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ESC/EAS GUIDELINES

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR)

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Councils: Council on Cardiovascular Nursing and Allied Professions, Council for Cardiology Practice, Council on Cardiovascular Primary Care, Council on Hypertension

Working Groups: Atherosclerosis & Vascular Biology, Cardiovascular Pharmacotherapy, Coronary Pathophysiology & Microcirculation, E-cardiology, Myocardial and Pericardial Diseases, Peripheral Circulation, Thrombosis.

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Table of Contents

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List of abbreviations

ABI	ankle-brachial index
ACC	American College of Cardiology
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 syndrome
AFCAPS/TEXCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
AHA	American Heart Association
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes
ALT	alanine aminotransferase
Apo	apolipoprotein

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ART	antiretroviral treatment
ASSIGN	CV risk estimation model from the Scottish Intercollegiate Guidelines Network
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
BIP	Bezafibrate Infarction Prevention study
BMI	body mass index
CABG	coronary artery bypass graft surgery
CAC	coronary artery calcium
CAD	coronary artery disease
CARE	Cholesterol and Recurrent Events
CETP	cholesteryl ester transfer protein
CHD	coronary heart disease
CIMT	carotid intima-media thickness
CK	creatine kinase
CKD	chronic kidney disease
CTT	Cholesterol Treatment Trialists
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
4D	Die Deutsche Diabetes Dialyse
DASH	Dietary Approaches to Stop Hypertension
DGAT-2	diacylglycerol acyltransferase-2
DHA	docosahexaenoic acid
DLCN	Dutch Lipid Clinic Network
EAS	European Atherosclerosis Society
EMA	European Medicines Agency
EPA	eicosapentaenoic acid
ER	extended release
ESC	European Society of Cardiology
ESRD	end-stage renal disease
EU	European Union
FACE-BD	Fondamental Academic Centers of Expertise in Bipolar Disorders
FATS	Familial Atherosclerosis Treatment Study
FCH	familial combined hyperlipidaemia
FDA	US Food and Drug Administration
FDC	fixed-dose combination
FH	familial hypercholesterolaemia
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
FOCUS	Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention
GFR	glomerular filtration rate
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GP	general practitioner
GWAS	genome-wide association studies
HAART	highly active antiretroviral treatment
HATS	HDL-Atherosclerosis Treatment Study
HbA1C	glycated haemoglobin
HeFH	heterozygous familial hypercholesterolaemia
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HHS	Helsinki Heart Study
HIV	human immunodeficiency virus
HMG-CoA	hydroxymethylglutaryl-coenzyme A
HPS	Heart Protection Study
HPS2-THRIVE	Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events
HoFH	homozygous familial hypercholesterolaemia
HTG	hypertriglyceridaemia
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICD	International Classification of Diseases
IDEAL	Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial
IDL	intermediate-density lipoproteins
ILLUMINATE	Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
KDIGO	Kidney Disease: Improving Global Outcomes
LAL	lysosomal acid lipase
LCAT	lecithin cholesterol acyltransferase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LEAD	lower extremities arterial disease
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
LPL	lipoprotein lipase
Lp	lipoprotein
MetS	metabolic syndrome
MI	myocardial infarction
MTP	microsomal triglyceride transfer protein
MUFA	monounsaturated fatty acid
NICE	National Institute for Health and Care Excellence
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
NYHA	New York Heart Association
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PPAR-α	peroxisome proliferator-activated receptor-α
PROCAM	Prospective Cardiovascular Munster Study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PUFA	polyunsaturated fatty acid
RAAS	renin–angiotensin–aldosterone system
RCT	randomized controlled trial
REACH	Reduction of Atherothrombosis for Continued Health
REDUCE-IT	Reduction of Cardiovascular Events with EPA-Intervention Trial

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REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid modification
RR	relative risk
RYR	red yeast rice
4S	Scandinavian Simvastatin Survival Study
SALTIRE	Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression
SAGE	Studies Assessing Goals in the Elderly
SCORE	Systemic Coronary Risk Estimation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SFA	saturated fatty acid
SHARP	Study of Heart and Renal Protection
SLE	systemic lupus erythematosus
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
TIA	transient ischaemic attack
TC	total cholesterol
T2DM	type 2 diabetes mellitus
TG	triglyceride
TNT	Treatment to new targets
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

Preamble

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 for Cardiovascular Prevention & Rehabilitation (EACPR), and 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, 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

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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

completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

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.

Table 2 Levels of evidence

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

1. What is cardiovascular disease prevention?

1.1 Definition and rationale

Cardiovascular disease (CVD) kills >4 million people in Europe each year. It kills more women [2.2 million (55%)] than men [1.8 million (45%)], although cardiovascular (CV) deaths before the age of 65 years are more common in men (490 000 vs. 193 000).[1] Prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, aimed at eradicating, eliminating or minimizing the impact of CV diseases and their related disability. CVD remains a leading cause of morbidity and mortality, despite improvements in outcomes for CVD. 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 CVD prevention remains undisputed and should be delivered at different levels: (i) in the general population by promoting healthy lifestyle behaviour[2] and (ii) at the individual level, in those at moderate to high risk of CVD or patients with established CVD, by tackling an unhealthy lifestyle (e.g. poor-quality diet, physical inactivity, smoking) and by reducing increased levels of CV risk factors such as increased lipid or blood pressure levels. Prevention is effective in reducing the impact of CVD; the elimination of health risk behaviours would make it possible to prevent at least 80% of CVD and even 40% of cancers, thus providing added value for other chronic diseases.[3,4]

1.2 Development of the Joint Task Force guidelines

The present guidelines represent an evidence-based consensus of the European Task Force including the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS).

By appraising the current evidence and identifying remaining knowledge gaps in managing the prevention of dyslipidaemias, the Task Force formulated recommendations to guide actions to prevent CVD in clinical practice by controlling elevated lipid plasma levels. The Task Force followed the quality criteria for development of

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guidelines, which can be found at http://www.escardio.org/Guidelines-&-Education/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines. Recommendations are graded in classes (*Table 1*) and in levels of evidence (*Table 2*).

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 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 is considered.[6] This implies that apart from improving lifestyle habits and reducing risk factor levels in patients with established CVD and in those at increased risk of developing CVD, healthy people of all ages should be encouraged to adopt or sustain a healthy lifestyle. Healthcare professionals play an important role in achieving this in their clinical practice.

1.3 Cost-effectiveness of prevention

Box 1 Key messages

- Prevention of CVD, either by lifestyle changes or medication, is cost-effective in many scenarios, including population-based approaches and actions directed at high-risk individuals.
- Cost-effectiveness depends on several factors, including baseline CV risk, cost of drugs or other interventions, reimbursement procedures, and uptake of preventive strategies.

CV = cardiovascular; CVD = cardiovascular disease.

In 2009, healthcare costs related to CVD in Europe amounted to €106 billion, representing ~9% of the total healthcare expenditure across the European Union (EU).[8] In the USA, direct annual costs of CVD are projected to triple between 2010 and 2030.[9] Thus, CVD represents a considerable economic burden to society, and this necessitates an effective approach to CVD prevention. There is consensus in favour of an approach combining strategies to improve CV health across the population at large from childhood onwards, with actions to improve CV health in individuals at increased risk of CVD or with established CVD.

Most studies assessing the cost-effectiveness of prevention of CVD combine evidence from clinical research with simulation approaches, while data from randomized controlled trials (RCTs) are relatively scarce.[7,10,11] Cost-effectiveness results strongly depend on parameters such as the target population's age, the overall population risk of CVD and the cost of interventions. Hence, results obtained in one country might not be valid in another. Furthermore, changes such as the introduction of generic drugs can considerably change cost-effectiveness.[12] In general, lifestyle changes may be more cost effective at the population level than drug treatments (*Table 3*).

Table 3 Suggestions for implementing healthy lifestyles

Recommendation	Class[a]	Level[b]	Ref[c]
Measures aimed at implementing healthy lifestyles are more cost-effective than drug interventions at the population level.	IIa	B	7

[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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 cholesterol and blood pressure levels and smoking.[13–16] This favourable trend is partly offset by increases in other major risk factors, such as obesity and type 2 diabetes.[13–16] Ageing of the population also contributes to increasing the absolute number of CVD events.[17]

Several population-level interventions have proven to efficiently affect lifestyle in individuals, leading to this success: awareness and knowledge of how lifestyle risk factors lead to CVD increased in recent decades and undoubtedly contributed to the decline in smoking and cholesterol levels. Moreover, legislation promoting a healthy lifestyle, such as reduced salt intake and smoking bans, are cost effective in preventing CVD.[18–22]

Lowering blood cholesterol levels using statins[10,11,23–25] and improving blood pressure control are also cost effective.[26,27] Importantly, a sizable portion of patients on hypolipidaemic or antihypertensive drug treatment fail to take their treatment adequately or to reach their therapeutic goals,[28,29] with clinical and economic consequences.[30] Reinforcing measures aimed at improving adherence to treatment is cost effective.[31,32]

It has been suggested that the prescription to the whole population older than 55 years of age of a single pill containing a combination of CV drugs (the polypill) could prevent as much as 80% of CVD events[33] and be cost effective.[34] Part of the cost-effectiveness of the polypill is due to improvement in adherence to treatment, but which combination of drugs is most cost effective in which target population remains to be assessed.[35]

Considerable evidence has quantified the relative efforts and costs in relation to health impact. The efforts may be depicted in the health impact pyramid (*Figure 1*), where interventions with the broadest impact on populations represent the base and interventions with considerable individual effort are at the top.[36]

The cost-effectiveness of CVD prevention has been calculated in various contexts. According to the WHO, policy and environmental changes could reduce CVD in all countries for <US$1 per person per year, while interventions at the individual level are considerably more expensive.[37]. A report from the National Institute for Health and Care Excellence (NICE) estimated that a UK national programme reducing population CV risk by 1% would prevent 25 000 CVD cases and generate savings of €40 million per year.[38] Coronary artery disease (CAD) mortality rates could be halved by only

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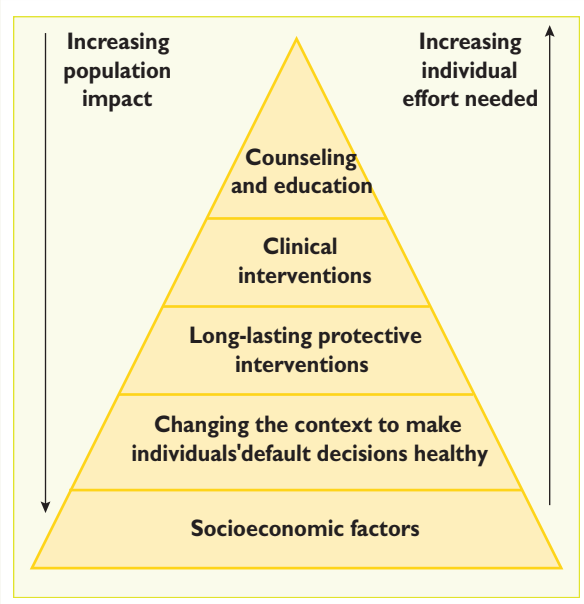

Figure 1 Health impact pyramid.

modest risk factor reduction,[39] and it has been suggested that eight dietary priorities alone could halve CVD death.[40]

There is consensus that all the levels of the pyramid should be targeted but that emphasis should be put on the second level. Targeting lower levels in the health impact pyramid will also address the socio-economic divide in CV health, which has not diminished despite major improvements in the treatment of CVD in recent decades.[9,10]

Box 2 Gaps in evidence

- Most cost-effectiveness studies rely on simulation. More data are needed, particularly from randomized controlled trials.
- The effectiveness of the polypill in primary prevention awaits further investigation.

2. Total cardiovascular risk

2.1 Total cardiovascular risk estimation

CV risk in the context of these guidelines means the likelihood of a person developing a fatal or non-fatal atherosclerotic CV event over a defined period of time.

2.1.1 Rationale for assessing total cardiovascular disease risk

All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CAD or CV risk, because atherosclerotic CVD is usually the product of a number of risk factors, and prevention of CVD in a given person should be adapted to his/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, including different Framingham models,[41] Systemic Coronary Risk Estimation (SCORE),[42] ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network),[43] Q-Risk,[44] Prospective Cardiovascular Munster Study (PROCAM),[45] Reynolds,[46,47] CUORE,[48] the Pooled Cohort equations[49] and Globorisk.[50] Most guidelines use one of these risk estimation systems.[50–52]

One of the advantages of the SCORE system is that it can be recalibrated for use in different populations by adjustment for secular changes in CVD mortality and risk factor prevalences. Calibrated country-specific versions exist for Belgium, Cyprus, Czech Republic, Germany, Greece, Poland, Slovakia, Spain, Switzerland and Sweden, and country-specific electronic versions for Bosnia and Herzegovina, Croatia, Estonia, France, Romania, Russian Federation and Turkey can be found at http://www.heartscore.org. Other risk estimation systems can also be recalibrated, but the process is easier for mortality than for total events. The European Guidelines on CVD prevention in clinical practice (version 2012)[6] recommend use of the SCORE system because it is based on large, representative European cohort datasets.

Risk charts such as SCORE are intended to facilitate risk estimation in apparently healthy persons with no documented CVD. Patients who have had a clinical event such as acute coronary syndrome (ACS) or a stroke are at very high risk of a further event and automatically qualify for risk factor evaluation and management (*Table 6*).

Simple principles of risk assessment, developed in these guidelines, can be defined as follows:

(1) Persons with
- documented CVD
- type 1 or type 2 diabetes
- very high levels of individual risk factors
- chronic kidney disease (CKD) (refer to section 9.9)

are automatically at very high or high total CV risk. No risk estimation models are needed for them; they all need active management of all risk factors.

(2) For all other people, the use of a risk estimation system such as SCORE is recommended to estimate total CV risk since many people have several risk factors that, in combination, may result in unexpectedly high levels of total CV risk.

The SCORE system estimates the 10-year cumulative risk of a first fatal atherosclerotic event, whether heart attack, stroke or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high- and low-risk regions in Europe (*Figures 2* and *3*). All International Classification of Diseases (ICD) codes that are related to deaths from vascular origin caused by atherosclerosis are included. Some other systems estimate CAD risk only.

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

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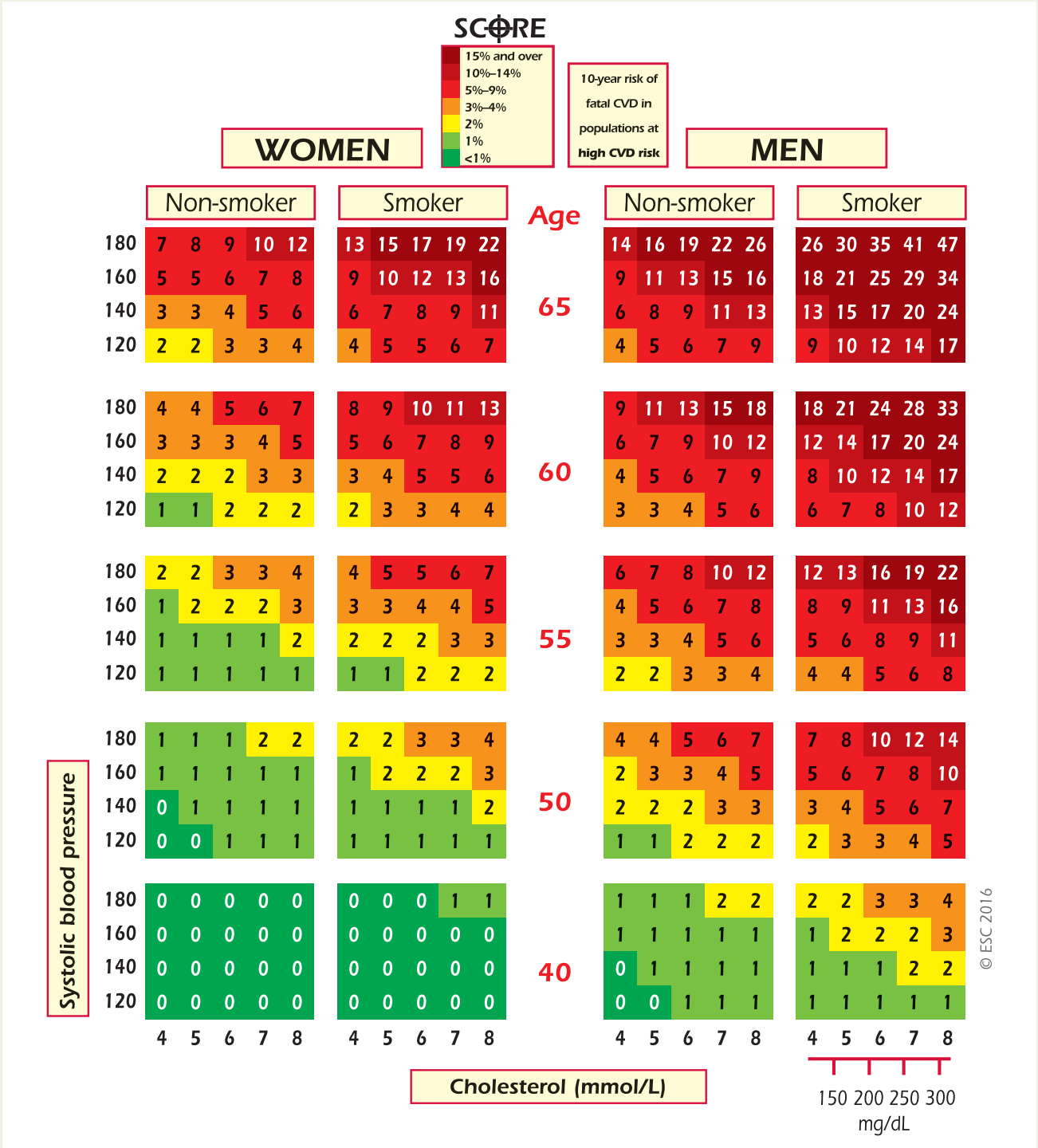

Figure 2 **SCORE chart:** 10-year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + nonfatal) hard CVD, multiply 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, 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.

variable multipliers to convert fatal to total events. In addition, total event charts, in contrast to those based on mortality, cannot easily be recalibrated to suit different populations.

Naturally, the risk of total fatal and non-fatal events is higher, and clinicians frequently ask for this to be quantified. The SCORE data indicate that the total CVD event risk is about three times higher

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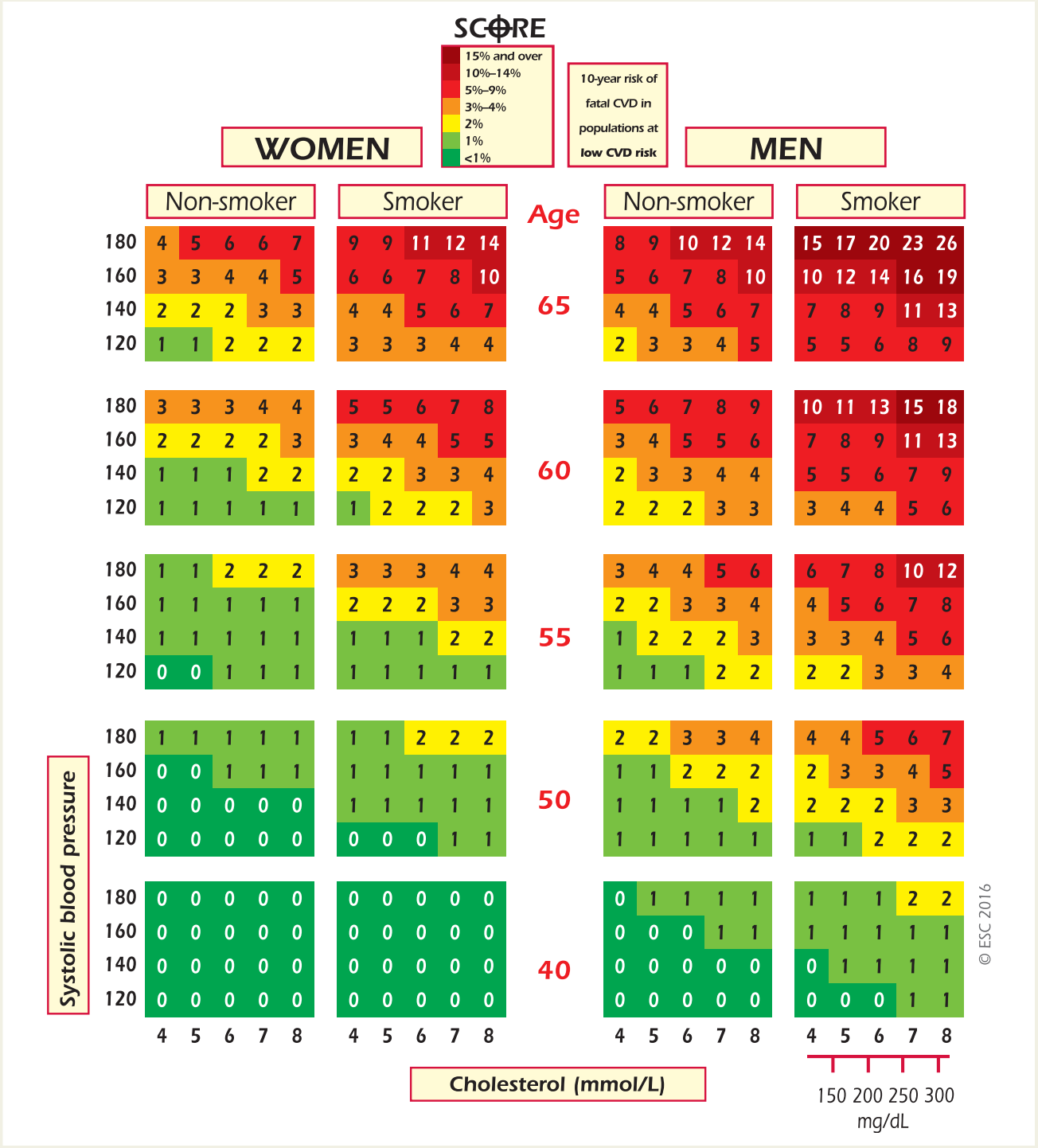

Figure 3 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 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, 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.

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) hard CVD endpoints; the multiplier is ~4 in women and lower in older persons.

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

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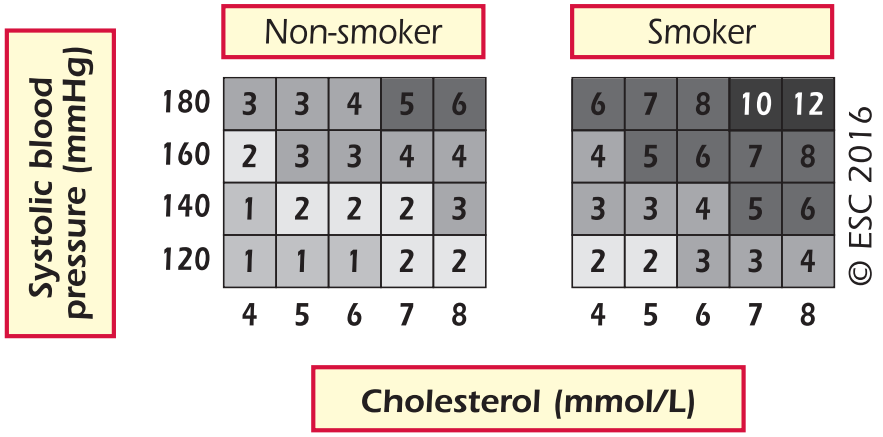

Figure 4 **Relative risk chart for 10-year cardiovascular mortality.** Please note that this chart shows RELATIVE not absolute risk. The risks are RELATIVE to 1 in the bottom left. Thus, a person in the top right hand box has a relative risk that is 12 times higher than a person in the bottom left.

systolic blood pressure. 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 intensive lifestyle advice. To motivate young people 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 (*Figure 4*).

Another approach to this problem in young people is to use CV 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 may have a risk age $\geq$60 years. Risk age is an intuitive and easily understood way of illustrating the likely reduction in life expectancy that a young person with a low absolute but high relative risk of CVD will be exposed to if preventive measures are not adopted. Risk age can be estimated visually by looking at the SCORE chart (as illustrated in *Figure 5*). In this chart, the risk age is calculated compared with someone with ideal risk factor levels, which have been taken as non-smoking, total cholesterol of 4 mmol/L (155 mg/dL) and systolic blood pressure of 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 endpoint used,[51,52] which bypasses the dilemma of whether to use a risk estimation system based on CVD mortality or on the more attractive but less reliable endpoint of total CVD events. Risk age can be used in any population regardless of baseline risk or secular changes in mortality, and therefore avoids the need for recalibration. At present, risk age is recommended for helping to communicate about risk, especially to younger people with a low absolute risk but a high relative risk. It is not currently recommended to base treatment decisions on risk age.

Lifetime risk is another approach to illustrating the impact of risk factors that may be useful in younger people.[53] 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 and such an approach would likely lead to excessive use of drugs in young people.

Another problem relates to old people. In some age categories the majority, especially of men, will have estimated CV death risks exceeding the 5–10% level, based on age (and gender) only, even when other CV risk factor levels are relatively low. This could lead to excessive use of drugs in the elderly and should be evaluated carefully by the clinician. Recent work has shown that β-coefficients are not constant with ageing and that SCORE overestimates risk in older people.[54] This article includes illustrative charts in subjects older than 65 years of age. While such subjects benefit from smoking cessation and control of hypertension and hyperlipidaemia, clinical judgement is required to avoid side effects from overmedication.

SCORE charts are available for both total cholesterol (TC) and the TC:high-density lipoprotein cholesterol (HDL-C) ratio. However, subsequent work on the SCORE database has shown that HDL-C can contribute more to risk estimation if entered as a separate variable as opposed to the ratio. For example, HDL-C modifies risk at all levels of risk as estimated from the SCORE cholesterol charts.[55] Furthermore, this effect is seen in both genders and in all age groups, including older women. This is particularly important at levels of risk just below the 5% threshold for intensive risk modification; many of these subjects will qualify for intensive advice if their HDL-C is low. Charts including HDL-C are available on the ESC website (http://www.escardio.org/guidelines). The additional impact of HDL-C on risk estimation is illustrated in *Figures 6* and *7*. 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

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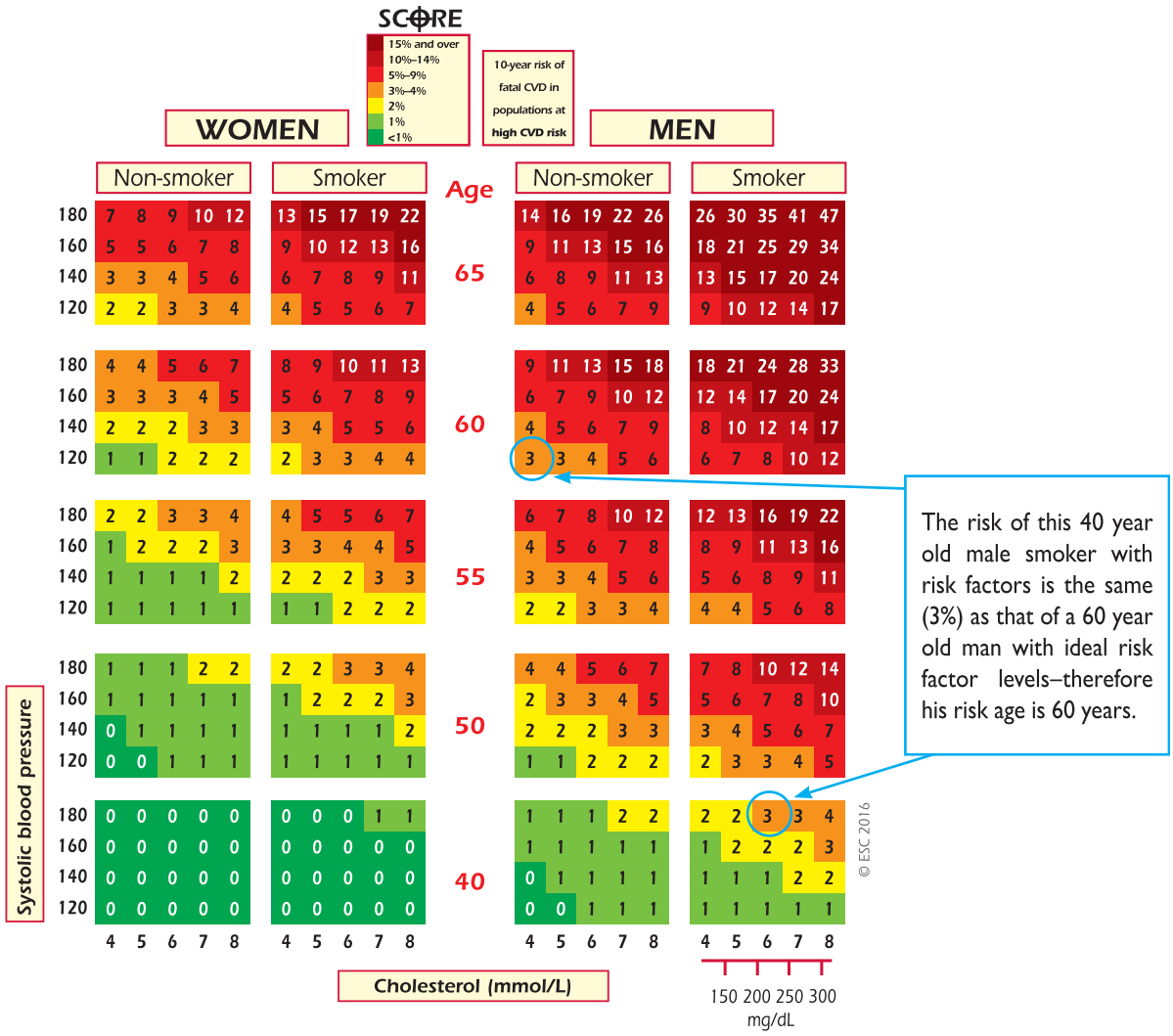

Figure 5 Illustration of the risk age concept.

into account on a continuous basis, which is even better; we recommend its use in order to increase the accuracy of the risk evaluation. Overall, HDL-C has a modest but useful effect in refining risk estimation,[56] but this may not be universal, as its effect may not be seen in some low-risk populations, particularly with a relatively high mean HDL-C level.[57]

2.1.2 How to use the risk estimation charts

When it comes to European countries and to countries with cardiology societies that belong to the ESC, the low-risk charts should be considered for use in Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. While any cut-off point is arbitrary and open to debate, in these guidelines the cut-off points for calling a country 'low risk' are based on age-adjusted 2012 CVD mortality rates (<225/100 000 in men and <175/100 000 in women) (http://apps.who.int/gho/data/node.main.A865CARDIOVASCULAR?lang=en).

The high-risk charts should be considered in all other countries. Of these, some are at very high risk, and the high-risk chart may underestimate risk in these countries. These are countries with a CVD mortality rate more than double the cut-off of low-risk countries according to 2012 WHO statistics (http://apps.who.int/gho/data/node.main.A865CARDIOVASCULAR?lang=en): ≥450/100 000 for men or ≥350/100 000 for women (Albania, Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, Latvia, FYR Macedonia, Republic of Moldova, Russian Federation, Syrian Arab Republic, Tajikistan, Turkmenistan, Ukraine and Uzbekistan). The remaining high-risk countries are Bosnia and Herzegovina, Croatia, Estonia, Hungary, Lithuania, Montenegro, Morocco, Poland, Romania, Serbia, Slovakia, Tunisia and Turkey. Note that several countries have undertaken national recalibrations

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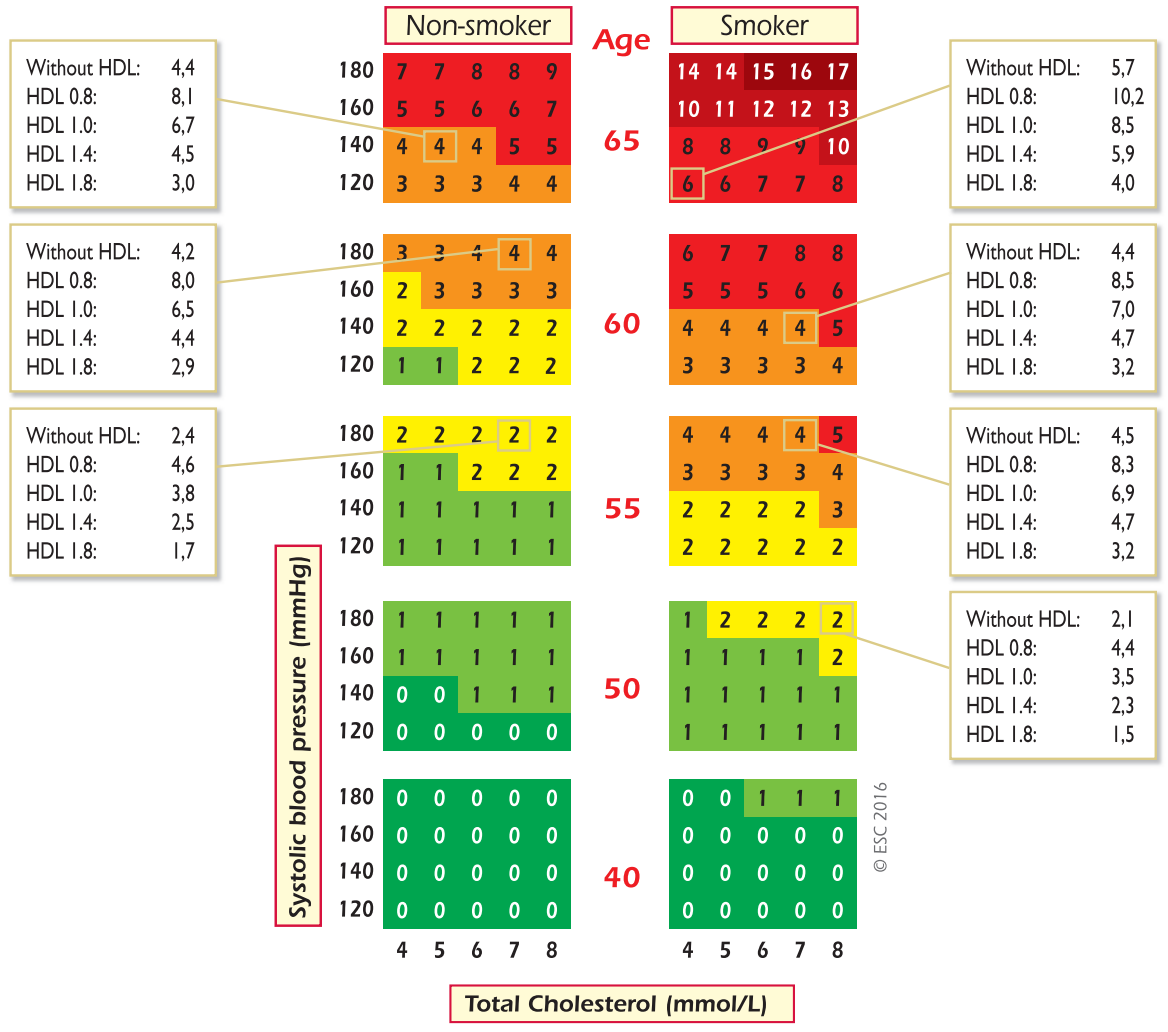

Figure 6 Risk function without high-density lipoprotein-cholesterol (HDL-C) for women in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.

Box 3 How to use the risk estimation charts

To estimate a person's 10-year risk of 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 and 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 blood pressure 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 blood pressure is not known, if the total 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 will be a time lag before the risk reduces and that the results of randomized controlled trials in general give better estimates of benefits. In general, those who stop smoking rapidly halve their cumulative risk.

Box 4 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 appear 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 (**Figure 4**) and the estimated risk age (**Figure 5**) may be helpful in identifying and counselling such persons.

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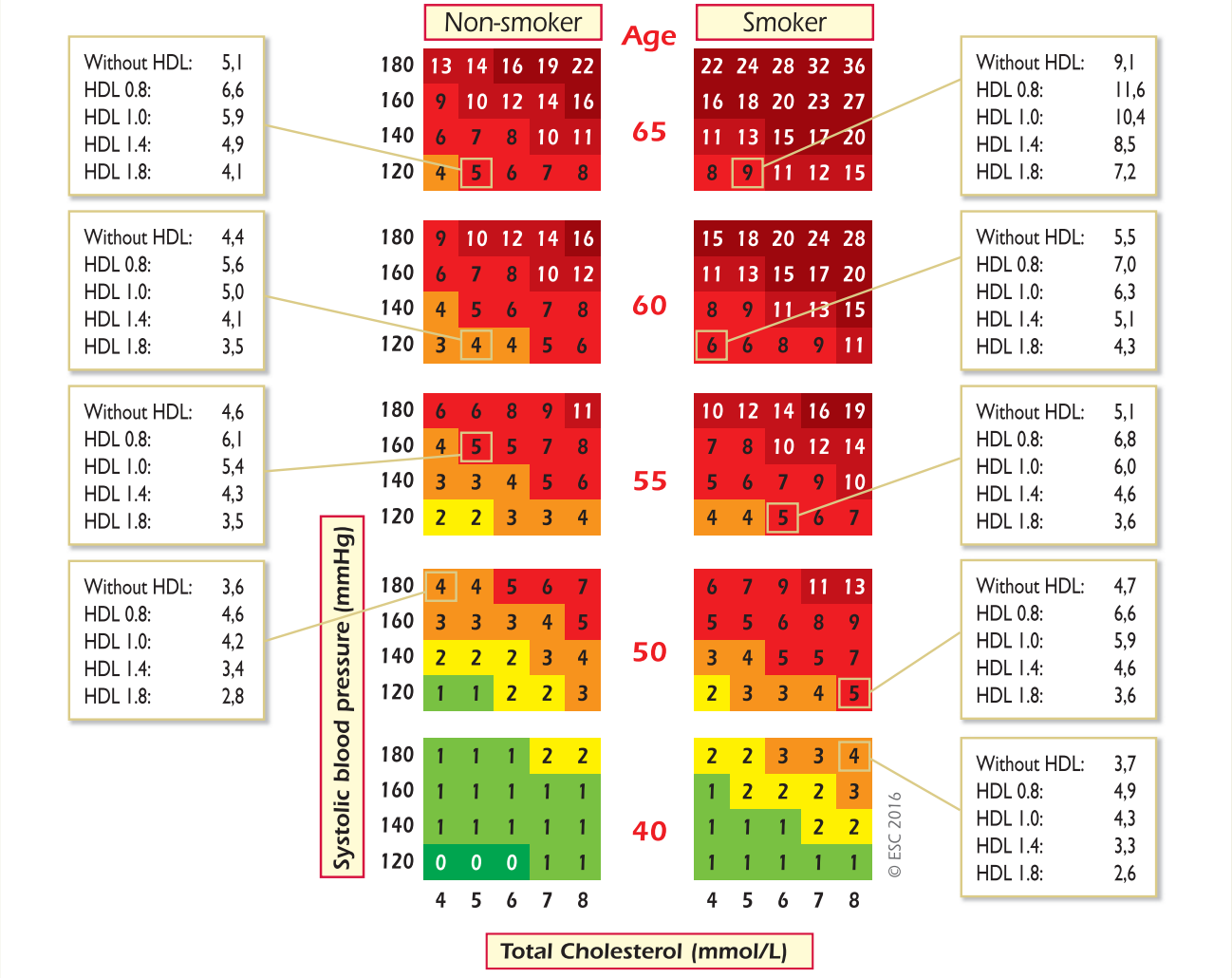

Figure 7 Risk function without high-density lipoprotein-cholesterol (HDL-C) for men in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.

Box 5 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).
Autoimmune and other inflammatory disorders.
Major psychiatric disorders.
Treatment for human immunodeficiency virus (HIV) infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.

to allow for time trends in mortality and risk factor distributions. Such charts are likely to represent current risk levels better.

Social deprivation and psychosocial stress set the scene for increased risk.[57] For those at intermediate risk, other factors, including metabolic factors such as increased apolipoprotein B (apoB), lipoprotein(a) (Lp(a)), triglycerides (TGs) or high-sensitivity C-reactive protein (hs-CRP) or the presence of albuminuria, 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 detected by coronary artery calcium (CAC), ankle-brachial index (ABI), pulse wave velocity or carotid ultrasonography. In studies comparing these markers, CAC had the best reclassification ability.[58–60]

Subjects in need of reclassification are those belonging to the intermediate CV risk group. Therefore the use of methods to detect

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Box 6 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- or 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 or CKD.
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 perfection cannot be achieved with one risk factor, risk can still be reduced by trying harder with the others.

these markers should be of interest in that group (class IIa, level of evidence B). Cut-off values that should be used in considering these markers as modifiers of total CV risk are CAC score >400 Agatston units, ABI <0.9 or >1.40, aortic pulse wave velocity of 10 m/s and the presence of plaques on carotid ultrasonography. Some factors such as a high HDL-C or apoA1 and a family history of longevity can also reduce risk.

2.2 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 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 and health insurance systems. Not only should those at high risk be identified and managed, but those at moderate risk should also receive professional advice regarding life-style changes; in some cases drug therapy will be needed to control their plasma lipids.

In these subjects we realistically can

- prevent further increase in total CV risk,
- increase awareness of the danger of CV risk,
- improve risk communication and
- promote primary prevention efforts.

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. This raises the issue that most older people in high-risk countries who smoke would be candidates for lipid-lowering drug treatment even if they have satisfactory blood pressure levels. The clinician is strongly recommended to use clinical judgment in making therapeutic decisions in older people, with a firm commitment to implementing lifestyle measures such as smoking cessation in the first instance.

With these considerations one can propose the following levels of total CV risk (*Table 4*).

Table 4 Risk categories

Very high-risk	Subjects with any of the following: • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m^2). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type 1 diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m^2). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

ACS = acute coronary syndrome; AMI = acute myocardial infarction; BP = blood pressure; CKD = chronic kidney disease; DM = diabetes mellitus; GFR = glomerular filtration rate; PAD = peripheral artery disease; SCORE = systematic coronary risk estimation; TIA = transient ischaemic attack.

2.2.1 Risk-based intervention strategies

Table 5 presents suggested intervention strategies as a function of total CV risk and low-density lipoprotein cholesterol (LDL-C) level. This graded approach is based on evidence from multiple meta-analyses and individual RCTs, which show a consistent and graded reduction in CVD risk in response to reductions in TC and LDL-C levels.[61–71] These trials are consistent in showing that the higher the initial LDL-C level, the greater the absolute reduction in risk, while the relative risk reduction remains constant at any given baseline LDL-C level. Advice on individual drug treatments is given in section 6.

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Table 5 Intervention strategies as a function of total cardiovascular risk and low-density lipoprotein cholesterol level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	I/C	I/C	IIa/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class[a]/Level[b]	I/C	I/C	IIa/A	IIa/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider 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
≥10 or very high-risk	Lifestyle intervention, consider 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/A	IIa/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.
[c]In patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels

Table 6 Recommendations for risk estimation

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 and very high-risk individuals can be detected 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 high priority for intensive advice with regard to all risk factors.	I	C

CVD = cardiovascular disease; SCORE = Systemic Coronary Risk Estimation.
[a]Class of recommendation.
[b]Level of evidence.

3. Evaluation of laboratory lipid and apolipoprotein parameters

Screening for dyslipidaemia is always indicated in subjects with clinical manifestations of CVD, in clinical conditions associated with increased risk for CVD and whenever risk factor screening is considered. In several clinical conditions, dyslipidaemia may contribute to an increased risk of developing CVD. Autoimmune chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE) and psoriasis are associated with increased CV risk and dyslipidaemia. Furthermore, in women, diabetes or hypertension during pregnancy are risk indicators, and in men, erectile dysfunction. Patients with CKD are also at increased risk for CVD events and should be screened for dyslipidaemias. Clinical manifestations of genetic dyslipidaemias, including xanthomas, xanthelasmas and premature arcus cornealis (<45 years), should be sought because they may signal the presence of a severe lipoprotein disorder, especially familial hypercholesterolaemia (FH), which is the most frequent monogenic disorder

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associated with premature CVD. Antiretroviral therapies may be associated with accelerated atherosclerosis. Screening for dyslipidaemias is also indicated in patients with peripheral arterial disease (PAD) or in the presence of increased carotid intima-media thickness (CIMT) or carotid plaques.

Screening for dyslipidaemias should be considered in all adult men ≥40 years of age and in women ≥50 years of age or post-menopausal, particularly in the presence of other risk factors (see section 2.2). It is also indicated to screen offspring of patients with severe dyslipidaemia and to follow them in specialized clinics if affected. Similarly, screening for significant lipoprotein disorders of family members of patients with premature CVD is recommended (see section 10) (*Table 7*).

Table 7 Recommendations for lipid analyses in 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
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C
ApoB should be considered as an alternative risk marker whenever available, especially in subjects with high TG.	IIa	C
Lp(a) should be considered in selected cases at high-risk, in patients with a family history of premature CVD, and for reclassification in subjects with borderline risk.	IIa	C
The ratio apoB/apoA1 may be considered as an alternative analysis for risk estimation.	IIb	C
The ratio non-HDL-C/HDL-C may be considered as an alternative but HDL-C used in HeartScore gives a better risk estimation.	IIb	C

Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; SCORE = Systemic Coronary Risk Estimation; TC = total cholesterol; TG = triglycerides.
[a]Class of recommendation.
[b]Level of evidence.

The suggested analyses used for baseline lipid evaluation are TC, TGs, HDL-C, LDL-C calculated with the Friedewald formula unless TGs are elevated (>4.5 mmol/L or >400 mg/dL) or with a direct method, and non-HDL-C. When available, apoB can be considered as an equivalent to non-HDL-C. Additional plasma lipid analyses that may be considered are Lp(a), apoB:apoA1 ratio and non-HDL-C:HDL-C ratio (*Tables 7* and *8*).

Table 8 Recommendations for lipid analyses for characterization of dyslipidaemias before treatment

Recommendations	Class [a]	Level [b]
LDL-C has to be used as the primary lipid analysis.	I	C
It is recommended to analyse HDL-C before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
When available, apoB should be an alternative to non-HDL-C.	IIa	C
Lp(a) should be recommended in selected cases at high-risk, for reclassification at borderline risk, and in subjects with a family history of premature CVD (**see Box 7**).	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

Apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; TC = total cholesterol; TG = triglycerides.
[a]Class of recommendation.
[b]Level of evidence.

The direct methods for HDL-C and LDL-C analysis are currently widely used and are reliable in patients with normal lipid levels.[72] However, in hypertriglyceridaemia (HTG) these methods have been found to be unreliable, with variable results and variations between the commercially available methods. Therefore, under these conditions, the values obtained with direct methods may be over- or underestimating the LDL-C and HDL-C levels. The use of non-HDL-C may overcome some of these problems, but it is still dependent on a correct analysis of HDL-C. An alternative to non-HDL-C may be the analysis of apoB. The analysis of apoB is accurate, with small variations, and is recommended as an alternative when available. Near patient testing is also available using dry chemistry methods. These methods may give a crude estimate, but should be verified by analysis in an established certified laboratory.

3.1 Fasting or non-fasting?

Traditionally blood samples for lipid analysis have been drawn in the fasting state. As recently shown, fasting and non-fasting sampling give similar results for TC, LDL-C and HDL-C. TGs are affected by food, resulting in, on average, an ~0.3 mmol/L (27 mg/dL) higher plasma level, depending on the composition and the time frame of the last meal. For risk estimation, non-fasting has a prediction strength similar to fasting, and non-fasting lipid levels can be used in screening and in general risk estimation.[73–76] It should be emphasized, however, that the risk may be underestimated in patients with diabetes, because in one study, patients with diabetes had up to 0.6 mmol/L lower LDL-C in non-fasting samples.[77] Furthermore, to characterize

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severe dyslipidaemias further, and for follow-up of patients with HTG, fasting samples are recommended.

3.2 Intra-individual variation

There is a considerable intra-individual variation in plasma lipids. Variations of 5–10% for TC and >20% for TGs have been reported, particularly in those patients with HTG. This is to some extent due to analytical variation, but is also due to environmental factors such as diet and physical activity, and a seasonal variation, with higher levels of TC and HDL-C during the winter.[78]

3.3. Lipid and lipoprotein analyses

Throughout this section it should be noted that most risk estimation systems and virtually all drug trials are based on TC and LDL-C, and that clinical benefit from using other measures, including apoB, non-HDL-C and various ratios, while sometimes logical, has largely been based on post hoc analyses. Non-HDL-C has recently been proposed by locally developed guidelines such as NICE using the QRISK2 risk calculator.[79,80] While the role of the alternative analyses is being established, traditional measures of risk such as TC, LDL-C and HDL-C remain robust and supported by a major evidence base. Furthermore, multiple clinical trials have established beyond all reasonable doubt that, at least in high-risk subjects, reduction of TC or LDL-C is associated with statistically and clinically significant reductions in CV events and mortality. Therefore, TC and LDL-C remain the primary targets recommended in these guidelines. However, for several reasons non-HDL-C and apoB are recommended as secondary targets. In patients with elevated TG levels, the extra risk carried with TG-rich lipoproteins is taken into account. Furthermore, some of the methodological problems with the direct methods for HDL-C and LDL-C may be reduced.

3.3.1 Total cholesterol

TC is recommended to be used to estimate total CV risk by means of the SCORE system. In individual cases, however, TC may be misleading. This is especially so in women, who often have higher HDL-C levels, and in subjects with diabetes or with high TGs, who often have low HDL-C levels. For an adequate risk analysis, at least LDL-C and HDL-C should be analysed. Note that assessment of total risk is not required in patients with familial hyperlipidaemia (including FH) or those with TC >7.5 mmol/L (290 mg/dL). These patients are always at high risk and should receive special attention.

3.3.2 Low-density lipoprotein cholesterol

In most clinical studies LDL-C has been calculated using the Friedewald formula.

Friedewald formula, in mmol/L: LDL-C = TC − HDL-C − (TG/2.2); in mg/dL: LDL-C = TC − HDL-C − (TG/5).

The calculated value of LDL-C is based on a number of assumptions:

- Methodological errors may accumulate since the formula necessitates three separate analyses of TC, TGs and HDL-C.
- A constant cholesterol:TG ratio in very low-density lipoprotein (VLDL) is assumed. With high TG values (>4.5 mmol/L or >400 mg/dL), the formula cannot be used.
- The Friedewald formula may be unreliable when blood is obtained under non-fasting conditions. Under these conditions, non-HDL-C may be determined.

Despite its limitations, the calculated LDL-C value is still widely used. With very low LDL-C or in patients with high TGs, the Friedewald formula may underestimate LDL-C, even giving negative values. Direct methods for the determination of LDL-C are available and are now widely used. In general, comparisons between calculated and direct LDL-C show good agreement.[81] Several of the limitations of the Friedewald formula may be overcome with the direct methods. However, the direct methods have been found to be unreliable in patients with HTG and should be used with caution in these cases[72]; also, they may underestimate very low values of LDL-C. Non-HDL-C or apoB should, under these circumstances, be considered as an alternative.

3.3.3 Non-high-density lipoprotein cholesterol

Non-HDL-C is used as an estimation of the total amount of atherogenic lipoproteins in plasma (VLDL, VLDL remnants, intermediate-density lipoprotein (IDL), LDL, Lp(a)) and relates well to apoB levels. Non-HDL-C is easily calculated from TC minus HDL-C. Some recent guidelines recommend non-HDL-C as a better risk indicator than LDL-C.[82]

Several analyses have been published comparing these variables in risk algorithms, but data are inconclusive. In some reports non-HDL-C is superior, but in others, LDL-C and non-HDL-C are reported to give similar information.[83–85]

Non-HDL-C has been shown to have a strong predictive power, and although the scientific background from randomized trials is weaker, there are practical aspects of using non-HDL-C instead of LDL-C in certain situations. Non-HDL-C is simple to calculate and does not require additional analyses. Both Friedewald's formula and direct LDL-C estimations have limitations in subjects with HTG and in subjects with very low LDL-C. Non-HDL-C also includes the atherogenic TG-rich lipoproteins (VLDL, IDL and remnants), which is essential considering the recent information from genome-wide association studies (GWASs) and Mendelian randomization[76,86–89] supporting TGs and remnant particles as causative factors in atherogenesis.

Since all trials use LDL-C, we still recommend this as the primary treatment target. However, non-HDL-C should be used as a secondary target when the LDL-C goal is reached. Goals for non-HDL-C are easily calculated as LDL-C goals plus 0.8 mmol/L (30 mg/dL).

3.3.4 High-density lipoprotein cholesterol

Low HDL-C has been shown to be a strong and independent risk factor in several studies and is included in most of the risk estimation tools available, including HeartScore. Very high levels of HDL-C have consistently not been found to be associated with atheroprotection.[90] Based on epidemiological data, levels of HDL-C associated with increased risk for men are <1.0 mmol/L (40 mg/dL) and for women are <1.2 mmol/L (48 mg/dL). The causative role of HDL-C for protection against CVD has been questioned in several studies utilizing Mendelian randomization.[87,89,91,92] Recent studies suggest that HDL has a complex role in atherogenesis and that the presence of dysfunctional HDL may be more relevant to the

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development of atherosclerosis than the HDL-C level.[93–95] Most available assays are of high quality, but the method used should be evaluated against the available reference methods and controlled in international quality programmes. It should also be considered that HTG might interfere with the direct HDL-C assays.[72]

3.3.5 Triglycerides

TGs are determined by accurate enzymatic techniques. A rare error occurs in patients with hyperglycerolaemia, where falsely very high values for TGs are detected.

High TG levels are often associated with low HDL-C and high levels of small dense LDL particles. In a number of meta-analyses, TGs has been shown to be an independent risk factor.[96,97] Furthermore, recent genetic data support the contention that elevated TG levels are a direct cause of CV disease.[76,88]

Recent studies suggest that non-fasting TGs may carry information regarding remnant lipoproteins associated with increased risk.[76,86,98,99] For general screening and risk evaluation, non-fasting TGs can be used.

3.3.6 Apolipoproteins

From a technical point of view, there are advantages in the determination of apoB and apoA1. Good immunochemical methods are available and easily run in conventional autoanalysers. The analytical performance is good and the assays do not require fasting conditions and are not sensitive to markedly elevated TG levels.

Apolipoprotein B. ApoB is the major apolipoprotein of the atherogenic lipoprotein families (VLDL, IDL and LDL). ApoB is a good estimate of the number of these particles in plasma. This might be of special importance in the case of high concentrations of small dense LDL. Several prospective studies have shown that apoB is equal to LDL-C and non-HDL-C in risk prediction. ApoB has not been evaluated as a primary treatment target in clinical trials, but several post hoc analyses of clinical trials suggest that apoB may be not only a risk marker, but also a treatment target.[100] A major disadvantage of apoB is that it is not included in algorithms for calculation of global risk, and it has not been a predefined treatment target in controlled trials. Recent data from a meta-analysis[83,90] indicate that apoB does not provide any benefit beyond non-HDL-C or traditional lipid ratios.[101] Likewise, apoB provided no benefit beyond traditional lipid markers in people with diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.[102] In contrast, in another meta-analysis of LDL-C, non-HDL-C and apoB, the latter was superior as a marker of CV risk.[103] ApoB can be used as a secondary target, as suggested for non-HDL-C, when analysis for apoB is available.

Apolipoprotein A1. ApoA1 is the major protein of HDL-C and provides a satisfactory estimate of HDL-C concentration. However, each HDL particle may carry from one to five apoA1 molecules. Plasma apoA1 levels $<$120 mg/dL for men and $<$140 mg/dL for women correspond approximately to what is considered as low for HDL-C.

Apolipoprotein B:apolipoprotein A1 ratio, total cholesterol:high-density lipoprotein cholesterol ratio and non-high-density lipoprotein cholesterol:high-density lipoprotein cholesterol ratio. Ratios between atherogenic lipoproteins and HDL-C or apoA1 (TC:HDL-C, non-HDL-C:HDL-C, apoB:apoA1) are useful for risk estimation, but not for diagnosis or as treatment targets. The components of the ratio have to be considered separately.

Apolipoprotein CIII. ApoCIII has been identified as a potentially important new risk factor.[104–106] ApoCIII is a key regulator of TG metabolism, and high apoCIII plasma levels are associated with high plasma VLDL and plasma TGs. Furthermore, loss of function mutations are associated with low TGs as well as with reduced risk for CVD.[106,107] ApoCIII has been identified as a new potential therapeutic target that is currently being studied, but whether it has a role in clinical practice is unknown and its measurements on a routine basis are not encouraged.[108]

3.3.7 Lipoprotein(a)

Lp(a) has been found in several studies to be an additional independent risk marker; indeed, genetic data show it to be causal in the pathophysiology of atherosclerotic vascular disease and aortic stenosis.[109–111] Lp(a) has properties in common with LDL, but it contains a unique protein, apolipoprotein(a) [apo(a)], that is structurally homologous to plasminogen. The plasma level of Lp(a) is to a major extent genetically determined. Several methods for determination of Lp(a) are available, but standardization between assays is needed.[112] The measurement of Lp(a) is particularly stable over time. Plasma Lp(a) is not recommended for risk screening in the general population; however, Lp(a) measurement should be systematically considered in people with high CVD risk or a strong family history of premature atherothrombotic disease (Box 7).[109] The risk is regarded as significant when Lp(a) is above the 80th percentile (50 mg/dL).[109] Including Lp(a) in risk evaluation has been shown to give a correct reclassification[113,114] and should be considered in patients on the borderline between high and moderate risk.

Box 7 Individuals who should be considered for lipoprotein(a) screening

Individuals with:
• Premature CVD
• Familial hypercholesterolaemia
• A family history of premature CVD and/or elevated Lp(a)
• Recurrent CVD despite optimal lipid-lowering treatment
• ≥5% 10-year risk of fatal CVD according to SCORE

Reduction of Lp(a) has been shown with several of the emerging lipid-lowering drugs. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and nicotinic acid reduce Lp(a) by ~30%.[115–117] An effect on CVD events targeting Lp(a) has not been shown. Antisense drugs targeting the Lp(a) gene reduce the circulating levels of this protein by up to 80%. A reasonable option for patients at risk with high Lp(a) is an intensified treatment of the modifiable risk factors, including LDL-C.

3.3.8 Lipoprotein particle size

Lipoproteins are heterogeneous, and evidence suggests that subclasses of LDL and HDL may contribute differently to estimation

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of the risk of CVD.[118] However, the causal relation of subclasses to atherosclerosis is unclear. Determination of small dense LDL may be regarded as an emerging risk factor and may be used in the future, but it is not currently recommended for risk estimation.[119]

3.3.9 Genotyping

Several genes have been associated with CVD. Large GWASs have been published for coronary heart disease (CHD), as well as for associated biomarkers and risk factors. At present, the use of genotyping for risk estimation is not recommended since known risk loci account for only a small proportion of risk.[120] For the diagnosis of specific genetic hyperlipidaemias, genotyping of apolipoprotein E (apoE) and of genes associated with FH [low-density lipoprotein receptors (LDLRs), apoB and PCSK9] should be considered. In FH, a genetic diagnosis is important for family screening, to establish the diagnosis in patients with borderline LDL-C and to improve patient adherence to therapy.[121]

ApoE is present in three isoforms (apoE2, apoE3 and apoE4). ApoE genotyping is used primarily for the diagnosis of dysbetalipoproteinaemia (apoE2 homozygosity) and is indicated in cases with severe combined hyperlipidaemia. With increasing knowledge about common polymorphisms and lipoproteins, the importance of a polygenic background to familial hyperlipidaemias is emphasized.[67,122]

Table 7 lists recommendations for lipid analyses in CVD risk estimation, *Table 8* lists recommendations for lipid analyses for characterization of dyslipidaemias before treatment and *Table 9* lists recommendations for lipid analyses as treatment targets in the prevention of CVD.

Table 9 Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease

Recommendations	Class [a]	Level [b]	Ref [c]
LDL-C is recommended as the primary target for treatment.	I	A	64, 68
TC should be considered as a treatment target if other analyses are not available.	IIa	A	64, 123
Non-HDL-C should be considered as a secondary treatment target.	IIa	B	103
ApoB should be considered as a secondary treatment target, when available.	IIa	B	103, 124
HDL-C is not recommended as a target for treatment.	III	A	92, 93
The ratios apoB/apoA1 and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B	103

Apo = apolipoprotein; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

4. Treatment targets

In both the 2011 EAS/ESC guidelines for the management of dyslipidaemias[125] and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults,[71] the importance of LDL-C lowering to prevent CVD is strongly emphasized. The approaches that are proposed to reach that LDL-C reduction are different. The task force charged with the development of the 2016 EAS/ESC updated guidelines on dyslipidaemias examined this issue in depth. It was recognized that the US expert panel confined itself to a simple, hard source of evidence coming from results in RCTs. Despite this, there has not been an RCT to support the AHA/ACC recommendation for the use of high-dose statins in all high-risk people regardless of baseline LDL-C level. 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 CVD. 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 CVD 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. Indeed, the task force accepts that the choice of any given target goal for LDL-C may be open to debate given the continuous nature of the relationship between LDL-C reduction and reduction in risk. Particular consideration was given to results from systematic reviews confirming the dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.[65,66] The benefits related to LDL-C reduction are not specific for statin therapy.[63] 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,[61] 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 likely 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 defined, 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 CVD events.[126] Therefore, it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high CV risk.

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The lipid goals are part of a comprehensive CV risk reduction strategy, summarized in *Table 10*. The rationale for the non-lipid targets are given in the 2016 ESC Joint Prevention guidelines.[485]

Table 10 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	2.5–5 h 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]
Lipids LDL-C is the primary target[b]	**Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL)** or a reduction of at least 50% if the baseline[b] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline[b] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk.
	TG: no target 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).

BMI = body mass index; HbA1C = glycated haemoglobin; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglycerides.
[a]The BP target can be lower in some patients with type 2 diabetes127 and in some high-risk patients without diabetes who can tolerate multiple antihypertensive drugs.[70]
[b]The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.

The targeted approach to lipid management is primarily aimed at reducing LDL-C. For patients at a very high total CV risk, the goal is an LDL-C <1.8 mmol/L (70 mg/dL). At least a 50% reduction from baseline (if >1.8 mmol/L) should also be achieved. For subjects at high total CV risk, the goal is an LDL-C level <2.6 mmol/L (100 mg/dL). At least a 50% reduction from baseline [if >2.6 mmol/L (100 mg/dL)] should also be achieved. In people at moderate total CV risk, the LDL-C goal is <3 mmol/L (115 mg/dL) (*Table 11*).

Box 8 Recommendations for treatment goals for lowdensity lipoprotein-cholesterol (LDL-C)–examples

Patient A	Very high-risk, LDL-C >1.8 mmol/L (>70 mg/dL) on statin: the goal is still <1.8 mmol/L (70 mg/dL).
Patient B	High-risk, LDL-C >2.6 mmol/L (>100 mg/dL) on statin: the goal is still <2.6 mmol/L (100 mg/dL).
Patient C	Very high-risk, LDL-C 1.8–3.5 mmol/L (70–135 mg/dL) not on pharmacological therapy: the goal is at least a 50% reduction.
Patient D	High-risk, LDL-C 2.6–5.2 mmol/L (100–200 mg/dL) not on pharmacological therapy: the goal is at least a 50% reduction.
Patient E	Very high-risk, LDL-C >3.5 mmol/L (135 mg/dL) not in pharmacological therapy: the goal is <1.8 mmol/L (70 mg/dL).
Patient F	High-risk LDL-C >5.2 mmol/L (200 mg/dL) not in pharmacological therapy: the goal is <2.6 mmol/L (100 mg/dL).

Table 11 Recommendations for treatment goals for low-density lipoprotein-cholesterol

Recommendations	Class[a]	Level[b]	Ref[c]
In patients at VERY HIGH CV risk[d], an LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C[e] is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B	61, 62, 65, 68, 69, 128
In patients at HIGH CV risk[d], an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C[e] is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B	65, 129
In subjects at LOW or MODERATE risk[d] an LDL-C goal of <3.0 mmol/L (<115 mg/dL) should be considered.	IIa	C	-

CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]For definitions see section 2.2.
[e]The term "baseline LDL-C" refers to the level in a subject not taking any lipid lowering medication.

When secondary targets are used the recommendations are

- non-HDL-C <2.6 mmol/L (100 mg/dL) and <3.4 mmol/L (130 mg/dL) in subjects at very high and high total CV risk, respectively (Class IIa, Level B).[100,130]
- apoB <80 mg/dL and <100 mg/dL in those at very high and high total CV risk, respectively (Class IIa, Level B).[100,131]

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Secondary targets 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. Clinicians who are using apoB in their practice can use targets levels of <100 mg/dL and <80 mg/dL for subjects at high or at very high total CV risk, respectively. 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 targets 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. 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 CAD patients, even when LDL-C is <1.8 mmol/L (70 mg/dL). However, clinical trial evidence is lacking on the effectiveness of intervening in these variables to reduce CV risk further.

Clinicians should use clinical judgment when considering further treatment intensification in patients at high or very high total CV risk.

5. Lifestyle modifications to improve the plasma lipid profile

The role of nutrition in the prevention of CVD has been extensively reviewed.[132–134] There is strong evidence showing that dietary factors may influence atherogenesis directly or through effects on traditional risk factors such as plasma lipids, blood pressure or glucose levels.

Results from RCTs relating dietary patterns to CVD have been reviewed.[132] Some interventions resulted in significant CVD prevention, whereas others did not. In order to get an overall estimate of the impact of dietary modifications on the CV risk, different meta-analyses have been performed, sometimes with inconsistent outcomes.[135,136] This is due not only to methodological problems, particularly inadequate sample size or the short duration of many trials included in the systematic revision, but also to the difficulty of evaluating the impact of a single dietary factor independently of any other changes in the diet. Such studies rarely allow attribution of reduction in CV risk to a single dietary component. These

Table 12 Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence	References
Lifestyle interventions to reduce TC and LDL-C levels			
Reduce dietary trans fat	+++	A	136, 139
Reduce dietary saturated fat	+++	A	136, 137
Increase dietary fibre	++	A	140, 141
Use functional foods enriched with phytosterols	++	A	142, 143
Use red yeast rice supplements	++	A	144–146
Reduce excessive body weight	++	A	147, 148
Reduce dietary cholesterol	+	B	149
Increase habitual physical activity	+	B	150
Use soy protein products	+/-	B	151
Lifestyle interventions to reduce TG-rich lipoprotein levels			
Reduce excessive body weight	+++	A	147, 148
Reduce alcohol intake	+++	A	152, 153
Increase habitual physical activity	++	A	150, 154
Reduce total amount of dietary carbohydrate	++	A	148, 155
Use supplements of n-3 polyunsaturated fat	++	A	156, 157
Reduce intake of mono- and disaccharides	++	B	158, 159
Replace saturated fat with mono- or polyunsaturated fat	+	B	136, 137
Lifestyle interventions to increase HDL-C levels			
Reduce dietary trans fat	+++	A	136, 160
Increase habitual physical activity	+++	A	150, 161
Reduce excessive body weight	++	A	147, 148
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A	148, 162
Modest consumption in those who take alcohol may be continued	++	B	152
Quit smoking	+	B	163
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+/-	C	164
Reduce intake of mono- and disaccharides	+/-	C	158, 159

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

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limitations suggest that caution is required in interpreting the results of meta-analyses of RCTs in relation to the impact of a single dietary change on CVD, particularly where they conflict with the existing global research, including clinical studies on risk factors and epidemiological observations. In this respect, it is relevant that a meta-analysis of the relationship between improvement of the plasma lipoprotein profile and the rate of CV events has demonstrated that non-HDL-C lowering translates into a reduction in risk independent of the mechanisms (statins, resins, diet and ileal bypass) involved.[131]

In summary, the available evidence from RCTs addressing the issue of how to modify the habitual diet in order to contribute to CVD prevention shows that the dietary patterns that have been more extensively evaluated are the Dietary Approaches to Stop Hypertension (DASH) diet, particularly in relation to blood pressure control, and the Mediterranean diet; both have been proven to be effective in reducing CV risk factors and, possibly, to contribute to CVD prevention.[133] They are characterized by high consumption of fruits, vegetables and wholegrain cereal products; frequent intake of legumes, nuts, fish, poultry and low fat dairy products and limited intake of sweets, sugar-sweetened drinks and red meat. The DASH diet and the Mediterranean diet derive a large proportion of dietary fat from non-tropical vegetable oil rather than from animal sources; the most relevant difference between them is the emphasis on extra virgin olive oil given in the Mediterranean diet. This latter dietary pattern has been proven in RCTs to be effective in reducing CV diseases in primary and secondary prevention.[137,138] In particular, the PREDIMED trial, a multicentre randomized intervention study conducted in Spain, evaluated the impact of a Mediterranean type of diet, supplemented with either extra-virgin olive oil or mixed nuts, on the rate of major CV events [myocardial infarction (MI), stroke or death from CV causes) in individuals at high CV risk but with no CVD at enrolment. The Mediterranean diet supplemented with extra-virgin olive oil or nuts significantly reduced the incidence of major CV events by almost 30%.[137] However, despite the strong support of lifestyle intervention for CVD prevention coming from the PREDIMED and other intervention studies with CVD endpoints, most evidence linking nutrition to CVD is based on observational studies and investigations of the effects of dietary changes on CV risk factors.

The influence of lifestyle changes and functional foods on lipoproteins is evaluated and summarized in *Table 12*; in this table the magnitude of the effects and the levels of evidence refer to the impact of dietary modifications on the specific lipoprotein class and not to CVD endpoints.

5.1 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).[165] Stearic acid, in contrast to other SFAs (lauric, myristic and palmitic), does not increase TC levels. 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.[166] 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.[137] If 1% of the dietary energy derived from SFAs is replaced by n-6 polyunsaturated fatty acids (PUFAs), LDL-C decreases by 0.051 mmol/L (2.0 mg/dL); if replaced by monounsaturated fatty acids (MUFAs), the decrease would be 0.041 mmol/L (1.6 mg/dL); and if replaced by carbohydrate, it would be 0.032 mmol/L (1.2 mg/dL). PUFAs of

Table 13 Dietary recommendations 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 skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
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

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the n-3 series have no hypocholesterolaemic effect; conversely, when they are used at high dosages (>3 g/day), the effect on LDL-C levels is either neutral or a slight increase [particularly with docosahexaenoic acid (DHA)] with a concomitant decrease of TGs.[165]

A positive relationship exists between dietary cholesterol and CAD mortality, which is partly independent of TC levels. Several experimental studies in humans have evaluated the effects of dietary cholesterol on cholesterol absorption and lipid metabolism and have revealed marked variability among individuals.[167,168] Dietary carbohydrate is 'neutral' on LDL-C; therefore, carbohydrate-rich foods represent one of the possible options to replace saturated fat in the diet. However, the major drawback of their excessive consumption is represented by untoward effects on plasma TGs and on HDL-C levels.[165] Dietary fibre (particularly of the soluble type), which is present in legumes, fruits, vegetables, and wholegrain cereals (oats, barley), has a direct hypocholesterolaemic effect. Therefore, carbohydrate foods rich in fibre represent a good dietary substitute for saturated fat in order 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.[140] Conversely, refined carbohydrate foods and beverages should not be recommended to replace saturated fat since they may contribute to elevated plasma TGs and lower HDL-C levels.

Body weight reduction also influences TC and LDL-C, but the magnitude of the effect is rather small; in grossly obese subjects, a decrease in LDL-C concentration of ~0.2 mmol/L (8 mg/dL) is observed for every 10 kg of weight loss; the reduction of LDL-C is greater if weight loss is achieved with a low fat diet.[147,148] Even smaller is the reduction of LDL-C levels induced by regular physical exercise.[150,169] However, the beneficial effects of weight reduction and physical exercise on the CV risk profile go beyond LDL-C reduction and involve not only other lipoprotein classes but also other risk factors.

In *Table 13*, lifestyle interventions to lower TC and LDL-C are summarized. Given the cultural diversity of the European populations, they should be translated into practical behaviours, taking into account local habits and socio-economic factors.

5.2 The influence of lifestyle on triglyceride levels

A high monounsaturated fat diet significantly improves insulin sensitivity compared with a high saturated fat diet.[170] This goes in parallel with a reduction in TG levels, mostly in the post-prandial period.[171] A more relevant hypotriglyceridaemic effect is observed when saturated fat is replaced by n-6 PUFA. A marked reduction of TGs can be obtained with a high dosage of long chain n-3 PUFAs; however, a dietary approach based exclusively on natural foods will seldom reach an intake adequate to achieve a clinically significant effect. To this aim, either pharmacological supplements or foods artificially enriched with n-3 PUFAs may be utilized.[172] In people with severe HTG, in whom chylomicrons are equally present in the fasting state, it is appropriate to reduce the total amount of dietary fat as much as possible (<30 g/day). In these patients, the use of medium chain TGs (from C6 to C12) that avoid the formation of chylomicrons may be considered since they are directly transported and metabolized in the liver following transport in the portal vein.

Glucose and lipid metabolism are strongly related, and any perturbation of carbohydrate metabolism induced by a high carbohydrate diet will also lead to an increase in TG concentrations.[148,165] The greater and more rapid this perturbation, the more pronounced are the metabolic consequences. Most detrimental effects of a high carbohydrate diet could be minimized if carbohydrate digestion and absorption were slowed down. The glycaemic index permits identification, among carbohydrate-rich foods, of those with 'fast' and 'slow' absorption. In particular, 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).[173,174]

Habitual consumption of significant amounts (>10% energy) of dietary fructose contributes to TG elevations, particularly in people with HTG. These effects are dose dependent; with a habitual fructose consumption between 15 and 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.[158,175]

Weight reduction improves insulin sensitivity and decreases TG levels. In many studies the reduction of TG levels due to weight reduction is between 20–30%; this effect is usually preserved as long as weight is not regained. Regular physical exercise reduces plasma TG levels over and above the effect of weight reduction.[150,169,176]

Alcohol intake has a major impact on TG levels. While in individuals with HTG even a small amount of alcohol can induce a further elevation of TG concentrations, in the general population alcohol exerts detrimental effects on TG levels only if the intake is excessive.[152,177]

5.3 The influence of lifestyle on high-density lipoprotein cholesterol levels

SFAs increase HDL-C levels in parallel with LDL-C; in contrast, trans fats decrease them.[137] MUFA consumption as a replacement for SFAs has almost no effect on HDL-C, while n-6 PUFAs induce a slight decrease. In general, n-3 fatty acids have limited (<5%) or no effect on HDL-C levels.[156,172]

Increased carbohydrate consumption as an isocaloric substitution for fat is associated with a significant decrease in HDL-C [0.01 mmol/L (0.4 mg/dL) for every 1% energy substitution]. In this respect, both the glycaemic index and the fibre content do not seem to play a relevant role.[178,179] The impact of fructose/sucrose intake on HDL-C does not seem different from that of other refined carbohydrates.[158,159] Moderate alcohol consumption is associated with increased HDL-C levels as compared with abstainers, with a dose-response relationship. Weight reduction has a beneficial influence on 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 corresponding to a total energy expenditure of 1500–2200 kcal/week, such as 25–30 km of brisk walking per week (or any equivalent activity), may

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increase HDL-C levels by 0.08–0.15 mmol/L (3.1–6 mg/dL).[176] Smoking cessation may also contribute to HDL-C elevation, provided that weight gain is prevented; this is often observed soon after quitting smoking.[163]

5.4 Lifestyle recommendations to improve the plasma lipid profile

LDL-C represents the primary lipoprotein target for reducing CV risk and therefore it deserves special emphasis in the evaluation of lifestyle measures useful for CVD prevention. However, it may be appropriate that the diet recommended to the general population, and particularly to people at increased CV risk, should not only lower LDL-C, but should also be able to improve plasma TG and HDL-C levels (*Table 12*). This section focuses on dietary and other lifestyle factors that have an effect on lipids. It has to be kept in mind that dietary components, other lifestyle factors and weight loss also contribute to reducing the overall CV risk through their influence on other risk factors, e.g. hypertension, subclinical inflammation or impaired insulin sensitivity.

5.4.1 Body weight and physical activity

Since overweight, obesity and abdominal adiposity often contribute to dyslipidaemia, caloric intake should be reduced and energy expenditure increased in those with excessive weight and/or abdominal adiposity. Overweight is defined as a body mass index (BMI) $\geq$25–30 kg/m^2 and obesity as a BMI $\geq$30 kg/m^2.

Abdominal adiposity can be detected easily by measuring waist circumference; this should be performed in all individuals who are either overweight, have dyslipidaemia or are at increased CV risk. Measurements of waist circumference >80 cm for women of any ethnicity and >94 cm for men of European ancestry or >90 cm for men of Asian origin indicate the presence of abdominal adiposity, even in people of normal weight (*Table 14*).[180] 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.[147] An even more marked hypolipidaemic effect occurs when weight reduction is more relevant, as observed in severely obese patients who undergo bariatric surgery. This treatment seems to induce beneficial effects not only on the overall risk factor profile, but also on CV events.[181]

Weight reduction can be achieved by decreasing the consumption of energy-dense foods, inducing a caloric deficit of 300–500 kcal/day. To be effective in the long run, this advice should be incorporated into structured, intensive lifestyle education programmes. In order to facilitate the maintenance of body weight close to the target, it is always appropriate to advise people with dyslipidaemia to engage in regular physical exercise of moderate intensity.[150]

Modest weight reduction and regular physical exercise of moderate intensity are very effective in preventing type 2 diabetes and improving all the metabolic abnormalities and CV risk factors clustering with insulin resistance, which are often associated with abdominal adiposity. Physical activity should be encouraged, with a goal of regular physical exercise for at least 30 min/day every day.[169]

Table 14 Definition of central obesity

	Waist circumference
Caucasians (Europids)	Men ≥94 cm, women ≥80 cm
South Asians, Chinese, Japanese	Men ≥90 cm, women ≥80 cm
South and Central Americans	Use recommendations for South Asians until more specific data are available.
Sub-Saharan Africans	Use European data until more specific data are available.
Eastern Mediterranean and Middle East (Arabic populations)	Use European data until more specific data are available.

5.4.2 Dietary fat

Limiting as much as possible the intake of trans fat is a key measure of the dietary prevention of CVD. Trying to avoid the consumption of foods made with processed sources of trans fats provides the most effective means of reducing the intake of trans fats to <1% of energy. Because the trans fatty acids produced in the partial hydrogenation of vegetable oils account for 80% of total intake, the food industry has an important role in decreasing the trans fatty acid content of the food supply. 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 >35% 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 to unfavourable changes in HDL-C.[165]

Fat intake should predominantly come from sources of MUFAs and both n-6 and n-3 PUFAs. However, the intake of n-6 PUFAs should be limited to <10% of the energy intake, both to minimize the risk of lipid peroxidation of plasma lipoproteins and to avoid any clinically relevant HDL-C decrease.[182] Not enough data are available to make a recommendation regarding the optimal n-3:n-6 fatty acid ratio.[182,183] The cholesterol intake in the diet should be reduced (<300 mg/day), particularly in people with high plasma cholesterol levels.

5.4.3 Dietary carbohydrate and fibre

Carbohydrate intake should range between 45 and 55% of total energy intake. Consumption of vegetables, legumes, fruits, nuts and wholegrain cereals should be particularly encouraged, together with all the other foods rich in dietary fibre and/or with a low glycaemic index. 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.[164]

Intake of sugars 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

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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.[158,159]

5.4.4 Alcohol

Moderate alcohol consumption [up to 20 g/day (2 units) for men and 10 g/day (1 unit) for women] is acceptable for those who drink alcoholic beverages, provided that TG levels are not elevated.

5.4.5 Smoking

Smoking cessation has clear benefits on the overall CV risk, and specifically on HDL-C, but special attention should be paid in order to prevent weight gain in people who stop smoking.[163]

5.5 Dietary supplements and functional foods for the treatment of dyslipidaemias

Innovative nutritional strategies to improve dyslipidaemias have been developed. They are based on either changing some 'risky' dietary components or encouraging the consumption of specifically targeted 'healthy' functional foods and/or dietary supplements; these so-called nutraceuticals can be used either as alternatives or in addition to lipid-lowering drugs.[184] 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 and the absence of major undesirable effects. The substantiation of health claims relevant for each food should be based on results from intervention studies in humans that are consistent with the proposed claims. 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 sufficient duration to be relevant for the natural history of dyslipidaemia and CVD.

5.5.1 Phytosterols

The principal phytosterols are sitosterol, campesterol and stigmasterol; they occur naturally in vegetable oils and in smaller amounts in vegetables, fresh fruits, chestnuts, 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.

Phytosterols have been added to spreads and vegetable oils (functional margarine, butter and cooking oils), as well as yoghurt and other foods; however, food matrices do not significantly influence the cholesterol-lowering efficacy of phytosterols at equivalent doses.[142] 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.[143] Although the effect of plant sterol consumption on TC levels has been clearly shown, no studies have been performed yet on the subsequent effect on CVD. However, the meta-analysis of Robinson *et al.*[131] indicates that LDL-C reduction translates into CV benefits, independent of the mechanism involved. Long-term surveillance is also needed to guarantee the safety of the regular use of phytosterol-enriched products. The possible decrease in carotenoid and fat-soluble vitamin levels by sterols/stanols can be prevented with a balanced diet rich in these nutrients.[185] 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 pharmacologic therapy in high- and very high-risk patients who fail to achieve LDL-C goals on statins or are statin intolerant; and (iii) in adults and children (>6 years) with FH, in line with current guidance.[142]

5.5.2 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,[145] but the long-term safety of the regular consumption of these products is not fully documented. However, side effects similar to those observed with statins have been reported in some people using these nutraceuticals. Furthermore, their quality may vary widely.

In one RCT from China in patients with CAD, a partially purified extract of RYR reduced recurrent events by 45%.[144] No other trial has been performed to confirm this finding. A clinically relevant hypocholesterolaemic effect (up to a 20% reduction) is observed with RYR preparations providing a daily dose of ~2.5–10 mg monacolin K.[146] 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.

5.5.3 Dietary fibre

Available evidence consistently demonstrates a TC- and LDL-C-lowering effect of water-soluble fibre from oat and barley beta-glucan. Foods enriched with these fibres are well tolerated, effective and recommended for LDL-C lowering at a daily dose of at least 3 g/day.[186,187]

5.5.4 Soy protein

Soy protein has been indicated as being able to induce a modest LDL-C-lowering effect when replacing animal protein foods.[151] However, this was not confirmed when changes in other dietary components were taken into account.

5.5.5 Policosanol and berberine

Policosanol is a natural mixture of long chain aliphatic alcohols extracted primarily from sugarcane wax.[188] Studies show that policosanol from sugarcane, rice or wheat germ has no significant effect on LDL-C, HDL-C, TGs, apoB, Lp(a), homocysteine, hs-CRP, fibrinogen or blood coagulation factors.[189]

As for berberine, a recent meta-analysis has evaluated its effects on plasma lipids in humans; six trials were available for this purpose: the berberine group contained 229 patients and the control group contained 222 patients.[190] The studies, showing a statistically

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significant heterogeneity, were all performed in China in people of Asian ethnicity. 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.

5.5.6 n-3 unsaturated fatty acids

Observational evidence supports the recommendation that the intake of fish (at least twice a week) and long chain n-3 fatty acids supplements at low dosage may reduce the risk of CV death and stroke in primary prevention, but have no major effects on plasma lipoprotein metabolism.[183] Pharmacological doses of n-3 fatty acids (2–3 g/day) reduce TG levels up to 30%, but a higher dosage may increase LDL-C. Alfa-linolenic acid (a medium chain n-3 fatty acid present in chestnuts, some vegetables and some seed oils) is less effective on TG levels. Long chain n-3 PUFAs also reduce the postprandial lipaemic response.[156,172]

5.6 Other features of a healthy diet contributing to cardiovascular disease prevention

The results of the PREDIMED trial are clearly in support of a diet inspired by the traditional Mediterranean diet as an effective approach to the lifestyle prevention of CVDs. 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; wine is consumed in moderation with meals.[137] Dietary choices inspired by this model should be recommended for both primary and secondary prevention of CVD.

One of the important features of this type of diet is represented by the consumption of large amounts of fruits and vegetables of different types providing 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.

As for the consumption of fish, at least two portions per week are recommended to the general population for the prevention of CVD, together with the regular consumption of other food sources of n-3 PUFAs (nuts, soy and flaxseed oil). For secondary prevention of CVD, the use of n-3 PUFA supplements is no longer recommended in view of the recent evidence showing no benefit on CVD of this supplementation in people who have already experienced a CV event. Previous RCTs where omega-3 supplementation was beneficial were not blinded or had low use of standard CV medications (such as statins).

Salt intake should be limited to <5 g/day, 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.[132–134]

Food choices to lower TC and LDL-C are summarized in *Table 13*. Box 9 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 subjects, in particular those with dyslipidaemia, should receive specialist dietary advice, if feasible.

Box 9 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 or saturated fat (hard margarines, 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 trans fats <1.0% of total energy and saturated fat <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 <20 g/day for men) and patients with hypertriglyceridaemia should abstain.
The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, 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.

6. Drugs for treatment of hypercholesterolaemia

6.1 Statins

6.1.1 Mechanism of action

Statins reduce the synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity. The reduction in intracellular cholesterol concentration induces an increased expression of LDLR on the surface of the hepatocytes, which results in increased uptake of LDL-C from the blood and a decreased plasma concentration of LDL-C and other apoB-containing lipoproteins, including TG-rich particles.

The degree of LDL-C reduction is dose dependent and varies between the different statins (supplementary *Figure A* and supplementary *Table A*).[191] There is also considerable interindividual variation in LDL-C reduction with the same dose of drug.[61] Poor response to statin treatment in clinical studies is to some extent caused by poor compliance, but may also be explained by a genetic background involving variations in genes of both

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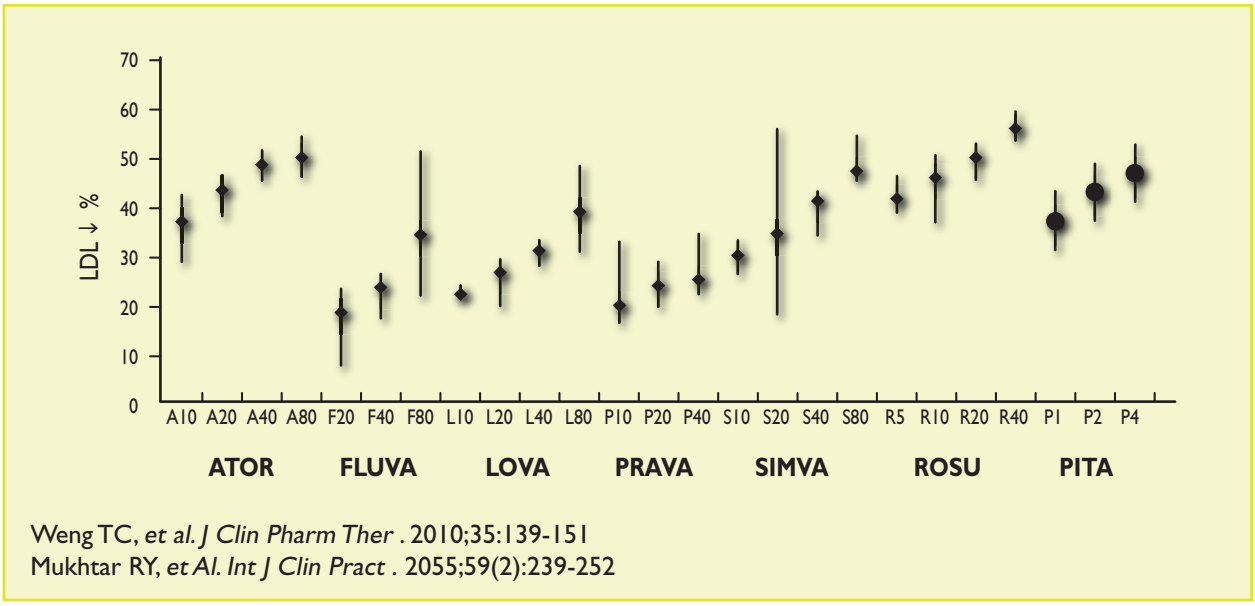

Weng TC, *et al. J Clin Pharm Ther* . 2010;35:139-151
Mukhtar RY, *et Al. Int J Clin Pract* . 2055;59(2):239-252

Supplementary Figure A A systematic review and meta-analysis of the therapeutic equivalence of statins. ATOR = atorvastatin; FLUVA = fluvastatin; LOVA = lovastatin; PRAVA = pravastatin; SIMVA = simvastatin; ROSU = rosuvastatin; PITA = pitavastatin.

Supplementary Table A Percentage reduction of low-density lipoprotein cholesterol (LDL-C) requested to achieve goals as a function of the starting value.

Starting LDL-C		Reduction to reach LDL-C goal, %		
mmol/L	~mg/dL	<1.8 mmol/L (~70 mg/dL)	<2.6 mmol/L (~100 mg/dL)	<3 mmol/L (~115 mg/dL)
>6.2	>240	>70	>60	>55
5.2–6.2	200–240	65–70	50–60	40–55
4.4–5.2	170–200	60–65	40–50	30–45
3.9–4.4	150–170	55–60	35–40	25–30
3.4–3.9	130–150	45–55	25–35	10–25
2.9–3.4	110–130	35–45	10–25	<10
2.3–2.9	90–110	22–35	<10	–
1.8–2.3	70–90	<22	–	–

cholesterol metabolism and of statin uptake and metabolism in the liver.[192,193] Furthermore, conditions causing high cholesterol (e.g. hypothyroidism) should be considered. Indeed, interindividual variations in statin response warrant monitoring of individual response on initiation of therapy.

6.1.2 Efficacy of cardiovascular disease prevention in clinical studies

Statins are among the most studied drugs in CVD prevention, and dealing with single studies is beyond the scope of the present guidelines. A number of large-scale trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention, in both genders and in all age groups. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis.

Meta-analyses. A large number of meta-analyses have been performed to analyse the effects of statins in larger populations and in subgroups.[64–66,68,129,194–200] In the large Cholesterol Treatment Trialists (CTT) analysis data, >170 000 participants and 26 RCTs with statins were included.[64] A 10% proportional reduction in all-cause mortality and 20% proportional reduction in CAD death per 1.0 mmol/L (40 mg/dL) LDL-C reduction was reported. The risk of major coronary events was reduced by 23% and the risk of stroke was reduced by 17% per 1 mmol/L (40 mg/dL) LDL-C

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reduction. The benefits were similar in all subgroups examined. The benefits were significant within the first year, but were greater in subsequent years. There was no increased risk for any non-CV cause of death, including cancer, in those receiving statins. Other meta-analyses have confirmed these results, coming to essentially the same conclusions. Most of the meta-analyses include studies in primary as well as secondary prevention. The absolute benefit from statin treatment may be less evident in patients in primary prevention, who are typically at lower risk. Several meta-analyses have specifically studied statins in primary prevention.[66,68,199] The largest of these was published as a Cochrane review in 2013.[200] The analysis included 19 studies with different statins and with somewhat varying inclusion criteria. In this analysis, all-cause mortality was reduced by 14%, CVD events by 27%, fatal and non-fatal coronary events by 27% and stroke by 22% per 1 mmol/L (40 mg/dL) LDL-C reduction. The relative risk reduction in primary prevention is about the same as that observed in secondary prevention. Similar results were also observed in analyses of statin treatment in people with low risk of vascular disease.[66] However, it should be emphasized that in subjects with lower risk, the absolute risk reduction is also lower.

Current available evidence from meta-analyses suggests that the clinical benefit is largely independent of the type of statin but depends on the extent of LDL-C lowering, therefore the type of statin used should reflect the LDL-C goal in a given patient.

The following scheme may be proposed.

- Evaluate the total CV risk of the subject.
- Involve the patient with decisions on CV risk management.
- Identify the LDL-C goal for that risk level.
- Calculate the percentage reduction of LDL-C required to achieve that goal.
- Choose a statin and a dose that, on average, can provide this reduction.
- Response to statin treatment is variable, therefore up-titration of the dose may be required.
- If the highest tolerated statin dose does not reach the goal, consider drug combinations.
- In addition, for subjects at very high and high risk, a $\geq$50% reduction in LDL-C should be achieved.

Of course, 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.

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).[201,202] Among such effects that are potentially relevant for the prevention of CVD are anti-inflammatory and anti-oxidant effects of statin treatment. Effects have been shown *in vitro* and in experimental systems, but their clinical relevance remains controversial.[203]

Furthermore, the effects of statins on a number of other clinical conditions have been evaluated, including dementia,[204] hepatic steatosis,[205] cancer,[206,207] venous thromboembolism[208] and polycystic ovary syndrome.[209] Available data are controversial and thus far no clinically relevant effect on these conditions has been demonstrated. Statins also reduce TGs by 30–50% and may increase HDL-C by 5–10%. For indications for statins in HTG, see section 7.4.

The suggested effect on Alzheimer's disease was recently reviewed in a Cochrane analysis reporting no conclusive positive effect from statins. Furthermore, case reports on neurocognitive side effects of statins have not been confirmed in analyses of larger patient populations or in meta-analyses.[210]

6.1.3 Adverse effects of statins

Statins differ in their absorption, bioavailability, plasma protein binding, excretion and solubility. Lovastatin and simvastatin are prodrugs, whereas the other available statins are administered in their active form. Their absorption rate varies between 20 and 98%. 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 well tolerated, there are adverse effects to be considered when statins are prescribed.

Muscle. Muscle symptoms are the most commonly described clinically relevant adverse effect of statin treatment.[57] Rhabdomyolysis is the most severe form of statin-induced myopathy, 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, often up to 40 times the upper limit of normal.[211] The frequency of rhabdomyolysis has been estimated to represent 1–3 cases/100$\sqrt{}$000 patient-years.[212] A more commonly described form of muscular adverse effect is muscular pain and tenderness (myalgia) without CK elevation or major functional loss. The actual frequency of this adverse effect, however, is unclear, and varies between different reports. In meta-analyses of RCTs, no increased frequency in statin-treated groups has been shown.[213,214] On the other hand, the reported frequency varies between 10 and 15% in observational studies.[215,216] One study, designed specifically to study the effects of statins on muscle symptoms, suggests that the frequency of muscle-related complaints is ~5%.[217] The diagnosis is based on the clinical observation and whether symptoms disappear after discontinuation of statins and recur with statin rechallenge. The symptoms are often vague and the association with statin treatment is often difficult to confirm. In patients with a high risk for CVD, it is essential to confirm the diagnosis before leaving the patient without the benefits of statin treatment. Risk factors for muscular adverse effects have been identified. Among these, the interaction with concomitant drug therapy should especially be considered (see below). Suggested practical management of muscular symptoms is given in supplementary material. In patients with high or very high risk for CVD, treatment with the highest tolerable dose of statin should be considered, in combination with a cholesterol absorption inhibitor, and if available a PCSK9 inhibitor may also be considered.[218,219] 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.[57,220] Although no clinical endpoint trials are available, this treatment should be considered in high-risk patients who do not tolerate daily doses of statin treatment.

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

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commonly with potent statins or high doses. The common definition of clinically relevant ALT elevation has been an increase of three times the upper limit of normal (ULN) on two 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.[221] 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.[222–224]

Diabetes. Patients on statin treatment have been shown to exhibit an increased risk of dysglycaemia and development of diabetes type 2. In a meta-analysis including 91 140 subjects, the relative risk was increased by 9% relative to placebo. The absolute risk was increased by 0.2%.

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.[225] However, the risk is higher with the more potent statins in high doses,[226] and the risk for diabetes is higher in the elderly and in the presence of other risk factors for diabetes such as overweight or insulin resistance.[227] Overall, the absolute reduction in the risk of CVD in high-risk patients outweighs the possible adverse effects of a small increase in the incidence of diabetes.

Kidney. The effect of statin treatment on renal function is still being debated. A recent Cochrane analysis could not find support for beneficial effects on renal function based on studies where creatinine clearance was available, and no deleterious effects were observed.[228] An increased frequency of proteinuria has been reported for all statins, but has been analysed in more detail for rosuvastatin, probably due to the high frequency of proteinuria observed with a higher dose (80 mg). 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 and is supposed to be due to reduced tubular reabsorption and not to glomerular dysfunction.[229] In experimental systems, reduced pinocytosis has been shown in renal cells. The statin-induced reduced pinocytosis is directly related to the inhibition of cholesterol synthesis.[230] In clinical trials the frequency of proteinuria is in general low and in most cases is not higher than for placebo.[231]

6.1.4 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 15*. 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. CYP3A 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 15 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[232] and Wiklund *et al.*[233]

Combinations of statins with fibrates may enhance the risk for myopathy. This risk is highest for gemfibrozil, and the association of gemfibrozil with statins should be avoided. The increased risk for myopathy when combining statins with other fibrates such as fenofibrate, bezafibrate or ciprofibrate seems to be small.[234,235]

The increased risk for myopathy with nicotinic acid has been debated, but in recent reviews no increased risk of myopathy was found with this agent.[236,237]

6.2 Bile acid sequestrants

6.2.1 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. Recently the synthetic drug colesevelam was introduced. The bile acid sequestrants are not systemically absorbed or altered by digestive enzymes, therefore the beneficial clinical effects are indirect. By binding the bile acids, the drugs prevent the entry of bile acids 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 stores of cholesterol. The decrease in bile acid returned to the liver leads to upregulation of key enzymes responsible for bile acid synthesis from cholesterol, particularly CYP7A1. The increase in cholesterol catabolism to bile acids results in a compensatory increase in hepatic LDLR activity, clearing LDL-C from the circulation and thus reducing LDL-C levels. These agents also reduce glucose levels in hyperglycaemic patients. A recent Cochrane review found that colesevelam, when added to other antidiabetic agents, showed significant effects on glycaemic control; however, more research on the impact of CV risk is required.[238]

6.2.2 Efficacy in clinical studies

At the top 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.

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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 subjects, with a benefit proportional to the degree of LDL-C lowering. However, this study was performed before many of the modern treatment options were available.[239–241]

6.2.3 Adverse effects and interactions

Gastrointestinal 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 many commonly prescribed drugs and should therefore be administered either 4 h before or 1 h after other drugs. Colesevelam represents a newer formulation of the bile acid sequestrant, which may be better tolerated than cholestyramine. Colesevelam has fewer interactions with other drugs and can be taken together with statins and several other drugs.[242]

6.3 Cholesterol absorption inhibitors

6.3.1 Mechanism of action

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine [by interaction with the Niemann-Pick C1-like protein 1 (NPC1L1)], 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-C from the blood.

6.3.2 Efficacy in clinical studies

In clinical studies, ezetimibe in monotherapy reduces LDL-C in hypercholesterolaemic patients by 15–22%. Combined therapy with ezetimibe and a statin provides an incremental reduction in LDL-C levels of 15–20%. The efficacy of ezetimibe in association with simvastatin has been addressed in subjects with aortic stenosis in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study[243] and in patients with CKD in the Study of Heart and Renal Protection (SHARP) (see sections 9.7.3 and 9.9.2). In both the SEAS and SHARP trials, a reduction in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.[243,244]

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) ezetimibe was added to simvastatin (40 mg) in patients after ACS.[63] A total of 18 144 patients were randomized and 5314 patients over 7 years experienced a CVD 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 in the simvastatin group and 1.4 mmol/L 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 the further LDL-C reduction. In this group of patients already treated with statins to reach goals, the absolute benefit from added ezetimibe was small, although significant. However, the study supports the proposition that LDL-C lowering by means other than statins is beneficial and can be performed without adverse effects. 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.[245]

Taken together with other studies such as the PRECISE-IVUS study,[246] 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 patients intolerant of statins or with contraindications to these drugs.

6.3.3 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 without regard to 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. Ezetimibe can be co-administered with any dose of any statin. No major adverse effects have been reported; the most frequent adverse effects are moderate elevations of liver enzymes and muscle pain.

6.4 PCSK9 inhibitors

6.4.1 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.[247] Elevated levels/functions of this protein in plasma reduce LDLR expression by promoting, upon binding, the LDLR lysosomal catabolism and increase plasma LDL-C concentration, while lower levels/functions of PCSK9 are related to lower plasma LDL-C levels.[248] Therapeutic strategies have been developed mainly using monoclonal antibodies that reduce LDL-C levels by ~60% independent from the presence of a background lipid-lowering therapy. 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.[248]

6.4.2 Efficacy in clinical studies

The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have recently approved two monoclonal antibodies (Mabs) for the control of elevated plasma LDL-C. The efficacy at reducing LDL-C is in the range of 50–70%, independent of the presence of a background therapy (statins, ezetimibe, etc.); preliminary data from phase 3 trials suggest a reduction of CV events in line with the LDL-C reduction achieved.[115,116] A recent meta-analysis confirmed these findings.[249] No major effects are

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reported on HDL-C or plasma TGs. However, the TG effect must be reconfirmed in populations with higher starting plasma TG levels.

Given the mechanism of action, these drugs are effective at reducing LDL-C in all patients with the capability of expressing LDLRs in the liver. Therefore this pharmacological approach is effective in the vast majority of patients, including those with heterozygous FH (HeFH) and, albeit to a lower level, those with homozygous FH (HoFH) with residual LDLR expression. Receptor-deficient HoFH responds poorly to the therapy.

People at very high total CV risk, people with HeFH (and some with HoFH) on maximally tolerated doses of first- and second-line therapy and/or in apheresis and who are statin 'intolerant' with persistent high levels of LDL-C are reasonable candidates for the use of these drugs.

6.4.3 Adverse effects and interactions

Anti-PCSK9 Mabs are injected subcutaneously, usually every other week, at doses up to 150 mg. The potential for interaction with orally absorbed drugs is absent, as they will not interfere with pharmacokinetics or pharmacodynamics. Anti-PCSK9 Mabs do not modulate pathways involved in biotransformation or drug uptake/extrusion from cells. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms. In some studies an increase of patient-reported neurocognitive effects was described. This finding requires further scrutiny.[250]

6.5 Nicotinic acid

Nicotinic acid has broad lipid-modulating action, raising HDL-C in a dose-dependent manner by up to 25% and reducing LDL-C by 15–18% and TGs by 20–40% at the 2 g/day dose. Nicotinic acid is unique in lowering Lp(a) levels by up to 30% at this dose. After two large studies with nicotinic acid, one with extended-release niacin[251] and one with niacin plus laropiprant,[252] showed no beneficial effect, but rather an increased frequency of serious adverse effects, no medication containing nicotinic acid is currently approved in Europe. For the role of niacin in hypertriglyceridaemia, see section 7.6.

6.6 Drug combinations

Although the LDL-C goals are attained with monotherapy in many patients, a significant proportion of high-risk subjects or patients with very high LDL-C levels need additional treatment. There are also patients who are statin intolerant or are not able to tolerate higher statin doses. In these cases, combination therapy should be considered (*Table 19*). More information on statin intolerance is provided in Supplementary *Figure C*.

6.6.1 Statins and cholesterol absorption inhibitors

The combination of statins and ezetimibe is discussed above (see section 6.3.2).

6.6.2 Statins and bile acid sequestrants

The combination of a statin and cholestyramine, colestipol or colesevelam could be useful in achieving LDL-C goals. On average, the addition of a bile acid sequestrant to a statin reduces LDL-C by an additional 10–20%. However, there are no published clinical outcome trials with either conventional bile acid sequestrants or colesevelam in combination with other drugs. The combination has been found to reduce atherosclerosis, as evaluated by coronary angiography.[253]

6.6.3 Other combinations

In high-risk patients such as those with FH, or in cases of statin intolerance, other combinations may be considered. Co-administration of ezetimibe and bile acid sequestrants (colesevelam, colestipol or cholestyramine) resulted in an additional reduction of LDL-C levels without any additional adverse effects when compared with the stable bile acid sequestrant regimen alone.[254] Clinical outcome studies with these combinations have not been performed.

Functional foods containing phytosterols as well as plant sterol–containing tablets additionally reduce LDL-C levels by up to 5–10% in patients taking a stable dose of a statin, and this combination is also well tolerated and safe.[142,255] Phytosterols and plant sterols should be taken after a meal. However, it is still not known whether this could reduce the risk of CVD since no trials with plant sterols or stanols in combination with other lipid-lowering drugs are available for CVD outcomes. The combination of red yeast with statins is not recommended.

In patients at very high risk, with persistent high LDL-C despite being treated with a maximal statin dose in combination with ezetimibe, or in patients with statin intolerance, a PCSK9 inhibitor may be considered.

Recommendations for the treatment of hypercholesterolaemia are shown in *Table 16*.

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
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.	IIb	C	115, 116

LDL-C = low-density lipoprotein-cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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7. Drugs for treatment of hypertriglyceridaemia

7.1 Triglycerides and cardiovascular disease risk

Although the role of TGs as a risk factor for CVD has been strongly debated, recent data favour the role of TG-rich lipoproteins as a risk factor for CVD.[87] Large prospective studies have reported that non-fasting TGs predict CAD risk more strongly than fasting TGs.[98,99] Recent data from genetic studies utilizing a Mendelian randomization design have consistently linked both non-fasting TG levels as well as remnant cholesterol to increased risk of CVD events and all-cause mortality.[86,107] Remnant cholesterol is a calculated parameter in these studies and equals TC − (HDL-C + LDL-C). These genetic data have strengthened the position of remnant cholesterol as a causal factor driving atherosclerosis and CVD events.[75] Recently, remnant cholesterol has turned out to be a good surrogate marker of TGs and remnants.[90] The burden of HTG as a CVD risk factor is highlighted by the fact that about one-third of adult individuals have TG levels >1.7 mmol/L (150 mg/dL).[258] HTG can have different causes (*Table 17*), among which its polygenic nature is most important in relation to CVD prevention.

Table 17 Possible causes of hypertriglyceridaemia

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens (protease inhibitors) • Psychotropic medications: phenothiazines, second generation antipsychotics

7.2 Definition of hypertriglyceridaemia

The definition of different categories for elevated fasting TG levels seems to be slightly variable in different guidelines and recommendations.[67,259] According to the EAS consensus document, mild to moderate HTG is defined as TGs >1.7 mmol/L (150 mg/dL) and <10 mmol/L (880 mg/dL); TGs >10 mmol/L is defined as severe HTG.[260] Age/gender, race/ethnicity and lifestyle are modulating factors at the population level for serum TGs. In the Copenhagen general population ~27% had TGs >1.7 mmol/L.[75] Severe HTG is rare and is typically associated with monogenic mutations. Severe HTG is associated with an increased risk for pancreatitis.

7.3 Strategies to control plasma triglycerides

A level of fasting TGs ≤1.7 mmol/L (150 mg/dL) is desirable. The first step is to consider possible causes of HTG and to evaluate the total CV risk. The primary goal is to achieve the LDL-C level recommended based on the total CV risk level. As compared with the overwhelming evidence for the benefits of LDL-C reduction, the evidence on the benefits of lowering elevated TG levels is still modest, and is primarily derived from subgroup or post hoc analyses. However, recent evidence of TGs as a causal risk factor may encourage TG lowering (*Table 18*).

Table 18 Recommendations for drug treatments of hypertriglyceridaemia

Recommendations	Class [a]	Level [b]	Ref [c]
Drug treatment should be considered in high-risk patients with TG >2.3 mmol/L (200 mg/dL).	IIa	B	261, 262
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	IIb	B	263, 264
In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins.	IIb	C	261–264

CVD = cardiovascular disease; TG = triglycerides.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Although the CVD risk is increased if fasting TGs are >1.7 mmol/L (150 mg/dL),[87] the use of drugs to lower TGs may only be considered in high-risk subjects 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.

For information on lifestyle management, please refer to section 5.

7.4 Statins

Since statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to

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reduce both total CVD risk and moderately elevated TG levels. More potent statins (atorvastatin, rosuvastatin and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with elevated TGs. In subgroup analyses from statin trials, the risk reduction is the same in subjects with HTG as in normotriglyceridaemic subjects.

7.5 Fibrates

7.5.1 Mechanism of action

Fibrates are agonists of peroxisome proliferator-activated receptor-α (PPAR-α), acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. By interacting with PPAR-α, fibrates recruit different cofactors and regulate gene expression. 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. The HDL-C raising effects of fibrates are modest.[263]

7.5.2 Efficacy in clinical trials

The clinical effects of fibrates are primarily illustrated by five prospective RCTs: Helsinki Heart Study (HHS), Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT), Bezafibrate Infarction Prevention (BIP) study, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, where fenofibrate was added to statin therapy.[261,262,265–267]

Although the Helsinki Heart Study reported a significant reduction in CVD outcomes with gemfibrozil, neither the FIELD nor the ACCORD study showed a reduction in total CVD outcomes. 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 subjects 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.[268,269] 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.[270–272] Thus the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Overall, the possible benefits of fibrates require confirmation.

7.5.3 Adverse effects and interactions

Fibrates are generally well tolerated with mild adverse effects, gastrointestinal disturbances being reported in <5% of patients and skin rashes in 2%.[273] In general, myopathy, liver enzyme elevations and cholelithiasis represent the most well-known adverse effects associated with fibrate therapy.[273] In the FIELD study, small but significant increases in the incidence of pancreatitis (0.8% vs. 0.5%) and pulmonary embolism (1.1% vs. 0.7%) and a non-significant trend toward an increase in deep vein thrombosis (1.4% vs. 1.0%) were seen in those taking fenofibrate compared with placebo; this is in line with data from other fibrate studies.[261] Elevations of both CK (>5 times above the ULN) and ALT (>3 times above the ULN) were reported more frequently for patients on fenofibrate than on placebo, but the incidence of these abnormalities remained <1% in both treatment groups. In the FIELD study, one case of rhabdomyolysis was reported in the placebo group and three cases in the fenofibrate group.[261] The risk of myopathy has been reported to be 5.5-fold greater with fibrate use as a monotherapy compared with statin use. The risk of myopathy is greater in patients with CKD, and it varies with different fibrates and statins used in combination. This is explained by the pharmacological interaction between different fibrates and glucuronidation of statins. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to highly increased plasma concentrations of statins. As fenofibrate does not share the same pharmacokinetic pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy.[273]

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.[274] The increase in homocysteine by fibrates has been considered to be relatively innocent with respect to CVD risk. However, the fibrate-induced increase in homocysteine may blunt the increases in both HDL-C and apoA1, and this may contribute to the smaller than estimated benefits of fenofibrate in the outcome parameters.[275] High homocysteine also promotes thrombosis, and the increased trend to deep vein thrombosis seen in the FIELD study was associated with the baseline homocysteine levels, but no interaction was observed between the increase of homocysteine by fibrate and venous thromboembolic events.[276]

7.6 Nicotinic acid

7.6.1 Mechanism of action

Nicotinic acid has been reported to decrease fatty acid influx to the liver and the secretion of VLDL by the liver. This effect appears to be mediated in part by the action on hormone-sensitive lipase in the adipose tissue. 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 from the liver, which is also reflected in reductions of both IDL and LDL particles.[277] Nicotinic acid raises HDL-C and apoA1 primarily by stimulating apoA1 production in the liver.[277] The effects of nicotinic acid on lipolysis and fatty acid mobilization in adipocytes are well established.

7.6.2 Efficacy in clinical trials

Nicotinic acid has multiple effects on serum lipids and lipoproteins.[277] Nicotinic acid effectively reduces not only TGs, but also LDL-C, reflecting its effect on all apoB-containing proteins. Nicotinic acid increases apoA1-containing lipoproteins, reflected in increases of HDL-C and apoA1. At a daily dose of 2 g it reduces TGs by 20–40% and LDL-C by 15–18% and increases HDL-C by 15–35%.[257,277,278] The favourable effect on angiographic measures has been reported in the Familial Atherosclerosis Treatment Study (FATS) and in the HDL-Atherosclerosis Treatment Study (HATS).[279]

Two large randomized clinical trials [the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and the Heart

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Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)] using, respectively, extended release (ER) nicotinic acid vs. placebo in addition to simvastatin, and ER nicotinic acid/laropiprant vs. placebo in patients treated with simvastatin (plus, if indicated, ezetimibe), failed to report positive benefits of the therapies on CV outcomes and have challenged the position and benefits of niacin in lipid management.[251,252] Furthermore, there was an increased frequency of severe adverse effects in the niacin groups. Since the EMA suspended ER nicotinic acid/laropiprant, this therapeutic option is unavailable in Europe.

7.7 n-3 fatty acids

7.7.1 Mechanism of action

n-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.

7.7.2 Efficacy in clinical trials

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.[280] The recommended doses of total EPA and DHA to lower TGs have varied between 2 and 4 g/day. Three recent studies in subjects with high TGs using EPA reported a significant reduction in serum TG levels of up to 45% in a dose-dependent manner.[281–283] The efficacy of omega-3 fatty acids to lower serum TGs has also been reported in meta-analyses.[284] One meta-analysis included 63 030 subjects from 20 trials and reported no overall effect of omega-3 fatty acids on composite CV events {relative risk [RR] 0.96 [95% confidence interval (CI) 0.90, 1.02]; $P = 0.24$} or total mortality [RR 0.95 (95% CI 0.86, 1.04); $P = 0.28$]. A major side effect was gastrointestinal disturbances.[285] The FDA has approved the use of n-3 fatty acids (prescription products) as an adjunct to diet if TGs are >5.6 mmol/L (496 mg/dL). Although a recent Japanese study in patients with hypercholesterolaemia reported a 19% reduction in CVD outcome,[286] the data remain inconclusive and their clinical efficacy appears to be related to non-lipid effects.[287,288] Two randomized placebo-controlled trials [Reduction of Cardiovascular Events with EPA-Intervention Trial (REDUCE-IT) and Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk PatienTs with Hypertriglyceridemia (STRENGTH)] to study the potential benefits of EPA on CVD outcomes in subjects with elevated serum TGs are ongoing. REDUCE-IT aims to recruit ~8000 subjects and STRENGTH 13 000 subjects.

7.7.3 Safety and interactions

The administration of n-3 fatty acids appears to be safe and devoid of clinically significant interactions. However, the antithrombotic effects may increase the propensity to bleed, 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.[289]

Table 19 Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.
If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

TG = triglycerides.

8. Drugs affecting high-density lipoprotein cholesterol (*Table 20*)

Low levels of HDL-C constitute a strong, independent and inverse predictor of the risk of premature development of atherosclerosis.[83] Moreover, the increase in CV risk relative to low HDL-C levels is especially dramatic over the range of HDL-C from 0.65 to 1.17 mmol/L (25 to 45 mg/dL).[260] Results from a meta-analysis of four intervention trials, which involved the use of intravascular ultrasound to evaluate changes in coronary atheroma volume, indicated that elevation ≥7.5% in HDL-C, together with a reduction in LDL-C to a target of 2.0 mmol/L (<80 mg/dL), represented the minimum requirement for plaque regression.[290]

Table 20 Recommendations if drug treatment of low high-density lipoprotein cholesterol is considered

Recommendations	Class [a]	Level [b]	Ref [c]
Statins and fibrates raise HDL-C with a similar magnitude and these drugs may be considered.	IIb	B	262, 292
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	IIb	B	261, 262

HDL-C = high-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

Subjects with type 2 diabetes or those with mixed or combined dyslipidaemia, renal and hepatic insufficiency states or autoimmune diseases often present with low plasma concentrations of HDL-C. In addition to low HDL-C, these disease states feature a moderate or marked degree of HTG. The intravascular metabolism of TG-rich lipoproteins (principally VLDL) is intimately linked to that of HDL. Drug-induced elevation of HDL-C may lead to reductions in the cholesterol content of both VLDL and LDL. The magnitude of reduction in VLDL cholesterol (VLDL-C) and LDL-C under these circumstances tends to differ markedly as a function of the specific mechanism of action of the pharmacological agent concerned, as

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well as the dose employed and the baseline lipid phenotype. Furthermore, the percentage increase in HDL-C following treatment tends to be greater in subjects with the lowest baseline levels.

The available options for elevating low HDL-C levels are relatively few. While HDL-C levels may be increased by up to 10% by implementing therapeutic lifestyle changes, including weight reduction, exercise, smoking cessation and moderate alcohol consumption, many patients will also require pharmacological intervention if an HDL-C increase is sought. However, until now there has been no clear direct evidence that raising HDL-C really results in CVD prevention. Recent studies aimed at testing this hypothesis have failed to show any beneficial effect [ILLUMINATE (torcetrapib), Dalcetrapib Outcomes (dal-OUTCOMES), ACCELERATE (evacetrapib), HPS2-THRIVE (nicotinic acid plus statin), AIM-HIGH (nicotinic acid on background statin)], although the population selection in the last two studies may not have been optimal. The ongoing study with a cholesteryl ester transfer protein (CETP) inhibitor, the Randomized Evaluation of the Effects of Anacetrapib Through Lipid modification (REVEAL), will provide more information.

8.1 Statins

Statins produce modest elevations in HDL-C. In a meta-analysis[291] of several intervention studies in dyslipidaemic patients, elevations in HDL-C varied with dose among the respective statins; such elevations were typically in the range of 5–10%. As a result of the marked reductions in atherogenic apoB-containing lipoproteins by statins, it is difficult to assess the extent to which the effect on HDL-C levels might contribute to the overall observed reductions in CV risk consistently seen in statin intervention trials. Despite such an effect, however, the elevated CV risk associated specifically with low HDL-C levels was only partially corrected by statin treatment in the Treatment to New Targets (TNT) trial.[292]

8.2 Fibrates

As a class, fibrates differ in their potential to modulate the atherogenic lipid profile by concomitantly lowering TG levels (up to 50%) and by raising those of HDL-C (up to 10–15% in short-term studies). However, the HDL-raising effect has been markedly less (~5%) in the long-term intervention trials in people with type 2 diabetes[261,262]; such differences appear to reflect distinctions in their relative binding affinities for PPARs, and notably for PPAR-α.[293]

8.3 Nicotinic acid

Nicotinic acid appears to increase HDL-C by partially reducing HDL catabolism and by mainly increasing apoA1 synthesis by the liver. The latter effect is regarded as the most relevant for the HDL functions.[263] Itsefficacy in clinical trials and adverse effects and drug interactions are described in section 7.6.

8.4 Cholesteryl ester transfer protein inhibitors

To date, the most efficacious pharmacological approach to elevation of low HDL-C levels has involved direct inhibition of CETP by small molecule inhibitors, which may induce an increase in HDL-C by ≥100% on a dose-dependent basis. Of the three CETP inhibitors developed originally (torcetrapib, dalcetrapib and anacetrapib), torcetrapib was withdrawn following an excess of mortality in the torcetrapib arm of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial.[294] The Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE) trial of evacetrapib in acute coronary syndrome subjects on statins was terminated due to futility.

Retrospectively, it appears that the deleterious effects of torcetrapib arose primarily from off-target toxicity related to activation of the renin–angiotensin–aldosterone system (RAAS). The results of the dalcetrapib trial (Dal-OUTCOMES) shows no effects in ACS patients. Phase III trials with anacetrapib (REVEAL) are ongoing.

8.5 Future perspectives

Major developments in the search for efficacious agents to raise HDL-C and apoA1 with concomitant benefit in atherosclerosis and CV events are on the horizon. Among them, major interest is focused on apoA1 mimetic peptides, which are not only active in cellular cholesterol efflux, but may also exert a vast array of biological activities including anti-inflammatory and immune-modulating effects. However, the genetic studies suggesting that low HDL-C is not causative for CVD may cast doubt on the possibilities of these treatment options.

9. Management of dyslipidaemia 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 hyperlipidaemia. A number of monogenic lipid disorders have been identified; among these, FH is most common and strongly related to CVD. 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, but rather that it stems from inheriting more than one lipoprotein gene variant 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.[295] It is common to find that high LDL-C, high TGs or low HDL-C affect several family members.

9.1.1 Familial combined hyperlipidaemia

Familial combined hyperlipidaemia (FCH) is a highly prevalent dyslipidaemia (1:100) and an important cause of premature CAD. FCH is characterized by elevated levels of LDL-C, TGs or both. The phenotype varies even among members of the same family. FCH shares considerable phenotype overlap with type 2 diabetes and MetS. FCH is a complex disease and the phenotype is determined by interaction of multiple susceptibility genes and the environment. The phenotype even within a family shows high inter- and intraperson variability based on lipid values (TGs, LDL-C, HDL-C and apoB). 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 subjects who most probably have FCH.[296] Currently, research is ongoing to define genetic markers;

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hopefully this approach will facilitate diagnosis of this frequent genetic dyslipidaemia.

The concept of FCH 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 are riskier 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 monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C. If left untreated, men and women with heterozygous FH (HeFH) typically develop CAD before the ages of 55 and 60 years, respectively. However, if diagnosed early and properly treated, the risk for CAD may be dramatically reduced, with some studies even suggesting a normal life expectancy.

Table 21 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia[301]

Criteria	Points
1) Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or	
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 (see 9.1.2.3)	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	
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 (diagnosis is based on the total number of points obtained)	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

FH = familial hypercholesterolaemia; LDL-C = low-density lipoproteincholesterol.
[a]Exclusive of each other (i.e. maximum 6 points if both are present)

The frequency of HeFH in the population has earlier been estimated at 1/500; however, recent studies from whole populations suggest that the frequency is higher, in some populations as high as 1/137.[297] Based on extrapolations from available data, the frequency of HeFH can be estimated to be between 1/200 and 1/250, putting the total number of cases at between 14 and 34 million worldwide.[121,298] Only a minor fraction of these are identified and properly treated. The risk of CHD among individuals with definite or probable HeFH is estimated to be increased at least 10-fold.

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; 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. Complete loss of receptor function is associated with more severe disease. A total of 4–5% of FH is caused by mutations in *apoB* causing reduced binding to LDLR and ~1% is caused by mutations in *PCSK9* causing increased catabolism of LDLR.

The diagnosis of FH is in most cases based on the clinical picture. Different criteria for the diagnosis have been developed. The commonly used criteria from the Dutch Lipid Clinic Network (DLCN) are shown in *Table 21*. Other criteria are the Simon Broome register or the WHO criteria.[299,300]

The clinical diagnosis of HeFH is based on family history of hypercholesterolaemia or premature CHD, clinical history of the patient regarding CVD and clinical signs. Finally, the diagnosis can be verified by showing causative mutations in the three pathogenic genes. However, in most studies the frequency of detectable mutations in patients with a clinically definite or probable HeFH is only 60–70%. This suggests that a considerable fraction of patients with FH have either a polygenic cause of the disease or that other genes, not yet identified, are involved.

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

- plasma cholesterol ≥8 mmol/L (310 mg/dL) 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

The most effective way to identify new cases is to undertake cascade screening of family members of a known index case. Cascade screening is best performed by a lipid clinic with trained nurses and physicians. 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 since affected individuals may present with TC below the clinical diagnostic criteria.

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. LDL-C goals are

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<2.6 mmol/L (100 mg/dL) or <1.8 mmol/L (70 mg/dL) if CVD is present.

PCSK9 antibodies have recently been registered for use in FH patients. The drugs very efficiently lower LDL-C by up to 60% on top of the statin. Randomized controlled studies have yet to report clinical endpoints and therefore the use of these drugs should be limited. PCSK9 inhibitors should be considered in patients with FH at very high risk due to the presence of CVD, a family history of CAD at a very young age or an LDL-C level far from goal even on maximal other therapy. PCSK9 inhibitors should also be considered in HeFH patients who cannot tolerate statins and in FH patients with high Lp(a).

Recommendations for the detection and treatment of patients with HeFH are shown in *Table 22*.

Table 22 Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia

Recommendations	Class [a]	Level [b]
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
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.	IIa	C
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.	IIa	C
In children, testing is recommended from age 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 statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).
[a]Class of recommendation.
[b]Level of evidence.

9.1.2.2 Homozygous familial hypercholesterolaemia

Homozygous FH (HoFH) is a rare and life-threatening disease. The clinical picture is characterized by extensive xanthomas, marked premature and progressive CVD and total cholesterol >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. For a more detailed discussion of HoFH, including the role of PCSK9 inhibitors and the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide, see the EAS consensus paper on HoFH.[302]

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.[303] Testing during childhood is optimal to discriminate between FH and non-FH using LDL-C. LDL-C ≥5 mmol/L (190 mg/dL) is most probably FH. In children with a family history of high cholesterol or premature CHD, the cut-off point may be put at ≥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).

Although placebo-controlled trials are missing 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.[303] 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 8–10 years of age. Statin treatment should be started with low doses and the dose should be increased to reach goals. 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. It is rare for it to be expressed 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, apoE2 homozygosity does not generally cause familial dysbetalipoproteinaemia syndrome. The syndrome often develops in the presence of dyslipidaemia associated with HTG, diabetes mellitus, obesity or hypothyroidism.

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 xanthomata, 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 detection of apoE2 homozygosity in a dyslipidaemic patient is diagnostic and analysis of apoE isoforms is now available in most clinical laboratories. In older patients with xanthomata resembling those of familial dysbetalipoproteinaemia, who prove not to be

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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

The genetic aetiology for HTG seems to be very complex, with effects of both common and rare genetic variants.[67,304] 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. In CVD prevention, polygenic moderate TG elevation is to be considered. Monogenic severe HTG causes 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. A 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. Recently, gene therapy for LPL deficiency has been developed and tested in clinical trials[305] and the alipogene tiparvovec was approved by the EMA in 2013. 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.[306] These findings have raised the possibility of apoC3 as a novel lipid drug target. In summary, the development of new therapeutic options for this rare disease raises the need for awareness and screening of these patients.

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), and actions to prevent acute pancreatitis are mandatory. 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 study ($n = 33\,346$) 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.[307] 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.[67] 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.[308]

9.1.5 Other genetic disorders of lipoprotein metabolism (*Table 23*)

Sometimes patients are encountered with extremely low levels of LDL-C or HDL-C. The most common genetic hypolipidaemia is hypobetalipoproteinaemia, which is dominantly inherited and often due to truncation of apoB. Serum LDL-C is typically between 0.5 and 1.5 mmol/L (20–60 mg/dL). It is generally of no medical significance. 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

Table 23 Genetic disorders of lipoprotein metabolism

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 200–250	*LDLR* *APO B* *PCSK9*	↑LDL-C
HoFH	1 in 160 000–320 000	*LDLR* *APO B* *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* *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 lipoproteincholesterol; VLDL = very low-density lipoprotein-cholesterol.

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(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 CVD in these patients, but it cannot stop the progression of liver damage. Enzyme replacement therapy with sebelipase alfa might offer a treatment solution in the near future.[309]

9.2 Children

Only children with FH should be considered for lipid-lowering drug treatment. In other cases of dyslipidaemia in children, focus should be on diet and treatment of underlying metabolic disorders. HoFH patients should be treated with lipid-lowering drugs as early as possible, and the same is true for HeFH patents with extremely high LDL-C, i.e. ≥400 mg/dL (~10.3 mmol/L).[310] In the case of other HeFH children, statin treatment is generally withheld until sometime between the ages of 8 and 10 years. There is evidence from carotid ultrasound measurements that increased CIMT in children with HeFH compared with siblings who have not inherited HeFH can be detected from the age of 6 years onwards, and that the progression of increasing CIMT can be ameliorated with statin therapy and/or apheresis.[311] However, the exact age at which to start statin treatment is a matter of clinical judgement.

9.3 Women

Among several studies that have evaluated the impact of lipid-lowering therapy on primary and secondary prevention of CAD, only a few have included women, usually in small numbers, and the results have often not been separately reported by gender.[312] The most recent CTT meta-analysis, however, indicates a similar relative benefit in men and women.[65]

9.3.1 Primary prevention

The benefit of statins in primary prevention is less well-established in women than in men. This may be because of their lower baseline risk and their underrepresentation in trials, and points to the need to include gender balance and sufficient numbers to detect modest absolute treatment effects in future trials.

The 2013 Cochrane analysis showed reductions of all-cause mortality, vascular events and revascularisations with statins in primary prevention. Effects in women were similar to those in men.[200] In postmenopausal women, plaque rupture was found to be a more common cause of ACS than plaque erosion and is correlated with TC levels.[313]

A recent meta-analysis of statin trials in the CTT database compared the effects of statin therapy between men and women.[65] The proportional (relative risk) reductions in major coronary events, coronary revascularisations and stroke did not differ significantly by gender. All-cause mortality reductions were seen in both women and men, showing that statin therapy is of similar effectiveness. Significant decreases in vascular events in primary prevention were seen in both women and men. Thus statin use should be considered for primary prevention in women at high CV risk with the same indications as for men.

9.3.2 Secondary prevention

More data coming from large RCTs of secondary prevention are available for women. The results of these trials concordantly show that lipid-lowering therapy substantially reduces CV events in these patients, although no reduction in total mortality risk could be demonstrated. The meta-analysis of Walsh and Pignone[314] reported a 26% reduction of CV mortality, a 29% reduction of MI and a 20% reduction of total CAD events in a cohort of 8272 females with previous CVD mainly treated with statins. The CTT meta-analysis also indicates that the benefit overall is similar in men and women.[65] Therefore, secondary prevention of CV events in women should routinely include a statin-based lipid-lowering regimen, with the same recommendations and therapeutic goals that are applied to men.

9.3.3 Non-statin lipid-lowering drugs

No definitive evidence of cardioprotective effects was available until recently. The IMPROVE-IT study[63] included patients at least 50 years of age who had been hospitalized within the preceding 10 days for an ACS (24% women). The combination of simvastatin–ezetimibe was compared with simvastatin monotherapy. The rate of the composite endpoint of death from CV causes, MI or stroke was significantly lower, by 1.8 percentage points, in the combination group and the benefit of simvastatin–ezetimibe was consistent for women.[63]

The ACCORD lipid study showed less primary event reduction with combination therapy in women, but the recent FIELD study analysis showed consistent CV event reduction in women and men.[315] Ezetimibe, or fibrates, alone or in combination with statins, can be used, depending on the type of dyslipidaemia and adverse effect profiles. Recent data with PCSK9 inhibitors indicate a similar efficacy in reducing LDL-C in women vs. men.[115,116]

9.3.4 Hormone therapy

Currently used third-generation low-dose oestrogen–progestin oral contraceptives do not appear to increase adverse coronary events[316] 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.[317] 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.[318] No lipid-lowering drugs should be administered during pregnancy and the period of breastfeeding since data on possible adverse effects are lacking. However, bile acid sequestrants may be considered.

Box 10 lists the main measures in the management of dyslipidaemia in women.

Box 10 Management of dyslipidaemia in women

Statin treatment is recommended for primary prevention of CAD in high-risk women.[64,65]
Statins are recommended for secondary prevention in women with the same indications and targets as in men.[64,65]
Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breastfeeding period. However, bile acid sequestrants (which are not absorbed) may be considered.

9.4 Older persons

The proportion of older people 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.[319] Coronary care has also been improved for

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