



# ESC/EAS Guidelines for the management of dyslipidaemias

## The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)

Developed with the special contribution of: European Association for Cardiovascular Prevention & Rehabilitation<sup>†</sup>

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## Keywords

Dyslipidaemia • Cholesterol • Triglycerides • Treatment • Cardiovascular diseases • Guidelines

## Table of Contents

1. Preamble . . . . .	1772	9.2 Fibrates . . . . .	1797
2. Introduction . . . . .	1773	9.3 Nicotinic acid . . . . .	1797
2.1 Scope of the problem . . . . .	1773	9.4 Cholesterylester transfer protein inhibitors . . . . .	1797
2.2 Dyslipidaemias . . . . .	1773	9.5 Future perspectives . . . . .	1797
3. Total cardiovascular risk . . . . .	1774	10. Management of dyslipidaemias in different clinical settings . . . . .	1798
3.1 Total cardiovascular risk estimation . . . . .	1774	10.1 Familial dyslipidaemias . . . . .	1798
3.2 Risk levels . . . . .	1778	10.1.1 Familial combined hyperlipidaemia . . . . .	1798
4. Evaluation of laboratory lipid and apolipoprotein parameters . . . . .	1779	10.1.2 Familial hypercholesterolaemia . . . . .	1798
5. Treatment targets . . . . .	1783	10.1.3 Familial dysbetalipoproteinaemia . . . . .	1800
6. Lifestyle modifications to improve the plasma lipid profile . . . . .	1784	10.1.4 Familial lipoprotein lipase deficiency . . . . .	1800
6.1 The influence of lifestyle on total cholesterol and low-density lipoprotein-cholesterol levels . . . . .	1785	10.1.5 Other genetic disorders of lipoprotein metabolism . . . . .	1800
6.2 The influence of lifestyle on triglyceride levels . . . . .	1785	10.2 Children . . . . .	1801
6.3 The influence of lifestyle on high-density lipoprotein-cholesterol levels . . . . .	1786	10.3 Women . . . . .	1801
6.4 Dietary supplements and functional foods active on plasma lipid values . . . . .	1787	10.4 The elderly . . . . .	1802
6.5 Lifestyle recommendations . . . . .	1787	10.5 Metabolic syndrome and diabetes . . . . .	1803
7. Drugs for treatment of hypercholesterolaemia . . . . .	1789	10.6 Patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention . . . . .	1804
7.1 Statins . . . . .	1790	10.7 Heart failure and valvular disease . . . . .	1805
7.2 Bile acid sequestrants . . . . .	1791	10.8 Autoimmune diseases . . . . .	1805
7.3 Cholesterol absorption inhibitors . . . . .	1792	10.9 Renal disease . . . . .	1806
7.4 Nicotinic acid . . . . .	1792	10.10 Transplantation patients . . . . .	1807
7.5 Drug combinations . . . . .	1792	10.11 Peripheral arterial disease . . . . .	1808
7.5.1 Statins and bile acid sequestrants . . . . .	1792	10.12 Stroke . . . . .	1809
7.5.2 Statins and cholesterol absorption inhibitors . . . . .	1792	10.13 Human immunodeficiency virus patients . . . . .	1809
7.5.3 Other combinations . . . . .	1792	11. Monitoring of lipids and enzymes in patients on lipid-lowering drug therapy . . . . .	1810
7.6 Low-density lipoprotein apheresis . . . . .	1793	12. How to improve adherence to lifestyle changes and compliance with drug therapy . . . . .	1811
7.7 Future perspectives . . . . .	1793	13. References . . . . .	1812
8. Drugs for treatment of hypertriglyceridaemia . . . . .	1793		
8.1 Management of hypertriglyceridaemia . . . . .	1793	Addenda on the ESC website:	
8.2 Fibrates . . . . .	1794	Addendum I. SCORE charts with high-density lipoprotein-cholesterol	
8.3 Nicotinic acid . . . . .	1795	Addendum II. Practical approach to reach low-density lipoprotein-cholesterol goal	
8.4 <i>n</i> -3 fatty acids . . . . .	1795	Addendum III. Inhibitors and inducers of enzymatic pathways involved in statin metabolism	
8.5 Drug combinations . . . . .	1795	Addendum IV. Additional references	
8.5.1 Statins and fibrates . . . . .	1795		
8.5.2 Statins and nicotinic acid . . . . .	1796		
8.5.3 Statins and <i>n</i> -3 fatty acids . . . . .	1796		
9. Drugs affecting high-density lipoprotein . . . . .	1796		
9.1 Statins . . . . .	1797		

## Abbreviations and acronyms

4D	Die Deutsche Diabetes Dialyse Studie	FATS	Familial Atherosclerosis Treatment Study
4S	Scandinavian Simvastatin Survival Study	FCH	familial combined hyperlipidaemia
ABC-1	ATP-binding cassette transporter 1	FDA	Food and Drug Administration
ACCORD	Action to Control Cardiovascular Risk in Diabetes	FH	familial hypercholesterolaemia
ACS	acute coronary syndrome	FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
AIM-HIGH	Atherothrombosis Intervention in Metabolic syndrome with Low HDL-C/High Triglyceride and Impact on Global Health Outcomes	GFR	glomerular filtration rate
ALT	alanine aminotransferase	GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Effect of rosuvastatin in patients with chronic Heart Failure
apo (a)	apolipoprotein (a)	GISSI-P	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione
apo A1	apolipoprotein A1	GP	general practitioner
apo B	apolipoprotein B	GPR	G protein-coupled receptor
apo E	apolipoprotein E	HAART	highly active antiretroviral treatment
apo C	apolipoprotein C	HATS	HDL-Atherosclerosis Treatment Study
ARBITER-6	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis	Hb <sub>A1c</sub>	glycated haemoglobin
HALTS		HDL	high-density lipoprotein
ARMYDA	Atorvastatin for Reduction of Myocardial Damage During Angioplasty	HDL-C	high-density lipoprotein-cholesterol
ASSIGN	CV risk estimation model from the Scottish Intercollegiate Guidelines Network	HeFH	heterozygous familial hypercholesterolaemia
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events	HF	heart failure
BIP	Bezafibrate Infarction Prevention	HHS	Helsinki Heart Study
BMI	body mass index	HIV	human immunodeficiency virus
CABG	coronary artery bypass graft	HMG-CoA	hydroxymethylglutaryl coenzyme A
CAD	coronary artery disease	HoFH	homozygous familial hypercholesterolaemia
CARE	Cholesterol and Recurrent Events	HPS	Heart Protection Study
CETP	cholesterylester transfer protein	HPS2-THRIVE	Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events
CI	confidence interval	hs-CRP	high sensitivity C-reactive protein
CIMT	carotid intima-media thickness	HTG	hypertriglyceridaemia
CK	creatine phosphokinase	ICD	International Classification of Diseases
CKD	chronic kidney disease	IDL	intermediate-density lipoprotein
CORONA	COntrolled ROsuvastatin multiNAtional study in heart failure	ILLUMINATE	Investigation of Lipid Levels Management to Understand its Impact in Atherosclerotic Events
CPG	ESC Committee for Practice Guidelines	JUPITER	Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin Study
CTT	Cholesterol Treatment Trialists' Collaboration	LCAT	lecithin-cholesterol acyltransferase
CV	cardiovascular	LDL	low-density lipoprotein
CVD	cardiovascular disease	LDLR	low-density lipoprotein receptor
CYP	cytochrome P450 isoenzyme	LDL-C	low-density lipoprotein-cholesterol
Dal-OUTCOMES	Dalcetrapib Outcomes trial	Lp(a)	lipoprotein(a)
DALYs	disability-adjusted life years	LPL	lipoprotein lipase
DHA	docosahexaenoid acid	MetS	metabolic syndrome
DGAT-2	diacylglycerol acyltransferase-2	MI	myocardial infarction
EAS	European Atherosclerosis Society	MTP	microsomal transfer protein
EMA	European Medicines Agency	MUFA	monounsaturated fatty acid
EPA	eicosapentaenoic acid	NICE	National Institute for Health and Clinical Excellence
ER	extended release form	NNT	number needed to treat
ESC	European Society of Cardiology	Non-HDL-C	non-HDL-cholesterol
ESRD	end-stage renal disease	NYHA	New York Heart Association
		PAD	peripheral arterial disease
		PCI	percutaneous coronary intervention
		PCSK9	proprotein convertase subtilisin/Kexin 9

PPAR	peroxisome proliferator-activated receptor
PPP	Pravastatin Pooling Project
PROCAM	Prospective Cardiovascular Munster study
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PUFA	polyunsaturated fatty acid
RAAS system	renin–angiotensin–aldosterone system
RCT	randomized controlled trial
REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification
RRR	relative risk reduction
RYR	red yeast rice
SCORE	Systematic Coronary Risk Estimation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SFA	saturated fatty acids
SHARP	Study of Heart And Renal Protection
SLE	systemic lupus erythematosus
TC	total cholesterol
TG	triglyceride
TIA	transient ischaemic attack
TNT	Treating to New Targets Trial
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
USF 1	upstream transcription factor 1
VA-HIT	Veterans Affairs High-density lipoprotein Intervention Trial
VLDL	very low density lipoprotein
VLDL-C	very low density lipoprotein-cholesterol
WHO	World Health Organization

## Conversion factors

$$\text{mg/dL cholesterol} = \text{mmol/L} \times 38.6$$

$$\text{mg/dL triglycerides} = \text{mmol/L} \times 88.5$$

$$\text{mg/dL glucose} = \text{mmol/L} \times 18$$

## 1. Preamble

Guidelines summarize and evaluate all available evidence at the time of the writing process on a particular issue with the aim of assisting physicians 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 are not substitutes but are complements for textbooks and cover the ESC Core Curriculum topics. Guidelines and recommendations should help physicians to make decisions in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible physician(s).

A large number of Guidelines have been issued in recent years by the European Society of Cardiology (ESC) as well as by other societies and organizations. 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-surveys/esc-guidelines/about/Pages/rules-writing.aspx>). 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 to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a

**Table I** Classes of recommendations

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

**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.

comprehensive review of the published evidence for diagnosis, management, and/or prevention of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. 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 recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in Tables 1 and 2.

The experts of the writing and reviewing panels filled in declarations of interest forms of all relationships which 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 updated. The Task Force received its entire financial support from the ESC 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. After appropriate revisions, it is approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the *European Heart Journal*.

The task of developing Guidelines covers not only the 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 guidelines versions, summary slides, booklets with essential messages, and 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 the ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines,

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

The guidelines do not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patients, in consultation with that patient, and, where appropriate and necessary, the patient's guardian or carer. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

## 2. Introduction

### 2.1 Scope of the problem

Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and to thrombosis is the foremost cause of premature mortality and of disability-adjusted life years (DALYs) in Europe, and is also increasingly common in developing countries.<sup>1</sup> In the European Union, the economic cost of CVD represents annually ~€192 billion<sup>1</sup> in direct and indirect healthcare costs.

The main clinical entities are coronary artery disease (CAD), ischaemic stroke, and peripheral arterial disease (PAD).

The causes of these CVDs are multifactorial. Some of these factors relate to lifestyles, such as tobacco smoking, lack of physical activity, and dietary habits, and are thus modifiable. Other risk factors are also modifiable, such as elevated blood pressure, type 2 diabetes, and dyslipidaemias, or non-modifiable, such as age and male gender.

These guidelines deal with the management of dyslipidaemias as an essential and integral part of CVD prevention.

Prevention and treatment of dyslipidaemias should always be considered within the broader framework of CVD prevention, which is addressed in guidelines of the Joint European Societies' Task forces on CVD prevention in clinical practice.<sup>2–5</sup> The latest version of these guidelines was published in 2007<sup>5</sup>; an update will become available in 2012.

These Joint ESC/European Atherosclerosis Society (EAS) guidelines on the management of dyslipidaemias are complementary to the guidelines on CVD prevention in clinical practice and address not only physicians [e.g. general practitioners (GPs) and cardiologists] interested in CVD prevention, but also specialists from lipid clinics or metabolic units who are dealing with dyslipidaemias that are more difficult to classify and treat.

### 2.2 Dyslipidaemias

Lipid metabolism can be disturbed in different ways, leading to changes in plasma lipoprotein function and/or levels. This by itself and through interaction with other cardiovascular (CV) risk factors may affect the development of atherosclerosis.

Therefore, dyslipidaemias cover a broad spectrum of lipid abnormalities, some of which are of great importance in CVD prevention. Dyslipidaemias may be related to other diseases (secondary dyslipidaemias) or to the interaction between genetic predisposition and environmental factors.

Elevation of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) has received most attention, particularly because it can be modified by lifestyle changes and drug

therapies. The evidence showing that reducing TC and LDL-C can prevent CVD is strong and compelling, based on results from multiple randomized controlled trials (RCTs). TC and LDL-C levels continue therefore to constitute the primary targets of therapy.

Besides an elevation of TC and LDL-C levels, several other types of dyslipidaemias appear to predispose to premature CVD. A particular pattern, termed the atherogenic lipid triad, is more common than others, and consists of the co-existence of increased very low density lipoprotein (VLDL) remnants manifested as mildly elevated triglycerides (TG), increased small dense low-density lipoprotein (LDL) particles, and reduced high-density lipoprotein-cholesterol (HDL-C) levels. However, clinical trial evidence is limited on the effectiveness and safety of intervening in this pattern to reduce CVD risk; therefore, this pattern or its components must be regarded as optional targets of CVD prevention.

Dyslipidaemias may also have a different meaning in certain subgroups of patients which may relate to genetic predisposition and/or co-morbidities. This requires particular attention complementary to the management of the total CV risk.

### 3. Total cardiovascular risk

#### 3.1 Total cardiovascular risk estimation

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

##### *Rationale for 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, in most people, atherosclerotic CVD is the product of a number of risk factors. Many risk assessment systems are available, and have been comprehensively reviewed, including Framingham, SCORE (Systemic Coronary Risk Estimation), ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), Q-Risk, PROCAM (Prospective Cardiovascular Munster Study), and the WHO (World Health Organization).<sup>6,7</sup>

Most guidelines use risk estimation systems based on either the Framingham or the SCORE projects.<sup>8,9</sup>

In practice, most risk estimation systems perform rather similarly when applied to populations recognizably similar to that from which the risk estimation system was derived,<sup>6,7</sup> and can be re-calibrated for use in different populations.<sup>6</sup> The current joint European Guidelines on CVD prevention in clinical practice<sup>5</sup> recommend the use of the SCORE system because it is based on large, representative European cohort data sets.

Risk charts such as SCORE are intended to facilitate risk estimation in apparently healthy persons with no signs of clinical or pre-clinical disease. Patients who have had a clinical event such as an acute coronary syndrome (ACS) or stroke are at high risk of a further event and automatically qualify for intensive risk factor evaluation and management.

Thus, although refined later in this chapter, very simple principles of risk assessment can be defined as follows<sup>5</sup>:

##### (1) Those with

- known CVD
- type 2 diabetes or type 1 diabetes with microalbuminuria
- very high levels of individual risk factors
- chronic kidney disease (CKD)

are automatically at VERY HIGH or HIGH TOTAL CARDIOVASCULAR RISK and 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 because many people have several risk factors which, in combination, may result in unexpectedly high levels of total CV risk.

SCORE differs from earlier risk estimation systems in several important ways, and has been modified somewhat for the present guidelines.

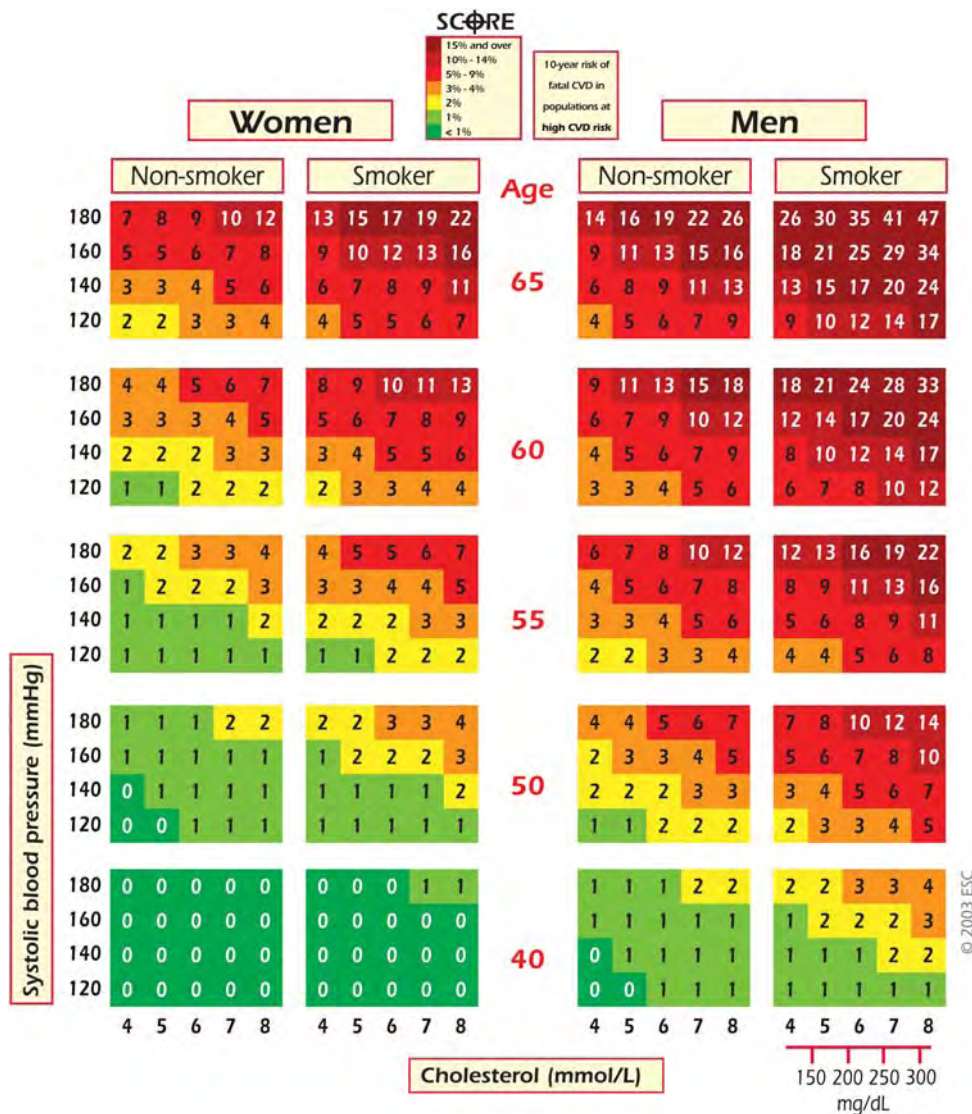
The SCORE system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe (see Figures 1 and 2). All International Classification of Diseases (ICD) codes that could reasonably be assumed to be atherosclerotic are included. Most other systems estimate CAD risk only.

The new nomenclature in the 2007 guideline<sup>5</sup> is that everyone with a 10 year risk of CV death of  $\geq 5\%$  has an increased risk. The reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that non-fatal events are dependent on definition, developments in diagnostic tests, and methods of ascertainment, all of which can vary, resulting in very variable multipliers to convert fatal to total events. In addition, total event charts, in contrast to those based on mortality, cannot easily be re-calibrated 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 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 plus non-fatal) hard CVD endpoints; the multiplier is slightly higher in women and lower in older persons.

Clinicians often ask for thresholds to trigger certain interventions, but this is problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated, and this is true for all continuous risk factors such as plasma cholesterol or systolic blood pressure. Therefore, the targets 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. Therefore, a relative risk chart has been added to the absolute risk charts to illustrate that, particularly in younger persons, lifestyle changes can reduce relative risk substantially as well as reducing the increase in absolute risk that will occur with ageing (Figure 3).

Another problem relates to old people. In some age categories the vast majority, especially of men, will have estimated CV death

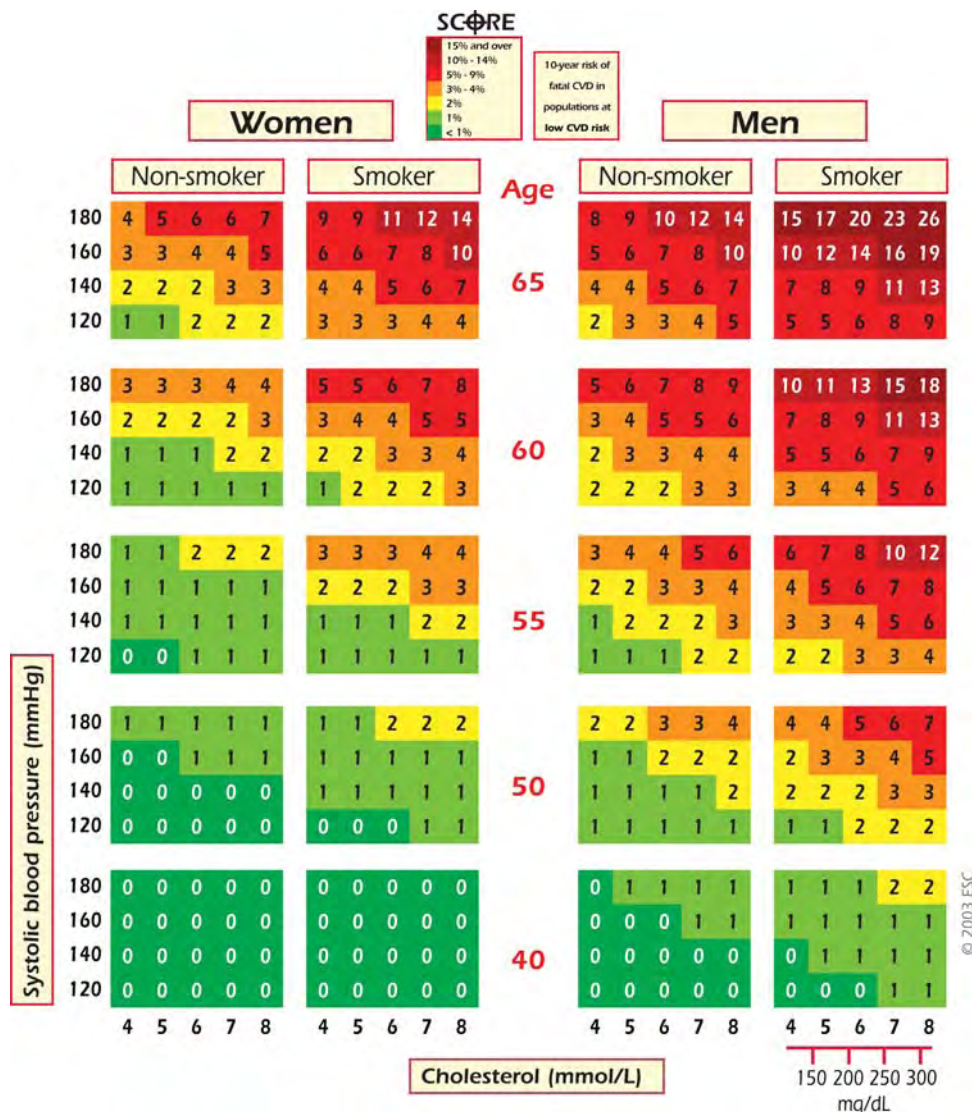


**Figure 1** SCORE chart: 10 year risk of fatal cardiovascular disease (CVD) in populations at **high CVD risk** based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply 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, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice.

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 usage of drugs in the elderly and should be evaluated carefully by the clinician.

Charts are presented for TC. However, subsequent work on the SCORE database<sup>10,11</sup> has shown that HDL-C can contribute substantially 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.<sup>10</sup> Furthermore, this effect is seen in both genders and in all age groups, including older women.<sup>11</sup> 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.<sup>10</sup> Charts including HDL-C are available as Addendum I to these guidelines on the ESC website ([www.escardio.org/guidelines](http://www.escardio.org/guidelines)). The additional impact of HDL-C on risk estimation is illustrated in Figures 4 and 5. The electronic version of SCORE, HeartScore, is being modified to take HDL-C into account, and we recommend its use by using the [www.heartscore.org](http://www.heartscore.org) in order to increase the accuracy of the risk evaluation. HeartScore will also include new data on body mass index (BMI).



**Figure 2** 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, or very high levels of individual risk factors because such people are already at high risk and need intensive risk factor advice.

The role of a raised plasma TG level as a predictor of CVD has been debated for many years. Fasting TG levels relate to risk in univariate analyses, but the effect is attenuated by adjustment for other factors, especially HDL-C. More recently, attention has focused on non-fasting TG, which may be more strongly related to risk independently of the effects of HDL-C.<sup>12</sup> Currently TG levels are not included in the risk charts. The effect of additional risk factors such as high sensitivity C-reactive protein (hs-CRP) and homocysteine levels was also considered. Their contribution to absolute CV risk estimations for individual patients (in addition to the older risk factors) is generally modest.

The impact of self-reported diabetes has been re-examined. The impact of diabetes on risk appears greater than in risk estimation

systems based on the Framingham cohort, with relative risks of ~5 in women and ~3 in men.

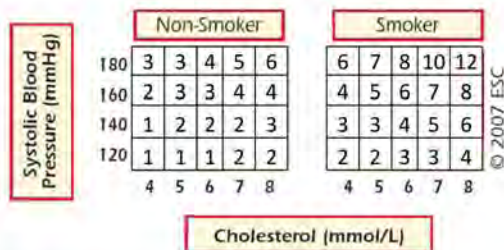
In Figures 1–5 the approximate (~) equivalent values for TC are:

mmol/L	~mg/dl
4	150
5	190
6	230
7	270
8	310



### Relative Risk Chart

This chart may be used to show younger people at low absolute risk that, relative to others in their age group, their risk may be many times higher than necessary. This may help to motivate decisions about avoidance of smoking, healthy nutrition and exercise, as well as flagging those who may become candidates for medication



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 risk that is 12 times higher than a person in the bottom left

Figure 3 Relative risk chart.

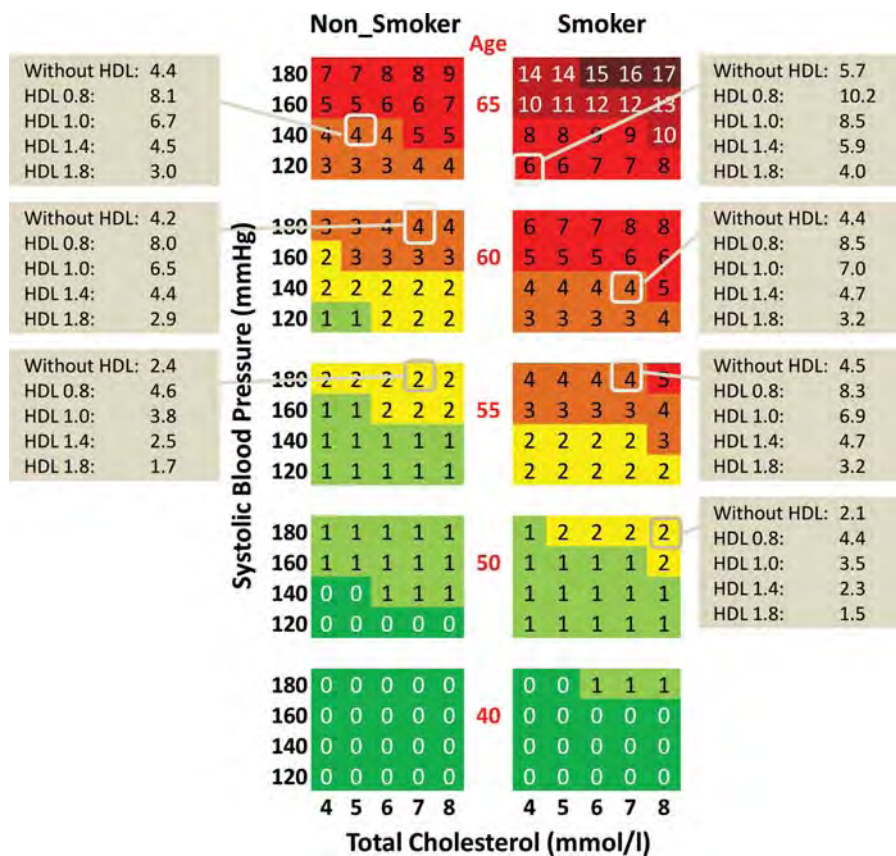


Figure 4 Risk function without high-density lipoprotein-cholesterol (HDL-C) for women in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.

### How to use the risk estimation charts

- The low risk charts should be considered for use in Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland and Portugal and also in countries which have recently experienced a substantial lowering of the CV mortality rates (see <http://www.ehnheart.org/> (CVD statistics) for recent mortality data). The high risk charts should be considered in all other countries of Europe. NOTE that several countries have undertaken national recalibrations to allow for time trends in mortality and risk factor distributions. Such charts are likely to represent current risk levels better.
- To estimate a person's 10 year risk of CVD death, find the table for their 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.
- 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.
- Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low. The relative risk chart (Figure 3) may be helpful in identifying and counselling such persons.
- 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 risk reduces and that the results of randomized controlled trials in general give better estimates of benefits. Those who stop smoking in general halve their risk.
- The presence of additional risk factors increases the risk (such as low HDL-C, high TG).

### Qualifiers

- The charts can assist in risk assessment and management but must be interpreted in the 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 falling CVD mortality, and underestimated in countries in which mortality is increasing.
- At any given age, risk estimates are lower for women than for men. This may be misleading since, eventually, at least as many women as men die of CVD. Inspection of the charts indicates that risk is merely deferred in women, with a 60-year-old woman resembling a 50-year-old man in terms of risk.

### Risk will also be higher than indicated in the charts in:

- Socially deprived individuals; deprivation drives many other risk factors.
- Sedentary subjects and those with central obesity; these characteristics determine many of the other aspects of risk listed below.
- Individuals with diabetes: re-analysis of the SCORE database indicates that those with known diabetes are at greatly increased risk; five times higher in women and three times higher in men.
- Individuals with low HDL-C or apolipoprotein A1 (apo A1), increased TG, fibrinogen, homocysteine, apolipoprotein B (apo B), and lipoprotein(a) [Lp(a)] levels, familial hypercholesterolaemia (FH), or increased hs-CRP; these factors indicate a higher level of risk in both genders, all age groups and at all levels of risk. As mentioned above, supplementary material (see Addendum I) illustrates the additional impact of HDL-C on risk estimation.
- Asymptomatic individuals with preclinical evidence of atherosclerosis, for example, the presence of plaques or increased carotid intima-media thickness (CIMT) on carotid ultrasonography.
- Those with impaired renal function.
- Those with a family history of premature CVD, which is considered to increase the risk by 1.7-fold in women and by 2.0-fold in men.
- Conversely, risk may be lower than indicated in those with very high HDL-C levels or a family history of longevity.

### 3.2 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.

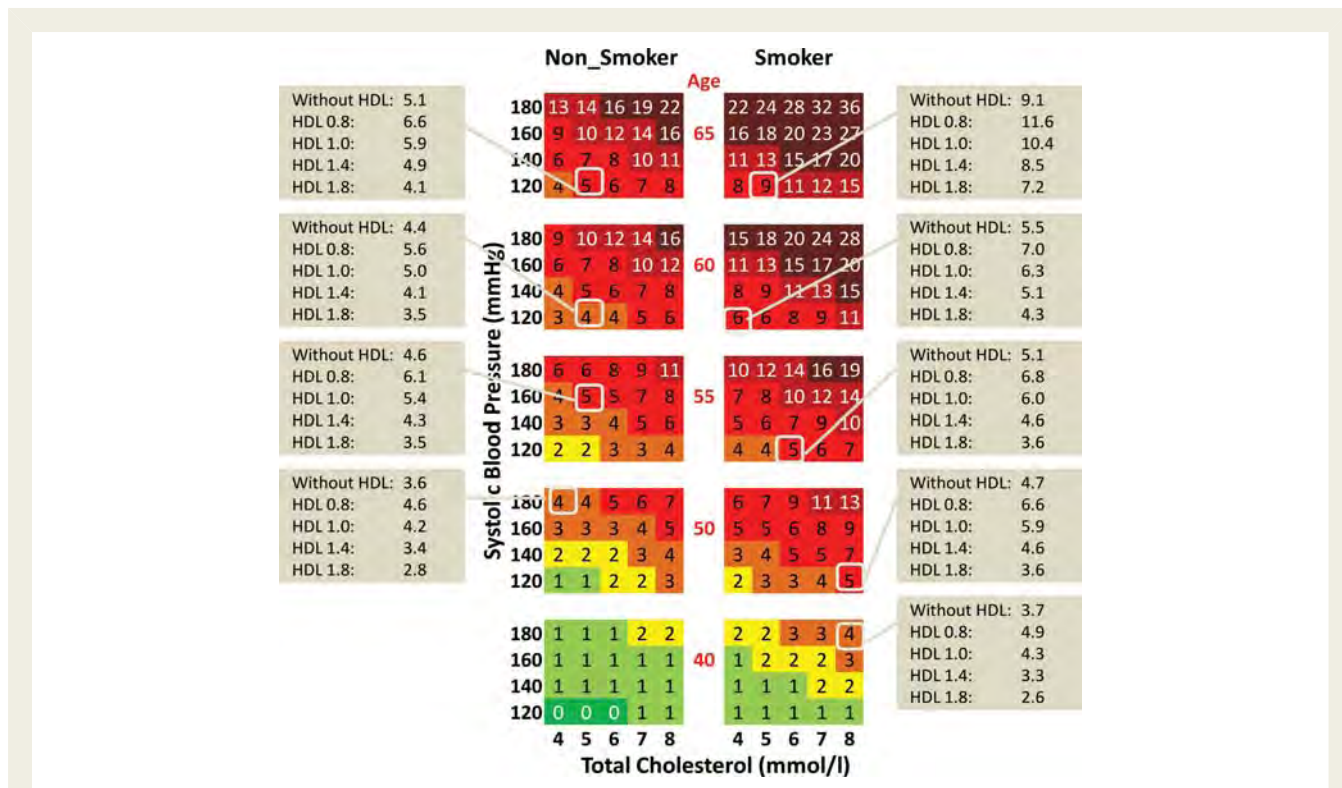
Not only should those at high risk be identified and managed; those at moderate risk should also receive professional advice regarding lifestyle changes, and in some cases drug therapy will be needed to control their plasma lipids.

In these subjects we should do all we realistically can to:

- 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.

With these considerations one can propose the following levels of total CV risk:



**Figure 5** 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.

**1. Very high risk**

Subjects with any of the following:

- Documented CVD by invasive or non-invasive testing (such as coronary angiography, nuclear imaging, stress echocardiography, carotid plaque on ultrasound), previous myocardial infarction (MI), ACS, coronary revascularization [percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)] and other arterial revascularization procedures, ischaemic stroke, PAD.
- Patients with type 2 diabetes, patients with type 1 diabetes with target organ damage (such as microalbuminuria).
- Patients with moderate to severe CKD [glomerular filtration rate (GFR) <60 mL/min/1.73 m<sup>2</sup>].
- A calculated 10 year risk SCORE ≥10%.

**2. High risk**

Subjects with any of the following:

- Markedly elevated single risk factors such as familial dyslipidaemias and severe hypertension.
- A calculated SCORE ≥5% and <10% for 10 year risk of fatal CVD.

**3. Moderate risk**

Subjects are considered to be at moderate risk when their SCORE is ≥1% and <5% at 10 years. Many middle-aged subjects belong to this risk category. This risk is further modulated by a family history of premature CAD, abdominal obesity, physical

activity pattern, HDL-C, TG, hs-CRP, Lp(a), fibrinogen, homocysteine, apo B, and social class.

**4. Low risk**

The low risk category applies to individuals with SCORE <1%.

In Table 3 different intervention strategies are presented as a function of the total CV risk and the LDL-C level.

*Risk intervention in older people.* The strongest driver of CVD risk is age, which may be regarded as ‘exposure time’ to risk factors. This raises the issue that Table 3 might suggest that most older men in high risk countries who smoke would be candidates for drug treatment, even if they have satisfactory blood pressure and lipid levels. To date, this is not supported by trial evidence, and the clinician is strongly recommended to use clinical judgement in making therapeutic decisions in older people, with a firm commitment to lifestyle measures such as smoking cessation in the first instance.

**4. Evaluation of laboratory lipid and apolipoprotein parameters**

Risk factor screening, including the lipid profile, may be considered in adult men ≥40 years of age, and in women ≥50 years of age or post-menopausal, particularly in the presence of other risk factors. In addition, all subjects with evidence of atherosclerosis in any vascular bed or with type 2 diabetes, irrespective of age, are regarded as being at high risk; it is recommended to assess their lipid profile. Individuals with a family history of premature CVD also deserve early screening. Several other medical conditions are associated

**Table 3** Intervention strategies as a function of total CV risk and LDL-C level

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.5 mmol/L	100 to <155 mg/dL 2.5 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	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled
Class <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	I/C	I/C	I/a/A
≥1 to <5	Lifestyle intervention	Lifestyle intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class <sup>a</sup> /Level <sup>b</sup>	I/C	I/C	I/a/A	I/a/A	I/A
>5 to <10, or high risk	Lifestyle intervention, consider drug*	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	I/a/A	I/a/A	I/a/A	I/A	I/A
≥10 or very high risk	Lifestyle intervention, consider drug*	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention	Lifestyle intervention and immediate drug intervention
Class <sup>a</sup> /Level <sup>b</sup>	I/a/A	I/a/A	I/A	I/A	I/A

\*In patients with MI, statin therapy should be considered irrespective of LDL-C levels.<sup>13,14</sup>

<sup>a</sup>Class of recommendation

<sup>b</sup>Level of evidence. References to level A: 15–41.

CV = cardiovascular; LDL-C = low-density lipoprotein-cholesterol; MI = myocardial infarction.

with premature CVD. Patients with arterial hypertension should be carefully assessed for concomitant metabolic disorders and dyslipidaemias. Patients with central obesity, as defined for Europeans by an increased waist circumference of ≥94 cm for men (90 cm for Asian males) and ≥80 cm for women, or with a BMI ≥25 kg/m<sup>2</sup> but <30 kg/m<sup>2</sup> (overweight), or ≥30 kg/m<sup>2</sup> (obesity), should also be screened—although one should recognize that the risk for CVD increases more rapidly as the BMI increases, becoming almost exponential from 27 kg/m<sup>2</sup> upwards.

Autoimmune chronic inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis are associated with increased CV risk. Patients with CKD (GFR <60 mL/min/1.73 m<sup>2</sup>) 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, should be sought because they may signal the presence of a severe lipoprotein disorder, especially FH, the most frequent monogenic disorder associated with premature CVD. Antiretroviral therapies may be associated with accelerated atherosclerosis. It is also indicated to screen for dyslipidaemias in patients with PAD or in the presence of increased CIMT or carotid plaques.

Finally, it is indicated to screen offspring of patients with severe dyslipidaemia [FH, familial combined hyperlipidaemia (FCH) or chylomicronaemia] 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.

The recommendations for lipid profiling in order to assess total CV risk are presented in Table 4.

The baseline lipid evaluation suggested is: TC, TG, HDL-C, and LDL-C, calculated with the Friedewald formula unless TG are elevated (>4.5 mmol/L or greater than ~400 mg/dL) or with a direct method, non-HDL-C and the TC/HDL-C ratio.

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

Alternatively apo B and the apo B/apo A1 ratio can be used, which have been found to be at least as good risk markers compared with traditional lipid parameters.<sup>42</sup>

For these analyses, most commercially available methods are well standardized. Methodological developments may cause shifts in values, especially in patients with highly abnormal lipid levels or in the presence of interacting proteins. Recent progression in dry chemistry has made possible analysis of lipids on site in clinical practice. Among such available methods, only certified and well standardized products should be used whenever possible.

#### Fasting or non-fasting?

If possible, blood sampling should be made after 12 h fasting, but this is requested only for the evaluation of TG, which is also

**Table 4 Recommendations for lipid profiling in order to assess total CV risk**

Condition	Class <sup>a</sup>	Level <sup>b</sup>
Lipid profiling is indicated in subjects with: Type 2 diabetes mellitus	I	C
Established CVD	I	C
Hypertension	I	C
Smoking	I	C
BMI $\geq 30$ kg/m <sup>2</sup> or waist circumference >94 cm (90 cm <sup>2</sup> ) for men, >80 cm for women	I	C
Family history of premature CVD	I	C
Chronic inflammatory disease	I	C
Chronic kidney disease	I	C
Family history of familial dyslipidaemia	I	C
Lipid profiling may be considered in men >40 and women >50 years of age	IIb	C

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

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

<sup>c</sup>For Asian males.

BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease.

needed for the calculation of LDL-C with the Friedewald formula. TC, apo B, apo A1, and HDL-C can be determined in non-fasting samples.<sup>43</sup> Fasting state is also essential if blood glucose is measured in screening programmes.

#### Intraindividual variation

There is considerable intraindividual variation in plasma lipids. For TC, a variation of 5–10% and for TG >20% has been reported, particularly in those with hypertriglyceridaemia (HTG). This variation 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.

#### 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 apo B, non-HDL-C, and various ratios, while sometimes logical, has not been proven. While their role is being established, traditional measures of risk such as TC and LDL-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 a statistically and clinically significant reduction in cardiovascular mortality. Therefore, TC and LDL-C remain the primary targets recommended in these guidelines.

#### Total cholesterol

In screening programmes, TC is recommended to be used to estimate total CV risk by means of the SCORE system. In the individual case, however, TC may be misleading. This is especially so in women who often have high HDL-C levels and in subjects with diabetes or the metabolic syndrome (MetS) who often have low HDL-C levels. For an adequate risk analysis, at least HDL-C and LDL-C should be analysed. Note that assessment of total risk does not include patients with familial hyperlipidaemia (including FH and FCH) or those with TC >8.0 mmol/L (~310 mg/dL). These patients are always at high risk and should receive special attention.

#### Low-density lipoprotein-cholesterol

In most clinical studies LDL-C has been calculated using Friedewald's formula (unless TG are elevated >4.5 mmol/L or more than ~400 mg/dL).

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, TG, and HDL-C.
- A constant cholesterol/TG ratio in VLDL is assumed. With high TG values (>4.5 mmol/L or more than ~400 mg/dL), the formula cannot be used.
- The use of Friedewald's formula is not indicated when blood is obtained under non-fasting conditions (class III C). Under these conditions, non-HDL-C may be determined.

Despite its limitations, the calculated LDL-C is still widely used. However, direct methods for determining LDL-C should be used whenever available.

A number of commercially available methods for direct determination of LDL-C have appeared. The modern generation of these methods have good reproducibility and specificity, and have the advantage that the analysis is made in one step and they are not sensitive to variations in TG levels to the same extent. Comparisons between calculated LDL-C and direct LDL-C show good agreement; considering the limitations of calculated LDL-C, direct LDL-C is recommended, although most trials have been performed with calculated LDL-C.

A large amount of data is the basis for the current recommendations, and internationally there is a good agreement between different target levels. Non-HDL-C or apo B may give a better estimate of the concentration of atherogenic particles, especially in high risk patients with diabetes or MetS.

#### Non-high-density lipoprotein-cholesterol

Non-HDL-C is used as an estimation of the total number of atherogenic particles in plasma [VLDL + intermediate-density lipoprotein (IDL) + LDL] and relates well to apo B levels. Non-HDL-C is easily calculated from TC minus HDL-C.

Non-HDL-C can provide a better risk estimation compared with LDL-C, in particular in HTG combined with diabetes, the MetS, or CKD. This is supported by a recent meta-analysis including 14 statin trials, seven fibrate trials, and six nicotinic acid trials.<sup>44</sup>

### High-density lipoprotein-cholesterol

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.

### Triglycerides

TG are determined by accurate and cheap enzymatic techniques. A very rare error is seen in patients with hyperglycerolaemia where falsely very high values for TG are obtained.

High TG are often associated with low HDL-C and high levels of small dense LDL particles.

Recently studies have been published suggesting that non-fasting TG may carry information regarding remnant lipoproteins associated with increased risk.<sup>12,45</sup> How this should be used in clinical practice is still debated.

### Apolipoproteins

From a technical point of view there are advantages in the determination of apo B and apo A1. Good immunochemical methods are available and easily run in conventional autoanalysers. The analytical performance is good. The assay does not require fasting conditions and is not sensitive to moderately high TG levels.

**Apolipoprotein B.** Apo B is the major apolipoprotein of the atherogenic lipoprotein families VLDL, IDL, and LDL. The concentration of apo B 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. Apo B has been shown in several prospective studies to be equal to LDL-C in risk prediction. Apo B has not been evaluated as a primary treatment target in statin trials, but several post-hoc analyses of statin trials suggest that apo B may be not only a risk marker but also a better treatment target than LDL-C.<sup>46</sup> The major disadvantages of apo B are that it is not included in algorithms for calculation of global risk, and it has not been a pre-defined treatment target in controlled trials. Recent data from a meta-analysis by the Emerging Risk Factor Collaboration<sup>42</sup> indicate that apo B does not provide any benefit beyond non-HDL-C or traditional lipid ratios. Likewise, apo B provided no benefit beyond traditional lipid markers in people with diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study.<sup>47</sup> In contrast, in another meta-analysis of LDL-C, non-HDL-C, and apo B, the latter was superior as a marker of CV risk.<sup>48</sup>

**Apolipoprotein A1.** Apo A1 is the major protein of HDL and provides a good estimate of HDL concentration. Each HDL particle may carry several apo A1 molecules. Plasma apo A1 of <120 mg/dL for men and <140 mg/dL for women approximately correspond 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

The different ratios give similar information. The ratio between apo B and apo A1 has been used in large prospective studies as an indicator of risk. Ratios between atherogenic lipoproteins and HDL-C (TC/HDL-C, non-HDL-C/HDL-C, apo B/apo A1) are useful for risk estimation, but for diagnosis and as treatment targets the components of the ratio have to be considered separately.

### Lipoprotein(a)

Lp(a) has been found in several studies to be an additional risk marker.<sup>49</sup> Lp(a) has properties in common with LDL but contains a unique protein, apolipoprotein (a) [apo(a)], which is structurally different from other apolipoproteins. 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 as well as use of size-insensitive assays. Lp(a) is generally expressed as total Lp(a) mass; however, it is recommended to express it as mmol/L (or mg/dL) of Lp(a) protein.<sup>50</sup> Plasma Lp(a) is not recommended for risk screening in the general population; however, **Lp(a) measurement should be considered in people with high CVD risk or a strong family history of premature atherothrombotic disease.**<sup>51</sup>

Table 5 lists the recommendations for lipid analyses for screening for CVD risk and Table 6 the recommendations for lipid analyses for characterization of dyslipidaemias; Table 7 gives the

**Table 5 Recommendations for lipid analyses for screening for CVD risk**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
TC is recommended 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 and risk estimation.	I	C
TG adds information on risk and is indicated for risk estimation.	I	C
HDL-C is a strong risk factor and is recommended to be used for risk estimation.	I	C
Non-HDL-C should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
Apo B should be considered as an alternative risk marker, especially in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	C
The ratio apo B/apo A1 combines the risk information of apo B and apo A1 and may be recommended as an alternative analysis for risk screening.	IIb	C
The ratio non-HDL-C/HDL-C may be recommended as an alternative analysis for risk screening.	IIb	C

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

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

Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

**Table 6** Recommendations for lipid analyses for characterization of dyslipidaemias before treatment

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
LDL-C is recommended to be used as the primary lipid analysis.	I	C
TG adds information to risk and is indicated for diagnosis and choice of treatment.	I	C
HDL-C is recommended to be analysed before initiation of treatment.	I	C
Non-HDL-C should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Apo B should be recommended for further characterization of combined hyperlipidaemias and dyslipidaemia in diabetes, the MetS or CKD.	IIa	C
Lp(a) should be recommended in selected cases at high risk and in subjects with a family history of premature CVD.	IIa	C
TC may be considered but is usually not enough for the characterization of dyslipidaemia before initiation of treatment.	IIb	C

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

recommendations for lipid analyses as treatment target in the prevention of CVD.

#### Lipoprotein particle size

Lipoproteins are heterogeneous classes of particles, and a lot of evidence suggests that the different subclasses of LDL and HDL may bear different risks for atherosclerosis.<sup>54</sup>

Determination of small dense LDL may be regarded as an emerging risk factor that may be used in the future<sup>54</sup> but is not currently recommended for risk estimation.<sup>55</sup>

#### Genotyping

Several genes have been associated with CVD. At present the use of genotyping for risk estimation is not recommended. However, studies suggest that in the future a panel of genotypes may be used for identification of high risk subjects.<sup>56</sup>

For the diagnosis of specific genetic hyperlipidaemias, genotyping of apolipoprotein E (apo E) and of genes associated with FH may be considered.

Apo E is present in three isoforms (apo E2, apo E3, and apo E4). Apo E genotyping is primarily used for the diagnosis of dysbetalipoproteinaemia (apo E2 homozygosity) and is indicated in cases with severe combined hyperlipidaemia.

**Table 7** Recommendations for lipid analyses as treatment target in the prevention of CVD

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
LDL-C is recommended as target for treatment.	I	A	15, 16, 17
TC should be considered as treatment target if other analyses are not available.	IIa	A	5, 15
TG should be analysed during the treatment of dyslipidaemias with high TG levels.	IIa	B	52
Non-HDL-C should be considered as a secondary target in combined hyperlipidaemias, diabetes, the MetS or CKD.	IIa	B	48
Apo B should be considered as a secondary treatment target.	IIa	B	48, 53
HDL-C is not recommended as a target for treatment.	III	C	-
The ratios apo B/apo A I and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	C	-

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.

Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; MetS = metabolic syndrome; TC = total cholesterol; TG = triglyceride.

Tools for genetic screening in families with FH are now available and should be used in specialized clinics.<sup>57</sup>

## 5. Treatment targets

Treatment targets of dyslipidaemia are primarily based on results from clinical trials. In nearly all lipid-lowering trials the LDL-C level has been used as an indicator of response to therapy. Therefore, **LDL-C remains the primary target of therapy in most strategies of dyslipidaemia management.**

**The most recent Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis of several trials involving >170 000 patients confirmed the dose-dependent reduction in CVD with LDL-C lowering.**<sup>15</sup>

The overall guidelines on CVD prevention in clinical practice strongly recommend modulating the intensity of the preventive intervention according to the level of the total CV risk. Therefore, the targets should be less demanding when the total CV risk decreases from very high to high or moderate.

Every 1.0 mmol/L (~40 mg/dL) reduction in LDL-C is associated with a corresponding 22% reduction in CVD mortality and morbidity.<sup>15</sup>

Extrapolating from the available data, an absolute reduction to an LDL-C level <1.8 mmol/L (less than ~70 mg/dL) or at least a 50% relative reduction in LDL-C provides the best benefit in terms of CVD reduction.<sup>15</sup> In the majority of patients, this is achievable with statin monotherapy. Therefore, for patients with very high CV risk, the treatment target for LDL-C is <1.8 mmol/L (less than ~70 mg/dL) or a ≥50% reduction from baseline LDL-C.

Target levels for subjects at high risk are extrapolated from several clinical trials.<sup>15</sup> An LDL-C level of <2.5 mmol/L (less than ~100 mg/dL) should be considered for them. Secondary targets of therapy in the high risk category are based on data extrapolation; therefore, clinical judgement is required before a final treatment plan is implemented. Clinicians again should exercise judgement to avoid premature or unnecessary implementation of lipid-lowering therapy. Lifestyle interventions will have an important long-term impact on health, and the long-term effects of pharmacotherapy must be weighed against potential side effects. For subjects at moderate risk, an LDL-C target of <3 mmol/L (less than ~115 mg/dL) should be considered.

#### Targets other than low-density lipoprotein-cholesterol

Because apo B levels have also been measured in outcome studies in parallel with LDL-C, apo B can be substituted for LDL-C. Based on the available evidence, apo B appears to be a risk factor at least as good as LDL-C and a better index of the adequacy of LDL-lowering therapy than LDL-C.<sup>46</sup> Also, there now appears to be less laboratory error in the determination of apo B than of LDL-C, particularly in patients with HTG. However, apo B is not presently being measured in all clinical laboratories. Clinicians who are using apo B in their practice can do so; the apo B treatment targets for subjects at very high or high total CV risk are <80 and <100 mg/dL, respectively.

The specific target for non-HDL-C should be 0.8 mmol/L (~30 mg/dL) higher than the corresponding LDL-C target; this corresponds to the LDL-C level augmented by the cholesterol fraction which is contained in 1.7 mmol/L (~150 mg/dL) of TG, which is the upper limit of what is recommended.

Adjusting lipid-lowering therapy to optimize one or more of the secondary and optional targets may be considered in patients at very high CV risk after achieving a target LDL-C (or apo B), but the clinical advantages of this approach, with respect to patient outcomes, remain to be addressed.

To date, no specific targets 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 lower than 1.8 mmol/L or ~70 mg/dL. However, clinical trial evidence is lacking on the effectiveness of intervening on these variables to reduce CV risk further, and thus they must be regarded as secondary and optional. The hypothesis of a specific target for hs-CRP in secondary prevention is based on results from pre-determined analyses of the Pravastatin Or Atorvastatin

**Table 8** Recommendations for treatment targets for LDL-C

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
In patients at VERY HIGH CV risk (established CVD, type 2 diabetes, type 1 diabetes with target organ damage, moderate to severe CKD or a SCORE level ≥10%) the LDL-C goal is <1.8 mmol/L (less than ~70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached.	I	A	15, 32, 33
In patients at HIGH CV risk (markedly elevated single risk factors, a SCORE level ≥5 to <10%) an LDL-C goal <2.5 mmol/L (less than ~100 mg/dL) should be considered.	IIa	A	15, 16, 17
In subjects at MODERATE risk (SCORE level >1 to ≤5%) an LDL-C goal <3.0 mmol/L (less than ~115 mg/dL) should be considered.	IIa	C	-

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

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

<sup>c</sup>References.

CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol.

Evaluation and Infection Therapy (PROVE-IT) and the A-to-Z trials<sup>58</sup> and from the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial,<sup>59</sup> which showed that patients who have reached both an LDL-C level <2.0 mmol/L (less than ~80 mg/dL) and an hs-CRP level <2.0 mg/L had the lowest CVD event rate. Presently, hs-CRP as a secondary target of therapy is not recommended for everybody; based on available data, however, it may be useful in people close to the high risk category to better stratify their total CV risk. Clinicians should use clinical judgement when considering further treatment intensification in secondary prevention or in high risk primary prevention.

Table 8 lists the recommendations for treatment targets for LDL-C.

If non-HDL-C is used, the targets should be <2.6 mmol/L (less than ~100 mg/dL) and <3.3 mmol/L (less than ~130 mg/dL) in those at very high and high total CV risk, respectively (class IIa B<sup>46</sup>).

If apo B is available, the targets are <80 mg/dL and <100 mg/dL in those at very high and high total CV risk, respectively (class IIa B<sup>46</sup>).

## 6. Lifestyle modifications to improve the plasma lipid profile

The role of nutrition in the prevention of CVD has been extensively reviewed.<sup>60–62</sup> There is strong evidence showing that



dietary factors may influence atherogenesis directly or through effects on traditional risk factors such as lipid levels, blood pressure, or glucose levels.

Results from RCTs relating dietary pattern to CVD have been reviewed.<sup>60</sup> Some interventions resulted in significant CVD prevention, whereas others did not. Most evidence linking nutrition to CVD is based on observational studies and on investigations of the effects of dietary changes on lipid levels. In this section, the influence of lifestyle changes and of functional foods on lipoproteins is considered and summarized in *Table 9*.

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

Dietary saturated fatty acids (SFAs) are the dietary factor with the strongest 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).<sup>63</sup>

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 in western countries is between 2 and 5% of the total energy intake. Quantitatively, dietary trans fatty acids have a similar raising effect on LDL-C to that of SFAs.<sup>64</sup>

If 1% of the dietary energy derived from SFAs is replaced by monounsaturated fatty acids (MUFAs), LDL-C decreases by 0.041 mmol/L (1.6 mg/dL); if replaced by *n*-6 polyunsaturated fatty acids (PUFAs) the decrease would be 0.051 mmol/L (2.0 mg/dL); and if replaced by carbohydrate it would be 0.032 mmol/L (1.2 mg/dL).<sup>63</sup> PUFAs of the *n*-3 series have no direct hypocholesterolaemic effect; however, habitual fish consumption is associated with a reduced CV risk that is mostly independent of any effect on plasma lipids. When consumed in pharmacological doses (>2 g/day) the effect of *n*-3 PUFAs on LDL-C levels is either neutral or a slight increase with a concomitant decrease of TG.<sup>63</sup> A positive relationship exists between dietary cholesterol and CAD mortality, which is partly independent of TC levels. Several experimental studies on humans have evaluated the effects of dietary cholesterol on cholesterol absorption and lipid metabolism and have revealed marked variability among individuals.<sup>66,82</sup> Dietary carbohydrate is ‘neutral’ on LDL-C; therefore, carbohydrate-rich foods represent one of the possible options to replace saturated fat in the diet.<sup>83</sup> Dietary fibre (particularly of the soluble type), which is present in legumes, fruit, vegetables, and wholemeal cereals, has a direct hypocholesterolaemic effect.<sup>65</sup> Therefore, carbohydrate foods rich in fibres represent an optimal dietary substitute for saturated fat to maximize the effects of the diet on LDL-C levels and to minimize possible untoward effects of a high carbohydrate diet on other lipoproteins.<sup>65</sup>

Body weight reduction also influences TC and LDL-C, but the magnitude of the effect is rather small; in grossly obese subjects

a drop in LDL-C concentration of ~0.2 mmol/L (~8 mg/dL) is observed for every 10 kg of weight loss. Even smaller is the reduction of LDL-C levels induced by regular physical exercise.<sup>68,70</sup>

In *Table 9* dietary recommendations to lower TC and LDL-C are summarized; given the cultural diversity of diets in Europe, these recommendations should be translated into practical cooking recipes, taking into account local habits and socioeconomic factors.

## 6.2 The influence of lifestyle on triglyceride levels

A high monounsaturated fat diet significantly improves insulin sensitivity compared with a high saturated fat diet.<sup>84</sup> This goes in parallel with a reduction in TG levels, particularly in the post-prandial period.

Another dietary effect on TG is observed 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.<sup>84</sup>

In people with severe HTG with chylomicrons present, also 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 TG that avoid the formation of chylomicrons may be considered since they are directly transported and metabolized in the liver.

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. The greater and more rapid this perturbation is, 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 TG occur mainly when carbohydrate-rich foods with a high glycaemic index/low fibre content are consumed, while they are much less prominent if the diet is based largely on fibre-rich, low glycaemic index foods.<sup>85</sup>

The beneficial effects on plasma lipid metabolism induced by low glycaemic index/high fibre foods cannot be automatically extrapolated to foods in which fructose (a sugar with a low glycaemic index) represents the major source of carbohydrates. In contrast, dietary fructose contributes to TG elevations; these effects are dose dependent and become clinically relevant when the intake is >10% energy daily—with a habitual fructose consumption between 15 and 20% of the 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.<sup>76</sup>

Weight reduction improves insulin sensitivity and decreases TG levels. In many studies the reduction of TG levels due to weight reduction is between 20 and 30%; this effect is usually preserved as long as weight is not regained.<sup>70</sup>

Alcohol intake has a major negative impact on TG levels. While in individuals with HTG even a small amount of alcohol can induce

**Table 9** Impact of specific lifestyle changes on lipid levels

	Magnitude of the effect	Level of evidence	References
<b>Lifestyle interventions to reduce TC and LDL-C levels</b>			
Reduce dietary saturated fat	+++	A	63
Reduce dietary trans fat	+++	A	64
Increase dietary fibre	++	A	65
Reduce dietary cholesterol	++	B	66
Utilize functional foods enriched with phytosterols	+++	A	67
Reduce excessive body weight	+	B	68
Utilize soy protein products	+	B	69
Increase habitual physical activity	+	A	70
Utilize red yeast rice supplements	+	B	71, 72
Utilize polycosanols supplements	-	B	73
<b>Lifestyle interventions to reduce TG levels</b>			
Reduce excessive body weight	+++	A	68
Reduce alcohol intake	+++	A	74
Reduce intake of mono- and disaccharides	+++	A	75, 76
Increase habitual physical activity	++	A	77
Reduce total amount of dietary carbohydrate	++	A	78
Utilize supplements of <i>n-3</i> polyunsaturated fat	++	A	79
Replace saturated fat with mono- or polyunsaturated fat	+	B	63
<b>Lifestyle interventions to increase HDL-C levels</b>			
Reduce dietary trans fat	+++	A	64
Increase habitual physical activity	+++	A	77
Reduce excessive body weight	++	A	68
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A	78
Use alcohol with moderation	++	B	80
Among carbohydrate-rich foods prefer those with low glycaemic index and high fibre content	+	C	-
Quit smoking	+	B	81
Reduce intake of mono- and disaccharides	+	C	-

+++ = general agreement on the effects on lipid levels.

++ = less pronounced effects on lipid levels; weight of evidence/opinion is in favour of efficacy.

+ = conflicting evidence; efficacy is less well established by evidence/opinion.

- = not effective and/or uncertainties regarding safety.

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride.

a further elevation of TG concentrations, in the general population alcohol exerts detrimental effects on TG levels only if the intake exceeds what is considered a moderate consumption (up to 1–2 drinks/day corresponding to 10–30 g/day).<sup>74</sup>

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

SFAs increase HDL-C levels in parallel with LDL-C; in contrast, trans fatty acids reduce the former and increase the latter.

MUFA consumption as a replacement for SFAs has a small or no effect on HDL-C; *n*-6 PUFAs induce a slight decrease. In general, *n*-3 fatty acids have limited (<5%) effect on HDL-C levels.<sup>63,86</sup>

Increased carbohydrate consumption, as isocaloric substitution for fat, is associated with a significant decrease in HDL-C (0.1 mmol/L or ~4 mg/dL for every 10% energy substitution). However, when the carbohydrate-rich foods have a low glycaemic index and a high fibre content, the reduction of HDL-C is either not observed or is very small.<sup>63,87</sup> Usually a high fructose/sucrose intake is associated with a more pronounced decrease of HDL-C.

Moderate ethanol consumption (up to 20–30 g/day in men and 10–20 g/day in women) is associated with increased HDL-C levels as compared with abstainers.<sup>86</sup>

Weight reduction has a beneficial influence on HDL-C levels: a 0.01 mmol/L (~0.4 mg/dL) increase is observed for every kg decrease in body weight when weight reduction has stabilized. Aerobic physical activity corresponding to a total energy expenditure of between 1500 and 2200 kcal/week, such as ~25–30 km of brisk walking per week (or any equivalent activity) may increase HDL-C levels by 0.08–0.15 mmol/L (3.1–6 mg/dL).<sup>77</sup> Smoking cessation may also contribute to HDL-C elevation.<sup>5,81</sup>

## 6.4 Dietary supplements and functional foods active on plasma lipid values

Innovative nutritional strategies to improve dyslipidaemias have been developed; they are based either on changing some 'risky' dietary components or on encouraging the consumption of specifically targeted 'healthy' functional foods and/or dietary supplements; these so-called 'nutriceuticals' can be used either as alternatives or in addition to lipid-lowering drugs.<sup>69</sup>

Nutritional evaluation of functional foods includes not only the search for the 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.<sup>88</sup>

Overall, the available evidence on functional foods so far identified in this field is lacking; 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.

### Phytosterols

The principal phytosterols are sitosterol, campesterol, and stigmasterol, and 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, thus 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. The daily consumption of 2 g of phytosterols can effectively lower TC and LDL-C by 7–10% in humans, with little or no effect

on HDL-C and TG levels when consumed with the main meal.<sup>67</sup> Currently there are no data available indicating that cholesterol lowering through plant sterol ingestion results in prevention of CVD. 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 diet rich in these nutrients.<sup>89</sup>

### Soy protein

Soy protein has a modest LDL-C-lowering effect. Soy foods can be used as a plant protein substitute for animal protein foods high in SFAs, but expected LDL-C lowering may be modest (3–5%) and most likely in subjects with hypercholesterolaemia.<sup>90</sup>

### Dietary fibre

Available evidence consistently demonstrates a TC- and LDL-C-lowering effect of water-soluble fibre from oat bran,  $\beta$ -glucan, and psyllium. Foods enriched with these fibres are well tolerated, effective, and recommended for LDL-C lowering at a daily dose of 5–15 g/day soluble fibre.<sup>91</sup>

### *n*-3 unsaturated fatty acids

Supplementation with 2–3 g/day of fish oil (rich in long chain *n*-3 fatty acids) can reduce TG levels by 25–30% in both normolipidaemic and hyperlipidaemic individuals.  $\alpha$ -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. Long chain *n*-3 PUFAs, at doses of ~3 g/day given as supplements, may increase LDL-C by ~5% in severely hypertriglyceridaemic patients.<sup>85</sup> However, a low dose supplementation of a margarine with *n*-3 PUFAs (400 mg/day) or  $\alpha$ -linolenic acid (2 g/day) did not significantly reduce TG levels in an RCT involving 4837 post-MI patients; neither did this supplementation reduce the rate of major CV events.<sup>92</sup>

### Policosanol and red yeast rice

Policosanol is a natural mixture of long chain aliphatic alcohols extracted primarily from sugarcane wax.<sup>93</sup> Studies show that policosanol from sugarcane, rice, or wheat germ has no significant effect on LDL-C, HDL-C, TG, apo B, Lp(a), homocysteine, hs-CRP, fibrinogen, or blood coagulation factors.<sup>94</sup>

'Red yeast rice' (RYR) is a source of fermented pigment used in China as a food colourant and flavour enhancer for centuries. Possible bioactive effects of RYR are related to a statin-like mechanism [inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase]. Different commercial preparations of RYR have different concentrations of monacolins, the bioactive ingredients, and lower TC and LDL-C,<sup>71</sup> but the long-term safety of the regular consumption of these products is not fully documented. In one RCT from China in patients with CAD, a partially purified extract of RYR reduced recurrent events by 45%.<sup>72</sup>

## 6.5 Lifestyle recommendations

### Body weight and physical activity

Since overweight, obesity, and central obesity often contribute to dyslipidaemia, caloric intake should be reduced and energy

**Table 10** Definition of central obesity

	Waist circumference
Caucasians (Europids)	Men $\geq 94$ cm; women $\geq 80$ cm
South Asians, Chinese, Japanese	Men $\geq 90$ cm; women $\geq 80$ cm
Ethnic South and Central Americans	Use South Asian recommendations 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

expenditure increased in those with excessive weight and/or abdominal adiposity. Overweight is defined as a BMI  $\geq 25$  to  $< 30$  kg/m<sup>2</sup> and obesity as a BMI  $\geq 30$  kg/m<sup>2</sup>. Criteria for central obesity as defined by the International Diabetes Federation are given in Table 10.<sup>95</sup> 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. 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 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.<sup>5</sup> Modest weight reduction and regular physical exercise of moderate intensity is very effective in preventing type 2 diabetes and improving all the metabolic abnormalities and the CV risk factors clustering with insulin resistance, often associated with abdominal adiposity. Physical activity should be encouraged, aiming at regular physical exercise for at least 30 min/day every day.

#### Dietary fat

The recommended total fat intake is between 25 and 35% of calories for adults.<sup>96,97</sup> For most individuals, a wide range of intakes is acceptable and will depend upon individual preferences and characteristics. Fat intakes that exceed 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.<sup>5</sup>

The type of fat intake should predominantly come from sources of MUFAs and both *n*-6 and *n*-3 PUFAs. To improve plasma lipid levels, saturated fat intake should be lower than 10% of the total caloric intake. The optimal intake of SFAs should be further reduced ( $< 7\%$  of energy) in the presence of hypercholesterolaemia. 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.<sup>5</sup>

Observational evidence supports the recommendation that intake of fish and *n*-3 fatty acids from plant sources ( $\alpha$ -linolenic

acid) may reduce the risk of CV death and stroke but has no major effects on plasma lipoprotein metabolism. Supplementation with pharmacological doses of *n*-3 fatty acids ( $> 2\text{--}3$  g/day) reduces TG levels, but a higher dosage may increase LDL-C; not enough data are available to make a recommendation regarding the optimal *n*-3/*n*-6 fatty acid ratio.<sup>98</sup>

The cholesterol intake in the diet should ideally be  $< 300$  mg/day.

Limited consumption of foods made with processed sources of trans fats provides the most effective means of reducing intake of trans fats below 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.

#### Dietary carbohydrate and fibre

Carbohydrate intake may range between 45 and 55% of total energy. Consumption of vegetables, legumes, fruits, nuts, and wholegrain cereals should be particularly encouraged, together with all the other foods rich in dietary fibre 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 a very low carbohydrate diet.

Intake of sugars should not exceed 10% of total energy (in addition to the amount present in natural foods such as fruit and dairy products); more restrictive advice concerning sugars may be useful for those needing to lose weight or with high plasma TG values. Soft drinks should be used with moderation by the general population and should be drastically limited in those individuals with elevated TG values.

#### Alcohol and smoking

Moderate alcohol consumption (up to 20–30 g/day for men and 10–20 g/day for women) is acceptable for those who drink alcoholic beverages, provided that TG levels are not elevated. Smoking cessation has clear benefits on the overall CV risk and specifically on HDL-C.<sup>5</sup>

#### Dietary supplements and functional foods

There are many functional foods and dietary supplements that are currently promoted as beneficial for people with dyslipidaemia or for reducing the risk of CVD. Some of these products have been shown to have potentially relevant functional effects but have not been tested in long-term clinical trials, and should therefore be utilized only when the available evidence clearly supports their beneficial effects on plasma lipid values and their safety. Based on the available evidence, foods enriched with phytosterols (1–2 g/day) may be considered for individuals with elevated TC and LDL-C values in whom the total CV risk assessment does not justify the use of cholesterol-lowering drugs.<sup>99</sup>

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

The diet should be varied and rich in fruit and vegetables of different types to obtain a sufficient amount and variety of antioxidants.

**Table 11** Dietary recommendations to lower TC and LDL-C

	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		Vegetables prepared in butter or cream
Legumes	All (including soy and soy protein)		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, fructose, glucose, chocolate, candies	Cakes, ice creams
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	Skimmed milk and yogurt, egg white	Low fat milk, low fat cheese and other milk products	Regular cheese, cream, egg yolk, whole milk and yoghurt
Cooking fat and dressings	Vinegar, ketchup, mustard, fat-free dressings	Vegetable oils, soft margarines, salad dressing, mayonnaise	Butter, solid margarines, trans fats, palm and coconut oils; lard, bacon fat, dressings made with egg yolks
Nuts/seeds		All	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

LDL-C = LDL-cholesterol; TC = total cholesterol.

At least two or three portions of fish per week are recommended to the general population for the prevention of CVD, together with regular consumption of other food sources of n-3 PUFAs (nuts, soy, and flaxseed oil); for secondary prevention of CVD, the recommended amount of n-3 unsaturated fat should be 1 g/day, which is not easy to derive exclusively from natural food sources, and use of nutraceuticals and/or pharmacological supplements may be considered. Salt intake should be limited to <5 g/day, not only by reducing the amount of salt used for food seasoning but also by reducing the consumption of foods preserved by the addition of salt; this recommendation should be more stringent in people with hypertension or MetS.<sup>5</sup> Dietary recommendations to lower TC and LDL-C are summarized in Table 11. Table 12 summarizes 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.

## 7. Drugs for treatment of hypercholesterolaemia

Cholesterol levels are determined by multiple genetic factors as well as environmental factors, primarily dietary habits. Hypercholesterolaemia can also be secondary to other medical conditions.

Secondary dyslipidaemia can have different causes; the possibility of secondary hypercholesterolaemia (Table 13) should be

**Table 12** 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 fruit, vegetables, legumes, nuts, wholegrain cereals and bread, fish (especially oily) should be encouraged.
- Saturated fat should be replaced with the above foods and with monounsaturated and polyunsaturated fats from vegetable sources, in order to reduce energy intake from total fat to <35% of energy, saturated fat to <7% of total energy, trans fats to <1% of total energy, and dietary cholesterol to <300 mg/day.
- Salt intake should be reduced below 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 (<10–20 g/day for women and <20–30 g/day for men) and patients with hypertriglyceridaemia (HTG) should abstain.
- The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, particularly for patients with HTG.
- Physical activity should be encouraged, aiming at regular physical exercise for at least 30 minutes/day every day.
- Use and exposure to tobacco products should be avoided.

**Table 13** Examples of causes of secondary hypercholesterolaemia

• Hypothyroidism
• Nephrotic syndrome
• Pregnancy
• Cushing syndrome
• Anorexia nervosa
• Immunosuppressant agents
• Corticosteroids

considered before initiating therapy. As an example, mild hypothyroidism is rather frequent and associated with cholesterol elevation; the latter will be solved once thyroid function is normalized.

## 7.1 Statins

### Mechanism of action

Statins reduce synthesis of cholesterol in the liver by competitively inhibiting HMG-CoA reductase activity. The reduction in intracellular cholesterol concentration induces low-density lipoprotein receptor (LDLR) expression on the hepatocyte cell surface, which results in increased extraction of LDL-C from the blood and a decreased concentration of circulating LDL-C and other apo B-containing lipoproteins including TG-rich particles.

### Efficacy in clinical studies

Statins are among the most studied drugs in CV prevention, and dealing with single studies is beyond the scope of the present guidelines.

A number of large-scale clinical trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and secondary prevention.<sup>15–17</sup> Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis.<sup>18–40</sup>

### Meta-analyses

In the CTT meta-analyses of individual participant data from >170 000 participants in 26 randomized trials of statins,<sup>15</sup> 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 is reported. The risk for major coronary events was reduced by 23% and the risk for stroke was reduced by 17% per mmol/L (40 mg/dL) LDL-C reduction. The proportional reductions in major CV event rates per mmol/L (mg/dL) LDL-C reduction were very similar in all of the subgroups examined. The benefits were significant within the first year, but were greater in subsequent years. There was no increased risk for any specific non-CV cause of death, including cancer, in those receiving statins. The excess risk of rhabdomyolysis with statins was small and not significant. Information on episodes of increased liver enzymes was not examined in this meta-analysis. Other

meta-analyses<sup>16,17,41</sup> addressed the issue of primary prevention, with results regarding efficacy and safety that are, in general, consistent with the conclusions from the CTT.<sup>15</sup> Regarding cost-effectiveness and quality of life, caution is still needed in prescribing statins for primary prevention among people at low total CV risk.<sup>41</sup>

At maximal recommended doses the different statins differ in their LDL-C-lowering capacity.

Current available evidence 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 degree of LDL-C reduction that is required to reach the target LDL-C in a given patient.<sup>15,100</sup> More details on this are provided in Addendum II to these guidelines.

The following scheme is proposed:

- Evaluate the total CV risk of the subject
- Involve the patient with decisions on CV risk management
- Identify the LDL-C target for that risk level
- Calculate the percentage reduction of LDL-C required to achieve that goal
- Choose a statin that, on average, can provide this reduction
- Since the response to statin treatment is variable, up-titration to reach target is mandatory
- If the statin cannot reach the goal, consider drug combinations.

Of course these will be only general criteria for the choice of drug. The clinical conditions of the subjects, concomitant treatments, and drug tolerability will play a major role in determining the final choice of drug and dose.

### Side effects and interactions

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 statin treatment has beneficial effects in the prevention of CVD, interindividual variation exists in response to statin therapy, as well as in the incidence of adverse effects.

### Muscle

Statins are generally well tolerated, and serious adverse events are rare. Over 129 000 patients have been systematically studied in controlled trials with blinded randomized assignment to statin vs. placebo treatment groups.<sup>15</sup> Factors such as advanced age, small body size, female gender, renal and hepatic dysfunction, perioperative periods, hypothyroidism, multisystem disease, and alcohol abuse increase the likelihood of side effects with statins.

The most serious adverse effect associated with statin therapy is myopathy, which may progress to rhabdomyolysis, and that, in turn, can lead to renal failure and death. Creatine phosphokinase (CK) elevation has become the primary marker for ongoing muscle cell death and destruction. The myoglobin release from these cells can directly damage the kidneys. An elevation of CK is the best indicator, although not unequivocal, of statin-induced

myopathy. The common definition of a tolerable elevation has been a rise of five times the upper limit of normal (ULN) of this enzyme measured on two occasions. How statins injure skeletal muscle is not clear. **The incidence of myopathy is low (<1/1000 patients treated) and the excess risk in comparison with placebo-treated patients has been <1/10 000 patients treated in clinical trials.**

Myopathy is most likely to occur in persons with complex medical problems and/or who are taking multiple medications, or in elderly persons, especially women. Myalgia (without CK elevation) occurs in 5–10% of patients in clinical practice. Patients should be instructed on promptly reporting unexpected muscle pain or weakness. However, patients complaining of myalgia without elevated CK levels can continue the medication if their symptoms are tolerable. If the symptoms are not tolerable or are progressive, the drug should be stopped. The possibility of re-challenge to verify the cause of the pain should be discussed with the patient, as well as dose reduction, drug substitution, and/or drug combinations. Potent drugs such as atorvastatin and rosuvastatin can often be used on intermittent days to reduce side effects.

#### Liver

The activity of alanine aminotransferase (ALT) and aspartate aminotransferase in blood plasma is commonly used by clinicians to assess hepatocellular damage. These measures have been monitored in all significant statin trials. **Elevated hepatic transaminases occur in 0.5–2.0% of statin-treated patients and are dose dependent.** The common definition of a meaningful elevation has been a rise of three times the ULN of these enzymes on two occasions, usually measured within a short interval of days to a few weeks. Whether transaminase elevation with statins constitutes true hepatotoxicity has not been determined. Progression to liver failure is exceedingly rare. Reversal of transaminase elevation is frequently noted with reduction of dose; thus, a patient who develops increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality returns to normal. Should an increase in transaminase levels of >3 times the ULN or greater persist, therapy should be discontinued.

#### Type 2 diabetes

The recent finding that the incidence of diabetes may increase with statins should not discourage institution of treatment; **the absolute reduction in the risk of CVD in high risk patients outweighs the possible adverse effects of a very small increase in the incidence of diabetes.**<sup>101</sup>

#### Other effects

Results from observational studies have suggested other unintended benefits and adverse effects related to statin therapy<sup>102,103</sup> such as multiple sclerosis, Alzheimer disease, and respiratory diseases. These results need confirmation, preferably in RCTs, and emphasize the need for long-term pharmaco-surveillance.

#### Interactions

A number of important drug interactions with statins have been described that may increase the risk of side effects. Inhibitors and inducers of enzymatic pathways involved in statin metabolism are summarized in a table in Addendum III of these guidelines. All currently available statins, except pravastatin, rosuvastatin, and pitavastatin, undergo major hepatic metabolism via the CYPs. These isoenzymes are mainly expressed in 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 CYP3A4, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 are also 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.

**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.**<sup>104,105</sup> **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.**<sup>106,107</sup>

## 7.2 Bile acid sequestrants

### Mechanism of action

Bile acids are synthesized in the liver from cholesterol. The bile acids 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 colesevelam has been introduced into the market. 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 acid 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 up-regulation 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; however, the mechanism behind this reduction is not completely clear.

### Efficacy in clinical studies

At the top dose of 24 g of cholestyramine, 20 g of colestipol, or 4.5 g of cholestagel, a reduction in LDL-C of 18–25% has been observed. No major effect on HDL-C has been reported, while TG may increase in some predisposed patients.

In clinical trials, bile acid sequestrants have contributed greatly to the original 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.<sup>108</sup>

### Side effects and interactions

**Gastrointestinal adverse effects** (most commonly flatulence, constipation, dyspepsia and nausea) are often present with these drugs even at low doses, which limit their practical use. These side 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 TG in certain patients.

Bile acid sequestrants have important 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**. **The drug reduces LDL-C and also improves glycated haemoglobin (Hb<sub>A1C</sub>) in patients with type 2 diabetes.**<sup>109,110</sup> **Colesevelam has fewer interactions with other drugs and can be taken together with statins.** For other drugs, however, the same general rules for administration as for other sequestrants should be applied.

## 7.3 Cholesterol absorption inhibitors

### 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 (most probably by interacting with the NPC1L1 protein), ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by up-regulating LDLR, which in turn leads to increased clearance of LDL from the blood.

### 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**<sup>38</sup> **and in patients with CKD in the Study of Heart and Renal Protection (SHARP) (see Sections 7.5.2 and 10.9).** **In the SHARP study a reduction of 17% in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.**<sup>111</sup>

Ezetimibe can be used as second-line therapy in association with statins when the therapeutic target is not achieved at maximal tolerated statin dose or in patients intolerant of statins or with contraindications to these drugs.

### Side effects and interactions

Ezetimibe is rapidly absorbed and extensively metabolized to the 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 side effects have been reported; the most frequent side effects are moderate elevations of liver enzymes, and muscle pain.

## 7.4 Nicotinic acid

Nicotinic acid has broad lipid-modulating action, raising HDL-C in a dose-dependent manner by ~25%, and reducing both LDL-C by 15–18% and TG 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. It is therefore primarily used in subjects with low HDL-C levels as typical of mixed hyperlipidaemia, HTG, or in FCH, but may also be used in subjects with insulin resistance (type 2 diabetes and MetS). Nicotinic acid may be used in combination with statins (see also Sections 8.3 and 8.5.2).<sup>112</sup>

## 7.5 Drug combinations

Although the target levels of LDL-C are reached with monotherapy in many patients, a 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.<sup>113</sup>

### 7.5.1 Statins and bile acid sequestrants

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 further by 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.<sup>113–115</sup>

### 7.5.2 Statins and cholesterol absorption inhibitors

**Combining ezetimibe with a statin reduces LDL-C by an additional 15–20%.**<sup>116</sup> The results of the SEAS study in patients with asymptomatic aortic stenosis showed that ezetimibe and simvastatin applied concomitantly reduce the incidence of ischaemic CVD events (up to 46% in the patients with less severe aortic stenosis) but not events related to aortic valve stenosis.<sup>38</sup> Recently the data of the SHARP trial were presented with positive results in CKD patients (see Section 10.9).<sup>111</sup>

### 7.5.3 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. Adding **ezetimibe to nicotinic acid** further reduces LDL-C and does not affect nicotinic acid-induced HDL-C increase. **Also triple therapy (bile acid sequestrant, statin, and ezetimibe or nicotinic acid)** will further reduce LDL-C. Clinical outcome studies with these combinations have not been performed.

Functional food 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<sup>67</sup> (see also Section 6.4). However, it is still not known whether this could reduce the risk of CVD since no trials with plant sterols in combination with other lipid-lowering drugs are available for CVD outcomes.

## 7.6 Low-density lipoprotein apheresis

Rare patients with severe hyperlipidaemias, especially homozygous and severe heterozygous FH, require specialist evaluation and consideration of the need for LDL apheresis. By this expensive but effective technique, LDL and Lp(a) are removed from plasma during extracorporeal circulation weekly or every other week. Clearly this is a procedure that is only performed in highly specialized centres.

## 7.7 Future perspectives

Recently a number of promising new drugs have reached phase III in clinical trials and have been reported to lower LDL-C effectively in severe hypercholesterolaemias, including microsomal transfer protein (MTP) inhibitors,<sup>117</sup> thyroid hormone mimetics with liver selectivity,<sup>118</sup> and oligonucleotides such as mipomersen that specifically suppress apo B.<sup>119</sup> All these approaches may further help in achieving therapeutic targets in people with severe or familial forms of hyperlipidaemia, especially FH patients.

Recommendations for the pharmacological treatment of hypercholesterolaemia are shown in Table 14.

## 8. Drugs for treatment of hypertriglyceridaemia

### Triglycerides and cardiovascular disease risk

Although the role of TG as a risk factor for CVD has been strongly debated, recent data strongly favour the role of TG-rich lipoproteins as a risk factor for CVD.<sup>121</sup> Recent large prospective studies reported that non-fasting TG predict CHD risk more strongly than fasting TG.<sup>12,45</sup> Whether the impact of high TG levels on CVD risk is explained by the burden of remnant particles, small dense LDL particles or associated low HDL remains unsettled.<sup>121</sup> Recently, non-HDL-C has turned out to be a good surrogate marker of TG and remnants.<sup>42</sup> The burden of HTG as a CVD risk factor is highlighted by the fact that about one-third of adult individuals have TG >1.7 mmol/L (more than ~150 mg/dL).<sup>122</sup> HTG can have different causes (Table 15).

### 8.1 Management of hypertriglyceridaemia

#### Action to prevent acute pancreatitis

One of the major clinical risks of dramatically elevated TG is acute pancreatitis. The risk of pancreatitis is clinically significant if TG exceed 10 mmol/L (more than ~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 between 5 and 10 mmol/L (~440–880 mg/dL).

**Table 14** Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Prescribe statin up to the highest recommended dose, or highest tolerable dose to reach the target level.	I	A	15, 16, 17
In the case of statin intolerance, bile acid sequestrants or nicotinic acid should be considered.	IIa	B	108, 120
A cholesterol absorption inhibitor, alone or in combination with bile acid sequestrants or nicotinic acid, may also be considered in the case of statin intolerance.	IIb	C	-
If target level is not reached, statin combination with a cholesterol absorption inhibitor or bile acid sequestrant or nicotinic acid may be considered.	IIb	C	-

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

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

<sup>c</sup>References.

Admit the patient to the hospital if symptomatic or secure a careful and close follow-up of the patient's TG values. Restriction of calories and fat content (10–15% recommended) of the diet and alcohol abstinence are obligatory. Initiate fibrate therapy (fenofibrate) with *n*-3 fatty acids (2–4 g/day) as adjunct therapy or nicotinic acid. In patients with diabetes, initiate insulin therapy to achieve a good glycaemic control. In general a sharp decrease of TG values is seen within 2–5 days. In the acute setting apheresis is able to lower TG levels rapidly.<sup>123</sup>

#### Strategies to control plasma triglycerides

Even though the role of TG as a risk factor of CVD remains uncertain, a level of fasting TG <1.7 mmol/L or less than ~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 will be to achieve the LDL-C target 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.

#### Lifestyle management

The influence of lifestyle management on TG levels is well documented. Weight reduction together with a regular physical activity programme of moderate intensity can reduce TG between 20 and 30%, and should be mandatory for all patients with obesity, MetS, or type 2 diabetes.

**Table 15** Possible causes of HTG

• Genetic predisposition
• Obesity
• Type 2 diabetes
• Alcohol consumption
• Diet high in simple carbohydrates
• Renal disease
• Hypothyroidism
• Pregnancy (physiological TG concentrations double during the third trimester)
• Autoimmune disorders, such as a paraproteinemia or SLE
• Multiple medications, including
> Corticosteroids
> Oestrogens, especially those taken orally
> Tamoxifen
> Antihypertensives: e.g. $\beta$ -adrenergic blocking agents (except carvedilol), thiazides
> Isotretinoin
> Bile acid-binding resins
> Ciclosporin
> Antiretroviral regimens (protease inhibitors)
> Psychotropic medications: phenothiazines, second-generation antipsychotics

HTG = hypertriglyceridaemia; SLE = systemic lupus erythematosus, TG = triglyceride.

### Pharmacological therapy

Although the CVD risk is increased if fasting TG are  $>1.7$  mmol/L (more than  $\sim 150$  mg/dL),<sup>121</sup> the use of drugs to lower TG should only be considered in subjects with TG  $>2.3$  mmol/L (more than  $\sim 200$  mg/dL) who cannot lower them by lifestyle measures, and if the subject is at high total CV risk.

The available pharmacological interventions include statins, fibrates, nicotinic acid, and *n-3* PUFAs. As statins have significant effects on mortality as well as most CVD outcome parameters, these drugs are the first choice to 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 TG.

## 8.2 Fibrates

### Mechanism of action

Fibrates are agonists of peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. By interacting with PPAR- $\alpha$ , 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 TG and triglyceride-rich lipoprotein (TRL) remnant particles. The HDL-C-raising effects of fibrates are modest.<sup>112</sup>

### Efficacy in clinical trials

The clinical benefits of fibrates in monotherapy are primarily illustrated by four prospective, randomized, placebo-controlled, clinical trials: Helsinki Heart Study (HHS), Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT), Bezafibrate Infarction Prevention study (BIP), and FIELD.<sup>124–127</sup> The data from these trials have shown consistent decreases in the rates of non-fatal MI (although often as a result of post-hoc analyses), the effect being most robust in subjects with elevated TG/low HDL-C levels. However, the data on other outcome parameters have remained equivocal. Thus, the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Recent meta-analyses reported that fibrate therapy reduced major CVD events by 13% [95% confidence interval (CI) 7–19], the benefits being most robust in patients with elevated TG levels ( $>2.3$  mmol/L or more than  $\sim 200$  mg/dl).<sup>52</sup>

### Side effects and interactions

Fibrates are generally well tolerated with mild side effects, gastrointestinal disturbance being reported in  $\sim 5\%$  of the patients and skin rashes in 2%.<sup>128</sup> In general, myopathy, liver enzyme elevations, and cholelithiasis represent the most well known safety issues associated with fibrate therapy.<sup>128</sup> In the FIELD study, small but significant increases in the incidence of pancreatitis (0.8% vs. 0.5%) and of 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.<sup>127</sup>

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.<sup>127</sup> The risk of myopathy has been reported to be 5.5-fold greater with fibrate use as a monotherapy compared with statin use.<sup>128</sup> 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 that 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 the combination therapy.<sup>128</sup>

As a class, fibrates have been reported to raise both serum creatinine and homocysteine in both short-term and long-term studies, but the effect seems to be fibrate specific. Whether the increase of serum creatinine reflects kidney dysfunction or not is a matter of ongoing debate, but clearly an annual monitoring of creatinine levels particularly in people with type 2 diabetes is necessary.

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 apo A1, and this may contribute to the smaller than estimated benefits of fenofibrate in the outcome parameters.<sup>129</sup> High homocysteine also promotes thrombosis, and this may explain the increased trend to deep vein

thrombosis and the increase in pulmonary embolism seen in the FIELD study.

### 8.3 Nicotinic acid

#### 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 effects 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 is reported to inhibit diacylglycerol acyltransferase-2 (DGAT-2) that results in the decreased secretion of VLDL particles from the liver, which is also reflected in reductions of both IDL and LDL particles.<sup>130</sup> Nicotinic acid raises HDL-C and apo A1 primarily by stimulating apo A1 production in the liver.<sup>130</sup> The effects of nicotinic acid on lipolysis and fatty acid mobilization in adipocytes are well established.

#### Efficacy in clinical trials

Nicotinic acid has multiple beneficial effects on serum lipids and lipoprotein.<sup>130</sup> Nicotinic acid reduces effectively not only TG but also LDL-C, reflecting its effect on all apo B-containing proteins. Nicotinic acid increases apo A1-containing lipoproteins, reflected in increases of HDL-C and apo A1. Nicotinic acid is currently used mostly as an extended release (ER) form. At the daily dose of 2 g it reduces TG by ~20–40% and LDL-C by 15–18%, and increases HDL-C by ~15–35%.<sup>130</sup> Currently available outcome data for nicotinic acid from randomized clinical trials are still limited.<sup>120,131</sup> The favourable effect on angiographic measures has been reported in the Familial Atherosclerosis Treatment Study (FATS) and in the HDL-Atherosclerosis Treatment Study (HATS).<sup>132</sup> In statin-treated patients with low HDL-C, high dose, modified release nicotinic acid, compared with placebo, significantly reduced carotid wall area, quantified by magnetic resonance imaging after 1 year.<sup>133</sup> Two large ongoing trials (the AIM-HIGH and the HPS2-THRIVE) using, respectively, 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) will provide additional data on the effects of nicotinic acid on CVD risk in combination with statin therapy.

In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6: HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER-6 HALTS) trial with 315 patients, ER nicotinic acid was shown to be more effective than ezetimibe at reducing CIMT on a background of statin therapy in patients with LDL-C <2.5 mmol/L (less than ~100 mg/dL).<sup>134</sup>

#### Side effects and interactions

In clinical practice, skin reactions (flushing) are the most frequent and troublesome side effect of nicotinic acid and its derivatives, often preventing titration of the dose to maximal efficacy, even using aspirin as a modulator of flushing. Other side effects of nicotinic acid include hyperuricaemia, liver toxicity, and acanthosis nigricans. Recently, specific receptors [G protein-coupled receptor (GPR) 109A and GPR 109B] for nicotinic acid were discovered in adipocytes. Interestingly, the presence of these receptor in macrophages in the skin seems to be the link to the most robust side effect of nicotinic acid, the flushing phenomenon associated with

itching and tingling. The mediator is prostaglandin D2 released from arachidonic acid. Laropiprant is a selective antagonist of prostaglandin D2 action at the receptor level. A nicotinic acid/laropiprant combination has been approved by the European Medicines Agency (EMA) for clinical use. A recent survey revealed that <15% of new users of ER nicotinic acid were still using the drug after 1 year. The recently introduced association with laropiprant might help in reducing the incidence of this side effect. Elevation of liver enzymes in users of ER nicotinic acid is less common (<1%) than with previous nicotinic acid compounds. The issue that nicotinic acid may interfere with glycaemic control by increasing blood glucose levels is of concern in treating people with diabetes. In clinical practice, the titration of glucose-lowering medication can be utilized to overcome these unfavourable effects.

### 8.4 n-3 fatty acids

#### Mechanism of action

n-3 fatty acids [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] are components of fish oil and the Mediterranean diet, and have been used to lower TG. n-3 fatty acids at pharmacological doses (>2 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 apo B.

#### Efficacy in clinical trials

Fish oil reduces TG by ~30%, but the effects on other lipoproteins are trivial in their magnitude. More detailed data on clinical outcomes are needed to justify the use of prescription n-3 fatty acids.<sup>135</sup> The recommended doses of total EPA and DHA to lower TG have varied between 2 and 4 g/day. The Food and Drug Administration (FDA) has approved the use of n-3 fatty acids (prescription products) as an adjunct to the diet if TG exceed 5.6 mmol/L (496 mg/dL). The average reduction of TG is ~30% and the benefit seems to be dose dependent, being ~45% in subjects with baseline TG values >5.6 mmol/L (496 mg/dL).<sup>135</sup> Although a recent Japanese study in patients with hypercholesterolaemia reported a 19% reduction in CVD outcome,<sup>136</sup> the data remain inconclusive<sup>137</sup> and their clinical efficacy appears to be related to non-lipid effects.<sup>138</sup>

#### 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.

### 8.5 Drug combinations

#### 8.5.1 Statins and fibrates

Clinical trials have shown that the combination of a statin and a fibrate, particularly fenofibrate, bezafibrate, or ciprofibrate, results in a significantly stronger reduction in LDL-C and TG as well as a greater elevation of HDL-C than monotherapy with either.<sup>139</sup> Since both fibrate and statin monotherapy are associated with an increased risk of myopathy, the risk could be increased when these drugs are taken together, particularly if the doses of statin are very high. However, the risk is 15-fold higher if

gemfibrozil is used than if fenofibrate is co-administered with any of five commonly used statins.<sup>140</sup> Therefore, it seems that this is most probably not a class effect of fibrates but rather a problem only with gemfibrozil. Based upon data from many trials, fibrates, particularly fenofibrate due to its lower myopathic potential, can be prescribed concomitantly with statins to improve achievement of lipid goals in patients with atherogenic combined dyslipidaemia, especially patients with MetS and/or diabetes. Patients should still be instructed about warning symptoms (myalgia), but since such adverse effects are very rare they should not be the reason to deny the combined treatment to patients who really need it. This combination should be prescribed with caution to patients who are also receiving other drugs metabolized through cytochrome P450. Fibrates should preferably be taken in the morning and statins in the evening to minimize peak dose concentrations. Avoidance of adding gemfibrozil to a statin regimen is advised.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,<sup>141</sup> in patients with type 2 diabetes the combination therapy of fenofibrate with simvastatin did not reduce the rates of CVD as compared with simvastatin alone when all the patients were analysed together. However, patients who had both TG levels in the higher third ( $\geq 2.3$  mmol/L or  $\geq 204$  mg/dL) and an HDL-C level below the lower third ( $\leq 0.88$  mmol/L or  $\leq 34$  mg/dL)—representing 17% of all participants—appeared to benefit from the combination therapy. These results are similar to those from post-hoc analyses performed in the HHS,<sup>124</sup> BIP,<sup>126</sup> and FIELD studies.<sup>127</sup> Therefore, these results from ACCORD and from previous trials suggest that the addition of fenofibrate to a statin may benefit certain patients with type 2 diabetes with a high TG/low HDL-C dyslipidaemic pattern.

### 8.5.2 Statins and nicotinic acid

The combination of ER nicotinic acid with moderate doses of a statin provides a significantly better increase in HDL-C and decrease in TG than either a high dose of a statin or the combination of a statin and ezetimibe.<sup>142</sup> Patients taking concomitant statin therapy, mostly simvastatin or atorvastatin, with nicotinic acid report a similar incidence of all-cause adverse events, and the incidence of flushing is similar in patients with and without statin treatment. Triple combination therapy with nicotinic acid, simvastatin, and ezetimibe showed a stronger lowering of LDL-C and a stronger increase in HDL-C than with either drug alone or with statin/ezetimibe treatment.<sup>143</sup> Several studies have shown that the combination of nicotinic acid and colestipol causes a higher frequency of absolute regression of atherosclerotic lesions than colestipol alone.<sup>144</sup> The HATS study showed not only a small regression of angiographically measured coronary plaques due to combined nicotinic acid and statin treatment as compared with progression observed on placebo, but also 90% lower risk of CV events, although in a very small number of patients.<sup>145</sup>

### 8.5.3 Statins and n-3 fatty acids

Treatment with a combination of 4 g/day n-3 fatty acids and simvastatin caused a stronger reduction of TG concentrations and a small but significant increase in HDL-C when compared with statin alone.<sup>146</sup> Adding n-3 fatty acids to pravastatin and fenofibrate in a triple combination further decreased TG concentrations and homocysteine as well in patients with diabetic dyslipidaemia. No

**Table 16 Recommendations for drug treatment of HTG**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
In particular high risk patients (see above), lowering of HTG by using the following drugs:			
is recommended: fibrates	I	B	127
should be considered: nicotinic acid	IIa	B	131
nicotinic acid + laropiprant	IIa	C	-
n-3 fatty acids	IIa	B	135, 136
statin + nicotinic acid <sup>d</sup>	IIa	A	142, 145
statin + fibrate <sup>d</sup>	IIa	C	-
may be considered: combinations with n-3 fatty acids <sup>e</sup>	IIb	B	146

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

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

<sup>c</sup>References.

<sup>d</sup>Evidence for additional lipid-lowering, compared with monotherapy.

<sup>e</sup>The evidence for prevention of CVD using combination therapy is in general limited.

CVD = cardiovascular disease; HTG = hypertriglyceridaemia.

significant interactions of any drug with n-3 fatty acids have been described. In one study EPA combined with low dose pravastatin or simvastatin compared with statin therapy alone reduced major coronary events without altering rates of sudden cardiac death.<sup>136</sup> However, since these effects were achieved without any significant changes in TC, LDL-C, or HDL-C, and just a small decrease in TG, EPA may lower CAD risk by mechanisms other than LDL-C lowering. In a subgroup analysis, such a combined treatment also reduced the incidence of CAD events in high risk patients with MetS and therefore a high TG/low HDL-C dyslipidaemic pattern.<sup>147</sup>

Recommendations for the drug treatment of HTG are shown in Table 16.

## 9. Drugs affecting high-density lipoprotein

### High-density lipoprotein and cardiovascular disease risk

Low levels of HDL-C constitute a strong, independent, and inverse predictor of the risk of premature development of atherosclerosis and CVD.<sup>11</sup> Moreover, the decrease in CV risk relative to HDL-C levels is especially dramatic over the range of HDL-C from  $\sim 0.65$  to 1.17 mmol/L (25–45 mg/dL).<sup>148</sup> Elevation of  $\geq 7.5\%$  in HDL-C, together with a reduction in LDL-C to a target of  $< 2.0$  mmol/L (less than  $\sim 80$  mg/dL), represented the minimum requirement

for plaque regression in a meta-analysis of four intervention trials, which involved use of intravascular ultrasound to evaluate changes in coronary atheroma volume.<sup>149</sup>

Low plasma concentrations of HDL-C are frequently a characteristic of type 2 diabetes as well as mixed or combined dyslipidaemia, renal and hepatic insufficiency states, and autoimmune diseases. 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 raising of HDL-C may lead to beneficial reduction 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 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.<sup>150</sup>

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 target levels should be set. However, there is until now no clear direct evidence that raising HDL-C really results in CVD prevention. This is being tested in the Dalcetrapib Outcomes (dal-OUTCOMES), HPS2-THRIVE (nicotinic acid plus statin), AIM-HIGH (nicotinic acid on background statin), and Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) trials.

### 9.1 Statins

Statins produce modest elevations in HDL-C. In the recent meta-analysis<sup>146</sup> of several intervention studies in dyslipidaemic patients, elevations in HDL-C varied with dose among the respective statins; such elevations were typically limited to the range of 5–10%.

As a result of the marked reductions in atherogenic apo B-containing lipoproteins by statins, it is difficult to assess the extent to which the smaller 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.<sup>151</sup>

### 9.2 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<sup>127,141</sup>; such differences appear to reflect distinctions in their relative binding affinities for PPARs and notably for PPAR- $\alpha$ .<sup>152</sup>

### 9.3 Nicotinic acid

Nicotinic acid appears to increase HDL-C by partially reducing HDL catabolism and mainly by increasing apo A1 synthesis by the liver. The latter effect is regarded as the most relevant for the HDL functions.<sup>112</sup>

Efficacy in clinical trials and side effects and drug interactions have been described in Section 8.3.

### 9.4 Cholesteryl ester transfer protein inhibitors

To date, the most efficacious pharmacological approach to elevation of low HDL-C levels has involved direct inhibition of cholesteryl ester transfer protein (CETP) by small molecule inhibitors, which may induce an increase in HDL-C by  $\geq 100\%$  on a dose-dependent basis. Among 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 Levels Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial.<sup>153</sup>

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). Development of dalcetrapib and anacetrapib is ongoing, and the Dal-OUTCOMES trial has recently been launched; this trial is a safety and outcomes trial of dalcetrapib in ACS patients. A phase III trial (REVEAL) with anacetrapib will start in 2011.

### 9.5 Future perspectives

Major developments in the search for efficacious agents to raise HDL-C and apo A1 with concomitant benefit on atherosclerosis and CV events are on the horizon. Among them, major interest is focused on apo A1 mimetic peptides which are not only active in cellular cholesterol efflux, but may also exert anti-inflammatory effects.

**Table 17 Recommendations if drug treatment of low HDL-C is considered**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Nicotinic acid is currently the most efficient drug to raise HDL-C and should be considered.	<b>IIa</b>	<b>A</b>	112
Statins and fibrates raise HDL-C with similar magnitude and these drugs may be considered.	<b>IIb</b>	<b>B</b>	141, 151
The efficacy of fibrates to increase HDL-C may be attenuated in people with type 2 diabetes.	<b>IIb</b>	<b>B</b>	127, 141

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

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

<sup>c</sup>References.

HDL-C = high-density lipoprotein-cholesterol.

**Table 18 Summary of the efficacy of drug combinations for the management of mixed dyslipidaemias**

- In combined dyslipidaemia an increase of HDL-C and a decrease of TG, on top of the LDL-C reduction that can be achieved with a statin, may be considered. Therefore a combination of statin with nicotinic acid can be considered, but the adverse effect of flushing may affect compliance.
- 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.

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglyceride.

Table 17 lists the recommendations when considering drug treatment of low HDL-C.

Table 18 summarizes the efficacy of drug combinations in the management of mixed dyslipidaemias.

## 10. Management of dyslipidaemias in different clinical settings

### 10.1 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, and among those FH is most common and strongly related to CVD. 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 which, on its own, might have relatively little effect, but in combination with another or others has a greater influence on TC, TG, or HDL-C. This pattern of inheritance is called polygenic. It is very common to find that high LDL-C, high TG, or low HDL-C affect several family members.

#### 10.1.1 Familial combined hyperlipidaemia

FCH is a highly prevalent genetic dyslipidaemia (1:100) and an important cause of premature CAD. FCH is characterized by elevated levels of LDL-C, TG, or both. The phenotype varies even among members from 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 (TG, LDL-C, HDL-C, and apo B). Therefore, the diagnosis is commonly missed in clinical practice; the combination of apo B >120 mg/dL + TG >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.<sup>154</sup> Currently research is ongoing to define genetic markers; 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 raised LDL-C levels are riskier when HTG is also present. Statin treatment has been shown to decrease 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.

#### 10.1.2 Familial hypercholesterolaemia

Heterozygous familial hypercholesterolaemia (HeFH) affects ~1 in 500 people of European descent. It is a dominantly inherited condition and is generally fully penetrant. Affected individuals typically have LDL-C levels which are about double that of their unaffected siblings. This is because the proportion of circulating LDL they can catabolize is decreased. Most commonly this is due to a mutation of the LDLR. Occasionally HeFH syndrome can be caused by mutations of genes other than the LDLR. One of these is proprotein convertase subtilisin/Kexin 9 (PCSK9) and the other apo B.

Clinically, HeFH can be recognized by particularly high levels of LDL-C in the range of 5–10 mmol/L (~200–400 mg/dL) in adulthood. Generally TG levels are normal, but can occasionally be raised in adults, particularly if they are obese. The typical HeFH patient may not in appearance conform at all to the clinician's concept of a coronary-prone individual. CVD risk estimation methods based on multivariate risk equations alone are not sufficient to estimate the risk of individuals with FH. Furthermore, the risk related to HeFH can be substantially ameliorated by early treatment. Untreated, the majority of affected men and women will have symptomatic coronary disease by 60 years and half of the men and 15% of the women will have died. On the other hand, patients who start attending a lipid clinic before they develop clinical CAD may enjoy a normal life expectancy if well managed.<sup>155</sup> An extensive review of the literature and treatment of FH is found in a report of the National Institute for Health and Clinical Excellence (NICE).<sup>156</sup>

#### Strategy for heterozygous familial hypercholesterolaemia case finding

**Family history.** Often attention is drawn to the possibility that HeFH may be running in a family because of the occurrence of a coronary event in a family member early in life. Occasionally, however, because, even in HeFH, women have a lower risk of CAD, a male patient may inherit HeFH from his mother and himself have a CAD event before she has any symptoms of CAD. A family history of early-onset CVD is also, of course, all too common in countries with a high prevalence of CVD for reasons other than HeFH. Reliance on family history can thus be misleading in the diagnosis of HeFH. However, raised TC in the presence of CAD in a male before 50 or a female before 60 years of age should always prompt a family screening for other cases of raised TC.

**Tendon xanthomata.** Corneal arcus or xanthelasmata in a young person should always prompt the measurement of TC, but

**Table 19** Diagnostic criteria for the clinical diagnosis of HeFH according to MedPed and WHO<sup>158</sup>

	Criteria	Score
<b>Family history</b>	First-degree relative known with premature CAD* and/or first-degree relative with LDL-C >95th centile	1
	First-degree relative with Tx and/or children <18 with LDL-C >95th centile	2
<b>Clinical history</b>	Patient has premature CAD*	2
	Patient has premature cerebral/peripheral vascular disease	1
<b>Physical examination</b>	Tx	6
	Arcus cornealis below the age of 45 years	4
<b>LDL-C</b>	>8.5 mmol/L (more than ~330 mg/dL)	8
	6.5–8.4 mmol/L (~250–329 mg/dL)	5
	5.0–6.4 mmol/L (~190–249 mg/dL)	3
	4.0–4.9 mmol/L (~155–189 mg/dL)	1
<b>Definite FH</b>		Score >8
<b>Probable FH</b>		Score 6–8
<b>Possible FH</b>		Score 3–5
<b>No diagnosis</b>		Score <3

\*Premature CAD: male before 55, women before 60 years of age. CAD = coronary artery disease; FH = familial hypercholesterolaemia; HeFH = heterozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol; Tx = tendon xanthomata; WHO = World Health Organization.

neither is specific for HeFH. The presence of tendon xanthomata is, however, virtually diagnostic of HeFH. Other causes are homozygous FH (HoFH), cerebrotendinous xanthomatosis, and sitosterolaemia, all of which are exceedingly rare. The most common sites to find tendon xanthomata are in the extensor tendons on the dorsum of the hand and in the Achilles tendon. The MedPed and WHO criteria have been used extensively to identify the HeFH phenotype (Table 19).<sup>157</sup> Other commonly used criteria are the Dutch criteria<sup>158</sup> and the criteria from the Simon Broome register.<sup>159</sup> The use of age-related LDL-C levels in the Dutch criteria does assist the childhood diagnosis.

**Childhood screening.** High TC levels are present from birth in HeFH. Because there are few other causes of high cholesterol in childhood, the finding of increased LDL-C is virtually diagnostic of HeFH. It is best to avoid measurement of TC in the first 6 weeks after birth because high levels of HDL-C may obscure the high LDL-C levels in HeFH. After that, measurement of TC can be virtually diagnostic, unlike in adults. The TC level in childhood rises

until the prepubertal growth spurt, when it declines until the accelerated growth subsides, after which it begins to increase to adult levels. It should, however, be remembered that children in families where one family member is already affected by HeFH are likely to be on a particular diet, so borderline cases from such families should be viewed with caution. It is under these circumstances that a DNA diagnosis may be most valuable.

**Cascade family screening using phenotype.** Screening for CVD risk at the national level generally does not start before the age of 40–50 years. In cascade family screening an extensive family history is obtained from patients with definite HeFH attending a lipid clinic. The family history, which includes contact details of relatives, is generally taken by a specially trained nurse who then arranges for lipoprotein profiles on these relatives. The expected yield of cases is ~50% of the relatives screened, which is close to what is observed in practice. The process can be repeated for any new cases detected (cascading). The system requires that a national network of lipid clinics is established and that GPs, cardiologists, and other physicians and nurses are aware of the process and of the necessity of referring suspected cases to lipid clinics.

**Genotyping.** Identification of the mutation causing HeFH in individual patients is much easier to contemplate when the mutations likely to be encountered are relatively few in number. Of course, once the mutation in a particular family has been discovered, the process of screening other family members becomes easier and much less costly. Identification of the mutation in the others would require sequencing of LDLR, PCSK9, and apo B. Specialized lipid clinics and laboratories can provide this service.

**Treatment.** It cannot be overemphasized that the management of HeFH does not simply involve advice about a healthy lifestyle and the prescription of lipid-lowering drugs, but also involves ensuring that patients have prompt access to investigations to detect the presence of significant atherothrombotic disease. Ideally management of HeFH should involve a lipid clinic. Lifestyle advice, particularly about diet and the avoidance of smoking, is important in HeFH.

**Drug treatment should be rigorous but should be used cautiously in women with childbearing potential.**<sup>155</sup> There seems no reason to adopt LDL-C targets for statin treatment different from those in other markedly increased risk patients. It should, however, be realized that even with maximum doses of therapies, one cannot expect in patients with particularly high pre-treatment LDL-C levels to achieve levels <1.8 mmol/L (less than ~70 mg/dL); a maximal reduction of LDL-C that can be achieved without side effects should be the target. **Generally atorvastatin or rosuvastatin titrated to maximum doses is required. For those whose LDL-C remains too high despite this, combination therapy should be considered (see above).**

Table 20 lists the recommendations for the detection and treatment of patients with HeFH.

**Homozygous familial hypercholesterolaemia.** HoFH is rare in European populations (~1 in 10<sup>6</sup> births) unless there is a founder gene effect or consanguinity, which is encountered, for example, in migrants from Asia. Both parents will have HeFH and there is a one in four chance that a child born to them will have HoFH. If the heterozygous parents are unrelated, they are generally unlikely to have the same mutation and thus a child

**Table 20** Recommendations for detection and treatment of patients with HeFH

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
FH is suspected in patients with CVD aged <50 years among men or <60 years among women, in subjects with relatives with premature CVD or in subjects with known FH in the family.	I	C
It is recommended to confirm the diagnosis with clinical criteria or whenever the resources are available with DNA analysis.	I	C
Family screening is indicated when a patient with HeFH is diagnosed; if resources are available it is recommended to perform this as cascade screening.	I	C
In HeFH high dose statin is recommended and whenever needed in combination with cholesterol absorption inhibitors and/or a bile acid sequestrant.	I	C
Children of parents with FH are recommended: <ul style="list-style-type: none"> <li>• to be diagnosed as early as possible</li> <li>• to be educated to adopt a proper diet</li> <li>• to receive pharmacological treatment in late childhood or in adolescence.</li> </ul>	I	C
Children with HoFH need special attention already from the first year of life.	I	C
Treatment is aimed at reaching the LDL-C goals for high risk subjects (<2.5 mmol/L, less than ~100 mg/dL) or in the presence of CVD of very high risk subjects (<1.8 mmol/L, less than ~70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations in tolerated doses.	IIa	C

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

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

CVD = cardiovascular disease; FH = familial hypercholesterolaemia; HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol.

with the clinical diagnosis of HoFH will in strict genetic terms be a compounded heterozygote. Regardless of this, HoFH is always an extremely serious disease, which untreated leads to death typically in adolescence or early adulthood due to myocardial ischaemia or aortic stenosis. The worst prognosis occurs when both mutations lead to complete failure of expression of LDLR rather than to defective LDLR expression.<sup>160</sup> Prenatal diagnosis is possible. When pregnancy is planned the partners of known cases of HeFH should have their TC levels checked to exclude the possibility that they also have HeFH.

Affected children develop florid tendon xanthomata and orange-yellow subcutaneous planar and tuberoso xanthomata on the buttocks, antecubital fossae, knees, and hands, typically in the webspaces between the fingers. Treatment with statins and LDL apheresis should be undertaken at a specialist centre from an

early age. MTP inhibitors and apo B antisense approaches might be used to increase LDL reduction. CABG is frequently necessary in the late teens or early 20s. If cardiac transplantation is undertaken, consideration should also be given to liver transplantation to provide functioning hepatic LDLRs.

### 10.1.3 Familial dysbetalipoproteinaemia

Familial dysbetalipoproteinaemia (syn. type III hyperlipoproteinaemia; remnant removal disease) is rare and is generally inherited as an autosomal recessive disorder with variable penetrance. It is rare in women before the menopause. The majority of cases are homozygous for apo E2. Apo E is important for hepatic clearance of chylomicron remnants and LDL. Apo E2 binds less readily than E3 or E4 to hepatic receptors. However, without some coincidental cause of dyslipidaemia, apo E2 homozygosity does not generally cause the 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 TG are raised before treatment. Patients develop tubero-eruptive xanthomata, particularly over the elbows and knees, and palmar xanthomata in the skin creases of their hands and wrists. The risk of CAD is very high, and accelerated atherosclerosis of the femoral and tibial arteries is also prevalent. A simple screening test for familial dysbetalipoproteinaemia is to measure the ratio of apo B to TC. If this is <0.15 (using g/L for apo B and mmol/L for TC) familial dysbetalipoproteinaemia is highly likely.

Generally, the detection of apo E2 homozygosity in a dyslipidaemic patient is a reliable confirmation of the diagnosis and can be easily performed in a specialized lipid clinic. In older patients with xanthomata resembling those of familial dysbetalipoproteinaemia, who prove not to be homozygote for apo E2, a paraprotein should be sought.

The treatment of familial dysbetalipoproteinaemia should be undertaken in a specialist clinic. Many cases respond well to fibrate and statin drugs, increasingly employed in combination.

### 10.1.4 Familial lipoprotein lipase deficiency

A profound defect in the catabolism of chylomicrons and VLDL results in chylomicronaemia and TG levels >15 mmol/L (~1330 mg/dL). It occurs in patients who are homozygous or compound heterozygote for mutations of the enzyme lipoprotein lipase (LPL). A similar defect in TG catabolism can be produced by inheritance of apo C2 deficiency. Mutations of the gene for other apolipoproteins (apo CIII and apo A5) or interacting proteins are also emerging as a cause of severe hypertriglyceridaemia.

Familial LPL deficiency is a rare cause of severe HTG which may cause severe disorders of the pancreas.

### 10.1.5 Other genetic disorders of lipoprotein metabolism (see Table 21)

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 apo B. Serum LDL-C is typically between 0.5 and 1.5 mmol/L (~20–60 mg/dL). It is generally of



**Table 21 Genetic disorders of lipoprotein metabolism**

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 500	<i>LDLR</i> <i>PCSK9</i> <i>APO B</i>	↑LDL
HoFH	1 in 10 <sup>6</sup>	<i>LDLR</i>	↑↑LDL
FCH	1 in 100/200	<i>USF1</i> + modifying genes	↑LDL, ↑VLDL ↑ apo B
Familial dysbetalipoproteinaemia	1 in 5000	<i>APO E</i>	↑↑IDL and chylomicron remnants (βVLDL)
Familial lipoprotein lipase deficiency	1 in 10 <sup>6</sup>	<i>LPL</i> <i>APO C2</i>	↑↑chylomicrons andVLDL
Tangier disease (analphalipoproteinaemia)	1 in 10 <sup>6</sup>	<i>ABC-I</i>	↓↓HDL
Familial LCAT deficiency (fish eye disease)	1 in 10 <sup>6</sup>	<i>LCAT</i>	↓HDL

FH = familial hypercholesterolaemia; HeFH = heterozygous familial hypercholesterolaemia; HoFH = homozygous familial hypercholesterolaemia; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin cholesterol acyltransferase; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

no medical significance. A more profound deficiency of apo B occurs in abetalipoproteinaemia when steatorrhea, neurological and 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 of 5 mmol/L (~200 mg/dL) or above are observed in homozygotes. This is not associated with disease.

## 10.2 Children

Diet is the mainstay of treatment for dyslipidaemia in childhood. Only in FH should consideration be given to lipid-lowering drug treatment. In other cases of dyslipidaemia in children, focus should be on diet and treatment of underlying metabolic disorders.

In the case of HeFH, statin treatment is generally withheld until sometime between the ages of 10 and 18 years. There is evidence from carotid ultrasound measurements that increased CIMT compared with siblings who have not inherited HeFH can be detected from the age of 10 years onwards, and that the progression of increasing CIMT can be ameliorated with statin therapy and/or apheresis.<sup>161</sup> The exact age at which to start statin treatment is,

however, a matter for clinical judgement. Generally treatment before the age of 18 years would be indicated in boys with a particularly adverse family history, because it is known that the age at which first-degree relatives develop symptomatic CAD is fairly closely correlated.

Although evidence that statin treatment causes fetal harm is inconclusive, women should be advised to avoid pregnancy while they are receiving such treatment. When pregnancy is planned, the statin should be stopped 3 months before conception is attempted and not recommenced until breastfeeding has been completed.

## 10.3 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.<sup>162</sup> The most recent CTT meta-analysis,<sup>15</sup> however, indicates that the benefit overall is similar in men and women.

### Primary prevention

Evidence for protective effects of lipid-lowering treatment in high risk patients without previous CAD has been definitively demonstrated in men. In contrast, such evidence remains less firm in women. Two meta-analyses have addressed the effects of different lipid-lowering treatments on primary prevention of CV events in women with a broad range of TC from normal to elevated, and concordantly found no major effects on total mortality and CAD events in women as opposed to men.<sup>15,163</sup> A more recent meta-analysis that included the large female subgroup from the JUPITER trial reported a 12% relative risk reduction (RRR) of total mortality with statin use in high risk subjects without established CVD, with no heterogeneity in treatment effect between men and women.<sup>16</sup> Thus, statin use should be considered for primary prevention in women at high CV risk with the same indications as for men.

### Secondary prevention

More data coming from large RCTs of secondary prevention are available for women. The results of these trials concordantly showed that lipid-lowering therapy substantially reduces CV events in these patients, although no reduction in total mortality risk could be demonstrated.<sup>164</sup> The meta-analysis of Walsh *et al.*<sup>164</sup> reported, in a cohort of 8272 females with previous CVD mainly treated with statins, a 26% reduction of CV mortality, a 29% reduction of MI, and a 20% reduction of total CAD events. The CTT meta-analysis also indicates that the benefit overall is similar in men and women.<sup>15</sup> Therefore, secondary prevention of CV events in women should routinely include a statin-based lipid-lowering regimen, with the same recommendations and therapeutic targets that are applied to men.

### Non-statin lipid-lowering drugs

The role of other pharmacological treatments for primary and secondary prevention of CAD in women remains undetermined. In particular, nicotinic acid, ezetimibe, or fibrates, alone or in combination with statins, can be used, depending on the type of

**Table 22 Management of dyslipidaemia in women**

- Statin treatment is recommended for primary prevention of CAD in high risk women.<sup>16</sup>
- Statins are recommended for secondary prevention in women with the same indications and targets as in men.<sup>15, 164</sup>
- Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breast feeding period.

CAD = coronary artery disease.

dyslipidaemia and side effect profiles, although no definitive evidence of cardioprotective effects is available.

### Hormone therapy

Currently used third-generation low oestrogen–progestin dose oral contraceptives do not appear to increase adverse coronary events, 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, more than ~160 mg/dL), or with multiple risk factors and in those at high risk of thrombotic events.<sup>165</sup> Oestrogen replacement therapy, despite some favourable effects on the lipid profile, has not been demonstrated to reduce CV risk and cannot be recommended for CV prevention in women.<sup>166</sup>

No lipid-lowering drugs should be administered during pregnancy and the period of breastfeeding because data on possible adverse effects are lacking.

Table 22 lists the main measures in the management of dyslipidaemia in women.

## 10.4 The elderly

The proportion of elderly people in society is increasing. More than 80% of individuals who die of CAD are older than 65 years. Smoking, hypertension, hyperlipidaemia, and diabetes mellitus are leading risk factors for CVD at all ages, but the absolute risk increases exponentially with advancing age.

Risk reduction in individuals older than 65 years is essential because two-thirds to three-quarters of them have either clinical CAD or subclinical atherosclerotic disease. Almost 25% of men and 42% of women older than 65 years have a TC level >6 mmol/L (more than ~240 mg/dL). According to published data, elderly individuals are a high risk group who could benefit significantly from lipid-lowering therapy to reduce CV morbidity and mortality.<sup>15</sup> Evidence for treatment above the age of 80–85 years is very limited, and clinical judgement should guide decisions in the very old.

### Primary prevention

The optimal approach is lifetime prevention and the goal is to reduce the total burden of CVD in the population. Lifetime prevention includes no smoking, healthy eating habits, regular exercise, and eliminating excess body weight. Primary prevention

measures in the elderly should not differ from those undertaken in younger subjects. In fact, although there is no evidence that hypolipidaemic treatment in elderly people prolongs life in patients without previous CVD, treatment reduces CV morbidity (stroke, MI) in elderly people in primary prevention.<sup>16</sup> The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first trial to evaluate older people prospectively. Patients between 70 and 82 years of age who had a history of risk factors for vascular disease were randomized to pravastatin 40 mg/day or placebo. After 3 years of follow-up, pravastatin reduced LDL-C levels by 34%, TG by 13%, and the risk from coronary death, non-fatal MI, and stroke by 15%. It could not reduce total mortality or improve cognitive dysfunction.<sup>26</sup> The CTT meta-analysis showed no significant differences in RRR between younger and older people,<sup>15</sup> and neither did a recent meta-analysis of primary prevention trials.<sup>16</sup>

### Secondary prevention

Despite including few elderly participants, multiple prospective clinical trials have shown good outcomes of lipid-lowering therapy in elderly patients with CAD.<sup>15</sup> The Scandinavian Simvastatin Survival Study (4S) showed that simvastatin decreased total mortality by 35% and coronary mortality by 42% in both sexes and in individuals aged ≥60 years over 5 years.<sup>18</sup> The Cholesterol and Recurrent Events (CARE) trial evaluated the effect of pravastatin on coronary events after MI and showed major coronary events, coronary death, and stroke were reduced by, respectively, 32, 45, and 40% in elderly patients; the number needed to treat (NNT) of older patients for 5 years was 11 in order to prevent one major coronary event and 22 to prevent one coronary death.<sup>20</sup>

Results from an MI registry study in Sweden demonstrate that statin treatment is associated with lower CV mortality in very elderly post-MI patients without increasing the risk of the development of cancer.<sup>167</sup>

### Side effects and interactions

The safety and side effects of statins are a matter of special concern in the elderly because older adults often have co-morbidities, take multiple medications, and have altered pharmacokinetics and pharmacodynamics. Statin–drug interactions are a concern primarily because of their potential to increase statin-associated side effects such as myalgia without CK elevation, myopathy with CK elevation, and the rare but serious rhabdomyolysis with marked CK elevation. Medication should be started at a low dose to avoid adverse events, and then titrated to achieve optimal LDL-C levels with an appropriate dose.

### Adherence

Elderly individuals are less likely to receive lipid-lowering medications or adhere to statin therapy. Cost, adverse effects, coronary events occurring despite being on lipid-lowering agents, and the perception that the drug is not beneficial may be the reasons for non-compliance. Improving patient understanding of CV risk, the medication regimen, and potential benefits of persistence with statin therapy may further enhance compliance.

**Table 23** Recommendations for treatment of dyslipidaemia in the elderly

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Treatment with statins is recommended for elderly patients with established CVD in the same way as for younger patients.	I	B	15, 16
Since elderly people often have comorbidities and have altered pharmacokinetics, it is recommended to start lipid-lowering medication at a low dose and then titrate with caution to achieve target lipid levels which are the same as in the younger subjects.	I	C	-
Statin therapy may be considered in elderly subjects free of CVD, particularly in the presence of at least one other CV risk factor besides age.	I <b>b</b>	B	20, 167

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

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

<sup>c</sup>References.

CV = cardiovascular; CVD = cardiovascular disease.

Table 23 lists the recommendations for treatment of dyslipidaemia in the elderly.

## 10.5 Metabolic syndrome and diabetes

The term MetS refers to the tendency for certain risk factors to cluster together: central obesity, raised serum TG, reduced HDL-C, glucose intolerance, and hypertension. Scoring systems which dichotomize these variables, and require, for instance, three out of five to make a diagnosis, may miss some of the associated risk; a practical approach is that if one component is identified, a systematic search should be made for others.

MetS identifies people at a higher risk of CVD than the general population. Data from recent meta-analyses indicate that people with MetS have a 2-fold increase in CV outcomes and 1.5-fold increase in all-cause mortality.<sup>168</sup> How to capture the extra risk beyond the traditional risk factors in clinical practice is a debated issue; even the definition of MetS is not fully harmonized. A combination of high waist circumference and elevation of TG is a simple and inexpensive screening tool to discriminate people with MetS at high CVD risk for global risk evaluation.<sup>95</sup>

Since CVD is the major cause of both morbidity and mortality in people with diabetes, the global epidemic of type 2 diabetes foresees a daunting increase of CVD. Diabetes itself is an independent risk factor for CVD and is associated with higher risk of CVD, even more so in women. Hypertension, dyslipidaemia, and abdominal obesity commonly co-exist with type 2 diabetes and further aggravate the risk that is highest in people with type 2 diabetes and features of MetS.<sup>169</sup> Importantly, diabetes confers excess mortality risk following ACS despite modern therapies highlighting the

**Table 24** Summary of dyslipidaemia in MetS and in type 2 diabetes

- Dyslipidaemia in MetS represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial TGs, apo B, and small dense LDL, and low HDL-C and apo A1.
- Non-HDL-C or apo B are good surrogate markers of TRLs and remnants and are a secondary objective of therapy. Non-HDL-C <3.3 mmol/L (less than ~130 mg/dL) or apo B <100 mg/dL is desirable.
- Increased waist circumference and elevation of TGs seems to be a simple tool to capture the high risk subjects with MetS.
- Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes.

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

poor prognosis of coronary patients with type 2 diabetes<sup>170</sup> and the need for aggressive therapy.

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

Diabetic dyslipidaemia is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated. HTG or low HDL-C or both is seen in about half of subjects with type 2 diabetes. The increase in large VLDL particles in type 2 diabetes initiates a sequence of events that generates atherogenic remnants, small dense LDL and small dense HDL particles.<sup>171</sup> These components are not isolated abnormalities but are metabolically closely linked to each other. Together these components comprise the atherogenic lipid triad that is also characterized by an increase in apo B concentration due to an increased number of apo B-containing particles. Importantly, TRLs including chylomicrons, VLDL, and their remnants carry a single apo B molecule, also like LDL particles. Therefore, the malignant nature of diabetic dyslipidaemia is not always revealed by the lipid measures used in clinical practice as LDL-C remains within the normal range. Elevation of TG or low HDL-C is seen in about half of subjects with type 2 diabetes.<sup>172</sup> The abnormal features of the lipid profile precede type 2 diabetes by several years and are common in subjects with central obesity, MetS, and type 2 diabetes.

Table 24 summarizes the role of dyslipidaemia in MetS and type 2 diabetes.

### Treatment strategies for subjects with type 2 diabetes and metabolic syndrome

Lifestyle therapy to improve the atherogenic lipid profile should be recommended to all subjects with type 2 diabetes and MetS.<sup>173</sup> Dietary advice should be tailored according to individuals needs.

If targets are not achieved on maximally tolerated doses of statins, drug combinations may offer additional lowering of LDL-C, but the evidence from outcome studies is limited.

Patients with type 2 diabetes younger than 40 years, with a short duration of therapy, without other risk factors, without

complications, and with an LDL-C level  $<2.5$  mmol/L ( $<100$  mg/dL) may not need lipid-lowering drugs.

### Evidence for lipid-lowering therapy

#### Low-density lipoprotein-cholesterol

Trials specifically performed in subjects with type 2 diabetes as well as subsets of individuals with diabetes in major statin trials have consistently demonstrated significant benefits of statin therapy on CVD events in people with type 2 diabetes.<sup>15</sup> Statin therapy reduces the 5 year incidence of major CVD events by  $\sim 20\%$  per mmol/L reduction in LDL-C regardless of initial LDL-C or other baseline characteristics based on meta-analysis.<sup>15</sup>

The CTT meta-analysis further indicates that subjects with type 2 diabetes will benefit from cholesterol-lowering therapy in RRR to a similar degree as non-diabetic patients, but being at higher absolute risk the absolute benefit will be greater resulting in a lower NNT. Recent studies have suggested an increased incidence of diabetes in patients treated with statins.<sup>101</sup> This effect must not lessen our attention to the treatment of patients as the overall benefit in CV events reduction still remains.

#### Triglycerides and high-density lipoprotein-cholesterol

Recent data from patients with type 2 diabetes in the FIELD study revealed that traditional lipid ratios (non-HDL-C/HDL-C, TC/HDL-C) were as strong predictors for CVD risk as the apo B/apo A1 ratio, and captured the impact of both atherogenic and anti-atherogenic particles on CVD risk.<sup>47</sup> Clinical benefits achieved by treatment of the atherogenic dyslipidaemia (high TG and low HDL-C) are still a matter of discussion. The FIELD trial failed to reduce significantly the primary endpoint of CAD events (CAD death or non-fatal MI). CVD events were reduced significantly by 11%. In a post-hoc analysis of the FIELD study, fenofibrate reduced CVD events by 27% in those with raised TG ( $>2.3$  mmol/L or more than  $\sim 204$  mg/dL) and reduced HDL-C (NNT = 23).<sup>172</sup> The ACCORD trial has confirmed this: patients who had both TG levels in the higher third ( $\geq 2.3$  mmol/L,  $\geq 204$  mg/dL) and an HDL-C level below the lower third ( $\leq 0.88$  mmol/L,  $\leq 34$  mg/dL)—representing 17% of all participants—appeared to benefit from adding fenofibrate to simvastatin.<sup>141</sup>

A post-hoc analysis of patients with low HDL-C  $<1$  mmol/L (less than  $\sim 40$  mg/dL) and elevated TG  $>1.80$  mmol/L (more than  $\sim 160$  mg/dL) in the 4S trial demonstrated a relative risk for major coronary events of 0.48 with simvastatin. The respective relative risk for overall mortality was 0.44.<sup>174</sup> Consistent with these findings, a meta-analysis of fibrates in the prevention of CVD in 11 590 people with type 2 diabetes showed that fibrates reduced the risk of non-fatal MI significantly by  $\sim 21\%$ , but had no effect on the risk of overall mortality or coronary mortality.<sup>175</sup>

The concept of raising HDL-C seems attractive based on the strength of the relationship between low HDL-C and increased CVD risk in observational studies. The available tools to raise HDL-C in clinical practice are limited, lifestyle modification providing the first option. At present, nicotinic acid provides the best drug strategy to raise HDL-C, although fibrates can also be used. The impairment of glycaemic control by nicotinic acid is seen at high doses, but at modest doses glycaemic control can in general be maintained by adjustment of diabetes therapy.<sup>176</sup>

### Type 1 diabetes

Type 1 diabetes is associated with high CVD risk, in particular in patients with microalbuminuria and renal disease.<sup>177</sup> Conclusive evidence supports the proposition that hyperglycaemia accelerates atherosclerosis.

The lipid profile in type 1 diabetic subjects with good glycaemic control is 'supernormal' and characterized by subnormal TG and LDL-C, whereas HDL-C is usually within the upper normal range or slightly elevated. This is explained by administration of subcutaneous insulin therapy that increases LPL activity in adipose tissue and skeletal muscle and consequently the turnover rate of VLDL particles. However, there are potentially atherogenic changes in the composition of both HDL and LDL particles. In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.

Recommendations for the treatment of dyslipidaemia in diabetes are shown in Table 25.

**Table 25 Recommendations for treatment of dyslipidaemia in diabetes**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
In all patients with type 1 diabetes and in the presence of microalbuminuria and renal disease, LDL-C lowering (at least 30%) with statins as the first choice (eventually drug combination) is recommended irrespective of the basal LDL-C concentration.	I	C	
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are over the age of 40 years with one or more other CVD risk factors or markers of target organ damage, the recommended goal for LDL-C is $<1.8$ mmol/L (less than $\sim 70$ mg/dL) and the secondary goal for non-HDL-C is $<2.6$ mmol/L (100 mg/dL) and for apo B is $<80$ mg/dL.	I	B	15, 16
In all people with type 2 diabetes LDL-C $<2.5$ mmol/L (less than $\sim 100$ mg/dL) is the primary target. Non-HDL-C $<3.3$ mmol/L (130 mg/dL) and apo B $<100$ mg/dL are the secondary targets.	I	B	15, 16

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

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

<sup>c</sup>References.

apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; LDL-C = low-density lipoprotein-cholesterol.

## 10.6 Patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention

Patients who have presented recently with an ACS are at high risk of experiencing further CV events. In these patients, lipid management should be undertaken in the context of a comprehensive global risk management strategy that includes lifestyle adaptations,

management of risk factors, and the use of cardioprotective drugs in certain subgroups. Ideally, this can be well coordinated through participation in a multidisciplinary cardiac rehabilitation programme.

### Specific lipid management issues in acute coronary syndrome

Data from specific trials<sup>23,30,35</sup> and meta-analysis support routine early use of prompt and intensive statin therapy. Thus, we recommend that high dose statin therapy be initiated during the first 1–4 days of hospitalization for the index ACS; if basal LDL-C values are known, the dose should aim at reaching the LDL-C target of <1.8 mmol/L (less than ~70 mg/dL). The use of lower intensity statin therapy should be considered in patients at increased risk of side effects with high doses of statin (e.g. the elderly, hepatic impairment, renal impairment, or potential for interaction with essential concomitant therapy). Lipids should be re-evaluated 4–6 weeks after the ACS to determine whether target levels have been reached and regarding safety issues; the statin dose can then be adapted accordingly.

The consumption of *n*-3 PUFAs, as either increased (oily) fish intake or a highly purified *n*-3 acid ethyl ester prescription medication, has in one study been shown to reduce mortality in survivors of MI,<sup>178</sup> but not in another.<sup>92</sup> Post-hoc analysis of the GISSI-P (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione) study has shown particular benefit from highly purified *n*-3 supplementation in those post-MI patients with left ventricular dysfunction who are at an increased risk of mortality. However, this cannot be attributed to their antilipidaemic effect but predominantly to their antiarrhythmic effects.

### Lipid management issues in patients undergoing percutaneous coronary intervention

Short-term pre-treatment with atorvastatin reduces the extent of MI during PCI in statin-naïve patients with both stable angina and ACS. More recently, the Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA)<sup>179</sup> trial demonstrated that reloading with high dose atorvastatin reduces the frequency of periprocedural MI, even in patients receiving chronic statin therapy undergoing PCI for management of stable angina or low–intermediate risk ACS. Thus, a strategy of routine reload with high intensity statin shortly before PCI may be considered even on the background of chronic therapy (class IIb B<sup>179</sup>).

## 10.7 Heart failure and valvular diseases

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

Onset of heart failure (HF) increases the risk of mortality and morbidity 3–4 times compared with patients without HF. Pooling of results from RCTs suggested that cholesterol lowering with statin treatment reduced incident HF by 9–45% in patients with CAD.<sup>22,180</sup>

Five key prospective RCTs compared more intensive vs. less intensive drug regimens. The more intense approach reduced the incidence of hospitalization due to HF by an average of 27% ( $P < 0.0001$ ) in patients with acute and stable CAD without previous HF. This demonstrated that a more intensive statin therapy is more

effective than less intensive statin therapy for prevention of incident HF.<sup>23,26,181–183</sup> However, there is no evidence that statins can prevent HF in patients with non-ischaemic cardiomyopathy.

### Chronic heart failure

HF patients have lower TC and LDL-C than patients without HF. In contrast to patients without HF, a low TC portends a poor prognosis in HF. Although non-controlled observational studies have shown favourable effects among statin users in HF trials, RCT studies do not support this notion. Observational studies are subject to confounding, and treatment with statins should not be started in patients with moderate to severe HF [New York Heart Association (NYHA) classification III–IV].<sup>36,39</sup> However, there is no evidence for harm in patients on statin treatment after the occurrence of HF. The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Effect of Rosuvastatin in Patients with Chronic Heart Failure (GISSI-HF) trials in patients with symptomatic HF did not demonstrate any benefit on CV mortality and non-fatal MI and stroke, in spite of a marked reduction of LDL-C and hs-CRP.<sup>36,39</sup>

One RCT has demonstrated a small but significant effect of *n*-3 PUFAs on primary endpoints (all-cause death and hospitalization for HF).<sup>184</sup> This effect was significant only after adjustment for baseline imbalance between randomized groups.

### Valvular disease

There is an association between aortic stenosis, LDL-C, and Lp(a), and also between aortic stenosis and increased risk for CV events and mortality. There is also suggestive evidence for an association between cholesterol and increased risk for calcification of bioprosthetic valves. Early observational non-controlled trials show beneficial effects of aggressive lipid lowering in slowing the progression of aortic stenosis. This was not confirmed in a recent RCT, yet the CAD was significantly reduced.<sup>38</sup>

The SEAS trial randomized 1873 patients with mild to moderate asymptomatic aortic stenosis to the combination of simvastatin 40 mg plus ezetimibe 10 mg, and simvastatin 40 mg alone. Despite marked LDL-C lowering (61%), progression of aortic stenosis was similar in the two treatment groups.<sup>38</sup> Ischaemic events were reduced by 21%. One small observational study suggested a benefit of statin treatment among patients with bioprosthetic valves.<sup>185</sup>

Table 26 lists the recommendations for treatment of dyslipidaemia in HF or valvular disease.

## 10.8 Autoimmune diseases

Autoimmune diseases, including rheumatoid arthritis, SLE, psoriasis, and antiphospholipid syndrome, are characterized by enhanced atherosclerosis and consequently higher CV morbidity and mortality rates compared with the general population.<sup>186–188</sup>

The immune system is believed to be involved in the pathogenesis of atherosclerosis. Inflammatory components of the immune response, as well as autoimmune elements (e.g. autoantibodies, autoantigens, and autoreactive lymphocytes) are involved in these processes. The diseases are characterized by inflammatory vasculitis and endothelial dysfunction.

**Table 26** Recommendations for treatment of dyslipidaemia in HF or valvular disease

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
n-3 PUFAs 1 g/day may be considered to be added to optimal treatment in patients with HF (NYHA classification II-IV).	I <b>IIb</b>	<b>B</b>	184
Cholesterol-lowering therapy with statins is not indicated in patients with moderate to severe HF (NYHA classification III-IV).	<b>III</b>	<b>A</b>	36,39
Lipid-lowering treatment is not indicated in patients with valvular disease without CAD.	<b>III</b>	<b>B</b>	38

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.

CAD = coronary heart disease; HF = heart failure; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.

**Table 27** Recommendations for treatment of dyslipidaemia in autoimmune diseases

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
As yet there is no indication for the preventive use of lipid-lowering drugs only on the basis of the presence of autoimmune diseases.	<b>III</b>	<b>C</b>

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.

Table 27 lists the recommendations for the treatment of dyslipidaemia in autoimmune diseases.

## 10.9 Renal disease

The prevalence of CKD, in particular mild to moderate CKD, is rapidly increasing worldwide. A decreasing GFR is associated with CVD independently of other risk factors.<sup>189</sup> In a recent survey in Europe the standardized CV mortality rate was 38 per 1000 person years (95% CI 37.2–39.0) higher in patients starting dialysis than in the general population.<sup>190</sup>

### Lipoprotein profile in chronic kidney disease

The lipid profile shows both quantitative and qualitative abnormalities that worsen with declining GFR, being most pronounced in subjects with end-stage renal disease (ESRD). Dyslipidaemia comprises typically elevations of TG and lowering of HDL-C, whereas the changes of TC and LDL-C are less marked in stage 1–2 CKD. The elevation of TG is caused by both increased production and impaired removal of TRLs due to changes in

regulatory enzymes and proteins. Consequently non-HDL-C and apo B levels are clearly increased. LDL subclasses display a shift to excess of small dense LDL particles. In patients with ESRD the catabolic rate of LDL is markedly prolonged, resulting in clear elevation of both TC and LDL-C levels. Plasma Lp(a) levels also start to increase early due to the prolonged residence times of these particles in the circulation. Altogether, most patients with stage 3–5 CKD have mixed dyslipidaemia and the lipid profile is highly atherogenic with adverse changes in all lipoproteins.

### Evidence for lipid management in patients with chronic kidney disease

Available data from post-hoc analyses of statin trials provide evidence for the beneficial effects of statin therapy on CVD outcomes in patients with stages 2 and 3 CKD. The Pravastatin Pooling Project (PPP) included 19 737 subjects with a median follow-up of 64 months.<sup>191</sup> The benefit was most marked in subjects with both CKD and diabetes. Notably there was also a significant reduction in the risk of all-cause mortality (relative risk 0.81, 95% CI 0.73–0.89). In the Heart Protection Study (HPS) the absolute risk reduction was 11% in a subgroup of subjects with mild CKD as compared with 5.4% in the total cohort.<sup>192</sup>

The results from patients with more advanced CKD (stage 4–5) and on dialysis are less clear. Two observational studies have reported benefits of statin use in subjects on haemodialysis. However, in the Die Deutsche Diabetes Dialyse studie (4D) trial<sup>31</sup> in a cohort of 1200 patients with diabetes on haemodialysis, atorvastatin had no positive effect on the primary composite endpoint of CVD. The results from AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events) involving 2776 patients on haemodialysis<sup>40</sup> show that rosuvastatin lowered LDL-C as expected but had no significant effect on the composite CVD endpoint. These negative results question the benefits of statins in these very high risk patients with poor outcomes. SHARP reported results in ~9500 high risk subjects with CKD. Major atherosclerotic events were reduced by 17% ( $P = 0.0022$ ) and major vascular events by 15.3% ( $P = 0.0012$ ) in patients on ezetimibe plus simvastatin as compared with placebo.<sup>111</sup> Importantly, although no significant heterogeneity existed between non-dialysis and dialysis subjects, this was also true for placebo vs. dialysis subjects.

### Therapeutic targets for patients with chronic kidney disease

CKD is acknowledged as a CAD risk equivalent. This has set the LDL-C reductions as the primary target of therapy. Non-HDL-C should be the second objective in the management of mixed dyslipidaemia. The treatment algorithm should be based on GFR. Drugs eliminated mainly by the hepatic route should be preferred (fluvastatin, atorvastatin, pitavastatin, and ezetimibe). Statins metabolized via CYP3A4 may result in adverse effects due to drug–drug interactions, and special caution is required.

Table 28 lists the recommendations for lipid-lowering drugs in patients with moderate to severe CKD.

**Table 28** Recommendations for lipid lowering drugs in patients with moderate to severe CKD (stages 2–4, GFR 15–89 mL/min/1.73 m<sup>2</sup>)

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
CKD is acknowledged as a CAD risk equivalent; in these patients LDL-C reduction is recommended as the primary target of therapy.	I	A	189, 190
LDL-C lowering reduces CVD risk in CKD subjects and should be considered.	IIa	B	111, 193
Statins should be considered to slow the rate of kidney function loss modestly and thus protect against the development of ESRD requiring dialysis.	IIa	C	-
Since statins have a beneficial effect on pathological proteinuria (>300 mg/day) they should be considered in patients with stage 2–4 CKD.	IIa	B	194
In moderate to severe CKD statins as monotherapy or in combination with other drugs should be considered to achieve LDL-C <1.8 mmol/L (less than ~70 mg/dL).	IIa	C	-

<sup>a</sup>Class of recommendation.<sup>b</sup>Level of evidence.<sup>c</sup>References.

CAD = coronary artery disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol.

**Lipid management in kidney failure (stage 5, glomerular filtration rate <15 mL/min/1.73 m<sup>2</sup>)**

The use of statins with limited renal excretion is mandatory at low doses. The use of prescription *n*-3 fatty acids to lower TG is an option.

**Safety of lipid management in patients with chronic kidney disease**

Statins are generally well tolerated at moderate doses in subjects with CKD stages 1–2. Safety issues and dose adjustment become important in more advanced stages of CKD (stages 3–5), as adverse events are commonly dose related and due to increased blood concentration of the compound. Statins with minimal renal excretion should be the drug of choice (atorvastatin, fluvastatin, and pitavastatin).

Growing evidence indicates that fibrates increase serum creatinine and homocysteine, both being established CVD risk factors. Effects of fenofibrate are more pronounced than those of gemfibrozil. As fibrates have no effect on creatinine excretion into urine, the estimation of GFR is hampered by the rise of creatinine

and is a problem in clinical practice. Fenofibrate is also non-dialysable and should not be used in patients with GFR <50 mL/min/1.73 m<sup>2</sup>. The dose of gemfibrozil is recommended to be reduced to 600 mg/day if GFR is <60 mL/min/1.73 m<sup>2</sup> and avoided if GFR is <15 mL/min/1.73 m<sup>2</sup>.

Recently the availability of prescription brand *n*-3 fatty acids provides an option to lower TG in patients with mixed dyslipidaemia.

**10.10 Transplantation patients**

Lipid abnormalities are common in patients who have undergone solid organ transplantation, and predispose to the development of both atherosclerotic disease and transplant arterial vasculopathy, resulting in major vascular events.

Common general causes of dyslipidaemia in these patients are diabetes, obesity, MetS, and CKD.

Immunosuppressive drug regimens also have important adverse effects on lipid metabolism. Glucocorticoid therapy causes weight gain and exacerbates insulin resistance, leading to increases in TC, VLDL, and TG, and in the size and density of LDL particles. Calcineurin inhibitors increase the activity of hepatic lipase, decrease LPL, and bind the LDLR, resulting in reduced clearance of atherogenic lipoproteins. A greater adverse impact on lipid profiles is seen with ciclosporin than with tacrolimus. Sirolimus, a structural analogue of tacrolimus, causes dyslipidaemia in almost half of the patients receiving it. Patients should receive healthy lifestyle advice as recommended for patients at increased risk of CVD. Statins have a similar effect on lipids in transplant recipients as in the general population. Although randomized trial data have shown that statins have the potential to improve outcomes in heart transplant patients<sup>195–197</sup> and renal transplant patients,<sup>198</sup> the amounts of outcome data are not extensive. A recent systematic review demonstrated a strong trend to reduced CVD events and mortality with statins in renal transplant patients.<sup>198</sup>

Several potential drug interactions must also be considered, especially with ciclosporin which is metabolized through CYP3A4 and may increase systemic statin exposure and the risk of myopathy. Fluvastatin, pravastatin, pitavastatin, and rosuvastatin have less potential for interaction.<sup>197</sup> Tacrolimus is also metabolized by CYP3A4 but appears to have less potential for harmful interaction with statins than ciclosporin. Other drugs that influence CYP3A4 activity should be avoided if possible and used with extreme caution in patients receiving both calcineurin inhibitors and statins.

Statins are recommended as the first-line agents for lipid lowering in transplant patients. Initiation should be at low doses with careful up-titration and caution regarding potential drug–drug interactions. Initiation of therapy with low dose pravastatin or fluvastatin is recommended for those on ciclosporin.

For those with dyslipidaemia who are unable to take statins, ezetimibe could be considered as an alternative in those with high LDL-C,<sup>199</sup> and nicotinic acid might be considered for lowering TG and raising HDL-C. No outcome data are available for these drugs, which should generally be reserved for second-line use. Care is required with use of fibrates as they can decrease ciclosporin levels and have the potential to cause myopathy. Extreme caution is required if fibrate therapy is planned in combination with a statin. Cholestyramine is not effective as a monotherapy

**Table 29** Recommendations for treatment of dyslipidaemia in transplant patients

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Global CV risk management strategies are a priority in transplant patients.	I	C	-
Statins should be considered as the first-line agents in transplant patients. Initiation should be at low doses with careful up-titration and with caution regarding potential drug–drug interactions, particularly for those on ciclosporin.	Ila	B	197
In patients who are intolerant of statins or those with significant dyslipidaemia and high residual risk despite a maximally tolerated dose of statin, alternative or additional therapy may be considered: ezetimibe for those where high LDL-C is the principal abnormality; fibrates or nicotinic acid for those where hypertriglyceridaemia and/or low HDL-C is the principal abnormality.	Ilb	C	-

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

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

<sup>c</sup>References.

CV = cardiovascular; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol.

in heart transplant patients and has the potential to reduce absorption of immunosuppressants, minimized by separate administration.

Table 29 lists the recommendations for treatment of dyslipidaemia in transplant patients.

### 10.11 Peripheral arterial disease

PAD is a common manifestation of atherosclerosis and may involve several vascular sites, including the carotid district, the aorta, the lower limb arteries, and, more rarely, the renal and mesenteric arterial vessels. Patients with PAD are at elevated risk of coronary events, and the presence of peripheral vascular atherosclerosis represents an independent risk factor for MI and CV death.<sup>200,201</sup> Elevated CV risk has led to inclusion of PAD among the list of ‘risk equivalent’ conditions, and therapeutic strategies of secondary prevention should be implemented. Yet, despite the high CV morbidity and mortality risk, PAD patients are usually inadequately managed compared with CAD patients.<sup>200</sup>

#### Occlusive arterial disease of the lower limbs

Cholesterol-lowering therapy reduces the risk of ischaemic CV events and worsening of claudication, and improves walking performance.

As for cardiac events, a recent systematic review<sup>202</sup> of 18 trials including > 10 000 patients, with cholesterol levels from normal to elevated, reported that lipid-lowering therapy in subjects affected by atherosclerosis of the lower limbs is associated with a 20% reduction in total CV events, together with a non-significant 14% reduction of all-cause mortality.

#### Carotid artery disease

Several trials have shown the beneficial effects of lipid-lowering therapy on the progression of CIMT and on the prevention of CV events. A meta-analysis of 10 studies including 3443 patients<sup>203</sup> reported a significant reduction in the progression of carotid atherosclerosis in statin-treated patients compared with placebo, and a more recent systematic review also showed a significant CIMT regression after statin therapy.<sup>204</sup> In a meta-analysis of RCTs enrolling > 90 000 patients, Amarenco *et al.* reported that statin therapy determines a 21% reduction in the incidence of all strokes in different populations, with a strong correlation between LDL-C reduction and CIMT, pointing to a 0.73% per year reduction of CIMT for each 10% decrease of LDL-C.<sup>205</sup> Recent studies also suggest that nicotinic acid may add to the protective effect of statins.<sup>131</sup>

However, there are currently no randomized studies that have assessed whether lipid-lowering treatments reduce the incidence of CV events in patients enrolled on the basis of carotid atherosclerotic disease and without previous CV events.

#### Retinal artery atherosclerosis

Atherosclerotic changes of retinal arteries correlate with TC, LDL-C, TG, and apo B levels and also with CAD. However, there are no studies assessing whether lipid-lowering treatments reduce these changes.<sup>206</sup>

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

Although the presence of abdominal aortic aneurysm represents a risk equivalent condition, there are currently no available clinical trials on CV risk reduction in patients affected by this condition. Two systematic reviews,<sup>204,207</sup> mostly based on retrospective non-randomized studies, reported that there is still inconclusive evidence that statin therapy reduces the perioperative CV morbidity and mortality in these patients. In an RCT comparing atorvastatin 20 mg with placebo, the composite endpoint of cardiac death, MI, stroke, and unstable angina was significantly reduced in 100 patients undergoing vascular non-cardiac surgery, including abdominal aortic aneurysm repair.<sup>208</sup> In another double-blind placebo-controlled trial in 497 patients undergoing vascular surgery, perioperative fluvastatin therapy (80 mg/day) was associated with an improvement in post-operative cardiac outcome.<sup>209</sup> Lipid-lowering therapy has never been tested in patients affected by renovascular atherosclerosis. Yet, despite lack of clinical trials, statin treatment should be considered for patients affected by aortic atherosclerotic disease.

The recommendations for lipid-lowering drugs in patients with PAD are shown in Table 30.



**Table 30 Recommendations for lipid-lowering drugs in patients with PAD**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
PAD is a high risk condition, and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A	202
Statin therapy is recommended to reduce the progression of carotid atherosclerosis.	I	A	203, 204
Statin therapy is recommended to prevent the progression of aortic aneurysm.	I	C	-

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 PAD = peripheral arterial disease.

**Table 31 Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke**

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
Statin therapy to reach established treatment goals is recommended in patients at high global risk.	I	A	210, 211
Statin therapy is recommended in patients with other manifestations of CVD.	I	A	210
Statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA.	I	A	34, 210

<sup>a</sup>Class of recommendation.  
<sup>b</sup>Level of evidence.  
<sup>c</sup>References.  
 CVD = cardiovascular disease; TIA = transient ischaemic attack.

### 10.12 Stroke

Stroke has a heterogeneous aetiology including cardiac thrombo-embolism (often associated with atrial fibrillation), carotid artery and proximal aortic atherosclerosis and thrombo-embolism, small vessel cerebrovascular disease, and intracranial haemorrhage (including intracerebral and subarachnoid haemorrhage). Dyslipidaemia may play a variable role in the pathogenesis of stroke according to the particular aetiology. The relationship between dyslipidaemia and atherothrombotic events including ischaemic stroke and transient ischaemic attack (TIA) is well recognized, while the association of dyslipidaemia with other types of stroke is uncertain.

#### Primary prevention

The use of cholesterol-lowering therapy in adults at high risk of CVD due to LDL-C or other CV risk factors, including arterial hypertension, reduces the risk of stroke or TIA.<sup>26,30,33,210,211</sup> More intensive lipid lowering with statins is associated with lower risk of stroke compared with less intensive regimens.<sup>210</sup>

Primary prevention of stroke contributes to the overall indication for starting treatment with statins in all patients with established atherosclerotic disease and in patients at high risk for developing CVD.

Statin therapy<sup>28,32,37</sup> should be considered for reducing the risk of ischaemic stroke and other CV events in accordance with the recommendations given in Table 3. The value of other lipid-lowering therapies in the primary prevention of stroke is uncertain.

#### Secondary prevention

Following stroke or TIA,<sup>34</sup> patients are at risk not only of recurrent cerebrovascular events but also of other major CV events including MI. Secondary prevention therapy with statins reduces the risk of stroke, MI, and vascular death. However, the aetiology of stroke

may influence the response to statins, and those patients with evidence of atherothrombosis underlying their cerebrovascular events appear to benefit most, while those with haemorrhagic stroke may not benefit or may even be harmed by statins, particularly if patients do not have evidence of atherosclerotic disease.<sup>210</sup>

A recent meta-analysis suggests that nicotinic acid alone or in combination with statin may add further benefit in stroke prevention.<sup>133</sup>

Table 31 lists the recommendations for lipid-lowering drugs for primary and secondary prevention of stroke.

### 10.13 Human immunodeficiency virus patients

Human immunodeficiency virus (HIV)-infected patients often have low TC and LDL-C as well as low HDL-C and increased TG. Highly active antiretroviral treatment (HAART) causes an increase of LDL-C and TG, and predominance of small, dense LDL particles, thus doubling their CAD risk when compared with HIV-negative subjects.<sup>212</sup> Since HAART also increases blood pressure and insulin resistance, this could contribute to the increased CAD risk too. Lipoprotein metabolism is influenced to a lesser extent by nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. HAART, including protease inhibitors, may particularly accelerate the onset of CAD-related events in young male heavy smokers with dyslipidaemia.

Dietary changes and regular physical activity as well as switching to another HAART regimen may act favourably on dyslipidaemia, but most patients still need pharmacological therapy to reach the lipid goals. There were safety concerns because of potential interactions for the association of lipid-lowering drugs with HAART. However, no significant toxicity has been observed and statins are the treatment of choice for increased LDL-C, while fibrates

**Table 32** Recommendations for lipid-lowering drugs in HIV patients

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Lipid-lowering therapy, mostly statins, should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high risk subjects.	Ila	C

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

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

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

may be prescribed when HTG is predominant.<sup>213</sup> Different statin brands could have different interactions with HAART; according to the European AIDS Clinical Society simvastatin is contraindicated in patients receiving ritonavir-boosted protease inhibitor-based antiretroviral treatment<sup>214</sup>; the combination of rosuvastatin with lopinavir/ritonavir should also be used with caution.<sup>215</sup> For patients who cannot tolerate statin treatment, ezetimibe could be an option.<sup>216</sup> Use of bile acid sequestrants is not recommended because they increase TG and their effects on the absorption of antiretroviral drugs have not been studied.

There are no data on effects of statins, ezetimibe, nicotinic acid, or fibrates on CV events in dyslipidaemic HIV-infected patients.

The recommendations for lipid-lowering drugs in HIV patients are shown in Table 32.

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

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

Response to therapy can be assessed at 6–8 weeks from initiation or dose increases for statins, but response to fibrates and lifestyle may take longer. Standard practice for subsequent follow-up monitoring is 6–12 months, but such monitoring intervals are arbitrary. As a minimum, TC should be assessed, but better management decisions will probably occur if a full lipid profile is performed including HDL-C, TG, and LDL-C. Epidemiological studies show that non-HDL-C and apo B measurement may correlate modestly better with outcomes, but there are no data on the use in routine clinical settings.

A separate issue is the impact of regular lipid monitoring in promoting patient adherence to lifestyle changes or drug regimens that impact positively on their health, as found in a range of studies.<sup>217</sup> It is unclear if only the process of monitoring is critical in achieving this, or a combination of education, regular contact, and adherence assessment.

**Table 33** Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy

Testing lipids
<p><b>How often should lipids be tested?</b></p> <ul style="list-style-type: none"> <li>Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where immediate drug treatment is suggested such as in ACS.</li> </ul>
<p><b>How often should patients' lipids be tested after starting lipid-lowering treatment?</b></p> <ul style="list-style-type: none"> <li>8 (±4) weeks after starting drug treatment.</li> <li>8 (±4) weeks after adjustments to treatment until within the target range.</li> </ul>
<p><b>How often should cholesterol or lipids be tested once a patient has reached target or optimal cholesterol?</b></p> <ul style="list-style-type: none"> <li>Annually (unless there is adherence problems or another specific reason for more frequent reviews).</li> </ul>
Monitoring liver and muscle enzymes
<p><b>How often should liver enzymes (ALT) be routinely measured in patients taking lipid-lowering drugs?</b></p> <ul style="list-style-type: none"> <li>Before treatment</li> <li>8 weeks after starting drug treatment or after any dose increase</li> <li>Annually thereafter if liver enzymes are &lt;3×ULN</li> </ul>
<p><b>What if liver enzymes become raised in a person taking lipid-lowering drugs?</b></p> <p>If &lt;3×ULN:</p> <ul style="list-style-type: none"> <li>Continue therapy</li> <li>Recheck liver enzymes in 4–6 weeks</li> </ul> <p>If values rise to ≥3×ULN:</p> <ul style="list-style-type: none"> <li>Stop statin or reduce dose, recheck liver enzymes within 4–6 weeks</li> <li>Cautious reintroduction of therapy may be considered after ALT has returned to normal</li> </ul>
<p><b>How often should CK be measured in patients taking lipid-lowering drugs?</b></p> <p><i>Pre-treatment</i></p> <ul style="list-style-type: none"> <li>Before starting treatment</li> <li>If baseline CK level &gt;5×ULN, do not start drug therapy; recheck</li> </ul> <p><i>Monitoring</i></p> <ul style="list-style-type: none"> <li>Routine monitoring of CK is not necessary</li> <li>Check CK if patient develops myalgia</li> </ul> <p>Increase alertness regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease.</p>
<p><b>What if CK becomes raised in a person taking lipid-lowering drugs?</b></p> <p>If &gt;5×ULN:</p> <ul style="list-style-type: none"> <li>Stop treatment, check renal function and monitor CK every 2 weeks.</li> <li>Consider the possibility of transient CK elevation for other reasons such as muscle exertion.</li> <li>Consider secondary causes of myopathy if CK remains elevated.</li> </ul> <p>If ≤5×ULN:</p> <ul style="list-style-type: none"> <li>If no muscle symptoms, continue statin (patients should be alerted to report symptoms; consider further checks of CK)</li> <li>If muscle symptoms, monitor symptoms and CK regularly</li> </ul>

ACS = acute coronary syndrome; ALT = alanine aminotransferase; CK = creatine phosphokinase; ULN = upper limit of normal.

**Follow-up safety assessments**

Where statins are used, safety blood tests are advised by regulators, including ALT and CK at baseline to identify the limited number of patients where treatment is contraindicated. CK should at least be checked in patients with high risk for myopathy such as the very elderly with co-morbidities, patients with earlier muscle symptoms, or patients on interacting drugs. Follow-up is advised at 6 or 12 monthly intervals to monitor potential toxic side effects, but such assessments have a limited scientific basis. A systematic review<sup>218</sup> found that the incidence of drug-induced hepatotoxicity in patients taking lipid-lowering drugs is unknown, with few cases occurring in large-scale randomized trials. Recent reviews<sup>219</sup> are encouraging about the safety of long-term lipid-lowering therapy.

There is no predictive value of routine repeat CK testing for rhabdomyolysis since the test can rise with muscle injury or excess muscular exercise. However, CK must be assessed immediately in patients, especially the elderly, presenting with muscle pains and weakness, and treatment stopped if >5 times the ULN. In patients whose liver function tests rise above three times the ULN, explanations such as alcohol ingestion or non-alcoholic fatty liver disease should be sought and the levels monitored. If levels remain elevated, then statins should be stopped but may be cautiously re-introduced under monitoring after levels have returned to normal. There is limited evidence to suggest that some statins have more likelihood of being associated with muscle symptoms (but not CK change), or liver enzyme changes.

Table 33 summarizes the recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy.

## 12. How to improve adherence to lifestyle changes and compliance with drug therapy

No smoking, healthy eating, and being physically active are the foundations of preventive cardiology. These lifestyles are most effectively achieved through formal programmes of preventive care; such programmes are also more appropriate for initiating and up-titrating drug therapies, achieving the treatment goals, and adherence over the long-term which in turn improves event-free survival.<sup>220</sup> However, in everyday care, statins are usually prescribed at the lowest dose and often not up-titrated to achieve goals. In addition, adherence over the long term is poor, with up to a third of patients or more stopping their statin treatment within a year. Not up-titrating the dose of statin, and poor adherence to this therapy, are the main reasons why over half of all coronary patients, and four out of five of all high risk patients, are not achieving the lipid goals and, as a consequence, are not achieving the maximum benefits of these preventive strategies.<sup>221</sup>

So, the challenges for clinical practice are to initiate treatment in both vascular patients and those at high risk of developing CVD, up-titrate the dose to achieve the lipid goals wherever feasible, and achieve adherence.

Most of the problems related to adherence to lifestyles are currently assumed to be similar to those related to compliance with lipid-lowering drug therapy. Two of the most important factors

**Table 34 Hints to help adherence to lifestyle changes**

• Develop a good alliance with the patient.
• Make sure that the patient understands how lifestyles affect cardiovascular disease and use this to gain commitment to the change in behaviour.
• Explore potential barriers to the change.
• Design with the patient a lifestyle change plan that is realistic and encouraging.
• Reinforce the patient's efforts to change.
• Involve other experts wherever needed and possible.
• Arrange a schedule of follow-up visits.

**Table 35 Tips to help compliance with multiple drug therapies**

• Simplify the dosing regimen if possible by reducing daily doses and concomitant medications.
• Choose cheaper alternatives.
• Provide clear written and oral instructions.
• Undertake a dialogue with the patient regarding adherence.
• Tailor the regimen to the patient's lifestyle and needs.
• Involve the patient as partner in the treatment.
• Use behavioural strategies (reminder systems, cues, self-monitoring, feedback, reinforcement)

contributing to poor adherence are undoubtedly the asymptomatic and lifelong nature of the disease. Other potential determinants of adherence may be related to:

- demographic factors such as age and education
- the patient's understanding and perception of dyslipidaemia
- the healthcare provider's mode of delivering treatment
- the relationships between patients and healthcare professionals
- influences from the health systems, and
- complex chronic drug regimens.

Poor socioeconomic status, illiteracy, and unemployment are important risk factors for poor adherence. Other important patient-related factors may include understanding and acceptance of the disease, perception of the health risk related to the disease, awareness of the costs and benefits of treatment, and active participation in monitoring and decision-making in relation to management of the disease.<sup>222</sup>

In Table 34 some hints are given that may help improve patient adherence to lifestyle changes.

The responsibility for adherence must be shared between the healthcare provider, the patient, and the healthcare system.

Good relationships between the patients and their healthcare providers are therefore imperative for good adherence. Empathetic and non-judgemental attitude and assistance, ready availability, and good quality of communication and interaction are some of the important attributes of healthcare professionals that have been shown to be determinants of the adherence of patients.<sup>223</sup>

Issues related to health systems also play an important role in the promotion of adherence. In most low income countries, supplies of medications are limited and they often have to be bought out-of-pocket. Strategies for improving access to drugs such as sustainable financing, affordable prices, and reliable supply systems have an important influence on patient adherence. Some of the better recognized determinants of adherence to hypolipidaemic therapy are related to aspects of the drug treatment itself, and include drug tolerability, regimen complexity, drug costs, and treatment duration. In Table 35 some tips are given that may help improve compliance with multiple drug therapies.

The complexity of the regimen is, for instance, a treatment-related factor that has been identified as a possible cause of poor adherence. Frequency of dosing, number of concurrent medications, and changes in medications are some of the factors that contribute to the complexity of a regimen, and these have been investigated in many observational studies. Fewer daily doses of drugs, monotherapies, and fewer changes in medications have all been associated with better adherence.

Until better insight into adherence is obtained, multifaceted measures to assist patients to follow treatment with lipid-lowering drugs have to be adopted. Healthcare providers need to be made aware of the low rates of adherence of

patients with dyslipidaemia. They should receive training on how to counsel patients in a constructive and non-judgemental manner, with the primary goal of helping the patient to adhere better to the treatment schedule.

Patients need to understand the importance of maintaining lipid control during the day and to use their drugs rationally. Furthermore, they need to learn how to deal with missed doses, how to identify adverse events, and what to do when they occur.

While many interventions (e.g. education in self-management; pharmacy management programmes; nurse, pharmacist, and other non-medical health professional intervention protocols; counselling; behavioural interventions; follow-up; and reminders) have been shown to be effective in significantly improving adherence rates,<sup>224</sup> they have tended to be used alone. A single factor approach might be expected to have limited effectiveness if the factors determining adherence interact and potentiate each other's influence, as they are likely to do.

The most effective approaches have been shown to be multilevel—targeting more than one factor with more than one intervention. Several programmes have demonstrated good results using multilevel team approaches. In fact, adequate evidence exists to support the use of innovative, modified healthcare system teams rather than traditional, independent physician practice and minimally structured systems.<sup>221</sup>

Most of the statements in these guidelines are supported by published evidence. Only a minority of the publications that support the written text can be listed in the following abridged reference list of the guidelines. A full list of the references is available on the ESC website ([www.escardio.org/guidelines](http://www.escardio.org/guidelines)).

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CME questions for this article are available at: *European Heart Journal* [http://cme.oxfordjournals.org/cgi/hierarchy/oupcme\\_node:ehj](http://cme.oxfordjournals.org/cgi/hierarchy/oupcme_node:ehj) and European Society of Cardiology <http://www.escardio.org/guidelines>.

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