

2016 ESC/EAS Guidelines for the Management of Dyslipidaemias

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

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

Authors/Task Force Members: Alberico L. Catapano* (Chairperson) (Italy), Ian Graham* (Chairperson) (Ireland), Guy De Backer (Belgium), Olov Wiklund (Sweden), M. John Chapman (France), Heinz Drexel (Austria), Arno W. Hoes (The Netherlands), Catriona S. Jennings (UK), Ulf Landmesser (Germany), Terje R. Pedersen (Norway), Željko Reiner (Croatia), Gabriele Riccardi (Italy), Marja-Riita Taskinen (Finland), Lale Tokgozoglu (Turkey), W. M. Monique Verschuren (The Netherlands), Charalambos Vlachopoulos (Greece), David A. Wood (UK), Jose Luis Zamorano (Spain)

Additional Contributor: Marie-Therese Cooney (Ireland)

Document Reviewers: Lina Badimon (CPG Review Coordinator) (Spain), Christian Funck-Brentano (CPG Review Coordinator) (France), Stefan Agewall (Norway), Gonzalo Barón-Esquivias (Spain), Jan Borén (Sweden), Eric Bruckert (France), Alberto Cordero (Spain), Alberto Corsini (Italy), Pantaleo Giannuzzi (Italy),

* Corresponding authors: Alberico L. Catapano, Department of Pharmacological and Biomolecular Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, and Multimedica IRCCS (MI) Italy. Tel: +39 02 5031 8401, Fax: +39 02 5031 8386, E-mail: alberico.catapano@unimi.it; Ian Graham, Cardiology Department, Hermitage Medical Clinic, Old Lucan Road, Dublin 20, Dublin, Ireland. Tel: +353 1 6459715, Fax: +353 1 6459714, E-mail: ian@grahams.net

ESC Committee for Practice Guidelines (CPG) and National Cardiac Society Reviewers can be found in the Appendix.

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), European Association for Cardiovascular Prevention & Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), Heart Failure Association (HFA)

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

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

The content of these European Society of Cardiology (ESC) and European Atherosclerosis Society Guidelines has been published for personal and educational use only. No commercial use is authorized. No part of the ESC Guidelines may be translated or reproduced in any form without written permission from the ESC. Permission can be obtained upon submission of a written request to Oxford University Press, the publisher of the European Heart Journal and the party authorized to handle such permissions on behalf of the ESC (journals.permissions@oup.com).

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

© 2016 European Society of Cardiology and European Atherosclerosis Association. All rights reserved. For permissions please email: journals.permissions@oup.com.

François Gueyffier (France), Goran Krstacic (Croatia), Maddalena Lettino (Italy), Christos Lionis (Greece), Gregory Y. H. Lip (UK), Pedro Marques-Vidal (Switzerland), Davor Milicic (Croatia), Juan Pedro-Botet (Spain), Massimo F. Piepoli (Italy), Angelos G. Rigopoulos (Germany), Frank Ruschitzka (Switzerland), José Tuñón (Spain), Arnold von Eckardstein (Switzerland), Michal Vrablik (Czech Republic), Thomas W. Weiss (Austria), Bryan Williams (UK), Stephan Windecker (Switzerland), and Reuven Zimlichman (Israel)

The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines.

Online publish-ahead-of-print 28 August 2016

Keywords

dyslipidaemias • cholesterol • triglycerides • low-density lipoproteins • high-density lipoproteins • apolipoprotein B • lipoprotein remnants • total cardiovascular risk • treatment, lifestyle • treatment, drugs • treatment, adherence

Table of Contents

List of abbreviations	3	5.4.5 Smoking	25
Preamble	5	5.5 Dietary supplements and functional foods for the treatment of dyslipidaemias	25
1. What is cardiovascular disease prevention?	6	5.5.1 Phytosterols	26
1.1 Definition and rationale	6	5.5.2 Monacolin and red yeast rice	26
1.2 Development of the Joint Task Force guidelines	6	5.5.3 Dietary fibre	26
1.3 Cost-effectiveness of prevention	7	5.5.4 Soy protein	26
2. Total cardiovascular risk	8	5.5.5 Policosanol and berberine	26
2.1 Total cardiovascular risk estimation	8	5.5.6 n-3 unsaturated fatty acids	26
2.1.1 Rationale for assessing total cardiovascular disease risk	8	5.6 Other features of a healthy diet contributing to cardiovascular disease prevention	26
2.1.2 How to use the risk estimation charts	12	6. Drugs for treatment of hypercholesterolaemia	27
2.2 Risk levels	13	6.1 Statins	27
2.2.1 Risk- based intervention strategies	13	6.1.1 Mechanism of action	27
3. Evaluation of laboratory lipid and apolipoprotein parameters	14	6.1.2 Efficacy of cardiovascular disease prevention in clinical studies	27
3.1 Fasting or non-fasting?	16	6.1.3 Adverse effects of statins	29
3.2 Intra-individual variation	16	6.1.4 Interactions	30
3.3 Lipid and lipoprotein analyses	16	6.2 Bile acid sequestrants	30
3.3.1 Total cholesterol	16	6.2.1 Mechanism of action	30
3.3.2 Low-density lipoprotein cholesterol	16	6.2.2 Efficacy in clinical studies	30
3.3.3 Non-high-density lipoprotein cholesterol	17	6.2.3 Adverse effects and interactions	30
3.3.4 High-density lipoprotein cholesterol	18	6.3 Cholesterol absorption inhibitors	30
3.3.5 Triglycerides	18	6.3.1 Mechanism of action	30
3.3.6 Apolipoproteins	18	6.3.2 Efficacy in clinical studies	31
3.3.7 Lipoprotein(a)	19	6.3.3 Adverse effects and interactions	31
3.3.8 Lipoprotein particle size	19	6.4 PCSK9 inhibitors	31
3.3.9 Genotyping	19	6.4.1 Mechanism of action	31
4. Treatment targets	20	6.4.2 Efficacy in clinical studies	31
5. Lifestyle modifications to improve the plasma lipid profile	21	6.4.3 Adverse effects and interactions	31
5.1 The influence of lifestyle on total cholesterol and low-density lipoprotein cholesterol levels	23	6.5 Nicotinic acid	31
5.2 The influence of lifestyle on triglyceride levels	24	6.6 Drug combinations	32
5.3 The influence of lifestyle on high-density lipoprotein cholesterol levels	24	6.6.1 Statins and cholesterol absorption inhibitors	32
5.4 Lifestyle recommendations to improve the plasma lipid profile	24	6.6.2 Statins and bile acid sequestrants	32
5.4.1 Body weight and physical activity	24	6.6.3 Other combinations	32
5.4.2 Dietary fat	25	7. Drugs for treatment of hypertriglyceridaemia	32
5.4.3 Dietary carbohydrate and fibre	25	7.1 Triglycerides and cardiovascular disease risk	32
5.4.4 Alcohol	25	7.2 Definition of hypertriglyceridaemia	33
		7.3 Strategies to control plasma triglycerides	33

7.4	Statins	33	9.7	Heart failure and valvular diseases	44
7.5	Fibrates	33	9.7.1	Prevention of incident heart failure in coronary artery disease patients	44
7.5.1	Mechanism of action	33	9.7.2	Chronic heart failure	44
7.5.2	Efficacy in clinical trials	33	9.7.3	Valvular disease	45
7.5.3	Adverse effects and interactions	34	9.8	Autoimmune diseases	45
7.6	Nicotinic acid	34	9.9	Chronic kidney disease	45
7.6.1	Mechanism of action	34	9.9.1	Lipoprotein profile in chronic kidney disease	45
7.6.2	Efficacy in clinical trials	34	9.9.2	Evidence for lipid management in patients with chronic kidney disease	46
7.7	n-3 fatty acids	34	9.9.3	Safety of lipid management in patients with chronic kidney disease	46
7.7.1	Mechanism of action	34	9.9.4	Recommendations of lipid management for patients with chronic kidney disease	46
7.7.2	Efficacy in clinical trials	34	9.10	Transplantation (Table 31)	46
7.7.3	Safety and interactions	35	9.11	Peripheral arterial disease	47
8	Drugs affecting high-density lipoprotein cholesterol (Table 20)	35	9.11.1	Lower extremities arterial disease	47
8.1	Statins	35	9.11.2	Carotid artery disease	47
8.2	Fibrates	35	9.11.3	Retinal vascular disease	48
8.3	Nicotinic acid	35	9.11.4	Secondary prevention in patients with aortic abdominal aneurysm	48
8.4	Cholesteryl ester transfer protein inhibitors	36	9.11.5	Renovascular atherosclerosis	48
8.5	Future perspectives	36	9.12	Stroke	48
9	Management of dyslipidaemia in different clinical settings	36	9.12.1	Primary prevention of stroke	48
9.1	Familial dyslipidaemias	36	9.12.2	Secondary prevention of stroke	49
9.1.1	Familial combined hyperlipidaemia	36	9.13	Human immunodeficiency virus patients	49
9.1.2	Familial hypercholesterolaemia	36	9.14	Mental disorders	49
9.1.2.1	Heterozygous familial hypercholesterolaemia	36	10	Monitoring of lipids and enzymes in patients on lipid-lowering therapy (Table 36)	51
9.1.2.2	Homozygous familial hypercholesterolaemia	38	11	Strategies to encourage adoption of healthy lifestyle changes and adherence to lipid-modifying therapies	51
9.1.2.3	Familial hypercholesterolaemia in children	38	11.1	Achieving and adhering to healthy lifestyle changes	51
9.1.3	Familial dysbetalipoproteinaemia	38	11.2	Adhering to medications	54
9.1.4	Genetic causes of hypertriglyceridaemia	38	12	To do and not to do messages from the Guidelines	57
9.1.4.1	Action to prevent acute pancreatitis in severe hypertriglyceridaemia	39	13	Appendix	58
9.1.5	Other genetic disorders of lipoprotein metabolism (Table 23)	39	14	References	59
9.2	Children	40	List of abbreviations		
9.3	Women	40	ABI	ankle-brachial index	
9.3.1	Primary prevention	40	ACC	American College of Cardiology	
9.3.2	Secondary prevention	40	ACCELERATE	Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes	
9.3.3	Non-statin lipid-lowering drugs	40	ACCORD	Action to Control Cardiovascular Risk in Diabetes	
9.3.4	Hormone therapy	40	ACS	acute coronary syndrome	
9.4	Older persons	40	AFCAPS/	Air Force/Texas Coronary Atherosclerosis Prevention Study	
9.4.1	Primary prevention	41	TEXCAPS		
9.4.2	Secondary prevention	41	AHA	American Heart Association	
9.4.3	Adverse effects, interactions and adherence	41	AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes	
9.5	Diabetes and metabolic syndrome	42	ALT	alanine aminotransferase	
9.5.1	Specific features of dyslipidaemia in insulin resistance and type 2 diabetes (Table 25)	42	Apo	apolipoprotein	
9.5.2	Evidence for lipid-lowering therapy	42			
9.5.2.1	Low-density lipoprotein cholesterol	42			
9.5.2.2	Triglycerides and high-density lipoprotein cholesterol	42			
9.5.3	Treatment strategies for subjects with type 2 diabetes and metabolic syndrome	43			
9.5.4	Type 1 diabetes	43			
9.6	Patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention	43			
9.6.1	Specific lipid management issues in acute coronary syndrome	43			
9.6.2	Lipid management issues in patients undergoing percutaneous coronary intervention	44			

ART	antiretroviral treatment	HF	heart failure
ASSIGN	CV risk estimation model from the Scottish Intercollegiate Guidelines Network	HHS	Helsinki Heart Study
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin	HIV	human immunodeficiency virus
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events	HMG-CoA	hydroxymethylglutaryl-coenzyme A
BIP	Bezafibrate Infarction Prevention study	HPS	Heart Protection Study
BMI	body mass index	HPS2-THRIVE	Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events
CABG	coronary artery bypass graft surgery	HoFH	homozygous familial hypercholesterolaemia
CAC	coronary artery calcium	HTG	hypertriglyceridaemia
CAD	coronary artery disease	HR	hazard ratio
CARE	Cholesterol and Recurrent Events	hs-CRP	high-sensitivity C-reactive protein
CETP	cholesteryl ester transfer protein	ICD	International Classification of Diseases
CHD	coronary heart disease	IDEAL	Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial
CIMT	carotid intima-media thickness	IDL	intermediate-density lipoproteins
CK	creatinine kinase	ILLUMINATE	Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events
CKD	chronic kidney disease	IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
CTT	Cholesterol Treatment Trialists	JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
CV	cardiovascular	KDIGO	Kidney Disease: Improving Global Outcomes
CVD	cardiovascular disease	LAL	lysosomal acid lipase
CYP	cytochrome P450	LCAT	lecithin cholesterol acyltransferase
4D	Die Deutsche Diabetes Dialyse	LDL-C	low-density lipoprotein cholesterol
DASH	Dietary Approaches to Stop Hypertension	LDLR	low-density lipoprotein receptor
DGAT-2	diacylglycerol acyltransferase-2	LEAD	lower extremities arterial disease
DHA	docosahexaenoic acid	LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
DLCN	Dutch Lipid Clinic Network	LPL	lipoprotein lipase
EAS	European Atherosclerosis Society	Lp	lipoprotein
EMA	European Medicines Agency	MetS	metabolic syndrome
EPA	eicosapentaenoic acid	MI	myocardial infarction
ER	extended release	MTP	microsomal triglyceride transfer protein
ESC	European Society of Cardiology	MUFA	monounsaturated fatty acid
ESRD	end-stage renal disease	NICE	National Institute for Health and Care Excellence
EU	European Union	NNRTI	non-nucleoside reverse transcriptase inhibitor
FACE-BD	Fondamental Academic Centers of Expertise in Bipolar Disorders	NNT	number needed to treat
FATS	Familial Atherosclerosis Treatment Study	NPC1L1	Niemann-Pick C1-like protein 1
FCH	familial combined hyperlipidaemia	NSTE-ACS	non-ST elevation acute coronary syndrome
FDA	US Food and Drug Administration	NYHA	New York Heart Association
FDC	fixed-dose combination	PAD	peripheral arterial disease
FH	familial hypercholesterolaemia	PCI	percutaneous coronary intervention
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes	PCSK9	proprotein convertase subtilisin/kexin type 9
FOCUS	Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention	PPAR- α	peroxisome proliferator-activated receptor- α
GFR	glomerular filtration rate	PROCAM	Prospective Cardiovascular Munster Study
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico	PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
GP	general practitioner	PUFA	polyunsaturated fatty acid
GWAS	genome-wide association studies	RAAS	renin–angiotensin–aldosterone system
HAART	highly active antiretroviral treatment	RCT	randomized controlled trial
HATS	HDL-Atherosclerosis Treatment Study	REACH	Reduction of Atherothrombosis for Continued Health
HbA1C	glycated haemoglobin	REDUCE-IT	Reduction of Cardiovascular Events with EPA-Intervention Trial
HeFH	heterozygous familial hypercholesterolaemia		
HDL-C	high-density lipoprotein cholesterol		

REVEAL	Randomized Evaluation of the Effects of Anacetrapib Through Lipid modification
RR	relative risk
RYR	red yeast rice
4S	Scandinavian Simvastatin Survival Study
SALTIRE	Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression
SAGE	Studies Assessing Goals in the Elderly
SCORE	Systemic Coronary Risk Estimation
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SFA	saturated fatty acid
SHARP	Study of Heart and Renal Protection
SLE	systemic lupus erythematosus
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
STEMI	ST elevation myocardial infarction
STRENGTH	Outcomes Study to Assess STatin Residual Risk Reduction with EpaNova in HiGh CV Risk Patients with Hypertriglyceridemia
TIA	transient ischaemic attack
TC	total cholesterol
T2DM	type 2 diabetes mellitus
TG	triglyceride
TNT	Treatment to new targets
TRL	triglyceride-rich lipoprotein
ULN	upper limit of normal
UMPIRE	Use of a Multidrug Pill In Reducing cardiovascular Events
VA-HIT	Veterans Affairs High-density lipoprotein Intervention Trial
VLDL	very low-density lipoprotein
WHO	World Health Organization

Preamble

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

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

Guidelines represent the official position of the ESC on a given topic and are regularly updated.

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

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (<http://www.escardio.org/guidelines>). Any changes in declarations of interest that arise during the writing period must be notified to the ESC and EAS and updated. The Task Force received its entire financial support from the ESC and EAS without any involvement from the healthcare industry.

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

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

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

Table 1 Classes of recommendations

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

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

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

1. What is cardiovascular disease prevention?

1.1 Definition and rationale

Cardiovascular disease (CVD) kills >4 million people in Europe each year. It kills more women [2.2 million (55%)] than men [1.8 million (45%)], although cardiovascular (CV) deaths before the age of 65 years are more common in men (490 000 vs. 193 000).¹ Prevention is defined as a coordinated set of actions, at the population level or targeted at an individual, aimed at eradicating, eliminating or minimizing the impact of CV diseases and their related disability. CVD remains a leading cause of morbidity and mortality, despite improvements in outcomes for CVD. More patients are surviving their first CVD event and are at high risk of recurrences. In addition, the prevalence of some risk factors, notably diabetes and obesity, is increasing. The importance of CVD prevention remains undisputed and should be delivered at different levels: (i) in the general population by promoting healthy lifestyle behaviour² and (ii) at the

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.

individual level, in those at moderate to high risk of CVD or patients with established CVD, by tackling an unhealthy lifestyle (e.g. poor-quality diet, physical inactivity, smoking) and by reducing increased levels of CV risk factors such as increased lipid or blood pressure levels. Prevention is effective in reducing the impact of CVD; the elimination of health risk behaviours would make it possible to prevent at least 80% of CVD and even 40% of cancers, thus providing added value for other chronic diseases.^{3,4}

1.2 Development of the Joint Task Force guidelines

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

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

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

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

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

1.3 Cost-effectiveness of prevention

Box 1 Key messages

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

CV = cardiovascular; CVD = cardiovascular disease.

In 2009, healthcare costs related to CVD in Europe amounted to €106 billion, representing ~9% of the total healthcare expenditure across the European Union (EU).⁸ In the USA, direct annual costs of CVD are projected to triple between 2010 and 2030.⁹ Thus, CVD represents a considerable economic burden to society, and this necessitates an effective approach to CVD prevention. There is consensus in favour of an approach combining strategies to improve CV health across the population at large from childhood onwards, with actions to improve CV health in individuals at increased risk of CVD or with established CVD.

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

Table 3 Suggestions for implementing healthy lifestyles

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

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

More than half of the reduction in CV mortality in the last three decades has been attributed to population-level changes in CV risk factors, primarily reductions in cholesterol and blood pressure levels and smoking.^{13–16} This favourable trend is partly offset by increases in other major risk factors, such as obesity and type 2 diabetes.^{13–16} Ageing of the population also contributes to increasing the absolute number of CVD events.¹⁷

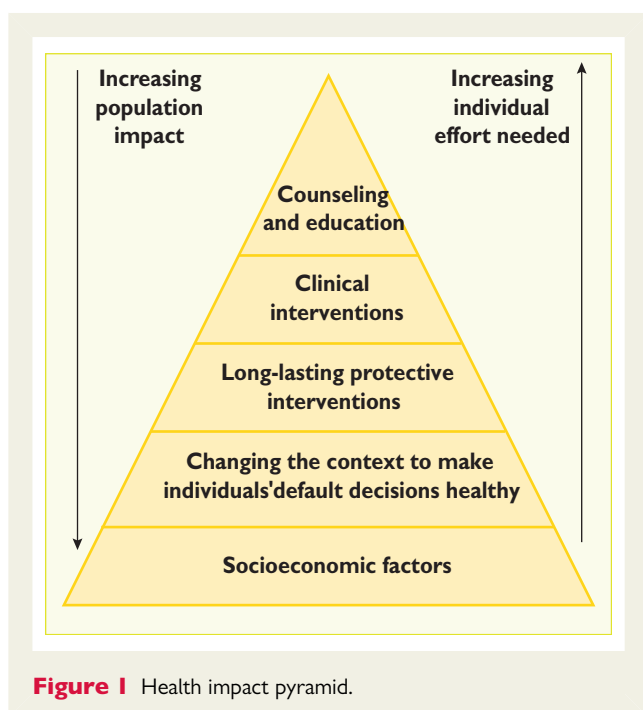
Several population-level interventions have proven to efficiently affect lifestyle in individuals, leading to this success: awareness and knowledge of how lifestyle risk factors lead to CVD increased in recent decades and undoubtedly contributed to the decline in smoking and cholesterol levels. Moreover,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

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

It has been suggested that the prescription to the whole population older than 55 years of age of a single pill containing a combination of CV drugs (the polypill) could prevent as much as 80% of CVD events³³ and be cost effective.³⁴ Part of the cost-effectiveness of the polypill is due to improvement in adherence to treatment, but which combination of drugs is most cost effective in which target population remains to be assessed.³⁵

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

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



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

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

Box 2 Gaps in evidence

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

2. Total cardiovascular risk

2.1 Total cardiovascular risk estimation

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

2.1.1 Rationale for assessing total cardiovascular disease risk

All current guidelines on the prevention of CVD in clinical practice recommend the assessment of total CAD or CV risk, because atherosclerotic CVD is usually the product of a number of risk factors, and prevention of CVD in a given person should be adapted to

his/her total CV risk: the higher the risk, the more intense the action should be.

Many risk assessment systems are available and have been comprehensively reviewed, including different Framingham models,⁴¹ Systemic Coronary Risk Estimation (SCORE),⁴² ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network),⁴³ Q-Risk,⁴⁴ Prospective Cardiovascular Munster Study (PROCAM),⁴⁵ Reynolds,^{46,47} CUORE,⁴⁸ the Pooled Cohort equations⁴⁹ and Globorisk.⁵⁰ Most guidelines use one of these risk estimation systems.^{50–52}

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

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

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

(1) Persons with

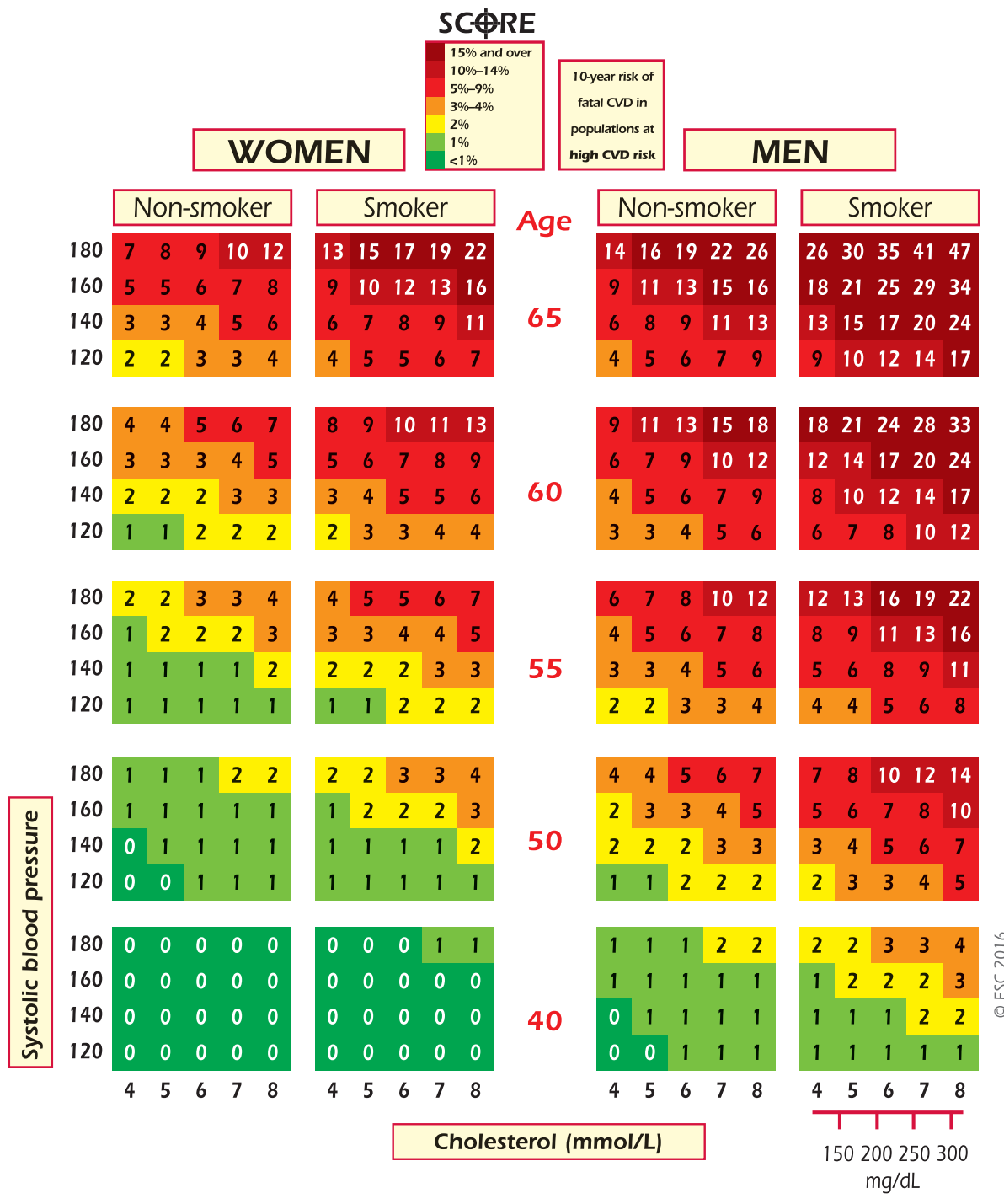
- documented CVD
- type 1 or type 2 diabetes
- very high levels of individual risk factors
- chronic kidney disease (CKD) (refer to section 9.9)

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

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

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

The reasons for retaining a system that estimates fatal as opposed to total fatal + non-fatal events are that non-fatal events are dependent on definition, developments in diagnostic tests and methods of ascertainment, all of which can vary, resulting in very



Downloaded from <http://eurheartj.oxfordjournals.org/> by guest on December 19, 2016

Figure 2 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in populations at high CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + nonfatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, familial hypercholesterolaemia or very high levels of individual risk factors because such people are already at high-risk and need intensive risk factor advice.

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

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

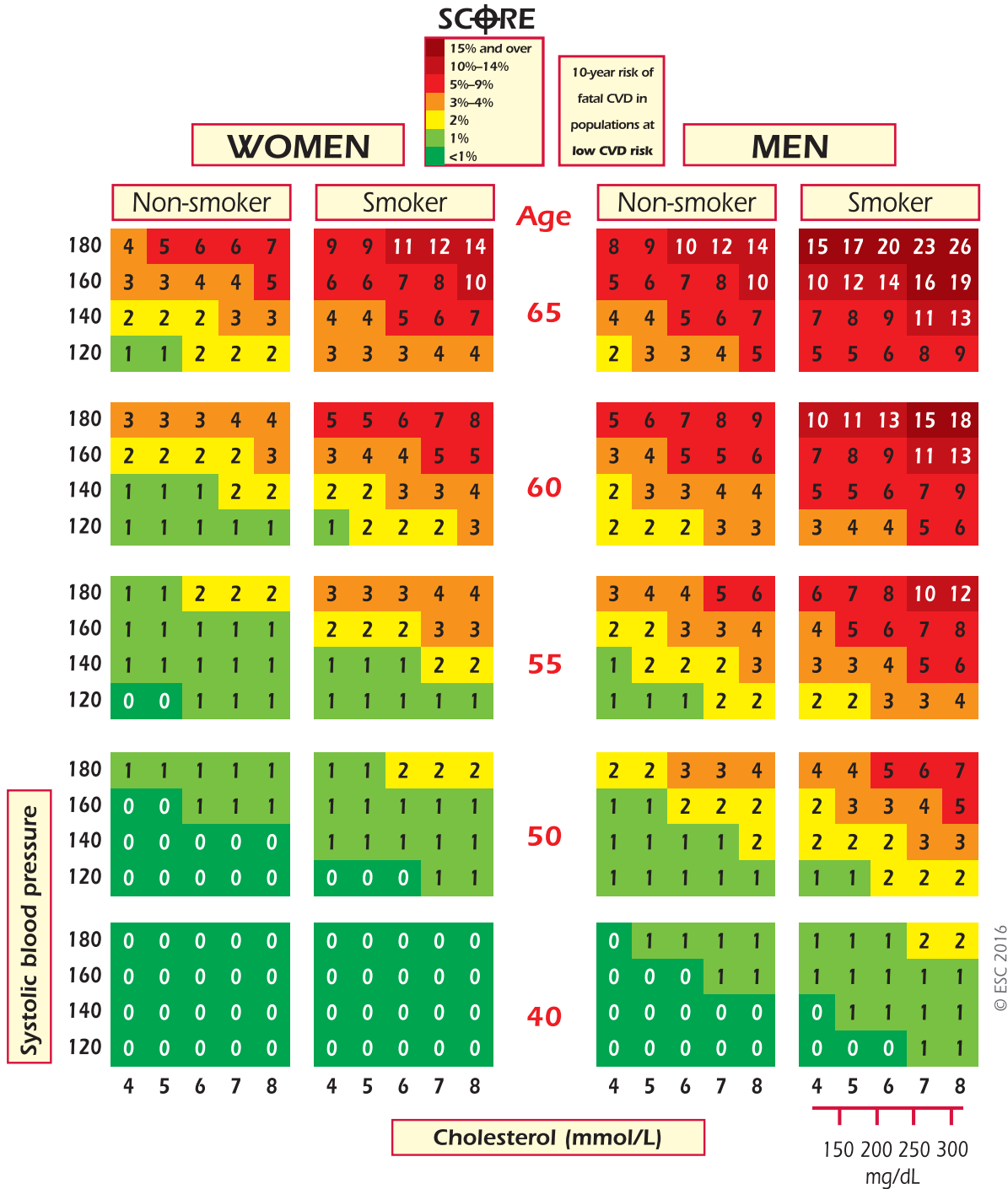


Figure 3 SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in populations at low CVD risk based on the following risk factors: age, gender, smoking, systolic blood pressure, and total cholesterol. To convert the risk of fatal CVD to risk of total (fatal + non-fatal) hard CVD, multiply by 3 in men and 4 in women, and slightly less in old people. Note: the SCORE chart is for use in people without overt CVD, diabetes, chronic kidney disease, familial hypercholesterolaemia, or very high levels of individual risk factors because such people are already at high-risk and need intensive risk factor advice.

than the risk of fatal CVD for men, so that a SCORE risk of 5% translates into a CVD risk of ~15% of total (fatal + non-fatal) hard CVD endpoints; the multiplier is ~4 in women and lower in older persons.

Clinicians often ask for thresholds to trigger certain interventions. This is problematic since risk is a continuum and there is no threshold at which, for example, a drug is automatically indicated. This is true for all continuous risk factors such as plasma cholesterol or

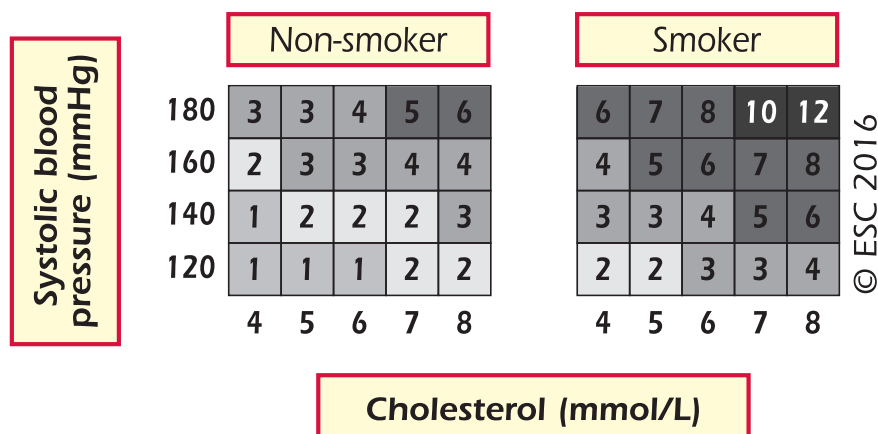


Figure 4 Relative risk chart for 10-year cardiovascular mortality. Please note that this chart shows RELATIVE not absolute risk. The risks are RELATIVE to 1 in the bottom left. Thus, a person in the top right hand box has a relative risk that is 12 times higher than a person in the bottom left.

systolic blood pressure. Therefore, the goals that are proposed in this document reflect this concept.

A particular problem relates to young people with high levels of risk factors; a low absolute risk may conceal a very high relative risk requiring intensive lifestyle advice. To motivate young people not to delay changing their unhealthy lifestyle, an estimate of their relative risk, illustrating that lifestyle changes can reduce relative risk substantially, may be helpful (Figure 4).

Another approach to this problem in young people is to use CV risk age. The risk age of a person with several CV risk factors is the age of a person with the same level of risk but with ideal levels of risk factors. Thus a high-risk 40-year-old may have a risk age ≥ 60 years. Risk age is an intuitive and easily understood way of illustrating the likely reduction in life expectancy that a young person with a low absolute but high relative risk of CVD will be exposed to if preventive measures are not adopted. Risk age can be estimated visually by looking at the SCORE chart (as illustrated in Figure 5). In this chart, the risk age is calculated compared with someone with ideal risk factor levels, which have been taken as non-smoking, total cholesterol of 4 mmol/L (155 mg/dL) and systolic blood pressure of 120 mmHg. Risk age is also automatically calculated as part of the latest revision of HeartScore (<http://www.HeartScore.org>).

Risk age has been shown to be independent of the CV endpoint used,^{51,52} which bypasses the dilemma of whether to use a risk estimation system based on CVD mortality or on the more attractive but less reliable endpoint of total CVD events. Risk age can be used in any population regardless of baseline risk or secular changes in mortality, and therefore avoids the need for recalibration. At present, risk age is recommended for helping to communicate about risk, especially to younger people with a low absolute risk but a high relative risk. It is not currently recommended to base treatment decisions on risk age.

Lifetime risk is another approach to illustrating the impact of risk factors that may be useful in younger people.⁵³ The greater the

burden of risk factors, the higher the lifetime risk. This approach produces higher risk figures for younger people because of their longer exposure times. It is therefore more useful as a way of illustrating risk than as a guide to treatment because therapeutic trials have been based on a fixed follow-up period and not on lifetime risk and such an approach would likely lead to excessive use of drugs in young people.

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

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

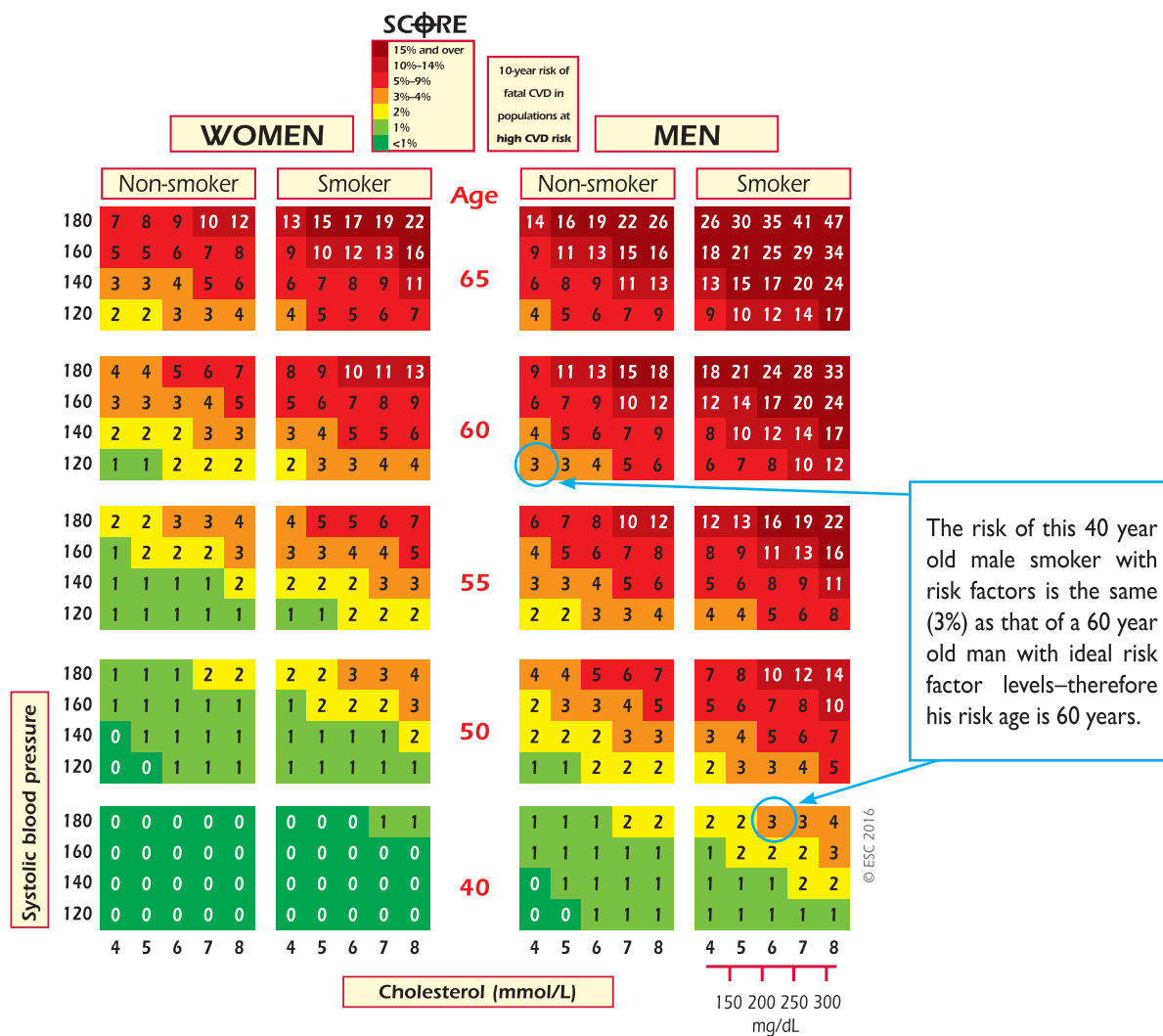


Figure 5 Illustration of the risk age concept.

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

2.1.2 How to use the risk estimation charts

When it comes to European countries and to countries with cardiology societies that belong to the ESC, the low-risk charts should be considered for use in Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom. While any cut-off point is arbitrary and open to debate, in these guidelines the cut-off points for calling a country 'low risk' are based on age-adjusted 2012 CVD mortality rates

(<225/100 000 in men and <175/100 000 in women) (<http://apps.who.int/gho/data/node.main.A865CARDIOVASCULAR?lang=en>).

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

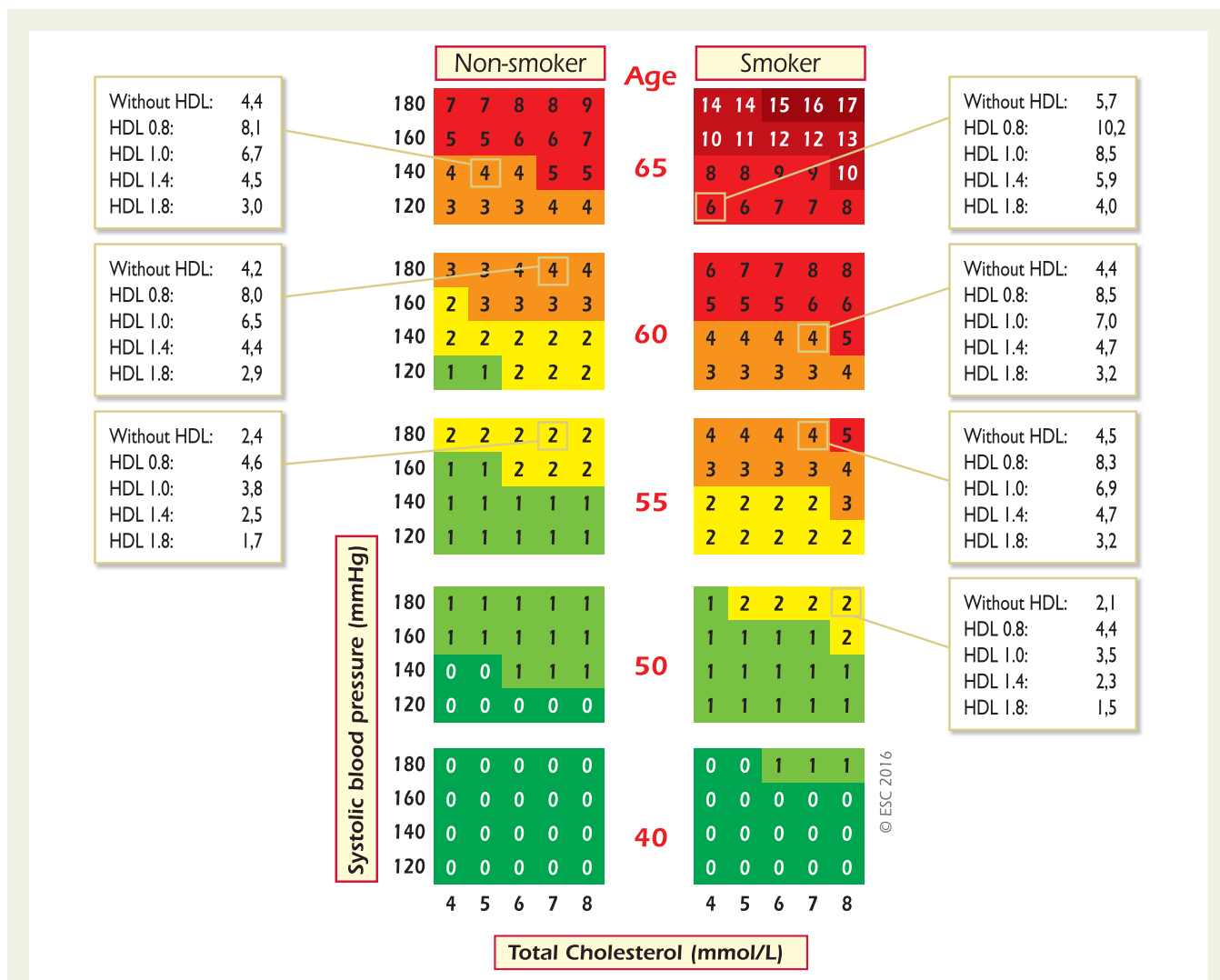


Figure 6 Risk function without high-density lipoprotein-cholesterol (HDL-C) for women in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.

Box 3 How to use the risk estimation charts

To estimate a person's 10-year risk of CVD death, find the table for his/her gender, smoking status, and age. Within the table find the cell nearest to the person's blood pressure and TC. Risk estimates will need to be adjusted upwards as the person approaches the next age category.

Risk is initially assessed on the level of TC and systolic blood pressure before treatment, if known. The longer the treatment and the more effective it is, the greater the reduction in risk, but in general it will not be more than about one-third of the baseline risk. For example, for a person on antihypertensive drug treatment in whom the pre-treatment blood pressure is not known, if the total CV SCORE risk is 6%, then the pre-treatment total CV risk may have been 9%.

Low-risk persons should be offered advice to maintain their low-risk status. While no threshold is universally applicable, the intensity of advice should increase with increasing risk.

The charts may be used to give some indication of the effects of reducing risk factors, given that there will be a time lag before the risk reduces and that the results of randomized controlled trials in general give better estimates of benefits. In general, those who stop smoking rapidly halve their cumulative risk.

Box 4 Qualifiers

The charts can assist in risk assessment and management but must be interpreted in light of the clinician's knowledge and experience and of the patient's pre-test likelihood of CVD.

Risk will be overestimated in countries with a decreasing CVD mortality, and underestimated in countries in which mortality is increasing. This is dealt with by recalibration (www.heartscore.org).

Risk estimates appear lower in women than in men. However, risk is only deferred in women; the risk of a 60-year-old woman is similar to that of a 50-year-old man. Ultimately more women die from CVD than men.

Relative risks may be unexpectedly high in young persons, even if absolute risk levels are low. The relative risk chart (Figure 4) and the estimated risk age (Figure 5) may be helpful in identifying and counselling such persons.

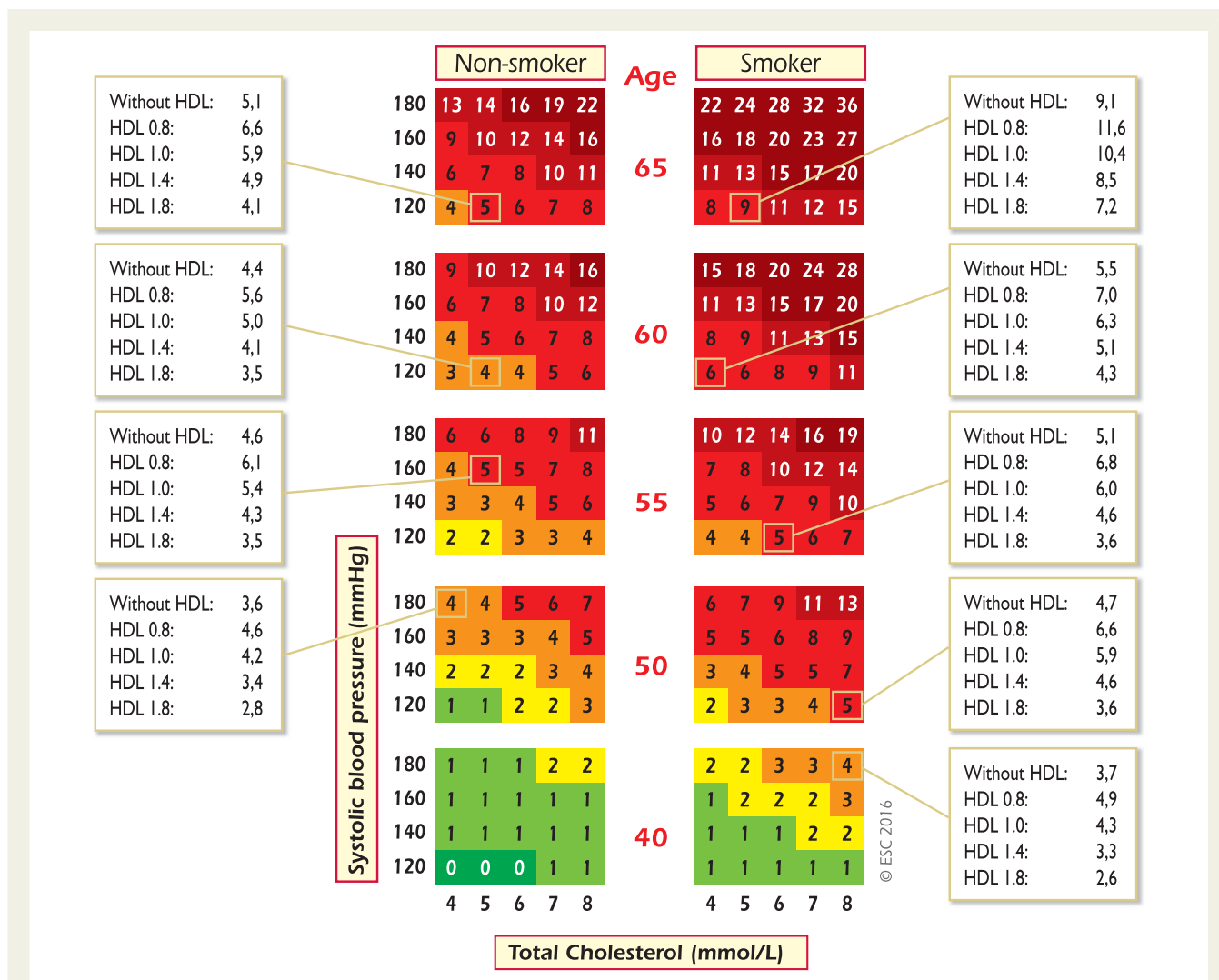


Figure 7 Risk function without high-density lipoprotein-cholesterol (HDL-C) for men in populations at high cardiovascular disease risk, with examples of the corresponding estimated risk when different levels of HDL-C are included.

Box 5 Factors modifying SCORE risks

Social deprivation—the origin of many of the causes of CVD.
Obesity and central obesity as measured by the body mass index and waist circumference, respectively.
Physical inactivity.
Psychosocial stress including vital exhaustion.
Family history of premature CVD (men: <55 years; women: <60 years).
Autoimmune and other inflammatory disorders.
Major psychiatric disorders.
Treatment for human immunodeficiency virus (HIV) infection.
Atrial fibrillation.
Left ventricular hypertrophy.
Chronic kidney disease.
Obstructive sleep apnoea syndrome.

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

Social deprivation and psychosocial stress set the scene for increased risk.⁵⁷ For those at intermediate risk, other factors, including metabolic factors such as increased apolipoprotein B (apoB), lipoprotein(a) (Lp(a)), triglycerides (TGs) or high-sensitivity C-reactive protein (hs-CRP) or the presence of albuminuria, may improve risk classification. Many other biomarkers are also associated with increased CVD risk, although few of these have been shown to be associated with appreciable reclassification. Total CV risk will also be higher than indicated in the SCORE charts in asymptomatic persons with abnormal markers of subclinical atherosclerotic vascular damage detected by coronary artery calcium (CAC), ankle-brachial index (ABI), pulse wave velocity or carotid ultrasonography. In studies comparing these markers, CAC had the best reclassification ability.^{58–60}

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

Box 6 Key messages

In apparently healthy persons, CVD risk is most frequently the result of multiple, interacting risk factors. This is the basis for total CV risk estimation and management.

Risk factor screening including the lipid profile should be considered in men >40 years old and in women >50 years of age or post-menopausal.

A risk estimation system such as SCORE can assist in making logical management decisions, and may help to avoid both under- or over-treatment.

Certain individuals declare themselves to be at high or very high CVD risk without needing risk scoring and require immediate attention to all risk factors.

This is true for patients with documented CVD, diabetes or CKD.

All risk estimation systems are relatively crude and require attention to qualifying statements.

Additional factors affecting risk can be accommodated in electronic risk estimation systems such as HeartScore (www.heartscore.org).

The total risk approach allows flexibility—if perfection cannot be achieved with one risk factor, risk can still be reduced by trying harder with the others.

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

2.2 Risk levels

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

In these subjects we realistically can

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

Low-risk people should be given advice to help them maintain this status. Thus the intensity of preventive actions should be tailored to the patient's total CV risk. The strongest driver of total CV risk is age, which can be considered as 'exposure time' to risk factors. This raises the issue that most older people in high-risk countries who smoke would be candidates for lipid-lowering drug treatment even if they have satisfactory blood pressure levels. The clinician is strongly recommended to use clinical judgment in making

therapeutic decisions in older people, with a firm commitment to implementing lifestyle measures such as smoking cessation in the first instance.

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

Table 4 Risk categories

Very high-risk	Subjects with any of the following: <ul style="list-style-type: none"> • Documented cardiovascular disease (CVD), clinical or unequivocal on imaging. Documented CVD includes previous myocardial infarction (MI), acute coronary syndrome (ACS), coronary revascularisation (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)) and other arterial revascularization procedures, stroke and transient ischaemic attack (TIA), and peripheral arterial disease (PAD). Unequivocally documented CVD on imaging is what has been shown to be strongly predisposed to clinical events, such as significant plaque on coronary angiography or carotid ultrasound. • DM with target organ damage such as proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia. • Severe CKD (GFR <30 mL/min/1.73 m²). • A calculated SCORE ≥10% for 10-year risk of fatal CVD.
High-risk	Subjects with: <ul style="list-style-type: none"> • Markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg. • Most other people with DM (some young people with type I diabetes may be at low or moderate risk). • Moderate CKD (GFR 30–59 mL/min/1.73 m²). • A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	SCORE is ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	SCORE <1% for 10-year risk of fatal CVD.

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

2.2.1 Risk-based intervention strategies

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

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

Total CV risk (SCORE) %	LDL-C levels				
	<70 mg/dL <1.8 mmol/L	70 to <100 mg/dL 1.8 to <2.6 mmol/L	100 to <155 mg/dL 2.6 to <4.0 mmol/L	155 to <190 mg/dL 4.0 to <4.9 mmol/L	≥190 mg/dL ≥4.9 mmol/L
<1	No lipid intervention	No lipid intervention	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled
Class ^a /Level ^b	I/C	I/C	I/C	I/C	Ia/A
≥1 to <5	No lipid intervention	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention, consider drug if uncontrolled
Class ^a /Level ^b	I/C	I/C	Ia/A	Ia/A	I/A
≥5 to <10, or high-risk	No lipid intervention	Lifestyle intervention, consider drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	Ia/A	Ia/A	Ia/A	I/A	I/A
≥10 or very high-risk	Lifestyle intervention, consider drug ^c	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	Ia/A	Ia/A	I/A	I/A	I/A

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.

^aClass of recommendation.

^bLevel of evidence.

^cIn patients with myocardial infarction, statin therapy should be considered irrespective of total cholesterol levels

Table 6 Recommendations for risk estimation

Recommendations	Class ^a	Level ^b
Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia.	I	C
High and very high-risk individuals can be detected on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, familial hypercholesterolaemia or a high SCORE risk and are a high priority for intensive advice with regard to all risk factors.	I	C

CVD = cardiovascular disease; SCORE = Systemic Coronary Risk Estimation.

^aClass of recommendation.

^bLevel of evidence.

3. Evaluation of laboratory lipid and apolipoprotein parameters

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

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

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

Table 7 Recommendations for lipid analyses in cardiovascular disease risk estimation

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

Apo = apolipoprotein; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; SCORE = Systemic Coronary Risk Estimation; TC = total cholesterol; TG = triglycerides.

^aClass of recommendation.

^bLevel of evidence.

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

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

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

Apo = apolipoprotein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; Lp = lipoprotein; TC = total cholesterol; TG = triglycerides.

^aClass of recommendation.

^bLevel of evidence.

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

3.1 Fasting or non-fasting?

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

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

3.2 Intra-individual variation

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

3.3. Lipid and lipoprotein analyses

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

3.3.1 Total cholesterol

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

3.3.2 Low-density lipoprotein cholesterol

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

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

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

- Methodological errors may accumulate since the formula necessitates three separate analyses of TC, TGs and HDL-C.
- A constant cholesterol:TG ratio in very low-density lipoprotein (VLDL) is assumed. With high TG values (>4.5 mmol/L or >400 mg/dL), the formula cannot be used.

- The Friedewald formula may be unreliable when blood is obtained under non-fasting conditions. Under these conditions, non-HDL-C may be determined.

Despite its limitations, the calculated LDL-C value is still widely used. With very low LDL-C or in patients with high TGs, the Friedewald formula may underestimate LDL-C, even giving negative values. Direct methods for the determination of LDL-C are available and are now widely used. In general, comparisons between calculated and direct LDL-C show good agreement.⁸¹ Several of the limitations of the Friedewald formula may be overcome with the direct methods. However, the direct methods have been found to be unreliable in patients with HTG and should be used with caution in these cases⁷²; also, they may underestimate very low values of LDL-C. Non-HDL-C or apoB should, under these circumstances, be considered as an alternative.

3.3.3 Non-high-density lipoprotein cholesterol

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

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

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

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

3.3.4 High-density lipoprotein cholesterol

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

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

3.3.5 Triglycerides

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

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

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

3.3.6 Apolipoproteins

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

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

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

Apolipoprotein B:apolipoprotein A1 ratio, total cholesterol:high-density lipoprotein cholesterol ratio and non-high-density lipoprotein cholesterol:high-density lipoprotein cholesterol ratio. Ratios between atherogenic lipoproteins and HDL-C or apoA1 (TC:HDL-C, non-HDL-C:HDL-C, apoB:apoA1) are useful for risk

estimation, but not for diagnosis or as treatment targets. The components of the ratio have to be considered separately.

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

3.3.7 Lipoprotein(a)

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

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

Individuals with:

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

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

3.3.8 Lipoprotein particle size

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

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

3.3.9 Genotyping

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

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

Table 7 lists recommendations for lipid analyses in CVD risk estimation, Table 8 lists recommendations for lipid analyses for characterization of dyslipidaemias before treatment and Table 9 lists

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

4. Treatment targets

In both the 2011 EAS/ESC guidelines for the management of dyslipidaemias¹²⁵ and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the treatment of blood cholesterol to reduce atherosclerotic CV risk in adults,⁷¹ the importance of LDL-C lowering to prevent CVD is strongly emphasized. The approaches that are proposed to reach that LDL-C reduction are different. The task force charged with the development of the 2016 EAS/ESC updated guidelines on dyslipidaemias examined this issue in depth. It was recognized that the US expert panel confined itself to a simple, hard source of evidence coming from results in RCTs. Despite this, there has not been an RCT to support the AHA/ACC recommendation for the use of high-dose statins in all high-risk people regardless of baseline LDL-C level. The European Task Force felt that limiting the current knowledge on CV prevention only to results from RCTs reduces the exploitation of the potential that is available for prevention of CVD. It is the concordance of the conclusions from many different approaches (from basic science, clinical observations, genetics, epidemiology, RCTs, etc.) that contributes to the understanding of the causes of CVD and to the potential of prevention. The task force is aware of the limitations of some of the sources of evidence and accepts that RCTs have not examined different LDL-C goals systematically, but felt that it was appropriate to look at the totality of the evidence. Indeed, the task force accepts that the choice of any given target goal for LDL-C may be open to debate given the continuous nature of the relationship between LDL-C reduction and reduction in risk. Particular consideration was given to results from systematic reviews confirming the dose-dependent reduction in CVD with LDL-C lowering; the greater the LDL-C reduction, the greater the CV risk reduction.^{65,66} The benefits related to LDL-C reduction are not specific for statin therapy.⁶³ No level of LDL-C below which benefit ceases or harm occurs has been defined.

There is considerable individual variability in the LDL-C response to dietary and drug treatments,⁶¹ which is traditionally taken to support a tailored approach to management. Total CV risk reduction should be individualized, and this can be more specific if goals are defined. The use of goals can also aid patient–doctor communication. It is judged likely that a goal approach may facilitate adherence to treatment, although this consensus opinion has not been fully tested. For all these reasons the European Task Force retains a goal approach to lipid management and treatment goals are defined, tailored to the total CV risk level. There is also evidence suggesting that lowering LDL-C beyond the goals that were set in the previous EAS/ESC guidelines is associated with fewer CVD events.¹²⁶ Therefore, it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high CV risk.

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

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

Apo = apolipoprotein; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

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

Table 10 Treatment targets and goals for cardiovascular disease prevention

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	2.5–5 h moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m ² , waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg ^a
Lipids LDL-C is the primary target	Very high-risk: LDL-C <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline ^b is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL).
	High-risk: LDL-C <2.6 mmol/L (100 mg/dL) or a reduction of at least 50% if the baseline ^b is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL).
	Low to moderate risk: LDL-C <3.0 mmol/L (115 mg/dL).
	Non-HDL-C secondary targets are <2.6, 3.4 and 3.8 mmol/L (100, 130 and 145 mg/dL) for very high-, high- and moderate-risk subjects, respectively.
	HDL-C: no target, but >1.0 mmol/L (40 mg/dL) in men and >1.2 mmol/L (48 mg/dL) in women indicates lower risk. TG: no target but <1.7 mmol/L (150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

BMI = body mass index; HbA1C = glycated haemoglobin; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TG = triglycerides.

^aThe BP target can be lower in some patients with type 2 diabetes¹²⁷ and in some high-risk patients without diabetes who can tolerate multiple antihypertensive drugs.⁷⁰

^bThe term “baseline LDL-C” refers to the level in a subject not taking any lipid lowering medication.

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

Box 8 Recommendations for treatment goals for low-density lipoprotein-cholesterol (LDL-C)—examples

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

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

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

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

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

^dFor definitions see section 2.2.

^eThe term “baseline LDL-C” refers to the level in a subject not taking any lipid lowering medication.

When secondary targets are used the recommendations are

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

Secondary targets have also been defined by inference for non-HDL-C and for apoB; they receive a moderate grading, as they have not been extensively studied in RCTs. Clinicians who are using apoB in their practice can use targets levels of <100 mg/dL and <80 mg/dL for subjects at high or at very high total CV risk, respectively. The specific goal for non-HDL-C should be 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-C goal; adjusting lipid-lowering therapy in accordance with these secondary targets may be considered after having achieved an LDL-C goal in patients at very high CV risk, although the clinical advantages of this approach with respect to outcomes remain to be addressed. To date, no specific goals for HDL-C or TG levels have been determined in clinical trials, although increases in HDL-C predict atherosclerosis regression and low HDL-C is associated with excess events and mortality in CAD patients, even when LDL-C is <1.8 mmol/L (70 mg/dL). However, clinical trial evidence is lacking on the effectiveness of intervening in these variables to reduce CV risk further.

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

5. Lifestyle modifications to improve the plasma lipid profile

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

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

Table 12 Impact of specific lifestyle changes on lipid levels

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

HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol; TG = triglycerides.

The magnitude of the effect (+++ = marked effects, ++ = less pronounced effects, + = small effects, – = not effective) and the level of evidence refer to the impact of each dietary modification on plasma levels of a specific lipoprotein class.

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

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

significantly reduced the incidence of major CV events by almost 30%.¹³⁷ However, despite the strong support of lifestyle intervention for CVD prevention coming from the PREDIMED and other intervention studies with CVD endpoints, most evidence linking nutrition to CVD is based on observational studies and investigations of the effects of dietary changes on CV risk factors.

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

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

Saturated fatty acids (SFAs) are the dietary factor with the greatest impact on LDL-C levels (0.02–0.04 mmol/L or 0.8–1.6 mg/dL of LDL-C increase for every additional 1% energy coming from saturated fat).¹⁶⁵ Stearic acid, in contrast to other SFAs (lauric, myristic and palmitic), does not increase TC levels. Trans unsaturated fatty acids can be found in limited amounts (usually <5% of total fat) in dairy products and in meats from ruminants. 'Partially hydrogenated fatty acids' of industrial origin represent the major source of trans fatty acids in the diet; the average consumption of trans fatty acids ranges from 0.2% to 6.5% of the total energy intake in different populations.¹⁶⁶ Quantitatively, dietary trans fatty acids have a similar elevating effect on LDL-C to that of SFAs; however, while SFAs increase HDL-C levels, trans fats decrease them.¹³⁷ If 1% of the dietary energy derived from SFAs is replaced by n-6 polyunsaturated fatty acids (PUFAs), LDL-C decreases by 0.051 mmol/L (2.0 mg/dL); if replaced by monounsaturated fatty acids (MUFAs), the decrease would be 0.041 mmol/L (1.6 mg/dL); and if replaced by carbohydrate, it would be 0.032 mmol/L (1.2 mg/dL). PUFAs of

Table 13 Dietary recommendations to lower low-density lipoprotein-cholesterol and improve the overall lipoprotein profile

	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

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

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

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

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

5.2 The influence of lifestyle on triglyceride levels

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

are directly transported and metabolized in the liver following transport in the portal vein.

Glucose and lipid metabolism are strongly related, and any perturbation of carbohydrate metabolism induced by a high carbohydrate diet will also lead to an increase in TG concentrations.^{148,165} The greater and more rapid this perturbation, the more pronounced are the metabolic consequences. Most detrimental effects of a high carbohydrate diet could be minimized if carbohydrate digestion and absorption were slowed down. The glycaemic index permits identification, among carbohydrate-rich foods, of those with 'fast' and 'slow' absorption. In particular, the detrimental effects of a high carbohydrate diet on TGs occur mainly when refined carbohydrate-rich foods are consumed, while they are much less prominent if the diet is based largely on fibre-rich, low glycaemic index foods. This applies particularly to people with diabetes or with metabolic syndrome (MetS).^{173,174}

Habitual consumption of significant amounts ($>10\%$ energy) of dietary fructose contributes to TG elevations, particularly in people with HTG. These effects are dose dependent; with a habitual fructose consumption between 15 and 20% of the total energy intake, plasma TG increases as much as 30–40%. Sucrose, a disaccharide-containing glucose and fructose, represents an important source of fructose in the diet.^{158,175}

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

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

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

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

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

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

5.4 Lifestyle recommendations to improve the plasma lipid profile

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

5.4.1 Body weight and physical activity

Since overweight, obesity and abdominal adiposity often contribute to dyslipidaemia, caloric intake should be reduced and energy expenditure increased in those with excessive weight and/or abdominal adiposity. Overweight is defined as a body mass index (BMI) ≥ 25 –30 kg/m² and obesity as a BMI ≥ 30 kg/m².

Abdominal adiposity can be detected easily by measuring waist circumference; this should be performed in all individuals who are either overweight, have dyslipidaemia or are at increased CV risk. Measurements of waist circumference > 80 cm for women of any ethnicity and > 94 cm for men of European ancestry or > 90 cm for men of Asian origin indicate the presence of abdominal adiposity, even in people of normal weight (Table 14).¹⁸⁰ Body weight reduction, even if modest (5–10% of basal body weight), improves lipid abnormalities and favourably affects the other CV risk factors often present in dyslipidaemic individuals.¹⁴⁷ An even more marked hypolipidaemic effect occurs when weight reduction is more relevant, as observed in severely obese patients who undergo bariatric surgery. This treatment seems to induce beneficial effects not only on the overall risk factor profile, but also on CV events.¹⁸¹

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

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

Table 14 Definition of central obesity

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

5.4.2 Dietary fat

Limiting as much as possible the intake of trans fat is a key measure of the dietary prevention of CVD. Trying to avoid the consumption of foods made with processed sources of trans fats provides the most effective means of reducing the intake of trans fats to $< 1\%$ of energy. Because the trans fatty acids produced in the partial hydrogenation of vegetable oils account for 80% of total intake, the food industry has an important role in decreasing the trans fatty acid content of the food supply. As for saturated fat, its consumption should be $< 10\%$ of the total caloric intake and should be further reduced ($< 7\%$ of energy) in the presence of hypercholesterolaemia. For most individuals, a wide range of total fat intakes is acceptable and will depend upon individual preferences and characteristics. However, fat intakes that $> 35\%$ of calories are generally associated with increased intakes of both saturated fat and calories. Conversely, a low intake of fats and oils increases the risk of inadequate intakes of vitamin E and of essential fatty acids, and may contribute to unfavourable changes in HDL-C.¹⁶⁵

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

5.4.3 Dietary carbohydrate and fibre

Carbohydrate intake should range between 45 and 55% of total energy intake. Consumption of vegetables, legumes, fruits, nuts and wholegrain cereals should be particularly encouraged, together with all the other foods rich in dietary fibre and/or with a low glycaemic index. A fat-modified diet that provides 25–40 g of total dietary fibre, including at least 7–13 g of soluble fibre, is well tolerated, effective and recommended for plasma lipid control; conversely, there is no justification for the recommendation of very low carbohydrate diets.¹⁶⁴

Intake of sugars should not exceed 10% of total energy (in addition to the amount present in natural foods such as fruits and dairy products); more restrictive advice concerning sugars may be useful

for those needing to lose weight or with high plasma TG values, MetS or diabetes. Soft drinks should be used with moderation by the general population and should be drastically limited in those individuals with elevated TG values.^{158,159}

5.4.4 Alcohol

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

5.4.5 Smoking

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

5.5 Dietary supplements and functional foods for the treatment of dyslipidaemias

Innovative nutritional strategies to improve dyslipidaemias have been developed. They are based on either changing some 'risky' dietary components or encouraging the consumption of specifically targeted 'healthy' functional foods and/or dietary supplements; these so-called nutraceuticals can be used either as alternatives or in addition to lipid-lowering drugs.¹⁸⁴ Nutritional evaluation of functional foods includes not only the search for clinical evidence of beneficial effects relevant to improved health or reduction of disease risk, but also the demonstration of good tolerability and the absence of major undesirable effects. The substantiation of health claims relevant for each food should be based on results from intervention studies in humans that are consistent with the proposed claims. Overall, the available evidence on functional foods so far identified in this field is incomplete; the major gap is the absence of diet-based intervention trials of sufficient duration to be relevant for the natural history of dyslipidaemia and CVD.

5.5.1 Phytosterols

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

Phytosterols have been added to spreads and vegetable oils (functional margarine, butter and cooking oils), as well as yoghurt and other foods; however, food matrices do not significantly influence the cholesterol-lowering efficacy of phytosterols at equivalent doses.¹⁴² The daily consumption of 2 g of phytosterols can effectively lower TC and LDL-C by 7–10% in humans (with a certain degree of heterogeneity among individuals), while it has little or no effect on HDL-C and TG levels.¹⁴³ Although the effect of plant sterol consumption on TC levels has been clearly shown, no studies have been performed yet on the subsequent effect on CVD. However, the meta-analysis of Robinson *et al.*¹³¹ indicates that LDL-C reduction translates into CV benefits, independent of the mechanism involved. Long-term surveillance is also needed to guarantee the safety of the regular use of phytosterol-enriched products. The

possible decrease in carotenoid and fat-soluble vitamin levels by sterols/stanols can be prevented with a balanced diet rich in these nutrients.¹⁸⁵ Based on LDL-C lowering and the absence of adverse signals, functional foods with plant sterols/stanols (at least 2 g/day with the main meal) may be considered: (i) in individuals with high cholesterol levels at intermediate or low global CV risk who do not qualify for pharmacotherapy; (ii) as an adjunct to pharmacologic therapy in high- and very high-risk patients who fail to achieve LDL-C goals on statins or are statin intolerant; and (iii) in adults and children (>6 years) with FH, in line with current guidance.¹⁴²

5.5.2 Monacolin and red yeast rice

Red yeast rice (RYR) is a source of fermented pigment that has been used in China as a food colorant and flavour enhancer for centuries. Hypocholesterolaemic effects of RYR are related to a statin-like mechanism, inhibition of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, of monacolins, which represent the bioactive ingredient. Different commercial preparations of RYR have different concentrations of monacolins, and lower TC and LDL-C to a variable extent,¹⁴⁵ but the long-term safety of the regular consumption of these products is not fully documented. However, side effects similar to those observed with statins have been reported in some people using these nutraceuticals. Furthermore, their quality may vary widely.

In one RCT from China in patients with CAD, a partially purified extract of RYR reduced recurrent events by 45%.¹⁴⁴ No other trial has been performed to confirm this finding. A clinically relevant hypocholesterolaemic effect (up to a 20% reduction) is observed with RYR preparations providing a daily dose of ~2.5–10 mg monacolin K.¹⁴⁶ Nutraceuticals containing purified RYR may be considered in people with elevated plasma cholesterol concentrations who do not qualify for treatment with statins in view of their global CV risk.

5.5.3 Dietary fibre

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

5.5.4 Soy protein

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

5.5.5 Picosanol and berberine

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

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

significant heterogeneity, were all performed in China in people of Asian ethnicity. The comparative evaluation of berberine and lifestyle intervention or placebo indicated that in the berberine group, LDL-C and plasma TG levels were more effectively reduced than in the control group. However, due to the lack of high-quality randomized clinical trials, the efficacy of berberine for treating dyslipidaemia needs to be further validated.

5.5.6 n-3 unsaturated fatty acids

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

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

The results of the PREDIMED trial are clearly in support of a diet inspired by the traditional Mediterranean diet as an effective approach to the lifestyle prevention of CVDs. This type of diet is characterized by the regular consumption of extra-virgin olive oil, fruits, nuts, vegetables and cereals; a moderate intake of fish and poultry and a low intake of dairy products, red meat, processed meats and sweets; wine is consumed in moderation with meals.¹³⁷ Dietary choices inspired by this model should be recommended for both primary and secondary prevention of CVD.

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

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

Salt intake should be limited to <5 g/day, not only by reducing the amount of salt used for food seasoning, but especially by reducing the consumption of foods preserved by the addition of salt; this recommendation should be more stringent in people with hypertension or MetS.^{132–134}

Food choices to lower TC and LDL-C are summarized in *Table 13. Box 9* lists lifestyle measures and healthy food choices for managing total CV risk. All individuals should be advised on lifestyles associated with a lower CVD risk. High-risk subjects, in particular those with dyslipidaemia, should receive specialist dietary advice, if feasible.

Box 9 Summary of lifestyle measures and healthy food choices for managing total cardiovascular risk

Dietary recommendations should always take into account local food habits; however, interest in healthy food choices from other cultures should be promoted.

A wide variety of foods should be eaten. Energy intake should be adjusted to prevent overweight and obesity.

Consumption of fruits, vegetables, legumes, nuts, wholegrain cereal foods and fish (especially oily) should be encouraged.

Foods rich in trans or saturated fat (hard margarines, tropical oils, fatty or processed meat, sweets, cream, butter, regular cheese) should be replaced with the above foods and with monounsaturated fat (extra virgin olive oil) and polyunsaturated fat (non-tropical vegetable oils) in order to keep trans fats <1.0% of total energy and saturated fat <10% (<7% in the presence of high plasma cholesterol values).

Salt intake should be reduced to <5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt.

For those who drink alcoholic beverages, moderation should be advised (<10 g/day for women and <20 g/day for men) and patients with hypertriglyceridaemia should abstain.

The intake of beverages and foods with added sugars, particularly soft drinks, should be limited, especially for persons who are overweight, have hypertriglyceridaemia, metabolic syndrome or diabetes.

Physical activity should be encouraged, aiming at regular physical exercise for at least 30 min/day every day.

Use of and exposure to tobacco products should be avoided.

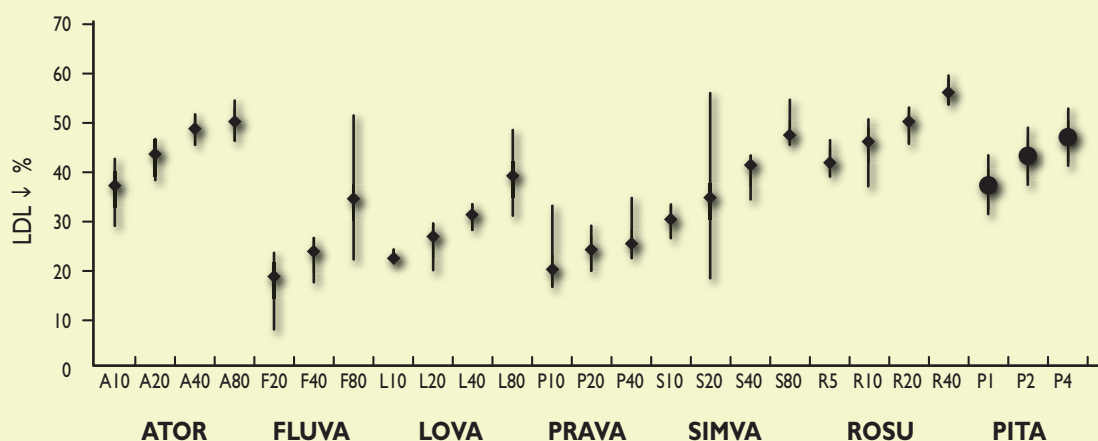
6. Drugs for treatment of hypercholesterolaemia

6.1 Statins

6.1.1 Mechanism of action

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

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



Weng TC, et al. *J Clin Pharm Ther*. 2010;35:139-151

Mukhtar RY, et al. *Int J Clin Pract*. 2005;59(2):239-252

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

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

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

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

6.1.2 Efficacy of cardiovascular disease prevention in clinical studies

Statins are among the most studied drugs in CVD prevention, and dealing with single studies is beyond the scope of the present guidelines. A number of large-scale trials have demonstrated that statins substantially reduce CV morbidity and mortality in both primary and

secondary prevention, in both genders and in all age groups. Statins have also been shown to slow the progression or even promote regression of coronary atherosclerosis.

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

reduction. The benefits were similar in all subgroups examined. The benefits were significant within the first year, but were greater in subsequent years. There was no increased risk for any non-CV cause of death, including cancer, in those receiving statins. Other meta-analyses have confirmed these results, coming to essentially the same conclusions. Most of the meta-analyses include studies in primary as well as secondary prevention. The absolute benefit from statin treatment may be less evident in patients in primary prevention, who are typically at lower risk. Several meta-analyses have specifically studied statins in primary prevention.^{66,68,199} The largest of these was published as a Cochrane review in 2013.²⁰⁰ The analysis included 19 studies with different statins and with somewhat varying inclusion criteria. In this analysis, all-cause mortality was reduced by 14%, CVD events by 27%, fatal and non-fatal coronary events by 27% and stroke by 22% per 1 mmol/L (40 mg/dL) LDL-C reduction. The relative risk reduction in primary prevention is about the same as that observed in secondary prevention. Similar results were also observed in analyses of statin treatment in people with low risk of vascular disease.⁶⁶ However, it should be emphasized that in subjects with lower risk, the absolute risk reduction is also lower.

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

The following scheme may be proposed.

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

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

Other effects of statins. Although the reduction of LDL-C is the major effect of statins, a number of other, potentially important effects have been suggested (pleiotropic effects of statins).^{201,202} Among such effects that are potentially relevant for the prevention of CVD are anti-inflammatory and anti-oxidant effects of statin treatment. Effects have been shown *in vitro* and in experimental systems, but their clinical relevance remains controversial.²⁰³

Furthermore, the effects of statins on a number of other clinical conditions have been evaluated, including dementia,²⁰⁴ hepatic steatosis,²⁰⁵ cancer,^{206,207} venous thromboembolism²⁰⁸ and polycystic ovary syndrome.²⁰⁹ Available data are controversial and thus far no clinically relevant effect on these conditions has been demonstrated. Statins also reduce TGs by 30–50% and may increase

HDL-C by 5–10%. For indications for statins in HTG, see section 7.4.

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

6.1.3 Adverse effects of statins

Statins differ in their absorption, bioavailability, plasma protein binding, excretion and solubility. Lovastatin and simvastatin are prodrugs, whereas the other available statins are administered in their active form. Their absorption rate varies between 20 and 98%. Many statins undergo significant hepatic metabolism via cytochrome P450 isoenzymes (CYPs), except pravastatin, rosuvastatin and pitavastatin. These enzymes are expressed mainly in the liver and gut wall. Although statins are generally well tolerated, there are adverse effects to be considered when statins are prescribed.

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

Liver. The activity of alanine aminotransferase (ALT) in plasma is commonly used to assess hepatocellular damage. Mild elevation of ALT occurs in 0.5–2.0% of patients on statin treatment, more

commonly with potent statins or high doses. The common definition of clinically relevant ALT elevation has been an increase of three times the upper limit of normal (ULN) on two occasions. Mild elevation of ALT has not been shown to be associated with true hepatotoxicity or changes in liver function. Progression to liver failure is exceedingly rare, therefore routine monitoring of ALT during statin treatment is no longer recommended.²²¹ Patients with mild ALT elevation due to steatosis have been studied during statin treatment and there is no indication that statins cause any worsening of liver disease.^{222–224}

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

A minor, not clinically relevant elevation of glycated haemoglobin (HbA1C) has also been observed. The number needed to cause one case of diabetes was estimated at 255 over 4 years.²²⁵ However, the risk is higher with the more potent statins in high doses,²²⁶ and the risk for diabetes is higher in the elderly and in the presence of other risk factors for diabetes such as overweight or insulin resistance.²²⁷ Overall, the absolute reduction in the risk of CVD in high-risk patients outweighs the possible adverse effects of a small increase in the incidence of diabetes.

Kidney. The effect of statin treatment on renal function is still being debated. A recent Cochrane analysis could not find support for beneficial effects on renal function based on studies where creatinine clearance was available, and no deleterious effects were observed.²²⁸ An increased frequency of proteinuria has been reported for all statins, but has been analysed in more detail for rosuvastatin, probably due to the high frequency of proteinuria observed with a higher dose (80 mg). With a dose of 80 mg, a frequency of 12% was reported. With the approved doses up to 40 mg, the frequency is much lower and in line with the frequency for other statins. The proteinuria induced by statins is of tubular origin and is supposed to be due to reduced tubular reabsorption and not to glomerular dysfunction.²²⁹ In experimental systems, reduced pinocytosis has been shown in renal cells. The statin-induced reduced pinocytosis is directly related to the inhibition of cholesterol synthesis.²³⁰ In clinical trials the frequency of proteinuria is in general low and in most cases is not higher than for placebo.²³¹

6.1.4 Interactions

A number of important drug interactions with statins have been described that may increase the risk of adverse effects. Inhibitors and inducers of enzymatic pathways involved in statin metabolism are summarized in Table 15. All currently available statins, except pravastatin, rosuvastatin and pitavastatin, undergo major hepatic metabolism via the CYPs. These isoenzymes are mainly expressed in the liver and intestine. Pravastatin does not undergo metabolism through the CYP system, but is metabolized by sulfation and conjugation. CYP3A isoenzymes are the most abundant, but other isoenzymes such as CYP2C8, CYP2C9, CYP2C19 and CYP2D6 are frequently involved in the metabolism of statins. Thus other pharmacological substrates of these CYPs may interfere with statin metabolism. Conversely, statin therapy may interfere with the catabolism of other drugs that are metabolized by the same enzymatic system.

Table 15 Drugs potentially interacting with statins metabolized by CYP3A4 leading to increased risk of myopathy and rhabdomyolysis

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

Adapted from Egan and Colman²³² and Wiklund *et al.*²³³

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

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

6.2 Bile acid sequestrants

6.2.1 Mechanism of action

Bile acids are synthesized in the liver from cholesterol and are released into the intestinal lumen, but most of the bile acid is returned to the liver from the terminal ileum via active absorption. The two older bile acid sequestrants, cholestyramine and colestipol, are both bile acid-binding exchange resins. Recently the synthetic drug colesevelam was introduced. The bile acid sequestrants are not systemically absorbed or altered by digestive enzymes, therefore the beneficial clinical effects are indirect. By binding the bile acids, the drugs prevent the entry of bile acids into the blood and thereby remove a large portion of the bile acids from the enterohepatic circulation. The liver, depleted of bile, synthesizes more from hepatic stores of cholesterol. The decrease in bile acid returned to the liver leads to upregulation of key enzymes responsible for bile acid synthesis from cholesterol, particularly CYP7A1. The increase in cholesterol catabolism to bile acids results in a compensatory increase in hepatic LDLR activity, clearing LDL-C from the circulation and thus reducing LDL-C levels. These agents also reduce glucose levels in hyperglycaemic patients. A recent Cochrane review found that colesevelam, when added to other antidiabetic agents, showed significant effects on glycaemic control; however, more research on the impact of CV risk is required.²³⁸

6.2.2 Efficacy in clinical studies

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

In clinical trials, bile acid sequestrants have contributed greatly to the demonstration of the efficacy of LDL-C lowering in reducing CV events in hypercholesterolaemic subjects, with a benefit proportional to the degree of LDL-C lowering. However, this study was performed before many of the modern treatment options were available.^{239–241}

6.2.3 Adverse effects and interactions

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

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

6.3 Cholesterol absorption inhibitors

6.3.1 Mechanism of action

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

6.3.2 Efficacy in clinical studies

In clinical studies, ezetimibe in monotherapy reduces LDL-C in hypercholesterolaemic patients by 15–22%. Combined therapy with ezetimibe and a statin provides an incremental reduction in LDL-C levels of 15–20%. The efficacy of ezetimibe in association with simvastatin has been addressed in subjects with aortic stenosis in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study²⁴³ and in patients with CKD in the Study of Heart and Renal Protection (SHARP) (see sections 9.7.3 and 9.9.2). In both the SEAS and SHARP trials, a reduction in CV events was demonstrated in the simvastatin–ezetimibe arm vs. placebo.^{243,244}

In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) ezetimibe was added to simvastatin (40 mg) in patients after ACS.⁶³ A total of 18 144 patients were randomized and 5314 patients over 7 years experienced a CVD event; 170 fewer events (32.7 vs. 34.7%) were recorded in the group taking simvastatin plus ezetimibe ($P = 0.016$). The average LDL-C during the study was 1.8 mmol/L in the simvastatin group and 1.4 mmol/L in patients taking ezetimibe plus simvastatin. Also, ischaemic stroke was reduced by 21% in this trial ($P = 0.008$). There was no evidence

of harm caused by the further LDL-C reduction. In this group of patients already treated with statins to reach goals, the absolute benefit from added ezetimibe was small, although significant. However, the study supports the proposition that LDL-C lowering by means other than statins is beneficial and can be performed without adverse effects. The beneficial effect of ezetimibe is also supported by genetic studies of mutations in NPC1L1. Naturally occurring mutations that inactivate the protein were found to be associated with reduced plasma LDL-C and reduced risk for CAD.²⁴⁵

Taken together with other studies such as the PRECISE-IVUS study,²⁴⁶ IMPROVE-IT supports the proposal that ezetimibe should be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant of statins or with contraindications to these drugs.

6.3.3 Adverse effects and interactions

Ezetimibe is rapidly absorbed and extensively metabolized to pharmacologically active ezetimibe glucuronide. The recommended dose of ezetimibe of 10 mg/day can be administered in the morning or evening without regard to food intake. There are no clinically significant effects of age, sex or race on ezetimibe pharmacokinetics, and no dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe renal insufficiency. Ezetimibe can be co-administered with any dose of any statin. No major adverse effects have been reported; the most frequent adverse effects are moderate elevations of liver enzymes and muscle pain.

6.4 PCSK9 inhibitors

6.4.1 Mechanism of action

Recently a new class of drugs, PCSK9 inhibitors, has become available that targets a protein (PCSK9) involved in the control of the LDLR.²⁴⁷ Elevated levels/functions of this protein in plasma reduce LDLR expression by promoting, upon binding, the LDLR lysosomal catabolism and increase plasma LDL-C concentration, while lower levels/functions of PCSK9 are related to lower plasma LDL-C levels.²⁴⁸ Therapeutic strategies have been developed mainly using monoclonal antibodies that reduce LDL-C levels by ~60% independent from the presence of a background lipid-lowering therapy. The mechanism of action relates to the reduction of plasma levels of PCSK9, which in turn is not available to bind the LDLR. Since this interaction triggers the intracellular degradation of the LDLR, lower levels of circulating PCSK9 will result in a higher expression of LDLRs at the cell surface and therefore in a reduction of circulating LDL-C levels.²⁴⁸

6.4.2 Efficacy in clinical studies

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

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

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

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

6.4.3 Adverse effects and interactions

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

6.5 Nicotinic acid

Nicotinic acid has broad lipid-modulating action, raising HDL-C in a dose-dependent manner by up to 25% and reducing LDL-C by 15–18% and TGs by 20–40% at the 2 g/day dose. Nicotinic acid is unique in lowering Lp(a) levels by up to 30% at this dose. After two large studies with nicotinic acid, one with extended-release niacin²⁵¹ and one with niacin plus laropiprant,²⁵² showed no beneficial effect, but rather an increased frequency of serious adverse effects, no medication containing nicotinic acid is currently approved in Europe. For the role of niacin in hypertriglyceridaemia, see section 7.6.

6.6 Drug combinations

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

6.6.1 Statins and cholesterol absorption inhibitors

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

6.6.2 Statins and bile acid sequestrants

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

found to reduce atherosclerosis, as evaluated by coronary angiography.²⁵³

6.6.3 Other combinations

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

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

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

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

Table 16 Recommendations for the pharmacological treatment of hypercholesterolaemia

Recommendations	Class ^a	Level ^b	Ref ^c
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A	62, 64, 68
In the case of statin intolerance, ezetimibe or bile acid sequestrants, or these combined, should be considered.	IIa	C	239, 256, 257
If the goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	IIa	B	63
If the goal is not reached, statin combination with a bile acid sequestrant may be considered.	IIb	C	
In patients at very high-risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	IIb	C	115, 116

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

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

7. Drugs for treatment of hypertriglyceridaemia

7.1 Triglycerides and cardiovascular disease risk

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

Table 17 Possible causes of hypertriglyceridaemia

Genetic predisposition
Obesity
Type 2 diabetes
Alcohol consumption
Diet high in simple carbohydrates
Renal disease
Hypothyroidism
Pregnancy (physiological triglyceride concentrations double during the third trimester)
Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus
Multiple medications including: <ul style="list-style-type: none"> • Corticosteroids • Oestrogens, especially those taken orally • Tamoxifen • Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides • Isotretinoin • Bile acid-binding resins • Ciclosporin • Antiretroviral regimens (protease inhibitors) • Psychotropic medications: phenothiazines, second generation antipsychotics

7.2 Definition of hypertriglyceridaemia

The definition of different categories for elevated fasting TG levels seems to be slightly variable in different guidelines and

recommendations.^{67,259} According to the EAS consensus document, mild to moderate HTG is defined as TGs >1.7 mmol/L (150 mg/dL) and <10 mmol/L (880 mg/dL); TGs >10 mmol/L is defined as severe HTG.²⁶⁰ Age/gender, race/ethnicity and lifestyle are modulating factors at the population level for serum TGs. In the Copenhagen general population ~27% had TGs >1.7 mmol/L.⁷⁵ Severe HTG is rare and is typically associated with monogenic mutations. Severe HTG is associated with an increased risk for pancreatitis.

7.3 Strategies to control plasma triglycerides

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

Table 18 Recommendations for drug treatments of hypertriglyceridaemia

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

CVD = cardiovascular disease; TG = triglycerides.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

Although the CVD risk is increased if fasting TGs are >1.7 mmol/L (150 mg/dL),⁸⁷ the use of drugs to lower TGs may only be considered in high-risk subjects when TGs are >2.3 mmol/L (200 mg/dL) and cannot be lowered by lifestyle measures. The available pharmacological interventions include statins, fibrates, PCSK9 inhibitors and n-3 PUFAs.

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

7.4 Statins

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

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

7.5 Fibrates

7.5.1 Mechanism of action

Fibrates are agonists of peroxisome proliferator-activated receptor- α (PPAR- α), acting via transcription factors regulating various steps in lipid and lipoprotein metabolism. By interacting with PPAR- α , fibrates recruit different cofactors and regulate gene expression. As a consequence, fibrates have good efficacy in lowering fasting TG levels as well as post-prandial TGs and TG-rich lipoprotein (TRL) remnant particles. The HDL-C raising effects of fibrates are modest.²⁶³

7.5.2 Efficacy in clinical trials

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

Although the Helsinki Heart Study reported a significant reduction in CVD outcomes with gemfibrozil, neither the FIELD nor the ACCORD study showed a reduction in total CVD outcomes. Decreases in the rates of non-fatal MI were reported, although often as a result of post hoc analyses. The effect was most evident in subjects with elevated TG/low HDL-C levels. However, the data on other outcome parameters have remained equivocal. Only one study, ACCORD, has analysed the effect of a fibrate as an add-on treatment to a statin. No overall benefit was reported in two recent meta-analyses.^{268,269} Results from other meta-analyses suggest reduced major CVD events in patients with high TGs and low HDL-C in fibrate-treated patients, but no decrease in CVD or total mortality.^{270–272} Thus the overall efficacy of fibrates on CVD outcomes is much less robust than that of statins. Overall, the possible benefits of fibrates require confirmation.

7.5.3 Adverse effects and interactions

Fibrates are generally well tolerated with mild adverse effects, gastrointestinal disturbances being reported in <5% of patients and skin rashes in 2%.²⁷³ In general, myopathy, liver enzyme elevations and cholelithiasis represent the most well-known adverse effects associated with fibrate therapy.²⁷³ In the FIELD study, small but significant increases in the incidence of pancreatitis (0.8% vs. 0.5%) and pulmonary embolism (1.1% vs. 0.7%) and a non-significant trend toward an increase in deep vein thrombosis (1.4% vs. 1.0%) were seen in those taking fenofibrate compared with placebo; this is in line with data from other fibrate studies.²⁶¹ Elevations of both CK (>5 times above the ULN) and ALT (>3 times above the ULN) were reported more frequently for patients on fenofibrate than on placebo, but the incidence of these abnormalities remained <1% in both treatment groups. In the FIELD

study, one case of rhabdomyolysis was reported in the placebo group and three cases in the fenofibrate group.²⁶¹ The risk of myopathy has been reported to be 5.5-fold greater with fibrate use as a monotherapy compared with statin use. The risk of myopathy is greater in patients with CKD, and it varies with different fibrates and statins used in combination. This is explained by the pharmacological interaction between different fibrates and glucuronidation of statins. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to highly increased plasma concentrations of statins. As fenofibrate does not share the same pharmacokinetic pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy.²⁷³

As a class, fibrates have been reported to raise both serum creatinine and homocysteine in both short-term and long-term studies. The increase of serum creatinine by fibrate therapy seems to be fully reversible when the drug is stopped. Data from meta-analyses suggest that a reduction of calculated glomerular filtration rate (GFR) does not reflect any adverse effects on kidney function.²⁷⁴ The increase in homocysteine by fibrates has been considered to be relatively innocent with respect to CVD risk. However, the fibrate-induced increase in homocysteine may blunt the increases in both HDL-C and apoA1, and this may contribute to the smaller than estimated benefits of fenofibrate in the outcome parameters.²⁷⁵ High homocysteine also promotes thrombosis, and the increased trend to deep vein thrombosis seen in the FIELD study was associated with the baseline homocysteine levels, but no interaction was observed between the increase of homocysteine by fibrate and venous thromboembolic events.²⁷⁶

7.6 Nicotinic acid

7.6.1 Mechanism of action

Nicotinic acid has been reported to decrease fatty acid influx to the liver and the secretion of VLDL by the liver. This effect appears to be mediated in part by the action on hormone-sensitive lipase in the adipose tissue. Nicotinic acid has key action sites in both liver and adipose tissue. In the liver, nicotinic acid inhibits diacylglycerol acyltransferase-2 (DGAT-2), resulting in decreased secretion of VLDL particles from the liver, which is also reflected in reductions of both IDL and LDL particles.²⁷⁷ Nicotinic acid raises HDL-C and apoA1 primarily by stimulating apoA1 production in the liver.²⁷⁷ The effects of nicotinic acid on lipolysis and fatty acid mobilization in adipocytes are well established.

7.6.2 Efficacy in clinical trials

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

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

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

7.7 n-3 fatty acids

7.7.1 Mechanism of action

n-3 fatty acids [eicosapentaenoic acid (EPA) and DHA] are used at pharmacological doses to lower TGs. n-3 fatty acids (2–4 g/day) affect serum lipids and lipoproteins, in particular VLDL concentration. The underlying mechanism is poorly understood, although it may be related, at least in part, to their ability to interact with PPARs and to a decreased secretion of apoB.

7.7.2 Efficacy in clinical trials

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

7.7.3 Safety and interactions

The administration of n-3 fatty acids appears to be safe and devoid of clinically significant interactions. However, the antithrombotic effects may increase the propensity to bleed, especially when given in addition to aspirin/clopidogrel. Recently the data from one study associated the risk of prostate cancer with high dietary intake of n-3 PUFAs.²⁸⁹

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

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.

If TG are not controlled by statins or fibrates, prescription of n-3 fatty acids may be considered to decrease TG further, and these combinations are safe and well tolerated.

TG = triglycerides.

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

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

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

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

HDL-C = high-density lipoprotein cholesterol.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

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

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

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

8.1 Statins

Statins produce modest elevations in HDL-C. In a meta-analysis²⁹¹ of several intervention studies in dyslipidaemic patients, elevations in HDL-C varied with dose among the respective statins; such elevations were typically in the range of 5–10%. As a result of the marked reductions in atherogenic apoB-containing lipoproteins by statins, it is difficult to assess the extent to which the effect on HDL-C levels might contribute to the overall observed reductions in CV risk consistently seen in statin intervention trials. Despite such an effect, however, the elevated CV risk associated specifically with low HDL-C levels was only partially corrected by statin treatment in the Treatment to New Targets (TNT) trial.²⁹²

8.2 Fibrates

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

8.3 Nicotinic acid

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

8.4 Cholesteryl ester transfer protein inhibitors

To date, the most efficacious pharmacological approach to elevation of low HDL-C levels has involved direct inhibition of CETP by small molecule inhibitors, which may induce an increase in HDL-C by $\geq 100\%$ on a dose-dependent basis. Of the three CETP inhibitors developed originally (torcetrapib, dalcetrapib and anacetrapib),

torcetrapib was withdrawn following an excess of mortality in the torcetrapib arm of the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events (ILLUMINATE) trial.²⁹⁴ The Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes (ACCELERATE) trial of evacetrapib in acute coronary syndrome subjects on statins was terminated due to futility.

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

8.5 Future perspectives

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

9. Management of dyslipidaemia in different clinical settings

9.1 Familial dyslipidaemias

Plasma lipid levels are to a very large extent determined by genetic factors. In its more extreme forms this is manifested as familial hyperlipidaemia. A number of monogenic lipid disorders have been identified; among these, FH is most common and strongly related to CVD. In general in patients with dyslipidaemia, most commonly the pattern of inheritance does not suggest that there is a major single gene disorder (monogenic) causing the abnormality, but rather that it stems from inheriting more than one lipoprotein gene variant that, on its own, might have relatively little effect, but in combination with another or others has a greater influence on TC, TGs or HDL-C. The pattern of inheritance is polygenic.²⁹⁵ It is common to find that high LDL-C, high TGs or low HDL-C affect several family members.

9.1.1 Familial combined hyperlipidaemia

Familial combined hyperlipidaemia (FCH) is a highly prevalent dyslipidaemia (1:100) and an important cause of premature CAD. FCH is characterized by elevated levels of LDL-C, TGs or both. The phenotype varies even among members of the same family. FCH shares considerable phenotype overlap with type 2 diabetes and MetS. FCH is a complex disease and the phenotype is determined by interaction of multiple susceptibility genes and the environment. The phenotype even within a family shows high inter- and intraindividual variability based on lipid values (TGs, LDL-C, HDL-C and apoB). Therefore, the diagnosis is commonly missed in clinical practice; the combination of apoB >120 mg/dL + TGs >1.5 mmol/L (133 mg/dL) with a family history of premature CVD can be used to identify subjects who most probably have FCH.²⁹⁶ Currently, research is ongoing to define genetic markers;

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

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

9.1.2 Familial hypercholesterolaemia

9.1.2.1 Heterozygous familial hypercholesterolaemia

FH is a common monogenic dyslipidaemia causing premature CVD due to lifelong elevation of plasma levels of LDL-C. If left untreated, men and women with heterozygous FH (HeFH) typically develop CAD before the ages of 55 and 60 years, respectively. However, if

diagnosed early and properly treated, the risk for CAD may be dramatically reduced, with some studies even suggesting a normal life expectancy.

The frequency of HeFH in the population has earlier been estimated at 1/500; however, recent studies from whole populations suggest that the frequency is higher, in some populations as high as 1/137.²⁹⁷ Based on extrapolations from available data, the frequency of HeFH can be estimated to be between 1/200 and 1/250, putting the total number of cases at between 14 and 34 million worldwide.^{121,298} Only a minor fraction of these are identified and properly treated. The risk of CHD among individuals with definite or probable HeFH is estimated to be increased at least 10-fold.

FH is a monogenic disease caused by loss of function mutations in the *LDLR* or *apoB* genes or a gain of function mutation in the *PCSK9* gene; 95% of FH is caused by mutations in *LDLR*. More than a thousand different mutations have been identified in *LDLR* causing FH. The different mutations cause reduced function or complete loss of function. Complete loss of receptor function is associated with more severe disease. A total of 4–5% of FH is caused by mutations in *apoB* causing reduced binding to LDLR and ~1% is caused by mutations in *PCSK9* causing increased catabolism of LDLR.

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

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

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

- plasma cholesterol ≥ 8 mmol/L (310 mg/dL) in an adult or adult family member (or >95 th percentile by age and gender for country),
- premature CHD in the subject or a family member,
- tendon xanthomas in the subject or a family member or
- sudden premature cardiac death in a family member

The most effective way to identify new cases is to undertake cascade screening of family members of a known index case. Cascade screening is best performed by a lipid clinic with trained nurses and physicians. In most families the cases may be identified with TC or LDL-C analysis. However, when the causative mutation is known, genetic testing is recommended since affected individuals may present with TC below the clinical diagnostic criteria.

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

Table 21 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia³⁰¹

Criteria	Points
1) Family history	
First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or	
First-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
children <18 years of age with LDL-C above the 95th percentile (see 9.1.2.3)	2
2) Clinical history	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels	
LDL-C ≥ 8.5 mmol/L (325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>apoB</i> or <i>PCSK9</i> gene	8
Choose only one score per group, the highest applicable	
Diagnosis (diagnosis is based on the total number of points obtained)	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

FH = familial hypercholesterolaemia; LDL-C = low-density lipoproteincholesterol.

^aExclusive of each other (i.e. maximum 6 points if both are present)

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

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

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

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

Recommendations	Class ^a	Level ^b
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Diagnosis is recommended to be confirmed with clinical criteria and, when available, with DNA analysis.	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (100 mg/dL) or in the presence of CVD <1.8 mmol/L (70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	IIa	C
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very high-risk for CHD, such as other CV risk factors, family history, high Lp(a) or statin intolerance.	IIa	C
In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with statin from 8–10 years of age. Targets for treatment should be LDL-C <3.5 mmol/L (135 mg/dL) at >10 years of age.	IIa	C

CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein-cholesterol; Lp(a) = lipoprotein(a).

^aClass of recommendation.

^bLevel of evidence.

9.1.2.2 Homozygous familial hypercholesterolaemia

Homozygous FH (HoFH) is a rare and life-threatening disease. The clinical picture is characterized by extensive xanthomas, marked premature and progressive CVD and total cholesterol >13 mmol/L (500 mg/dL). Most patients develop CAD and aortic stenosis before the age of 20 years and die before 30 years of age. The frequency of HoFH is estimated to be 1/160 000–1/300 000. The early identification of these children and prompt referral to a specialized clinic is crucial. The patients should be treated with available cholesterol-lowering drugs and, when available, with lipoprotein apheresis. For a more detailed discussion of HoFH, including the role of PCSK9 inhibitors and the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide, see the EAS consensus paper on HoFH.³⁰²

9.1.2.3 Familial hypercholesterolaemia in children

FH is diagnosed in children based on phenotypic criteria including elevated LDL-C plus a family history of elevated LDL-C, premature CAD and/or positive genetic testing.³⁰³ Testing during childhood is optimal to discriminate between FH and non-FH using LDL-C. LDL-C ≥5 mmol/L (190 mg/dL) is most probably FH. In children with a family history of high cholesterol or premature CHD, the cut-off point may be put at ≥4.0 mmol/L (160 mg/dL). If a parent has a known genetic defect, the diagnostic level for the child is ≥3.5 mmol/L (130 mg/dL).

Although placebo-controlled trials are missing in children, there are observational studies suggesting that early treatment can reduce LDL-C burden, improve endothelial function, substantially attenuate development of atherosclerosis and improve coronary outcomes.³⁰³ Treatment of children with FH includes a healthy lifestyle and statin treatment. A heart-healthy diet should be adopted early in life and statin treatment should be considered at 8–10 years of age. Statin treatment should be started with low doses and the dose should be increased to reach goals. The goal in children >10 years of age is an LDL-C <3.5 mmol/L (135 mg/dL) and at younger ages at least a 50% reduction of LDL-C.

9.1.3 Familial dysbetalipoproteinaemia

Familial dysbetalipoproteinaemia (i.e. type III hyperlipoproteinaemia; remnant removal disease) is rare and is generally inherited as an autosomal recessive disorder with variable penetrance. It is rare for it to be expressed in women before menopause. The majority of cases are homozygous for the E2 isoform of apoE. ApoE is important for hepatic clearance of chylomicron remnants and IDL. ApoE2 binds less readily than isoforms E3 or E4 to hepatic receptors. However, without some coincidental cause of dyslipidaemia, apoE2 homozygosity does not generally cause familial dysbetalipoproteinaemia syndrome. The syndrome often develops in the presence of dyslipidaemia associated with HTG, diabetes mellitus, obesity or hypothyroidism.

Familial dysbetalipoproteinaemia produces a characteristic clinical syndrome in which both TC and TGs are elevated before treatment, usually both in the range of 7–10 mmol/L. In severe cases, patients develop tuberoeruptive xanthomata, particularly over the elbows and knees, and palmar xanthomata in the skin creases of the hands and wrists. The risk of CAD is very high, and accelerated atherosclerosis of the femoral and tibial arteries is also prevalent.

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

homozygous for apoE2, a paraprotein should be sought. The treatment of familial dysbetalipoproteinaemia should be undertaken in a specialist clinic. Most cases respond well to treatment with a statin or, if dominated by high TGs, a fibrate; often a combination of a statin and a fibrate may be needed.

9.1.4 Genetic causes of hypertriglyceridaemia

The genetic aetiology for HTG seems to be very complex, with effects of both common and rare genetic variants.^{67,304} Moderate elevation of TG levels (between 2.0–10.0 mmol/L) is caused by the polygenic effect of multiple genes influencing both VLDL production and removal. In CVD prevention, polygenic moderate TG elevation is to be considered. Monogenic severe HTG causes pancreatitis and lipid deposits. Thus far, mutations in six genes (*LPL*, *apoC2*, *apoA5*, *LMF1*, *GPIHBP1* and *GPD1*) with monogenic effect have been recognized to lead to severe elevation of serum TGs due to disruption of the chylomicron removal pathways. These mutations are inherited as an autosomal recessive trait and are rare. A profound defect in the catabolism of chylomicrons and VLDL results in chylomicronaemia and TG levels >11.2 mmol/L (1000 mg/dL), with turbid and milky serum. Severe HTG is seen in patients who are homozygous or compound heterozygous for mutations of the enzyme lipoprotein lipase (LPL) and in the other genes linked to catabolism of TG-rich lipoproteins. Recently, gene therapy for LPL deficiency has been developed and tested in clinical trials³⁰⁵ and the alipogene tiparvovec was approved by the EMA in 2013. A gain of function mutation in *apoC3* leading to high apoC3 levels can also cause severe HTG by the inhibition of LPL activity, whereas loss of function mutations are associated with a favourable lipid profile with low TG levels.³⁰⁶ These findings have raised the possibility of apoC3 as a novel lipid drug target. In summary, the development of new therapeutic options for this rare disease raises the need for awareness and screening of these patients.

9.1.4.1 Action to prevent acute pancreatitis in severe hypertriglyceridaemia

The risk of pancreatitis is clinically significant if TGs exceed 10 mmol/L (880 mg/dL), and actions to prevent acute pancreatitis are mandatory. Notably, HTG is the cause of ~10% of all cases with pancreatitis, and patients can develop pancreatitis even when their TG

concentration is 5–10 mmol/L (440–880 mg/dL). Recent data from a prospective cohort study ($n = 33\,346$) reported that the risk of acute pancreatitis increased significantly over the quartiles of serum TGs, highlighting that serum TGs as a risk factor may have been underestimated.³⁰⁷ Any factor that increases VLDL production can aggravate the risk of pancreatitis, with alcohol consumption being the most common contributing factor. The patient should be admitted to hospital if symptomatic, or careful and close follow-up of the patient's TG values should be undertaken. Restriction of calories and fat content (10–15% recommended) in the diet and alcohol abstinence are obligatory. Fibrate therapy (fenofibrate) should be initiated, with n-3 fatty acids (2–4 g/day) as adjunct therapy or nicotinic acid. Lomitapide may also be considered in severe cases.⁶⁷ In patients with diabetes, insulin therapy should be initiated to achieve good glycaemic control. In general, a sharp decrease of TG values is seen within 2–5 days. In the acute setting, plasmapheresis is able to rapidly lower TG levels.³⁰⁸

9.1.5 Other genetic disorders of lipoprotein metabolism (Table 23)

Sometimes patients are encountered with extremely low levels of LDL-C or HDL-C. The most common genetic hypolipidaemia is hypobetalipoproteinaemia, which is dominantly inherited and often due to truncation of apoB. Serum LDL-C is typically between 0.5 and 1.5 mmol/L (20–60 mg/dL). It is generally of no medical significance. A more profound deficiency of apoB occurs in abetalipoproteinaemia when steatorrhea and neurological or other complications require specialist treatment. Almost absent levels of HDL-C occur in Tangier disease (analphalipoproteinaemia) and very low levels of HDL-C occur in lecithin cholesterol acyltransferase (LCAT) deficiency. Both these conditions are associated with distinct clinical syndromes and require specialist investigation. Very high levels of HDL-C are detected in patients with CETP deficiency. In the heterozygous form, typically levels of 2.0–2.4 mmol/L (80–90 mg/dL) are observed, and levels ≥ 5 mmol/L (200 mg/dL) are observed in homozygotes. This is not associated with atherosclerotic disease and may be associated with reduced risk.

Lysosomal acid lipase (LAL) deficiency or cholesterol ester storage disease (in children with Wolman disease) is a rare cause

Table 23 Genetic disorders of lipoprotein metabolism

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

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

(recessive transmission) of elevated LDL-C and low HDL-C accompanied by hepatomegaly and microvesicular hepatosteatosis. Statin treatment does decrease LDL-C, and therefore could prevent CVD in these patients, but it cannot stop the progression of liver damage. Enzyme replacement therapy with sebelipase alfa might offer a treatment solution in the near future.³⁰⁹

9.2 Children

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

9.3 Women

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

9.3.1 Primary prevention

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

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

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

9.3.2 Secondary prevention

More data coming from large RCTs of secondary prevention are available for women. The results of these trials concordantly show that lipid-lowering therapy substantially reduces CV events in these patients, although no reduction in total mortality risk could be

demonstrated. The meta-analysis of Walsh and Pignone³¹⁴ reported a 26% reduction of CV mortality, a 29% reduction of MI and a 20% reduction of total CAD events in a cohort of 8272 females with previous CVD mainly treated with statins. The CTT meta-analysis also indicates that the benefit overall is similar in men and women.⁶⁵ Therefore, secondary prevention of CV events in women should routinely include a statin-based lipid-lowering regimen, with the same recommendations and therapeutic goals that are applied to men.

9.3.3 Non-statin lipid-lowering drugs

No definitive evidence of cardioprotective effects was available until recently. The IMPROVE-IT study⁶³ included patients at least 50 years of age who had been hospitalized within the preceding 10 days for an ACS (24% women). The combination of simvastatin–ezetimibe was compared with simvastatin monotherapy. The rate of the composite endpoint of death from CV causes, MI or stroke was significantly lower, by 1.8 percentage points, in the combination group and the benefit of simvastatin–ezetimibe was consistent for women.⁶³

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

9.3.4 Hormone therapy

Currently used third-generation low-dose oestrogen–progestin oral contraceptives do not appear to increase adverse coronary events³¹⁶ and can be used, after baseline lipid profile assessment, in women with acceptable TC levels. In contrast, alternative contraceptive measures should be recommended in women with hypercholesterolaemia [LDL-C >4 mmol/L (160 mg/dL)] or with multiple risk factors and in those at high risk of thrombotic events.³¹⁷ Oestrogen replacement therapy, despite some favourable effects on the lipid profile, has not been demonstrated to reduce CV risk and cannot be recommended for CVD prevention in women.³¹⁸ No lipid-lowering drugs should be administered during pregnancy and the period of breastfeeding since data on possible adverse effects are lacking. However, bile acid sequestrants may be considered.

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

Box 10 Management of dyslipidaemia in women

Statin treatment is recommended for primary prevention of CAD in high-risk women.^{64,65}

Statins are recommended for secondary prevention in women with the same indications and targets as in men.^{64,65}

Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breastfeeding period. However, bile acid sequestrants (which are not absorbed) may be considered.

9.4 Older persons

The proportion of older people in society is increasing and, as a consequence, $>80\%$ of individuals who die from CVD are >65 years of age. The proportion of patients with MI >85 years of age has increased several fold.³¹⁹ Coronary care has also been improved for

older adults, with improving prognosis after the first MI.³²⁰ To target the older population with risk reduction is important since CVD or subclinical atherosclerosis is common and dyslipidaemia is frequent.

Results from a meta-analysis on blood cholesterol and vascular mortality indicates that high TC is a significant risk factor for CAD mortality at all ages, but this association is attenuated in older adults; 1 mmol/L (38.7 mg/dL) lower TC was associated with about one-half [hazard ratio (HR) 0.44] lower CAD mortality in the age group 40–49 years compared with an HR of 0.85 in those 80–89 years old.^{321,322} However, although a relative risk reduction is seen in the oldest subjects, the increased frequency of CAD means that the absolute number of cases associated with cholesterol is highest in this group. Evidence for treatment in this group, particularly for those >80–85 years of age, is limited, and clinical judgement should guide decisions in the very old.

9.4.1 Primary prevention

The most important way to prevent CVD in older adults is to promote a healthy lifestyle and reduction of risk factors early in life. Several studies have shown that a healthy lifestyle early in life prevents CVD in older age and reduces lifetime risk for CVD.^{53,323–325} Lifetime prevention includes no smoking, control of blood pressure, healthy eating habits, regular exercise and controlling body weight. No primary prevention study has specifically targeted the older population.³²⁶ Available data are based on subgroup analyses from controlled studies. In a recent meta-analysis, subjects >65 years of age ($n = 24\,674$) from eight studies were included.³²⁷ Statin treatment reduced MI (RR 0.61) and stroke (RR 0.76). The reduction in all-cause mortality was not significant (RR 0.94). In the Air Force/Texas Coronary Atherosclerosis Prevention (AFCAPS-TEXCAP) study, risk reduction was similar above and below the median age (57 years for men and 62 years for women).³²⁸ In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial a post hoc analysis of subjects older and younger than 70 years showed that the relative risk reduction for a composite CVD endpoint was similar in the two groups. The number needed to treat for 4 years to prevent one major event was 24 in the older group and 36 in the younger age group.³²⁹

9.4.2 Secondary prevention

Also in secondary prevention, very few studies have targeted the older population. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study included patients 70–82 years of age with CVD or at high risk for CVD.³³⁰ Patients were treated with pravastatin 40 mg daily or placebo. The relative risk reduction for a combined CAD endpoint was reduced by 15%, whereas no reduction was shown for stroke. In the Studies Assessing Goals in the Elderly (SAGE) trial, 893 patients 65–83 years of age with stable CAD were recruited to treatment with atorvastatin 80 mg or pravastatin 40 mg.³³¹ The atorvastatin group had a lower all-cause mortality (HR 0.33) and a non-significant trend towards reduction in major CAD events.

Subgroup analyses in randomized trials have been performed for several studies. In the Scandinavian Simvastatin Survival Study (4S) trial, patients >65 years of age had a similar relative risk reduction as younger patients.³³² In the Heart Protection Study (HPS), 20 536 individuals were allocated to simvastatin or placebo. After 5 years the relative risk reduction was 18% for coronary death and 25% for coronary events. The reduction was similar in age groups

<65, 65–70 and >70 years.³³³ Similar results were found in subgroup analyses of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID),³³⁴ Cholesterol and Recurrent Events (CARE)³³⁵ and TNT trials.³³⁶ From data in the LIPID trial the authors calculated that per 1000 persons treated, 45 deaths and 47 major coronary events would be prevented in the older group over 6 years compared with 22 deaths and 32 major coronary events in younger patients over the same time period.

In a CTT meta-analysis, rate ratios for the effects of statins on major vascular events were 0.78, 0.78 and 0.84 in age groups <65, 65–75 and >75 years, respectively.⁶⁴ Results from an MI registry study in Sweden demonstrate that statin treatment is associated with lower CV mortality in very old post-MI patients without (which is important to stress) increasing the risk of cancer.³³⁷

9.4.3 Adverse effects, interactions and adherence

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

Older adults are less likely to be prescribed lipid-lowering medications, or adhere to statin therapy, than younger or middle-age subjects. Cost, adverse effects, coronary events occurring despite being on lipid-lowering agents and the wrong perception that the drug is not beneficial are among the reasons for non-adherence. Improving patient understanding of CV risk, the medication regimen and potential benefits of persistence with statin therapy may enhance adherence.

Table 24 Recommendations for the treatment of dyslipidaemia in older adults

Recommendations	Class ^a	Level ^b	Ref ^c
Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	I	A	334, 337
Since older people often have co-morbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger subjects.	IIa	C	
Statin therapy should be considered in older adults free from CVD, particularly in the presence of hypertension, smoking, diabetes and dyslipidaemia.	IIa	B	62, 64, 65

CVD = cardiovascular disease.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

Table 24 lists the recommendations for treatment of dyslipidaemia in older adults.

9.5 Diabetes and metabolic syndrome

Diabetes seems to be the fastest increasing disease in the world and it is estimated that the number of people with diabetes will increase from ~350 million today up to 550 million by 2030.³³⁸ Despite significant advantages in the management strategies that lessen CVD risk factors, CVD has remained the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). It has been estimated that the years of life lost for a 50-year-old person with diabetes averages at 6 years and ~58% of this difference is due to excess vascular disease.³³⁹ Diabetes itself is an independent risk factor for CVD and is associated with a higher risk of CVD, even more so in women. Although the difference in CVD risk between individuals with and without diabetes has narrowed substantially over the last decades, there are strong associations between diabetes and vascular outcomes.^{340,341} Recent data indicate that diabetes per se increases CVD risk about two-fold on average, but the risk is subject to wide variation depending on the population.³⁴² Importantly, those with diabetes and CAD are at substantially higher CVD risk for future events. Hypertension, dyslipidaemia and abdominal obesity commonly co-exist with T2DM and further aggravate the risk, which is highest in people with T2DM and features of MetS.^{343,344} Importantly, diabetes confers excess mortality risk following ACS despite modern therapies, highlighting the poor prognosis of coronary patients with T2DM and the need for intensive therapy.³⁴⁵

Even more frequent are conditions predisposing to diabetes, such as the so-called metabolic syndrome. The term MetS refers to the clustering of different cardiometabolic risk factors: central obesity, raised serum TGs, reduced HDL-C, glucose intolerance and high blood pressure.^{346,347} Scoring systems that dichotomize these variables 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 two-fold increase in CV outcomes and a 1.5-fold increase in all-cause mortality.³⁴⁸ How to capture the extra risk beyond the traditional risk factors in clinical practice is a debated issue. A combination of large waist circumference and elevation of TGs is a simple and inexpensive screening tool to discriminate people with MetS at high CVD risk for global risk evaluation.¹⁸⁰

9.5.1 Specific features of dyslipidaemia in insulin resistance and type 2 diabetes (Table 25)

Diabetic dyslipidaemia is a cluster of plasma lipid and lipoprotein abnormalities that are metabolically interrelated. The increase in large VLDL particles in T2DM initiates a sequence of events that generates atherogenic remnants, small dense LDL and small TG-rich dense HDL particles.³⁴⁹ These components are not isolated abnormalities but are closely linked to each other. Both LDL and HDL particles show variable compositional changes that are reflected in their functions. Notably apoCIII levels are increased in subjects with T2DM.³⁵⁰ Together, TRL remnants, small dense LDL and small dense HDL comprise the atherogenic lipid profile, which is also characterized by an increase in apoB concentration due to an increased number of apoB-containing particles. Importantly, TRLs,

Table 25 Summary of dyslipidaemia in metabolic syndrome and in type 2 diabetes

Dyslipidaemia in MetS represents a cluster of lipid and lipoprotein abnormalities including elevation of both fasting and postprandial TG, apoB, and small dense LDL and low HDL-C and apoA1.

Non-HDL-C or apoB are good surrogate markers of TRLs and remnants and are a secondary objective of therapy. Non-HDL-C <3.4 mmol/L (<130 mg/dL) or apoB <100 mg/dL is desirable in those at high-risk, and <2.6 mmol/L (<100 mg/dL) and <80 mg/dL, respectively, in those at very high-risk.

Increased waist circumference and elevation of TG 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.

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

including chylomicrons, VLDL and their remnants, carry a single apoB molecule, also like LDL particles. Therefore the malignant nature of diabetic dyslipidaemia is not always revealed by the lipid measures used in clinical practice, as LDL-C may remain within the normal range. It may be better revealed by non-HDL-C. Elevation of TGs or low HDL-C is seen in about half of subjects with T2DM.³⁵¹ The abnormal features of the lipid profile precede the onset of T2DM by several years and are common in subjects with central obesity, MetS and T2DM.

9.5.2 Evidence for lipid-lowering therapy

9.5.2.1 Low-density lipoprotein cholesterol

LDL-C is stipulated to be the primary target of lipid-lowering therapy in diabetes. Trials specifically performed in subjects with T2DM as well as subsets of individuals with diabetes in major statin trials have consistently demonstrated significant benefits of statin therapy on CVD events in people with T2DM.⁶⁴ Statin therapy reduces the 5-year incidence of major CVD events by 23% per 1 mmol/L reduction in LDL-C, regardless of the initial LDL-C or other baseline characteristics based on meta-analysis.⁶⁴ The CTT meta-analysis further indicates that subjects with T2DM will have a relative risk reduction that is comparable to that seen in non-diabetic patients, but being at higher absolute risk, the absolute benefit will be greater, resulting in a lower number needed to treat (NNT). Recent studies have suggested an increased incidence of diabetes in patients treated with statins.²²⁵ This effect must not lessen our attention to the treatment of patients, as the overall benefit in CV events reduction remains.

9.5.2.2 Triglycerides and high-density lipoprotein cholesterol

Clinical benefits achieved by the treatment of atherogenic dyslipidaemia (high TGs and low HDL-C) are still a matter of discussion. Although the Helsinki Heart Study reported a significant reduction in CVD outcomes with gemfibrozil, neither the FIELD nor the ACCORD study showed a reduction in total CVD outcomes.^{261,262,265} 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 elevated TGs

[>2.3 mmol/L (~204 mg/dL)] and reduced HDL-C (NNT = 23).³⁵¹ The ACCORD trial confirmed this: patients who had both TG levels in the higher third [≥ 2.3 mmol/L (204 mg/dL)] and an HDL-C level in the lower third [≤ 0.88 mmol/L (34 mg/dL)], representing 17% of all participants, appeared to benefit from adding fenofibrate to simvastatin.²⁶²

A post hoc analysis of patients with low HDL-C [< 1 mmol/L (~40 mg/dL)] and elevated TGs [> 1.80 mmol/L (~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 0.44.³⁵² Consistent with these findings, a meta-analysis of fibrates in the prevention of CVD in 11 590 people with T2DM showed that fibrates significantly reduced the risk of non-fatal MI by 21%, but had no effect on the risk of overall mortality or coronary mortality.³⁵³

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. Evidence for a beneficial clinical effect of raising HDL-C is lacking, with lifestyle modification providing the first option due to its multifaceted effects.

9.5.3 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 T2DM and MetS (see section 5). Dietary advice should be tailored according to the individual's needs. If LDL-C goals 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.³⁵⁴ Patients with T2DM <40 years of age, with a short duration of therapy, without other risk factors, without complications and with an LDL-C level <2.6 mmol/L (100 mg/dL) may not need lipid-lowering drugs.

9.5.4 Type 1 diabetes

Type 1 diabetes is associated with high CVD risk, in particular in patients with microalbuminuria and renal disease.³⁵⁵ Conclusive evidence supports the proposition that hyperglycaemia accelerates atherosclerosis. Emerging evidence highlights the frequent coexistence of MetS with type 1 diabetes, resulting in this so-called double diabetes increasing CVD risk.³⁵⁶

The lipid profile in type 1 diabetic subjects with good glycaemic control is 'supernormal' and characterized by subnormal TGs and LDL-C, whereas HDL-C is usually within the upper normal range or slightly elevated. This is explained by subcutaneous administration of insulin that increases LPL activity in adipose tissue and skeletal muscle and consequently the turnover rate of VLDL particles. 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 (drug combination may be considered if needed) is recommended irrespective of the basal LDL-C concentration.

Recommendations for the treatment of dyslipidaemia in diabetes are shown in Table 26.

Table 26 Recommendations for the treatment of dyslipidaemia in diabetes

Recommendations	Class ^a	Level ^b	Ref ^c
In all patients with type 1 diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration.	I	C	64, 357
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age 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 (<70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (<100 mg/dL) and for apoB is <80 mg/dL.	I	B	62, 64
In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.	I	B	62, 64

apoB = apolipoprotein B; CKD = chronic kidney disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein-cholesterol; LDL-C = low-density lipoprotein-cholesterol; MetS = metabolic syndrome; TG = triglycerides.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.6 Patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention

Patients who have presented recently with 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.

9.6.1 Specific lipid management issues in acute coronary syndrome

Data from specific trials^{358–360} and meta-analysis support routine early use of prompt, intensive and prolonged statin therapy. Thus we recommend that high-intensity statin therapy be initiated during the first 1–4 days of hospitalization for the index ACS; the dose should aim at reaching the LDL-C goal of <1.8 mmol/L (~70 mg/dL) or a 50% reduction of LDL-C as indicated in Table 11 on treatment goals. The use of lower-intensity statin therapy should be considered in patients at increased risk of adverse effects with high-intensity statins (e.g. the elderly, hepatic impairment, renal impairment or potential for interaction with essential concomitant therapy). Ezetimibe further

reduced LDL-C and offered additional benefit (6.4% relative risk reduction in composite clinical endpoint) in association with simvastatin in post-ACS patients.⁶³ Results in studies with PCSK9 inhibitors that included post-ACS/very high-risk patients were promising^{115,116} and definitive outcome studies are awaited.

Lipids should be re-evaluated 4–6 weeks after ACS to determine whether lipid goals have been reached and whether there are any safety issues; the therapeutic regimen can then be adapted accordingly.

Supplementation with highly purified n-3 PUFAs reduced mortality in survivors of MI in one study (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)), but failed to affect clinical outcomes in two more recent trials using modern evidence-based prevention therapies (most patients were on statins), and therefore cannot be recommended in routine practice.³⁶¹ Furthermore, in patients who had experienced a recent ACS, the CETP inhibitor dalcetrapib did not reduce the risk of recurrent CV events.³⁶²

9.6.2 Lipid management issues in patients undergoing percutaneous coronary intervention

In an individual patient meta-analysis of 13 randomized studies that included 3341 patients, it was shown that either pretreatment

with high-dose statin (ranging from >2 weeks to a single dose) in statin-naïve patients (11 studies) or loading of a high-dose statin in patients receiving chronic statin therapy decreased periprocedural MI and 30-day adverse events in patients undergoing percutaneous coronary intervention (PCI).^{363–365} In all but one study, PCI was performed in the setting of stable angina, or in a non-emergent fashion in non-ST elevation ACS (NSTEMI-ACS). In one study in the setting of primary PCI that was included in the meta-analysis, coronary flow was improved.³⁶⁶ Thus a strategy of routine short pretreatment or loading (on the background of chronic therapy) with high-dose statin before PCI should be considered in elective PCI or in NSTEMI-ACS (class IIa, level of evidence A).^{363–365} High-dose statin pretreatment or loading before primary or delayed PCI for ST elevation MI (STEMI) requires further study. Statin pretreatment is also effective in reducing the risk of contrast-induced acute kidney injury after coronary angiography or intervention.³⁶⁷

Recommendations for lipid-lowering therapy in patients with ACS and patients undergoing PCI are shown in Table 27.

Table 27 Recommendations for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention

Recommendations	Class ^a	Level ^b	Ref ^c
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A	64, 358–360
If the LDL-C target is not reached with the highest tolerable statin dose, ezetimibe should be considered in combination with statins in post-ACS patients.	IIa	B	63
If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin intolerant patients or in whom a statin is contra-indicated.	IIb	C	115, 116
Lipids should be re-evaluated 4–6 weeks after ACS to determine whether target levels of LDL-C <1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) have been reached and whether there are any safety issues. The therapy dose should then be adapted accordingly.	IIa	C	
Routine short pretreatment or loading (on the background of chronic therapy) with high-dose statins before PCI should be considered in elective PCI or in NSTEMI-ACS.	IIa	A	363–365

ACS = acute coronary syndrome; LDL-C = low-density lipoprotein-cholesterol; NSTEMI-ACS = non-ST elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.7 Heart failure and valvular diseases

9.7.1 Prevention of incident heart failure in coronary artery disease patients

The onset of heart failure (HF) increases the risk of mortality and morbidity three to four 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.^{368,369} Four 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% in patients with acute and stable CAD without previous HF.^{358,370–372} However, there is no evidence that statins can prevent HF of non-ischæmic origin.

9.7.2 Chronic heart failure

HF patients have lower TC and LDL-C than patients without HF. In contrast to patients without HF, low TC portends a poor prognosis in HF. Routine administration of statins in patients with HF is not advised. In two large RCTs^{373,374} there was no benefit on hard endpoints, such as CV mortality and non-fatal MI and stroke, in spite of a decrease in hospitalizations^{373,375} and a marked reduction of LDL-C and hs-CRP in patients with mainly systolic heart failure. In any case, there is no evidence for harm in patients on statin treatment after the occurrence of HF, and therefore there is no need for discontinuation if patients are already on this medication. n-3 PUFAs may have a small benefit. In the GISSI-HF RCT, a significant effect on primary endpoints (all-cause death and hospitalization for

HF) was found in HF patients with New York Heart Association (NYHA) classifications II–IV.³⁷⁶

9.7.3 Valvular disease

Aortic stenosis increases the risk of CV events and mortality. Suggestions for an association between aortic stenosis, LDL-C and Lp(a), as well as between cholesterol and increased risk for calcification of bioprosthetic valves, were matched with early observational non-controlled trials that showed beneficial effects of aggressive lipid lowering in slowing the progression of aortic stenosis. However, this was not confirmed in RCTs.^{243,377,378} The Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE; 155 patients, 80 mg atorvastatin or placebo), the SEAS (1873 patients, simvastatin 40 mg plus ezetimibe 10 mg or placebo) and the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER; 269 patients, rosuvastatin 40 mg or placebo) trials failed to show a reduction in the progression of aortic stenosis or related events in patients with mild to moderate aortic stenosis. Notably, ischaemic events were reduced by 21% in the SEAS trial. Furthermore, in a post hoc analysis of the RCTs Incremental Decrease In Endpoints Through Aggressive Lipid-lowering Trial (IDEAL) and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), high-dose versus usual-dose statin therapy or placebo did not impact the incidence of aortic valve stenosis among patients without known aortic valve stenosis.³⁷⁹ Aortic valve sclerosis (calcification of the aortic leaflets without impairment in leaflet excursion or a significant transvalvular pressure gradient) is associated with an increased risk of CAD even in the absence of increased risk profiles. In such patients, statins, acting at an earlier disease stage, may be useful both for aortic valve disease and CAD progression; however, this warrants further investigation.³⁸⁰ Regarding rheumatic mitral stenosis and bioprosthetic valves, small observational studies suggest a benefit of statin treatment.^{381,382}

Recommendations for lipid-lowering therapy in patients with HF and valvular diseases are shown in *Table 28*.

Table 28 Recommendations for the treatment of dyslipidaemia in heart failure or valvular disease

Recommendations	Class ^a	Level ^b	Ref ^c
Cholesterol-lowering therapy with statins is not recommended (but is not harmful either) in patients with heart failure in the absence of other indications for their use.	III	A	373, 374
n-3 PUFAs 1 g/day may be considered for addition to optimal treatment in patients with heart failure.	IIb	B	376
Cholesterol-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD in the absence of other indications for their use.	III	A	243, 377, 378

CAD = coronary artery disease; PUFAs = polyunsaturated fatty acids.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.8 Autoimmune diseases

Autoimmune diseases, including rheumatoid arthritis, SLE, psoriasis and anti-phospholipid syndrome, are characterized by enhanced atherosclerosis and consequently higher CV morbidity and mortality rates compared with the general population.^{383–385} 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 auto-reactive lymphocytes) are involved in these processes. These diseases are characterized by inflammatory vasculitis and endothelial dysfunction. Therefore particular attention should be paid to conventional CVD risk factor treatment, including dyslipidaemia, in these patients. Statins are effective in reducing disease activity, CV events and mortality (particularly in primary prevention) in this setting, while their discontinuation increases MI and mortality.³⁸⁶ However, there is no firm indication to use lipid-lowering therapy only on the basis of the presence of the disease (*Table 29*). Furthermore, no specific LDL-C goal beyond that indicated by individual total risk has been set for such patients.

Table 29 Recommendation for the treatment of dyslipidaemia in autoimmune diseases

Recommendation	Class ^a	Level ^b
The universal use of lipid-lowering drugs is not recommended	III	C

^aClass of recommendation.

^bLevel of evidence.

9.9 Chronic kidney disease

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. CKD can be classified on the basis of the GFR into five categories.³⁸⁷ In the adult population, a decreasing GFR is associated with an increased CVD risk, independent of other CV risk factors.^{388–391} The CV mortality in patients with stage 3 and stage 4 CKD is two-fold and three-fold higher, respectively, when compared with patients with normal renal function.³⁹¹ Patients with CKD and established CVD have a much higher mortality rate compared with patients with CVD and normal renal function.³⁹² Therefore patients with CKD are considered high risk (stage 3 CKD) or very high risk (stage 4–5 CKD or on dialysis) and there is no need to use risk estimation models in these patients.

9.9.1 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). In the initial stages of CKD, TGs are specifically elevated and HDL-C lowered; the elevation of TGs is caused by both increased production and impaired removal of TRLs due to changes in regulatory enzymes and proteins. Consequently, non-HDL-C and apoB levels are clearly increased. LDL subclasses display a shift to an 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.

9.9.2 Evidence for lipid management in patients with chronic kidney disease

In a systematic review of 50 studies including 45 285 participants, the benefits and harms of statins were evaluated in comparison with placebo or no treatment (47 studies) or another statin (3 studies) in adults with CKD and no CVD at baseline.³⁹³ Statins consistently lowered the death rate and major coronary events by 20%; statin-related effects on stroke and kidney function were found to be uncertain. These results are in line with those from a meta-analysis of 11 RCTs including 21 293 patients with CKD, of whom 6857 were receiving dialysis.³⁹⁴ In patients with CKD not on dialysis, treatment with statins reduced all-cause mortality by 34%, CV mortality by 31%, CV events by 45% and stroke by 34%. In patients receiving dialysis, treatment with statins had no effect on all-cause mortality and stroke, but reduced CV mortality by 21% and CV events by 19%. Stage 5 CKD (or on dialysis) is indeed a very high-risk condition in which different factors influence outcome; results from RCTs of lipid-altering therapies have not provided convincing evidence of reduced CVD events in such patients.

In the 4D trial (Die Deutsche Diabetes Dialyse studie) involving a cohort of 1200 patients with diabetes on haemodialysis, atorvastatin had no positive effect on the primary composite endpoint of CVD.³⁹⁵ 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, show that rosuvastatin lowered LDL-C as expected but had no significant effect on the composite CVD endpoint.³⁹⁶ The neutral results question the benefits of statins in these very high-risk patients with poor outcomes.

In the SHARP study³⁹⁷ simvastatin and ezetimibe combination therapy was associated with lower risk for major atherosclerotic events (coronary death, MI, non-haemorrhagic stroke or any revascularization) compared with placebo in persons with CKD stage 3A–5. The trial did not have sufficient power to assess the effects in the primary outcome separately in dialysis and non-dialysis patients, but there was no good statistical evidence that the proportional effects in dialysis patients differed from those seen in patients not on dialysis; in general, CV risk was much lower in the patients in the SHARP trial compared with those of the AURORA and 4D trials, reflected in the lower event and mortality rates.

A cost-effectiveness analysis of statins for primary CVD prevention in CKD³⁹⁸ showed that statins reduced absolute CVD risk in patients with CKD but that the increased risk for rhabdomyolysis, and competing risks associated with progressive CKD, partly offset these gains. A systematic review of the benefits and harms of statins in patients with a functioning kidney transplant included 3465 patients, free of CHD, from 22 studies. The authors concluded that statins may reduce CV events, although treatment effects were imprecise; due to heterogeneity, different statin regimens could not be compared and additional studies are recommended.²²⁸

9.9.3 Safety of lipid management in patients with chronic kidney disease

Safety issues and dose adjustment are important in advanced stages of CKD (stages 3–5), as adverse events are commonly dose related

and due to increased blood concentration of the compound. Preference should be given to regimens and doses that have been shown to be beneficial in RCTs conducted specifically in such patients.³⁹⁹ Prevention of coronary events has been documented with fluvastatin 80 mg, atorvastatin 20 mg, rosuvastatin 10 mg, simvastatin/ezetimibe 20/10 mg, pravastatin 40 mg and simvastatin 40 mg. Lower doses than those used in the trials may be appropriate in Asian countries and in patients on polypharmacy and with co-morbidities. Furthermore, statins that are eliminated mainly by the hepatic route may be preferred (fluvastatin, atorvastatin, pitavastatin). Statins metabolized via CYP3A4 may result in adverse effects due to drug–drug interactions, and special caution is required.

9.9.4 Recommendations of lipid management for patients with chronic kidney disease

Based on the evidence for lipid management in patients with CKD, the Kidney Disease: Improving Global Outcomes (KDIGO) organization developed an updated clinical practice guideline for lipid management in CKD.³⁹⁹ In line with this, but with a focus on those patients at high or very high risk for developing CVD, recommendations are summarized in Table 30.

Table 30 Recommendations for lipid management in patients with moderate to severe chronic kidney disease

Recommendations	Class ^a	Level ^b	Ref ^c
Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	I	A	388–392
The use of statins or statin/ezetimibe combination is indicated in patients with non-dialysis-dependent CKD.	I	A	393, 394, 397
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A	395, 396
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, these drugs should be continued, particularly in patients with CVD.	IIa	C	
In adult kidney transplant recipients treatment with statins may be considered.	IIb	C	

CKD = chronic kidney disease; CV = cardiovascular.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.10 Transplantation (Table 31)

Lipid abnormalities are common in patients who have undergone solid organ transplantation and predispose patients 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 TGs and in the size and density of LDL particles. Calcineurin inhibitors increase the activity of hepatic lipase, decrease LPL and bind 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^{400–402} and renal transplant patients,⁴⁰³ the amounts of outcome data are not extensive. A recent systematic review demonstrated a strong trend towards reduced CVD events and mortality with statins in renal transplant patients.⁴⁰³ 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.⁴⁰² 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 patients with dyslipidaemia who are unable to take statins, ezetimibe could be considered as an alternative in those with high LDL-C.⁴⁰⁴ No outcome data are available for this drug, which should generally be reserved for second-line use. Care is required with the use of fibrates, as they can decrease ciclosporin levels and have the potential to cause myopathy. Extreme caution is required if fibrate therapy is planned in combination with a statin. Cholestyramine is not effective as monotherapy in heart transplant patients and has the potential to reduce absorption of immunosuppressants, minimized by separate administration.

9.11 Peripheral arterial disease

The term PAD encompasses all vascular sites, including carotid, vertebral, upper extremity, mesenteric, renal and lower extremity arteries. The aorta is often included in the term.⁴⁰⁵ PAD is a common manifestation of atherosclerosis, and such patients are at elevated risk of coronary events, with PAD representing an independent risk factor for MI and CV death.^{405,406} 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.⁴⁰⁶

9.11.1 Lower extremities arterial disease

A low ABI (<0.90) is diagnostic for lower extremities arterial disease (LEAD). Either a low (<0.90) or a high (>1.40, related to stiffened arteries) ABI is predictive of CV morbidity and mortality. Cholesterol-lowering therapy reduces the risk of ischaemic CV events and worsening of claudication, while it also improves walking performance. As for cardiac events, a systematic review of 18 trials including >10 000 patients, with cholesterol levels ranging from normal to elevated, reported that lipid-lowering therapy in 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.⁴⁰⁷ Regarding limb prognosis, in the Reduction of Atherothrombosis for Continued Health (REACH) registry, statin use was associated with an ~18% lower rate of adverse limb outcomes.⁴⁰⁸ Even in the most advanced stages of the disease (critical limb ischaemia), statin therapy improved rates of 1-year mortality and major adverse CV events and increased amputation-free survival.⁴⁰⁹

9.11.2 Carotid artery disease

While there are currently no randomized studies that have assessed whether lipid-lowering treatments reduce the incidence of CV events in patients enrolled on the basis of carotid atherosclerotic disease and without previous CV events, lipid-lowering therapy reduced stroke in numerous studies. In a meta-analysis of RCTs enrolling >90 000 patients, Amarenco *et al.*⁴¹⁰ reported that statin therapy leads to a 21% reduction in the incidence of all strokes in different populations and that this effect is mainly driven by the extent of LDL-C reduction. CIMT is reduced with statins in RCTs,^{410,411} yet the predictive role of this biomarker (but not of carotid plaque) is somewhat compromised in light of recent data.⁶⁰ Modest regression of carotid atherosclerosis with niacin in most (but not all) imaging studies was not supported by clinical benefit in the AIM-HIGH and HPS2-THRIVE trials.^{251,252}

Table 31 Recommendations for the treatment of dyslipidaemia in transplant patients

Recommendations	Class ^a	Level ^b	Ref ^c
Global CV risk management strategies have to be developed 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	402
In patients who are intolerant of statins or those with significant dyslipidaemia and high residual risk despite a maximally tolerated statin dose, alternative or additional therapy may be considered: ezetimibe for those where high LDL-C is the principal abnormality; or; fibrates for those where hypertriglyceridaemia and/or low HDL-C is the principal abnormality.	Ilb	C	

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

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.11.3 Retinal vascular disease

Atherosclerotic changes of retinal arteries correlate with TC, LDL-C, TG and apoB levels and also with CAD.⁴¹² Fenofibrate reduces the progression of diabetic retinopathy.^{413,414}

9.11.4 Secondary prevention in patients with aortic abdominal aneurysm

The presence of an abdominal aortic aneurysm represents a risk-equivalent condition and is associated with age, male gender, personal history of atherosclerotic CVD, smoking, hypertension and dyslipidaemia,⁴¹⁵ while, in contrast, diabetic patients are at decreased risk.

There are currently no available clinical trials on the reduction of CV risk with lipid-lowering therapy in patients affected by this condition. Systematic reviews,⁴¹⁶ mostly based on retrospective non-randomized studies, have reported that there is still inconclusive evidence that statin therapy reduces perioperative CV morbidity and mortality. In an RCT comparing atorvastatin 20 mg with placebo, the composite 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.⁴¹⁷ In another double-blind placebo-controlled trial in 497 patients undergoing vascular surgery, perioperative fluvastatin therapy (80 mg/day) was associated with an improvement in postoperative cardiac outcome.⁴¹⁸

Based on a recent meta-analysis, statin therapy is likely effective in the prevention of growth of small (<55 mm in diameter) abdominal aortic aneurysms.⁴¹⁹

9.11.5 Renovascular atherosclerosis

Although lipid-lowering therapy has never been tested in an RCT in patients affected by renovascular atherosclerosis, a recent population-based study showed that in patients >65 years of age with atherosclerotic renovascular disease, the risk of a major cardio-renal composite endpoint (MI, stroke, HF, acute renal failure, dialysis and death) was significantly lower in statin users than in non-users.⁴²⁰

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

Table 32 Recommendations for lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)

Recommendations	Class ^a	Level ^b	Ref ^c
PAD is a very-high-risk condition and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A	407, 421
Statin therapy should be considered to prevent the progression of abdominal aortic aneurysm.	IIa	B	419

PAD = peripheral arterial disease.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.12 Stroke

Stroke has a heterogeneous aetiology, including cardiac thromboembolism (often associated with atrial fibrillation), carotid artery and proximal aortic atherosclerosis and thromboembolism, 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 TIA, is well recognized, while the association of dyslipidaemia with other types of stroke is uncertain. Notwithstanding, concomitant control of other aetiological factors, such as hypertension, is of paramount importance.

9.12.1 Primary prevention of stroke

The use of statin therapy in adults at high risk of CVD due to LDL-C or other CV risk factors, including arterial hypertension, as well as in the setting of established CVD, reduces the risk of ischaemic stroke or TIA.^{64,69,128,330,422–426} Risk reduction for a first ischaemic stroke is 21% per 1.0 mmol/L LDL-C reduction,⁶⁴ and it is similar between men and women.⁶⁵ Beneficial effects are retained over long-term follow-up.⁴²⁷ A recent meta-analysis of RCTs in subjects >65 years of age at high CV risk without established CV disease showed that statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term.³²⁷ More intensive lipid lowering with statins is associated with a lower risk of stroke compared with less intensive regimens.^{64,65,128,422} Concerns for increased risk of haemorrhagic stroke with statin treatment do not appear to be justified.⁴²³ The addition of ezetimibe to simvastatin in post-ACS patients had an incremental beneficial effect for ischaemic stroke or all strokes (marginal statistical significance for the latter).⁶³ Niacin did not reduce stroke over long-term follow-up in patients with CVD in the AIM-HIGH and HPS2-THRIVE trials.^{251,252} In fact, the increased rate of ischaemic stroke in the AIM-HIGH trial and the trend ($P = 0.08$) for increased haemorrhagic stroke in the HPS2-THRIVE trial raised concerns and contributed to halting of the AIM-HIGH trial before its planned conclusion. 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, in accordance with the recommendations given in Table 33.

Table 33 Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke

Recommendations	Class ^a	Level ^b	Ref ^c
Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.	I	A	64, 65, 422, 426
Lipid-lowering therapy is recommended in patients with other manifestations of CVD for primary prevention of stroke.	I	A	63–65, 422, 426
Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke	I	A	422, 428

CVD = cardiovascular disease; TIA = transient ischaemic attack.

^aClass of recommendation.

^bLevel of evidence.

^cReference(s) supporting recommendations.

9.12.2 Secondary prevention of stroke

Following stroke or TIA, patients are at risk not only of recurrent cerebrovascular events, but also of other major CV events, including MI. Secondary prevention therapy with statins reduces the risk of recurrent stroke (by 12%), MI and vascular death.^{422,428} Statin pretreatment at TIA onset was associated with reduced recurrent early stroke risk in patients with carotid stenosis in a pooled data analysis, supporting an as-early-as-possible initiation of statins after stroke.⁴²⁹ 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.⁴²²

9.13 Human immunodeficiency virus patients

HIV-infected patients typically have low TC and LDL-C, as well as low HDL-C and increased TGs.^{430,431} Antiretroviral treatment (ART) or highly active antiretroviral treatment (HAART; when drugs are used in combination) causes marked increases in TC, LDL-C and TGs and a predominance of small dense LDL particles, while HDL-C remains low. The extent of lipid changes differs between and within antiretroviral drug classes. Newer protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) or integrase inhibitors affect lipoprotein metabolism to a lesser extent. ART also reduces insulin sensitivity and promotes hypertension and body fat redistribution (lipodystrophy that involves lipoatrophy, which refers to a loss of fat in the face, buttocks and limbs, and/or lipohypertrophy, in which there is an accumulation of fat in the breasts, neck, back or stomach region) that additionally contribute to CVD risk. HIV-infected patients have a higher risk for CVD when compared with HIV-uninfected individuals [RR 1.61 (95% CI 1.43, 1.83)], while ART (and especially older protease inhibitors) further increases this risk, up to two-fold [RR 2.00 (95% CI 1.70, 2.37)].^{431–433} CVD risk remains high even after adjusting for traditional risk factors.⁴³⁴ ART may particularly accelerate the onset of CAD-related events in young male heavy smokers with dyslipidaemia. Nevertheless, absolute CVD risk increase with ART is moderate and should be put into perspective with the benefits of HIV treatment.

Dietary changes and regular physical activity, as well as switching to another ART regimen, may act favourably on dyslipidaemia, but most patients still need pharmacological therapy to reach lipid goals. Statins are effective, but drug interactions with ART need to be considered. Statins metabolized in the liver via the CYP3A4 or CYP2C9 are susceptible to drug interactions with protease inhibitors and the NNRTI efavirenz. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore a preferred statin in HIV-infected individuals. Preferred statins include atorvastatin, fluvastatin, pitavastatin and rosuvastatin, although caution should be exercised. Combination of simvastatin or lovastatin with any protease inhibitor or efavirenz is not recommended. The HIV drug interaction database of the University of Liverpool (<http://www.hiv-druginteractions.org>) is a very helpful tool for checking drug interactions (Supplementary Figure B). For patients who cannot tolerate statin treatment, ezetimibe could be an option.⁴³⁵ Fibrates and fish oil may be prescribed when HTG is predominant.⁴³⁶ Use of bile

acid sequestrants is not recommended because they increase TGs and their effects on the absorption of antiretroviral drugs have not been studied.

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

The recommendations for lipid-lowering drugs in HIV patients are shown in Table 34.

Table 34 Recommendation for lipid-lowering drugs in human immunodeficiency virus patients

Recommendation	Class ^a	Level ^b
Lipid lowering therapy (mostly statins) should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high-risk subjects	Ia	C

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

^aClass of recommendation.

^bLevel of evidence.

9.14 Mental disorders

The presence of a major mental illness such as schizophrenia or bipolar disorder has deleterious effects on the risk of developing CVD. This is related to an unhealthy lifestyle in the majority of these patients (sedentary behaviour, unbalanced diet, smoking), but also to drug treatment. Some antipsychotics, antidepressants, anxiolytics and mood stabilizers are associated with weight gain and cardiometabolic disturbances, including dyslipidaemia and dysglycaemia.

In patients with first-episode schizophrenia spectrum disorders, cardiometabolic risk factors were present early in the illness; this was related to the underlying disorder, unhealthy lifestyle and antipsychotic medications, which interact with each other.⁴³⁷ All this explains the higher prevalence of obesity, MetS, diabetes and dyslipidaemia in patients with these psychiatric diseases.⁴³⁸ It also results in a greater incidence of CVD and in more CV deaths in psychiatric patients suffering from these disorders.

In a Finnish cohort of patients with schizophrenia, life expectancy was about 2 decades less than in persons of similar age from the general population.⁴³⁹ In patients with bipolar disorder there was a reduction in life expectancy of 12–14 years.⁴⁴⁰ Among 654 patients with bipolar disorder in the Fundamental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD) cohort, 18.5% met the criteria for MetS; only 11% and 28% of the patients with hypercholesterolaemia and high fasting glycaemia, respectively, were treated for these conditions.⁴⁴¹ Patients with the aforementioned psychiatric diseases are in general less compliant with chronic drug treatments and therefore have their CV risk factors less well controlled.

CVD accounts for much of the excess mortality in psychiatric patients.⁴⁴² CVD develops more than a decade earlier in patients with bipolar disorders than in controls.⁴⁴³ Therefore it could be recommended to start primary prevention earlier rather than later in these patients. This is well summarized in a position paper of the European

Lipid-Lowering Treatment Selector
Charts revised August 2013. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org

		ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Statins	Atorvastatin	↑	↑	↑153%	↑	↑490%	↑	↓43%	↓37%	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Fluvastatin	↔	↔	↔	↑	↔	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Lovastatin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Pravastatin	↔	↑81%	↔	↑	↔	↓50%	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Rosuvastatin	↑213%	↑48%	↑8%	↑	↑107%	↑	↔	↑	↔	↔	↔	↔	↑48%	↔	↔	↔	↔	↔
	Simvastatin	↑	↑	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔
Fibrates	Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑↑
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Gemfibrozil	↓	↓	↓	↓	↓41%	↓	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔
	Ezetimibe	↑ ^a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour Legend

- No clinically significant interaction expected.
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

Text Legend

- ↑ Potential increased exposure of the lipid-lowering drug
- ↓ Potential decreased exposure of the lipid-lowering drug
- ↔ No significant effect
- ↑↑ Potential increased exposure of HIV drug
- ↓↓ Potential decreased exposure of HIV drug

^aUnboosted atazanavir

Numbers refer to increased or decreased AUC of the lipid-lowering drug as observed in drug-drug interaction studies.

Supplementary figure B HIV-drug interaction database of the University of Liverpool.

Psychiatric Association supported by the European Association for the Study of Diabetes and by the ESC.⁴⁴⁴

Statins are equally effective in lowering LDL-C in psychiatric patients treated with second-generation antipsychotics⁴⁴⁵; however, in only a limited number of these patients are preventive actions taken both in regard to lifestyle and to the use of cardioprotective drugs. The odds of the use of statins was approximately halved in patients with schizophrenia compared with controls.⁴⁴⁶

Unfortunately, no RCTs with 'hard' CV outcome measures have so far been conducted in patients with these major mental diseases. It is reasonable to expect that the favourable metabolic effects of treatment that have been demonstrated result in the prevention of CV events in the long term. However, several questions remain that need to be addressed in further studies in patients with these major mental disorders, regarding long-term safety of statins in association with antipsychotics that also predispose to diabetes and prevention of premature CV mortality and incidence.

Table 35 lists the recommendations for the lipid-lowering drug treatment of patients with mental disorders.

Table 35 Recommendations for lipid-lowering pharmacological treatment in patients with mental disorders

Recommendations	Class ^a	Level ^b
Major psychiatric disorders are modifiers for estimating total CV risk.	I	C
The management of total CV risk in patients with a psychiatric disorder is not different from what is recommended in patients at high/very high CV risk.	I	C
In patients with psychiatric disorders particular attention has to be paid to adherence to lifestyle changes and compliance with drug treatment.	I	C

CV = cardiovascular.

^aClass of recommendation.^bLevel of evidence.^cReference(s) supporting recommendations.

10. Monitoring of lipids and enzymes in patients on lipid-lowering therapy (Table 36)

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

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

Where lipid-lowering therapy is implemented, safety blood tests are advised, including ALT and CK at baseline, to identify the limited number of patients where treatment is contraindicated. CK should be checked in patients with high risk for myopathy, such as the very elderly with co-morbidities, patients with earlier muscle symptoms or patients on interacting drugs. A systematic review found that the incidence of drug-induced hepatotoxicity in patients taking statins is unknown, with very few cases occurring in large-scale RCTs.^{212,214} Recent reviews are encouraging about the safety of long-term statin therapy.^{221,222} ALT is recommended 8–12 weeks after the start of lipid-lowering therapy or dose change, but routine control of ALT during treatment is not recommended and should be performed, if indicated, based on clinical observations. 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 lipid-lowering therapy should be stopped, but may be cautiously reintroduced under monitoring after levels have returned to normal.

There is no predictive value of routine repeat CK testing for rhabdomyolysis since the level can increase for many reasons, including muscle injury or excess muscular exercise. However, CK must be assessed immediately in patients, especially the elderly, presenting with muscle pain and weakness, and treatment stopped if >10 times the ULN. Strategies to handle CK elevations are given in Table 35 and in the supplementary material. Due to the increased frequency of diabetes during statin treatment, regular checks of HbA1C should be considered in patients at high risk of developing diabetes, such as the elderly or those with MetS, obesity or signs of insulin resistance.

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

Terminology to describe the way patients follow their medication regimens and sustain behavioural changes has evolved over the years to include terms such as compliance, adherence and concordance. *Compliance* (<http://medical-dictionary.thefreedictionary.com/Compliance>) is defined as a 'willingness to follow a prescribed course of treatment', but also has connotations of obeying orders in a subservient way. *Adherence* (<http://apps.who.int/medicinedocs/en/d/Js4883e/6.html>) is defined as 'the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider' and is literally defined as sticking to something. Finally, *concordance* (<http://www.drugs.com/dict/concordance.html>) is defined as 'a negotiated, shared agreement between clinician and patient concerning treatment regimen(s), outcomes, and behaviours; a more cooperative relationship than those based on issues of compliance and noncompliance'.

While the terms adherence and concordance are today considered more acceptable than compliance, for the purposes of this guideline, the term adherence will be used, as it is most commonly used in practice and research today.

11.1 Achieving and adhering to healthy lifestyle changes

Behavioural strategies to promote the adoption of healthy lifestyle habits are covered in brief in this section; however, more detail is available in the ESC Guidelines on cardiovascular disease prevention in clinical practice.⁶

No smoking, healthy eating and being physically active are the foundations of preventive cardiology because of their favourable impact on CV risk, including modification of the lipid profile. Healthy lifestyle habits will also enhance effectiveness and reduce the need for drug therapy.

Helping patients to change to healthier lifestyle habits is most effectively achieved through formal programmes of preventive care, possibly because of the intensive follow-up and multidisciplinary expertise they provide.⁴⁴⁷ However, in everyday care, adherence to both healthy lifestyle changes and medication regimens is a challenge to both professionals and patients.

A comprehensive patient- and family-centred approach located in one healthcare setting is recommended rather than addressing single risk factors with more than one intervention in different locations. Drawing on expertise from different disciplines in smoking cessation, dietetics, physical activity, exercise and health psychology is also essential, regardless of whether these experts have direct involvement with patients as dedicated members of a team or whether this expertise is achieved by the provision of training to doctors and nurses delivering care.⁴⁴⁷

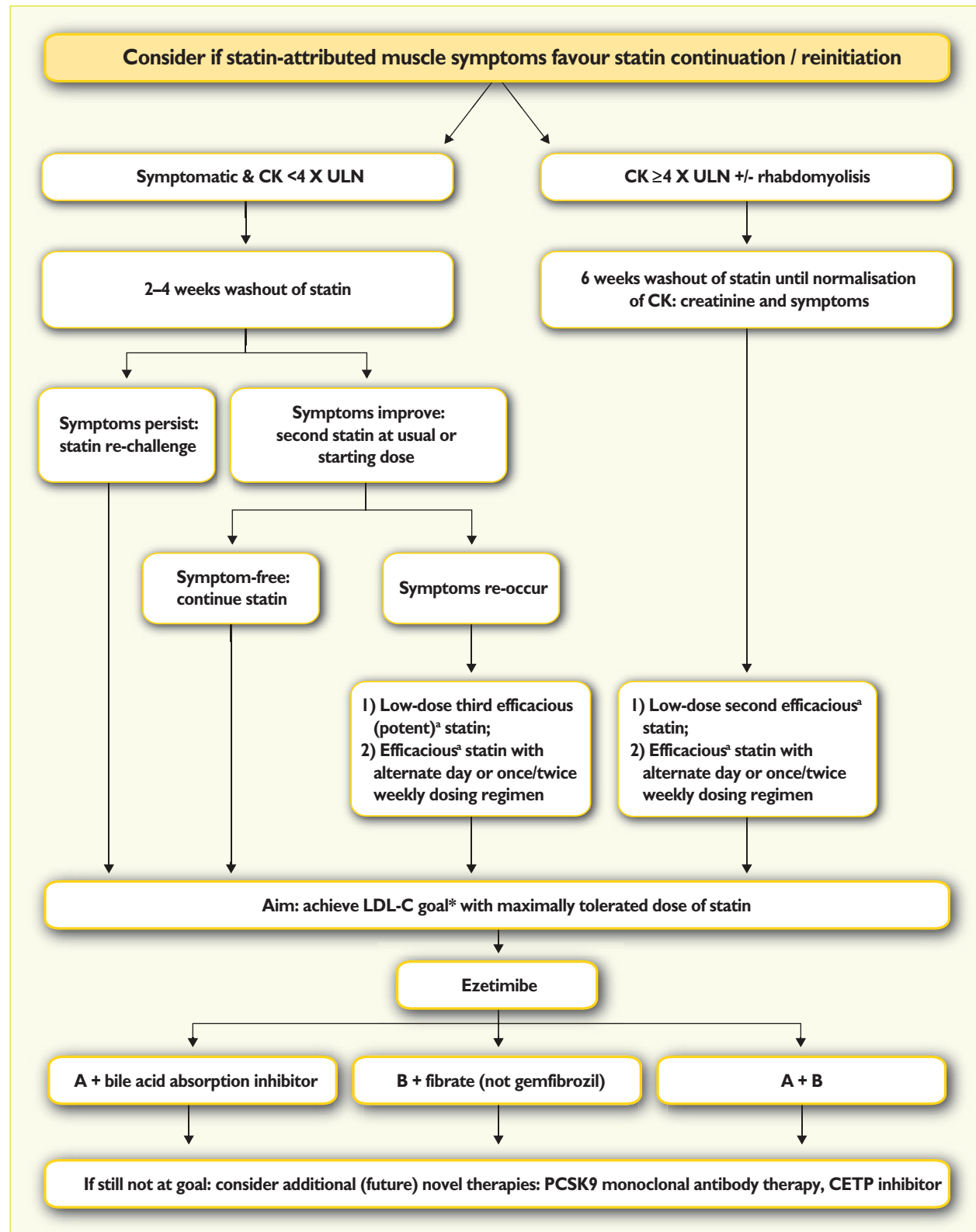
Table 36 Summary of recommendations for monitoring lipids and enzymes in patients on lipid-lowering therapy

Testing lipids
<p>How often should lipids be tested?</p> <ul style="list-style-type: none"> • Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested such as ACS and very high-risk patients.
<p>How often should a patient's lipids be tested after starting lipid-lowering treatment?</p> <ul style="list-style-type: none"> • 8 (±4) weeks after starting treatment. • 8 (±4) weeks after adjustment of treatment until within the target range.
<p>How often should lipids be tested once a patient has reached the target or optimal lipid level?</p> <ul style="list-style-type: none"> • Annually (unless there is adherence problems or other specific reasons for more frequent reviews).
Monitoring liver and muscle enzymes
<p>How often should liver enzymes (ALT) be routinely measured in patients on lipid-lowering drugs?</p> <ul style="list-style-type: none"> • Before treatment. • Once 8–12 weeks after starting a drug treatment or after dose increase. • Routine control of ALT thereafter is not recommended during lipid-lowering treatment.
<p>What if liver enzymes become elevated in a person taking lipid-lowering drugs?</p> <p>If ALT <3x ULN:</p> <ul style="list-style-type: none"> • Continue therapy. • Recheck liver enzymes in 4–6 weeks. <p>If value rises to ≥3x ULN</p> <ul style="list-style-type: none"> • Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks. • Cautious reintroduction of therapy may be considered after ALT has returned to normal. • If ALT remains elevated check for the other reasons.
<p>How often should CK be measured in patients taking lipid-lowering drugs?</p> <p><i>Pre-treatment</i></p> <ul style="list-style-type: none"> • Before starting therapy. • If baseline CK is 4x ULN, do not start drug therapy; recheck. <p><i>Monitoring:</i></p> <ul style="list-style-type: none"> • Routine monitoring of CK is not necessary. • Check CK if patient develops myalgia. <p>Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease or sport athletes.</p>
<p>What if CK becomes elevated in a person taking lipid-lowering drugs?</p> <p>Re-evaluate indication for statin treatment.</p> <p>If ≥4 x ULN:</p> <ul style="list-style-type: none"> • If CK >10x ULN: stop treatment, check renal function and monitor CK every 2 weeks. • If CK <10x ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK. • If CK <10x ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose. • Consider the possibility of transient CK elevation for other reasons such as exertion. • Consider myopathy if CK remains elevated. • Consider combination therapy or an alternative drug. <p>If <4 x ULN:</p> <ul style="list-style-type: none"> • If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK). • If muscle symptoms, monitor symptoms and CK regularly. • If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment. • Consider re-challenge with the same or another statin. • Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy. <p>For details on CK elevation and treatment of muscular symptoms during statin treatment see algorithm in supplementary figure C.</p>

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

The adoption of effective strategies to help patients to change behaviours is now made easier with the development of a hierarchical taxonomy of behaviour change strategies.⁴⁴⁸ The taxonomy has

developed a system of standardized labelling of behavioural strategies, which allows a clear description of complex interventions⁴⁴⁹ in research reports and their subsequent translation into clinical practice initiatives.



CETP = cholesteryl ester transfer protein; CK = creatine kinase; LDL-C= low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; ULN = upper limit of the normal range.

*Efficacious statin such as atorvastatin or rosuvastatin.

*Reiner Z et al. (2011).

Web Figure C Algorithm for treatment of muscular symptoms during statin treatment.²¹¹

Box 11 includes some useful techniques when counselling patients for behavioural change.

Box 11 Hints to aid adherence to lifestyle changes

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

In addition, it is important to be aware of the following barriers to change:

- Healthy choices are not always easy choices.
- Socio-economic status and cultural and environmental factors influence behaviour change.
- Your agenda for change as a health professional may conflict with that of the person you are trying to help.
- Helping people to change requires dedicated time from the health professional to provide support and follow-up.
- People may have feelings of ambivalence towards changing behaviour that need exploring.

11.2 Adhering to medications

Despite a wealth of evidence on the efficacy and effectiveness of statins in both primary and secondary prevention, adherence remains a consistent barrier, with rates of <50% demonstrated in several studies. Adherence declines over the duration of treatment^{450–454}; however, this is truer in patients treated for primary compared with secondary prevention of CVD, with reported rates of up to 77% discontinuing their statins within 2 years. Adherence is better in patients recruited to clinical trials compared with those treated in the real world.^{455,456} Not surprisingly, this non-adherence has an impact on healthcare costs, morbidity, hospital readmissions and mortality.^{457–461} Poor adherence rates are not only limited to statins but are also true of other lipid-lowering drugs and all medications used to prevent CVD, as demonstrated in a systematic review and meta-analysis.⁴⁶²

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

In the UK in 2014, controversy was sparked among general practitioners (GPs) and other physicians⁴⁶³ in relation to the recent updated recommendation from NICE to offer atorvastatin 20 mg for the primary prevention of CVD to people who have an estimated $\geq 10\%$ absolute 10-year risk of developing CVD using the QRISK2 assessment tool (<http://www.nice.org.uk/guidance/cg181>). Together

with the additional controversy generated by Abramson *et al.*^{464,465} regarding their analysis of the adverse effects of statins, which was subsequently corrected, it is not surprising that GPs, in particular, have a certain degree of reluctance to proceed with the NICE strategy. If there is a lack of local consensus on the prescription of statins in primary prevention, then GPs may be less inclined to prescribe them, let alone encourage patients to adhere to their statin therapy, even in the face of minor adverse effects.

Various empirical models of health behaviour and behaviour change theory have been shown to predict adherence, including the Theory of Planned Behaviour⁴⁶⁶ and the Health Belief Model.⁴⁶⁷ Studies that investigated adherence to medications in long-term conditions identified factors such as high susceptibility, severity of the condition, strong intentions and high self-efficacy as being associated with good adherence, while poor lifestyle habits and low perceived behavioural control were associated with poor adherence.^{468,469} However, these theoretical models are limited in that they do not take into account important social, economic, health system and therapy-related factors. Most recently, the COM-B (Capability, Opportunity and Motivation) theoretical model,⁴⁷⁰ developed by Michie *et al.*,⁴⁷¹ which takes a broader look at factors influencing adherence, proposed a framework for assessing and addressing adherence, taking the interaction between capability (defined as both the psychological and physical capacity of an individual to engage in a behaviour), opportunities (defined as factors outside the control of an individual) and their motivation to do so.

Predictors of non-adherence with statins have been identified^{450,472–474} and include their use in individuals for primary prevention as compared with their use in patients with disease or with multiple risk factors, lower income, being elderly, complex polypharmacy, cost and forgetfulness due to a lack of symptoms and psychological co-morbidities. In addition, reasons for reluctance to collect a first prescription of statin medication were investigated in a cross-sectional telephone survey conducted in California from recruits to an RCT.⁴⁷⁵ The most commonly reported reasons included general concerns about the medication, wanting to try lifestyle measures first and fear of adverse effects; however, a significant proportion reported financial hardship, a lack of understanding of why they needed to take the medication and what the medication was for (indicating a need to address the patient–professional relationship and poor health literacy). Health literacy is defined as ‘the degree to which individuals have the capacity to obtain, process and understand basic health info and services needed to make appropriate health decisions’ (<http://nnlm.gov/outreach/consumer/hlthlit.html>).

Poor health literacy is of particular concern in regard to medication adherence.⁴⁷⁵ Elderly patients and those with low socio-economic status and chronic health conditions may be especially vulnerable. These patients may get confused, especially when their regimens are complex and include many drugs (polypharmacy) that need to be taken on more than one occasion per day. Important steps to empower patients to get more benefit from health interventions include the following⁴⁷⁶:

1. Use good interpersonal skills (good eye contact, warm manner) and an empathetic, non-judgmental attitude.
2. Provide clear and simple instructions on a drug regimen backed up with written instructions, which can also be seen by a spouse or caregiver.

Need to know and do
e.g. Important information about diagnosis,
key treatment and management of prescribed medications

Nice to know and do
Information that may be covered but can wait for
a second consultation

Not necessary now, do later
e.g. Provide information, using leaflets, booklets or
web-based resources, about additional services
that can be provided

Figure 8 Prioritising information when educating patients.

3. Speak slowly in plain language and avoid medical jargon when giving instructions.
4. Limit the number of instructions to no more than three key points—principle of ‘need to know’ (Figure 8).
5. Use ‘teachback’ to confirm understanding; e.g. ‘I want to make sure that I explained things clearly. Let’s review what we discussed. What are the three strategies that will help keep your cholesterol down?’
6. Use supplemental materials, e.g. images, videos and audio sources, to improve recall (Figure 9).
7. Encourage questions and discussion—enlist the family or others important to the individual.
8. Motivational interviewing skills may be helpful in communicating with patients who are ambivalent or seem against starting or continuing with medications:^{37,477}
 - (a) Counsel patients using the OARS method (Box 11).
 - (b) Use the ‘elicit–provide–elicit’ model to tailor the information you give (elicit what the patient wants to know, provide that


















Names of pills	What it's for	 Morning/Breakfast	 Afternoon/Lunch	 Evening/Dinner	 Night/Bedtime
Lisinopril 20 mg 1 pill once a day	Blood pressure 				
Simvastatin 40 mg 1 pill at bedtime	Cholesterol 				
Metformin 500 mg 2 pills twice a day	Diabetes 				
Gabapentin 300 mg 1 pill every 8 hours	Nerve pain 				
Aspirin EC 81 mg 1 pill once a day	Heart 				

Figure 9 Images to improve recall.

information, elicit from the patient how they can use this new knowledge to their benefit).

- (c) Acknowledge and reflect your patient's resistance.
 - (d) Support your patient's autonomy to make their own decisions about their health and treatment.
 - (e) Explore your patient's ambivalence to adhere to their treatment.
 - (f) Develop a plan of action together and share decision-making.
9. Build self-efficacy and confidence, drawing on social learning theory.⁴⁷⁸

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

Interventions to improve adherence have been reviewed in a Cochrane review from 2010,⁴⁷⁹ which looked at interventions to improve adherence to all forms of lipid-lowering therapy, including reminders, simplification of drug regimens and provision of information and education. Most effective was reminders, such as setting alarms, connecting medication-taking to other tasks to trigger memory and phone reminders from nurses. Reminder systems have the potential to be developed with the help of innovations in technology, like the use of text messaging, the Internet and applications for mobile phones or tablets to assist in self-monitoring and management. Adherence research is weak in this area, mainly because it has not kept abreast of the rapid developments in technology;⁴⁸⁰ however, these methods may come into their own in the future with a stronger knowledge base.

Prescription of a statin should include a shared decision-making approach⁴⁸¹ that engages the patient in a discussion before initiating treatment, especially when it is being considered for primary prevention of CVD. This discussion should be based on risk estimation and adequate communication of this risk to patients. Involving the patient in such a way is likely to be empowering and motivate adherence. This discussion is not exclusively about the prescription of a statin to manage lipids; a comprehensive approach includes addressing all lifestyle and other biomedical factors that contribute to CV risk.

Once treatment has been prescribed, communication should focus on conveying achievements in reaching goals, assessment of adherence and possible reasons for non-adherence, such as adverse effects. In relation to lipid-lowering medications, and statins in particular, misconceptions and misleading media reports are in abundance. Many patients report adverse effects of statins to their GPs and this may be because of an increased likelihood to anticipate them. However, a recent large review of RCTs²¹³ found that in 83 880 patients receiving blinded placebo-controlled statin therapy, few reported adverse effects were actually due to the drug. This study calculated the PSN, defined as the proportion of symptoms not attributable to its pharmacological action, in order to provide GPs with a clear metric to use in advising their patients on whether reported symptoms are genuinely likely to be pharmacologically caused by the statin or not.

Recently, promising results for improving adherence have been demonstrated in the use of a fixed-dose combination (FDC) drug or 'polypill' in both primary and secondary prevention. The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE)

RCT⁴⁸² compared an FDC containing aspirin, statin and two blood pressure-lowering agents with usual care in both primary and secondary prevention in 2004 randomized patients in India and Europe. At 15 months, statistically significant differences between intervention and usual care were seen in self-reported adherence and changes in systolic blood pressure and LDL-C. The Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study⁴⁸³ had a cross-sectional first phase, which identified factors contributing to non-adherence after MI in 2118 patients from five countries in South America and Europe. In the second phase, 695 patients from the first phase were randomized to receive either a polypill containing aspirin, statin and ramipril in varying doses or were given the three drugs separately. Adherence was measured with the self-reported Morisky-Green questionnaire and pill counts and was statistically significantly superior in the intervention group compared with usual care at 9 months. In phase 1, factors associated with non-adherence were younger age, depression, complex regimen, poorer health insurance coverage and low social support.

Given the benefits for adherence demonstrated with simplified dosing reported in a Cochrane overview of interventions to improve safe and effective medicines use by consumers,⁴⁸⁴ it makes sense that a pill that contains multiple medications in one tablet will enhance adherence. This overview also found that the use of self-management or self-monitoring programmes, as well as a regular pharmacy review of prescribed medications with a view to taking out unnecessary medications, was helpful.

Many of the studies included in the Cochrane review of interventions to improve medication adherence⁴⁸⁰ drew on the support of allied professionals such as nurses and pharmacists to deliver complex interventions, which may include telephone follow-up, interim appointments and monitoring of repeat prescriptions. The reviewed interventions may be difficult to replicate in everyday clinical care due to the cost and the availability of personnel. Drawing on the support of non-professional people within the social context of the patient, such as spouses, other family members, caregivers or other key figures, as well as lay groups in the community, may prove to be a cost-effective way to improve adherence.

Box 12 lists a number of tips to use when prescribing multiple medications to patients in order to help them adhere.

Box 12 Tips to aid adherence to multiple drug therapies

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

12. To do and not to do messages from the Guidelines

Recommendations	Class ^a	Level ^b
Recommendations for risk estimation		
Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, diabetes, CKD or familial hypercholesterolaemia.	I	C
High and very high-risk individuals can be detected on the basis of documented CVD, diabetes mellitus, moderate to severe renal disease, very high levels of individual risk factors, familial hypercholesterolaemia or a high SCORE risk and are a high priority for intensive advice with regard to all risk factors.	I	C
Recommendations for lipid analyses in cardiovascular disease risk estimation		
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
LDL-C is recommended to be used as the primary lipid analysis for screening, risk estimation, diagnosis and management. HDL-C is a strong independent risk factor and is recommended to be used in the HeartScore algorithm.	I	C
Non-HDL-C is a strong independent risk factor and should be considered as a risk marker, especially in subjects with high TG.	I	C
Recommendations for lipid analyses for characterization of dyslipidaemias before treatment		
LDL-C has to be used as the primary lipid analysis.	I	C
It is recommended to analyse HDL-C before treatment.	I	C
TG adds information about risk, and is indicated for diagnosis and choice of treatment.	I	C
Non-HDL-C is recommended to be calculated, especially in subjects with high TG.	I	C
Recommendations for lipid analyses as treatment targets in the prevention of cardiovascular disease		
LDL-C is recommended as the primary target for treatment.	I	A
HDL-C is not recommended as a target for treatment.	III	A
The ratios apoB/apoAI and non-HDL-C/HDL-C are not recommended as targets for treatment.	III	B
Recommendations for treatment goals for low-density lipoprotein-cholesterol		
In patients at VERY HIGH CV risk ^c , an LDL-C goal of <1.8 mmol/L (70 mg/dL), or a reduction of at least 50% if the baseline LDL-C ^d is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) is recommended.	I	B
In patients at HIGH CV risk ^c , an LDL-C goal of <2.6 mmol/L (100 mg/dL), or a reduction of at least 50% if the baseline LDL-C ^d is between 2.6 and 5.2 mmol/L (100 and 200 mg/dL) is recommended.	I	B
Recommendations for the pharmacological treatment of hypercholesterolaemia		
Prescribe statin up to the highest recommended dose or highest tolerable dose to reach the goal.	I	A
Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia		
FH is recommended to be suspected in patients with CHD before the age of 55 years for men and 60 years for women, in subjects with relatives with premature fatal or non-fatal CVD, in subjects with relatives having tendon xanthomas, and in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL), in children >4 mmol/L (150 mg/dL)].	I	C
Family cascade screening is recommended to be performed when an index case of FH is diagnosed.	I	C
FH patients are recommended to be treated with intense-dose statin, often in combination with ezetimibe.	I	C
In children, testing is recommended from age 5 years, or earlier if homozygous FH is suspected.	I	C
Recommendations for the treatment of dyslipidaemia in older adults		
Treatment with statins is recommended for older adults with established CVD in the same way as for younger patients.	I	A
Recommendations for the treatment of dyslipidaemia in diabetes		
In all patients with type 1 diabetes and in the presence of microalbuminuria and/or renal disease, LDL-C lowering (at least 50%) with statins as the first choice is recommended irrespective of the baseline LDL-C concentration.	I	C
In patients with type 2 diabetes and CVD or CKD, and in those without CVD who are >40 years of age 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 (<70 mg/dL) and the secondary goal for non-HDL-C is <2.6 mmol/L (<100 mg/dL) and for apoB is <80 mg/dL.	I	B
In all patients with type 2 diabetes and no additional risk factors and/or evidence of target organ damage, LDL-C <2.6 mmol/L (<100 mg/dL) is the primary goal. Non-HDL-C <3.4 mmol/L (<130 mg/dL) and apoB <100 mg/dL are the secondary goals.	I	B
Recommendation for lipid-lowering therapy in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention		
It is recommended to initiate or continue high dose statins early after admission in all ACS patients without contra-indication or history of intolerance, regardless of initial LDL-C values.	I	A

To do or not to do lipid guidelines (continued)

Recommendations	Class ^a	Level ^b
Recommendations for the treatment of dyslipidaemia in heart failure or valvular disease		
Cholesterol lowering therapy with statins is not recommended (but is not harmful either) in patients with heart failure in the absence of other indications for their use.	III	A
Cholesterol-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD in the absence of other indications for their use.	III	A
Recommendations for the treatment of dyslipidaemia in autoimmune diseases		
The universal use of lipid-lowering drugs is not recommended.	III	C
Recommendations for lipid management in patients with moderate to severe chronic kidney disease		
Patients with stage 3–5 CKD have to be considered at high or very high CV risk.	I	A
The use of statins or statin/ezetimibe combination is indicated in patients with non-dialysis-dependent CKD.	I	A
In patients with dialysis-dependent CKD and free of atherosclerotic CVD, statins should not be initiated.	III	A
Recommendations for lipid-lowering drugs in patients with peripheral arterial disease (including carotid artery disease)		
PAD is a very high-risk condition and lipid-lowering therapy (mostly statins) is recommended in these patients.	I	A
Recommendations for lipid-lowering drugs for primary and secondary prevention of stroke		
Statin therapy to reach established treatment goals is recommended in patients at high or very high CV risk for primary prevention of stroke.	I	A
Lipid-lowering therapy is recommended in patients with other manifestations of CVD for primary prevention of stroke.	I	A
Intensive statin therapy is recommended in patients with a history of non-cardioembolic ischaemic stroke or TIA for secondary prevention of stroke.	I	A

^aClass of recommendation.^bLevel of evidence.

13. Appendix

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Victor Aboyans (France), Stephan Achenbach (Germany), Stefan Agewall (Norway), Lina Badimon (Spain), Gonzalo Barón-Esquivias (Spain), Helmut Baumgartner (Germany), Jeroen J. Bax (The Netherlands), Héctor Bueno (Spain), Scipione Carerj (Italy), Veronica Dean (France), Çetin Erol (Turkey), Donna Fitzsimons (UK), Oliver Gaemperli (Switzerland), Paulus Kirchhof (UK/Germany), Philippe Kolh (Belgium), Patrizio Lancellotti (Belgium), Gregory Y. H. Lip (UK), Petros Nihoyannopoulos (UK), Massimo F. Piepoli (Italy), Piotr Ponikowski (Poland), Marco Roffi (Switzerland), Adam Torbicki (Poland), António Vaz Carneiro (Portugal), Stephan Windecker (Switzerland).

ESC National Cardiac Societies actively involved in the review process of the 2016 ESC/EAS Guidelines for the management of dyslipidaemias:

Armenia: Armenian Cardiologists Association, Parounak H. Zelveian; **Austria:** Austrian Society of Cardiology, Peter Siostrzonek; **Azerbaijan:** Azerbaijan Society of Cardiology, Firdovsi Ibrahimov; **Belarus:** Belorussian Scientific Society of Cardiologists, Volha Sujayeva; **Belgium:** Belgian Society of Cardiology, Marc J. Claeys; **Bosnia and Herzegovina:** Association of Cardiologists of Bosnia and Herzegovina, Belma Pojskić; **Bulgaria:** Bulgarian

Society of Cardiology, Arman Postadzhiyan; **Croatia:** Croatian Cardiac Society, Davor Miličić; **Cyprus:** Cyprus Society of Cardiology, George C. Georgiou; **Czech Republic:** Czech Society of Cardiology, Hana Rosolova; **Denmark:** Danish Society of Cardiology, Christian Klausen; **Estonia:** Estonian Society of Cardiology, Margus Viigimaa; **Finland:** Finnish Cardiac Society, Kari Kervinen; **Former Yugoslav Republic of Macedonia:** Macedonian FYR Society of Cardiology, Sasko Kedev; **France:** French Society of Cardiology, Jean Ferrières; **Georgia:** Georgian Society of Cardiology, Shalva Petriashvili; **Germany:** German Cardiac Society, Ulrich Kintscher; **Greece:** Hellenic Cardiological Society, Loukianos Rallidis; **Hungary:** Hungarian Society of Cardiology, Róbert Gábor Kiss; **Iceland:** Icelandic Society of Cardiology, Thorarinn Guðnason; **Ireland:** Irish Cardiac Society, Vincent Maher; **Israel:** Israel Heart Society, Yaakov Henkin; **Italy:** Italian Federation of Cardiology, Gian Francesco Mureddu; **Kazakhstan:** Association of Cardiologists of Kazakhstan, Aisulu Mussagalieva; **Kosovo:** Kosovo Society of Cardiology, Pranvera Ibrahim; **Kyrgyzstan:** Kyrgyz Society of Cardiology, Erkin Mirrakhimov; **Latvia:** Latvian Society of Cardiology, Gustavs Latkovskis; **Libya:** Libyan Cardiac Society, Hisham Ben Lamin; **Lithuania:** Lithuanian Society of Cardiology, Rimvydas Slapikas; **Luxembourg:** Luxembourg Society of Cardiology, Laurent Visser; **Malta:** Maltese Cardiac Society, Philip Dingli; **Moldova:** Moldavian Society of Cardiology, Victoria Ivanov;

The Netherlands: Netherlands Society of Cardiology, Janneke Wittekoek; **Norway:** Norwegian Society of Cardiology, Anders Hovland; **Poland:** Polish Cardiac Society, Andrzej Rynkiewicz; **Portugal:** Portuguese Society of Cardiology, Quiteria Rato; **Russian Federation:** Russian Society of Cardiology, Marat Ezhov; **San Marino:** San Marino Society of Cardiology, Marco Zavatta; **Serbia:** Cardiology Society of Serbia, Milan A. Nedeljkovic; **Slovakia:** Slovak Society of Cardiology, Daniel Pella; **Slovenia:** Slovenian Society of Cardiology, Zlatko Fras; **Spain:** Spanish Society of Cardiology, Domingo Marzal; **Sweden:** Swedish Society of Cardiology, Lennart Nilsson; **Switzerland:** Swiss Society of Cardiology, Francois Mach; **Tunisia:** Tunisian Society of Cardiology and Cardio-Vascular Surgery, Faouzi Ad-dad; **Turkey:** Turkish Society of Cardiology, Meral Kaykcioglu; **Ukraine:** Ukrainian Association of Cardiology, Olena Mitchenko; **United Kingdom:** British Cardiovascular Society, David Wald.

14. References

- Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe—epidemiological update 2015. *Eur Heart J* 2015;**36**:2696–705.
- Cooney MT, Dudina A, Whincup P, Capewell S, Menotti A, Jousilahti P, Njølstad I, Oganov R, Thomsen T, Tverdal A, Wedel H, Wilhelmsen L, Graham I. Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:541–549.
- Liu K, Daviglius ML, Loria CM, Colangelo LA, Spring B, Moller AC, Lloyd-Jones DM. Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle age: the Coronary Artery Risk Development in (Young) Adults (CARDIA) study. *Circulation* 2012;**125**:996–1004.
- Ezzati M, Lopez AD, Rodgers A, Murray CJL. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva: World Health Organization, 2004.
- World Health Organization. Global status report on noncommunicable diseases 2010. Geneva: World Health Organization, 2011.
- Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syväne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;**33**:1635–1701.
- Mistry H, Morris S, Dyer M, Kotseva K, Wood D, Buxton M. Cost-effectiveness of a European preventive cardiology programme in primary care: a Markov modelling approach. *BMJ Open* 2012 Oct 11;**2**. pii: e001029.
- Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. *European Cardiovascular Disease Statistics, 2012*. Brussels: European Heart Network, 2012.
- Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 2011;**123**:933–944.
- McConnachie A, Walker A, Robertson M, Marchbank L, Peacock J, Packard CJ, Cobbe SM, Ford I. Long-term impact on healthcare resource utilization of statin treatment, and its cost effectiveness in the primary prevention of cardiovascular disease: a record linkage study. *Eur Heart J* 2014;**35**:290–298.
- Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, Yeo W, Payne N. A systematic review and economic evaluation of statins for the prevention of coronary events. *Health Technol Assess* 2007;**11**:1–160, iii–iv.
- Plans-Rubio P. The cost effectiveness of statin therapies in Spain in 2010, after the introduction of generics and reference prices. *Am J Cardiovasc Drugs* 2010;**10**:369–382.
- Bjorck L, Rosengren A, Bennett K, Lappas G, Capewell S. Modelling the decreasing coronary heart disease mortality in Sweden between 1986 and 2002. *Eur Heart J* 2009;**30**:1046–1056.
- Aspelund T, Gudnason V, Magnusdottir BT, Andersen K, Sigurdsson G, Thorsson B, Steingrimsdottir L, Critchley J, Bennett K, O'Flaherty M, Capewell S. Analysing the large decline in coronary heart disease mortality in the Icelandic population aged 25–74 between the years 1981 and 2006. *PLoS One* 2010;**5**:e13957.
- Pereira M, Azevedo A, Lunet N, Carreira H, O'Flaherty M, Capewell S, Bennett K. Explaining the decline in coronary heart disease mortality in Portugal between 1995 and 2008. *Circ Cardiovasc Qual Outcomes* 2013;**6**:634–642.
- Unal B, Sozmen K, Arik H, Gercekliloglu G, Altun DU, Simsek H, Doganay S, Demiral Y, Aslan Ö, Bennett K, O'Flaherty M, Capewell S, Critchley J. Explaining the decline in coronary heart disease mortality in Turkey between 1995 and 2008. *BMC Public Health* 2013;**13**:1135.
- Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, Naghavi M, Mensah GA, Murray CJ. Demographic and epidemiologic drivers of global cardiovascular mortality. *N Engl J Med* 2015;**372**:1333–1341.
- Cobiac LJ, Magnus A, Lim S, Barendregt JJ, Carter R, Vos T. Which interventions offer best value for money in primary prevention of cardiovascular disease? *PLoS One* 2012;**7**:e41842.
- Collins M, Mason H, O'Flaherty M, Guzman-Castillo M, Critchley J, Capewell S. An economic evaluation of salt reduction policies to reduce coronary heart disease in England: a policy modeling study. *Value Health* 2014;**17**:517–524.
- Mason H, Shoaibi A, Ghandour R, O'Flaherty M, Capewell S, Khatib R, Jabr S, Unal B, Sözmen K, Arfa C, Aissi W, Ben Romdhane H, Fouad F, Al-Ali R, Hussein A. A cost effectiveness analysis of salt reduction policies to reduce coronary heart disease in four Eastern Mediterranean countries. *PLoS One* 2014;**9**:e84445.
- O'Keefe C, Kabir Z, O'Flaherty M, Walton J, Capewell S, Perry IJ. Modelling the impact of specific food policy options on coronary heart disease and stroke deaths in Ireland. *BMJ Open* 2013;**3**. pii: e002837.
- Moreira PV, Baraldi LG, Moubarac JC, Monteiro CA, Newton A, Capewell S, O'Flaherty M. Comparing different policy scenarios to reduce the consumption of ultra-processed foods in UK: impact on cardiovascular disease mortality using a modelling approach. *PLoS One* 2015;**10**:e0118353.
- Neyt M, De Laet C, Van Brabant H, Franco O, Ramaekers D. Cost-effectiveness of statins in the primary prevention of cardiovascular disease: a systematic review and economic analysis for Belgium. *Acta Cardiol* 2009;**64**:1–10.
- Peura P, Martikainen J, Soini E, Hallinen T, Niskanen L. Cost-effectiveness of statins in the prevention of coronary heart disease events in middle-aged Finnish men. *Curr Med Res Opin* 2008;**24**:1823–1832.
- Ito MK, Nanchen D, Rodondi N, Paccaud F, Waeber G, Vollenweider P, Marques-Vidal P. Statins for cardiovascular prevention according to different strategies: a cost analysis. *Am J Cardiovasc Drugs* 2011;**11**:33–44.
- Stevanovic J, O'Prinsen AC, Verheggen BG, Schuiling-Veninga N, Postma MJ, Pechlivanoglou P. Economic evaluation of primary prevention of cardiovascular diseases in mild hypertension: a scenario analysis for the Netherlands. *Clin Ther* 2014;**36**:368–384.e5.
- Wisloff T, Selmer RM, Halvorsen S, Fretheim A, Norheim OF, Kristiansen IS. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease—a cost-effectiveness analysis. *BMC Cardiovasc Disord* 2012;**12**:26.
- Banegas JR, Lopez-Garcia E, Dallongeville J, Guallar E, Halcox JP, Borghi C, Massó-González EL, Jiménez FJ, Perk J, Steg PG, De Backer G, Rodríguez-Artalejo F. Achievement of treatment goals for primary prevention of cardiovascular disease in clinical practice across Europe: the EURIKA study. *Eur Heart J* 2011;**32**:2143–2152.
- Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Reiner Z, Keil U. EUROASPIRE III. Management of cardiovascular risk factors in asymptomatic high-risk patients in general practice: cross-sectional survey in 12 European countries. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:530–540.
- Cherry SB, Benner JS, Hussein MA, Tang SS, Nichol MB. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. *Value Health* 2009;**12**:489–497.
- Corrao G, Scotti L, Zambon A, Baio G, Nicotra F, Conti V, Capri S, Tragni E, Merlino L, Catapano AL, Mancia G. Cost-effectiveness of enhancing adherence to therapy with statins in the setting of primary cardiovascular prevention. Evidence from an empirical approach based on administrative databases. *Atherosclerosis* 2011;**217**:479–485.
- Dragomir A, Cote R, Roy L, Blais L, Lalonde L, Berard A, Perreault S. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Med Care* 2010;**48**:418–425.
- Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;**326**:1419.
- Gaziano TA, Opie LH, Weinstein MC. Cardiovascular disease prevention with a multidrug regimen in the developing world: a cost-effectiveness analysis. *Lancet* 2006;**368**:679–686.
- van Gils PF, Over EA, Hamberg-van Reenen HH, de Wit GA, van den Berg M, Schuit AJ, Engelfriet PM. The polypill in the primary prevention of cardiovascular disease: cost-effectiveness in the Dutch population. *BMJ Open* 2011;**1**:e000363.

36. Frieden TR. A framework for public health action: the health impact pyramid. *Am J Public Health* 2010;**100**:590–595.
37. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc* 2011; **86**:304–314.
38. National Institute for Health and Care Excellence. NICE Public Health Guidance 25. June 2010. <https://www.nice.org.uk/guidance/ph25>.
39. Capewell S, Ford ES, Croft JB, Critchley JA, Greenlund KJ, Labarthe DR. Cardiovascular risk factor trends and potential for reducing coronary heart disease mortality in the United States of America. *Bull World Health Org* 2010;**88**:120–130.
40. Mozaffarian D, Capewell S. United Nations' dietary policies to prevent cardiovascular disease. *BMJ* 2011;**343**:d5747.
41. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;**117**:743–753.
42. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetière P, Jousilahti P, Keil U, Njølstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;**24**:987–1003.
43. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart* 2007;**93**:172–176.
44. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, Brindle P. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ* 2008;**336**:1475–1482.
45. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation* 2002;**105**:310–315.
46. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;**118**:2243–2251.
47. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;**297**:611–619.
48. Ferrario M, Chiodini P, Chambless LE, Cesana G, Vanuzzo D, Panico S, Segà R, Pilotto L, Palmieri L, Giampaoli S. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol* 2005;**34**:413–421.
49. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**(25 Suppl 2):S49–S73.
50. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, Azizi F, Cifkova R, Di Cesare M, Eriksen L, Farzadfar F, Ikeda N, Khalili D, Khang YH, Lanska V, León-Muñoz L, Magliano D, Msyamboza KP, Oh K, Rodríguez-Artalejo F, Rojas-Martinez R, Shaw JE, Stevens GA, Tolstrup J, Zhou B, Salomon JA, Ezzati M, Danaei G. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol* 2015;**3**:339–355.
51. Cooney MT, Dudina AL, Graham IM. Value and limitations of existing scores for the assessment of cardiovascular risk: a review for clinicians. *J Am Coll Cardiol* 2009; **54**:1209–1227.
52. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? Do they make a difference? Can we see the future? *Circulation* 2010;**122**:300–310.
53. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006;**113**:791–798.
54. Cooney MT, Selmer R, Lindman A, Tverdal A, Menotti A, Thomsen T, DeBacker G, De Bacquer D, Tell GS, Njølstad I, Graham IM. Cardiovascular risk estimation in older persons: SCORE O.P. *Eur J Prev Cardiol* 2016;**23**: 1093–1103.
55. Cooney MT, Dudina A, De Bacquer D, Wilhelmsen L, Sans S, Menotti A, De Backer G, Jousilahti P, Keil U, Thomsen T, Whincup P, Graham IM. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis* 2009;**206**:611–616.
56. Cooney MT, Dudina A, De Bacquer D, Fitzgerald A, Conroy R, Sans S, Menotti A, De Backer G, Jousilahti P, Keil U, Thomsen T, Whincup P, Graham I. How much does HDL cholesterol add to risk estimation? A report from the SCORE Investigators. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:304–314.
57. Mortensen MB, Afzal S, Nordestgaard BG, Falk E. The high-density lipoprotein-adjusted SCORE model worsens SCORE-based risk classification in a contemporary population of 30,824 Europeans: the Copenhagen General Population Study. *Eur Heart J* 2015;**36**:2446–2453.
58. Kavousi M, Elias-Smale S, Rutten JH, Leening MJ, Vliegthart R, Verwoert GC, Krestin GP, Oudkerk M, de Maat MP, Leebeek FW, Mattace-Raso FU, Lindemans J, Hofman A, Steyerberg EW, van der Lugt A, van den Meiracker AH, Witteman JC. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med* 2012;**156**:438–444.
59. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;**308**:788–795.
60. Vlachopoulos C, Xaplanteris P, Aboyans V, Brodmann M, Cifkova R, Cosentino F, De Carlo M, Gallino A, Landmesser U, Laurent S, Lekakis J, Mikhailidis DP, Naka KK, Protogerou AD, Rizzoni D, Schmidt-Trucksäss A, Van Bortel L, Weber T, Yamashina A, Zimlichan R, Boutouyrie P, Cockcroft J, O'Rourke M, Park JB, Schillaci G, Sillesen H, Townsend RR. The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation: endorsed by the Association for Research into Arterial Structure and Physiology (ARTERY) Society. *Atherosclerosis* 2015;**241**:507–532.
61. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarencu P, Pedersen TR, LaRosa JC, Waters DD, DeMicco DA, Simes RJ, Keech AC, Colquhoun D, Hitman GA, Betteridge DJ, Clearfield MB, Downs JR, Colhoun HM, Gotto AM Jr, Ridker PM, Grundy SM, Kastelein JJ. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;**64**:485–494.
62. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009;**338**:b2376.
63. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tereshakovec AM, Musliner TA, Braunwald E, Califf RM. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
64. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
65. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–1405.
66. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;**380**:581–590.
67. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Borén J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A, Watts GF, Wiklund O. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. *Lancet Diabetes Endocrinol* 2014; **2**:655–666.
68. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 2008;**52**: 1769–1781.
69. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendixen FS, Lindahl C, Szarek M, Tsai J. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;**294**:2437–2445.
70. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC,

- Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
71. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**(25 Suppl 2):S1–S45.
 72. Langlois MR, Descamps OS, van der Laarse A, Weykamp C, Baum H, Pulkki K, von Eckardstein A, De Bacquer D, Borén J, Wiklund O, Laitinen P, Oosterhuis WP, Cobbaert C. Clinical impact of direct HDLc and LDLc method bias in hypertriglyceridemia. A simulation study of the EAS-EFLM Collaborative Project Group. *Atherosclerosis* 2014;**233**:83–90.
 73. Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, Perez-Martinez P, Bilianou H, Anagnostopoulou K, Panotopoulos G. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement. *Curr Vasc Pharmacol* 2011;**9**:258–270.
 74. Mihos C, Kolovou GD, Mikhailidis DP, Kovar J, Lairon D, Nordestgaard BG, Ooi TC, Perez-Martinez P, Bilianou H, Anagnostopoulou K, Panotopoulos G. Diagnostic value of postprandial triglyceride testing in healthy subjects: a meta-analysis. *Curr Vasc Pharmacol* 2011;**9**:271–280.
 75. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet* 2014;**384**:626–635.
 76. Jorgensen AB, Frikke-Schmidt R, West AS, Grande P, Nordestgaard BG, Tybjaerg-Hansen A. Genetically elevated non-fasting triglycerides and calculated remnant cholesterol as causal risk factors for myocardial infarction. *Eur Heart J* 2013;**34**:1826–1833.
 77. Langsted A, Nordestgaard BG. Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58 434 individuals from the Copenhagen General Population Study. *Clin Chem* 2011;**57**:482–489.
 78. Marti-Soler H, Gubelmann C, Aeschbacher S, Alves L, Bobak M, Bongard V, Clays E, de Gaetano G, Di Castelnuovo A, Elosua R, Ferrières J, Guessous I, Igländ J, Jørgensen T, Nikitin Y, O'Doherty MG, Palmieri L, Ramos R, Simons J, Sulo G, Vanuzzo D, Vila J, Barros H, Borglykke A, Conen D, De Bacquer D, Donfrancesco C, Gaspoz JM, Giampaoli S, Giles GG, Iacoviello L, Kee F, Kubinova R, Malyutina S, Marrugat J, Prescott E, Ruidavets JB, Scragg R, Simons LA, Tamosiunas A, Tell GS, Vollenweider P, Marques-Vidal P. Seasonality of cardiovascular risk factors: an analysis including over 230 000 participants in 15 countries. *Heart* 2014;**100**:1517–1523.
 79. Rabar S, Harker M, O'Flynn N, Wierzbicki AS, Guideline Development Group. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. *BMJ* 2014;**349**:g4356.
 80. JBS3. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;**100**(Suppl 2):ii1–ii67.
 81. Knopholz J, Disserol CC, Pierin AJ, Schirr FL, Streisky L, Takito LL, Massucheto Ledesma P, Faria-Neto JR, Olandoski M, da Cunha CL, Bandeira AM. Validation of the Friedewald formula in patients with metabolic syndrome. *Cholesterol* 2014;**2014**:261878.
 82. National Institute for Health and Care Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: National Institute for Health and Care Excellence, 2014.
 83. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundström J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'Agostino RB Sr, Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gómez-de-la-Cámara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;**307**:2499–2506.
 84. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM Jr, Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;**307**:1302–1309.
 85. Robinson JG, Wang S, Jacobson TA. Meta-analysis of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol* 2012;**110**:1468–1476.
 86. Varbo A, Benn M, Tybjaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol* 2013;**61**:427–436.
 87. Triglyceride Coronary Disease Genetics, Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010;**375**:1634–1639.
 88. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lytikäinen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravitto ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemssen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Feimer NB, Gieger C, Grove LC, Gudnason V, Gyllenstein U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimäki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolfenbutter BH, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JJ, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet* 2013;**45**:1345–1352.
 89. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Sverdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, UCLEB consortium, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almgueira B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karzewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimäki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 2015;**36**:539–550.
 90. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.

91. Haase CL, Tybjaerg-Hansen A, Grande P, Frikke-Schmidt R. Genetically elevated apolipoprotein A-I, high-density lipoprotein cholesterol levels, and risk of ischemic heart disease. *J Clin Endocrinol Metab* 2010;**95**:E500–510.
92. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante G, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed D, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buyschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeier J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altschuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a Mendelian randomisation study. *Lancet* 2012;**380**:572–580.
93. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* 2011;**364**:127–135.
94. Li XM, Tang WH, Mosior MK, Huang Y, Wu Y, Matter W, Gao V, Schmitt D, Didonato JA, Fisher EA, Smith JD, Hazen SL. Paradoxical association of enhanced cholesterol efflux with increased incident cardiovascular risks. *Arterioscler Thromb Vasc Biol* 2013;**33**:1696–1705.
95. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, Neeland JJ, Yuhanna IS, Rader DR, de Lemos JA, Shaul PW. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med* 2014;**371**:2383–2393.
96. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation* 2007;**115**:450–458.
97. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 1996;**3**: 213–219.
98. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women. *JAMA* 2007;**298**:309–316.
99. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA* 2007;**298**:299–308.
100. Charlton-Menys V, Betteridge DJ, Colhoun H, Fuller J, France M, Hitman GA, Livingstone SJ, Neil HA, Newman CB, Szarek M, DeMicco DA, Durrington PN. Targets of statin therapy: LDL cholesterol, non-HDL cholesterol, and apolipoprotein B in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS). *Clin Chem* 2009;**55**:473–480.
101. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 2007;**298**:776–785.
102. Taskinen MR, Barter PJ, Ehnholm C, Sullivan DR, Mann K, Simes J, Best JD, Hamwood S, Keech AC. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. *Diabetologia* 2010;**53**: 1846–1855.
103. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, Furberg CD. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011;**4**:337–345.
104. Onat A, Hergenç G, Sansoy V, Fobker M, Ceyhan K, Toprak S, Assmann G. Apolipoprotein C-III, a strong discriminant of coronary risk in men and a determinant of the metabolic syndrome in both genders. *Atherosclerosis* 2003;**168**:81–89.
105. Sacks FM, Alaupovic P, Moye LA, Cole TG, Sussex B, Stampfer MJ, Pfeffer MA, Braunwald E. VLDL, apolipoproteins B, CIII, and E, and risk of recurrent coronary events in the Cholesterol and Recurrent Events (CARE) trial. *Circulation* 2000;**102**: 1886–1892.
106. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute, Crosby J, Peloso GM, Auer PL, Crosslin DR, Stitzel NO, Lange LA, Lu Y, Tang ZZ, Zhang H, Hindy G, Masca N, Stirrups K, Kanoni S, Do R, Jun G, Hu Y, Kang HM, Xue C, Goel A, Farrall M, Duga S, Merlini PA, Asselta R, Girelli D, Olivieri O, Martinelli N, Yin W, Reilly D, Speliotes E, Fox CS, Hveem K, Holmen OL, Nikpay M, Farlow DN, Assimes TL, Franceschini N, Robinson J, North KE, Martin LW, DePristo M, Gupta N, Escher SA, Jansson JH, Van Zuydam N, Palmer CN, Wareham N, Koch W, Meitinger T, Peters A, Lieb W, Erbel R, König IR, Kruppa J, Degenhardt F, Gottesman O, Bottinger EP, O'Donnell CJ, Psaty BM, Ballantyne CM, Abecasis G, Ordovas JM, Melander O, Watkins H, Orho-Melander M, Ardissino D, Loos RJ, McPherson R, Willer CJ, Erdmann J, Hall AS, Samani NJ, Deloukas P, Schunkert H, Wilson JG, Kooperberg C, Rich SS, Tracy RP, Lin DY, Altschuler D, Gabriel S, Nickerson DA, Jarvik GP, Cupples LA, Reiner AP, Boerwinkle E, Kathiresan S. Loss-of-function mutations in APOC3, triglycerides, and coronary disease. *N Engl J Med* 2014;**371**:22–31.
107. Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG, Tybjaerg-Hansen A. Loss-of-function mutations in APOC3 and risk of ischemic vascular disease. *N Engl J Med* 2014;**371**:32–41.
108. Graham MJ, Lee RG, Bell TA 3rd, Fu W, Mullick AE, Alexander VJ, Singleton W, Viney N, Geary R, Su J, Baker BF, Burkey J, Crooke ST, Crooke RM. Antisense oligonucleotide inhibition of apolipoprotein C-III reduces plasma triglycerides in rodents, nonhuman primates, and humans. *Circ Res* 2013;**112**:1479–1490.
109. Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, Ginsberg H, Amarencu P, Catapano A, Descamps OS, Fisher E, Kovane PT, Kuivenhoven JA, Lesnik P, Masana L, Reiner Z, Taskinen MR, Tokgözoğlu L, Tybjaerg-Hansen A. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* 2010;**31**:2844–2853.
110. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Elevated lipoprotein(a) and risk of aortic valve stenosis in the general population. *J Am Coll Cardiol* 2014;**63**: 470–477.
111. Kronenberg F, Utermann G. Lipoprotein(a): resurrected by genetics. *J Intern Med* 2013;**273**:6–30.
112. Marcovina SM, Koschinsky ML, Albers JJ, Skarlatos S. Report of the National Heart, Lung, and Blood Institute Workshop on Lipoprotein(a) and Cardiovascular Disease: recent advances and future directions. *Clin Chem* 2003;**49**:1785–1796.
113. Willeit J, Kiechl S, Kronenberg F, Witztum JL, Santer P, Mayr M, Xu Q, Mayr A, Willeit J, Tsimikas S. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck Study. *J Am Coll Cardiol* 2014;**64**:851–860.
114. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol* 2013;**61**: 1146–1156.
115. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**372**:1489–1499.
116. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott R, Koren MJ, Stein EA. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;**727**:1500–1509.
117. Seed M, O'Connor B, Perombelon N, O'Donnell M, Revealey D, Knight BL. The effect of nicotinic acid and acipimox on lipoprotein(a) concentration and turnover. *Atherosclerosis* 1993;**101**:61–68.
118. Packard CJ. Small dense low-density lipoprotein and its role as an independent predictor of cardiovascular disease. *Curr Opin Lipidol* 2006;**17**:412–417.
119. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2007;**192**:211–217.
120. Whitfield JB. Genetic insights into cardiometabolic risk factors. *Clin Biochem Rev* 2014;**35**:15–36.
121. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovane PT, Boileau C, Averna M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;**34**:3478–3490a.
122. Futema M, Shah S, Cooper JA, Li K, Whittall RA, Sharifi M, Goldberg O, Drogari E, Mollaki V, Wiegman A, Defesche J, D'Agostino MN, D'Angelo A, Rubba P, Fortunato G, Waluś-Miarka M, Hegele RA, Aderayo Bamimore M, Durst R, Leitersdorf E, Mulder MT, Roeters van Lennep JE, Sijbrands EJ, Whittaker JC, Talmud PJ, Humphries SE. Refinement of variant selection for the LDL cholesterol

- genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. *Clin Chem* 2015;**61**: 231–238.
123. Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. *Eur Heart J* 2015;**36**: 2975–2983.
 124. Holme I, Cater NB, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Larsen ML, Lindahl C, Pedersen TR. Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease. Insights from the Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial (IDEAL). *Ann Med* 2008;**40**:456–464.
 125. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D. 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). *Eur Heart J* 2011;**32**:1769–1818.
 126. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *J Am Coll Cardiol* 2011;**57**:1666–1675.
 127. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998;**317**:703–713.
 128. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;**352**: 1425–1435.
 129. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999;**282**:2340–2346.
 130. Thompson A, Danesh J. Associations between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med* 2006;**259**:481–492.
 131. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol* 2009;**53**:316–322.
 132. Dalen JE, Devries S. Diets to prevent coronary heart disease 1957–2013: what have we learned? *Am J Med* 2014;**127**:364–369.
 133. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ, Kendall KA, Morgan LC, Trisolini MG, Velasco G, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;**129**(25 Suppl 2):S76–S99.
 134. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009;**169**:659–669.
 135. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**:398–406.
 136. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010;**7**:e1000252.
 137. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;**368**:1279–1290.
 138. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;**99**:779–785.
 139. Mozaffarian D, Aro A, Willett WC. Health effects of trans-fatty acids: experimental and observational evidence. *Eur J Clin Nutr* 2009;**63**(Suppl 2): S5–S21.
 140. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;**69**:30–42.
 141. Hollaender PL, Ross AB, Kristensen M. Whole-grain and blood lipid changes in apparently healthy adults: a systematic review and meta-analysis of randomized controlled studies. *Am J Clin Nutr* 2015;**102**:556–572.
 142. Gylling H, Plat J, Turley S, Ginsberg HN, Ellegård L, Jessup W, Jones PJ, Lütjohann D, Maerz W, Masana L, Silbernagel G, Staels B, Borén J, Catapano AL, De Backer G, Deanfield J, Descamps OS, Kovanen PT, Riccardi G, Tokgözoğlu L, Chapman MJ. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. *Atherosclerosis* 2014;**232**:346–360.
 143. Musa-Veloso K, Poon TH, Elliot JA, Chung C. A comparison of the LDL-cholesterol lowering efficacy of plant stanols and plant sterols over a continuous dose range: results of a meta-analysis of randomized, placebo-controlled trials. *Prostaglandins Leukot Essent Fatty Acids* 2011;**85**:9–28.
 144. Lu Z, Kou W, Du B, Wu Y, Zhao S, Brusco OA, Morgan JM, Capuzzi DM. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol* 2008;**101**: 1689–1693.
 145. Gordon RY, Cooperman T, Obermeyer W, Becker DJ. Marked variability of monacolin levels in commercial red yeast rice products: buyer beware. *Arch Intern Med* 2010;**170**:1722–1727.
 146. Li Y, Jiang L, Jia Z, Xin W, Yang S, Yang Q, Wand L. A meta-analysis of red yeast rice: an effective and relatively safe alternative approach for dyslipidemia. *PLoS One* 2014;**9**:e98611.
 147. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. *Am J Clin Nutr* 1992;**56**:320–328.
 148. Nordmann AJ, Nordmann A, Briel M, Keller U, Yancy WS Jr, Brehm BJ, Bucher HC. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;**166**:285–293.
 149. Keys A. Serum cholesterol response to dietary cholesterol. *Am J Clin Nutr* 1984;**40**: 351–359.
 150. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev* 2006;**4**:CD003817.
 151. Dewell A, Hollenbeck PL, Hollenbeck CB. Clinical review: a critical evaluation of the role of soy protein and isoflavone supplementation in the control of plasma cholesterol concentrations. *J Clin Endocrinol Metab* 2006;**91**:772–780.
 152. Rimm EB, Williams P, Fosher K, Criqui M, Stamper MJ. Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BMJ* 1999;**319**:1523–1528.
 153. Droste DW, Iliescu C, Vaillant M, Gantenbein M, De Bremaeker N, Lieunard C, Velez T, Meyer M, Guth T, Kuemmerle A, Gilson G, Chiotti A. A daily glass of red wine associated with lifestyle changes independently improves blood lipids in patients with carotid arteriosclerosis: results from a randomized controlled trial. *Nutr J* 2013;**12**:147.
 154. Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM. Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. *Am J Clin Nutr* 1999;**69**:632–646.
 155. Santos FL, Esteves SS, da Costa Pereira A, Yancy WS Jr, Nunes JP. Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. *Obes Rev* 2012;**13**:1048–1066.
 156. Rivellese AA, Maffettone A, Vessby B, Uusitupa M, Hermansen K, Berglund L, Louheranta A, Meyer BJ, Riccardi G. Effects of dietary saturated, monounsaturated and n-3 fatty acids on fasting lipoproteins, LDL size and post-prandial lipid metabolism in healthy subjects. *Atherosclerosis* 2003;**167**:149–158.
 157. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr* 1997;**65**(5 Suppl):1645S–1654S.
 158. Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Ai M, Otokozawa S, Nakajima K, Nakano T, Beyens C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. *J Clin Invest* 2009;**119**: 1322–1334.
 159. Kelishadi R, Mansourian M, Heidari-Beni M. Association of fructose consumption and components of metabolic syndrome in human studies: a systematic review and meta-analysis. *Nutrition* 2014;**30**:503–510.
 160. Gayet-Boyer C, Tenenhaus-Aziza F, Prunet C, Marmonier C, Malpuech-Brugere C, Lamarche B, Chardigny JM. Is there a linear relationship between the dose of ruminant trans-fatty acids and cardiovascular risk markers in healthy subjects: results from a systematic review and meta-regression of randomized clinical trials. *Br J Nutr* 2014;**112**:1914–1922.
 161. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: another look at a meta-analysis using prediction intervals. *Prev Med* 2009;**49**:473–475.

162. Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J Am Coll Cardiol* 2011;**57**:1299–1313.
163. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. *Prev Med* 2003;**37**:283–290.
164. Poli A, Marangoni F, Paoletti R, Mannarino E, Lupattelli G, Notarbartolo A, Aureli P, Bernini F, Cicero A, Gaddi A, Catapano A, Cricelli C, Gattone M, Marrocco W, Porrini M, Stella R, Vanotti A, Volpe M, Volpe R, Cannella C, Pinto A, Del Toma E, La Vecchia C, Tavani A, Manzato E, Riccardi G, Sirtori C, Zambon A. Non-pharmacological control of plasma cholesterol levels. *Nutr Metab Cardiovasc Dis* 2008;**18**:S1–S16.
165. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr* 2003;**77**:1146–1155.
166. Micha R, Khatibzadeh S, Shi P, Fahimi S, Lim S, Andrews KG, Engell RE, Powles J, Ezzati M, Mozaffarian D. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ* 2014;**348**:g2272.
167. Griffin JD, Lichtenstein AH. Dietary cholesterol and plasma lipoprotein profiles: randomized-controlled trials. *Curr Nutr Rep* 2013;**2**:274–282.
168. Ordovas JM. Genetic influences on blood lipids and cardiovascular disease risk: tools for primary prevention. *Am J Clin Nutr* 2009;**89**:1509S–1517S.
169. Huffman KM, Hawk VH, Henes ST, Ocampo CI, Orenduff MC, Slentz CA, Johnson JL, Houmard JA, Samsa GP, Kraus WE, Bales CW. Exercise effects on lipids in persons with varying dietary patterns—does diet matter if they exercise? Responses in Studies of a Targeted Risk Reduction Intervention through Defined Exercise I. *Am Heart J* 2012;**164**:117–124.
170. Vessby B, Uusitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Näslén C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffettone A, Pedersen E, Gustafsson IB, Storlien LH. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: the KANWU Study. *Diabetologia* 2001;**44**:312–319.
171. Rivellese AA, Giacco R, Annuzzi G, De Natale C, Patti L, Di Marino L, Minerva V, Costabile G, Santangelo C, Masella R, Riccardi G. Effects of monounsaturated vs. saturated fat on postprandial lipemia and adipose tissue lipases in type 2 diabetes. *Clin Nutr* 2008;**27**:133–141.
172. Jacobson TA, Glickstein SB, Rowe JD, Soni PN. Effects of eicosapentaenoic acid and docosahexaenoic acid on low-density lipoprotein cholesterol and other lipids: a review. *J Clin Lipidol* 2012;**6**:5–18.
173. Liu S, Manson JE, Stampfer MJ, Holmes MD, Hu FB, Hankinson SE, Willett WC. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. *Am J Clin Nutr* 2001;**73**:560–566.
174. De Natale C, Annuzzi G, Bozzetto L, Mazzarella R, Costabile G, Ciano O, Riccardi G, Rivellese AA. Effects of a plant-based high-carbohydrate/high-fiber diet versus high-monounsaturated fat/low-carbohydrate diet on postprandial lipids in type 2 diabetic patients. *Diabetes Care* 2009;**32**:2168–2173.
175. Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, Chen GX, Keim NL, Havel PJ. A dose-response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. *Am J Clin Nutr* 2015;**101**:1144–1154.
176. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, Bales CV, Henes S, Samsa GP, Otvos JD, Kulkarni KR, Slentz CA. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med* 2002;**347**:1483–1492.
177. Brien SE, Ronsley PE, Turner BJ, Mukamal KJ, Ghali WA. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 2011;**342**:d636.
178. Goff LM, Cowland DE, Hooper L, Frost GS. Low glycaemic index diets and blood lipids: a systematic review and meta-analysis of randomised controlled trials. *Nutr Metab Cardiovasc Dis* 2013;**23**:1–10.
179. Bazzano LA, Thompson AM, Tees MT, Nguyen CH, Winham DM. Non-soy legume consumption lowers cholesterol levels: a meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis* 2011;**21**:94–103.
180. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Fruchart JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;**120**:1640–1645.
181. Puzziferri N, Roshek TB 3rd, Mayo HG, Gallagher R, Belle SH, Livingston EH. Long-term follow-up after bariatric surgery: a systematic review. *JAMA* 2014;**312**:934–942.
182. Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation* 2009;**119**:902–907.
183. Mozaffarian D, Lemaitre RN, King IB, Song X, Huang H, Sacks FM, Rimm EB, Wang M, Siscovick DS. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. *Ann Intern Med* 2013;**158**:515–525.
184. Sirtori CR, Galli C, Anderson JW, Arnoldi A. Nutritional and nutraceutical approaches to dyslipidemia and atherosclerosis prevention: focus on dietary proteins. *Atherosclerosis* 2009;**203**:8–17.
185. Lea LJ, Hepburn PA. Safety evaluation of phytosterol-esters. Part 9: results of a European post-launch monitoring programme. *Food Chem Toxicol* 2006;**44**:1213–1222.
186. AbuMweis SS, Jew S, Ames NP. β -glucan from barley and its lipid-lowering capacity: a meta-analysis of randomized, controlled trials. *Eur J Clin Nutr* 2010;**64**:1472–1480.
187. Wolever TM, Tosh SM, Gibbs AL, Brand-Miller J, Duncan AM, Hart V, Lamarche B, Thomson BA, Duss R, Wood PJ. Physicochemical properties of oat beta-glucan influence its ability to reduce serum LDL cholesterol in humans: a randomized clinical trial. *Am J Clin Nutr* 2010;**92**:723–732.
188. Más R, Castaño G, Illnait J, Fernández L, Fernández J, Alemán C, Pontigas V, Lescaj M. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther* 1999;**65**:439–447.
189. Reiner Z, Tedeschi-Reiner E, Romic Z. Effects of rice policosanol on serum lipoproteins, homocysteine, fibrinogen and C-reactive protein in hypercholesterolaemic patients. *Clin Drug Investig* 2005;**25**:701–707.
190. Lan J, Zhao Y, Dong F, Yan Z, Zheng W, Fan J, Sun G. Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. *J Ethnopharmacol* 2015;**161**:69–81.
191. Weng TC, Yang YH, Lin SJ, Tai SH. A systematic review and meta-analysis on the therapeutic equivalence of statins. *J Clin Pharm Ther* 2010;**35**:139–151.
192. Chasman DI, Giulianini F, MacFadyen J, Barratt BJ, Nyberg F, Ridker PM. Genetic determinants of statin-induced low-density lipoprotein cholesterol reduction: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. *Circ Cardiovasc Genet* 2012;**5**:257–264.
193. Reiner Z. Resistance and intolerance to statins. *Nutr Metab Cardiovasc Dis* 2014;**24**:1057–1066.
194. Gould AL, Rossouw JE, Santanello NC, Heysse JF, Furberg CD. Cholesterol reduction yields clinical benefit. A new look at old data. *Circulation* 1995;**91**:2274–2282.
195. Gould AL, Rossouw JE, Santanello NC, Heysse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. *Circulation* 1998;**97**:946–952.
196. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**:1267–1278.
197. Genser B, Marz W. Low density lipoprotein cholesterol, statins and cardiovascular events: a meta-analysis. *Clin Res Cardiol* 2006;**95**:393–404.
198. Mills EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, Eyawo O, Guyatt G, Berwanger O, Briel M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *QJM* 2011;**104**:109–124.
199. Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, Sattar N. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. *Arch Intern Med* 2010;**170**:1024–1031.
200. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Abraham S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2013;**1**:CD004816.
201. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004;**109**(23 Suppl 1):III-39–III-43.
202. Zhou Q, Liao JK. Pleiotropic effects of statins. Basic research and clinical perspectives. *Circulation J* 2010;**74**:818–826.
203. Pedersen TR. Pleiotropic effects of statins: evidence against benefits beyond LDL-cholesterol lowering. *Am J Cardiovasc Drugs* 2010;**10**(Suppl 1):10–17.
204. McGuinness B, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. *Cochrane Database Syst Rev* 2014;**7**:CD007514.
205. Esлами L, Merat S, Malekzadeh R, Nasserri-Moghaddam S, Aramin H. Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Cochrane Database Syst Rev* 2013;**12**:CD008623.

206. Cholesterol Treatment Trialists' (CTT) Collaboration, Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhalra N, Holland L, Peto R, Keech A, Collins R, Simes J, Baigent C. Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy. *PLoS One* 2012;**7**:e29849.
207. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;**367**:1792–1802.
208. Li L, Sun T, Zhang P, Tian J, Yang K. Statins for primary prevention of venous thromboembolism. *Cochrane Database Syst Rev* 2011;**12**:CD008203.
209. Raval AD, Hunter T, Stuckey B, Hart RJ. Statins for women with polycystic ovary syndrome not actively trying to conceive. *Cochrane Database Syst Rev* 2011;**10**:CD008565.
210. Gauthier JM, Massicotte A. Statins and their effect on cognition: let's clear up the confusion. *Can Pharm J (Ott)* 2015;**148**:150–155.
211. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, Roden M, Stein E, Tokgözoğlu L, Nordestgaard BG, Bruckert E, De Backer G, Krauss RM, Laufs U, Santos RD, Hegele RA, Hovingh GK, Leiter LA, Mach F, März W, Newman CB, Wiklund O, Jacobson TA, Catapano AL, Chapman MJ, Ginsberg HN; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J* 2015;**36**:1012–1022.
212. Law M, Rudnicka AR. Statin safety: a systematic review. *Am J Cardiol* 2006;**97**(8A):52C–60C.
213. Finegold JA, Francis DP. What proportion of symptomatic side-effects in patients taking statins are genuinely caused by the drug? A response to letters. *Eur J Prev Cardiol* 2015;**22**:1328–1330.
214. Naci H, Bruggs J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013;**6**:390–399.
215. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;**19**:403–414.
216. Davidson MH, Clark JA, Glass LM, Kanumalla A. Statin safety: an appraisal from the adverse event reporting system. *Am J Cardiol* 2006;**97**(8A):32C–43C.
217. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of statins on skeletal muscle function. *Circulation* 2013;**127**:96–103.
218. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, Gipe D. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. *J Clin Lipidol* 2014;**8**:554–561.
219. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol* 2014;**63**:2541–2548.
220. Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. *Ann Pharmacother* 2013;**47**:398–404.
221. Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. *Am J Geriatr Pharmacother* 2012;**10**:264–271.
222. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology* 2004;**126**:1287–1292.
223. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. *Am J Med Sci* 2005;**329**:62–65.
224. Dongiovanni P, Petta S, Mannisto V, Mancina RM, Pipitone R, Karja V, Maggioni M, Kakela P, Wiklund O, Mozzi E, Grimaudo S, Kaminska D, Rametta R, Craxi A, Fargion S, Nobili V, Romeo S, Pihlajamäki J, Valenti L. Statin use and non-alcoholic steatohepatitis at risk individuals. *J Hepatol* 2015;**63**:705–712.
225. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchionni R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;**375**:735–742.
226. Preiss D, Seshasai SR, Welsh P, Murphy SA, Ho JE, Waters DD, DeMicco DA, Barter P, Cannon CP, Sabatine MS, Braunwald E, Kastelein JJ, de Lemos JA, Blazing MA, Pedersen TR, Tikkanen MJ, Sattar N, Ray KK. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;**305**:2556–2564.
227. Waters DD, Ho JE, Boekholdt SM, DeMicco DA, Kastelein JJ, Messig M, Breazna A, Pedersen TR. Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. *J Am Coll Cardiol* 2013;**61**:148–152.
228. Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev* 2014;**1**:CD005019.
229. Vidt DG. Statins and proteinuria. *Curr Atheroscler Rep* 2005;**7**:351–357.
230. Sidaway JE, Davidson RG, McTaggart F, Orton TC, Scott RC, Smith GJ, Brunskill NJ. Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase reduce receptor-mediated endocytosis in opossum kidney cells. *J Am Soc Nephrol* 2004;**15**:2258–2265.
231. Davidson MH. Rosuvastatin safety: lessons from the FDA review and post-approval surveillance. *Expert Opin Drug Saf* 2004;**3**:547–557.
232. Egan A, Colman E. Weighing the benefits of high-dose simvastatin against the risk of myopathy. *N Engl J Med* 2011;**365**:285–287.
233. Wiklund O, Pirazzi C, Romeo S. Monitoring of lipids, enzymes, and creatine kinase in patients on lipid-lowering drug therapy. *Curr Cardiol Rep* 2013;**15**:397.
234. Holoshitz N, Alsheikh-Ali AA, Karas RH. Relative safety of gemfibrozil and fenofibrate in the absence of concomitant cerivastatin use. *Am J Cardiol* 2008;**101**:95–97.
235. Franssen R, Vergeer M, Stroes ES, Kastelein JJ. Combination statin-fibrate therapy: safety aspects. *Diabetes Obes Metab* 2009;**11**:89–94.
236. Guyton JR, Bays HE. Safety considerations with niacin therapy. *Am J Cardiol* 2007;**99**(6A):22C–31C.
237. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, Jacobson TA, Davidson MH. Statin safety: an assessment using an administrative claims database. *Am J Cardiol* 2006;**97**(8A):61C–68C.
238. Ooi CP, Loke SC. Colesevelam for type 2 diabetes mellitus: an abridged Cochrane review. *Diabet Med* 2014;**31**:2–14.
239. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;**251**:351–364.
240. Pre-entry characteristics of participants in the Lipid Research Clinics' Coronary Primary Prevention Trial. *J Chronic Dis* 1983;**36**:467–479.
241. The Lipid Research Clinics Coronary Primary Prevention Trial. Results of 6 years of post-trial follow-up. The Lipid Research Clinics Investigators. *Arch Intern Med* 1992;**152**:1399–1410.
242. He L, Wickremasingha P, Lee J, Tao B, Mendell-Harary J, Walker J, Wight D. Lack of effect of colesvelam HCl on the single-dose pharmacokinetics of aspirin, atenolol, enalapril, phenytoin, rosiglitazone, and sitagliptin. *Diabetes Res Clin Pract* 2014;**104**:401–409.
243. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerds E, Gohlke-Bärwolf C, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008;**359**:1343–1356.
244. Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J* 2010;**160**:785–794 e10.
245. Myocardial Infarction Genetics Consortium Investigators, Stitzel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, Farrall M, Saleheen D, Ferrario P, König I, Asselta R, Merlini PA, Marziliano N, Notarangelo MF, Schick U, Auer P, Assimes TL, Reilly M, Wilensky R, Rader DJ, Hovingh GK, Meitinger T, Kessler T, Kastrati A, Laugwitz KL, Siscovick D, Rotter JJ, Hazen SL, Tracy R, Cresci S, Spertus J, Jackson R, Schwartz SM, Natarajan P, Crosby J, Muzny D, Ballantyne C, Rich SS, O'Donnell CJ, Abecasis G, Sunyaev S, Nickerson DA, Buring JE, Ridker PM, Denny JC, Roden DM, Palmer C, Deloukas P, Lin DY, Tang ZZ, Erdmann J, Schunkert H, Danesh J, Marrugat J, Elosua R, Ardisson D, McPherson R, Watkins H, Reiner AP, Wilson JG, Altshuler D, Gibbs RA, Lander ES, Boerwinkle E, Gabriel S, Kathiresan S. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med* 2014;**371**:2072–2082.
246. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, Komura N, Sakamoto K, Oka H, Nakao K, Nakamura S, Ishihara M, Matsui K, Sakaino N, Nakamura N, Yamamoto N, Koide S, Matsumura T, Fujimoto K, Tsunoda R, Morikami Y, Matsuyama K, Oshima S, Kaikita K, Hokimoto S, Ogawa H. Impact of dual lipid-lowering strategy with ezetimibe and atorvastatin on coronary plaque regression in patients with percutaneous coronary intervention: the multicenter randomized controlled PRECISE-IVUS trial. *J Am Coll Cardiol* 2015;**66**:495–507.
247. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D, Derré A, Villéger L, Farnier M, Beucler I, Bruckert E, Chambaz J, Chanu B, Lecerf JM, Luc G, Moulin P, Weissenbach J,

- Prat A, Krempf M, Junien C, Seidah NG, Boileau C. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet* 2003;**34**:154–156.
248. Norata GD, Tibolla G, Catapano AL. Targeting PCSK9 for hypercholesterolemia. *Annu Rev Pharmacol Toxicol* 2014;**54**:273–293.
249. Navarese EP, Kolodziejczak M, Kereiakes DJ, Tantry US, O'Connor C, Gurbel PA. Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies for acute coronary syndrome: a narrative review. *Ann Intern Med* 2016;**164**:600–607.
250. Zhang XL, Zhu L, Wei ZH, Zhu QQ, Qiao JZ, Dai Q, Huang W, Li XH, Xie J, Kang LN, Wang L, Xu B. Comparative efficacy and safety of everolimus-eluting bioresorbable scaffold versus everolimus-eluting metallic stents: a systematic review and meta-analysis. *Ann Intern Med* 2016;**164**:752–763.
251. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011;**365**:2255–2267.
252. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;**371**:203–212.
253. Zhao XQ, Krasuski RA, Baer J, Whitney EJ, Neradilek B, Chait A, Marcovina S, Albers JJ, Brown BG. Effects of combination lipid therapy on coronary stenosis progression and clinical cardiovascular events in coronary disease patients with metabolic syndrome: a combined analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS). *Am J Cardiol* 2009;**104**:1457–1464.
254. Jones MR, Nwose OM. Role of colesevelam in combination lipid-lowering therapy. *Am J Cardiovasc Drugs* 2013;**13**:315–323.
255. Abumweis SS, Barake R, Jones PJ. Plant sterols/stanols as cholesterol lowering agents: a meta-analysis of randomized controlled trials. *Food Nutr Res* 2008;**52**. ISSN 1654-661X. Available at <http://www.foodandnutritionresearch.net/index.php/fnr/article/view/1811>.
256. Tyroler HA. Cholesterol and cardiovascular disease. An overview of Lipid Research Clinics (LRC) epidemiologic studies as background for the LRC Coronary Primary Prevention Trial. *Am J Cardiol* 1984;**54**:14C–19C.
257. Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, Friedewald W. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;**8**:1245–1255.
258. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009;**16**:121–137.
259. Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;**97**:2969–2989.
260. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, Descamps OS, Fisher E, Kovanen P, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen MR, Tokgözoğlu L, Tybjaerg-Hansen A, Watts GF. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011;**32**:1345–1361.
261. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;**366**:1849–1861.
262. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC Jr, Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1563–1574.
263. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* 2010;**126**:314–345.
264. Catapano AL, Farnier M, Foody JM, Toth PP, Tomassini JE, Brudi P, Tershakovec AM. Combination therapy in dyslipidemia: where are we now? *Atherosclerosis* 2014;**237**:319–335.
265. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;**317**:1237–1245.
266. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schemtman G, Wilt TJ, Wittes J. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 1999;**341**:410–418.
267. Lipids and lipoproteins in symptomatic coronary heart disease. Distribution, inter-correlations, and significance for risk classification in 6,700 men and 1,500 women. The Bezafibrate Infarction Prevention (BIP) Study Group, Israel. *Circulation* 1992;**86**:839–848.
268. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. *BMJ* 2014;**349**:g4379.
269. Ip CK, Jin DM, Gao JJ, Meng Z, Meng J, Tan Z, Wang JF, Geng DF. Effects of add-on lipid-modifying therapy on top of background statin treatment on major cardiovascular events: a meta-analysis of randomized controlled trials. *Int J Cardiol* 2015;**191**:138–148.
270. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, Grobbee DE, Cass A, Chalmers J, Perkovic V. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet* 2010;**375**:1875–1884.
271. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis* 2011;**217**:492–498.
272. Bruckert E, Labreuche J, Deplanque D, Touboul PJ, Amarenco P. Fibrates effect on cardiovascular risk is greater in patients with high triglyceride levels or atherogenic dyslipidemia profile: a systematic review and meta-analysis. *J Cardiovasc Pharmacol* 2011;**57**:267–272.
273. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. *Am J Cardiol* 2007;**99**(6A):3C–18C.
274. Jun M, Zhu B, Tonelli M, Jardine MJ, Patel A, Neal B, Liyanage T, Keech A, Cass A, Perkovic V. Effects of fibrates in kidney disease: a systematic review and meta-analysis. *J Am Coll Cardiol* 2012;**60**:2061–2071.
275. Taskinen MR, Sullivan DR, Ehnholm C, Whiting M, Zannino D, Simes RJ, Keech AC, Barter PJ. Relationships of HDL cholesterol, ApoA-I, and ApoA-II with homocysteine and creatinine in patients with type 2 diabetes treated with fenofibrate. *Arterioscler Thromb Vasc Biol* 2009;**29**:950–955.
276. Herrmann M, Whiting MJ, Veillard AS, Ehnholm C, Sullivan DR, Keech AC. Plasma homocysteine and the risk of venous thromboembolism: insights from the FIELD study. *Clin Chem Lab Med* 2012;**50**:2213–2219.
277. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol* 2008;**101**(8A):20B–26B.
278. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. *Atherosclerosis* 2010;**210**:353–361.
279. Brown BG, Zhao XQ. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. *Am J Cardiol* 2008;**101**(8A):58B–62B.
280. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis* 2006;**189**:19–30.
281. Ballantyne CM, Bays HE, Kastelein JJ, Stein E, Isaacsohn JL, Braeckman RA, Soni PN. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high triglycerides (from the ANCHOR study). *Am J Cardiol* 2012;**110**:984–992.
282. Bays HE, Ballantyne CM, Kastelein JJ, Isaacsohn JL, Braeckman RA, Soni PN. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, placebo-controlled, Randomized, double-blind, 12-week study with an open-label Extension [MARINE] trial). *Am J Cardiol* 2011;**108**:682–690.
283. Kastelein JJ, Maki KC, Susekov A, Ezhov M, Nordestgaard BG, Machielse BN, Kling D, Davidson MH. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. *J Clin Lipidol* 2014;**8**:94–106.
284. Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. *Curr Atheroscler Rep* 2011;**13**:474–483.
285. Kotwal S, Jun M, Sullivan D, Perkovic V, Neal B. Omega 3 fatty acids and cardiovascular outcomes: systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012;**5**:808–818.
286. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;**369**:1090–1098.
287. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, Durrington PN, Higgins JP, Capps NE, Riemersma RA, Ebrahim SB, Davey Smith G. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 2006;**332**:752–760.

288. Marchioli R, Barzi F, Bomba E, Chieffo C, Di Gregorio D, Di Mascio R, Franzosi MG, Geraci E, Levantesi G, Maggioni AP, Mantini L, Marfisi RM, Mastrogiuseppe G, Mininni N, Nicolosi GL, Santini M, Schweiger C, Tavazzi L, Tognoni G, Tucci C, Valagussa F. Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* 2002;**105**:1897–1903.
289. Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, Meyskens FL Jr, Goodman GE, Minasian LM, Parnes HL, Klein EA, Kristal AR. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2013;**105**:1132–1141.
290. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007;**297**:499–508.
291. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDL-C: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER Database. *J Lipid Res* 2010;**51**:1546–1553.
292. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med* 2007;**357**:1301–1310.
293. Fruchart JC, Sacks FM, Hermans MP, Assmann G, Brown WV, Ceska R, Chapman MJ, Dodson PM, Fioretti P, Ginsberg HN, Kadowaki T, Lablanche JM, Marx N, Plutzky J, Reiner Z, Rosenson RS, Staels B, Stock JK, Sy R, Wanner C, Zambon A, Zimmet P. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in dyslipidaemic patient. *Diab Vasc Dis Res* 2008;**5**:319–335.
294. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007;**357**:2109–2122.
295. Global Lipids Genetics Consortium, Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Do R, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lytykäinen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravitto ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kleeberg P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stancáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllenstein U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Heem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimäki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Sieghart A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JJ, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Kathiresan S, Mohlke KL, Ingelsson E, Abecasis GR. Discovery and refinement of loci associated with lipid levels. *Nat Genet* 2013;**45**:1274–1283.
296. Veerkamp MJ, de Graaf J, Bredie SJ, Hendriks JC, Demacker PN, Stalenhoef AF. Diagnosis of familial combined hyperlipidemia based on lipid phenotype expression in 32 families: results of a 5-year follow-up study. *Arterioscler Thromb Vasc Biol* 2002;**22**:274–282.
297. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. *J Clin Endocrinol Metab* 2012;**97**:3956–3964.
298. de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). *Circulation* 2016;**133**:1067–1072.
299. Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. *BMJ* 1991;**303**:893–896.
300. World Health Organization. Human Genetics Programme. Familial hypercholesterolemia: report of a second WHO consultation. WHO/HGN/FH/Cons/992. Geneva: World Health Organization, 1999.
301. Defesche JC, Lansberg PJ, Umans-Eckenhausen MA, Kastelein JJ. Advanced method for the identification of patients with inherited hypercholesterolemia. *Semin Vasc Med* 2004;**4**:59–65.
302. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Borén J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. *Eur Heart J* 2014;**35**:2146–2157.
303. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Borén J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Wiklund O. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J* 2015;**36**:2425–2437.
304. Johansen CT, Wang J, Lanktree MB, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Cao H, Hegele RA. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. *Arterioscler Thromb Vasc Biol* 2011;**31**:1916–1926.
305. Gaudet D, Méthot J, Déry S, Brisson D, Essiembre C, Tremblay G, Tremblay K, de Wal J, Twisk J, van den Bulk N, Sier-Ferreira V, van Deventer S. Efficacy and long-term safety of alipogene tiparvovec (AAV1-LPLS447X) gene therapy for lipoprotein lipase deficiency: an open-label trial. *Gene Ther* 2013;**20**:361–369.
306. Huff MW, Hegele RA. Apolipoprotein C-III: going back to the future for a lipid drug target. *Circ Res* 2013;**112**:1405–1408.
307. Lindkvist B, Appellos S, Regner S, Manjer J. A prospective cohort study on risk of acute pancreatitis related to serum triglycerides, cholesterol and fasting glucose. *Pancreatol* 2012;**12**:317–324.
308. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol* 2009;**20**:497–504.
309. Reiner Z, Guardamagna O, Nair D, Soran H, Hovingh K, Bertolini S, Jones S, Ćorić M, Calandra S, Hamilton J, Eagleton T, Ros E. Lysosomal acid lipase deficiency—an under-recognized cause of dyslipidaemia and liver dysfunction. *Atherosclerosis* 2014;**235**:21–30.
310. National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics* 2011;**128**(Suppl 5):S213–S256.
311. Reiner Z. Impact of early evidence of atherosclerotic changes on early treatment in children with familial hypercholesterolemia. *Circ Res* 2014;**114**:233–235.
312. Jonsdottir LS, Sigfússon N, Gudnason V, Sigvaldason H, Thorgeirsson G. Do lipids, blood pressure, diabetes, and smoking confer equal risk of myocardial infarction in women as in men? The Reykjavik Study. *J Cardiovasc Risk* 2002;**9**:67–76.
313. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J* 2013;**34**:719–728.
314. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA* 2004;**291**:2243–2252.
315. d'Emden MC, Jenkins AJ, Li L, Zannino D, Mann KP, Best JD, Stuckey BG, Park K, Saltevo J, Keech AC. Favourable effects of fenofibrate on lipids and cardiovascular disease in women with type 2 diabetes: results from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetologia* 2014;**57**:2296–2303.

316. Spitzer WO, Faith JM, MacRae KD. Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. *Human Reprod* 2002;**17**: 2307–2314.
317. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. *J Am Coll Cardiol* 2009;**53**:221–231.
318. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, Trevisan M, Black HR, Heckbert SR, Detrano R, Strickland OL, Wong ND, Crouse JR, Stein E, Cushman M. Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2002;**349**:523–534.
319. Rosengren A. Better treatment and improved prognosis in elderly patients with AMI: but do registers tell the whole truth? *Eur Heart J* 2012;**33**:562–563.
320. Gale CP, Cattle BA, Woolston A, Baxter PD, West TH, Simms AD, Blaxill J, Greenwood DC, Fox KA, West RM. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003–2010. *Eur Heart J* 2012;**33**:630–639.
321. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;**370**:1829–1839.
322. Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other societies on coronary prevention. *Eur Heart J* 1998;**19**:1434–1503.
323. Berry JD, Dyer A, Cai X, Garside DB, Ning H, Thomas A, Greenland P, Van Horn L, Tracy RP, Lloyd-Jones DM. Lifetime risks of cardiovascular disease. *N Engl J Med* 2012;**366**:321–329.
324. Giang KW, Björck L, Novak M, Lappas G, Wilhelmsen L, Torén K, Rosengren A. Stroke and coronary heart diseases: predictive power of standard risk factors into old age—long-term cumulative risk study among men in Gothenburg, Sweden. *Eur Heart J* 2013;**34**:1068–1074.
325. Wilhelmsen L, Svärdsudd K, Eriksson H, Rosengren A, Hansson PO, Welin C, Odén A, Welin L. Factors associated with reaching 90 years of age: a study of men born in 1913 in Gothenburg, Sweden. *J Intern Med* 2011;**269**:441–451.
326. Reiner Z. Primary prevention of cardiovascular disease with statins in the elderly. *Curr Atheroscler Rep* 2014;**16**:420.
327. Savarese G, Gotto AM Jr, Paolillo S, D'Amore C, Losco T, Musella F, Scala O, Marciano C, Ruggiero D, Marsico F, De Luca G, Trimarco B, Perrone-Filardi P. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. *J Am Coll Cardiol* 2013;**62**:2090–2099.
328. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Krueger W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;**279**:1615–1622.
329. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med* 2010;**152**:488–496. W174.
330. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002;**360**:1623–1630.
331. Deedwania P, Stone PH, Bairey Merz CN, Cosin-Aguilar J, Koylan N, Luo D, Ouyang P, Piotrowicz R, Schenck-Gustafsson K, Sellier P, Stein JH, Thompson PL, Tzivoni D. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 2007;**115**: 700–707.
332. Miettinen TA, Pyörälä K, Olsson AG, Musliner TA, Cook TJ, Faergeman O, Berg K, Pedersen T, Kjekshus J. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1997;**96**:4211–4218.
333. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;**360**:7–22.
334. Hunt D, Young P, Simes J, Hague W, Mann S, Owensby D, Lane G, Tonkin A. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. *Ann Intern Med* 2001;**134**:931–940.
335. Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, Limacher M, Kell S, Glasser SP, Grant J, Davis BR, Pfeffer MA, Braunwald E. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998;**129**:681–689.
336. Wenger NK, Lewis SJ, Herrington DM, Bittner V, Welty FK. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. *Ann Intern Med* 2007;**147**:1–9.
337. Gränsbo K, Melander O, Wallentin L, Lindbäck J, Stenestrand U, Carlsson J, Nilsson J. Cardiovascular and cancer mortality in very elderly post-myocardial infarction patients receiving statin treatment. *J Am Coll Cardiol* 2010;**55**:1362–1369.
338. Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. *Lancet Diabetes Endocrinol* 2014;**2**:56–64.
339. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, Whincup PH, Mukamal KJ, Gillum RF, Holme I, Njølstad I, Fletcher A, Nilsson P, Lewington S, Collins R, Gudnason V, Thompson SG, Sattar N, Selvin E, Hu FB, Danesh J. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;**364**:829–841.
340. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, Williams DE, Geiss L. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl J Med* 2014;**370**:1514–1523.
341. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**:2215–2222.
342. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. *Diabetologia* 2013;**56**:686–695.
343. Liu J, Grundy SM, Wang W, Smith SC Jr, Vega GL, Wu Z, Zeng Z, Wang W, Zhao D. Ten-year risk of cardiovascular incidence related to diabetes, prediabetes, and the metabolic syndrome. *Am Heart J* 2007;**153**:552–558.
344. Despres JP. Body fat distribution and risk of cardiovascular disease: an update. *Circulation* 2012;**126**:1301–1313.
345. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM. Diabetes and mortality following acute coronary syndromes. *JAMA* 2007;**298**:765–775.
346. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev* 2013;**93**:359–404.
347. van Vliet-Ostapchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, Gaye A, Gögele M, Heier M, Hiekkalinna T, Joensuu A, Newby C, Pang C, Partinen E, Reischl E, Schwienbacher C, Tammesoo ML, Swertz MA, Burton P, Ferretti V, Fortier I, Giepmans L, Harris JR, Hillege HL, Holmen J, Jula A, Kootstra-Ros JE, Kvaløy K, Holmen TL, Männistö S, Metspalu A, Midthjell K, Murtagh MJ, Peters A, Pramstaller PP, Saaristo T, Salomaa V, Stolk RP, Uusitupa M, van der Harst P, van der Klauw MM, Waldenberger M, Perola M, Wolfenbützel BH. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. *BMC Endocr Disord* 2014;**14**:9.
348. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;**56**:1113–1132.
349. Adiels M, Olofsson SO, Taskinen MR, Borén J. Overproduction of very low-density lipoproteins is the hallmark of the dyslipidemia in the metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2008;**28**:1225–1236.
350. Taskinen MR, Boren J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis* 2015;**239**:483–495.
351. Scott R, O'Brien R, Fulcher G, Pardy C, D'Emden M, Tse D, Taskinen MR, Ehnholm C, Keech A. Effects of fenofibrate treatment on cardiovascular disease risk in 9,795 individuals with type 2 diabetes and various components of the metabolic syndrome: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. *Diabetes Care* 2009;**32**:493–498.
352. Ballantyne CM, Olsson AG, Cook TJ, Mercuri MF, Pedersen TR, Kjekshus J. Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. *Circulation* 2001;**104**:3046–3051.
353. Saha SA, Arora RR. Fibrates in the prevention of cardiovascular disease in patients with type 2 diabetes mellitus—a pooled meta-analysis of randomized placebo-controlled clinical trials. *Int J Cardiol* 2010;**141**:157–166.
354. Ilanne-Parikka P, Eriksson JG, Lindstrom J, Peltonen M, Aunola S, Hämmäläinen H, Keinänen-Kiukkaanniemi S, Laakso M, Valle TT, Lahtela J, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study Group. Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. *Diabetes Care* 2008;**31**:805–807.
355. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC. Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 2003;**46**:760–765.
356. Chillaron JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. *Metabolism* 2014;**63**:181–187.

357. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003;**361**:2005–2016.
358. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–1718.
359. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, Ramsey KE, Palmisano J, Bilheimer DW, Pfeffer MA, Califf RM, Braunwald E. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;**292**:1307–1316.
360. Ray KK, Cannon CP, McCabe CH, Cairns R, Tonkin AM, Sacks FM, Jackson G, Braunwald E. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol* 2005;**46**:1405–1410.
361. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012;**308**:1024–1033.
362. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**367**:2089–2099.
363. Di Sciascio G, Patti G, Pasceri V, Gaspardone A, Colonna G, Montinaro A. Efficacy of atorvastatin reload in patients on chronic statin therapy undergoing percutaneous coronary intervention: results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. *J Am Coll Cardiol* 2009;**54**:558–565.
364. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, Colombo A, Yun KH, Jeong MH, Kim JS, Choi D, Bozbas H, Kinoshita M, Fukuda K, Jia XW, Hara H, Cay S, Di Sciascio G. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 2011;**123**:1622–1632.
365. Briguori C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A. Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction. *J Am Coll Cardiol* 2009;**54**:2157–2163.
366. Kim JS, Kim J, Choi D, Lee CJ, Lee SH, Ko YG, Hong MK, Kim BK, Oh SJ, Jeon DW, Yang JY, Cho JR, Lee NH, Cho YH, Cho DK, Jang Y. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. *JACC Cardiovasc Interv* 2010;**3**:332–339.
367. Gandhi S, Mosleh W, Abdel-Qadir H, Farkouh ME. Statins and contrast-induced acute kidney injury with coronary angiography. *Am J Med* 2014;**127**:987–1000.
368. Kjekshus J, Pedersen TR, Olsson AG, Faergeman O, Pyörälä K. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail* 1997;**3**:249–254.
369. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;**339**:1349–1357.
370. Sacks FM, Pfeffer MA, Moyer LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wu CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;**335**:1001–1009.
371. Scirica BM, Morrow DA, Cannon CP, Ray KK, Sabatine MS, Jarolim P, Shui A, McCabe CH, Braunwald E. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 2006;**47**:2326–2331.
372. Khush KK, Waters DD, Bittner V, Deedwania PC, Kastelein JJ, Lewis SJ, Wenger NK. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. *Circulation* 2007;**115**:576–583.
373. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JG, Cornel JH, Dunselman P, Fonseca C, Goudev A, Grande P, Gullestad L, Hjalmarson A, Hradec J, Jánosi A, Kamenský G, Komajda M, Korewicki J, Kuusi T, Mach F, Mareev V, McMurray JJ, Ranjith N, Schaufelberger M, Vanhaecke J, van Veldhuisen DJ, Waagstein F, Wedel H, Wikstrand J. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
374. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1231–1239.
375. Rogers JK, Jhund PS, Perez AC, Böhm M, Cleland JG, Gullestad L, Kjekshus J, van Veldhuisen DJ, Wikstrand J, Wedel H, McMurray JJ, Pocock SJ. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). *JACC Heart Fail* 2014;**2**:289–297.
376. GISSI-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**372**:1223–1230.
377. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;**352**:2389–2397.
378. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. *Circulation* 2010;**121**:306–314.
379. Arsenault BJ, Boekholdt SM, Mora S, DeMicco DA, Bao W, Tardif JC, Amarencu P, Pedersen T, Barter P, Waters DD. Impact of high-dose atorvastatin therapy and clinical risk factors on incident aortic valve stenosis in patients with cardiovascular disease (from TNT, IDEAL, and SPARCL). *Am J Cardiol* 2014;**113**:1378–1382.
380. Milin AC, Vorobiof G, Aksoy O, Ardehali R. Insights into aortic sclerosis and its relationship with coronary artery disease. *J Am Heart Assoc* 2014;**3**:e001111.
381. Antonini-Canterin F, Moura LM, Enache R, Leiballi E, Pavan D, Piazza R, Popescu BA, Ghingina C, Nicolosi GL, Rajamannan NM. Effect of hydroxymethylglutaryl coenzyme-a reductase inhibitors on the long-term progression of rheumatic mitral valve disease. *Circulation* 2010;**121**:2130–2136.
382. Antonini-Canterin F, Zuppiroli A, Popescu BA, Granata G, Cervesato E, Piazza R, Pavan D, Nicolosi GL. Effect of statins on the progression of bioprosthetic aortic valve degeneration. *Am J Cardiol* 2003;**92**:1479–1482.
383. Goldberg RJ, Urowitz MB, Ibañez D, Nikpour M, Gladman DD. Risk factors for development of coronary artery disease in women with systemic lupus erythematosus. *J Rheumatol* 2009;**36**:2454–2461.
384. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, Troxel AB, Hennessy S, Kimmel SE, Margolis DJ, Choi H, Mehta NN, Gelfand JM. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;**74**:326–332.
385. Peters MJ, Symmons DP, McCarey D, Dijkman BA, Nicola P, Kvien TK, McInnes IB, Haentzschel H, Gonzalez-Gay MA, Provan S, Semb A, Sidiropoulos P, Kitas G, Smulders YM, Soubrier M, Szekanecz Z, Sattar N, Nurmohamed MT. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;**69**:325–331.
386. De Vera MA, Choi H, Abrahamowicz M, Kopec J, Goycochea-Robles MV, Lacaille D. Statin discontinuation and risk of acute myocardial infarction in patients with rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2011;**70**:1020–1024.
387. Barry R, James MT. Guidelines for classification of acute kidney diseases and disorders. *Nephron* 2015;**131**:221–226.
388. Olechnowicz-Tietz S, Gluba A, Paradowska A, Banach M, Rysz J. The risk of atherosclerosis in patients with chronic kidney disease. *Int Urol Nephrol* 2013;**45**:1605–1612.
389. Franczyk-Skóra B, Gluba A, Banach M, Rozenytr P, Polowski L, Rysz J. Acute coronary syndromes in patients with chronic kidney disease. *Curr Vasc Pharmacol* 2013;**11**:758–767.
390. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–352.
391. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**:2073–2081.
392. Loncar G, Barthelemy O, Berman E, Kerneis M, Petroni T, Payot L, Choussat R, Silvain J, Collet JP, Helft G, Montalescot G, Le Feuvre C. Impact of renal failure on all-cause mortality and other outcomes in patients treated by percutaneous coronary intervention. *Arch Cardiovasc Dis* 2015;**108**:554–562.
393. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2014;**5**:CD007784.
394. Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, Pencina MJ, Rizzo M, Rysz J, Abdollahi M, Nicholls SJ, Banach M. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy--a meta-analysis of 11

- randomized controlled trials involving 21,295 participants. *Pharmacol Res* 2013;**72**: 35–44.
395. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–248.
396. Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–1407.
397. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairitichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.
398. Erickson KF, Japa S, Owens DK, Chertow GM, Garber AM, Goldhaber-Fiebert JD. Cost-effectiveness of statins for primary cardiovascular prevention in chronic kidney disease. *J Am Coll Cardiol* 2013;**61**:1250–1258.
399. Tonelli M, Wanner C, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med* 2014;**160**:182.
400. Kobashigawa JA, Katznelson S, Laks H, Johnson JA, Yeatman L, Wang XM, Chia D, Terasaki PI, Sabad A, Cogert GA. Effect of pravastatin on outcomes after cardiac transplantation. *N Engl J Med* 1995;**333**:621–627.
401. Wenke K, Meiser B, Thiery J, Nagel D, von Scheidt W, Steinbeck G, Seidel D, Reichart B. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four-year randomized trial. *Circulation* 1997;**96**:1398–1402.
402. Page RL 2nd, Miller GG, Lindenfeld J. Drug therapy in the heart transplant recipient: part IV: drug-drug interactions. *Circulation* 2005;**111**:230–229.
403. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev* 2009;**2**:CD005019.
404. Shaw SM, Chaggar P, Ritchie J, Shah MK, Baynes AC, O'Neill N, Fildes JE, Yonan N, Williams SG. The efficacy and tolerability of ezetimibe in cardiac transplant recipients taking cyclosporin. *Transplantation* 2009;**87**:771–775.
405. European Stroke Organisation, Tenders M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, Cremonesi A, De Carlo M, Erbel R, Fowkes FG, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Rimbau V, Roffi M, Röther J, Sievert H, van Sambeek M, Zeller T. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2851–2906.
406. McDermott MM, Mandapat AL, Moates A, Albay M, Chiou E, Celic L, Greenland P. Knowledge and attitudes regarding cardiovascular disease risk and prevention in patients with coronary or peripheral arterial disease. *Arch Intern Med* 2003;**163**: 2157–2162.
407. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev* 2007;**4**: CD000123.
408. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, Banerjee S, Creager MA, Bhatt DL. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;**35**:2864–2872.
409. Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, Pevac WC, Amsterdam EA, Laird JR. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol* 2014;**63**:682–690.
410. Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* 2004;**35**:2902–2909.
411. Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. *J Atheroscler Thromb* 2013;**20**: 108–121.
412. Tedeschi-Reiner E, Strozzi M, Skoric B, Reiner Z. Relation of atherosclerotic changes in retinal arteries to the extent of coronary artery disease. *Am J Cardiol* 2005;**96**:1107–1109.
413. Keech AC, Mitchell P, Summanen PA, O'Day J, Davis TM, Moffitt MS, Taskinen MR, Simes RJ, Tse D, Williamson E, Merrifield A, Laatikainen LT, d'Emden MC, Crimet DC, O'Connell RL, Colman PG. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet* 2007;**370**:1687–1697.
414. ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, Lovato JF, Perdue LH, Goff DC Jr, Cushman WC, Ginsberg HN, Elam MB, Genuth S, Gerstein HC, Schubart U, Fine LJ. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med* 2010;**363**:233–244.
415. Golledge J, Muller J, Daugherty A, Norman P. Abdominal aortic aneurysm: pathogenesis and implications for management. *Arterioscler Thromb Vasc Biol* 2006;**26**: 2605–2613.
416. Paraskevas KI, Liapis CD, Hamilton G, Mikhailidis DP. Can statins reduce perioperative morbidity and mortality in patients undergoing non-cardiac vascular surgery? *Eur J Vasc Endovasc Surg* 2006;**32**:286–293.
417. Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leão P, Caramelli B. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004;**39**:967–975; discussion 975–976.
418. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, Verhagen HJ, Khan NA, Dunkelgrun M, Bax JJ, Poldermans D. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med* 2009;**361**: 980–989.
419. Takagi H, Yamamoto H, Iwata K, Goto S, Umemoto T, Group A. Effects of statin therapy on abdominal aortic aneurysm growth: a meta-analysis and meta-regression of observational comparative studies. *Eur J Vasc Endovasc Surg* 2012;**44**:287–292.
420. Hackam DG, Wu F, Li P, Austin PC, Tobe SW, Mamdani MM, Garg AX. Statins and renovascular disease in the elderly: a population-based cohort study. *Eur Heart J* 2011;**32**:598–610.
421. Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, Olsen AM, Jones WS, Torp-Pedersen C, Fosbol EL. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. *Eur J Prev Cardiol* 2015;**22**:317–325.
422. Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. *Lancet Neurol* 2009;**8**: 453–463.
423. McKinney JS, Kostis WJ. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. *Stroke* 2012;**43**:2149–2156.
424. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;**361**: 1149–1158.
425. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;**359**:2195–2207.
426. Byington RP, Davis BR, Plehn JF, White HD, Baker J, Cobbe SM, Shepherd J. Reduction of stroke events with pravastatin: the Prospective Pravastatin Pooling (PPP) Project. *Circulation* 2001;**103**:387–392.
427. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, Collins R. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet* 2011;**378**: 2013–2020.
428. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillensen H, Simunovic L, Szarek M, Welch KM, Zivin JA. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;**355**: 549–559.
429. Merwick Á, Albers GW, Arsava EM, Ay H, Calvet D, Coutts SB, Cucchiara BL, Demchuk AM, Giles MF, Mas JL, Olivot JM, Purroy F, Rothwell PM, Saver JL, Sharma VK, Tsvigoulis G, Kelly PJ. Reduction in early stroke risk in carotid stenosis with transient ischemic attack associated with statin treatment. *Stroke* 2013;**44**: 2814–2820.
430. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. *JAMA* 2003;**289**:2978–2982.

431. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. *Eur Heart J* 2014;**35**:1373–1381.
432. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: a systematic review and meta-analysis. *HIV Med* 2012;**13**:453–468.
433. Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, Wein N, Holodniy M, Hou N, Owens DK, Desai M. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One* 2013;**8**:e59551.
434. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007;**92**:2506–2512.
435. Wohl DA, Waters D, Simpson RJ Jr, Richard S, Schnell A, Napravnik S, Keys J, Eron JJ Jr, Hsue P. Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-infected patients receiving combination antiretroviral therapy. *Clin Infect Dis* 2008;**47**:1105–1108.
436. Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003;**17**:851–859.
437. Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn DL, Azrin S, Goldstein A, Severe J, Heinsen R, Kane JM. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 2014;**71**:1350–1363.
438. Andrade C. Primary prevention of cardiovascular events in patients with major mental illness: a possible role for statins. *Bipolar Disord* 2013;**15**:813–823.
439. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009;**374**:620–627.
440. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorder. *Schizophr Res* 2011;**131**:101–104.
441. Godin O, Etain B, Henry C, Bougerol T, Courtet P, Mayliss L, Passerieux C, Azorin JM, Kahn JP, Gard S, Costagliola D, Leboyer M. Metabolic syndrome in a French cohort of patients with bipolar disorder: results from the FACE-BD cohort. *J Clin Psychiatry* 2014;**75**:1078–1085; quiz 1085.
442. Lawrence D, Kisely S, Pais J. The epidemiology of excess mortality in people with mental illness. *Can J Psychiatry* 2010;**55**:752–760.
443. Goldstein BI, Fagiolini A, Houck P, Kupfer DJ. Cardiovascular disease and hypertension among adults with bipolar I disorder in the United States. *Bipolar Disord* 2009;**11**:657–662.
444. De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Möller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). *Eur Psychiatry* 2009;**24**:412–424.
445. Ojala K, Repo-Tiihonen E, Tiihonen J, Niskanen L. Statins are effective in treating dyslipidemia among psychiatric patients using second-generation antipsychotic agents. *J Psychopharmacol* 2008;**22**:33–38.
446. Mitchell AJ, Lord O. Do deficits in cardiac care influence high mortality rates in schizophrenia? A systematic review and pooled analysis. *J Psychopharmacol* 2010;**24**(4 Suppl):69–80.
447. Wood D, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faergeman O. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008;**371**:1999–2012.
448. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Ann Behav Med* 2013;**46**:81–95.
449. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *Int J Nurs Stud* 2013;**50**:587–592.
450. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;**288**:455–461.
451. Chodick G, Shalev V, Gerber Y, Heymann AD, Silber H, Simah V, Kokia E. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. *Clin Ther* 2008;**30**:2167–2179.
452. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002;**288**:462–467.
453. McGinnis BD, Olson KL, Delate TM, Stolcpart RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. *Am J Manag Care* 2009;**15**:689–695.
454. Huser MA, Evans TS, Berger V. Medication adherence trends with statins. *Adv Ther* 2005;**22**:163–171.
455. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, Daniel JG, Ekman I, Ho M, Johnson M, Kimmel SE, Liu LZ, Musaus J, Shrank WH, Whalley Buono E, Weiss K, Granger CB. Medication adherence: a call for action. *Am Heart J* 2011;**162**:412–424.
456. Hinchcliffe A. *Patient Adherence to Treatment with Statins for the Prevention of Cardiovascular Disease*. Cardiff: Public Health Wales NHS Trust, 2011.
457. Blackburn DF, Dobson RT, Blackburn JL, Wilson TW, Stang MR, Semchuk WM. Adherence to statins, beta-blockers and angiotensin-converting enzyme inhibitors following a first cardiovascular event: a retrospective cohort study. *Can J Cardiol* 2005;**21**:485–488.
458. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. *Heart* 2002;**88**:229–233.
459. Corrao G, Conti V, Merlino L, Catapano AL, Mancía G. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. *Clin Ther* 2010;**32**:300–310.
460. Aubert RE, Yao J, Xia F, Garavaglia SB. Is there a relationship between early statin compliance and a reduction in healthcare utilization? *Am J Manag Care* 2010;**16**:459–466.
461. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**:521–530.
462. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 2012;**125**:882–887.e1.
463. Wise J. Open letter raises concerns about NICE guidance on statins. *BMJ* 2014;**348**:g3937.
464. Abramson JD, Rosenberg HG, Jewell N, Wright JM. Should people at low risk of cardiovascular disease take a statin? *BMJ* 2013;**347**:f6123.
465. Huffman M, Taylor F, Ebrahim S. Huffman and colleagues' response to Abramson and colleagues' article on statins in low risk people. *BMJ* 2014;**348**:g1520.
466. Ajzen I. The Theory of Planned Behaviour. *Organ Behav Hum Decis Process* 1991;**50**:179–211.
467. Becker MH. The Health Belief Model and personal health behaviour. *Health Educ Monogr* 1974;**2**:324–508.
468. Rich A, Brandes K, Mullan B, Hagger MS. Theory of planned behavior and adherence in chronic illness: a meta-analysis. *J Behav Med* 2015;**38**:673–688.
469. Kamran A, Sadeghieh Ahari S, Biria M, Malepour A, Heydari H. Determinants of patient's adherence to hypertension medications: application of health belief model among rural patients. *Ann Med Health Sci Res* 2014;**4**:922–927.
470. Jackson C, Eliasson L, Barber N, Weinman J. Applying COM-B to medication adherence. *Eur Health Psychol* 2014;**16**:7–17.
471. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;**6**:42.
472. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. *Ann Pharmacother* 2010;**44**:1410–1421.
473. Latry P, Molimard M, Dedieu B, Couffinal T, Bégaud B, Martin-Latry K. Adherence with statins in a real-life setting is better when associated cardiovascular risk factors increase: a cohort study. *BMC Cardiovascular Disorders* 2011;**11**:46.
474. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. *Am Heart J* 2013;**165**:665–678.e1.
475. Harrison TN, Derosé SF, Cheatham TC, Chiu V, Vansomphone SS, Green K, Tunceli K, Scott RD, Marrett E, Reynolds K. Primary nonadherence to statin therapy: patients' perceptions. *Am J Manag Care* 2013;**19**:e133–e139.
476. DeWalt DA, Brouckou KA, Hawk V, Brach C, Hink A, Rudd R, Callahan L. Developing and testing the health literacy universal precautions toolkit. *Nurs Outlook* 2011;**59**:85–94.
477. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. *Br J Gen Pract* 2005;**55**:305–312.
478. Bandura A. *Self-Efficacy: The Exercise of Control*. New York: Freeman, 1997.
479. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev* 2010;**3**:CD004371.
480. Nieuwlaar R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2014;**11**:CD000011.
481. Martin SS, Sperling LS, Blaha MJ, Wilson PW, Gluckman TJ, Blumenthal RS, Stone NJ. Clinician-patient risk discussion for atherosclerotic cardiovascular

- disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. *J Am Coll Cardiol* 2015;**65**:1361–1368.
482. Thom S, Poulter N, Field J, Patel A, Prabhakaran D, Stanton A, Grobbee DE, Bots ML, Reddy KS, Cidambi R, Bompont S, Billot L, Rodgers A. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. *JAMA* 2013;**310**:918–929.
483. Castellano JM, Sanz G, Peñalvo JL, Bansilal S, Fernández-Ortiz A, Alvarez L, Guzmán L, Linares JC, García F, D'Aniello F, Arnáiz JA, Varea S, Martínez F, Lorenzatti A, Imaz I, Sánchez-Gómez LM, Roncaglioni MC, Baviera M, Smith SC Jr, Taubert K, Pocock S, Brotons C, Farkouh ME, Fuster V. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014;**64**:2071–2082.
484. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, Kaufman C, Cowie G, Taylor M. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev* 2014;**4**:CD007768.
485. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;**37**: 2315–2381.