regimen is not tolerated at any dosage, ezetimibe should be considered[200, | IIa | C |

| | | |
|---|---|---|
| 268, 358 | | |
| If a statin-based regimen is not tolerated at any dosage, a PCSK9 inhibitor added to ezetimibe may also be considered[200, 268, 358] | **IIb** | C |
| If the goal[c] is not achieved, statin combination with a bile acid sequestrant may be considered. | **IIb** | C |

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.
[c]For definitions see Table 3.

Although the LDL-C goals are attained with monotherapy in many patients, a significant proportion of patients at high-risk or with very high LDL-C levels need additional treatment. There are also patients who are not able to tolerate statins. In this case, combination therapy is reasonable. In patients at very high-risk and with persistent high-risk despite being treated with maximally tolerated statin, combination with ezetimibe is recommended, and if still not at goal, adding a PCSK9 inhibitor is recommended (**central illustration/recommendation table above**). Of note, adding a PCSK9 inhibitor directly to statin is also feasible.[122, 293]
(**Central illustration**).

As shown in *Figure 4*, the expected clinical benefit of treatment to lower LDL-C for any person can be estimated; it depends on the intensity of therapy, the baseline LDL-C level, and the baseline estimated risk of ASCVD. This simple algorithm can be used to help clinicians select the appropriate therapy and quantify the expected benefits of LDL-C lowering therapy to help inform discussions with patients. For ease of reference, *Supplementary table 3* provides a summary of the absolute LDL-C reductions that can be achieved with various therapeutic approaches at particular baseline levels of LDL-C

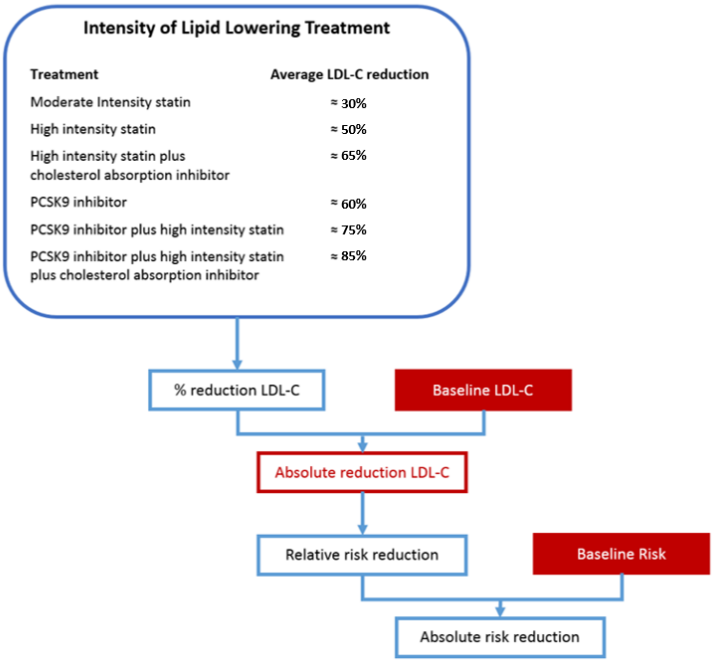
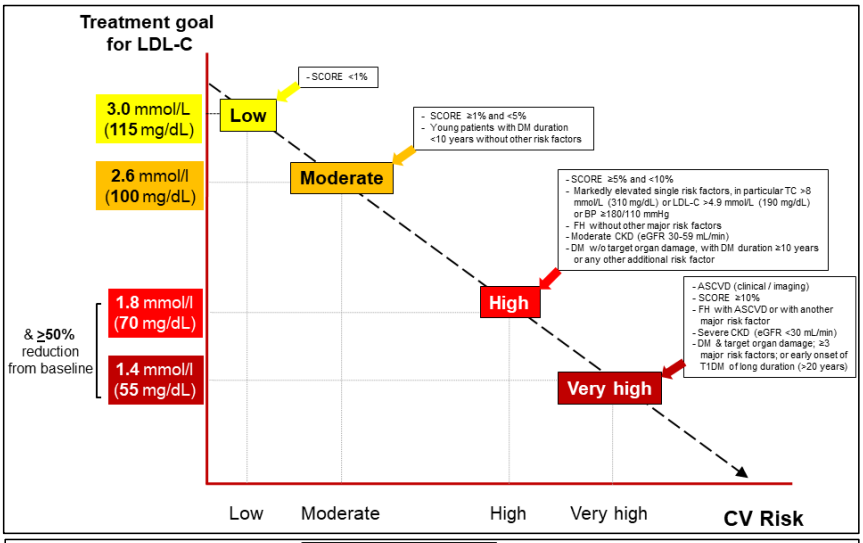



**Figure 4 Expected clinical benefit of low-density lipoprotein cholesterol (LDL-C) lowering therapies.** The expected clinical benefit of treatment to lower LDL-C for any person can be estimated; it depends on the intensity of therapy, the baseline LDL-C level, the absolute achieved reduction in LDL-C, and the baseline estimated risk of atherosclerotic cardiovascular disease (ASCVD). The intensity of therapy should be selected to achieve the recommended proportional reduction in LDL-C based on the person's estimated risk of ASCVD. Multiplying the proportional reduction in LDL-C by a person's baseline LDL-C level estimates the expected absolute reduction in LDL-C that is likely to be achieved with that therapy. Because each 1.0 mmol/L absolute reduction in LDL-C is associated with a 20% reduction in the risk of cardiovascular events, larger absolute reductions in LDL-C lead to larger proportional reductions in risk. Multiplying the proportional reduction in risk expected for the achieved absolute reduction in LDL-C by a person's estimated baseline risk of ASCVD determines the expected absolute risk reduction for that person.

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

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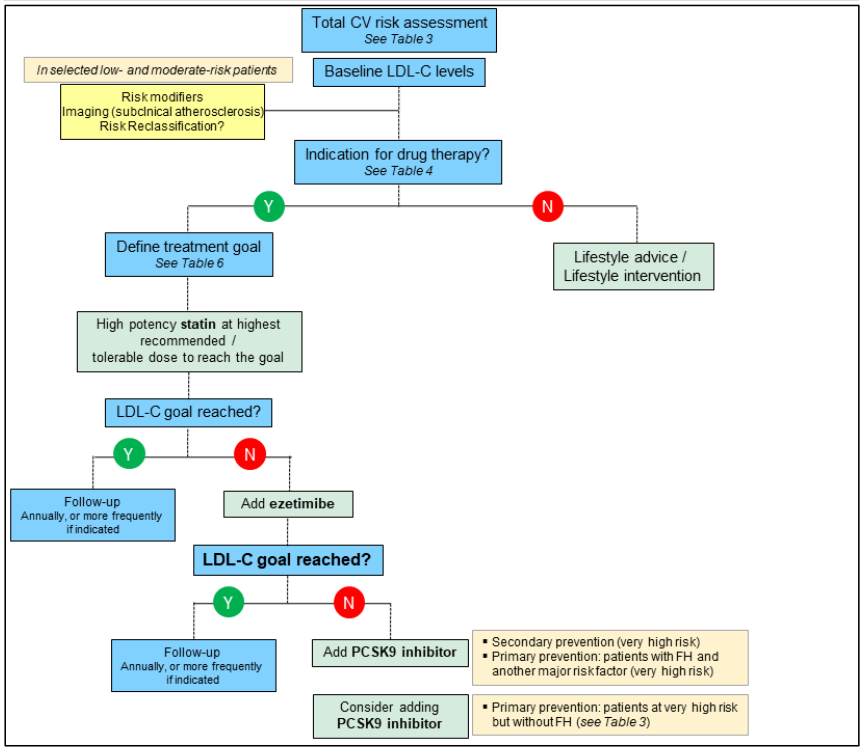


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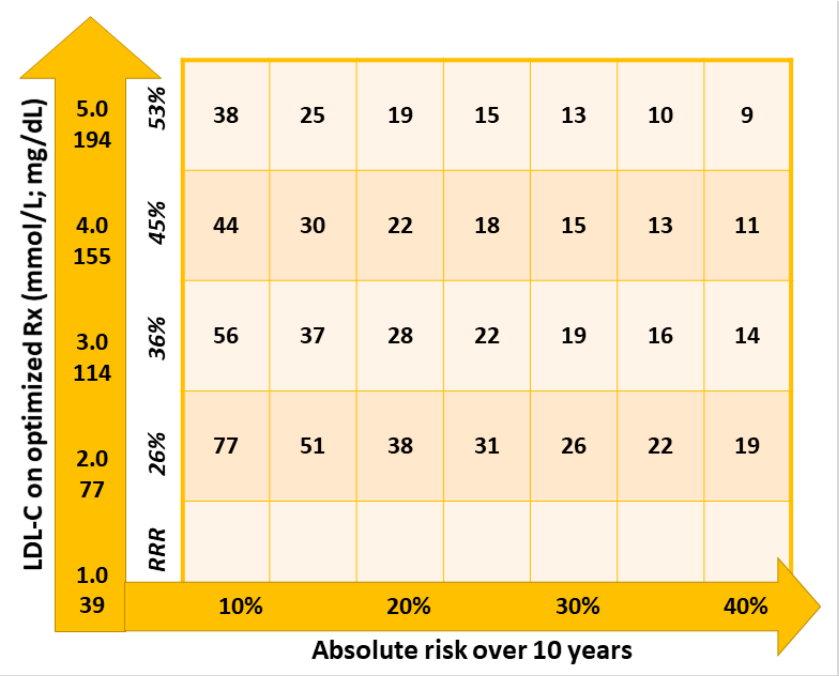
**Central illustration.** Upper panel: Treatment goals for LDL-C across categories of total CVD risk. Lower panel: Treatment algorithm for pharmacological LDL-C lowering.

**Supplementary table 3 Reduction of low-density lipoprotein cholesterol as a function of the therapeutic approach**

| LDL-C, mmol/L (mg/dL) | Reduction obtainable with different therapeutic strategies | | | | |
|---|---|---|---|---|---|
| | Moderate-intensity statins | | High-intensity statins | | PCSK9 inhibitor plus high-intensity statin |
| | | Plus ezetimibe | | Plus ezetimibe | |
| 4.5 (175) | 3.2 (123) | 2.5 (96) | 2.3 (88) | 1.6 (61) | 0.9 (35) |
| 4.3 (165) | 3.0 (116) | 2.4 (91) | 2.2 (83) | 1.5 (58) | 0.9 (33) |
| 4.0 (155) | 2.8 (109) | 2.2 (85) | 2.0 (78) | 1.4 (54) | 0.8 (31) |
| 3.7 (145) | 2.6 (102) | 2.0 (80) | 1.9 (73) | 1.3 (51) | 0.7 (29) |
| 3.5 (135) | 2.5 (95) | 1.9 (74) | 1.8 (68) | 1.2 (47) | 0.7 (27) |
| 3.2 (125) | 2.2 (88) | 1.8 (69) | 1.6 (63) | 1.1 (44) | 0.6 (25) |
| 3.0 (115) | 2.1 (81) | 1.7 (63) | 1.5 (58) | 1.1 (40) | 0.6 (23) |
| 2.7 (105) | 1.9 (74) | 1.5 (58) | 1.4 (53) | 0.9 (37) | 0.5 (21) |
| 2.5 (95) | 1.8 (67) | 1.4 (52) | 1.3 (48) | 0.9 (33) | 0.5 (19) |
| 2.2 (85) | 1.5 (60) | 1.2 (47) | 1.1 (43) | 0.8 (30) | 0.4 (17) |
| 1.9 (75) | 1.3 (53) | 1.0 (41) | 1.0 (38) | 0.7 (26) | 0.4 (15) |

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




**Supplementary figure 7 Number needed to treat (NNT, over 5 years) as a function of the estimated 10-year risk of a future ASCVD event, the starting LDL-C (on optimized statin/ezetimibe therapy), and the average RRR associated with a drug-induced LDL-C drop of 60% (with anti-PCSK9 mAbs).**

Predicted relative risk reduction (RRR) in the first column is associated with a PCSK9 inhibitor-induced 60% decrease in LDL-C, based on a 22% risk reduction per 1.0 mmol/L (38.7 mg/dL) drop in LDL-C. Modified from Annemans et al.[S18]

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

## 8.13 Strategies to control plasma triglycerides

Recommendations for the treatment of HTG are shown in the table below.

Although CVD risk is increased when fasting TGs are >1.7 mmol/L (150 mg/dL),[58] the use of drugs to lower TG levels may only be considered in high-risk patients when TGs are >2.3 mmol/L (200 mg/dL) and cannot be lowered by lifestyle measures. The available pharmacological interventions include statins, fibrates, PCSK9 inhibitors and n-3 PUFAs. A meta-analysis of 10 trials included people treated with various agents, which reduce serum TGs (fibrates, niacin and n-3 PUFAs), and reported a

12% reduction in CV outcomes.[359] Recently, the REDUCE-IT trial[197] demonstrated that in statin-treated patients with high CV risk with fasting TG levels between 135-499 mg/dL (1.52-1.63 mmol/L), high-dose icosapent-ethyl, a highly purified and stable EPA (2g) taken twice daily significantly reduced the risk of ischaemic events, including CV death, by about a quarter over a median follow-up of 4.9 years. In addition, the VITAL trial, showed that n-3 fatty acid at the lower dose of 1 g/day was not effective for primary prevention of CV or cancer events among healthy middle-aged men and women over 5 years of follow-up.[337]

**Recommendations for drug treatments of patients with hypertriglyceridaemia**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| ~~In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.~~[308, 310, 311, 360] | ~~IIb~~ | ~~B~~ |
| Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (200 mg/dL)).[360] | I | B |
| In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135-499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statin.[197] | IIa | B |
| In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[308, 310, 311, 361] | IIb | B |
| In high-risk patients who are at LDL-C goal with TG >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[308, 310, 311, 361] | IIb | C |

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = ; polyunsaturated fatty acids; TG = triglycerides.

[a]Class of recommendation.

[b]Level of evidence.

# 9. Management of dyslipidaemias in different clinical settings

## 9.1 Familial dyslipidaemias

Plasma lipid levels are to a very large extent determined by genetic factors. In its more extreme forms this is manifested as familial dyslipidaemias. A number of monogenic lipid disorders have been identified; among these, FH is most common and strongly related to CVD (*Table 10*). In general, in patients with dyslipidaemia, most commonly the pattern of inheritance does not suggest that there is a major single gene disorder (monogenic) causing the abnormality; rather, it stems from inheriting more than one gene variant affecting lipoprotein metabolism that, on its own, might have relatively little effect, but in combination with another or others has a greater influence on TC, TGs or HDL-C. The pattern of inheritance is polygenic.[362] It is common to find that high LDL-C, high TGs or low HDL-C affect several family members.

**Table 10 Genetic disorders of lipoprotein metabolism**

| Disorder | Prevalence | Gene(s) | Effect on lipoproteins |
|---|---|---|---|
| HeFH | 1 in 200–250 | *LDLR*<br>*APO B*<br>*PCSK9* | ↑LDL-C |
| HoFH | 1 in 160 000–320 000 | *LDLR*<br>*APO B*<br>*PCSK9* | ↑↑LDL-C |
| FCH | 1 in 100/200 | *USF1 + modifying genes* | ↑LDL-C ↑VLDL-C ↑apoB |
| Familial dysbetalipoproteinaemia | 1 in 5000 | *APO E* | ↑↑ IDL and chylomicron remnants (βVLDL) |
| Familial lipoprotein lipase deficiency | 1 in $10^6$ | *LPL*<br>*APO C2* | ↑↑ chylomicrons and VLDL-C |
| Tangier disease (analphalipoproteinaemia) | 1 in $10^6$ | *ABCA1* | ↓↓HDL-C |
| Familial LCAT deficiency | 1 in $10^6$ | *LCAT* | ↓HDL-C |

apo = apolipoprotein; FCH = familial combined hyperlipidaemia; HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia; HDL-C = high-density lipoprotein cholesterol; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyltransferase; LDL-C = low-density lipoprotein cholesterol; VLDL = very low-density lipoprotein cholesterol.

### 9.1.1 Familial combined hyperlipidaemia

Familial combined hyperlipidaemia (FCH) is a highly prevalent mixed dyslipidaemia (1:100-200) characterized by elevated levels of LDL-C, TGs or both and is an important cause of premature CAD. FCH is a complex disease and the phenotype is determined by interaction of multiple susceptibility genes and the environment. It has considerable overlap with the dyslipidaemic phenotype of type 2 diabetes and MetS. The phenotype even within a family shows high inter- and intraperson variability based on lipid values (TGs, LDL-C, HDL-C and apoB). FCH has no monogenic component and is not linked to a single genetic cause, but the phenotype is with high LDL and/or high TGs.[363, 364] Therefore, the diagnosis is commonly missed in clinical practice; the combination of apoB >120 mg/dL + TGs >1.5 mmol/L (133 mg/dL) with a family history of premature CVD can be used to identify people who most probably have FCH.[365]

The concept of mixed dyslipidaemia is also valuable clinically in assessing CV risk. It emphasizes both the importance of considering family history in deciding how rigorously to treat dyslipidaemia and that elevated LDL-C levels portend a higher risk when HTG is also present. Statin treatment decreases CV risk by the same relative amount in people with HTG as in those without. Because the absolute risk is often greater in those with HTG, they may therefore benefit greatly from hypocholesterolaemic therapy.

### 9.1.2 Familial hypercholesterolaemia

#### *9.1.2.1 Heterozygous familial hypercholesterolaemia*

FH is a common co-dominant monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C. If left untreated, men and women with HeFH typically develop early CAD, before the ages of 55 and 60 years, respectively. The risk of CHD among individuals with definite or probable HeFH is estimated to be increased at least 10-fold. However, an early diagnosis and appropriate treatment can dramatically reduce the risk for CAD.

The prevalence of HeFH in the population is estimated to be 1/200-250,[366] translating to a total number of cases at between 14 and 34 million worldwide.[367, 368] Only a minor fraction of these cases is identified and properly treated.

FH is a monogenic disease caused by loss of function mutations in the *LDLR* or *apoB* genes or a gain of function mutation in the *PCSK9* gene; up to 95% of FH is caused by mutations in *LDLR*. More than a thousand different mutations have been identified in *LDLR* causing FH. The different mutations cause reduced function or complete loss of function, the latter being associated with more severe hypercholesterolemia and CVD.

The diagnosis of FH is usually based on the clinical presentation. The commonly used criteria from the Dutch Lipid Clinic Network (DLCN) are shown in *Table 11*. Other criteria are the Simon Broome register or the WHO criteria.[369, 370]

**Table 11 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia**

| Criteria | Points |
|---|---|
| **1) Family history** | |
| First-degree relative with known premature (men <55 years; women <60 years) coronary or vascular disease, or<br>First-degree relative with known LDL-C above the 95th percentile | 1 |
| First-degree relative with tendinous xanthomata and/or arcus cornealis, or children <18 years of age with LDL-C above the 95th percentile | 2 |
| **2) Clinical history** | |
| Patient with premature (men <55 years; women <60 years) coronary artery disease | 2 |
| Patient with premature (men <55 years; women <60 years) cerebral or peripheral vascular disease | 1 |
| **3) Physical examination[a]** | |
| Tendinous xanthomata | 6 |
| Arcus cornealis before age 45 years | 4 |
| **4) LDL-C levels (without treatment)** | |
| LDL-C ≥8.5 mmol/L (325 mg/dL) | 8 |
| LDL-C 6.5-8.4 mmol/L (251-325 mg/dL) | 5 |
| LDL-C 5.0-6.4 mmol/L (191-250 mg/dL) | 3 |

| | |
|---|---|
| LDL-C 4.0-4.9 mmol/L (155-190 mg/dL) | 1 |
| **5) DNA analysis** | |
| Functional mutation in the *LDLR*, *apoB* or *PCSK9* gene | 8 |
| | |
| Choose only one score per group, the highest applicable. Diagnosis is based on the total number of points obtained | |
| A 'definite' FH diagnosis requires ≥8 points | |
| A 'probable' FH diagnosis requires 6-7 points | |
| A 'possible' FH diagnosis requires 3-5 points | |

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

[a]Exclusive of each other (i.e. maximum 6 points if both are present)

The diagnosis can be verified by showing causative mutations in the pathogenic genes. However, in most studies the frequency of detectable mutations in patients with a clinically definite or probable HeFH is between 60 and 80%. This suggests that a considerable fraction of patients with FH have either a polygenic cause of the disease or that other genes, yet to be identified, are involved.

*Genetic testing and cascade screening*. Probands (index cases) should be identified according to the following criteria:

- TC ≥8 mmol/L (310 mg/dL) without treatment in an adult or adult family member (or >95th percentile by age and gender for country),
- premature CHD in the subject or a family member,
- tendon xanthomas in the subject or a family member, or
- sudden premature cardiac death in a family member.

Cascade screening of family members of a known index case allows for an efficient identification of new cases. Cascade screening is best performed by a lipid clinic. In most families the cases may be identified with TC or LDL-C analysis. However, when the causative mutation is known, genetic testing is recommended.

Cholesterol-lowering treatment should be initiated as soon as possible after the diagnosis has been made. To improve risk assessment, use of imaging techniques to detect asymptomatic atherosclerosis is recommended. The concept of cumulative cholesterol burden illustrates the importance of early treatment (for children, see below). Treatment should be initiated with high-intensity statin treatment, in most cases in

combination with ezetimibe. In FH patients at very high risk of ASCVD due to a prior history of ASCVD or another major risk factor, LDL-C goals are at least a 50% reduction of LDL-C from baseline and an LDL-C <1.4 mmol/L (55 mg/dL). In the absence of ASCVD or another major risk factor, patients with FH are categorised as high-risk, and LDL-C goals are at least a 50% reduction of LDL-C from baseline and an LDL-C <1.8 mmol/L (70 mg/dL).

~~LDL-C goals are at least a 50% reduction of LDL-C from baseline and an LDL-C <1.8 mmol/L (70 mg/dL) if no signs of CVD (also by imaging) or <1.4 mmol/L (55 mg/dL), irrespective of whether signs of ASCVD (clinical or by imaging) are present or not if CVD is present~~

PCSK9 inhibitors lower LDL-C by up to 60% on top of statin. Two randomized controlled studies have reported a beneficial effect on clinical end points in ASCVD patients without FH.[121, 122] PCSK9 inhibitors ~~should be considered~~are recommended in very high-risk patients with FH if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe ~~at very high risk due to the presence of ASCVD, a family history of CAD at a very young age, with an LDL-C level far from goal even on maximal other therapy~~. PCSK9 inhibitors ~~s~~are also recommended ~~hould also be considered~~ in FH patients who cannot tolerate statins ~~and in FH patients with high Lp(a)~~.[371, 372]

Recommendations for the detection and treatment of patients with HeFH are shown in the table below.

**Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended to consider the diagnosis of FH in patients with CHD <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives having tendon xanthomas, in people with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)], and in first degree relatives of FH patients. | I | C |
| It is recommended to diagnose FH using clinical criteria and confirm, when available, with DNA analysis. | I | C |

| | | |
|---|---|---|
| Once the index case is diagnosed, family cascade screening is recommended. | **I** | **C** |
| It is recommended to treat FH patients with ASCVD or who have another major risk factor as very high-risk, and those with no prior ASCVD or other risk factors as high-risk. ~~It is recommended to treat FH patients (with or without clinical or imaging evidence of documented ASCVD) as high risk (without ASCVD) or very high risk (with ASCVD).~~ | **I** | **C** |
| For FH patients who are at very high risk, treatment ~~Treatment~~ to achieve at least a 50% reduction from baseline and an LDL-C ~~<1.8 mmol/L (70 mg/dL), or in the presence of ASCVD, at least a 50% reduction from baseline and an LDL-C~~ <1.4 mmol/L (55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended. | **I** | **C** |
| Treatment with a PCSK9 inhibitor is recommended in very high-risk FH patients ~~with ASCVD or with other factors putting them at very high risk for ASCVDCHD, such as other CV risk factors, family history, or high Lp(a), or~~ if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe ~~lipid lowering treatment~~. | **I** | **C** |
| In children, testing for FH is recommended from the age of 5 years, or earlier if homozygous FH is suspected. | **I** | **C** |
| Children with FH should be educated to adopt a proper diet and treated with a statin from 8-10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age. | **IIa** | **C** |

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = = proprotein convertase subtilisin/kexin type 9.

[a]Class of recommendation.

[b]Level of evidence.

*9.1.2.2 Homozygous familial hypercholesterolaemia*

HoFH is a rare and life-threatening disease. The clinical picture is characterized by extensive xanthomas, marked premature and progressive CVD and TC >13 mmol/L (500 mg/dL). Most patients develop CAD and aortic stenosis before the age of 20 years and die before 30 years of age. The frequency of HoFH is estimated to be 1/160 000-1/300 000. The early identification of these children and prompt referral to a specialized clinic

is crucial. The patients should be treated with available cholesterol-lowering drugs and, when available, with lipoprotein apheresis. This treatment (every 1/2 weeks) can decrease plasma LDL-C levels by 55-70%. . The procedure frequency may be adjusted for each patient as lipid levels, symptoms, and other disease-related parameters change. Maximally tolerated pharmacological therapy must be maintained.[373] For a more detailed discussion on HoFH, see the EAS consensus statements.[371, 373]

*9.1.2.3 Familial hypercholesterolaemia in children*

FH is diagnosed in children based on phenotypic criteria including elevated LDL-C plus a family history of elevated LDL-C, premature CAD and/or positive genetic testing.[374] Testing during childhood is optimal to discriminate between FH and non-FH using LDL-C. In children with a family history of high cholesterol or premature CHD, an accepted cut-off is ≥4.0 mmol/L (160 mg/dL). If a parent has a known genetic defect, the diagnostic level for the child is ≥3.5 mmol/L (130 mg/dL). If possible, a genetic test in the child is suggested

Although there are no placebo-controlled trials in children, there are observational studies suggesting that early treatment can reduce LDL-C burden, improve endothelial function, substantially attenuate development of atherosclerosis and improve coronary outcomes.[374-376] Treatment of children with FH includes a healthy lifestyle and statin treatment. A heart-healthy diet should be adopted early in life and statin treatment should be considered at 6-10 years of age. Statin treatment should be started with low doses and the dose should be increased to reach goals.[377] The goal in children >10 years of age is an LDL-C <3.5 mmol/L (135 mg/dL) and at younger ages at least a 50% reduction of LDL-C.

**9.1.3 Familial dysbetalipoproteinaemia**

Familial dysbetalipoproteinaemia (i.e. type III hyperlipoproteinaemia; remnant removal disease) is rare and is generally inherited as an autosomal recessive disorder with variable penetrance. Familial dysbetalipoproteinaemia produces a characteristic clinical syndrome in which both TC and TGs are elevated before treatment, usually both in the range of 7-10 mmol/L. In severe cases, patients develop tuberoeruptive xanthomas, particularly over the elbows and knees, and palmar xanthomata in the skin creases of the hands and wrists.

The risk of CAD is very high, and accelerated atherosclerosis of the femoral and tibial arteries is also prevalent. The syndrome is usually not expressed at young age or in women before menopause. The majority of cases are homozygous for the E2 isoform of apoE. ApoE is important for hepatic clearance of chylomicron remnants and IDL. ApoE2 binds less readily than isoforms E3 or E4 to hepatic receptors. However, without some coincidental cause of dyslipidaemia such as dyslipidaemia associated with HTG, diabetes mellitus, obesity or hypothyroidism.[378-380], apoE2 homozygosity does not generally cause familial dysbetalipoproteinaemia.

The detection of apoE2 homozygosity in a dyslipidaemic patient is diagnostic and analysis of apoE isoforms is now available in most clinical laboratories. The presence of cholesterol remnants characteristic of familial dysbetalipoproteinaemia can be reliably predicted on the basis of plasma levels of cholesterol, triglycerides and apoB.[381] If suspicion is confirmed, apoE genotyping can be performed. In older patients with xanthomata resembling those of familial dysbetalipoproteinaemia, who prove not to be homozygous for apoE2, a paraprotein should be sought. The treatment of familial dysbetalipoproteinaemia should be undertaken in a specialist clinic. Most cases respond well to treatment with a statin or, if dominated by high TGs, a fibrate; often a combination of a statin and a fibrate may be needed.

### 9.1.4 Genetic causes of hypertriglyceridaemia

Although the genetic aetiology for HTG seems to be very complex, recent data have extended the genetic understanding of HTG, in particular that of chylomicronaemia.[38, 382, 383] Moderate elevation of TG levels (between 2.0-10.0 mmol/L) is caused by the polygenic effect of multiple genes influencing both VLDL production and removal. Monogenic severe HTG causes chylomicronaemia, pancreatitis and lipid deposits. Thus far, mutations in six genes (*LPL*, *apoC2*, *apoA5*, *LMF1*, *GPIHBP1* and *GPD1*) with monogenic effect have been recognized to lead to severe elevation of serum TGs due to disruption of the chylomicron removal pathways. These mutations are inherited as an autosomal recessive trait and are rare. The profound defect in the catabolism of chylomicrons and VLDL results in chylomicronaemia and TG levels >11.2 mmol/L (1000 mg/dL), with turbid and milky serum. Severe HTG is seen in patients who are

homozygous or compound heterozygous for mutations of the enzyme lipoprotein lipase (LPL) and in the other genes linked to catabolism of TG-rich lipoproteins. The heterozygote carriers of these same gene mutations commonly express moderate elevations of serum TG levels that expose them to increased CVD risk.[384] Recently, gene therapy for LPL deficiency has been developed and tested in clinical trials[385] and the alipogene tiparvovec was approved by the European Medicines Agency (EMA) in 2013. This therapy however is no longer available. A gain of function mutation in *apoC3* leading to high apoC3 levels can also cause severe HTG by the inhibition of LPL activity, whereas loss of function mutations are associated with a favourable lipid profile with low TG levels.[386] These findings have raised the possibility of apoC3 as a novel lipid drug target.

*9.1.4.1 Action to prevent acute pancreatitis in severe hypertriglyceridaemia*

The risk of pancreatitis is clinically significant if TGs exceed 10 mmol/L (880 mg/dL), particularly when occurring in association with familial chylomicronaemia, and actions to prevent acute pancreatitis are mandatory.[387, 388] Notably, HTG is the cause of ~10% of all cases with pancreatitis, and patients can develop pancreatitis even when their TG concentration is 5-10 mmol/L (440-880 mg/dL). Recent data from a prospective cohort reported that the risk of acute pancreatitis increased significantly over the quartiles of serum TGs, highlighting that serum TGs as a risk factor may have been underestimated.[389] Any factor that increases VLDL production can aggravate the risk of pancreatitis, with alcohol consumption being the most common contributing factor. The patient should be admitted to hospital if symptomatic, or careful and close follow-up of the patient's TG values should be undertaken. Restriction of calories and fat content (10-15% recommended) in the diet and alcohol abstinence are obligatory. Fibrate therapy (fenofibrate) should be initiated, with n-3 fatty acids (2-4 g/day) as adjunct therapy or nicotinic acid. Lomitapide may also be considered in severe cases.[38] In patients with diabetes, insulin therapy should be initiated to achieve good glycaemic control. In general, a sharp decrease of TG values is seen within 2-5 days. In the acute setting, plasmapheresis is able to rapidly lower TG levels.[390]

**9.1.5 Other genetic disorders of lipoprotein metabolism**

Sometimes patients are encountered with extremely low levels of LDL-C or HDL-C. The most common form of genetic hypolipidaemia is hypobetalipoproteinaemia, which is dominantly inherited and often due to truncation of apoB. Serum LDL-C is typically between 0.5-1.5 mmol/L (20-60 mg/dL). A more profound deficiency of apoB occurs in abetalipoproteinaemia when steatorrhoea and neurological or other complications require specialist treatment. Almost absent levels of HDL-C occur in Tangier disease (analphalipoproteinaemia) and very low levels of HDL-C occur in lecithin cholesterol acyltransferase (LCAT) deficiency. Both these conditions are associated with distinct clinical syndromes and require specialist investigation. Very high levels of HDL-C are detected in patients with CETP deficiency. In the heterozygous form, typically levels of 2.0-2.4 mmol/L (80-90 mg/dL) are observed, and levels ≥5 mmol/L (200 mg/dL) are observed in homozygotes. This is not associated with atherosclerotic disease and may be associated with reduced risk.

Lysosomal acid lipase (LAL) deficiency or cholesterol ester storage disease (in children with Wolman disease) is a rare cause (recessive transmission) of elevated LDL-C and low HDL-C accompanied by hepatomegaly and microvesicular hepatosteatosis. Statin treatment does decrease LDL-C, and therefore could prevent ASCVD in these patients, but it cannot stop the progression of liver damage. Treatment with a PCSK9 inhibitor may lead to an even greater overload of lysosomes.[391] Enzyme replacement therapy with sebelipase alfa might offer a treatment solution in the near future.[392]

## 9.2 Women

Few randomized trials of statin therapy have reported independently significant CV benefits in women[393, 394] chiefly because women have not been adequately represented in statin trials.

### 9.2.1 Effects of statins in primary and secondary prevention

There has previously been controversy over whether statins are effective for primary prevention in women. Using published data, a 2013 Cochrane analysis showed that statin therapy reduced all-cause mortality, vascular events and revascularizations in primary prevention, and the proportional effects in women were similar to those in men.[216] The CTT collaboration has provided a more complete assessment of the evidence through a

comprehensive analysis of IPD from 22 trials of statin vs. control and five trials of more vs. less intensive statin therapy.[36] Overall, 46 675 (27%) of 174 149 participants were women, and after adjustment for non-gender differences, the proportional reductions per mmol/L reduction in LDL-C in major vascular events, major coronary events, coronary revascularization and stroke were similar in women and men.[36]

### 9.2.2 Non-statin lipid-lowering drugs

Definitive evidence of the cardioprotective effects of non-statin drugs that lower LDL-C is now available, and the beneficial effects are similar in both women and men. In the IMPROVE-IT study[34] the relative benefit of adding ezetimibe to simvastatin was similar in women and men.[34] In the ACCORD lipid study, there was no evidence that fenofibrate added to the effects of simvastatin in patients with type 2 diabetes mellitus (T2DM),[309] but an analysis of the FIELD study showed consistent CV event reduction in both women and men.[395] Several outcome trials assessing the effects of adding a PCSK9 inhibitor to high-intensity statin therapy have now been reported, with similar proportional reductions in major vascular events in women and men.[122, 289, 293]

### 9.2.3 Hormone therapy

Currently used third-generation low-dose oestrogen–progestin oral contraceptives do not appear to increase adverse coronary events[396] and can be used, after baseline lipid profile assessment, in women with acceptable TC levels. In contrast, alternative contraceptive measures should be recommended in women with hypercholesterolaemia [LDL-C >4 mmol/L (160 mg/dL)] or with multiple risk factors and in those at high risk of thrombotic events.[397] Oestrogen replacement therapy, despite some favourable effects on the lipid profile, has not been demonstrated to reduce CV risk and cannot be recommended for CVD prevention in women.[398] No lipid-lowering drugs should be administered during pregnancy and the period of breastfeeding because data on possible adverse effects are lacking. However, bile acid sequestrants may be considered.

*Box 6* lists the main measures in the management of dyslipidaemia in women.

**Box 6 Management of dyslipidaemia in women**

Statin treatment is recommended for primary prevention of

| |
|---|
| ASCVD in high-risk women.[35, 36] |
| Statins are recommended for secondary prevention in women with the same indications and goals as in men.[35, 36] |
| Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breastfeeding period. However, for severe FH patients, bile acid sequestrants (which are not absorbed) and/or LDL apheresis may be considered.. |

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL = low-density lipoprotein.

## 9.3 Older people

The proportion of older people (defined herein as those aged >65 years) in society is increasing and, as a consequence, >80% of individuals who die from CVD are >65 years of age. The proportion of patients with MI > 85 years of age has increased several-fold.[399]

A meta-analysis of observational studies has shown that higher TC is associated with increased CAD mortality at all ages.[63, 400] However, since the absolute risk of CAD is higher in older persons, the associated absolute increase in risk for a given increment in TC is larger with increasing age.[220]

### 9.3.1 Effects of statins in primary and secondary prevention

The use of statin therapy declines with increasing age, reflecting differences in both prescribing and compliance.[401, 402] This trend is even more prominent among older patients who do not have evidence of occlusive vascular disease.[402] One explanation for this pattern may be uncertainty about the effects of statins in older people due to the relatively small number of people aged >75 years included in statin trials.[236, 403, 404] The CTT collaboration has recently provided a comprehensive assessment of the randomized evidence on the effects of statin therapy at different ages.[220] Among 186 854 participants in 28 trials, 14 483 (8%) were aged >75 years at randomization. Overall, statin therapy produced a 21% relative reduction in major vascular events (RR 0.79, 95% CI 0.77 to 0.81) per 1.0 mmol/L reduction in LDL-C, and there was direct evidence of benefit among those aged >75. The relative reduction in major vascular events was similar, irrespective of age, among patients with pre-existing vascular disease, but appeared smaller among older individuals not known to have vascular disease. The available evidence from trials indicates, therefore, that statin therapy produces significant reductions in major vascular events irrespective of age. However, there is less direct

evidence of benefit among patients aged >75 who do not already have evidence of occlusive vascular disease, and this limitation is currently being addressed by the STAREE trial in Australia.

### 9.3.2 Adverse effects, interactions and adherence

The safety and adverse effects of statins are a matter of special concern in older adults because they often have co-morbidities, take multiple medications and have altered pharmacokinetics and pharmacodynamics. Statin–drug interactions are a concern primarily because of their potential to increase muscle-related statin-associated adverse effects such as myalgia without CK elevation, myopathy with CK elevation, and the rare but serious rhabdomyolysis. It is recommended that a statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

The recommendations for treatment of dyslipidaemias in older people are shown in the table below.

**Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[220] | I | A |
| Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged up to 75.[220] | I | A |
| Initiation of statin-treatment for primary prevention in older people aged over 75 may be considered.[220] | IIb | B |
| It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals. | I | C |

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.

## 9.4 Diabetes and metabolic syndrome

The number of people with diabetes will increase from ~415 million today up to 550 million by 2030, but the situation may get even worse.[405] Despite significant advantages in the management strategies that lessen atherosclerotic CVD risk factors, CVD has remained the leading cause of morbidity and mortality in patients with T2DM. The good news is that fatal CVD outcomes have declined significantly in both type 2 and type 1 diabetes between 1998 and 2014.[406] Diabetes itself is an independent risk factor for CVD and is associated with a higher risk of CVD, even more so in women. The difference in CVD risk between individuals with and without diabetes has narrowed substantially over the last decades,[407] and there are strong associations between diabetes and vascular outcomes.[408, 409] Recent data indicate that diabetes per se increases CVD risk about two-fold on average, but the risk is subject to wide variation depending on the population and current aggressive prophylactic therapy.[407, 410] Importantly, those with diabetes and CAD are at substantially higher CVD risk for future events. In T2DM the risk of ASCVD is strongly determined by the presence of target organ damage, including nephropathy (microalbuminuria), neuropathy or retinopathy, with the risks increasing in relation to the number of conditions present.[411] Hypertension, dyslipidaemia, abdominal obesity and non-alcoholic fatty liver disease (NAFLD) commonly co-exist with T2DM and further aggravate the risk, which is highest in people with T2DM and multiple cardiometabolic risk factors.[412-414] Importantly, diabetes confers excess mortality risk following ACS despite modern therapies, highlighting the poor prognosis of coronary patients with T2DM and the need for intensive therapy.[415]

How to capture the extra risk beyond the traditional risk factors in clinical practice is a debated issue. A practical approach is that if one component is identified, a systematic search should be made for the others.[416]

### 9.4.1 Specific features of dyslipidaemia in insulin resistance and type 2 diabetes

Diabetic dyslipidaemia is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated. The increase in large VLDL particles in T2DM initiates a sequence of events that generates atherogenic remnants, small dense LDL and small TG-rich dense HDL particles.[417] These components are not isolated abnormalities but are closely linked to each other. Both LDL and HDL particles show variable compositional

changes that are reflected in their functions. Notably apoCIII levels are increased in people with T2DM.[418] High apo CIII concentrations prevent the clearance of both TRLs and remnants resulting in prolonged residence time of these particles in the circulation.[419, 420] In fact the defective catabolism of TRLs seems to be a more important contributor to the elevation of plasma TGs than the increased production rate leading to an excess of remnant particles. Together, TRL remnants, small dense LDL and small dense HDL comprise the atherogenic lipid profile, which is also characterized by an increase in apoB concentration due to an increased number of apoB-containing particles. Importantly, TRLs, including chylomicrons, VLDL and their remnants, carry a single apoB molecule, also like LDL particles. Therefore, the malignant nature of diabetic dyslipidaemia is not always revealed by the lipid measures used in clinical practice, as LDL-C may remain within the normal range. It may be better revealed by non-HDL-C.[421] Elevation of TGs or low HDL-C in the fasting state or postprandial is seen in about half of the people with T2DM[422, 423] and is often present also in people with abdominal adiposity and insulin resistance or impaired glucose tolerance.[419]

*Box 7* summarises dyslipidaemia in metabolic syndrome and T2DM.

**Box 7 Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes**

| |
|---|
| Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial TG, apoB, small dense LDL and low HDL-C and apoA1. |
| Non-HDL-C or apoB are good markers of TRLs and remnants and are a secondary objective of therapy. Non-HDL-C <2.6 mmol/L (<100 mg/dL) and apoB <80 mg/dL are desirable in those at high risk, and non-HDL-C <2.2 mmol/L (<85 mg/dL) and apoB <65 mg/dL in those at very high risk. For those at very high risk with recurrent ASCVD events, a goal of non-HDL-C <1.8 mmol/L (70 mg/dL) and apoB <55 mg/dL can be considered. |
| Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes and in people with abdominal obesity and insulin resistance or impaired glucose tolerance. |

apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MetS=metabolic syndrome; TG=triglycerides; TRLs=triglyceride-rich lipoproteins.

### 9.4.2 Evidence for lipid-lowering therapy

#### *9.4.2.1 Low-density lipoprotein cholesterol*

LDL-C is the primary target of lipid-lowering therapy in diabetes. Trials specifically performed in people with T2DM as well as subsets of individuals with diabetes in major statin trials have consistently demonstrated significant benefits of statin therapy on CVD events in people with T2DM.[424] Statin therapy reduces the 5-year incidence of major CVD events by 23% per 1 mmol/L reduction in LDL-C, regardless of the initial LDL-C or other baseline characteristics based on meta-analysis.[424] The CTT meta-analysis further indicates that people with T2DM will have a relative risk reduction that is comparable to that seen in non-diabetic patients, but being at higher absolute risk, the absolute benefit will be greater, resulting in a lower number needed to treat (NNT). Thus statin therapy is the first-line treatment for LDL-C lowering and for reducing CVD burden.[425]

Ezetimibe lowers LDL-C by ~24% and when added to statin therapy decreases the risk of major vascular events.[34] The relative risk reduction in major vascular events is proportional to the absolute degree of LDL-C lowering and consistent with the relationship seen for statins. The subset of patients with diabetes in IMPROVE-IT had, as expected, a higher rate of major vascular events than did patients without diabetes (46% vs. 31% 7-year Kaplan Meier rate in the placebo arm). Ezetimibe appeared particularly efficacious in patients with diabetes, with a relative risk reduction of 15% (95% CI 6% to 22%) and an absolute risk reduction of 5.5%.[302]

The mAb PCSK9 inhibitors evolocumab and alirocumab lower LDL-C by ~60% and when added to statin therapy decrease the risk of major vascular events.[121] In FOURIER, the relative risk reduction for major vascular events was similar in patients with and without diabetes; however, given the higher baseline risk in patients with diabetes, the absolute risk reductions tended to be greater in patients with diabetes (2.7% absolute decrease in major vascular events over 3 years).[300] Of note, the achieved LDL-C in the evolocumab arm was 0.8 mmol/L.

Recent studies have suggested an increased incidence of diabetes in patients treated with statins.[250] These observations have been seen in Mendelian randomization studies and in clinical trials, although the effect appears greatest in patients already at high risk for diabetes (e.g. those with prediabetes). These observations should not lessen our attention to the treatment of patients, as the overall benefit in CV events reduction

remains and greatly outweighs the increase in diabetes. In the RCTs, neither ezetimibe nor the PCSK9 inhibitors increased the risk of diabetes.[300]

*9.4.2.2 Triglycerides and high-density lipoprotein cholesterol*

Lifestyle modification provides the first option to improve the atherogenic dyslipidaemia due to its multifaceted effects. Weight loss is in most cases the most effective measure since it is associated with very pronounced effects on plasma TG and HDL levels together with a modest decrease in TC and LDL-C. Moderate-to-heavy aerobic exercise is also associated with an improvement of the plasma lipid profile by reducing TG levels and increasing HDL-C concentrations. In relation to diet composition, besides the need to eliminate trans fat, the available evidence supports the reduction of saturated fat intake and its substitution with unsaturated fat as well as the replacement of a major proportion of refined starchy foods and simple sugars with fibre-rich foods like fruit, vegetables and wholegrain.[182]

The clinical benefits achieved by the treatment of atherogenic dyslipidaemia (high TGs and low HDL-C) are still a matter of debate as the effects of fenofibrate therapy on the major outcome (major adverse cardiovascular events [MACE]) remained negative in both the FIELD and the ACCORD studies performed in type 2 diabetic cohorts.[309, 310] In a post hoc analysis of the FIELD study, fenofibrate reduced CVD events by 27% in those with elevated TGs (~2.3 mmol/L [200 mg/dL]) and reduced HDL-C (NNT = 23).[422] The ACCORD trial confirmed this: patients who had both TG levels in the higher third (~2.3 mmol/L [200 mg/dL]) and an HDL-C level in the lower third (≤0.4 mmol/L [34 mg/dL]), representing 17% of all participants, appeared to benefit from adding fenofibrate to simvastatin.[309]

Recently post-trial follow-up of the ACCORD lipid trial participants reported the beneficial effect of fenofibrate in people with hypertriglyceridaemia and low HDL-C levels at baseline.[426] Consistent with these findings, a meta-analysis of fibrates in the prevention of CVD in 11 590 people with T2DM showed that fibrates significantly reduced the risk of non-fatal MI by 21%, but had no effect on the risk of overall mortality or coronary mortality.[427] In CV outcome trials of fibrates, the risk reduction appeared to simply be proportional to the degree of non-HDL-C lowering.[51]

Overall, available data indicate that diabetic people with atherogenic dyslipidaemia may derive clinical benefits from TG lowering therapy add-on statin.[359] The ongoing PROMINENT trial is exploring the efficacy of pemafibrate, a new selective PPAR-α modulator, to reduce CVD outcomes in about 10 000 diabetic patients with atherogenic dyslipidaemia on a statin.[321, 428]

There are limited data on the impact on CVDs of adding omega 3 fatty acids to statin therapy in patients with high plasma TG levels who are treated with statins. The REDUCE-IT trial examined the effects of icosapent-ethyl 2g twice daily on CV events in 8179 high-risk patients with hypertriglyceridaemia who were taking a statin. Over a median of 4.9 years, there was a significant ($p<0.001$) 25% reduction in the composite primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularisation or unstable angina, corresponding to an absolute reduction of 4.8%, which was offset by a 1% increased absolute risk of hospitalisation for atrial fibrillation or flutter.[197] The STRENGTH trial is investigating the effect of omega 3 fatty acids, in addition to a statin, in individuals with hypertriglyceridaemia and low HDL-C levels who are at high risk for CVD. The ASCEND trial was a randomized 2 × 2 factorial design study of aspirin and omega-3 fatty acid supplements for the primary prevention of CV events in people with diabetes, but not specifically with hypertriglyceridaemia. Among 15,480 people randomized to omega-3 fatty acid supplements versus placebo over a mean follow up of 7.4 years, there was no significant effect (HR 0.97; 95% CI 0.87-1.08) on serious vascular events (nonfatal MI, nonfatal stroke, TIA or vascular death).[429-432]

### 9.4.3 Type 1 diabetes

Type 1 diabetes is associated with high CVD risk, in particular in patients with microalbuminuria and renal disease.[433] Conclusive evidence supports the proposition that hyperglycaemia accelerates atherosclerosis. Emerging evidence highlights the frequent coexistence of MetS with type 1 diabetes, resulting in the so-called double diabetes increasing CVD risk.[434]

The lipid profile in type 1 diabetic patients with good glycaemic control is 'supernormal' and characterized by subnormal TGs and LDL-C, whereas HDL-C is usually within the upper normal range or slightly elevated. This is explained by

subcutaneous administration of insulin that increases LPL activity in adipose tissue and skeletal muscle and consequently the turnover rate of VLDL particles.[435] However, there are potentially atherogenic changes in the composition of both HDL and LDL particles.

Consistent data demonstrate the efficacy of statins in preventing CV events and reducing CV mortality in DM, with no evidence for sex differences.[436, 437] A meta-analysis including 18,686 patients with DM, demonstrated that a statin-induced reduction of LDL-C by 1.0 mmol/L (40 mg/dL) was associated with a 9% reduction in all-cause mortality and a 21% reduction in the incidence of major CV events.[424] Similar benefits were seen in both T1 and T2DM. In diabetic patients with ACS, intensive statin treatment led to a reduction in all-cause and CV death, and contributed to a reduction in atheroma progression.[438]

### 9.4.4 Management of dyslipidaemia for pregnant women with diabetes

In both T1DM and young onset T2DM, there is a paucity of evidence to indicate the age at which statin therapy should be initiated. To guide an approach, statins are not indicated in pregnancy[439] and should be avoided in both T1 and T2DM individuals who are planning pregnancy. If diabetes individuals up to the age of 30 have no evidence of vascular damage, and in particular, microalbuminuria, it seems reasonable to delay statin therapy in asymptomatic patients until the age of 30. Below this age, statin therapy should be managed on a case by case basis taking into account the presence of microalbuminuria, end organ damage and ambient LDL-C levels.

Recommendations for the treatment of dyslipidaemias in diabetes are shown in the table below.

**Recommendations for the treatment of dyslipidaemias in diabetes**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In patients with T2DM at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (55mg/dL) is recommended.[35, 424, 438] | I | A |
| In patients with T2DM at HIGH-risk[c] an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (< 70 mg/dL) is recommended.[424] | I | A |
| Statins are recommended in patients with T1DM who are at HIGH or VERY HIGH-risk[c].[433] | I | A |

| | | |
|---|---|---|
| Intensification of statin therapy should be considered before the introduction of combination therapy. | **IIa** | **C** |
| If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.[34, 302] | **IIa** | **B** |
| Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception | **III** | **C** |
| Statin therapy may be considered in both T1 and T2DM patients under the age of 30 years with evidence of end organ damage and/or LDL-C > 2.5 mmol/L as long as pregnancy is not being planned. | **IIb** | **C** |

LDL-C = low-density lipoprotein cholesterol; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 3*.

## 9.5 Patients with acute coronary syndromes and patients undergoing percutaneous coronary intervention

Patients who present with ACS are at increased risk of experiencing recurrent CV events. For these patients, lipid management should be undertaken in the context of a comprehensive global risk reduction strategy including lifestyle adaptations, risk factor management, and the implementation of cardioprotective drug strategies. Ideally, patients should be signed up to cardiac rehabilitation programmes to enhance the control of lipid levels[440] and improve overall survival following ACS.[441] Despite the acknowledged clinical benefits of lowering LDL-C in patients with ACS,[442] attainment of LDL-C target values remains suboptimal in this very high-risk setting.[443]

### 9.5.1 Lipid-lowering therapy in patients with acute coronary syndromes

LDL-C levels tend to decrease during the first days of ACS and therefore a lipid profile should be obtained as soon as possible after admission for ACS. Patients do not have to be fasting as this has little impact on LDL-C levels.[92] Lipid-lowering treatment should be initiated as early as possible to increase patient adherence after discharge. Lipid levels should be re-evaluated 4-6 weeks after ACS to determine whether treatment goals have been achieved and to check for any safety issues; the therapeutic regimen can then be adapted accordingly.

*9.5.1.1 Statins*

Data from RCTs and meta-analyses indicate that routine early use of high-intensity statin therapy is associated with rapid and sustained clinical benefits.[444-448] We recommend initiating high-intensity statin therapy in all statin-naïve ACS patients with no contra-indication, regardless of initial LDL-C values; the treatment goal is to reach a 50% LDL-C reduction from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL). In those with recurrent events within 2 years whilst taking maximally tolerated statin therapy, a goal of <1.0 mmol/L (40 mg/dL) for LDL-C should be considered. The intensity of statin therapy should be increased in those patients receiving low- or moderate-intensity statin treatment at presentation, unless there is a definite history of intolerance to high-intensity statin therapy. The use of lower-intensity statin therapy should be considered in patients at increased risk of adverse effects with high-intensity statin, such as in the elderly, patients diagnosed with hepatic or renal impairment, or in the case of a potential risk of drug–drug interactions with other essential concomitant therapy.

Regarding the timing of statin treatment initiation, the SECURE-PCI randomized, placebo-controlled trial recently assessed the impact of periprocedural loading with atorvastatin (2 loading doses of 80 mg, before and 24 hours after the planned percutaneous coronary intervention [PCI]) on MACE at 30 days in 4191 patients with ACS and planned invasive management.[449] All patients received atorvastatin 40 mg per day starting 24 hours after the second loading dose. The authors found no significant treatment benefit in the overall study population. In a prespecified analysis, a significant 28% relative risk reduction in MACE was observed among patients who underwent PCI (65% of all patients). The benefit was even more pronounced (46% relative risk reduction) in a post-hoc analysis including 865 ST-elevation MI (STEMI) patients undergoing reperfusion by primary PCI.[449] Based on current evidence, we recommend initiating high-intensity statin therapy during the first 1-4 days of hospitalization for the index ACS.[444-448] Moreover, pre-treatment (or loading dose for patients already on statin) with high-intensity statin may be considered in ACS patients with planned invasive management.[449]

*9.5.1.2 Ezetimibe*

In the IMPROVE-IT trial, adding ezetimibe to simvastatin therapy provided an additional benefit (6.4% relative risk reduction in the composite clinical end point) to post-ACS patients.[34] The clinical benefit of adding ezetimibe was consistent across patient subgroups[302, 450] and also led to a reduction of total CV events,[451] stroke[452] and rehospitalizations.[453] Patients at higher atherothrombotic risk (as assessed by the TIMI [Thrombolysis In Myocardial Infarction] Risk Score for Secondary Prevention) benefitted the most from the addition of ezetimibe.[454] In another randomized, open-label trial including 1734 patients with ACS, the addition of ezetimibe to moderate-intensity statin (pitavastatin 2 mg) failed to improve outcomes overall, but did reduce the composite primary end point (death, MI, stroke, unstable angina and ischaemia-driven revascularization) during a 3.9-year follow-up in patients with increased intestinal absorption of cholesterol (as assessed by elevated levels of sitosterol);[455] however, this finding requires further confirmation.

*9.5.1.3 PCSK9 inhibitors*

In the FOURIER trial including 27 564 patients with atherosclerotic CV disease, the addition of evolocumab to statin therapy (69% high-intensity) resulted in a 15% relative risk reduction of the composite primary end point throughout a 2.2-year follow-up. Results were consistent in the subgroup of patients with a history of MI (81% of all patients).[121, 456] A sub-analysis of FOURIER showed that patients who achieved the lowest LDL-C values under PCSK9 treatment also had the lowest risk of future MACE[457] In the ODYSSEY Outcomes trial including 18 924 patients with recent ACS (1-12 months prior to enrolment, median 2.6 months), alirocumab added to statin therapy (89% high-intensity) also resulted in a 15% relative risk reduction in the primary composite end point and was associated with a 15% relative reduction in all-cause mortality throughout a 2.8-year follow-up.[122] No serious side effects or safety concerns were reported in these two large trials. The optimal timing of initiating PCSK9 inhibition after ACS and its impact on clinical outcomes remain to be determined. Regarding the timing of PCSK9 inhibitor treatment initiation, post-hoc analyses from the FOURIER trial showed that the closer to the event this is done, the better. Treatment initiation with PCSK9 inhibitors during the acute phase of ACS is under investigation in the EVOPACS trial.[458] Based on

current evidence, we recommend initiation of treatment with PCSK9 inhibitors in patients with ACS who do not reach the respective LDL-C goals (as outlined in Table 6) after 4-6 weeks of maximum tolerated statin and ezetimibe therapy. In patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe prior to the event, adding a PCSK9 inhibitor early after the event (if possible, during the hospitalization for the ACS event) should be considered.

*9.5.1.4 n-3 polyunsaturated fatty acids*

Alimentary supplementation with highly purified n-PUFAs reduced mortality in survivors of myocardial infarction in one study (GISSI-P) but failed to affect clinical outcomes in subsequent trials using contemporary secondary prevention therapies. A recent meta-analysis of available RCTs showed no reduction in mortality, MI or major vascular events associated with n-3 PUFAs, including for the subgroup of patients with known CAD.[459] Therefore, routine treatment with n-3 PUFAs cannot be recommended.

*9.5.1.5 CETP inhibitors*

In 2007, a large prospective study using the CETP inhibitor torcetrapib failed to show any clinical benefit in more than 15 000 high-risk patients, and was even harmful.[340] The CETP inhibitors dalcetrapib (in more than 30 000 patients with recent ACS[66]) and evacetrapib (more than 12 000 high-risk patients[54]) were investigated in 2012 and 2017, respectively. Neither of these clinical studies was able to show any clinical benefit associated with CETP inhibitors.[66] More recently, the REVEAL study investigated anacetrapib in more than 30 000 patients with atherosclerotic vascular disease and resulted in a lower incidence of MACE compared to placebo after 4 years, with no safety concern.[55] However, because of the potential safety issue of life-long accumulation of anacetrapib within fat tissues, this compound was not filed for market authorisation.

### 9.5.2 Lipid-lowering therapy in patients undergoing a percutaneous coronary intervention

In a meta-analysis of 13 randomized studies including 3341 patients who were planned to undergo PCI, pre-treatment with high-dose statin (statin-naïve patients, 11 studies) or a

high-dose statin loading dose reduced the risk of MACE (death, MI, target vessel revascularization) by 44% both for periprocedural MI and MACE at 30 days.[460] In all but one study, PCI was performed in the setting of stable angina, or in a non-emergency setting in non-ST elevation ACS (NSTE-ACS). One of the studies that were included in the meta-analysis showed an improvement in coronary flow when primary PCI was used for the treatment of STEMI.[461] A routine strategy of either short pre-treatment or loading (on the background of pre-existing therapy) with high-dose statin before PCI should be considered in elective PCI or NSTE-ACS.[460, 462, 463]

In addition, pre-treatment with a statin has also been shown to reduce the risk of contrast-induced acute kidney injury after coronary angiography or intervention.[464]

Recommendations for lipid-lowering therapy in patients with ACS and patients undergoing PCI are summarized in the tables below.

**Recommendations for lipid-lowering therapy in very high-risk patients with acute coronary syndromes**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In all ACS patients without any contra-indication or definite history of intolerance, it is recommended to initiate or continue high dose statin as early as possible, regardless of initial LDL-C values.[444, 446, 448] | I | A |
| Lipid levels should be re-evaluated 4-6 weeks after ACS to determine whether a reduction of at least 50% from baseline and goal levels of LDL-C <1.4 mmol/L (55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly. | IIa | C |
| If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.[34] | I | B~~C~~ |
| If the LDL-C goal is not achieved after 4-6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.[121, 122] | I | B |
| In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered. | IIa | C |

| | | |
|---|---|---|
| For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered. | **IIa** | **C** |

ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.

**Recommendations for lipid-lowering therapy in very high-risk patients undergoing percutaneous coronary intervention**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Routine pre-treatment or loading (on the background of chronic therapy) with high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI.[449, 460, 462] | **IIa** | **B** |

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

## 9.6 Stroke

Stroke has a heterogeneous aetiology, including cardiac thromboembolism (often associated with atrial fibrillation, but also of uncertain source [embolic stroke of undetermined source]), carotid artery and proximal aortic atherosclerosis and thromboembolism, small vessel CVD and intracranial haemorrhage (including intracerebral and subarachnoid haemorrhage). Dyslipidaemia may play a variable role in the pathogenesis of stroke according to the particular aetiology. The relationship between dyslipidaemia and atherothrombotic events, including ischaemic stroke and transient ischaemic attack (TIA), is well recognized, while the association of dyslipidaemia with other types of stroke is uncertain. Notwithstanding, concomitant control of other aetiologic factors, such as hypertension, is of paramount importance.

Following ischaemic stroke or TIA, patients are at risk not only of recurrent cerebrovascular events, but also of other major CV events, including MI. Secondary prevention therapy with statins reduces the risk of recurrent stroke (by 12%), MI and vascular death.[465, 466] Statin pre-treatment at TIA onset was associated with reduced recurrent early stroke risk in patients with carotid stenosis in a pooled data analysis, supporting an as-early-as-possible initiation of statins after stroke.[467].[466, 468] Statin therapy

may yield a small increase in the risk of haemorrhagic stroke, but the evidence about this risk is uncertain.[35, 37, 254, 255]

**Recommendations for lipid-lowering therapy for prevention of ASCVD events in patients with prior ischaemic stroke**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Patients with a history of ischaemic stroke or TIA are at very high-risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy.[465, 466] | I | A |

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.

## 9.7 Heart failure and valvular diseases

### 9.7.1 Prevention of incident heart failure in coronary artery disease patients

Cholesterol lowering with statins reduces the incidence of heart failure (HF) in patients with CAD (stable CAD or a history of ACS) without previous HF; this has been shown consistently in RCTs that compared statin vs. no statin treatment[469, 470] as well as more-intensive vs. less-intensive statin therapy.[471-474] A large-scale meta-analysis of primary prevention and secondary prevention RCTs with statins showed a modest (10%) reduction in first non-fatal HF hospitalizations with statin treatment, with no effect on HF death within the limited RCT period.[475] There is no evidence that statins can prevent HF of non-ischaemic origin.

### 9.7.2 Chronic heart failure

Two large RCTs[472, 476] (including mainly patients with systolic HF) as well as a meta-analysis of 24 RCTs showed no benefit of statin treatment on CV mortality or stroke;[477] a reduction in HF hospitalizations[221, 477] as well as a small reduction in MI was observed in a pooled analysis of the CORONA and GISSI-HF trials.[478] Based on current evidence, routine administration of statins in patients with HF without other indications for their use (e.g. CAD) is not recommended. Because there is no evidence of harm in patients on

statin treatment after the occurrence of HF, there is no need for statin discontinuation for patients already on treatment.

There is no evidence on the effect of PCSK9 inhibition in patients with CHF. In the recent PCSK9 clinical outcomes trials, FOURIER[121] and ODYSSEY Outcomes,[122] PCSK9 inhibition in patients with atherosclerotic CVD or after an ACS did not reduce the risk of HF hospitalization. In the BIOSTAT-CHF study of 2174 patients with worsening HF, multivariable analysis revealed a positive linear association between PCSK9 levels and the risk of mortality and the composite of mortality and unplanned HF hospitalization.[479] Similarly, there was a negative association between LDLR levels and mortality, indicating a potential relationship between the PCSK9-LDLR axis and outcomes among patients with HF that requires further investigation.[479, 480]

n-3 PUFAs 1 g daily may confer a small benefit in patients with chronic HF, as shown by a significant 9% relative risk reduction for mortality in the GISSI-HF RCT.[481]

### 9.7.3 Valvular heart diseases

Aortic stenosis increases the risk of CV events and mortality and frequently coexists with atherosclerotic CVD. Life-long high levels of LDL-C[482] and Lp(a)[483] have been associated with incident aortic valve stenosis and aortic valve calcification in genetic Mendelian randomization studies. Observational studies have suggested possible beneficial effects of intensive lipid lowering in slowing the progression of native valve aortic stenosis.[484] This was, however, not confirmed in RCTs[269, 485-487] or in meta-analyses of observational and randomized trials.[488, 489] Three modestly sized trials[485-487] and one large randomized trial (SEAS, which included 1873 patients treated with simvastatin 40 mg plus ezetimibe 10 mg or placebo)[269] failed to show a reduction in the clinical progression of aortic stenosis in patients with mild to moderate native valve aortic stenosis. In a post-hoc analysis of the SEAS trial, the efficacy of lipid-lowering therapy on impeding the progression of aortic stenosis increased with higher pre-treatment LDL-C levels and lower peak aortic jet velocity (i.e. milder stenosis at baseline).[490] Similarly, a post hoc analysis of two RCTs including patients without known aortic valve stenosis at baseline (IDEAL and SPARCL) showed no impact of high-dose vs. usual-dose statin therapy on the incidence of aortic valve stenosis.[491] In patients who underwent

transcatheter aortic valve replacement, statin therapy was associated with improved outcomes in a small observational study.[492]

Aortic valve sclerosis (calcification of the aortic leaflets without significant transvalvular pressure gradient) is associated with an increased risk of CAD even in the absence of increased risk profiles. Whether statins may be useful both for aortic valve disease and CAD progression in such patients warrants further investigation.[493]

Recommendations for lipid-lowering therapy in patients with HF and valvular diseases are shown in the table below.

**Recommendations for the treatment of dyslipidaemias in chronic heart failure or valvular heart diseases**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Initiation of lipid-lowering therapy is not recommended in patients with heart failure in the absence of other indications for their use.[472, 476] | III | A |
| Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use.[269, 485-487] | III | A |

CAD = coronary artery disease.
[a]Class of recommendation.
[b]Level of evidence.

## 9.8 Chronic kidney disease

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD is classified on the basis of cause, GFR category and category of albuminuria.[494] In the adult population, a decreasing GFR is associated with an increased CVD risk, independent of other CV risk factors.[495-498] There is an increased risk of both atherosclerotic vascular disease and structural heart disease,.[498] Patients with CKD and established CVD have a much higher mortality rate compared with patients with CVD and normal renal function.[499] Therefore, patients with CKD are considered high-risk (stage 3 CKD) or very high-risk (stage 4-5 CKD or on dialysis) of CVD and there is no need to use risk estimation models in these patients.

### 9.8.1 Lipoprotein profile in chronic kidney disease

In the initial stages of CKD, TGs are specifically elevated and HDL-C lowered. LDL subclasses display a shift to an excess of small dense LDL particles. Studies suggest that the kidney has a role in Lp(a) catabolism, and that Lp(a) levels are increased in association with kidney disease. Such acquired abnormalities can be reversed by kidney transplantation or remission of nephrosis.

### 9.8.2 Evidence for risk reduction through statin-based therapy in patients with chronic kidney disease

In the 4D trial involving 1200 patients with diabetes on haemodialysis, atorvastatin had no significant effect on risk of CVD.[223] Similar results were obtained in AURORA, involving 2776 patients on haemodialysis.[224]

In the SHARP study[225] simvastatin and ezetimibe combination therapy reduced the risk for major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke or any revascularization) compared with placebo in persons with CKD stage 3A-5. The trial did not have sufficient power to assess the effects in the primary outcome separately in dialysis and non-dialysis patients. Although statin-based therapy is clearly effective in mild to moderate CKD, a major controversy that remained after the publication of 4D, AURORA and SHARP was whether statin therapy is effective in more advanced CKD, particularly dialysis patients. By combining data from the three CKD trials with other trials in the existing database, the CTT investigators found that, even after adjusting for the smaller LDL-C reductions achieved among patients with more advanced CKD, and for differences in outcome definitions between dialysis trials, there was a trend towards smaller relative reductions per mmol/L reduction in LDL-C in major atherosclerotic events as eGFR declines (with little evidence of benefit among dialysis patients).[217] This diminution in relative risk reduction as GFR declines implies that, at least in non-dialysis patients, more intensive LDL-lowering regimens are required to achieve the same benefit.

### 9.8.3 Safety of lipid management in patients with chronic kidney disease

Safety issues and dose adjustment are important in advanced stages of CKD (stages 3-5), as adverse events are commonly dose related and due to increased blood concentration of the compound. Although it has been suggested that preference should be given to regimens and doses that have been shown to be beneficial in RCTs conducted specifically

in such patients,[500] the CTT meta-analysis makes clear that the goal – as in patients without CKD – should be to achieve the largest possible absolute reduction in LDL-C safely. Although there were no specific safety concerns raised by the 4D, AURORA or SHARP trials, statins metabolized via CYP3A4 may result in adverse effects due to drug–drug interactions, and caution is required.

Based on the evidence for lipid management in patients with CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) organization developed an updated clinical practice guideline for lipid management in CKD.[500] In line with this, but with a focus on those patients at high or very high risk for developing CVD, recommendations are summarized in the table below.

**Recommendations for lipid management in patients with moderate to severe (KDOQI stages 3-5)* chronic kidney disease**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended that patients with stage 3-5 CKD are considered at high or very high risk of ASCVD.[495-499] | I | A |
| The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3-5 CKD.[217, 225, 501, 502] | I | A |
| ~~In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.[223, 224]~~ | ~~III~~ | ~~A~~ |
| In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD. | IIa | C |
| In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.[223, 224] | III | A |

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease.
[a]Class of recommendation.
[b]Level of evidence.
*Defined as eGFR < 60ml/min/1.73m$^2$ on two measurements more than 3 months apart.

## 9.9 Transplantation

Dyslipidaemias are very common in patients who have undergone heart, lung, liver, kidney or allogenic hematopoietic stem cell transplantation, and predispose these patients to an increased risk of developing ASCVD and transplant arterial vasculopathy.[503-507] In patients with CKD undergoing renal transplantation, the risk of ASCVD may be determined, at least in part, by the increased risk resulting from CKD itself.

Immunosuppressive drug regimens may have adverse effects on lipid metabolism leading to increases in TC, VLDL and TGs and in the size and density of LDL particles. These effects vary with different immunosuppressive drugs.[503, 504, 508-512]

The management of dyslipidaemias in transplant recipients is comparable to what is recommended for patients at high or very-high ASCVD risk, although more attention has to go into the causes of the lipid disturbances and into possible side-effects due to drug–drug interactions (*see Recommendations table below*).

The clinical effectiveness of statins in renal transplant patients is uncertain owing to a lack of randomized trials in this population. A systematic review of the benefits and harms of statins in patients with a functioning kidney transplant included 3465 patients, free of CHD, from 22 studies. Although the authors concluded that statins may reduce CV events, they also suggested the need for additional studies.[256] In patients with a functioning renal transplant at increased risk of CVD, however, it may be appropriate to extrapolate from the clear evidence of benefit from statin therapy, without safety concerns, in people with moderate reductions in GFR.[217]

Several potential drug interactions must also be considered, especially with ciclosporin, which is metabolized through CYP3A4 and may increase systemic statin exposure and the risk of myopathy. Ciclosporin increases the blood level of all statins.

Fluvastatin, pravastatin, pitavastatin and rosuvastatin are metabolized through different cytochrome P450 enzymes than the others and have less potential for interaction.[513]

Tacrolimus is also metabolized by CYP3A4, but appears to have less potential for harmful interaction with statins than ciclosporin. Other drugs that influence CYP3A4 activity should be avoided if possible and used with extreme caution in patients receiving both calcineurin inhibitors and statins.

For transplant patients with dyslipidaemia, ezetimibe could be considered as an alternative for patients unable to take statin or added to the highest tolerated statin dose.[513-515] No outcome data are available for this drug, which should generally be reserved for second-line use. Ciclosporin can induce a two- to 12-fold increase in the ezetimibe level.

Care is required with the use of fibrates, as they can decrease ciclosporin levels and have the potential to cause myopathy. Extreme caution is required if fibrate therapy is planned in combination with a statin. Cholestyramine is not effective as monotherapy in heart transplant patients and has the potential to reduce absorption of immunosuppressants; this potential is minimized by separate administration.

**Recommendations for low-density lipoprotein lowering in solid organ transplant patients**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Statins should be considered as first-line agents in transplant patients. Initiation should be at low doses with careful up-titration and with caution regarding potential drug–drug interactions, particularly for patients on ciclosporin.[513] | IIa | B |
| In patients who are intolerant of statins or those with significant dyslipidaemia despite maximally tolerated statin treatment, alternative or additional therapy with ezetimibe may be considered. | IIb | C |

[a]Class of recommendation.
[b]Level of evidence.

## 9.10 Peripheral arterial disease

The term ‘peripheral arterial disease’ (PAD) encompasses all vascular sites, including carotid, vertebral, upper extremity, mesenteric, renal and lower extremity arteries. The aorta is often included in the term.[516] PAD is a common manifestation of atherosclerosis, and such patients are at elevated risk of coronary events, with PAD representing an independent risk factor for MI and CV death.[516, 517] Patients with PAD are at very high-risk and should be managed according to recommendations in *Table 6*. Elevated CV risk has led to inclusion of PAD among the list of ‘risk equivalent’ conditions, and therapeutic

strategies of secondary prevention should be implemented (*see Recommendations table below*). Yet, despite the high CV morbidity and mortality risk, PAD patients are usually inadequately managed compared with CAD patients.[517]

### 9.10.1 Lower extremity arterial disease

A low ABI (0.90) is diagnostic for lower extremities arterial disease (LEAD). Either a low (0.90) or a high (1.40, related to stiffened arteries) ABI is predictive of CV morbidity and mortality. Lowering LDL-C reduces the risk of ischaemic CV events and worsening of claudication, while it also improves walking performance. As for cardiac events, a systematic review of 18 trials including 10 000 patients, with cholesterol levels ranging from normal to elevated, reported that lipid-lowering therapy in people affected by atherosclerosis of the lower limbs is associated with a 20% reduction in total CV events, together with a non-significant 14% reduction of all-cause mortality.[518] In the Heart Protection Study the need for non-coronary revascularization was reduced by 16% with statin therapy.[519]

In addition to statins, PSCK9 inhibitors have also been shown to reduce CV events in PAD patients. In a prespecified subgroup analysis of the FOURIER trial, evolocumab significantly reduced the primary end point in patients with PAD.[520] PAD had larger absolute risk reductions for the primary end point (3.5% with PAD, 1.6% without PAD). Evolocumab also reduced the risk of major adverse limb events by 42% in patients, with consistent effects in those with and without known PAD. In the FIELD trial, fenofibrate reduced the risk of amputations, particularly minor amputations without known large-vessel disease, probably through non-lipid mechanisms.[521]

### 9.10.2 Carotid artery disease

While there are currently no randomized studies that have assessed whether lipid-lowering treatments reduce the incidence of CV events in patients enrolled on the basis of carotid atherosclerotic disease and without previous CV events, lipid-lowering therapy reduced stroke in numerous studies. In a meta-analysis of RCTs enrolling more than 90 000 patients, statin therapy did lead to a 21% reduction in the incidence of all strokes in different populations; this effect was mainly driven by the extent of LDL-C reduction.[466]

### 9.10.3 Retinal vascular disease

Atherosclerotic changes of retinal arteries correlate with TC, LDL-C, TG and apoB levels and also with CAD.[522] Fenofibrate reduces the progression of diabetic retinopathy.[523, 524]

### 9.10.4 Secondary prevention in patients with aortic abdominal aneurysm

The presence of an abdominal aortic aneurysm represents a risk-equivalent condition and is associated with age, male gender, personal history of atherosclerotic CVD, smoking, hypertension and dyslipidaemia,[525] while, in contrast, diabetic patients are at decreased risk.

There are currently no available clinical trials on the reduction of CV risk with lipid-lowering therapy in patients affected by this condition. Systematic reviews,[526] mostly based on retrospective non-randomized studies, have reported that there is still inconclusive evidence that statin therapy reduces perioperative CV morbidity and mortality. In an RCT comparing atorvastatin 20 mg with placebo, the composite end point of cardiac death, MI, stroke and unstable angina was significantly reduced in 100 patients undergoing vascular non-cardiac surgery, including abdominal aortic aneurysm repair.[527] In another double-blind placebo-controlled trial in 497 patients undergoing vascular surgery, perioperative fluvastatin therapy (80 mg/day) was associated with an improvement in postoperative cardiac outcome.[528]

### 9.10.5 Renovascular atherosclerosis

Lipid-lowering therapy has never been tested in an RCT in patients affected by renovascular atherosclerosis; however, a recent population-based study showed that in patients 65 years of age with atherosclerotic renovascular disease, the risk of a major cardiorenal composite end point (MI, stroke, HF, acute renal failure, dialysis and death) was significantly lower in statin users than in non-users.[529]

**Recommendations for lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| In patients with PAD, lipid-lowering therapy is recommended to reduce the risk of ASCVD events.[518, 530] | I | A |

ASCVD = atherosclerotic cardiovascular disease; PAD = peripheral arterial disease.
[a]Class of recommendation.
[b]Level of evidence.

## 9.11 Other special populations at risk of ASCVD

In general, the effects of lowering LDL cholesterol are determined by the absolute risk of ASCVD and the achieved reduction in LDL cholesterol, so it is important to identify and treat all those at increased risk of ASCVD. There are a few specific groups of patients in whom an underlying disease confers such increased risk, and in addition in whom the standard treatments may themselves cause dyslipidaemia that may contribute to the risk of ASCVD. These include: (a) chronic immune-mediated inflammatory disease; (b) patients with HIV; and (c) patients with severe mental illness. The principles management are the same in these patient groups, but their management may need to address specific issues related to individual dyslipidaemias and drug safety. Details are provided in the Supplementary Appendix.

## Supplementary appendix.

### Chronic immune-mediated inflammatory diseases

Patients with chronic immune-mediated inflammatory diseases (CIID) are at increased risk of developing ASCVD; this has been demonstrated for inflammatory bowel diseases,[S19] rheumatoid arthritis (RA),S20 systemic lupus erythematosus (SLE),[S21] systemic sclerosis[S22] or ankylosing spondylitis.[S20]

In a large cohort study of 991 546 patients, free of ASCVD at baseline, systemic connective tissue diseases and RA were associated with an increased risk of incident ASCVD (HR 1.31, 95% CI 1.15 to 1.49, and HR 1.31, 95% CI 1.15 to 1.49, respectively) followed by inflammatory bowel diseases (HR 1.12, 95% CI 1.01 to 1.25), independent of age, sex, CV risk factors and drug use.[S23]

Some treatments for controlling CIID such as glucocorticoids have a deleterious effect on ASCVD risk.[S24] Some of the disease-modifying anti-rheumatic drugs may, on the contrary, have a cardioprotective effect through the inhibition of systemic inflammation.[S25-S27]

The increased ASCVD risk in patients with CIID is not fully explained by a higher prevalence of the traditional CVD risk factors or by the use of drugs[S23] The immune system is believed to be involved in the pathogenesis of atherosclerosis.[S28] A complex interaction between ASCVD risk factors and CIID-specific traits may lead to premature atherosclerosis and an increased ASCVD risk.[S29] When estimating risk of ASCVD in patients with CIID, it has been suggested that a factor of 1.5 should be applied in addition to known risk factors.[S30]

The presence of CIID by itself is not an indication to prescribe lipid-lowering drugs to all patients with CIID. Furthermore, no specific LDL-C goal beyond that indicated by individual total ASCVD risk has been set for such patients (*see Recommendations table below*).

**Recommendations for the treatment of dyslipidaemias in chronic immune-mediated inflammatory diseases**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| CIID is a risk modifier and should be considered when estimating total ASCVD risk. | IIa | C |
| The use of lipid-lowering drugs only on the basis of the presence of CIID is not recommended. | III | C |

ASCVD = atherosclerotic cardiovascular disease; CIID = chronic immune-mediated inflammatory diseases.
[a]Class of recommendation.
[b]Level of evidence.

## Human immunodeficiency virus patients

HIV-infected patients typically have low TC and LDL-C, as well as low HDL-C and increased TGs.[S31,S32] Antiretroviral treatment (ART) or highly active antiretroviral treatment (HAART; when drugs are used in combination) causes marked increases in TC, LDL-C and TGs and a predominance of small dense LDL particles, while HDL-C remains low. HIV-infected patients have a higher risk for CVD when compared with HIV-uninfected individuals (RR 1.61, 95% CI 1.43 to 1.83), while ART (and especially older protease inhibitors) further increases this risk, up to two-fold (RR 2.00, 95% CI 1.70 to 2.37).[S31, S33, S34] Nevertheless, the increase in absolute ASCVD risk with ART is moderate and should be considered in the context of the benefits of HIV treatment.

Statins are effective in reducing LDL cholesterol in patients with HIV infection, but drug interactions with ART need to be considered. Statins metabolized in the liver via CYP3A4 or CYP2C9 are susceptible to drug interactions with protease inhibitors and the NNRTI efavirenz. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore a preferred statin in HIV-infected individuals. A recent trial compared pravastatin with pitavastatin and showed that pitavastatin led to a greater reduction in markers of immune activation and arterial inflammation.[S35] Preferred statins include pravastatin, fluvastatin, pitavastatin and rosuvastatin, although caution should be exercised. Combination of simvastatin or lovastatin with any protease inhibitor or efavirenz is not recommended.

The recommendations for lipid-lowering drugs in HIV patients are shown in the table below.

**Recommendations for lipid-lowering drugs in human immunodeficiency virus patients**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| 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. | **IIa** | C |

HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.

## Severe mental illness

Patients with severe mental illness (SMI) such as schizophrenia, bipolar disorder or major depressive disorder have a life expectancy that is reduced by 10–17 years compared with the general population[S36-S38]; this is mainly due to premature mortality from non-communicable diseases among which ASCVD is a main contributor.

In 2017 results were published from a large-scale meta-analysis of 3 211 768 patients and 113 383 368 controls demonstrating that patients with SMI had a 53% higher risk for having ASCVD, a 78% higher risk for developing ASCVD and a 85% higher risk of dying from ASCVD compared to the regionally matched general population[S39] The

authors also identified some factors that increased the risk for ASCVD including antipsychotic drugs and an elevated BMI.

Some antipsychotics, antidepressants, anxiolytics and mood stabilizers are associated with weight gain and cardiometabolic disturbances, including dyslipidaemia and dysglycaemia; these effects vary with different antipsychotic drugs. Unhealthy lifestyle factors such as sedentary behaviour, unbalanced diet and smoking of tobacco are more prevalent in these patients and explain part of the increased ASCVD risk.[S40-S43]

Statins are equally effective in lowering LDL-C in psychiatric patients;[S44-S46] however, in only a limited number of these patients are preventive actions taken both in regard to lifestyle and to the use of cardioprotective drugs. The odds of the use of statins was approximately halved in patients with schizophrenia compared with controls.[S47]

The recommendations for the management of dyslipidaemias in patients with SMI are listed in the table below.

**Recommendations for the management of dyslipidaemias in patients with severe mental illness**

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| It is recommended that SMI are used as modifiers for estimating total ASCVD risk. | I | C |
| It is recommended that the same guidelines for the management of total ASCVD risk are used in patients with SMI as are used in patients without such disease. | I | C |
| It is recommended that in patients with SMI intensified attention is paid to adherence to lifestyle changes and to compliance with drug treatment. | I | C |

ASCVD = atherosclerotic cardiovascular disease, SMI = severe mental illness.
[a]Class of recommendation.
[b]Level of evidence.

# 10. Inflammation

Recent advances in basic science have established a fundamental role for low degree chronic inflammation in mediating all stages of atherosclerosis, from initiation through progression and, ultimately, to the rupture of plaque and ensuing thrombotic complications of atherosclerosis. The cellular and molecular interactions involved during atherogenesis are fundamentally not different from those in chronic inflammatory-

fibroproliferative diseases, such as RA, glomerulosclerosis or pulmonary fibrosis.[531] Almost all cell types of the immuno-inflammatory system, such as macrophages, T- and B-cells, as well as many pro- and anti-inflammatory cytokines and chemokines, have been identified during the process of atherosclerosis.[532] Interestingly cholesterol accumulation in cells triggers the inflammasome response and results in the production of inflammatory mediators such as interleukin (IL) 1β. Numerous animal studies, using the knock-out model, have demonstrated that inflammation and the immune system both play a crucial role during atherogenesis.[533]

During inflammatory processes, large numbers of acute phase proteins have been identified, and several clinical studies have identified CRP[534] as being the most useful serum marker of inflammation, even though it has a poor specificity for any particular inflammation process, including atherosclerosis. The high-sensitivity CRP (hsCRP) diagnostic test was developed to detect very low levels of CRP and thereby enable a more accurate and precise measure of chronic inflammation compared to standard CRP.[535] This diagnostic tool differs only in the range of CRP levels that it can detect. Several studies found that elevated levels of hsCRP in the blood were associated with an increased risk of CV events and could be used to predict clinical outcomes independently of cholesterol levels.[536, 537] Other studies were not able to show any relationship between low-grade chronic inflammation, as indicated by hsCRP levels, and increased risk of CV.[538-541] Finally, genetic studies of large population cohorts have not demonstrated that chronic elevated hsCRP increases the risk of atherosclerotic events.[542] Nevertheless, in some guidelines hsCRP has been added to traditional risk factors for prognostic information, especially for patients at intermediate-risk.[543, 544]

Statins have been shown to reduce CRP secretion by the hepatocytes,[545] and a series of clinical trials and post-hoc analyses found that beneficial outcomes after statin therapy relate both to a reduction in cholesterol levels and reduced inflammation.[546-550] The JUPITER trial[548] demonstrated that in primary prevention for individuals with chronically elevated CRP (above 2 mg/L), statin treatment markedly reduced cardiovascular events.[551] It is of note that other lipid-lowering agents, such as ezetimibe and more recently the anti-PCSK9 mAbs do not influence hsCRP levels,[552, 553] but lead to further significant reductions in CV events when added to statin therapy.

Specific anti-inflammatory treatment was tested in the CANTOS trial.[554] In patients with previous MI and chronic elevated hsCRP levels, all on optimal medical treatment, including statins, the anti-IL-1β mAb canakinumab dose-dependently reduced hsCRP and significantly lowered the rate of recurrent CV events compared to placebo, independently of the level of lipid-lowering. Not surprisingly, there was a slight increase in the risk of severe and fatal infections associated with canakinumab. This study was the first to highlight the positive correlation between hsCRP and CV events, where lower achieved hsCRP values were directly correlated with a lower risk of future CV events.[554] Nevertheless, the FDA declined to approve canakinumab for cardiovascular risk reduction on the strength of data from the CANTOS study. As canakinumab treatment has not been tested against anti-PCSK9 mAb and/or ezetimibe added to statin therapy, the question of residual risk remains for patients with elevated hsCRP despite achieving very low (below goal) LDL-C values, and whether patients with very low LDL-C would benefit from anti-IL-1β treatment or other anti-inflammatory agents. In addition, all currently recommended lipid-lowering drugs, including anti-PCSK9 mAbs, have demonstrated beneficial effects on atherosclerotic plaque composition as well as plaque volume regression; such results are still missing for anti-inflammatory treatment. Another anti-inflammatory approach using methotrexate was tested in CIRT (Cardiovascular Inflammation Reduction Trial).[555] Very-low-dose methotrexate (10 mg weekly), a proven anti-inflammatory regimen that reduces tumour necrosis factor (TNF), interleukin 6 (IL-6) and CRP levels and is widely used in the treatment of RA, was allocated vs. placebo to 7000 stable CAD patients. This study was stopped prematurely due to futility. Interestingly, this regimen of methotrexate had no effect on either IL-6 or hsCRP blood levels in this population, which could explain the neutral results of this trial.[556] Based on the current level of evidence, no further recommendations on the use of anti-inflammatory agents can be made.[557]

# 11. Monitoring of lipids and enzymes in patients on lipid-lowering therapy

Evidence from trials for what tests should be carried out to monitor lipids in patients on treatment is limited. Similar limited evidence applies to tests of possible toxicity, such as ALT and CK. Recommendations stem from consensus rather than evidence-based medicine.

Response to therapy can be assessed at 6–8 weeks from initiation of therapy, but response to lifestyle may take longer. Standard practice for subsequent follow-up monitoring is 6-12 months, but such monitoring intervals are arbitrary. As a minimum, LDL-C should be assessed whenever available, but better management decisions will probably occur if a full lipid profile is performed, including HDL-C and TGs. Non-HDL-C or apoB should also be analysed, and used as a secondary treatment target. A separate issue is the impact of regular lipid monitoring in promoting patient adherence to lifestyle changes or drug regimens that impact positively on their health, as found in a range of studies. It is unclear whether only the process of monitoring is critical in achieving this or whether a combination of education, regular contact and adherence assessment is required.

Where pharmacological lipid-lowering therapy is implemented, safety blood tests are advised, including ALT and CK at baseline, to identify the limited number of patients where treatment is contraindicated. CK should be checked in patients with high- risk for myopathy, such as the very elderly with co-morbidities, patients with antecedents of muscle symptoms or patients receiving interacting drugs. A mild and typically transient elevation of ALT is seen in up to 2% of patients and normalization is seen with continuing therapy.[243, 247, 558] Recent reviews are encouraging in regard to the safety of long-term statin therapy, and statin-induced liver injury is reported to be very uncommon.[246, 247, 559-561] ALT is recommended before the start of statin therapy; routine control of ALT during treatment is not recommended but should be performed, if indicated, based on clinical observations. During fibrate therapy, regular ALT control is still recommended. In patients whose liver function tests increase to above three times the ULN, explanations such as alcohol ingestion or non-alcoholic fatty liver disease should be sought and the levels monitored. If levels remain elevated then lipid-lowering therapy should be stopped, but may be cautiously reintroduced under monitoring after levels have returned to normal.

There is no predictive value of routine repeat CK testing for rhabdomyolysis since the level can increase for many reasons, including muscle injury or excess muscular exercise. However, CK must be assessed immediately in patients who present with muscle pain and weakness and especially in the elderly, and treatment stopped if CK rises to >10 times the ULN. Strategies to handle CK elevations are given in *Table 12*.

Due to the increased frequency of diabetes during statin treatment,[250, 252, 562, 563] regular checks of HbA1c should be considered in patients at high- risk of developing diabetes and under high-dose statin treatment. Groups to be considered for glucose control are the elderly or those with MetS, obesity or signs of insulin resistance.

**Table 12 Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy**

| **Testing lipids** |
|---|
| **How often should lipids be tested?**<br>• Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1-12 weeks, with the exception of conditions where concomitant drug treatment is suggested, such as acute coronary syndromes (ACS) and very high-risk patients. |
| **How often should a patient's lipids be tested after starting lipid-lowering treatment?**<br>• 8 (±4) weeks after starting treatment.<br>• 8 (±4) weeks after adjustment of treatment until the goal is achieved. |
| **How often should lipids be tested once a patient has achieved the target or optimal lipid level?**<br>• Annually (unless there are adherence problems or other specific reasons for more frequent reviews). |
| **Monitoring liver and muscle enzymes** |
| **How often should liver enzymes (alanine aminotransferase [ALT]) be routinely measured in patients on lipid-lowering drugs?**<br>• Before treatment.<br>• Once 8-12 weeks after starting a drug treatment or after dose increase.<br>• Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended. |
| **What if liver enzymes become elevated in a person taking lipid-lowering drugs?**<br><br>If ALT <3x upper limit of normal (ULN):<br>• Continue therapy.<br>• Recheck liver enzymes in 4-6 weeks.<br><br>If value rises to ≥3x ULN<br>• Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4-6 weeks. |

- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

**How often should creatine kinase (CK) be measured in patients taking lipid-lowering drugs?**

*Pre-treatment*

- Before starting therapy.
- If baseline CK is >4x ULN, do not start drug therapy; recheck.

*Monitoring:*

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease or athletes.

**What if CK becomes elevated in a person taking lipid-lowering drugs?**

Re-evaluate indication for statin treatment.

If ≥4 x ULN:

- If CK >10x ULN: stop treatment, check renal function and monitor CK every 2 weeks.
- If CK <10x ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK.
- If CK <10x ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

If <4x ULN:

- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider re-challenge with the same or another statin.
- Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy.

For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in *Supplementary figure 4*.

**In which patients should glycated haemoglobin (HbA1c) or blood glucose be checked?**

- Regular checks of HbA1c or glucose should be considered in patients at high-risk of developing diabetes, and on high-dose statin treatment.
- Groups to be considered for glucose control are the elderly and patients with MetS, obesity or other signs of insulin resistance.

# 12. Cost-effectiveness of cardiovascular disease prevention by lipid modification

In 2015, there were more than 85 million people in Europe living with CVD.[564] Aging populations[565], unhealthy diet, smoking, sedentary lifestyle, increasing obesity and diabetes[566-569] are the main contributors. CVD cost the European Union about €210 billion in 2015, half of which was in healthcare costs (~8% of total healthcare expenditure) and the other half in productivity losses and informal care.[564]

In this guideline, the Joint Task Force recommends a range of actions to reduce CVD by targeting plasma lipids, ranging from population-wide initiatives to promote healthy lifestyle to individual level interventions to reduce CVD risk factors such as unhealthy diet and high lipid levels. Cost-effectiveness analysis can help target resources for interventions where the net health gain is greatest in relation to the net resources, and is increasingly required across Europe.[570] However, cost-effectiveness depends on available resources, costs of services and disease risk in the population and results obtained in one country might not be valid in another.[571] In addition, to fully capture the long-term effects of interventions, cost-effectiveness studies combine evidence from RCTs with modelling and limitations in both could affect the reliability of findings. Here, the evidence for cost-effectiveness of ASCVD preventive interventions with respect to lipid modification is summarised; further scrutiny in view of local circumstances is recommended.

The health impact pyramid summarises the evidence on the relative efforts and costs in relation to health impact (*Figure 5*) with interventions with the broadest impact on populations at the base and interventions requiring considerable individual effort are at the top.[572] There is consensus that all the levels of the pyramid should be targeted but that emphasis should be placed on the lower levels. This would address the persistent socio-economic divide in CV health despite major improvements in ASCVD treatment.[564]

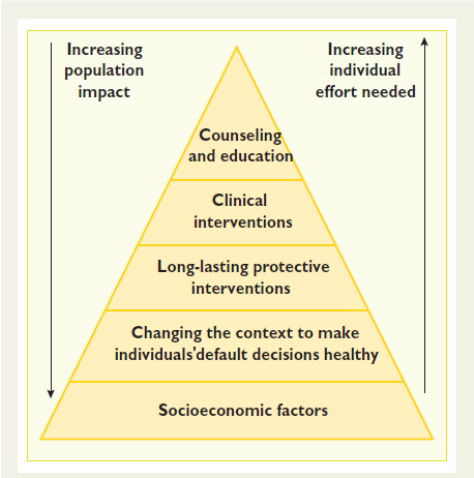



**Figure 5 Health impact pyramid**

More than half of the reduction in CV mortality in the last three decades has been attributed to population-level changes in CV risk factors, primarily reductions in plasma cholesterol, BP levels and smoking.[566-569, 573] Lifestyle changes at the population level may be more cost-effective than lifestyle and drug interventions at the individual level, particularly when targeted to populations at increased risk. Awareness and knowledge of how lifestyle risk factors lead to CVD has increased in recent decades. Moreover, legislation promoting a healthy lifestyle, such as reduced salt intake and smoking bans, has been reported to be cost-effective in preventing CVD[574-579] and initiatives to improve the infrastructure and promote physical activity have shown promise.[580, 581] A number of structural strategies at international, national, and regional levels combined can substantially reduce CVD morbidity and mortality.[582 583,584] Individual-level interventions to improve diet,[585, 586] increase physical activity[587] and stop smoking[588] could also be cost-effective.[589] However, suboptimal adherence limits benefits[590, 591] and interventions to improve adherence such as electronic device reminders to reinforce favourable health behaviours, are increasingly being investigated.[592]

All statin regimens and ezetimibe are now generically available across Europe. There is strong evidence that lowering blood cholesterol levels using low-cost statins is widely cost-effective[593-597] in many categories of patients. For secondary prevention of

CVD, the evidence suggests that statin treatments are highly cost-effective[593, 597, 598] and adding low-cost ezetimibe to high-intensity statin therapy further reduces LDL-C and CVD risk cost-effectively.[599] In primary ASCVD prevention, the cost-effectiveness evidence indicates that generic statin-based treatments are cost-effective for people at least down to 1% annual total CVD risk and could be cost-effective at even lower risk[596] with the highest tolerated statin intervention likely the most cost-effective.[598, 600, 601] Importantly, many patients on statin treatment fails to take their medications adequately and/or to reach their therapeutic goals,[311, 602] with clinical and economic consequences.[603, 604] Reinforcing measures aimed at improving adherence to treatment is cost-effective.[605-607]

Studies have shown that at mid-2018 prices PCSK9 inhibitors were largely not cost-effective .[608-611] Their cost-effectiveness is improved in selected high-risk patients, such as those with clinical CVD or FH, other co-morbidities and high LDL-C (see supplementary figure 5 ).[612, 613] At lower prices, however, PCSK9 inhibitors would become cost-effective in a wider range of high-risk patients: recent price reductions may therefore lead to increased use.[614] Cost-effectiveness evidence for other lipid-modifying therapies is lacking.

Effective interventions to prevent ASCVD, including statins, typically exhibit similar relative risk reductions across categories of patients, including by ASCVD risk; therefore, health benefits and cost-effectiveness are greater among people at higher ASCVD risk (*Figure 6*).[37, 236] Consequently, increased efforts and higher intensity interventions should be aimed at individuals and populations at higher ASCVD risk.

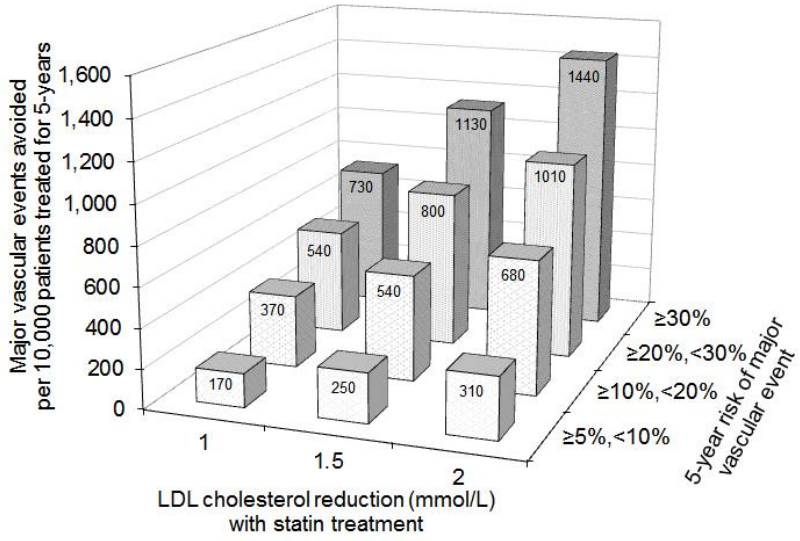



**Figure 6 Absolute reductions in major vascular events with statin therapy.**[236]
LDL = low-density lipoprotein.

*Box 8* lists the key messages regarding the cost-effectiveness of CVD prevention by lipid modification, and *Box 9* highlights gaps in the evidence.

**Box 8 Key messages**

| |
|---|
| Prevention of cardiovascular disease (CVD) by lifestyle changes, medication or both is cost-effective in many scenarios, including population-based approaches and actions directed at individuals at increased CVD risk. |
| Cost-effectiveness depends on several factors, including baseline CVD risk and LDL levels, cost of treatment, and uptake of preventive strategies. |
| Interventions to prevent CVD are more cost-effective among individuals and populations at higher CVD risk. |
| Cost-effectiveness analyses are importantly informed by assumptions about long-term disease prognosis and treatment effects. Strengthening the evidence to inform these assumptions is encouraged. |

**Box 9 Gaps in evidence**

| |
|---|
| Cost-effectiveness requires evidence for effects of interventions on health and healthcare over a long time period; modelling techniques fill gaps. More data are needed from randomized controlled and observational studies. |
| Direct evidence of effects of lipid-modifying treatments on overall mortality, particularly among people at low to moderate cardiovascular disease (CVD) risk, older people and for newer interventions, is lacking. Long-term post-trial follow-up in randomized controlled trials should be encouraged. |

The cost-effectiveness of using lifetime CVD risk and more precise CVD risk scores to target interventions needs further investigation.

# 13. Strategies to encourage adoption of healthy lifestyle changes and adherence to lipid-modifying therapies

Helping patients to change to healthier lifestyle habits is most effectively achieved through formal programmes of preventive care, possibly because of the intensive follow-up and multidisciplinary expertise they provide.[615] However, in everyday care, adherence to both healthy lifestyle changes and medication regimens is a challenge to patients and professionals.

A comprehensive patient- and family-centred approach located in one healthcare setting is recommended rather than addressing single risk factors with more than one intervention in different locations. *Box 10* includes some useful techniques when counselling patients for behavioural change.

**Box 10 Methods for enhancing adherence to lifestyle changes**

| |
|---|
| 1. Explore motivation and identify ambivalence. Weigh pros and cons for change, assess and build self-efficacy and confidence, avoid circular discussion. |
| 2. Offer support and establish an alliance with the patient and his/her family. |
| 3. Involve the partner, other household members or caregiver who may be influential in the lifestyle of the patient. |
| 4. Use the **OARS** method (**O**pen-ended questions, **A**ffirmation, **R**eflective listening, **S**ummarising; http://www.smartrecovery.org/ resources/UsingMIinSR.pdf) when discussing behaviour changes. |
| 5. Tailor advice to an individual patient's culture, habits and situation. |
| 6. Use **SMART** goal setting (negotiate goals for change that are **S**pecific, **M**easurable, **A**chievable, **R**ealistic and **T**imely). Follow up at goals and record progress on a shared record. |

A comprehensive approach to improving adherence to medication is described in the *Supplementary appendix*.

**Supplementary appendix. Adhering to medications**

Despite a wealth of evidence on the efficacy and effectiveness of statins in both primary and secondary prevention, adherence remains a consistent barrier, with rates of < 50% demonstrated in several studies. Adherence declines over the duration of treatment[S48-S52]; however, this is truer in patients treated for primary compared with secondary prevention of CVD, with reported rates of up to 77% discontinuing their statins within 2 years. Adherence is better in patients recruited to clinical trials compared with those treated in the real world.[S53, S54] Not surprisingly, this non-adherence has an impact on healthcare costs, morbidity, hospital readmissions and mortality.[S55-S59] Poor adherence rates are not only limited to statins but are also true of other lipid-lowering drugs and all medications used to prevent CVD, as demonstrated in a systematic review and meta-analysis.[S60]

The reasons for non-adherence are complex and include misconceptions about tolerability on the part of both patients and professionals alike. These barriers prevent patients from gaining the maximum benefit from their treatment.

Various empirical models of health behaviour and behaviour change theory have been shown to predict adherence, including the Theory of Planned Behaviour[S61] and the Health Belief Model.[S62] Studies that investigated adherence to medications in long-term conditions identified factors such as high susceptibility, severity of the condition, strong intentions and high self-efficacy as being associated with good adherence, while poor lifestyle habits and low perceived behavioural control were associated with poor adherence.[S63] However, these theoretical models are limited in that they do not take into account important social, economic, health system and therapy-related factors. Most recently, the COM-B (Capability, Opportunity and Motivation) theoretical model,[S65] developed by Michie *et al*,[S66] which takes a broader look at factors influencing adherence, proposed a framework for assessing and addressing adherence, taking the interaction between capability (defined as both the psychological and physical capacity of an individual to engage in a behaviour), opportunities (defined as factors outside the control of an individual) and their motivation to do so.

Predictors of non-adherence with statins have been identified[S48, S67-S69] and include their use in individuals for primary prevention as compared with their use in patients with disease or with multiple risk factors, lower income, being elderly, complex polypharmacy, cost and forgetfulness due to a lack of symptoms and psychological co-

morbidities. In addition, reasons for reluctance to collect a first prescription of statin medication were investigated in a cross-sectional telephone survey conducted in California from recruits to an RCT.[S70] The most commonly reported reasons included general concerns about the medication, wanting to try lifestyle measures first, and fear of adverse effects; however, a significant proportion reported financial hardship, a lack of understanding of why they needed to take the medication and what the medication was for (indicating a need to address the patient–professional relationship and poor health literacy). Health literacy is defined as "the degree to which individuals have the capacity to obtain, process and understand basic health info and services needed to make appropriate health decisions" (http://nnlm.gov/outreach/consumer/hlthlit.html).

Poor health literacy is of particular concern in regard to medication adherence.[S70] Elderly patients and those with low socio-economic status and chronic health conditions may be especially vulnerable. These patients may get confused, especially when their regimens are complex and include many drugs (polypharmacy) that need to be taken on more than one occasion per day. Important steps to empower patients to get more benefit from health interventions include the following[S71]

1. Use good interpersonal skills (good eye contact, warm manner) and an empathetic, non-judgmental attitude.
2. Provide clear and simple instructions on a drug regimen backed up with written instructions, which can also be seen by a spouse or caregiver.
3. Speak slowly in plain language and avoid medical jargon when giving instructions.
4. Limit the number of instructions to no more than three key points—principle of 'need to know' (*Supplementary figure 8*).
5. Use 'teachback' to confirm understanding; e.g. "I want to make sure that I explained things clearly. Let's review what we discussed. What are the three strategies that will help keep your cholesterol down?"
6. Use supplemental materials, e.g. images, videos and audio sources, to improve recall (*Supplementary figure 9*).
7. Encourage questions and discussion—enlist the family or others important to the individual.

8. Motivational interviewing skills may be helpful in communicating with patients who are ambivalent or seem against starting or continuing with medications[S72, S73]:

(a) Counsel patients using the OARS method (*Box 10*).

(b) Use the 'elicit–provide–elicit' model to tailor the information you give (elicit what the patient wants to know, provide that information, elicit from the patient how they can use this new knowledge to their benefit).

(c) Acknowledge and reflect your patient's resistance.

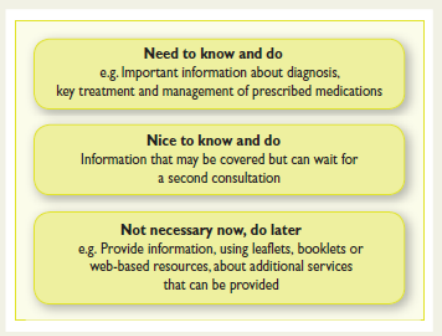
(d) Support your patient's autonomy to make their own decisions about their health and treatment.

(e) Explore your patient's ambivalence to adhere to their treatment.

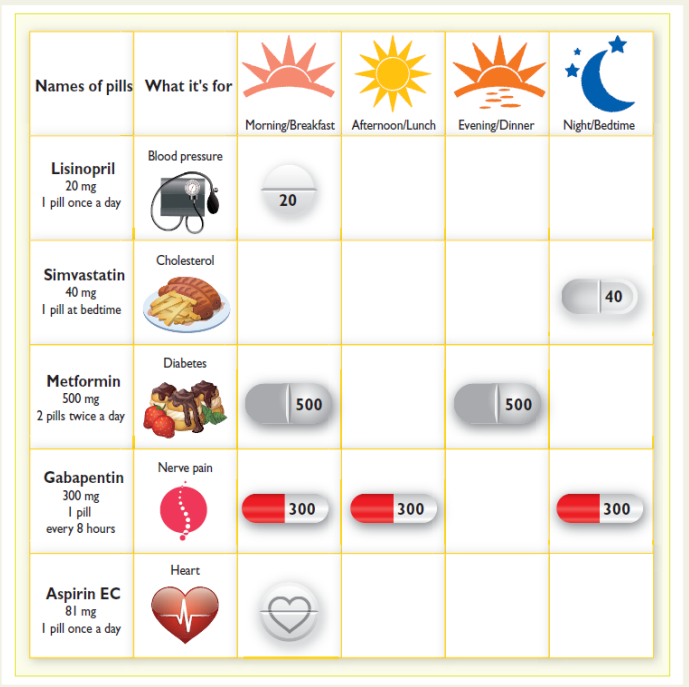
(f) Develop a plan of action together and share decision-making.

9. Build self-efficacy and confidence, drawing on social learning theory.[S74]

Being able to identify patients with low health literacy is important. Indicators may include seeking help when an illness is already advanced, inarticulacy in explaining concerns, making excuses like 'I forgot my glasses' to cover for the shame associated with illiteracy, being passive or aggressive and missing appointments.




**Supplementary figure 8. Prioritising information when educating patients.**




**Supplementary figure 9 Images to improve recall.**

Interventions to improve adherence were reviewed in a Cochrane review in 2010,[S75] which looked at interventions to improve adherence to all forms of lipid-lowering therapy, including reminders, simplification of drug regimens and provision of information and education. Most effective was reminders, such as setting alarms, connecting medication-taking to other tasks to trigger memory, and phone reminders from nurses. Reminder systems have the potential to be developed with the help of innovations in technology, like the use of text messaging, the internet and applications for mobile phones or tablets to assist in self-monitoring and management. Adherence research is weak in this area, mainly because it has not kept abreast of the rapid developments in technology[S76]; however, these methods may come into their own in the future with a stronger knowledge base. Using information technologies to increase adherence is becoming increasingly important, especially since the current methods are not increasing adherence sufficiently. Electronic health records and e-prescription is

being used increasingly. This can be used to flag high-risk patients, be a reminder for the patient and physician, and evaluate patient adherence and performance of the physician.[S77]

Mobile technologies can be used to remind or track medication, monitor activity and parameters like BP and provide education for the patient.[S78] The TEXTME trial showed that by using lifestyle-focused text messaging, it was possible to reduce BP, LDL-C, smoking and BMI.[S79] However, most trials assessing mobile technology on adherence are small and of short duration, and randomized clinical trials are lacking.

Prescription of a statin should include a shared decision-making approach[S80] that engages the patient in a discussion before initiating treatment, especially when it is being considered for primary prevention of CVD. This discussion should be based on risk estimation and adequate communication of this risk to patients. Involving the patient in such a way is likely to be empowering and motivate adherence. This discussion is not exclusively about the prescription of a statin to manage lipids; a comprehensive approach includes addressing all lifestyle and other biomedical factors that contribute to CV risk.

Once treatment has been prescribed, communication should focus on conveying achievements in reaching goals, assessment of adherence and possible reasons for non-adherence, such as adverse effects. In relation to lipid-lowering medications, and statins in particular, misconceptions and misleading media reports are in abundance. Many patients report adverse effects of statins to their GPs and this may be because of an increased likelihood to anticipate them. However, a recent large review of RCTs[S81] found that in 83 880 patients receiving blinded placebo-controlled statin therapy, few reported adverse effects were actually due to the drug. This study calculated the PSN, defined as the proportion of symptoms not attributable to its pharmacological action, in order to provide GPs with a clear metric to use in advising their patients on whether reported symptoms are genuinely likely to be pharmacologically caused by the statin or not.

Recently, promising results for improving adherence have been demonstrated in the use of a fixed-dose combination (FDC) drug or ‘polypill’ in both primary and secondary prevention. The UMPIRE (Use of a Multidrug Pill In Reducing cardiovascular Events) RCT[S82] compared an FDC containing aspirin, statin and two BP-lowering agents with usual care in both primary and secondary prevention in 2004 randomized patients in

India and Europe. At 15 months, statistically significant differences between intervention and usual care were seen in self-reported adherence and changes in SBP and LDL-C. The FOCUS (Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention) study[S83] had a cross-sectional first phase, which identified factors contributing to non-adherence after MI in 2118 patients from five countries in South America and Europe. In the second phase, 695 patients from the first phase were randomized to receive either a polypill, containing aspirin, statin and ramipril in varying doses, or were given the three drugs separately. Adherence was measured with the self-reported Morisky–Green questionnaire and pill counts and was statistically significantly superior in the intervention group compared with usual care at 9 months. In phase 1, factors associated with non-adherence were younger age, depression, complex regimen, poorer health insurance coverage and low social support.

Given the benefits for adherence demonstrated with simplified dosing reported in a Cochrane overview of interventions to improve safe and effective medicines use by consumers,[S84] it makes sense that a pill containing multiple medications in one tablet will enhance adherence. This overview also found that the use of self-management or self-monitoring programmes, as well as a regular pharmacy review of prescribed medications with a view to taking out unnecessary medications, was helpful.

Many of the studies included in the Cochrane review of interventions to improve medication adherence[S76] drew on the support of allied professionals such as nurses and pharmacists to deliver complex interventions, which may include telephone follow-up, interim appointments and monitoring of repeat prescriptions. The reviewed interventions may be difficult to replicate in everyday clinical care due to the cost and the availability of personnel. Team-based care, where nurse practitioners focus on chronic disease management, patient education and transitions of care, and the pharmacist assists with adherence to therapy and helps the patient with complex therapies, will increase adherence.[S85] Drawing on the support of non-professional people within the social context of the patient, such as spouses, other family members, caregivers or other key figures, as well as lay groups in the community, may prove to be a cost-effective way to improve adherence.

*Box S2* lists a number of tips to use when prescribing multiple medications to patients in order to help them adhere.

**Box S2 Tips to aid adherence to multiple drug therapies**

| |
|---|
| 1. 'Agree on' rather than 'dictate' a drug regimen to your patient and tailor it to his/her personal lifestyle and needs. |
| 2. Back up verbal instructions with clear written instructions. |
| 3. Simplify the dosing regimen and consider a fixed dose combination pill where available. |
| 4. Perform a regular review of medicines to minimize polypharmacy (or ask the pharmacist to assist). |
| 5. Encourage self-monitoring and use cues and technologies to act as reminders. |
| 6. Provide information on common side effects and discuss management strategies. |
| 7. Involve the partner, other family members or the caregiver in the patient's treatment. |

# 14. Gaps in evidence

- Prospective studies are needed to investigate the incremental value of re-classifying total CV risk and defining eligibility for lipid-lowering therapy based on coronary artery calcium score in individuals at moderate or high-risk.
- Outcomes-based comparison of coronary artery calcium score vs. assessment of arterial (carotid or femoral) plaque burden by ultrasonography for CV risk re-classification in people at moderate or high-risk is needed.
- Although calibrated country-specific versions of the SCORE system are available for many European countries, risk charts based on country-specific cohort data are missing for most countries. Regional total-event charts (vs. mortality-only charts) are needed.
- Total CV risk estimation by means of the SCORE system and, accordingly, recommendations on eligibility for statin as well as treatment goals are based on TC, whereas LDL-C is the primary lipid analysis for screening, diagnosis and management.
- There are no outcomes-based comparisons of LDL-C vs. ApoB as primary measurement for screening, diagnosis and management.
- Against a background of genetic and randomized clinical trial evidence showing no significant effect of increasing HDL levels on the risk of CVD events, the clinical impact of therapies altering the function of HDL particles is unknown. More evidence is needed regarding the apparently adverse association of extremely high levels of HDL-C with clinical outcomes.

- Dedicated studies assessing outcomes with specific Lp(a)-lowering therapies are warranted..
- More evidence is needed for PCSK9 inhibitors in specific populations, including patients with severe CKD and on dialysis, patients with HIV infection, in children and adolescents with FH, after heart transplantation and during pregnancy.
- The effects of inhibition of PCSK9 in all body compartments (as with siRNA or antisense) or only within plasma (as with monoclonal antibodies) remain to be established.
- How early should a PCSK9 inhibitor be initiated in patients with ACS or stroke? In view of evidence of sustained clinical benefit associated with the early initiation of statin treatment in the acute phase of ACS or stroke, the optimal timing of PCSK9 inhibitor treatment in ACS and stroke patients remains to be addressed in outcome studies.
- Whether very low LDL-C levels achieved with the combination of statin, ezetimibe and PCSK9i reduce the need for further PCI remains to be addressed in outcome studies.
- In patients with chronic heart failure, a small benefit of n-3 PUFAs has been shown in one RCT and merits further investigation.
- What is the optimal screening programme for detecting FH?
- In view of limited access to genetic testing in several environments, more evidence is needed regarding outcomes with clinical-only vs. genetic screening and diagnosis of FH.
- More RCT evidence is required to support the use of statin-based treatment in older people (aged 75 or over, but particularly aged 80 or over).
- More RCT evidence is needed for statin treatment in kidney transplant recipients.
- There are no data on the effects of statins, ezetimibe or fibrates on CV events in dyslipidaemic HIV-infected patients.
- More evidence is needed regarding attainment of recommended LDL goals among very high-risk patients in real-world practice in the era of increasingly prescribed combination therapies for LDL lowering.~~Prospective studies are needed to investigate the incremental value of re-classifying total CV risk and defining eligibility for statin therapy based on coronary artery calcium score in individuals at moderate or high risk.~~
- ~~Outcomes-based comparison of coronary artery calcium score vs. assessment of arterial (carotid or femoral) plaque burden by ultrasonography for CV risk re-classification in people at moderate or high risk is needed.~~
- ~~Although calibrated country-specific versions of the SCORE system are available for many European countries, risk charts based on country-specific cohort data are missing for most countries. Regional total-event charts (vs. mortality-only charts) are needed.~~
- ~~Total CV risk estimation by means of the SCORE system and, accordingly, recommendations on eligibility for statin as well as treatment goals are based on TC, whereas LDL-C is the primary lipid analysis for screening, diagnosis and management.~~
- ~~There are no outcomes-based comparisons of LDL-C vs. ApoB as primary measurement for screening, diagnosis and management.~~
- ~~Against a background of genetic and randomized clinical trial evidence showing no significant effect of increasing HDL levels on the risk of CVD events, the clinical impact of therapies altering the function of HDL particles is unknown. More evidence is needed regarding the association of extreme high levels of HDL-C with clinical outcomes.~~
- ~~The relative contribution of the Lp(a)-lowering effect of certain lipid-modifying therapies~~

(CETP inhibitors, PCSK9 inhibitors) on reducing the risk of ASCVD events remains to be addressed. Dedicated studies assessing outcomes with Lp(a)-lowering therapies are warranted, including trials with antisense oligonucleotides targeting apo(a).

- The long-term outcome benefits resulting from the recommended lifestyle modifications and dietary changes need to be further documented.
- In high-risk patients who do not tolerate daily doses of statin treatment, no clinical endpoint trials are available to test alternative dosing such as every other day or twice a week
- More evidence is needed for PCSK9 inhibitors in specific populations, including patients with severe CKD and on dialysis, patients with HIV infection, in children and adolescents with FH, after heart transplantation and during pregnancy.
- The effects of inhibition of PCSK9 in all body compartments (as with inclisiran) or only within plasma (as with monoclonal antibodies) remain to be established.
- How early should treatment with a PCSK9 inhibitor be initiated in patients with ACS? In view of evidence of early, sustained clinical benefit associated with the early initiation of statin treatment in the acute phase of ACS, the optimal timing of PCSK9 inhibitor treatment in ACS patients remains to be addressed in outcomes studies.
- In patients with chronic heart failure, a small benefit of n-3 PUFAs has been shown in one RCT and merits further investigation.
- What is the optimal screening programme for detecting FH?
- In view of limited access to genetic testing in several environments, more evidence is needed regarding outcomes with clinical-only vs. genetic screening and diagnosis of FH.
- More RCT evidence is required to support the use of statin-based treatment in older people (aged 75 or over, but particularly aged 80 or over), and to establish whether there are particular types of patients in whom such treatment should be stopped once commenced.
- In patients with CVD and on dialysis, whether continuation of statins and/or ezetimibe in those already on treatment at the time of dialysis initiation needs to be tested in a dedicated study.
- More evidence from RCT is needed for statin treatment in kidney transplant recipients.
- In transplant patients who are intolerant of statins or those with significantly elevated LDL-C despite maximally tolerated statin treatment, there are no studies of ezetimibe (alone or added to statin).
- There are no data on the effects of statins, ezetimibe or fibrates on CV events in dyslipidaemic HIV-infected patients.
- Anti-inflammatory treatment with canakinumab treatment has not been tested against anti-PCSK9 antibodies added to statin therapy. In very high-risk patients with elevated hsCRP, the clinical benefit of anti-inflammatory treatment with anti-IL1Beta-treatment with canakinumab (to address residual inflammatory risk) vs. intensive LDL-lowering treatment with PCSK9-inhibitors (to address residual cholesterol risk) remains to be evaluated.
- Evidence from trials is needed to assess which tests should be carried out to monitor lipids as well as possible muscle or liver toxicity in patients on statin treatment, as current recommendations are consensus-based.
- The impact of statin monotherapy vs. combination therapies on adherence to treatment requires further investigation.

- ~~More evidence is needed regarding attainment of recommended LDL goals among very high risk patients in real-world practice in the era of increasingly prescribed combination therapies for LDL lowering.~~

# 15. Key messages

1. **Cholesterol and risk.** Prospective studies, randomized trials, and Mendelian randomization studies have all shown that raised LDL-C is a cause of ASCVD. Throughout the range of LDL-C 'lower is better' with no lower threshold, at least down to around 1 mmol/L, lowering LDL-C may yield worthwhile benefit in patients with average or below average LDL-C who are already receiving LDL-C lowering treatment. The absolute reduction in ASCVD risk achieved by lowering LDL-C (e.g. with a statin, ezetimibe or PCSK9-inhibitor) depends on the absolute reduction in LDL-C, with each 1 mmol/L reduction corresponding to a reduction of about one fifth in ASCVD.
2. **Risk stratification.** Large trials have shown that PCSK9 inhibitors further reduce ASCVD risk when given on top of statin-based therapy and their use may need to be restricted to those at the highest ASCVD risk.
3. **Use of cardiac imaging for risk stratification.** CAC score assessment with CT may be helpful in reaching decisions about treatment in people who are at moderate risk of ASCVD. Obtaining such a score may assist in discussions about treatment strategy in patients where the LDL-C goal is not achieved with lifestyle intervention alone and there is a question of whether to institute LDL-C lowering treatment. Assessment of arterial (carotid or femoral) plaque burden on ultrasonography may also inform in these circumstances.
4. **Use of apoB in risk stratification.** ApoB may be a better measure of an individual's exposure to atherosclerotic lipoproteins, and hence its use may be particularly helpful for risk assessment in people where measurement of LDL-C underestimates this burden, such as those with high TG, diabetes, obesity or very low LDL-C.
5. **Use of Lp(a) in risk stratification**. A one-off measurement of Lp(a) may help to identify people with very high inherited Lp(a) levels who may have a substantial lifetime risk of ASCVD. It may also be helpful in further risk stratification of

patients at high risk of ASCVD, in patients with a family history of premature CVD, and for determining treatment strategy in people whose estimated risk is on the border of risk categories.

6. **Intensification of treatment goals.** It is important to ensure that treatment of the highest risk patients achieves the largest LDL-C reduction possible. These guidelines aim to support this by setting both a minimum percentage LDL-C reduction (50%), and an absolute LDL-C treatment goal of <1.4 mmol/L (55 mg/dL) for very high-risk patients, and <1.8 mmol/L (70 mg/dL) for high-risk patients. It is recommended to treat FH patients with ASCVD or who have another major risk factor as very high-risk, and those with no prior ASCVD or other risk factors as high-risk.
7. **Treatment of patients with recent ACS.** New randomized trials support a strategy of intensification of LDL-C lowering therapy in very high-risk patients with ACS (MI and unstable angina). If the specified LDL-C treatment goal is not achieved after 4-6 weeks with the highest tolerated statin dose and ezetimibe, it is appropriate to add a PCSK9 inhibitor.
8. **Safety of low LDL cholesterol concentrations.** There are no known adverse effects of very low LDL-C concentrations (e.g., below 1 mmol/L [40 mg/dL]).
9. **Management of statin 'intolerance'.** Whilst statins rarely cause serious muscle damage (myopathy, or rhabdomyolysis in the most severe cases), there is much public concern that statins may commonly cause less serious muscle symptoms. Such statin 'intolerance' is frequently encountered by practitioners and may be difficult to manage. However, placebo-controlled randomized trials have shown very clearly that true statin intolerance is rare, and that it is generally possible to institute some form of statin therapy (e.g., by changing the statin, or reducing the dose) in the overwhelming majority of patients at risk of ASCVD.
10. **Statin treatment for older people.** A meta-analysis of randomized trials has shown that the effects of statin therapy are determined by the absolute reduction in LDL-C as well as the baseline ASCVD risk, and are independent of all known risk factors, including age. Statin therapy in older people should therefore be considered according to the estimated level of risk and baseline LDL-C, albeit

with due regard to an individual's underlying health status and the risk of drug interactions. There is less certainty about the effects of statins above the age of 75, particularly in primary prevention. Statin therapy should be started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

# 16. Evidence-based 'to do' and 'not to do' messages from the Guidelines

| RECOMMENDATIONS | Class | Level of evidence |
|---|---|---|
| **Cardiovascular disease risk estimation** | | |
| Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, CKD or familial hypercholesterolaemia. | **I** | C |
| High-risk and very high-risk individuals may be identified on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, familial hypercholesterolaemia or a high SCORE risk and are a priority for advice and management of all risk factors. | **I** | C |
| Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM. | **III** | C |
| **Lipid analyses for cardiovascular disease risk estimation** | | |
| TC is to be used for the estimation of total CV risk by means of the SCORE system. | **I** | C |
| HDL-C analysis is recommended to further refine risk estimation using the online SCORE system. | **I** | C |
| LDL-C analysis is recommended as the primary lipid analysis for screening, diagnosis and management. | **I** | C |
| TG analysis is recommended as a part of the routine lipid analysis. | **I** | C |
| Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or very low LDL-C. | **I** | C |
| ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis and management, and may be preferred over non HDL-C in people with high TG, diabetes, obesity or very low LDL-C. | **I** | C |
| **Treatment goals for LDL-cholesterol** | | |

| | | |
|---|---|---|
| In secondary prevention patients at VERY HIGH-risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended. | I | A |
| In primary prevention, for individuals at VERY HIGH-risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (55 mg/dL) are recommended. | I | C |
| In patients at HIGH-risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (70 mg/dL) are recommended. | I | A |
| **Pharmacological LDL-C lowering** | | |
| It is recommended to prescribe a high intensity statin up to the highest tolerated dose to reach the goals set for the specific level of risk. | I | A |
| If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended. | I | B |
| For secondary prevention, patients at very high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. | I | A |
| ~~For patients with FH, either in primary or secondary prevention, not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.~~ For very high risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. | I | C |
| **Drug treatment of patients with hypertriglyceridaemia** | | |
| Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (200 mg/dL)). | I | B |
| **Management of patients with heterozygous familial hypercholesterolaemia** | | |
| It is recommended to consider the diagnosis of FH in patients with CHD <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives having tendon xanthomas, in people with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)], and in first degree relatives of FH patients. | I | C |
| It is recommended to diagnose FH using clinical criteria and confirm, when available, with DNA analysis. | I | C |
| Once the index case is diagnosed, family cascade screening is recommended. | I | C |
| It is recommended to treat FH patients with ASCVD or who have another major risk factor as very high~~-~~risk, and those with no prior ASCVD or other risk factors as high-risk. | I | C |
| For FH patients who are at very high risk, ~~T~~treatment to achieve at least a 50% | I | C |

| | | |
|---|---|---|
| reduction from baseline and an LDL-C <1.4 mmol/L (55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended. | | |
| Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients ~~with ASCVD or with other factors putting them at very high-risk for ASCVD, such as other CV risk factors, family history, or high Lp(a), or~~ if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe ~~lipid lowering treatment~~. | **I** | **C** |
| In children, testing for FH is recommended from the age of 5 years, or earlier if homozygous FH is suspected. | **I** | **C** |
| **Treatment of dyslipidaemias in older people** | | |
| Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients. | **I** | **A** |
| Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged up to 75. | **I** | **A** |
| It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals. | **I** | **C** |
| **Treatment of dyslipidaemias in diabetes** | | |
| In patients with T2DM at VERY HIGH-risk[c], an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (55mg/dL) is recommended. | **I** | **A** |
| In patients with T2DM at HIGH-risk[c] an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (< 70 mg/dL) is recommended. | **I** | **A** |
| Statins are recommended in patients with T1DM who are at HIGH or VERY HIGH-risk[c]. | **I** | **A** |
| Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception | **III** | **C** |
| **Management of patients with acute coronary syndromes** | | |
| In all ACS patients without any contra-indication or definite history of intolerance, it is recommended to initiate or continue high dose statin as early as possible, regardless of initial LDL-C values. | **I** | **A** |
| If the LDL-C goal is not achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended. | **I** | **C** |
| If the LDL-C goal is not achieved after 4-6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended. | **I** | **B** |
| **Lipid-lowering therapy for prevention of ASCVD events in patients with prior ischaemic stroke** | | |
| Patients with a history of ischaemic stroke or TIA are at very high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy. | **I** | **A** |

| | | |
|---|---|---|
| **Treatment of dyslipidaemias in chronic heart failure or valvular heart diseases** | | |
| Initiation of lipid-lowering therapy is not recommended in patients with heart failure in the absence of other indications for their use. | **III** | **A** |
| Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use. | **III** | **A** |
| **Lipid management in patients with moderate to severe (KDOQI stages 3-5) chronic kidney disease** | | |
| It is recommended that patients with stage 3-5 CKD are considered at high or very high risk of ASCVD. | **I** | **A** |
| The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3-5 CKD. | **I** | **A** |
| In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended. | **III** | **A** |
| **Lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)** | | |
| In patients with PAD, lipid-lowering therapy is recommended to reduce the risk of ASCVD events. | **I** | **A** |

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ACS=acute coronary syndrome; apo=apolipoproteins; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; CHD=coronary heart disease; CV=cardiovascular; CVD=cardiovascular disease; DM=diabetes mellitus; FH=familial hypercholesterolaemia; HDL=high-density lipoprotein; LDL=low-density lipoprotein; Lp(a)=lipoprotein(a); PCSK9=proprotein convertase subtilisin/kexin type 9; SCORE=Systemic Coronary Risk Estimation; TC=total cholesterol; TG=triglycerides; T1DM=type 1 diabetes mellitus; T2DM=type 2 diabetes mellitus.

# 17. Appendix

***WILL BE COMPLETED BY THE GUIDELINES STAFF AT THE PUBLICATION PHASE***

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