ESC European Society of Cardiology

JOINT GUIDELINES

2021 EUROPEAN GUIDELINES ON CARDIOVASCULAR DISEASE PREVENTION IN CLINICAL PRACTICE

Peer Review Round 3 – April/May 2021

Documents to review:

Pages 2 to 207

Guidelines Full Text

Pages 208 to 236

Supplementary data

Of note: the front page is not provided for review as the names of the Task Force Members and Reviewers are strictly confidential until publication of the guidelines. The front page will be added during the publication phase.

Please only submit your comments on the WORD comment form provided for this purpose.

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Contents

Recommendations

Tables

Figures

Abbreviations and acronyms

$\%HR_{max}$	percentage of a person's maximum heart rate
AAD	antiarrhythmic drug
ABC	Atrial fibrillation Better Care
ABI	ankle-brachial index
ABPM	ambulatory blood pressure monitoring
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	angiotensin-converting enzyme
ACR	albumin to creatinine ratio
ACS	acute coronary syndrome
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation
AF	atrial fibrillation
AMI	acute myocardial infarction
ARB	angiotensin-receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
ASCEND	A Study of Cardiovascular Events in Diabetes
ASCVD	atherosclerotic cardiovascular disease
b.i.d.	*bis in die* (twice a day)
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CAC	coronary artery calcium
CAD	coronary artery disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CANVAS	Canagliflozin cardioVascular Assessment Study
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events Investigators
CCB	calcium channel blocker
CCS	chronic coronary syndromes
CCTA	contrast computed tomography angiography
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CR	cardiac rehabilitation
CTT	Cholesterol Treatment Trialists'
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
CV	cardiovascular
CVD	cardiovascular disease
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DAPT	dual antiplatelet therapy
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DIAL	Diabetes Lifetime-perspective prediction
DM	diabetes mellitus
e-cigarettes	electronic cigarettes
EAGLES	Evaluating Adverse Events in a Global Smoking Cessation study
EAS	European Atherosclerosis Society
EBCR	exercise-based cardiac rehabilitation
ECG	electrocardiographic
ED	erectile dysfunction
eGFR	estimated glomerular filtration rate

ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EPA	eicosapentaenoic acid
EPIC	European Prospective Investigation into Cancer and Nutrition
EPIC-Norfolk	European Prospective Investigation of Cancer–Norfolk
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
FH	familial hypercholesterolaemia
GAD-2	Generalized Anxiety Disorder-2
GLP-1RA	glucagon like peptide-1 receptor agonist
HbA1c	glycated haemoglobin A1c
HBPM	home blood pressure monitoring
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HMOD	hypertension-mediated organ damage
HR	hazard ratio
IMT	intima-media thickness
INVEST	INternational VErapamil-SR/Trandolapril STudy
JBS3	Joint British Societies' consensus recommendations for the prevention of cardiovascular disease
LA	left atrium
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LEAD	lower extremity artery disease
LIFE-CVD	LIFEtime-perspective CardioVascular Disease
LNight	night-time hour exposure
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiovascular events
MET	metabolic equivalent
MRA	mineralocorticoid receptor antagonist
MUFA	monounsaturated fatty acid
N/A	not applicable
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NGO	non-governmental organization
NRI	net reclassification index
NRT	nicotine-replacement therapy
NYHA	New York Heart Association
o.d.	*omni die* (once a day)
OAC	oral anticoagulant therapy
OARS	Open ended questions, Affirmation, Reflecting listening and Summarizing
OR	odds ratio
ORBIT AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
OSA	obstructive sleep apnoea
PA	physical activity
PAD	peripheral artery disease
PAP	positive airway pressure
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PEGASUS	Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

PHQ	Patient Health Questionnaire
PLATO	PLATelet inhibition and patient Outcome
PM	particulate matter
PRC	polygenic risk score
PUFA	polyunsaturated fatty acid
PWV	pulse wave velocity
RAAS	renin–angiotensin–aldosterone system
RAS	renin–angiotensin system
RCT	randomized controlled trial
REACH	Reduction of Atherothrombosis for Continued Health
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
RPE	rate of energy expenditure
RR	relative risk
SAVOR-TIMI 53	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction
SBP	systolic blood pressure
SCORE	Systemic Coronary Risk Estimation
SCOT-HEART	Scottish Computed Tomography of the Heart
SFA	saturated fatty acid
SGLT2	sodium-glucose cotransporter 2
SHARP	Study of Heart and Renal Protection (SHARP),
SMART	Secondary Manifestations of Arterial Disease
SMART	Specific, Measurable, Achievable, Realistic, Timely
SMART-DATE	Safety of 6-month Duration of Dual Antiplatelet Therapy After Acute Coronary Syndrome
SMART-REACH	Secondary Manifestations of Arterial Disease–Reduction of Atherothrombosis for Continued Health
SNRI	selective serotonin noradrenaline reuptake inhibitor
SPRINT	Systolic Blood Pressure Intervention Trial
SSRI	selective serotonin reuptake inhibitor
STAREE	STAtin therapy for Reducing Events in the Elderly
SUPRIM	Secondary Prevention in Uppsala Primary Healthcare Project
SWITCHD	Stockholm Women's Intervention Trial for Coronary Heart Disease
THEMIS	Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study
TIA	transient ischaemic attack
TIMI	Thrombolysis In Myocardial Infarction
TRITON–TIMI	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
TRS 2°P	Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VITAL	Vitamin D and Omega-3 Trial
VO_2	oxygen consumption
WHO	World Health Organization

1. Preamble

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 divergence of opinion about the usefulness/efficacy of the given treatment or procedure	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

Levels of evidence

Level of evidence A	**Data derived from multiple randomized clinical trials or meta-analyses of randomized clinical trials**
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**

2. Introduction

Atherosclerotic cardiovascular disease (ASCVD) incidence and mortality rates are declining in many countries in Europe, but is still a major cause of morbidity and mortality. Over the past few decades, major ASCVD risk factors have been identified. The most important way to prevent ASCVD is to promote a healthy lifestyle throughout life, especially not smoking. Effective and safe risk factor treatments have been developed, and most drugs are now generic and available at low costs. Nevertheless, the prevalence of unhealthy lifestyle is still high, and ASCVD risk factors are often

poorly treated, even in patients considered to be at high (residual) ASCVD risk.[1]Prevention of CV events by reducing ASCVD risk is the topic of these Guidelines.

2.1. Definition and rationale

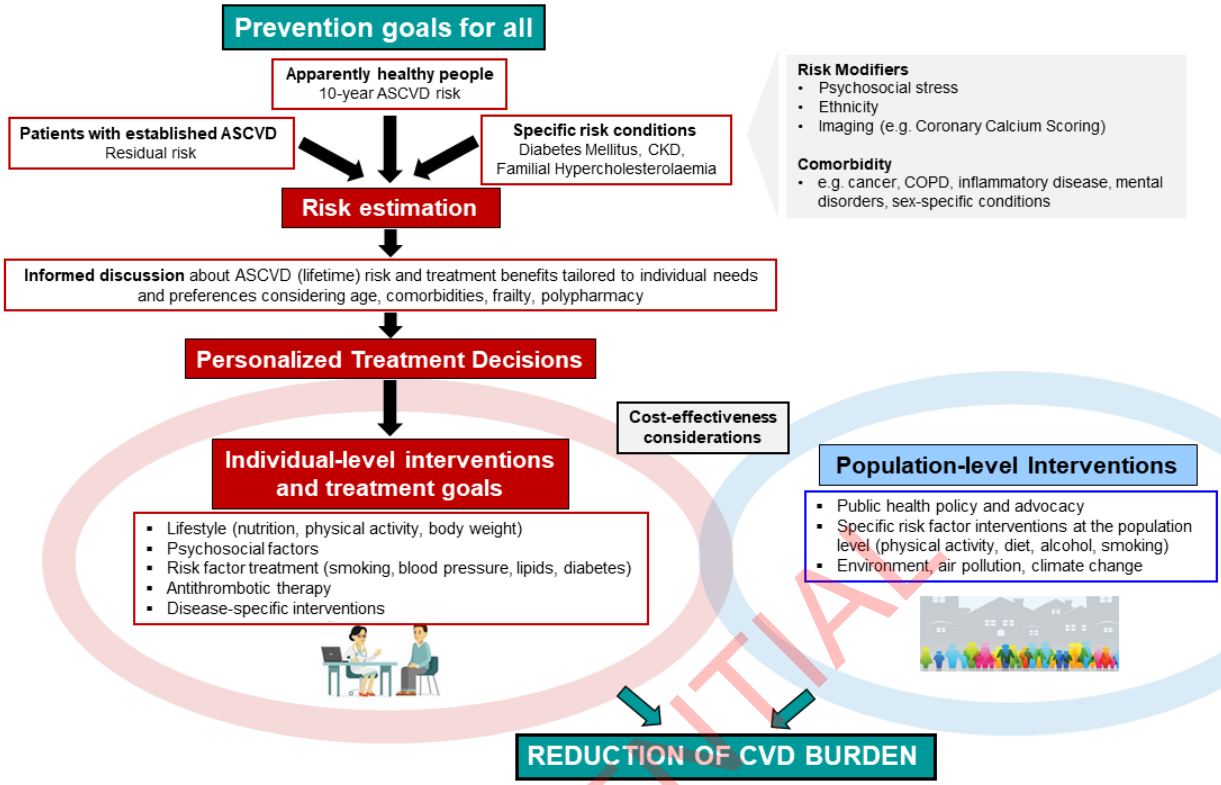
The present Guidelines have been developed to support healthcare professionals in their efforts to reduce the burden of ASCVD in both individual patients, as well as at a population level. The previous European Guidelines on ASCVD prevention in clinical practice were published in 2016.[2] Recent developments in prediction of ASCVD risk and treatment benefit, as well as novel treatments and treatment goals, necessitated new, up-to-date guidelines. The current guidelines on cardiovascular disease prevention in clinical practice concentrate principally but not exclusively on the risk factors, risk classification and prevention of ASCVD.

The current Guidelines provide recommendations on ASCVD prevention to support shared decision-making by the patient and their healthcare professional based on individual patient characteristics. Special considerations will be given to differences in age, sex and gender, life expectancy, risk factor profiles, ethnic and geographic differences. Estimating ASCVD risk not only in apparently healthy subjects, but also in older persons and in patients with established ASCVD or diabetes, provides information for tailored intervention on an individual level. Treatment goals can be individualized in a stepwise approach. 'Residual' ASCVD risk is defined as the risk estimated after initial lifestyle changes and risk factor treatment, and is mostly used in patients with established ASCVD. For younger apparently healthy subjects, lifetime ASCVD risk estimates are available to support treatment decisions, replacing 10-year risk algorithms that consistently estimate low 10-year risk even in the presence of high risk factor levels. In an ageing population, treatment decisions require a specific CV risk score that takes competing non-CV risk into account, as well as specific low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) treatment considerations. Estimating lifetime benefit in individual patients of smoking cessation, LDL-C lowering, and BP lowering provides opportunities to communicate benefit of treatment in an easy-to-understand way. Personalized treatment decisions using ASCVD risk estimations and a stepwise approach to treatment is more complex than a more general one-size fits all prevention strategy, but reflects the diversity in patients and patient characteristics in clinical practice.

Regarding LDL-C, blood pressure and glycemic control in diabetes, goals and targets remain as recommended in recent ESC Guidelines.[3] [4] [5] These guidelines propose a new, stepwise approach to treatment intensification as a tool to help physicians and patients pursue these targets in a way that fits patient profile and preferences. Of note, however, new evidence and/or new consensus may have resulted in some differences with these recent domain-specific ESC guidelines. New evidence on antithrombotic treatment regimens for ASCVD prevention is also presented. Sex and gender specific aspects are included.

Cardiovascular prevention needs an integrated, interdisciplinary approach including input from several disciplines and areas of expertise. We must work together in a patient and family centred way to address each of the core components of prevention and rehabilitation, including lifestyle modification, psychosocial factors, risk factor treatment and social determinants (Central Illustration).

Central Illustration.



2.2. Development

The Task Force chairs and members were appointed by the ESC Committee for Practice Guidelines. Each member of the Task Force was assigned specific writing tasks, which were reviewed by other (sub)section writers, the section coordinators, and the chairs. The text was developed over 11 months, during which the Task Force members met collectively on three occasions and corresponded intensively between meetings. The review panel consisted of experts selected by all the scientific societies that were involved in the development of these Guidelines, not only the ESC.

2.3. Cost effectiveness

The Task Force acknowledge the fact that healthcare budgets are in many circumstances limited and thus that certain recommendations and goals may not always be attainable. However, the current Guidelines do not provide cost-effectiveness analyses. Large national and regional differences in budget and costs associated with both interventions and diseases/events preclude valid universal cost-effectiveness analyses. However, some recommendations clearly have financial implications, either in terms of costs for individual patients and/or in terms of budget impact. Some of these recommendations pertain to diagnosis (e.g. large-scale use of expensive imaging tests such as computed tomography), others to intervention (e.g. expensive drugs, such as novel lipid-lowering of anti-diabetic drugs). For such recommendations, it is inappropriate to “unconditionally” implement them without first considering cost effectiveness in a national or regional context or, ideally, to

perform formal cost-effectiveness analyses with country-specific input parameters and cost-effectiveness thresholds.

2.4. What is new

New recommendations, and new and revised concepts, are presented in *Table 1*.

Table 1 New recommendations, and new and revised concepts

Most important new recommendations
Risk factors and clinical conditions – *section* 3
In apparently healthy people ≤70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and non-fatal ASCVD risk with SCORE2 is recommended.
In apparently healthy people >70 years of age without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorder, estimation of 10-year fatal and non-fatal ASCVD risk with SCORE2-OP is recommended.
Patients with established CVD and/or DM and/or moderate-to-severe renal disease and/or genetic/rare lipid or BP disorders are to be considered at high or very high ASCVD risk.
A stepwise treatment-intensification approach is recommended for apparently healthy people at high or very high ASCVD risk, as well as patients with established ASCVD and/or DM, with consideration of ASCVD risk, treatment benefit of risk factors, risk modifiers, comorbidities, and patient preferences.
In apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at very high risk (SCORE2 >7.5% for people aged under 50 years; SCORE2 >10% for people aged 50-70 years; SCORE2-OP >15% for people aged >70 years), treatment of ASCVD risk factors is recommended.
An informed discussion about ASCVD risk and treatment benefits tailored to the needs of a patient is recommended
It is recommended that mental disorders with either significant functional impairment or decreased use of healthcare systems be considered as influencing total CVD risk.
In apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at high risk (SCORE2 2.5-7.5% for people aged under 50 years; SCORE2 5-10% for people aged 50-70 years; SCORE2-OP 7.5-150% for people aged >70 years), treatment of risk factors should be considered taking ASCVD risk modifiers, lifetime risk and treatment benefit and patient preferences into account.
In apparently healthy people, after estimation of 10-year fatal and non-fatal ASCVD risk, lifetime risk and treatment benefit, risk modifiers, frailty, polypharmacy and patient preferences should be considered.
Presence of migraine with aura should be considered in ASCVD risk assessment.

Assessment of ASCVD risk should be considered in men with erectile dysfunction.
In women with a history of giving premature or stillbirth, periodic screening for hypertension and DM may be considered.
Assessment of total ASCVD risk may be considered in adults with chronic inflammatory conditions.
Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.
Interventions at the individual level – *section 4*
It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.
It is recommended to adopt a Mediterranean or similar diet to lower risk of ASCVD.
It is recommended to restrict alcohol consumption to a maximum of 100 grams per week.
It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.
Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.
Smoking cessation is recommended regardless of weight gain, as weight gain does not mitigate the ASCVD benefits of cessation.
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (<55 mg/dL) and a ≥50% reduction of LDL-C compared with baseline is recommended.
For secondary prevention patients not achieving their goals on a maximum tolerated dose of statin and ezetimibe, combination therapy with a PCSK9 inhibitor is recommended.
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe target organ damage), intensive lipid-lowering therapy ultimately aiming at ≥50% LDL-C reduction *and* an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.
In patients with type 2 DM >40 years at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.
It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific co-morbidities.
In treated patients aged 18-70 years, it is recommended that SBP should ultimately be lowered to a target range of 120−130 mmHg in most patients.
In treated patients aged over 70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.
In all treated patients, DBP is recommended to be lowered to <80 mmHg

In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes, without necessarily having to first commence metformin.
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended if no contraindications to improve ASCVD and/or cardiorenal outcomes.
In patients with type 2 DM and HF with reduced ejection fraction, use of an SGLT2 inhibitor with proven outcome benefits is recommended, if no contraindications, to lessen HF hospitalizations and CV death.
Participation in a medically supervised, structured, comprehensive, multidisciplinary EBCR and prevention programme for patients after ASCVD events and/or revascularization, and for patients with HF (mainly HFrEF), is recommended to improve patient outcomes.
Lifestyle interventions, such as group or individual education, behaviour-change techniques, telephone counselling, and use of consumer-based wearable activity trackers, should be considered to increase physical activity participation.
Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.
ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CV outcomes and reduce stress symptoms.
Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.
An ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of >50% from baseline should be considered in apparently healthy persons ≤70 years at very high risk.
An ultimate LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of >_50% from baselined should be considered in apparently healthy persons ≤70 years at high risk.
For those motivated to try, considerable weight loss with use of low-calorie diets followed by food reintroduction and weight-maintenance phases early after diagnosis can lead to diabetes remission and should be considered.
In patients with type 2 DM and target organ damage, the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits should be considered to reduce future CV and total mortality.
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 x 2 g/d) may be considered in combination with a statin.
Initiation of statin treatment for primary prevention in older people aged >70 may be considered, if at high risk or above.

Statin therapy may be considered in persons aged ≤40 years with type 1 or type 2 DM with evidence of end-organ damage and/or an LDL-C level >2.6 mmol/L (100 mg/dL), as long as pregnancy is not being planned.
In patients with DM at high or very high ASCVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.
Home-based CR, telehealth, and mHealth interventions may be considered to increase patient participation and long-term adherence to healthy behaviours.
In patients with HF and major depression, SSRI, SNRI, and tricyclic antidepressants are not recommended.
In patients with dialysis-dependent CKD who are free of ASCVD, commencing statin therapy is not recommended.
Policy interventions at the population level – *section 5*
Putting in place measures to reduce air pollution, including reducing particulate matter emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions are recommended to reduce CVD mortality and morbidity.
Disease-specific CVD risk management – *section 6*
It is recommended that patients with HF are enrolled in a comprehensive cardiac rehabilitation programme to reduce the risk of HF hospitalization and death.
It is recommended to screen patients with HF for both CV and non-CV comorbidities, which, if present, should be treated provided safe and effective interventions exist, not only to alleviate symptoms but also to improve prognosis.
In patients with a cerebrovascular event, improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.
Identification and management of risk factors and concomitant diseases are recommended to be considered an integral part of treatment in patients with AF.
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg b.i.d.) and aspirin (100 mg o.d.) may be considered.
Adding a second antithrombotic drug (a P2Y12 inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk.
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with a moderate risk of ischaemic events and without a high bleeding risk.

Changes in recommendations – upgrades – downgrades	
2016	**2021**
Risk factors and clinical conditions – *section 3*	**Risk factors and Clinical Conditions – *section 3***

ABI may be considered as a risk modifier in CV risk assessment.	The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than coronary calcium scoring or carotid ultrasound for plaque determination), is not recommended.
Interventions at the individual level – Chapter	**Interventions at the individual level – Chapter**
Drug treatment should be considered in patients with grade 1 or 2 hypertension who are at high CV risk.	For grade I hypertension, treatment initiation based on absolute ASCVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.
In patients with type 2 DM and CVD, use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.	In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes, without necessarily having to first commence metformin

ABI = ankle brachial index; ACS = acute coronary syndrome; AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; *b.i.d.* = *bis in die* (twice a day); BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; CR = cardiac rehabilitation; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EBCR = exercise-based cardiac rehabilitation; eGFR = estimated glomerular filtration rate; EPA = eicosapentaenoic acid; FH = familial hypercholesterolaemia; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HMOD = hypertension-mediated organ damage; IMT = intima-media thickness; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; *o.d.* = *omni die* (once a day); PA = physical activity; PCSK9 = proprotein convertase subtilisin/kexin type 9; PUFA = polyunsaturated fatty acid; SBP = systolic blood pressure; SCORE 2 = Systematic Coronary Risk Estimation 2; SGLT2 = sodium-glucose cotransporter 2; SNRI = selective serotonin noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TG = triglycerides.

554

New sections

Section 3

3.2.2. Sex and gender and their impact on health
3.2.3 Atherosclerotic Cardiovascular Disease (ASCVD) risk classification
3.2.3.1 A step-wise approach to risk factor treatment and treatment intensification
3.2.3.2 Risk estimation in apparently healthy people between 50–70 years of age
3.2.3.3 Translating risk thresholds to treatment thresholds
3.2.3.4 Risk estimation in apparently healthy people >70 years of age
3.2.3.5 Risk and treatment benefit estimation in apparently healthy people <50 years of age
3.2.3.6 Risk estimation in patients with established cardiovascular disease
3.2.4 Communication of cardiovascular disease risk
3.3.1. Psychosocial factors
3.3.4. Frailty
3.3.8. Environmental exposure
3.4. Clinical conditions
3.4.2. Atrial fibrillation
3.4.3. Heart failure
3.4.5. Chronic obstructive pulmonary disease
3.4.6. Inflammatory conditions
3.4.7. Infections (human immunodeficiency virus, influenza, periodontitis)
3.4.8. Migraine
3.4.9. Sleep disorders and obstructive sleep apnoea syndrome
3.4.10. Mental disorders
3.4.11. Non-alcoholic fatty liver disease
3.4.12. Sex-specific conditions

Section 4

4.10 Anti-inflammatory treatment
4.11. Cardiovascular rehabilitation and prevention programmes

Section 5

5.3. Environment, air pollution, and climate change

New /revised concepts

Section 3

- Systematic Coronary Risk Estimation 2 (SCORE2) and SCORE2-OP risk charts for fatal and non-fatal (MI, stroke) ASCVD.
- Estimating 10-year total ASCVD risk in apparently healthy people 50-70 years of age
- Estimating lifetime risk in apparently healthy people <50 years of age
- Estimating 10-year total ASCVD risk in apparently healthy people >70 years of age
- Cut-offs of 10-year ASCVD risk, based on SCORE-2 / SCORE2-OP, to define low-moderate risk, high risk, and very high risk for apparently healthy people at different age groups (< 50, 50-70, and > 70 years)
- Estimating 10-year CVD risk in patients with established CVD and/or diabetes mellitus.
- Lifetime benefit of stopping smoking and given reductions in LDL-C and SBP (*sections 3 and 4*)
- A two-step approach to attaining ultimate treatment goals (*sections 3 and 4*)

- Stepwise approach to risk factor treatment and treatment intensification.

Section 4

- Explicitly addressing cost-effectiveness (on a loco-regional or national level) before implementing some recommendations
- Non-fasting lipid measurement (*section 4.6.2.1*)
- A two-step approach to attaining treatment goals (*sections 3 and 4*)
- Anti-inflammatory treatment for very high risk patients

Section 5

- Taking into consideration population level interventions to mitigate the effects of pollution on CVD health

Section 6

- Risk management of disease-specific cardiovascular disease. This chapter addresses CVD prevention when certain underlying diseases are present and aims at providing guidance on how to prevent the worsening of existing, or the development of further comorbidities that could increase the overall risk of CVD.
- Subsections include: 6.1 Coronary artery disease; 6.2 Heart failure; 6.3 Cerebrovascular disease; 6.4 Lower extremity artery disease; 6.5 Chronic kidney disease; 6.6 Atrial fibrillation; 6.7 Multimorbidity

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

3. Risk factors and clinical conditions

3.1. Target population for assessing cardiovascular disease risk

ASCVD risk assessment or screening can be done opportunistically or systematically. Opportunistic screening means screening without a predefined strategy, but is done when a person presents for some other reason. Systematic screening can be done in the general population as part of a formal screening programme, with call and recall of patients, or in targeted subpopulations such as subjects with type 2 diabetes mellitus (DM), or family history of premature CVD. Systematic screening results in improvements in risk factors, but has no effect on CV outcomes.[6-9] Opportunistic screening for ASCVD risk factors, such as BP or lipids, is effective at increasing detection rates and is recommended.[10] Whilst ideally all adults would have their ASCVD risk assessed at some point, such as >40 years in men and >50 years in women, the decision about who to screen varies by country and is resource-dependent.

Structured national programs aiming to identify undocumented ASCVD risk factors in adults over 40 years of age without diabetes or ASCVD and treat them, have shown better risk factor control[11 12] A high-risk strategy of inviting the population predicted at the highest risk according to an integrated risk score would be equally effective in preventing new cases of CVD and had potential cost savings.[13] One large trial of mobile ultrasound screening for aortic aneurysm, peripheral artery disease, and hypertension in males between 65-74 showed a 7% mortality reduction at 5 years.[14]

A common criticism of screening in general is the potential of false positive and false negative results may cause harm. However, evidence on CV screening shows that those who participate do not report mental distress.[15-18]

Systematic CV assessment in the general population (adult men >40 and women >50 years of age) with no known CV risk factors appears not cost-effective in reducing subsequent vascular events and premature death, at least in short-term follow-up, but does increase detection of CV risk factors. Risk assessment is not a one-time event; it should be repeated, for example, every 5 years, although there are no empirical data to guide intervals.

Recommendations for cardiovascular disease risk assessment

Recommendations	Class[a]	Level[b]
Systematic global ASCVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, FH, ASCVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing ASCVD risk).	I	C
Systematic or opportunistic CV risk assessment in the general population in men >40 years of age and in women >50 years of age or postmenopausal with no known ASCVD risk factors may be considered.[9]	IIb	C
In those patients who have undergone ASCVD risk assessment in the context of systematic or opportunistic screening, a repetition of screening after 5 years (or sooner if risk was close to treatment thresholds) may be considered.	IIb	C
Opportunistic screening of BP in adults at risk for the development of hypertension, such as those who are overweight or with a known family history of hypertension, should be considered.[19]	IIa	B
Systematic ASCVD risk assessment in men <40 years of age and women <50 years of age with no known CV risk factors is not recommended.[9]	III	C

BP = blood pressure; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia.

[a] Class of recommendation.

[b] Level of evidence.

3.2. Risk factors and risk classification

3.2.1. Risk factors

The main causal and modifiable ASCVD risk factors are blood apo-B-containing lipoproteins (of which low-density lipoprotein [LDL] is most abundant), high BP, cigarette smoking, and DM. Another important risk factor is adiposity, which increases ASCVD risk via both major conventional risk factors

and other mechanisms. In addition to these, there are many other relevant risk factors, modifiers and clinical conditions, which are addressed under risk modifiers and clinical conditions (Chapters 3.3 and 3.4).

3.2.1.1 Cholesterol

The causal role of LDL-C, and other apo-B-containing lipoproteins, in the development of ASCVD is demonstrated beyond any doubt by genetic, observational, and interventional studies.[20] The key attributes of LDL-C as a risk factor for ASCVD are:

- Prolonged lower LDL-C is associated with lower risk of ASCVD throughout the range studied, and the results of RCTs indicate that lowering LDL-C safely reduces ASCVD risk even at low LDL-C levels (e.g. LDL-C <1.4 mmol/L [55 mg/dL]).[20]
- The relative reduction in ASCVD risk is proportional to the absolute size of the change in LDL-C, irrespective of the drug(s) used to achieve such change.[21]
- The absolute benefit of lowering LDL-C depends on the absolute risk of ASCVD and the absolute reduction in LDL-C, so even a small absolute reduction in LDL-C may be beneficial in a high- or very high-risk patient.[22]
- Non−HDL-C encompasses all atherogenic (apolipoprotein-B–containing) lipoproteins, and is calculated: total cholesterol – HDL-C = non−HDL-C. The relationship between non−HDL-C and CV risk is at least as strong as is the relationship with LDL-C. Non−HDL-C levels contain, in essence, the same information as a measurement of apo-B plasma concentration.[23, 24]

High-density lipoprotein cholesterol (HDL-C) is inversely associated with ASCVD risk. Very high HDL-C levels may signal an increased ASCVD risk. There is, however, no evidence from mendelian randomization studies, or randomized trials of cholesteryl ester transfer protein inhibitors, that raising plasma HDL-C reduces ASCVD risk.[25-28] HDL-C is nonetheless a useful biomarker to refine risk estimation using the Systemic Coronary Risk Estimation (SCORE2) algorithms. The SCORE2 algorithm cannot be used for patients with a genetic lipid disorder, such as familial hypercholesterolemia (FH). Specific LDL-C thresholds and targets are recommended irrespective of estimated CV risk for patients with FH or other rare/genetic lipid disorders.

3.2.1.1 Blood pressure

Longitudinal studies, genetic epidemiological studies, and RCTs have shown that raised BP is a major cause of both ASCVD and non-atherosclerotic CVD (particularly heart failure [HF]), accounting for 9.4 million deaths and 7% of global disability adjusted life-years.[29] Elevated BP is a risk factor for the development of CAD, HF, cerebrovascular disease, lower extremity arterial disease (LEAD), chronic kidney disease (CKD), and atrial fibrillation (AF). The risk of death from either CAD or stroke increases linearly from BP levels as low as 90 mmHg systolic and 75 mmHg diastolic upwards.[30, 31] The absolute benefit of reducing SBP depends on absolute risk and the absolute reduction in SBP, except that lower limits of SBP are imposed by tolerability and safety considerations. Management is determined by the category of hypertension (optimal, normal, high-normal, stages 1 to 3, and isolated systolic hypertension), defined according to seated office BP, ambulatory BP monitoring (ABPM), or home BP average values (see *section 4.7*). Evidence suggests that lifetime blood pressure evolution differs in

women as compared to men potentially resulting in an increased CVD risk at lower BP thresholds.[32-34] The SCORE2 algorithm cannot be used for patients with secondary causes and rarer forms of hypertension, such as primary hyperaldosteronism.

3.2.1.1 Cigarette smoking

Cigarette smoking is responsible for 50% of all avoidable deaths in smokers, half of these due to ASCVD. A lifetime smoker has a 50% probability of dying due to smoking, and on average will lose 10 years of life.[35] The ASCVD risk in smokers <50 years of age is fivefold higher than in non-smokers.[36] Prolonged smoking is more hazardous for women than for men.[37] Worldwide, after high SBP, smoking is the leading risk factor for disability adjusted life-years.[38] Second-hand smoke is associated with an increase in CVD risk.[39] Some smokeless tobacco is also associated with increased risk of CVD.[40]

3.2.1.1 Diabetes mellitus

Diabetes mellitus type 1 and type 2 are independent risk factors for ASCVD, increasing risk of ASCVD by about twofold, depending on the population and therapeutic control.[41] Women with type 2 DM appear to have a particularly higher risk for stroke.[42] Patients with type 2 DM are likely to have multiple ASCVD risk factors (including dyslipidaemia and hypertension), each of which mediates an increase in risk of both ASCVD and non-ASCVD.

3.2.1.1 Adiposity

Over recent decades BMI − measured as weight (in kg) divided by squared height (in m^2) − has increased substantially worldwide in children, adolescents, and adults.[43] Mendelian randomization analyses suggest a linear relation between BMI and mortality in non-smokers and a J-shaped relation in ever-smokers.[44] All-cause mortality is lowest at a BMI of 20−25 kg/m in apparently healthy people, with a J-shaped or U-shaped relation.[45, 46] In HF patients there is evidence for an obesity paradox with lower mortality risk in patients with higher BMI. A meta-analysis concluded that both BMI and waist circumference are similarly, strongly and continuously associated with ASCVD and type 2 DM.[47]

3.2.2. Sex and gender and their impact on health

The current prevention guidelines recognize the importance of integrating sex, gender and gender identity considerations into the risk assessment and clinical management of individuals and populations. These guidelines also acknowledge the complexity of the inter-relationship between these concepts and cardiovascular as well as psychological health. There is at present no official ESC position on the specific terminology to be used. According to the WHO, sex "refers to the different biological and physiological characteristics of females, males and intersex persons, such as chromosomes, hormones and reproductive organs.[48]

This is to be distinguished from gender which "refers to the characteristics of women, men, girls and boys that are socially constructed. This includes norms, behaviours and roles associated with being a

woman, man, girl or boy, as well as relationships with each other. As a social construct, gender varies from society to society and can change over time."[48] The Global Health 50/50 definition further states that gender refers "to the socially constructed norms that impose and determine roles, relationships, and positional power for all people across their lifetime.[49]

Where evidence exists on the risk modifying effect of sex or where sex-specific clinical conditions and clinical management strategies exist, this has been included into these guidelines.[50] The influence of gender on individual's experience and access to healthcare is paramount.[50] The specific health concerns related to gender are thus also acknowledged in these prevention guidelines.

Epigenetic effects of social constructs appear to condition the translation of biological sex into disease pathophysiology. Furthermore social constructs are also determinants of health access, healthcare utilisation, disease perception, decision making and perhaps therapeutic response[50], including in the field of cardiovascular disease and ASCVD prevention. Research is ongoing but gaps in evidence remain however and this has also been recognized in the guidelines.

Examples of specific topics regarding physiological, pathological and clinical differences related to sex and gender that have been studied include left ventricular ejection fraction, adverse drug reactions, trends in cardiovascular risk factors and awareness, sex disparities in the management of and outcomes after acute coronary syndromes.[51-58] Furthermore, cardiovascular health after menopause transition, pregnancy disorders, and gynaecologic conditions have recently been reviewed.[59]

3.2.3. Atherosclerotic Cardiovascular Disease (ASCVD) risk classification

The current guidelines on cardiovascular disease prevention in clinical practice concentrate principally but not exclusively on risk and prevention of atherosclerotic cardiovascular disease (ASCVD). This includes risk factors, risk prediction, risk modifiers, as well as clinical conditions that often increase the likelihood of ASCVD.

Identifying patients who will benefit most from ASCVD risk factor treatment is central to ASCVD prevention efforts. In general, the higher the absolute ASCVD risk, the higher the absolute benefit of risk factor treatment, and thus the lower the *number needed to treat* to prevent one CVD event during a period of time.[60, 61] With this in mind, the estimation of ASCVD risk remains the cornerstone of these guidelines and thus appears at the forefront of the proposed management schemes which are summarized in flowcharts.

Age is the major driver of ASCVD risk. Women below 50 years and men below 40 years of age are almost invariably at low 10-year ASCVD risk, but may have unfavourable modifiable risk factors that sharply increase their longer-term ASCVD risk. Conversely, men over 65 years and women over 75 years of age are almost always at high 10-year ASCVD risk. Only between the ages of 55-75 years in women and 40-65 years in men does the 10-year CVD risk vary around commonly used thresholds for intervention. The age categories <50, 50-70, >70 years should be used with common sense and flexibility. Different age ranges may be considered for men and women and may differ according to geographic region. Uncertainty around risk estimations should also be considered.

ASCVD risk can also be assessed in patients with type 2 DM and in patients with established CVD. The populations or patient groups in whom ASCVD risk needs to be considered are summarized and presented in *Table 3*. Lifetime ASCVD risk estimation is available for various groups of patients, and

enables estimation of lifetime benefit from preventive interventions such as smoking cessation (see 4.5.1), lipid-lowering (see 4.6.2.1), and BP treatment (see 4.7.5.2). Lifetime risk and benefit estimation may be used in the clinical decision-making process together with consideration of co-morbidities, frailty, patient preferences for initiating (STEP 1) and intensifying (STEP 2) risk factor treatment (*Figure 1*).

3.2.3.1 *A step-wise approach to risk factor treatment and treatment intensification*

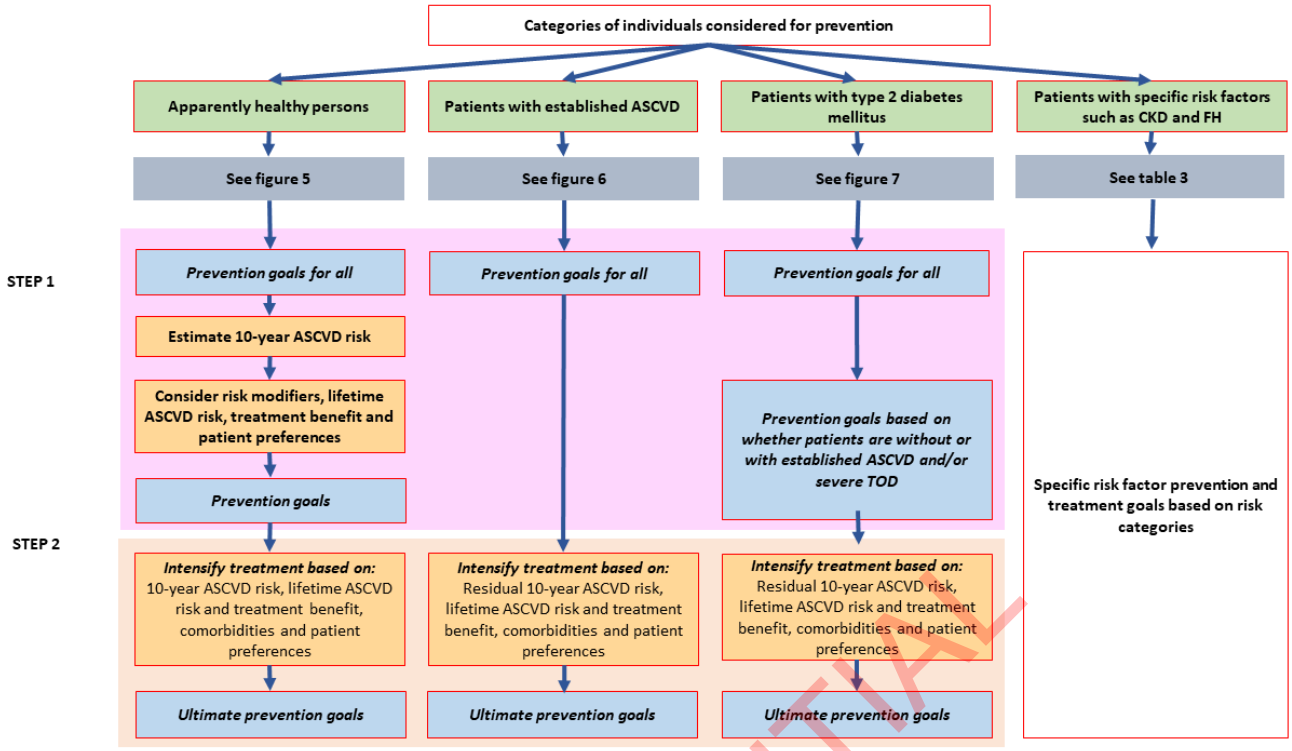
As explained before, targets and goals for LDL-C, blood pressure, and glycemic control in diabetes remain as recommended in recent ESC Guidelines.[5, 62, 63] These guidelines proposes a stepwise approach to treatment intensification as a tool to help physicians and patients pursue these targets in a way that fits patient profile and preferences. This principle (outlined in figure 1, using the example of a 2-step approach) is not conceptually novel, but rather reflects routine clinical practice, in which treatment strategies are initiated and then intensified, both as part of a shared decision making process involving both health care professionals and patients.

A stepwise approach starts with prevention goals for all, regardless of ASCVD risk. This is followed by ASCVD risk stratification and discussion of potential benefits of treatment with the patient. If treatment is initiated, its effect must be evaluated, and subsequent treatment intensification to reach ultimate risk factor goals must be considered in all patients taking into account additional benefit, co-morbidities, and frailty, all of which converge with patient preferences in a shared decision making process.

In the field of diabetes, studies have shown benefit of a stepwise approach to treatment intensification and do not support the contention of 'therapeutic nihilism' occurring in either physicians or patients. In fact it appears that attainment of treatment goals is similar, side effects are fewer, and patient satisfaction is significantly higher with a such an approach.[64, 65] We do, however, emphasize that stopping assessment of treatment goals and/or treatment routinely after the first step is inappropriate. The evidence-based ultimate targets of treatment intensification are optimal from the perspective of ASCVD risk reduction and are to be considered in all patients.

Figure 1 Examples of a stepwise approach to risk stratification and treatment options.

CKD = chronic kidney disease; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia.



3.2.3.2 Risk estimation in apparently healthy people with SCORE2 and SCORE2-OP

Apparently healthy people are those without established CVD, without DM2 and without severe co-morbidities. In the 2016 ESC Prevention Guidelines, the SCORE algorithm was used to estimate 10-year risk of CVD death. However, ASCVD morbidity (non-fatal myocardial infarction, non-fatal stroke) combined with ASCVD mortality better reflects the total burden of ASCVD. The updated SCORE algorithm – SCORE2 – used in these guidelines (see *Figure 2*), estimates an individual's 10-year risk of *fatal and non-fatal AS*CVD events (myocardial infarction, stroke) in apparently healthy people with risk factors that are untreated (or have been stable for several years).[66]

Several specific considerations apply to ASCVD risk estimation in older people. First, the gradient of the relationship between classical risk factors, such as lipids and BP, with ASCVD risk attenuates with age.[67] Second, ASCVD-free survival dissociates from overall survival progressively with increasing age, because risk for non-ASCVD mortality increases ("competing risk").[68] For these reasons, traditional risk models that do not take into account the competing risk of non-ASCVD mortality, tend to overestimate the actual 10-year risk of ASCVD, and hence overestimate the potential benefit of treatment.[69] The SCORE2-Older Person (SCORE2-OP) algorithm estimates 5-year and 10-year fatal and non-fatal ASCVD events (myocardial infarction, stroke) adjusted for competing risks in apparently healthy people aged >70 years.[70]

SCORE2 and SCORE2-OP are calibrated to four clusters of countries (low, moderate, high, and very high ASCVD risk) that are grouped based on national CV mortality rates published by the World Health Organization (*Supplementary Table 1* and *Figure 3*).[71] Low risk countries: France, Israel, Spain, Netherlands, Switzerland, Denmark, Norway, Luxembourg, Belgium, United Kingdom. Moderate risk countries: Iceland, Portugal, Sweden, Italy, San Marino, Ireland, Cyprus, Finland, Austria, Malta, Greece, Germany, Slovenia. High risk countries: Albania, Czech Republic, Turkey, Kazakhstan, Croatia, Poland, Estonia, Slovakia, Hungary, Bosnia and Herzegovina. Very high risk countries: Armenia,

Lithuania, Georgia, Latvia, Serbia, Romania, Montenegro, Russian Federation, TFYR Macedonia, Belarus, Azerbaijan, Bulgaria, Republic of Moldova, Ukraine, Kyrgyzstan, Uzbekistan, Egypt, Morocco, Syria, Tunisia, Lebanon, Algeria, Libya. A multiplier approach has been used for converting ASCVD mortality rates to fatal and non-fatal ASCVD events.[72] The SCORE2 algorithm can be accessed in the ESC CVD Risk app (freely available from app stores) and in risk charts for the four clusters of countries (*Figure 3*). The SCORE2 charts do not apply to persons with documented CVD or other high-risk conditions such as DM, FH, or other genetic or rare lipid or blood pressure disorders, chronic kidney disease (CKD) and in pregnant women.

To estimate a person's 10-year risk of total ASCVD events, one must first identify the correct cluster of countries and the accompanying risk table for their sex, smoking status, and (nearest) age. Within that table, one then finds the cell nearest to the person's BP and non-HDL cholesterol. Risk estimates then need to be adjusted upwards as the person approaches the next age category.

Figure 2 Systematic Coronary Risk Estimation 2 (SCORE2) and SCORE2-OP risk chart for fatal and non-fatal (MI, stroke) ASCVD.

ASCVD = atherosclerotic cardiovascular disease; SCORE = Systematic Coronary Risk Estimation.

For apparently healthy people 50-70 years the SCORE2 algorithm[66], is used to estimate 10-year risk of fatal and non- fatal (MI, stroke) ASCVD, and for apparently healthy people >70 years of age the SCORE2-Older Person (SCORE2-OP) is used.[70]

Low risk countries: France, Israel, Spain, Netherlands, Switzerland, Denmark, Norway, Luxembourg, Belgium, United Kingdom. **Moderate risk countries**: Iceland, Portugal, Sweden, Italy, San Marino, Ireland, Cyprus, Finland, Austria, Malta, Greece, Germany, Slovenia. **High risk countries**: Albania, Czech Republic, Turkey, Kazakhstan, Croatia, Poland, Estonia, Slovakia, Hungary, Bosnia and Herzegovina. **Very high risk countries**: Armenia, Lithuania, Georgia, Latvia, Serbia, Romania, Montenegro, Russian Federation, TFYR Macedonia, Belarus, Azerbaijan, Bulgaria, Republic of Moldova, Ukraine, Kyrgyzstan, Uzbekistan, Egypt, Morocco, Syria, Tunisia, Lebanon, Algeria, Libya.

SCORE2 & SCORE2-OP

10-year risk of (fatal and non-fatal) CV events in populations at *low* CVD risk

	<50 years	50-70 years	>70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

Women									Men								
Non-smoking				Smoking				Age	Non-smoking				Smoking				
160-179	28	29	30	31	31	32	33	34	85 - 89	29	35	42	49	29	35	42	49
140-159	26	27	28	29	29	30	31	32		28	33	40	47	27	33	40	47
120-139	24	25	26	27	27	28	29	30		26	32	38	45	26	32	38	45
100-119	23	24	25	26	25	26	27	28		25	30	36	43	25	30	36	43
160-179	20	21	22	23	25	26	28	29	80 - 84	23	27	32	37	26	31	36	41
140-159	18	19	20	21	23	24	25	26		21	25	29	34	24	28	33	38
120-139	16	17	18	19	20	21	22	23		19	22	26	31	22	25	30	34
100-119	15	15	16	17	18	19	20	21		17	20	24	28	19	23	27	31
160-179	15	15	16	17	21	22	23	24	75 - 79	19	21	24	27	24	27	31	34
140-159	13	13	14	15	18	19	20	21		16	18	21	23	21	23	26	30
120-139	11	11	12	13	15	16	17	18		14	15	18	20	18	20	23	26
100-119	9	10	10	11	13	14	15	15		12	13	15	17	15	17	19	22
160-179	10	11	12	12	17	18	19	20	70 - 74	15	16	18	19	22	24	26	28
140-159	9	9	10	10	14	15	16	16		12	13	14	16	18	19	21	23
120-139	7	7	8	8	11	12	13	14		10	11	12	13	14	16	17	19
100-119	6	6	6	7	9	10	10	11		8	8	9	10	12	13	14	15
160-179	8	8	9	9	12	12	13	13	65 - 69	11	12	12	13	15	16	17	19
140-159	7	7	7	7	10	10	11	11		9	10	11	11	13	14	15	16
120-139	5	6	6	6	8	9	9	9		8	8	9	10	11	12	13	13
100-119	5	5	5	5	7	7	7	8		6	7	7	8	9	10	11	11
160-179	6	6	7	7	10	10	11	11	60 - 64	8	9	10	11	13	14	15	17
140-159	5	5	5	6	8	8	9	9		7	8	8	9	10	11	13	14
120-139	4	4	4	5	6	7	7	8		6	6	7	8	9	10	10	11
100-119	3	3	4	4	5	6	6	6		5	5	6	6	7	8	9	10
160-179	4	5	5	5	8	8	9	10	55 - 59	7	7	8	9	10	12	13	15
140-159	3	4	4	4	6	7	7	8		5	6	7	8	9	10	11	12
120-139	3	3	3	3	5	5	6	6		4	5	5	6	7	8	9	10
100-119	2	2	3	3	4	4	5	5		4	4	4	5	6	6	7	8
160-179	3	4	4	4	6	7	7	8	50 - 54	5	6	7	8	9	10	11	13
140-159	3	3	3	3	5	5	6	6		4	5	5	6	7	8	9	10
120-139	2	2	2	3	4	4	5	5		3	4	4	5	6	6	7	8
100-119	2	2	2	2	3	3	4	4		3	3	3	4	4	5	6	7
160-179	2	3	3	3	5	5	6	7	45 - 49	4	5	6	6	7	8	10	11
140-159	2	2	2	3	4	4	5	5		3	4	4	5	6	7	8	9
120-139	1	2	2	2	3	3	4	4		2	3	3	4	4	5	6	7
100-119	1	1	1	1	2	2	3	3		2	2	3	3	3	4	5	5
160-179	2	2	2	3	4	4	5	6	40 - 44	3	4	5	5	6	7	8	10
140-159	1	2	2	2	3	3	4	4		2	3	3	4	5	5	6	8
120-139	1	1	1	1	2	3	3	3		2	2	3	3	3	4	5	6
100-119	1	1	1	1	2	2	2	2		1	2	2	2	3	3	4	5
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

SCORE2 & SCORE2-OP

10-year risk of (fatal and non-fatal) CV events in populations at *moderate* CVD risk

	<50 years	50-70 years	>70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

	Women								Age	Men							
	Non-smoking				Smoking					Non-smoking				Smoking			
160-179	37	39	40	42	41	43	44	46		37	45	53	62	37	45	53	61
140-159	35	36	38	39	39	40	42	43		36	43	51	59	35	43	51	59
120-139	32	34	35	37	36	38	39	41	85 - 89	34	41	49	57	34	41	48	57
100-119	30	32	33	34	34	35	37	38		32	39	47	55	32	39	46	55
160-179	27	28	30	31	34	35	37	39		30	35	41	47	34	40	46	53
140-159	24	25	27	28	30	32	33	35		27	32	37	43	31	36	42	48
120-139	21	22	24	25	27	28	30	31	80 - 84	25	29	34	40	28	33	38	44
100-119	19	20	21	22	24	25	27	28		22	26	31	36	25	30	35	40
160-179	19	20	21	23	27	29	30	32		24	27	31	35	31	35	39	44
140-159	16	17	18	19	24	25	26	28		21	23	27	30	27	30	34	38
120-139	14	15	15	16	20	21	22	24	75 - 79	17	20	23	26	23	26	29	33
100-119	12	12	13	14	17	18	19	20		15	17	19	22	19	22	25	29
160-179	13	14	15	16	22	23	25	26		19	21	23	25	28	31	34	36
140-159	11	11	12	13	18	19	20	22		15	17	18	20	23	25	28	30
120-139	9	9	10	11	15	16	17	18	70 - 74	12	13	15	16	19	20	22	24
100-119	7	7	8	8	12	13	13	14		10	11	12	13	15	16	18	20
160-179	10	10	11	12	15	16	17	18		14	15	17	18	20	22	23	25
140-159	8	9	9	9	13	13	14	15		12	13	14	15	17	18	20	21
120-139	7	7	7	8	10	11	12	12	65 - 69	10	11	12	13	14	15	17	18
100-119	5	6	6	6	9	9	9	10		8	9	10	10	12	13	14	15
160-179	7	8	8	9	12	13	14	15		11	12	13	15	17	18	20	22
140-159	6	6	7	7	10	11	11	12		9	10	11	12	14	15	17	18
120-139	5	5	5	6	8	8	9	10	60 - 64	7	8	9	10	11	13	14	15
100-119	4	4	4	5	6	7	7	8		6	7	7	8	9	10	11	12
160-179	5	6	6	7	10	11	11	12		9	10	11	12	14	16	17	20
140-159	4	4	5	5	8	8	9	10		7	8	9	10	11	13	14	16
120-139	3	3	4	4	6	7	7	8	55 - 54	5	6	7	8	9	10	11	13
100-119	3	3	3	3	5	5	6	6		4	5	6	6	7	8	9	10
160-179	4	4	5	5	8	8	9	10		7	8	9	10	11	13	15	17
140-159	3	3	4	4	6	6	7	8		5	6	7	8	9	10	12	14
120-139	2	2	3	3	5	5	6	6	50 - 54	4	5	5	6	7	8	9	11
100-119	2	2	2	2	3	4	4	5		3	4	4	5	5	6	7	8
160-179	3	3	3	4	6	7	8	9		5	6	7	8	9	11	13	15
140-159	2	2	3	3	5	5	6	6		4	5	5	6	7	8	10	12
120-139	2	2	2	2	3	4	4	5	45 - 49	3	4	4	5	5	7	8	9
100-119	1	1	1	2	3	3	3	4		2	3	3	4	4	5	6	7
160-179	2	2	3	3	5	5	6	7		4	5	6	7	8	9	11	13
140-159	1	2	2	2	3	4	5	5		3	4	4	5	6	7	8	10
120-139	1	1	1	2	3	3	3	4	40 - 44	2	3	3	4	4	5	6	8
100-119	1	1	1	1	2	2	2	3		2	2	2	3	3	4	5	6
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

SCORE2 & SCORE2-OP

10-year risk of (fatal and non-fatal) CV events in populations at *high* CVD risk

	<50 years	50-70 years	>70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

Women									Age	Men							
Non-smoking				Smoking						Non-smoking				Smoking			
160-179	53	55	57	58	58	59	61	63		42	49	57	65	41	49	56	65
140-159	50	52	54	55	55	56	58	60		40	47	55	63	40	47	54	62
120-139	47	49	51	52	52	53	55	57	85 - 89	38	45	53	61	38	45	52	60
100-119	44	46	48	50	49	51	52	54		36	43	51	58	36	43	50	58
160-179	40	42	44	45	49	51	53	55		34	40	45	51	38	44	50	56
140-159	36	38	39	41	44	46	48	50		31	36	42	47	35	40	46	52
120-139	32	34	36	37	40	42	44	46	80 - 84	29	33	38	44	32	37	42	48
100-119	29	31	32	34	36	38	40	41		26	30	35	40	29	34	39	44
160-179	29	31	32	34	41	43	45	47		28	32	35	39	35	39	44	48
140-159	25	27	28	29	35	37	39	41		24	27	31	34	31	34	38	43
120-139	22	23	24	25	31	32	34	36	75 - 79	21	24	27	30	27	30	34	37
100-119	18	19	20	22	26	28	29	31		18	20	23	26	23	26	29	33
160-179	21	22	24	25	33	35	37	39		23	25	27	29	33	35	38	41
140-159	17	18	19	20	28	29	31	33		19	20	22	24	27	29	32	34
120-139	14	15	16	17	23	24	26	27	70 - 74	15	17	18	20	22	24	26	28
100-119	11	12	13	14	19	20	21	22		12	14	15	16	18	20	22	23
160-179	15	16	17	18	26	27	29	30		17	18	20	22	25	28	30	32
140-159	12	13	14	14	21	22	23	24		14	15	16	18	21	23	25	27
120-139	10	10	11	11	16	17	18	19	65 - 69	11	12	13	15	17	19	20	22
100-119	8	8	8	9	13	14	14	15		9	10	11	12	14	15	17	18
160-179	11	11	12	13	20	21	23	25		13	14	16	18	20	23	25	28
140-159	8	9	9	10	15	16	18	19		10	11	13	14	16	18	20	23
120-139	6	7	7	8	12	13	14	15	60 - 64	8	9	10	11	13	15	16	18
100-119	5	5	6	6	9	10	11	11		6	7	8	9	10	12	13	15
160-179	7	8	9	10	15	16	18	20		9	11	12	14	16	19	21	24
140-159	5	6	7	7	11	12	14	15		7	8	10	11	13	15	17	19
120-139	4	4	5	5	8	9	10	11	55 - 59	6	6	7	9	10	11	13	15
100-119	3	3	4	4	6	7	8	8		4	5	6	7	8	9	10	12
160-179	5	5	6	7	11	13	14	16		7	8	10	11	13	15	18	21
140-159	3	4	4	5	8	9	10	12		5	6	7	9	10	12	14	16
120-139	3	3	3	4	6	7	8	9	50 - 54	4	5	5	6	7	9	10	12
100-119	2	2	2	3	4	5	6	6		3	3	4	5	6	7	8	9
160-179	3	4	4	5	8	10	11	13		5	6	8	9	10	13	15	18
140-159	2	3	3	4	6	7	8	9		4	5	6	7	8	9	11	14
120-139	2	2	2	2	4	5	6	6	45 - 49	3	3	4	5	6	7	8	10
100-119	1	1	2	2	3	3	4	5		2	2	3	4	4	5	6	7
160-179	2	3	3	4	6	7	9	10		4	5	6	7	8	10	13	16
140-159	1	2	2	2	4	5	6	7		3	3	4	5	6	7	9	11
120-139	1	1	1	2	3	4	4	5	40 - 44	2	2	3	4	4	5	7	8
100-119	1	1	1	1	2	2	3	3		1	2	2	3	3	4	5	6
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

SCORE2 & SCORE2-OP

10-year risk of (fatal and non-fatal) CV events in populations at *very high* CVD risk

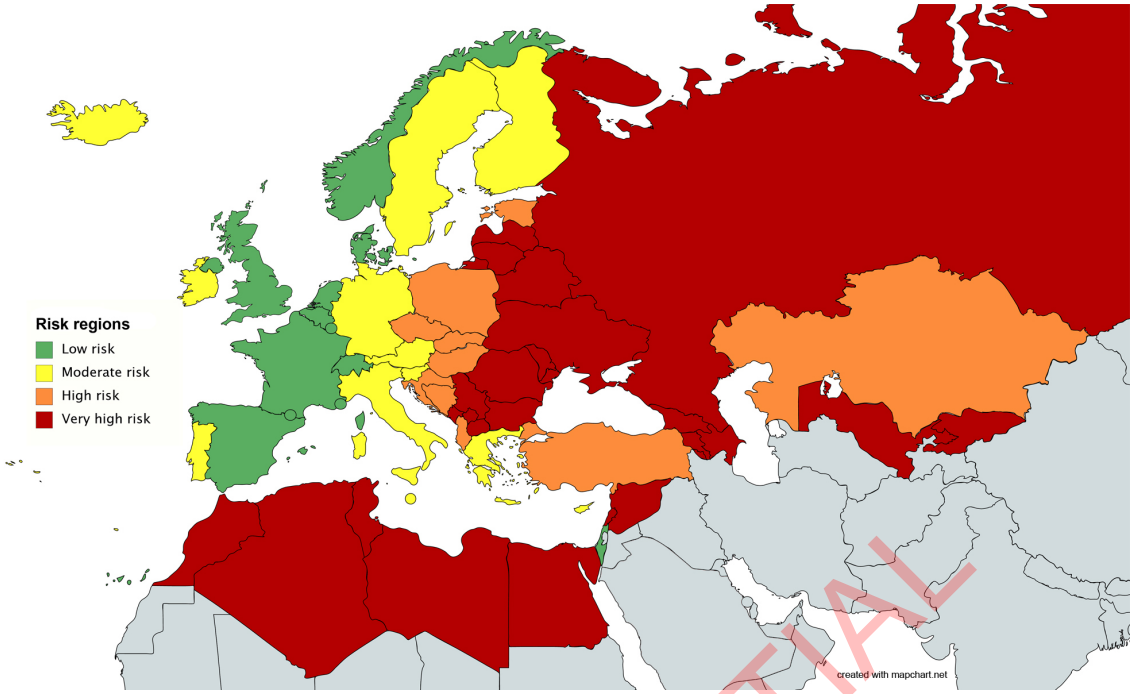
	<50 years	50-70 years	>70 years
	<2.5%	<5%	<7.5%
	2.5 to <7.5%	5 to <10%	7.5 to <15%
	≥7.5%	≥10%	≥15%

	Women								Age	Men							
	Non-smoking				Smoking					Non-smoking				Smoking			
160-179	62	63	64	65	65	66	67	68	85 - 89	49	54	59	64	49	54	59	64
140-159	60	61	62	63	63	64	65	66		48	53	58	63	48	53	58	63
120-139	58	59	60	61	61	62	63	65		47	52	56	61	47	52	56	61
100-119	56	57	58	60	59	60	61	63		46	50	55	60	46	50	55	60
160-179	53	54	55	57	59	60	62	63	80 - 84	44	48	52	56	47	51	55	59
140-159	50	51	52	54	56	57	59	60		42	46	49	53	45	49	52	56
120-139	47	48	49	51	53	54	56	57		40	43	47	51	43	46	50	54
100-119	44	45	47	48	50	51	53	54		38	41	45	48	40	44	48	51
160-179	44	46	47	48	53	55	56	58	75 - 79	40	42	45	48	45	48	51	54
140-159	41	42	43	45	49	51	52	53		37	39	42	44	42	44	47	50
120-139	37	39	40	41	46	47	48	49		34	36	39	41	39	41	44	47
100-119	34	35	36	37	42	43	44	46		31	33	36	38	36	38	41	43
160-179	37	38	39	41	48	49	51	52	70 - 74	35	37	39	40	43	45	47	49
140-159	33	34	35	36	43	44	46	47		32	33	35	36	39	41	42	44
120-139	29	30	31	32	39	40	41	43		28	30	31	33	35	36	38	40
100-119	26	27	28	29	34	36	37	38		25	26	28	29	31	33	34	36
160-179	27	28	30	31	41	42	44	46	65 - 69	26	28	30	32	36	39	42	44
140-159	22	23	24	26	34	36	37	39		22	24	26	27	31	33	36	38
120-139	18	19	20	21	28	30	31	33		18	20	21	23	26	28	30	33
100-119	15	16	16	17	23	24	26	27		15	17	18	19	22	24	26	28
160-179	20	21	22	24	33	35	37	39	60 - 64	20	23	25	27	31	33	36	40
140-159	16	17	18	19	27	29	30	32		17	19	20	22	25	28	31	33
120-139	12	13	14	15	22	23	25	26		14	15	17	18	21	23	25	28
100-119	10	11	11	12	17	18	20	21		11	12	14	15	17	19	21	23
160-179	14	15	17	18	26	28	31	33	55 - 54	16	18	20	23	25	28	32	35
140-159	11	12	13	14	21	23	24	26		13	14	16	18	21	23	26	29
120-139	8	9	10	11	16	18	19	21		10	11	13	15	17	19	21	24
100-119	7	7	8	9	13	14	15	16		8	9	10	12	13	15	17	19
160-179	10	11	12	14	21	23	25	28	50 - 54	12	14	16	19	21	24	28	31
140-159	8	9	9	11	16	18	19	22		10	11	13	15	17	19	22	25
120-139	6	6	7	8	12	13	15	17		7	9	10	12	13	15	17	20
100-119	4	5	5	6	9	10	11	13		6	7	8	9	10	12	14	16
160-179	7	8	9	10	16	18	21	23	45 - 49	9	11	13	16	17	20	24	28
140-159	5	6	7	8	12	14	15	17		7	8	10	12	13	16	18	22
120-139	4	4	5	6	9	10	12	13		5	6	8	9	10	12	14	17
100-119	3	3	4	4	7	8	9	10		4	5	6	7	8	9	11	13
160-179	5	6	7	8	13	15	17	19	40 - 44	7	9	11	13	14	17	20	24
140-159	4	4	5	6	9	11	12	14		5	6	8	10	11	13	16	19
120-139	3	3	3	4	7	8	9	10		4	5	6	7	8	10	12	14
100-119	2	2	2	3	5	6	6	7		3	4	4	5	6	7	9	11
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

Figure 3 Risk regions based on World Health Organization cardiovascular mortality rates.



3.2.3.3 Translating ASCVD risk to treatment thresholds

While no risk threshold is universally applicable, the intensity of treatment should increase with increasing ASCVD risk. In individual cases, however, no lower threshold of total CV risk precludes treatment of risk factors. Conversely, no high threshold for total ASCVD risk implies "mandatory" treatment. Across the entire range of ASCVD risk, the decision to initiate interventions remains a matter of individual consideration and shared decision-making (see also *section 4.1*). In general, risk factor treatment recommendations are based on categories of ASCVD risk ('low-to-moderate', 'high', and 'very high'). The cut-off risk levels for these categories are numerically different for various age groups to avoid undertreatment in the young and to avoid overtreatment in older persons. Because age is a major driver of ASCVD risk but lifelong risk factor treatment benefit is higher in younger people, the risk thresholds for considering treatment are lower for younger people (**Table 2**).

Risk categories do not 'automatically' translate into recommendations for starting drug treatment. In all age groups consideration of risk modifiers, lifetime ASCVD risk and treatment benefit, co-morbidities, frailty and patient preferences may further guide treatment decisions.

Also, note that many patients can move themselves towards a lower risk category without taking drugs just by stopping smoking. Finally, note that persons >70 years old may be at very high risk whilst being at target SBP, and primary prevention with lipid lowering drugs in older persons is a class IIb ('may consider') recommendation; see section 4.6.

In the 50-70 year age range, a 10-year ASCVD mortality risk threshold of 5% estimated with the previously used SCORE algorithm corresponds on average to a 10-year fatal and non-fatal ASCVD risk threshold of 10% estimated with SCORE2, as approximately the same number of people are above the risk threshold and would qualify for treatment.[66]

As the 10-year ASCVD risk thresholds guide treatment decisions and have an impact on healthcare costs and resources, countries or regions may decide on using higher or lower treatment thresholds.

Table 2. ASCVD risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

	<50 years	50-70 year	>70 years
Low-to-moderate ASCVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High ASCVD risk: risk factor treatment should be considered	2.5 - <7.5%	5 - < 10%	7.5 - <15%
Very high ASCVD risk: risk factor treatment generally recommended *	≥7.5%	≥10%	≥15%

* In apparently healthy patients >70 years old, the treatment recommendation for lipid lowering drugs is class IIb; 'may be considered'

The division of the population in 3 distinct age groups (<50, 50-70, and >70 years) results in a discontinuous increase in risk thresholds for low-to-moderate, high, and very high risk. In reality, age is obviously continuous, and a sensible application of the thresholds in clinical practice would require some flexibility in handling these risk thresholds as patients move towards the next age group, or recently passed the age cutoff. Figure 4 illustrates how a continuous increase in age relates to increasing risk thresholds, and may be used as a guide for daily practice.

Figure 4 Schematic representation of increasing 10-year ASCVD risk thresholds across age groups.

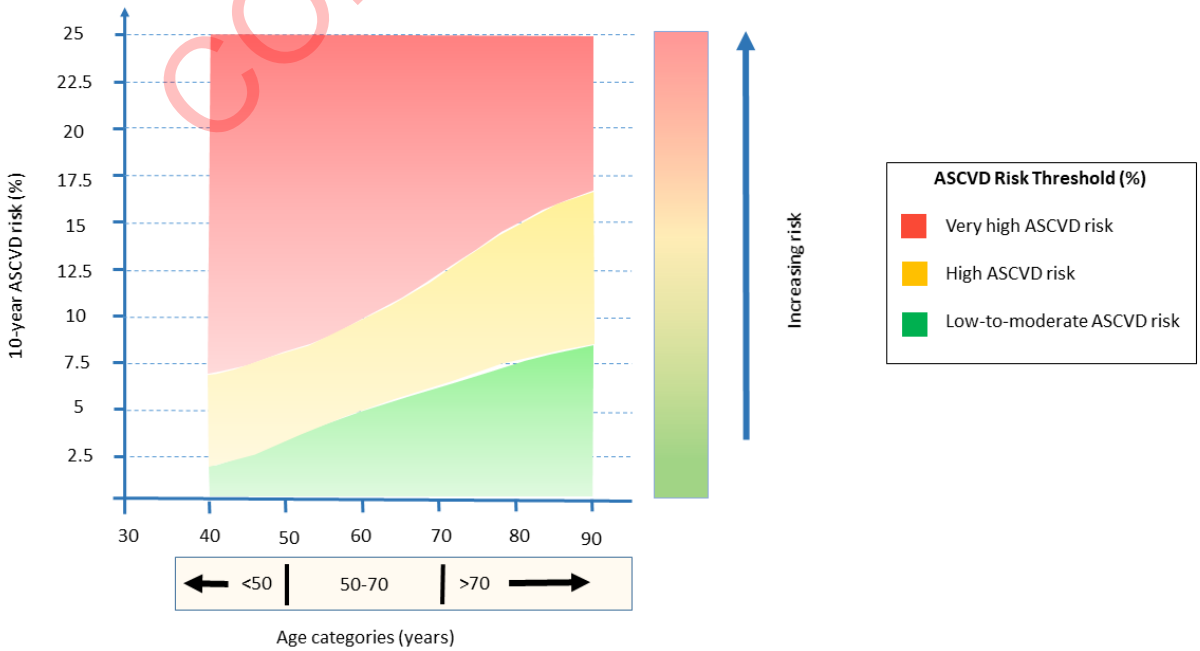


Figure 5 Flow chart of cardiovascular risk and risk factor treatment in apparently healthy persons.

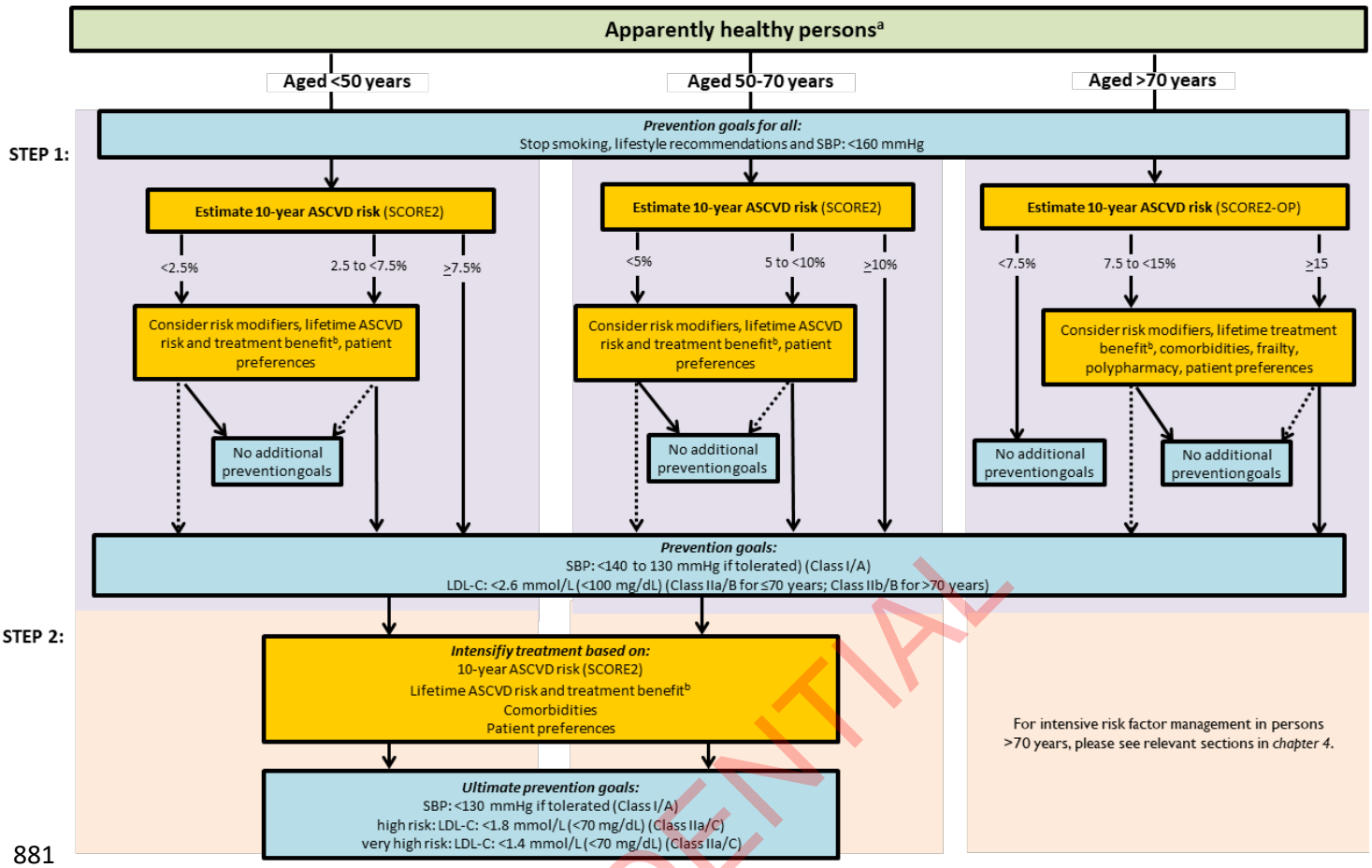
CKD = chronic kidney disease; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia; LDL-C =low-density lipoprotein cholesterol; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; SBP = systolic blood pressure; SCORE2 = Systematic Coronary Risk Estimation 2: SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons.

Solid lines represent default options for the majority of people. Dotted lines represent alternative choices for some, depending on the patient-specific characteristics and conditions indicated in the boxes.

Ultimate treatment goals for blood pressure (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued be as indicated. The stepwise approach has to be applied as a whole: after step 1, considering proceeding to the intensified goals of step 2 is mandatory. Risk Scores are available in the ESC CVD Risk Calculator app for mobile devices (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app) and at websites such as www.u-prevent.com.

[a] Does not include patients with CVD, DM, CKD, or FH.

[b] The LIFE-CVD model for estimating lifetime ASCVD risk and treatment benefit is calibrated for low- and moderate risk regions



3.2.3.4 Risk estimation and risk factor treatment in apparently healthy people 50-70 years of age

Stop smoking, lifestyle recommendations and a SBP <160 mmHg are recommended for all (figure 5). A 10-year ASCVD risk (fatal and non-fatal ASCVD events) ≥10% is generally considered "very high risk", and treatment of ASCVD risk factors is recommended. A 10-year ASCVD risk of 5 to <10% is considered "high risk", and treatment of risk factors should be considered taking ASCVD risk modifiers, lifetime risk and treatment benefit (in low and moderate risk regions, Box 1) and patient preferences into account. A 10-year ASCVD risk <5% is considered "low-to-moderate risk", and would generally not qualify for risk factor treatment unless one or several risk modifiers (Chapter 3.3) increase risk, or the estimated lifetime risk and treatment benefit is considered substantial.

3.2.3.5 Risk estimation and risk factor treatment estimation in apparently healthy people >70 years of age

Stop smoking, lifestyle recommendations and a SBP <160 mmHg are recommended for all (figure 5). Age is the dominant driver of ASCVD risk, and estimated 10-year ASCVD risk of almost all individuals >70 years exceeds conventional risk thresholds. Also, lifetime benefit of treatment in terms of time gained free of ASCVD is lower in older people. Therefore, the ASCVD risk thresholds for risk factor treatment are higher

in apparently healthy people >70 years. A 10-year ASCVD risk ≥15% is generally considered "very high risk", and treatment of ASCVD risk factors is recommended (note: the recommendation for lipid lowering treatment in apparently healthy people >70 years is class IIb; 'may be considered'; see section 4.6). A 10-year ASCVD risk of 7.5 to <15% is considered "high risk", and treatment of risk factors should be considered taking ASCVD risk modifiers, frailty, lifetime treatment benefit (in low and moderate risk regions, Box 1), co-morbidities, polypharmacy and patient preferences into account. Given the subjective nature of many of these factors, it is not possible to define strict criteria for these considerations. A 10-year ASCVD risk <7.5% is considered "low-to-moderate risk", and would generally not qualify for risk factor treatment unless one or several risk modifiers (Chapter 3.3) increase risk or the estimated lifetime risk and treatment benefit is considered substantial.)[73-77]

3.2.3.6 Risk estimation and risk factor treatment in apparently healthy people <50 years of age

Stop smoking, lifestyle recommendations and a SBP <160 mmHg are recommended for all (figure 5). The 10-year ASCVD risk in relatively young, apparently healthy people is on average low, even in the presence of high risk factor levels, but the lifetime ASCVD risk is in these circumstances very high. In apparently healthy people <50 years of age a 10-year ASCVD risk ≥7.5% is generally considered "very high risk" as this risk relates to a high lifetime risk, and treatment of ASCVD risk factors is recommended. A 10-year ASCVD risk of 2.5 to <7.5% is considered "high risk", and treatment of risk factors should be considered taking ASCVD risk modifiers, lifetime risk and treatment benefit (in low and moderate risk regions) and patient preferences into account. A 10-year ASCVD risk <2.5% is considered "low-to-moderate risk", and would generally not qualify for risk factor treatment unless one or several risk modifiers (Chapter 3.3) increase risk or the estimated lifetime risk and treatment benefit is considered substantial (see *Box 1*) (*Figure 5*).[73-76]

In risk communication with younger people, the lifetime benefit perspective may be useful, as well as discussing the potential of avoiding a devastating ASCVD event in the short to intermediate term, despite the fact that 10-year ASCVD risk may be very low.

ASCVD risk predictions as well as predictions of lifetime benefit of risk factor treatment are likely to be imprecise at very young age (<40 years). At that age lipid-lowering and blood pressure-lowering drug treatment are usually not considered, except for patients with Familial Hypercholesterolemia or specific blood pressure disorders. A healthy lifestyle that is maintained throughout life is more relevant for the very young. Mendelian randomization studies illustrate very nicely that relatively small differences in LDL-C or SBP maintained throughout life have large implications on cardiovascular risk over a lifespan.[78]

3.2.3.7 Risk estimation and risk factor treatment in patients with established ASCVD

Patients with clinically established ASCVD are, on average, at very high risk of recurrent ASCVD events if risk factors are not treated. Therefore, smoking cessation, adoption of a healthy lifestyle, and risk factor treatment is recommended in all patients (STEP 1). Further intensification of risk factor treatment by aiming at lower treatment goals (STEP 2) is beneficial in most patients and must be considered taking 10-year ASCVD risk, comorbidities, lifetime risk and treatment benefit (Box 1), frailty and patient preferences into account in a shared-decision making process (Figure 6).

After initial risk factor treatment and achieving risk factor treatment goals, the individual *residual* risk for recurrent ASCVD varies widely and should be considered.[79] It is evident that patients with a recent acute coronary syndrome (ACS) or progressive vascular disease, and patients with DM and vascular disease, are all at exceptionally high risk for recurrent ASCVD events. For other patients with established ASCVD the residual risk may be less evident and could be estimated based on clinical criteria such as age, (change in) risk factor levels, and risk modifiers, or by calculation of residual ASCVD risk with a calculator.

The risk of recurrent ASCVD is influenced mainly by classical risk factors, vascular disease site, and kidney function. Online available risk stratification tools for secondary prevention include the SMART risk score (available in the ESC CVD Risk app) for estimating 10-year residual ASCVD risk in patients with stable ASCVD, defined as coronary artery disease (CAD), PAD, or cerebrovascular disease,[79] and the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2°P), which estimates the 3-year risk of ASCVD in patients with a previous myocardial infarction.[80]

Occasionally, recurrent ASCVD risk is very high despite maximum (tolerated) conventional treatments. In such cases, novel but less-well established preventive treatments such as dual antithrombotic pathway inhibition,[81] eicosapentaenoic acid (EPA),[82] or anti-inflammatory therapy with colchicine (see chapter 4.10)[83, 84] may be considered.

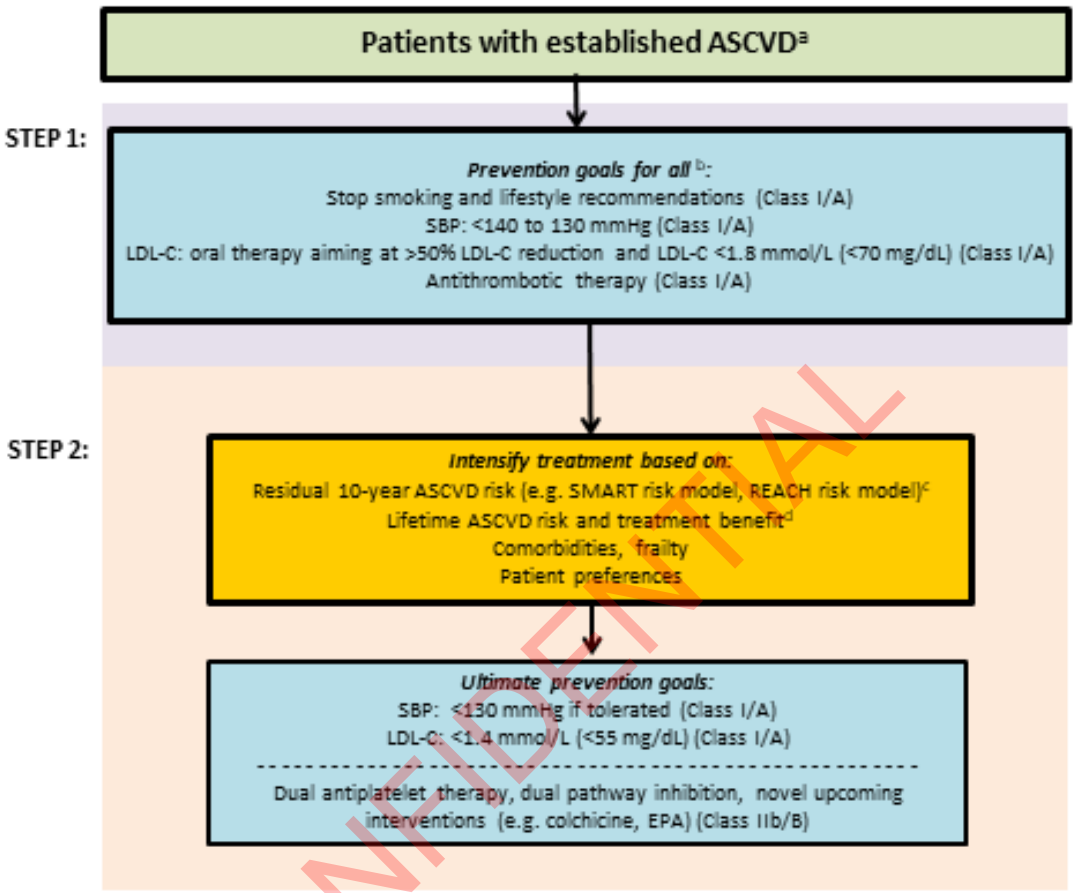
Figure 6 Flow chart of cardiovascular risk and risk factor treatment in patients with established cardiovascular disease.

Ultimate treatment goals for blood pressure (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued as indicated. The stepwise approach has to be applied as a whole: after step 1, considering proceeding to the intensified goals of step 2 is mandatory. ACS = acute coronary syndrome; CR = cardiac rehabilitation; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; EPA = icosapent ethyl; LDL-C =low-density lipoprotein cholesterol; REACH = Reduction of Atherothrombosis for Continued Health; SBP = systolic blood pressure; SMART = Secondary Manifestations of Arterial Disease.
Risk Scores are available in the ESC CVD Risk Calculator app for mobile devices (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app) and at websites such as www.u-prevent.com.

[a] For patients with DM see DM flow chart.
[b] For patients with recent ACS, these prevention goals are part of participation in cardiac rehabilitation (class I/A).

[c] For patients aged >70 years, a high 10-year risk may be associated with a lower absolute lifetime benefit from treatment due to limited life expectancy.

[d] Lifetime treatment benefit is expressed as extra CVD-free life gained from a certain intervention or treatment intensification.



3.2.3.8 Risk estimation and risk factor treatment in persons with type 2 diabetes mellitus

Most adults with type 2 diabetes are at high or very high risk for future ASCVD, particularly from middle age onwards. On average, type 2 DM doubles CVD risk and reduces life expectancy by 4–6 years, with absolute risks highest in those with any end-organ damage. Type 2 DM also increases the risk for cardiorenal outcomes, in particular heart failure and CKD. Relative risks for ASCVD in type 2 DM are higher at younger ages of onset and are modestly higher in women compared with men.[85] Smoking cessation and adoption of a healthy lifestyle are recommended for all people with type 2 DM, and risk factor treatment should be considered in all people with diabetes, at least those above the age of 40 years (see *sections 4.6* and *4.7*). Still, there is a wide range in individual risk for CVD events, especially after initial risk factor management.[86]

Persons with diabetes with severe target organ damage (TOD; for definition: see table 3) can be considered to be at very high ASCVD risk, similar to people with established CVD (see table 3). Most others with diabetes are considered to be at high ASCVD risk.[87] However, an exception can be made for

patients with well-controlled short-standing diabetes (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors, who may be considered being at moderate ASCVD risk.

In addition to the semi-quantitative division in 3 risk categories described above, diabetes-specific risk models may refine risk estimates and illustrate the impact of treatments. These models generally include duration of diabetes, glycated haemoglobin A1c (HbA1c) level, and presence of target organ damage. Examples are the ADVANCE risk score, which predicts 10-year ASCVD risk, and the UKPDS risk engine, which predicts fatal and non-fatal CVD risk and is available for use in the United Kingdom. However, we recommend cautious use of these calculators, since both are based on older cohort data[88, 89] (*Figure 7*).

Intensification of risk factor treatment in STEP 2 must be considered in all patients taking into account 10-year ASCVD risk, comorbidities, lifetime risk and treatment benefit (Box 1), frailty and patient preferences in a shared decision making process. [73]

3.2.3.9 Risk estimation and risk factor treatment in persons with type 1 diabetes mellitus

People with type 1 DM are at increased ASCVD risk, and early manifestation of type 1 diabetes relates to more life years lost in women than men mostly due to cardiovascular disease.[90] Relative risks of ASCVD are, on average, higher in type 1 versus type 2 DM, due to an average of three to four extra decades of hyperglycaemia and usual risk factors contribute strongly to CVD outcomes in type 1 DM.[91] CVD risks have declined over time, commensurate with improvements in life expectancy.[92] Lifetime ASCVD risks in type 1 DM are higher with poorer glycaemic control, lower social class, and younger age of onset. The absolute risk of ASCVD events or mortality is highest among those with any evidence of microvascular disease, particularly renal complications, and is strongly influenced by age. ASCVD risk stratification in persons with type 1 DM may be based on the same risk classification as for type 2 DM, summarized in table 3, although the level of evidence for type 1 is less strong.

Box 1 Lifetime ASCVD risk and treatment benefit estimation

Prevention of ASCVD by treating risk factors is usually done with a lifetime perspective. Lifetime ASCVD risk can be approximated by clinical experience with clinical criteria such as age, (change in) risk factor levels, risk modifiers, etc. or estimated in apparently healthy people, patients with established CVD and persons with type 2 DM with specific lifetime ASCVD risk scores.[73-75] Lifetime benefit from risk factor management can be estimated by combining lifetime risk models with HRs derived from RCTs, meta-analyses of RCTs, or mendelian randomization studies, which may provide estimates of the effects of longer-term treatment of risk factors. Online calculators (such as the ESC CVD Risk app) can be used to estimate the average lifetime benefit of smoking cessation (see also figure 10), lipid lowering (see also figure 11), and BP lowering (see also figure 14) on an individual patient level expressed as extra ASCVD-free life-years.[76] Average lifetime benefit is easy to interpret and may improve the communication of potential therapy benefits to patients in a shared decision-making process. This may in turn increase patient engagement, self-efficacy, and motivation to adhere to lifestyle changes and drug treatment.

The lifetime risk is an estimate of the age at which there is a 50% probability that a person will either have experienced an ASCVD event or have died. Lifetime benefit is the numerical difference between the predicted age at which there is a 50% probability that a person will either have experienced an

ASCVD event or have died with and without a proposed treatment. Currently there are no formal treatment thresholds for average lifetime benefit. In addition, the estimated individual lifetime benefit should be viewed in the light of the estimated duration of treatment. Duration of lifelong treatment will generally be longer in young persons compared to older people. Both treatment effect and treatment duration determine the individual 'return on investment' of risk factor treatment. In a shared decision-making process between healthcare provider and patient, the minimum desired benefit of a certain treatment needs to be established, a process in which patient preference, expected treatment harms and costs can be taken into account.

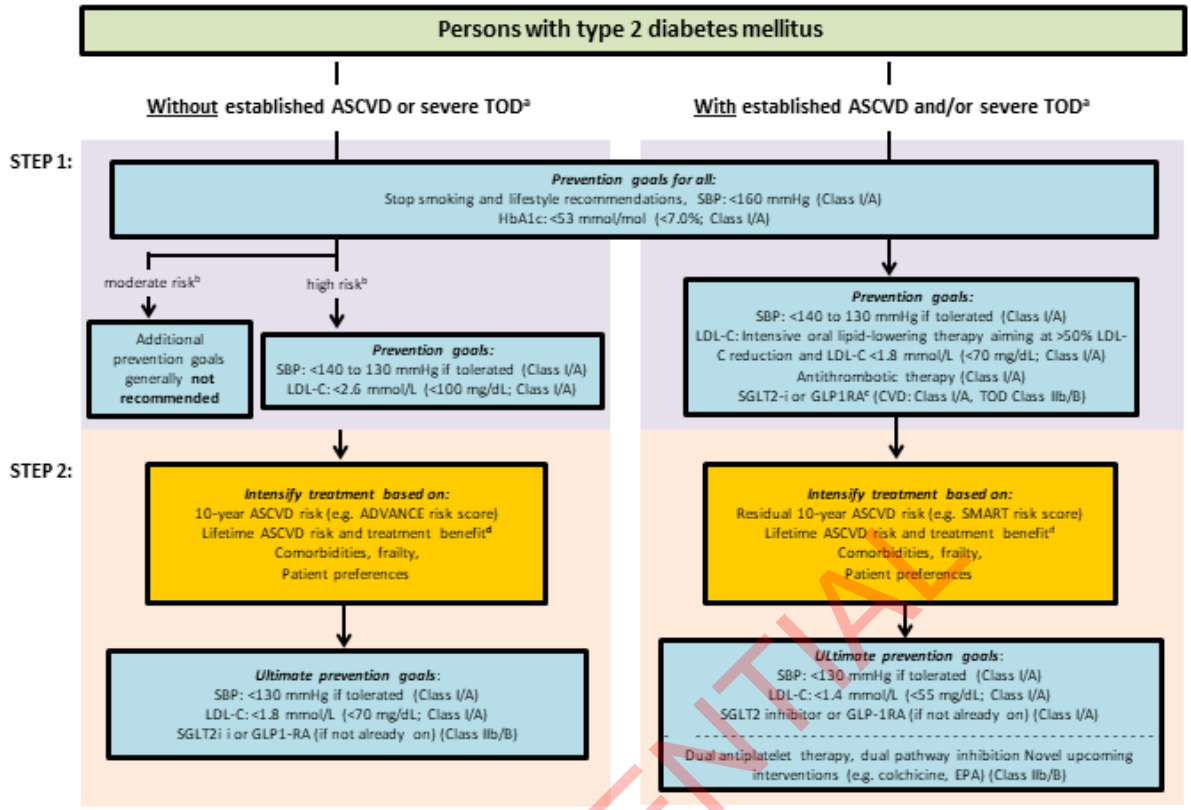
ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; ESC = European Society of Cardiology; HR = hazard ratio; RCT = randomized controlled trial.

Figure 7 Flow chart of cardiovascular risk and risk factor treatment in patients with type 2 diabetes mellitus.

Ultimate treatment goals for blood pressure (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines are to be pursued as indicated. The stepwise approach has to be applied as a whole: after step 1, considering proceeding to the intensified goals of step 2 is mandatory.

ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; CKD = chronic kidney disease; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DAPT = dual antiplatelet therapy; DIAL = Diabetes Lifetime-perspective prediction; DM = diabetes mellitus; EPA = icosapent ethyl; GLP-1RA = glucagon like peptide-1 receptor agonists; HbA1c = glycated haemoglobin; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; SMART = Secondary Manifestations of Arterial Disease; TOD = target organ damage (retinopathy, nephropathy, neuropathy).
Risk Scores are available in the ESC CVD Risk Calculator app for mobile devices (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app) and at websites such as www.u-prevent.com.
[a] Severe TOD is defined as 1 of these: eGFR <45 irrespective of presence or absence of albuminuria; eGFR 46-59 and microalbuminuria (ACR 30 -300 mg/g or 3-30 mg/mmol); proteinuria (ACR >300 mg/g or > 30 mg/mmol); presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)
[b] See table 3 and chapter 3.2.2.6 for ASCVD risk groups.
[c] Patients with prevalent HF or CKD are recommended for SGLT2 inhibitor, and patients post stroke recommended for GLP-1RA treatment.
[d] Lifetime treatment benefit is expressed as extra ASCVD-free life gained from a certain intervention or treatment intensification. See box 1.

1077



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1079

1080 **Recommendations for cardiovascular disease risk estimation**

Recommendations			Class[a]	Level[b]
In apparently healthy people without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders	<50 years	Estimation of 10-year fatal and non-fatal ASCVD risk with SCORE2 is recommended.[66]	I	B
	50–70 years	Estimation of 10-year fatal and non-fatal ASCVD risk with SCORE2 is recommended.[66]	I	B
	>70 years	Estimation of 10-year fatal and non-fatal ASCVD risk with SCORE2-OP is recommended.[70]	I	B
In apparently healthy people, after estimation of 10-year fatal and non-fatal ASCVD risk, lifetime risk and treatment benefit, risk modifiers, frailty, polypharmacy and patient preferences should be considered.			IIa	C

Patients with established CVD and/or DM and/or moderate-to-severe renal disease and/or genetic/rarer lipid or BP disorders are to be considered at high or very high CVD risk.[73, 75, 79, 86, 88, 89]	**I**	**A**
A stepwise treatment-intensification approach aiming at intensive risk factor treatment is recommended for apparently healthy people at high or very high ASCVD risk, as well as patients with established ASCVD and/or DM, with consideration of CVD risk, treatment benefit of risk factors, risk modifiers, comorbidities, and patient preferences.[64, 65]	**I**	**B**
In apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at very high risk (SCORE2 ≥7.5% for people aged under 50 years; SCORE2 ≥10% for people aged 50-70 years; SCORE2-OP ≥15% for people aged >70 years), treatment of ASCVD risk factors is recommended.	**I**	**C**
In apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at high risk (SCORE2 2.5 to <7.5% for people aged under 50 years; SCORE2 5 to <10% for people aged 50-70 years; SCORE2-OP 7.5 to <15% for people aged >70 years), treatment of risk factors should be considered taking ASCVD risk modifiers, lifetime risk and treatment benefit and patient preferences into account.	**IIa**	**C**

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease (see definition in table 3); DM = diabetes mellitus; SCORE2 = Systemic Coronary Risk Estimation 2.

[a] Class of recommendation.

[b] Level of evidence.

Gaps in evidence

- Country-specific risk algorithms for patients with established CVD and people with DM.
- Formal comparison of effectiveness and cost-effectiveness of CVD risk-guided treatment versus treatment guided by risk factor level.
- Comparison of the precision of competing risk-adjusted CVD risk models versus standard CVD risk models.
- Incorporating potential risk markers in conventional risk models, such as socio-economic status and ethnicity.
- Comparison of treatment benefit-guided strategy vs. risk-guided strategy in reducing risk factor levels and ASCVD risk
- Management of ASCVD risk in older people (> 85 years) with marked fragility, for whom no data currently exist.

Table 3. Patient categories and associated CVD risk.

Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Apparently healthy persons			
Persons without established ASCVD, diabetes mellitus, CKD, Familial Hypercholesterolemia	<50 years	Low- to high- risk	10-year ASCVD risk estimation (SCORE2). Lifetime risk and benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of ASCVD risk and treatment benefits.
	50-70 years	Low- to very high-risk	10-year ASCVD risk estimation (SCORE2). Lifetime benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits.
	>70 years	Low- to very high-risk	10-year ASCVD risk estimation (SCORE2-OP) lifetime benefit estimation of risk factor treatment (e.g. with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits.
Patients with CKD			
CKD without diabetes or ASCVD	Moderate CKD (eGFR 30–44 and ACR <30 or eGFR 45–59 and ACR 30–300 or eGFR ≥60 and ACR >300)	High-risk	N/A
	Severe CKD (eGFR<30 or eGFR 30-44 and ACR >30)	Very high-risk	N/A
Familial Hypercholesterolemia			
Associated with markedly elevated cholesterol levels	N/A	High-risk	N/A
Patients with type 2 diabetes mellitus			
Patients with type 1 DM above 40 years of age may also be classified according to these criteria	Patients with well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate-risk	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria.	High-risk	Residual 10-year ASCVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime benefit estimation of risk factor treatment (e.g. DIAL model).
	Patients with DM with established ASCVD and/or severe TOD*: • eGFR <45 irrespective of albuminuria • eGFR 46-59 and microalbuminuria (ACR 30 -300 mg/g or 3-30 mg/mmol) • Proteinuria (ACR >300 mg/g or >30 mg/mmol) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high-risk	Residual 10-year ASCVD risk estimation after general prevention goals (e.g. with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime benefit estimation of risk factor treatment (e.g. DIAL model).
Patients with established ASCVD			
Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), chronic coronary syndromes, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.	N/A	Very high-risk	Residual 10-year ASCVD risk estimation after general prevention goals (e.g. with the SMART risk score). Consider lifetime benefit estimation of risk factor treatment (e.g. SMART-REACH model; or DIAL model if diabetes).

ACR = albumin to creatinine ratio; ACS = acute coronary syndrome; ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; AMI = acute myocardial infarction; CKD = chronic kidney disease; CTA = computed tomography angiography; CV = cardiovascular; CVD = cardiovascular disease; DIAL = Diabetes Lifetime-perspective prediction; DM = diabetes mellitus; FH = familial hypercholesterolaemia; eGFR = estimated glomerular filtration rate; IMT = intima-media thickness; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; LVH = left ventricular hypertrophy; N/A = not applicable; PAD = peripheral artery disease; REACH = Reduction of Atherothrombosis for Continued Health; SBP = systolic blood pressure; SCORE = Systematic Coronary Risk Estimation; SMART = Secondary Manifestations of Arterial Disease; TIA = transient ischaemic attack.

[a] References: [87, 93-95]

3.2.4.Communication of cardiovascular disease risk

Reducing ASCVD risk at the individual level begins with appropriate assessment of individual risk (section 3) and effective communication of risk and anticipated risk reduction by risk factor treatment. Patient−doctor interactions are complex and communicating risk is challenging.[96, 97] There is no single "correct" approach; rather, it will depend on the individual's preferences and understanding, which in turn may differ with education status, numeracy. Risk perception is also strongly affected by emotional factors such as fear, optimism, etc. ("patients don't think risk, they feel risk")[98]

It is important to explore if patients understand their risk, the anticipated risk reduction, the pros and cons of intervention, and to identify what is important to them. For example, one patient may focus on living free of medications, whereas another may be less able to change lifestyle. In terms of outcomes, reducing mortality risk is crucial to some, whereas disease risk is more important to others. Short-term risk may motivate some patients, whereas lifetime benefit (see Box 1) will have more impact in others. In general, visual aids (graphs, etc.) improve risk understanding, absolute risk (reduction) is better understood than relative risk (reduction), and the use of "numbers needed to treat" is less well understood.

In apparently healthy people the standard approach is to report absolute 10-year risk of an ASCVD event with SCORE2 or SCORE2-OP, which can be found at the ESC CVD Risk Calculator app (https://www.escardio.org/Education/ESC-Prevention-of-CVD-Programme/Risk-assessment/esc-cvd-risk-calculation-app) or at http://www.heartscore.org or www.u-prevent.com. In specific situations, one may opt for expressing risk in terms other than absolute 10-year risk. Examples of such situations include risks in young or very old people. In young people lifetime risk might be more informative, as 10-year CVD risk is usually low even in the presence of risk factors. In older persons specific risk estimation is required taking competing non-CVD risk into account.[99] Direct translation of relative risks to treatment decisions is not recommended, as absolute risks remain the key criterion for starting treatment.

An alternative way of expressing individual risk is to calculate a person's "risk age".[98] The risk age of a person with several ASCVD risk factors is the age of a person of the same sex with the same level of risk but with low levels of risk factors. 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 ASCVD will be exposed to if preventive measures are not adopted. Risk age is also automatically calculated as part of HeartScore (http://www.heartscore.org/).[100-102]

ASCVD risk may also be expressed with a lifetime rather than a 10-year horizon, for example, the LIFE-CVD calculator (ESC CVD Risk Calculation app or http://www.u-prevent.com) (also see Box 1).[99] Lifetime ASCVD risk-prediction models identify high-risk individuals both in the short and long term. Such models account for predicted risk in the context of competing risks from other diseases over the remaining expected lifespan of an individual. A similar approach also employing lifetime perspective is to calculate lifetime benefit of preventive interventions.[99] Lifetime benefit of preventive interventions can be expressed as gain in ASCVD-free life (years), which is easier to communicate with a patient and may support the shared decision-making process.

Recommendation for cardiovascular disease risk communication

Recommendation	Class[a]	Level[b]
An informed discussion about ASCVD risk and treatment benefits tailored to the needs of a patient is recommended.[98]	I	C

ASCVD = atherosclerotic cardiovascular disease.

[a] Class of recommendation.

[b] Level of evidence.

3.3. Potential risk modifiers

Recommendations for risk modifiers

Recommendations	Class[a]	Level[b]
Stress symptoms and psychosocial stressors modify ASCVD risk. Assessment of these stressors should be considered.[103-105]	IIa	B
Coronary calcium scoring may be considered to improve risk classification around treatment decision thresholds. Plaque detection by carotid ultrasound is an alternative when CAC scoring is unavailable or not feasible.[106, 107]	IIb	B
Multiplication of calculated risk by relative risks for specific ethnic subgroups should be considered.[108]	IIa	B
The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than coronary calcium scoring or carotid ultrasound for plaque determination), is not recommended.	III	B

CAC = coronary artery calcium; ASCVD = atherosclerotic cardiovascular disease.

[a] Class of recommendation.

[b] Level of evidence.

Apart from the conventional CV risk factors included in the risk charts, additional risk factors or types of individual information can also modify calculated risk. Assessment of a potential modifier may be considered if:

- It improves measures of risk prediction, such as discrimination or reclassification (e.g. by calculation of net reclassification index [NRI]).
- Public health impact is clear (e.g. number needed to screen or net benefit).
- It is feasible in daily practice.

- Information is not just available on how risk increases with an unfavourable result, but also on how risk decreases if the modifier shows a favourable result.
- The literature on this potential modifier is not distorted by publication bias.

Very few potential modifiers meet all of these criteria. Meta-analyses in this field are, for example, susceptible to substantial publication bias.[109] Also, the exact way of integrating additional information on top of regular risk calculator input parameters is mostly unknown. Finally, RCTs to determine whether the added risk information eventually leads to improved health outcomes are generally lacking.

Assessment of potential risk modifiers seems particularly relevant if the individual's risk is close to a decision threshold, such as a SCORE risk close to 10%. In very high-risk or low-risk situations, additional information is less likely to alter management decisions. The number of individuals in this "grey zone" is large. Therefore, feasibility becomes a limitation as modifiers become more complex or expensive, such as some imaging techniques.

Care should be taken not to use risk modifiers solely to increase risk estimates when the modifier profile is unfavourable, but also vice versa. Although an unfavourable risk modifier may increase an individual's estimated risk, a more favourable profile than would be expected based on other patient's characteristics must have the opposite effect. Finally, it is important to acknowledge that the degree to which calculated absolute risk is affected by modifiers is generally much smaller than the (independent) relative risks reported for these modifiers in the literature.[110]

Taking the above into account, we summarize the literature on several popular risk modifiers in this chapter.

3.3.1. Psychosocial factors

Key message

- Psychosocial stress is associated with risk of ASCVD.

Psychosocial stress is associated in a dose-response pattern with the development and progression of ASCVD independently of conventional risk factors and gender. Psychosocial stress includes stress symptoms (i.e. symptoms of mental disorders), as well as stressors such as loneliness and critical life events. The relative risks of psychosocial stress are commonly between 1.2 and 2.0[111, 112] (*Supplementary Table 2*). Conversely, indicators of mental health, such as optimism and a strong sense of purpose, are associated with lower risk.[112] Psychosocial stress has direct biological effects, but is also highly correlated with socioeconomic and behavioural risk factors (e.g. smoking, poor adherence).[103, 112-116] Although the associations of psychosocial stress with CV health are robust, only "vital exhaustion" has been proven to improve risk reclassification.[104] Owing to the importance of stress symptoms among ASCVD patients, several guidelines and scientific statements recommend screening of ASCVD patients for psychological stress[116-118](*Box 2* and *Supplementary Table 3*). A recent prospective cohort study with a median follow-up of 8.4 years reported favourable effects of screening for depression on major ASCVD events.[105]

Gaps in evidence

- More evidence that psychosocial factors improve risk prediction beyond the classical risk factor models.

Box 2 Core topics for psychosocial assessment	
Simultaneous diagnostic assessment	At least one in five patients carries a diagnosis of a mental disorder, presenting usually with bodily symptoms (e.g., chest tightness, shortness of breath), Therefore, physicians should be equally attentive to somatic as to emotional causes of symptoms.
Screening	Screening instruments assessing depression, anxiety and insomnia are recommended (e.g. Patient Health Questionnaire[119], see *Supplementary Table 3*).[120, 121]
Stressors	There are simple questions to get into a conversation about significant stressors[122]: Are you bothered by stress at work, financial problems, difficulties in the family, loneliness, or any stressful events?
Need for mental health support	Are you interested in a referral to a psychotherapist or mental health service?

3.3.2. Ethnicity

Key message

- Current risk scores may under- or overestimate ASCVD risk in differing ethnic minority groups.

Europe harbours many citizens whose ethnic background originates in countries as India, China, North Africa, and Pakistan. Given the considerable variability in ASCVD risk factors between immigrant groups, no single ASCVD risk score performs adequately in all groups. Rather, the use of a multiplying factor would be helpful to take account of ASCVD risk imposed by ethnicity independent of other risk factors in the risk score. The most contemporary relevant data come from the QRISK3 findings in the UK,[108] although this focuses on a wider range of ASCVD outcomes and not simply ASCVD mortality.

Immigrants from South Asia (notably India and Pakistan) present higher ASCVD rates independent of other risk factors, whereas adjusted ASCVD risks appear lower in most other ethnic groups. The reasons for such differences remain inadequately studied. Based on such data, the following correction factors, based on data from the United Kingdom, could be applied when assessing ASCVD risk using SCORE.[108] Ideally, country and risk-calculator-specific relative risks should be used, as the impact of ethnicity may vary between regions and risk-calculators.

- Southern Asian: multiply the risk by 1.3 for Indians and Bangladeshis, and 1.7 for Pakistanis
- Other Asian: multiply the risk by 1.1
- Black Caribbean: multiply the risk by 0.85
- Black African and Chinese: multiply the risk by 0.70

Gaps in evidence

Whether recalibration of factors for ethnicity are homogeneous in various European countries.

3.3.3. Imaging

Key message

- Coronary calcium scoring is the best-established imaging modality to improve ASCVD risk stratification.

3.3.1.1 Coronary artery calcium

CAC scoring can reclassify ASCVD risk upwards and downwards in addition to conventional risk factors, and may thus be considered in men and women with calculated risks around decision thresholds.[106, 107] Availability and cost-effectiveness of large-scale CAC scanning must however be considered in a locoregional context (see section 3.2 on cost-effectiveness). If coronary calcium is detected, its extent should be compared with what would be expected for a patient of the same sex and age. Higher-than-expected CAC increases the person's calculated risk, whereas absent or lower-than-expected CAC is associated with lower than calculated risk. CAC scoring does not provide direct information on total plaque burden or stenosis severity, and can be low or even zero in middle-aged patients with soft non-calcified plaque. Clinicians are advised to consult existing protocols for details of how to assess and interpret CAC scores.

3.3.1.1 Computed tomography coronary angiography

Contrast computed tomography angiography (CCTA) allows identification of coronary stenoses and predicts cardiac events.[123] In the Scottish Computed Tomography of the Heart (SCOT-HEART) study, 5-year rates of coronary death or myocardial infarction were reduced when CCTA was used in patients with stable chest pain.[124] The relative reduction in myocardial infarction was similar in patients with non-cardiac chest pain. Whether CCTA improves risk classification or adds prognostic value over CAC scoring is unknown.

3.3.1.1 Carotid ultrasound

Intima-media thickness (IMT): systematic use of IMT to improve risk assessment is not recommended due to the lack of methodological standardization, and the absence of added value of IMT in predicting future ASCVD, even in the intermediate-risk group.[125]

Plaque is defined as the presence of a focal wall thickening that is ≥50% greater than the surrounding vessel wall, or as a focal region with an IMT measurement ≥1.5 mm that protrudes into the lumen.[126] Although the evidence is less extensive as it is for CAC, carotid artery plaque assessment using ultrasonography probably also reclassifies ASCVD risk,[107, 126] and may be considered as a risk modifier in patients at intermediate risk when a CAC score is not feasible.

3.3.1.1 Arterial stiffness

Arterial stiffness is commonly measured using either aortic pulse wave velocity (PWV) or arterial augmentation index. Studies suggest that arterial stiffness predicts future ASCVD and improves risk classification.[127] However, measurement difficulties and substantial publication bias[109] argue against widespread use.

3.3.1.1 Ankle-brachial index

Estimates are that 12–27% of middle-aged individuals have an ABI <0.9, around 50–89% of whom do not have typical claudication[128] . An individual patient-data meta-analysis concluded that the reclassification potential of ABI was limited, perhaps with the exception of women at intermediate risk.[129]

3.3.1.1 Echocardiography

In view of the lack of convincing evidence that it improves ASCVD risk reclassification, echocardiography is not recommended to improve CV risk prediction.

3.3.4. Frailty

Key messages

- Frailty is a functional risk factor of both CV and non-CV morbidity and mortality
- Frailty assessment is not a method to determine the eligibility for any particular treatment, but rather serves to build an individualized care plan with predefined priorities.

Frailty is a multidimensional state, independent of age and multimorbidity, that makes the individual more vulnerable to the effect of stressors. It constitutes a functional risk factor of unfavourable outcomes, including both high CV and non-CV morbidity and mortality.[130, 131]

Frailty is not the same as ageing and the two should not be confused. The incidence of frailty increases with age, but people of the same chronological age differ significantly in terms of health status and vitality. “Biological age” is much more important in the context of clinical status (including frailty features) and hard clinical outcomes (including ASCVD events).[130, 131] Similarly, although the presence of comorbidities can exacerbate frailty within an individual, frailty is not the same as multimorbidity (see *section 6.7*).

Frailty screening is indicated in every elderly patient, but should also be performed in every individual regardless of his/her age, when being at risk of accelerated ageing.[130, 131] Most of the tools relate to frail features, including slowness, weakness, low physical activity, exhaustion, and shrinking (e.g. Fried scale, Short Physical Performance Battery, Rockwood Clinical Frailty Scale, handgrip strength, gait speed).[130-133] Frailty assessment is important at each stage of an ASCVD trajectory. During an acute ASCVD event, however, frailty assessment is more difficult, and either relies on history taking or should be postponed to when patients return to a stable condition.

Frailty is a potential modifier of global CV risk. The impact of frailty on CV risk has been demonstrated across the spectrum of ASCVD, including people with ASCVD risk factors, patients with subclinical ASCVD, stable ASCVD, acute cerebral and coronary syndromes, and heart failure[130-134], with frailty itself rather than classical ASCVD risk factors predicting both all-cause and CV mortality in the very old.[134, 135] Importantly, the ability of frailty measures to improve ASCVD risk prediction has not been formally assessed. Hence, we do not recommend that frailty measures are integrated in the formal ASCVD risk assessment.

Importantly, frailty may influence treatment. Non-pharmacological interventions (e.g. balanced nutrition, micronutrient supplementation, exercise training, social activation) aiming to prevent, attenuate or reverse frailty are of utmost importance.[130, 131, 136] In terms of pharmacotherapy and device implantations, frailty assessment is not a method to determine the eligibility for any particular treatment, but rather serves to build an individualized care plan with predefined priorities. Frail individuals often have comorbidities, polypharmacy, and may be more susceptible to drug side-effects and serious complications during invasive and surgical procedures.[130, 131]

Gaps in evidence

- Consensus on a clinically orientated screening tool for frailty to be applied across the spectrum of ASCVD.
- Quantitative contribution of frailty to the global ASCVD risk prediction scheme.
- At which degree of frailty treatment of specific risk factors should be less aggressive.

3.3.5. Family history

Key message

- Family history should be enquired about routinely, and a positive family history of premature ASCVD should be followed by comprehensive ASCVD risk assessment.

Family history of premature ASCVD is a simple indicator of ASCVD risk, reflecting the genetic and environment interplay.[137] In the few studies that simultaneously assessed the effects of family history and genetics, family history remained significantly associated with ASCVD after adjusting for the genetic scores.[138, 139] However, family history only marginally improves the prediction of ASCVD beyond conventional ASCVD risk factors[140-145] Possible explanations are the varying definitions of family history applied and that conventional ASCVD risk factors largely explain the impact of family history.

A family history of premature ASCVD is simple, inexpensive information that can trigger comprehensive risk assessment in individuals with a family history of premature ASCVD.[140]

Gaps in evidence

- Disentangle the role and (genetic, socioeconomical, etc.) mechanisms of family history on ASCVD risk.

3.3.6. Genetics

Key message

- Current data does not support the use of genomic risk scores in ASCVD risk assessment in primary prevention.

The aetiology of ASCVD has a genetic component, but this information is not currently used in preventive approaches.[146] Advances on polygenic risk scores (PRSs) for risk stratification could increase the use of genetics in prevention.[147-149] For ASCVD, there is however a lack of consensus regarding which genes and corresponding single nucleotide polymorphisms should be included, and whether to use risk factor-specific or outcome-specific PRS.[150] PRS has shown some potential to improve ASCVD risk prediction for primary prevention,[151-153] but the incremental prediction accuracy is relatively modest and needs further evaluation in both men and women.[154, 155] Additional evidence is also needed to evaluate the clinical utility of PRSs in other clinical settings, such as in patients with pre-existing ASCVD.[156]

Gaps in evidence

- The potential of PRSs to complement existing risk scores.

3.3.7. Socioeconomic determinants

Key message

- ASCVD development and prognosis are linked to social gradients.

Low socioeconomic status and work stress are independently associated with ASCVD development and prognosis in both genders.[157,158] The strongest association has been found between low income and ASCVD mortality, with a relative risk of 1.76 (95% confidence interval [CI] 1.45–2.14).[159] Work stress is determined by job strain (i.e. the combination of high demands and low control at work) and effort–reward imbalance. There is preliminary evidence that the detrimental impact of work stress on ASCVD health is independent of conventional risk factors and their treatment.[160]

Gaps in evidence

- More evidence from different risk regions that the inclusion of socioeconomic factors improves risk prediction beyond classical risk factor models on both men and women.

3.3.8. Environmental exposure

Key message

- Air pollution is strongly associated with ASCVD.

Environmental exposures having ASCVD risk modifying potential include air and soil pollution as well as above threshold noise levels. Evaluating individual cumulative exposure to pollutants and noise remains challenging, but when available, might impact on individual risk assessment.

Components of outdoor air pollution include airborne particulate matter (PM; ranging in size from coarse particles 10-2.5 µm in diameter, to fine [<2.5 µm; $PM_{2.5}$], and ultrafine [<0.1 µm]) and gaseous pollutants (e.g. ozone, nitrogen dioxide [NO_2], volatile organic compounds, carbon monoxide, sulphur dioxide), produced primarily by combustion of fossil fuel. Soil and water pollutions are also ASCVD risk modifiers; increased exposure to lead, arsenic, and cadmium is associated with multiple ASCVD outcomes including hypertension, CHD, stroke, and ASCVD mortality.[161] Ambient PM pollution recently ranked as a leading modifiable mortality risk factor and also responsible for attributable disability adjusted life-years at the global level.[162] A recent model estimated that loss of life expectancy due to ambient air pollution is similar to, if not exceeded, that due to tobacco smoking, and accounting for a global excess mortality estimated at 8.8 million/year.[163]

The short-term attributable effects on mortality are linked primarily to exposure to PM, NO_2, and ozone, with an average 1.0% increase of all-cause mortality for an increment of 10µg/m^3 in exposure to $PM_{2.5}$; the long-term effects are associated mainly with $PM_{2.5}$. The evidence linking exposure to PM and ASCVD events is based on large-scale epidemiological studies and experimental studies. Associations with ASCVD mortality vary, but the majority of cohort studies link long-term air pollution with an increased risk of fatal or non-fatal CAD, and with subclinical atherosclerosis. Evidence suggests that reduction of $PM_{2.5}$ is associated with improvements in inflammation, thrombosis, and oxidative stress, and a decrease in death from ischaemic heart disease.[38, 164, 165] Because sufficiently precise individual exposure estimates are hard to obtain, formal risk reclassification is difficult to quantify at present.

Recommendations for cardiovascular disease risk related to air pollution

Recommendations	Class[a]	Level[b]
Patients at (very) high risk for ASCVD may be encouraged to try to avoid long-term exposure to areas with high air pollution.	IIb	C
In areas where people have long-term exposure to high levels of air pollution, (opportunistic) ASCVD risk screening programmes may be considered.	IIb	C

ASCVD = atherosclerotic cardiovascular disease.

[a] Class of recommendation.

[b] Level of evidence.

Gaps in evidence

- Whether air pollution reclassifies risk in individual patients.

3.3.9. Biomarkers in blood or urine

Key message

- Additional circulating and urine biomarkers should not be routinely measured.

Many biomarkers have been suggested to improve risk stratification. Some may be causal (e.g. lipoprotein[a] reflecting a pathogenic lipid fraction), whereas others may reflect underlying mechanisms (e.g. C-reactive protein reflecting inflammation) or indicate early cardiac damage (e.g. natriuretic peptides or high-sensitivity cardiac troponin).

In the 2016 Guidelines, we recommended against the routine use of biomarkers because most do not improve risk prediction, and publication bias seriously distorts the evidence.[109, 166] New studies confirm that CRP has limited additional value.[106] There is renewed interest in lipoprotein(a), but it too provides limited additional value in terms of reclassification potential.[167, 168] Cardiac biomarkers are promising,[169, 170] but further work is needed.

Gaps in evidence

- Added value of biomarkers in risk classification.

3.3.10. Body composition

Key Message

- Assess ASCVD risk in persons with obesity.

Worldwide, BMI has increased substantially in recent decades, in children, adolescents, and adults.[43] In observational studies, all-cause mortality is minimal at a BMI of 20–25 kg/m^2, with a J- or U-shaped relation in current smokers.[45, 46] Mendelian randomization analyses suggest a linear relation between BMI and mortality in never-smokers and a J-shaped relation in ever-smokers.[44] A meta-analysis concluded that both BMI and waist circumference are similarly strongly and continuously associated with ASCVD in elderly and young and in men and women.[47]

Among those with established ASCVD, the evidence is contradictory. Systematic reviews of patients with ACS or HF have suggested an “obesity paradox” whereby obesity appears protective.[171, 172 173] However, this evidence should be interpreted with caution as reverse causality and other biases may be operating.[45]

Which index of obesity is the best predictor of cardiovascular risk?

BMI can be measured easily, and is used extensively to define categories of body weight (see *Supplementary Table 4*). Body fat stored in visceral and other ectopic depots carries a higher risk than subcutaneous fat. Several measures of global and abdominal fat are available, of which waist circumference is the simplest to measure. The WHO thresholds for waist circumference are widely accepted in Europe. Two action levels are recommended:

- Waist circumference ≥94 cm in men and ≥80 cm in women: no further weight gain.
- Waist circumference ≥102 cm in men and ≥88 cm in women: weight reduction advised.

Different cut-offs for anthropometric measurements may be required in different ethnicities.

The phenotype of "metabolically healthy obesity", defined by the presence of obesity in the absence of metabolic risk factors, has gained interest. Long-term results support the notion that metabolically healthy obesity is a transient phase moving towards glucometabolic abnormalities rather than a specific "state".[174]

Risk reclassification

The associations between BMI, waist circumference, and waist-to-hip ratio and ASCVD are maintained after adjustment for conventional risk factors. However, these measures did not improve ASCVD risk prediction as assessed by reclassification.[47]

Assess risk factors and cardiovascular disease risk in persons with obesity

Comprehensive ASCVD risk assessment should be considered in individuals with unfavourable body composition. The main risk-related sequalae of adiposity include hypertension, dyslipidaemia, insulin resistance, systemic inflammation, a prothrombotic state, albuminuria, as well as a decline in estimated glomerular filtration rate (eGFR)[175] and the development of type 2 DM, ASCVD events, as well as heart failure and atrial fibrillation.

3.4. Clinical conditions

Individual calculated risks of ASCVD, as evaluated by conventional risk factors in risk scores, are subject to refinement by potential risk modifiers as highlighted in *section 3.3*. Beyond these potential modifiers, specific clinical conditions can influence ASCVD risk. These clinical conditions often increase the likelihood of ASCVD, or are associated with poorer clinical prognosis. The following chapter reviews some of these conditions, which are not often included in traditional risk scores but may be integrated in some national risk scores. Here we discuss how these conditions increase this risk.

Many clinical conditions share common CVD and ASCVD risk factors and therefore treating these allows a synergistic reduction in the overall burden of disease.

Recommendations for cardiovascular disease assessment in specific clinical conditions

Clinical condition	Recommendations	Class[a]	Level[b]

CKD	In all CKD patients, with or without diabetes, appropriate screening for ASCVD and kidney disease progression, including monitoring changes in albuminuria is recommended.[176]	**I**	**C**
Cancer	It is recommended to monitor cardiac dysfunction using imaging techniques and circulating biomarkers before, periodically during, and after cancer treatment.[177]	**I**	**B**
	Cardioprotection in high-risk patients (those receiving high cumulative doses or combined radiotherapy) receiving anthracyckine chemotherapy may be considered for prevention of LV dysfunction.[178, 179]	**IIb**	**B**
	Screening for CV risk factors and optimization of the CV risk profile is recommended in patients on treatment for cancer.	**I**	**C**
COPD	It is recommended that all COPD patients be investigated for ASCVD and ASCVD risk factors.	I	C
Inflammatory conditions	Assessment of total CVD risk may be considered in adults with chronic inflammatory conditions.[180]	IIb	B
	Multiplication of calculated total CVD risk by a factor of 1.5 should be considered in adults with rheumatoid arthritis.[181, 182]	IIa	B
Migraine	Presence of migraine with aura should be considered in CVD risk assessment.[183-185]	IIa	B
	Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.[186, 187]	IIb	B
Sleep disorders and OSAS	In patients with CVD, obesity, and hypertension, regular screening for non-restorative sleep is indicated (e.g. by the question: “how often have you been bothered by trouble falling or staying asleep, or sleeping too much?”).	I	C
	If there are significant sleep problems, which are not responding within 4 weeks to sleep hygiene, referral to a specialist is recommended.	I	C
Mental disorders	It is recommended that mental disorders with either significant functional impairment or decreased use of healthcare systems be considered as influencing total CVD risk.	I	C
Sex-specific conditions	In women with a history of preeclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered.[188-191]	IIa	B

	In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.[192-195]	IIa	B
	In women with a history of giving premature or stillbirth, periodic screening for hypertension and DM may be considered.[196, 197]	IIb	B
	Assessment of CVD risk should be considered in men with erectile dysfunction.	IIa	C

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; LV = left ventricular; OSA = obstructive sleep apnoea.

[a] Class of recommendation.

[b] Level of evidence.

3.4.1. Chronic kidney disease

Key messages

- CKD is an independent risk factor for ASCVD, and ASCVD is the leading cause of death in CKD.
- A short-term reduction in albuminuria by approximately 30% upon starting renin–angiotensin–aldosterone system (RAAS) inhibition is associated with improved CV and kidney outcomes.
- Similarly, SGLT2 inhibitors are associated with long-term benefits in CV and renal risks.

Worldwide, the total number of individuals with CKD who are not treated with kidney replacement therapy was approximately 850 million in 2017.[198] This number accounts for a prevalence of 10–12% among men and women. CKD is the third fastest growing cause of death globally.[199]

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with health implications. Criteria and markers of kidney damage, especially kidney disease due to diabetes, are albuminuria (albumin-to-creatinine ratio >30 mg/g in spot urine specimens) and glomerular filtration rate (GFR) (<60 mL/min/1.73 m^2). GFR can be estimated (eGFR) from calibrated serum creatinine and estimating equations using the CKD-EPI formula. Kidney disease severity is differentiated into stages (categories) according to the level of GFR and albuminuria; a patient with an eGFR <60 mL/min/1.73m^2 is classified as having CKD stage 3a, which represents an advanced kidney function impairment.[176]

Among persons with CKD, CVD is the leading cause of morbidity and death.[200] Even after adjustment for known CAD risk factors, including diabetes and hypertension, mortality risk progressively increases with worsening CKD.[201] As GFR declines below approximately 60–75 mL/min/1.73 m^2, the probability of developing CAD increases linearly[202] with up to triple the CVD mortality risk when reaching an eGFR of 15 mL/min/1.73 m^2. Kidney disease is associated with a very high ASCVD risk. Among persons with CKD, there is a high prevalence of traditional CAD risk factors such as diabetes

and hypertension. The use of CAC score to risk stratify patients with CKD might be a promising tool.[203-207] Furthermore, persons with CKD are also exposed to other non-traditional CV risk factors such as uraemia-related ones, including inflammation, oxidative stress, and promotors of vascular calcification. CKD and kidney failure not only increase the risk of CAD, they also modify its clinical presentation and cardinal symptoms.[208]

Gaps in evidence

- Identification of a good biomarker, besides albuminuria, and perhaps the use of CAC score to subclassify CV risk in CKD.
- Early and precise identification of progressive CKD with novel biomarkers that are more sensitive than eGFR and albuminuria.

3.4.2. Atrial fibrillation

Key messages

- AF is associated with an increased risk of death and an increased risk of ASCVD.

AF appears to be associated with an increased risk of death and of CV and kidney disease.[209] Furthermore, AF appears to be a stronger risk factor for CVD in women than in men.[210]

The prevalence of AF ranges between 2% and 4%, and a 2.3-fold rise is expected owing in part to ageing of the population and intensified search for undiagnosed AF, as well as lower CV death.[211] The age-adjusted incidence, prevalence and lifetime risk of AF are lower in women versus men and in non-white versus white cohorts.[212, 213] The lifetime AF risk estimate is now 1 in 3 individuals of European ancestry at an index age of 55 years.[214] Cardiovascular risk factor (CVRF) burden and comorbidities, including lifestyle factors, and age significantly affect the lifetime risk for AF development.[215-217] The observed effect of clinical CVRF burden and multiple comorbidity on the lifetime risk of AF (significantly increasing from 23.4% among individuals with an optimal clinical risk factor profile to 33.4% and 38.4%, respectively, in those with elevated clinical risk factors[214]) suggests that early intervention and control of modifiable CVRF could reduce incident AF. The continuum of unhealthy lifestyle, risk factor(s), and CVDs can contribute to atrial remodelling/cardiomyopathy and development of AF that commonly results from a combined effect of multiple interacting factors (*Figure 8*).[218] Risk factor and CVD management reduces AF burden. Targeted therapy of underlying conditions may significantly improve maintenance of sinus rhythm in patients with persistent AF and HF.[219] Studies addressing isolated management of specific conditions alone (e.g. hypertension) yielded inconsistent findings.[220]

The overall annual risk of ischaemic stroke in patients with AF is 5% but varies considerably according to comorbidities.[218] Cardioembolic strokes associated with AF are usually more severe, and often recurrent.[221] AF furthermore appears to be a stronger predictor of stroke in women than in men.[218] AF is also associated with impaired cognitive function ranging from mild cognitive impairment to dementia.[222] AF is independently associated with a twofold increased risk of all-cause mortality in women and a 1.5-fold increased risk in men.[223] In one population, the most common causes of death were HF (14.5%), malignancy (23.1%), and infection/sepsis (17.3%), while stroke-related mortality

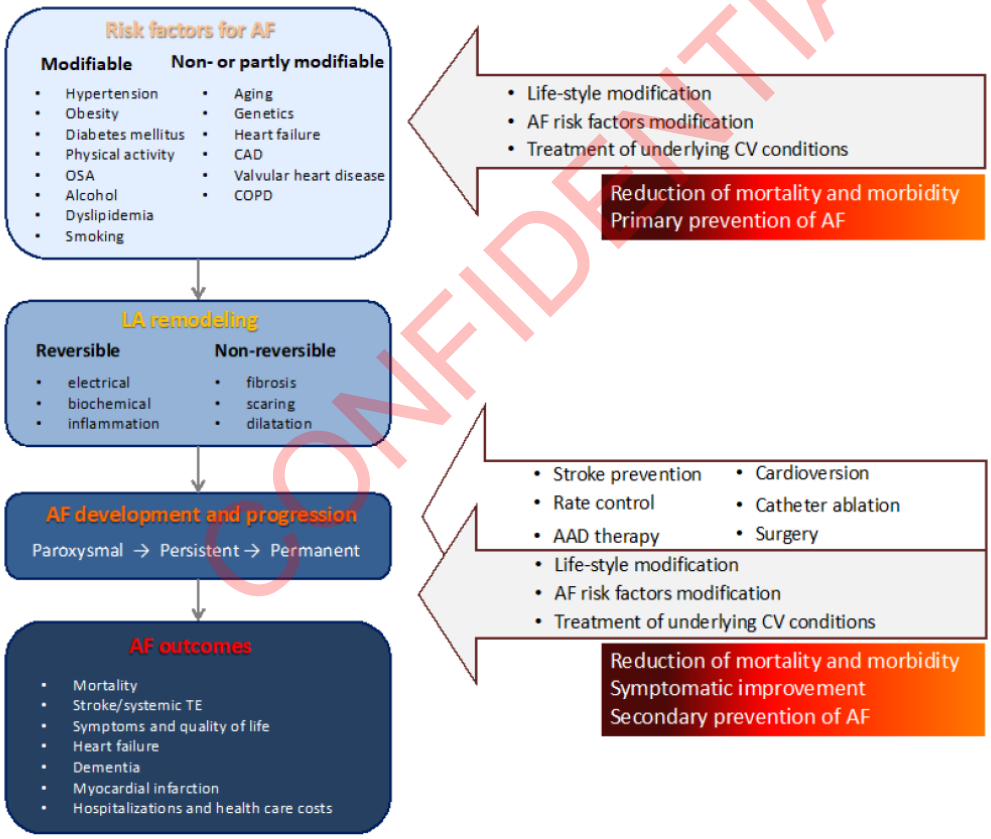
was only 6.5%.[224] These data indicate that, in addition to anticoagulation and HF treatment, comorbid conditions need to be actively treated to reduce AF-related mortality and morbidity.

Gaps in evidence

- Evaluate the effect of interventions aimed at reducing outcomes beyond stroke.
- Is AF a causal factor for increased ASCVD morbidity and mortality?
- Stroke risk-prediction for low-risk AF patients.
- Emerging evidence suggests that stroke can occur in patients with AF even after sinus rhythm is restored.

Figure 8 The role of risk factors and comorbidities in atrial fibrillation.[218]

AAD = antiarrhythmic drug; AF = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DM = diabetes mellitus; LA = left atrium; MI = myocardial infarction; OSA = obstructive sleep apnoea. [OUP: change TE to thromboembolism]



Regarding physical activity both sedentary lifestyles and very high levels of physical activity are associated with development of AF (U-shaped association), through different mechanisms. Furthermore, when AF develops in athletes it is not associated with the same increased risk of stroke.

3.4.3. Heart failure

Key messages

- Ischaemic HF constitutes the most advanced clinical manifestation of atherosclerosis within the myocardium.
- The diagnosis of overt HF as well as asymptomatic presentation with left ventricular (LV) dysfunction increases the risk of CVD events (myocardial infarction, ischaemic stroke, CV death).

HF of ischaemic origin constitutes a severe clinical manifestation of ASCVD. Conversely, HF itself (predominantly of ischaemic aetiology) increases the risk of CVD events (myocardial infarction, arrhythmias, ischaemic stroke, CV death).

Asymptomatic LV dysfunction (systolic or/and diastolic dysfunction) as well as overt symptomatic HF (across the spectrum of LVEF, i.e. HF with reduced ejection fraction [HFrEF], HF with mid-range ejection fraction, and HF with preserved ejection fraction [HFpEF]) increases the risk of urgent CV hospitalizations (including hospitalizations due to HF worsening), CV and all-cause deaths. These unfavourable effects on clinical outcomes have been demonstrated in asymptomatic subjects without overt CVD, in patients with acute and previous myocardial infarction, in patients with acute and previous stroke, and in patients with other clinical manifestations of CVD.[225]

The diagnosis of ischaemic HF positions individuals at very high CV risk, and justifies recommendations as for secondary prevention therapeutic strategies. Additionally, for patients with symptomatic HFrEF, several drugs are recommended to reduce the risk of CV morbidity and mortality (see *section 6.2*).

Gaps in evidence

- It remains unknown if patients with HFrEF of ischaemic origin should have different target LDL-C levels than those recommended for secondary prevention in individuals without HF.

3.4.4. Cancer

Key messages

- There is an overlap between cancer and CV risk factors; CV risk in patients with cancer depends on both the CV toxicity of treatments and patient-related factors.
- Signs or symptoms of cardiac dysfunction should be monitored before and periodically during and after treatment.
- Exercise should be strongly advised, in particular aerobic exercise, to prevent cardiotoxicity.

In patients with cancer, there is an overlap between cancer and ASCVD risk factors, with shared biological mechanisms, and genetic predispositions. Prevention and treatment of these is therefore beneficial in reducing both ASCVD as well as cancer risk. Moreover, the rates of the extent of CV risk depend on both the CV toxicity of treatments and patient-related factors. Owing to recent

improvements in clinical outcomes for many patients with cancer, CV mortality may ultimately exceed those from most forms of cancer recurrence.[226, 227]

The rapidly expanding variety of novel anticancer drugs/adjuvant therapies has demonstrated a wide range of both early and late CV side-effects, including cardiomyopathy, LV dysfunction, HF, hypertension, CAD, arrhythmias and other injuries. Therefore, effective strategies for the prediction and prevention of CV toxicities are critically important. The latency and severity of radiotherapy cardiotoxicity, as well as accelerated atherosclerosis and cerebral vascular disease, is related to multiple factors, including the dose (total per fraction), the volume of the heart irradiated, concomitant administration of other cardiotoxic drugs, and patient factors (which include amongst other factors younger age, traditional risk factors, history of heart disease).[228, 229] Furthermore, radio- and chemotherapy may exert direct vascular effects and increase atherosclerosis-related cardiovascular outcomes.[229, 230]

3.4.1.1 Diagnosis and screening

Signs or symptoms of cardiac dysfunction should be monitored before and periodically during and after cancer treatment for early detection of abnormalities in patients receiving potentially cardiotoxic chemotherapy. Detection of subclinical abnormalities using imaging and measurement of circulating biomarkers is currently recommended.[177, 231] Measures of myocardial strain, particularly systolic global longitudinal strain, may precede a significant decline in LVEF.[232-235]

3.4.1.1 Prevention of cardiotoxicity and cardiovascular risk factors

RCTs of preventive therapy with RAAS inhibitors and/or beta-blockers after Trastuzumab or anthracyclines have reported contradictory results.[232, 236, 237] The main benefits are less marked LV remodelling or a reduced decline in LVEF observed with cardiac magnetic resonance, but translation into better outcomes remains speculative.

Exercise should be strongly advised. In particular, aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy toxicity.[238] A study showed significantly higher risk of CVD in survivors of childhood cancer than in non-cancer adult controls, and particularly in survivors of adult-onset cancer with underlying CV risk factors.[239] Therefore, aggressive management of CV risk factors in this population is recommended.

Gaps in evidence

- RCTs using preventive therapy to demonstrate a clear effect on prevention of CV events.

3.4.5. Chronic obstructive pulmonary disease

Key messages

- COPD is a major risk factor for CVD, especially ASCVD, stroke, and HF.
- COPD patients are prone to arrhythmias (AF and VT) and sudden cardiac death (SCD).
- All COPD patients should be investigated for CVD.
- Common COPD medications are usually safe in terms of CV adverse events.

COPD is a complex, progressive respiratory disorder and currently the fourth leading cause of death worldwide. It is characterized by chronic airflow limitation with respiratory symptoms and is

associated with an increased inflammatory response and abnormalities of the airways caused by significant exposure to noxious particles or gases (mainly smoking). Although COPD is recognised and thoroughly investigated as a CVD comorbidity, its role as an ASCVD risk factor is not well established. Nevertheless, COPD patients have a 2–3-fold increased risk of ASCVD compared with age-matched controls when adjusted for tobacco smoking. Patients with mild-to-moderate COPD are 8–10 times more likely to die from ASCVD than respiratory failure, having higher rates of hospitalization and death due to ASCVD, stroke, and HF.[240, 241] ASCVD also runs undiagnosed; less than one-third of COPD patients with ECG evidence of myocardial infarction are diagnosed with CVD.[242] CV mortality increases by 28%, and the frequency of non-fatal coronary events by 20%, for every 10% decrease in FEV1 (forced expiratory volume in 1 second).[243] Acute COPD exacerbations, mainly due to infections, are frequent and are responsible for a fourfold hazard increase of CVD events .[244] The risk of both MI and ischaemic stroke is increased during the 3 months after an acute exacerbation.[245]

The high prevalence of CVD in COPD patients may be explained by the fact that both diseases share common risk factors such as smoking, ageing, hypertension and dyslipidaemia.[246] Metabolic syndrome and reduced physical activity is present in 34% of COPD patients, with its most prevalent components being hypertension (56%), abdominal obesity (39%), and hyperglycaemia (44%).[247] ASCVD may be caused by hypoxia during exercise due to lung hyperinflation, high resting heart rates, impaired vasodilatory capacity, and peripheral, cardiac, and neurohumoral sympathetic stress. Atherosclerosis and coronary artery calcification may be the result of oxidative stress and reductions in antiaging molecules causing both lung and vascular ageing.[248] Systemic inflammation is prominent in COPD with circulating biomarkers in high concentrations and associated with increased mortality.[249] Troponin is elevated during an acute exacerbation of COPD, and 10% of hospitalized patients meet the definition of AMI.[250] B-natriuretic peptide level, if elevated, increases the mortality risk.[251]

Systemic inflammation and oxidative stress caused by COPD promote vascular remodelling, stiffness, and atherosclerosis, and induce a “procoagulant” state that affects all vasculature types.[252] Cognitive impairment and dementia due to cerebral microvascular damage is correlated with COPD severity; patients have a 20% increased risk for both ischaemic and haemorrhagic stroke, which may be up to sevenfold higher following an acute exacerbation.[253] PAD is present in about 9% of COPD patients,[254] who have an almost doubled risk of developing PAD,[255] as well as an increased prevalence of carotid plaques related to the disease severity.[256] Finally, COPD is positively associated with abdominal aortic aneurysm, regardless of smoking status.[257]

Cardiac arrhythmias are common and may be due to the haemodynamic effects (pulmonary hypertension, diastolic dysfunction, atrial structural, and electrical remodelling) caused by the disease in combination with autonomic imbalance and abnormal ventricular repolarization.[258] AF is frequent, directly associated with FEV1, usually triggered by acute exacerbations of COPD, and an independent predictor of in-hospital COPD mortality.[259, 260] COPD is also a risk factor for ventricular tachycardia independent of LVEF,[261] and for SCD independent of CV risk profile.[262]

Unrecognised ventricular dysfunction is common in COPD,[263] although HF is 3.8 times more common in COPD patients than in controls.[264] Patients with frequent acute exacerbations show high frequency of diastolic dysfunction; HFpEF risk is higher because of a high prevalence of hypertension and DM.[265]

Considering these facts, it seems of upmost importance to screen COPD patients for ASCVD and ASCVD risk factors, bearing in mind that COPD affects the accuracy of CVD diagnostic tests. Achieving

adequate exercise is difficult, vasodilators for myocardial perfusion scanning may be contraindicated because of the risk of bronchospasm, and stress or transthoracic echocardiography is often disturbed by poor ultrasound windows. Computed tomography coronary angiography or magnetic resonance imaging may be alternatives, but remain expensive, time consuming, and not always available.

The use of COPD medication (i.e. long-acting muscarinic antagonists and long-acting beta agonists) is not associated with overall CV adverse events in patients with stable COPD. Olodaterol may reduce the risk of overall CV adverse events and formoterol may decrease the risk of cardiac ischaemia. Long-acting beta agonists may reduce the incidence of hypertension but may also increase the risk of HF, so should be used with caution in HF patients.[266]

Gaps in evidence

- Although common pathophysiological pathways between CVD and COPD are probable, they remain to be clarified.

3.4.6. Inflammatory conditions

Key message

- Chronic inflammatory conditions increase ASCVD risk.

Inflammatory conditions increase CVD risk both acutely and over time. The best evidence for chronic inflammation increasing CVD risk is available for rheumatoid arthritis (RA), which increases CVD risk by approximately 50% beyond established risk factors.[180] Hence, a low threshold for assessment of total CVD risk is appropriate in adults with RA, and one should consider increasing the risk estimate based on the level of disease activity.[180] There is also evidence for an approximately 20% increased ASCVD risk in patients with active inflammatory bowel disease.[267]

In other chronic inflammatory conditions, such as psoriasis[181] and ankylosing spondylitis,[182] ASCVD risk may also be increased. However, the strength of the evidence is less strong, as is the independence of such increased risks from the classical ASCVD risk factors. Nonetheless, it seems prudent to at least consider ASCVD risk assessment in patients with any chronic inflammatory condition, and to take into account the presence of such conditions when there is doubt regarding initiation of preventive interventions. The cumulative disease burden and recent degree of inflammation are important determinants of the risk-enhancing effect.

Apart from optimal anti-inflammatory treatment, ASCVD risk in inflammatory conditions should be treated with similar interventions as in the general high-risk population, as there is evidence that traditional methods to lessen risk (e.g. lipid-lowering treatment) are just as beneficial in preventing ASCVD.

Gaps in evidence

- The optimal way of integrating information on chronic inflammatory conditions in ASCVD risk assessment.

- The effect of modern anti-inflammatory drugs on cardiovascular risk (e.g. anti TNF, IL-1, IL-17. IL-23 biologics)

3.4.7. Infections (human immunodeficiency virus, influenza, periodontitis)

Key messages

- Infection with HIV is associated with an increased risk of LEAD and CAD.
- There is an association between influenza and periodontitis infections and ASCVD.

Infection with HIV is associated with a 19% increased risk of LEAD and CAD beyond that explained by traditional atherosclerotic risk factors [268, 269] However, for those with sustained CD4 cell counts <200 cells/mm^3, the risk of incident LEAD events is nearly twofold higher, whereas for those with sustained CD4 cell counts ≥500 cells/mm^3, there is no excess risk of incident LEAD events compared with uninfected people.[270]

CVD and influenza have long been associated, due to an overlap in the peak incidence of each disease during winter months. Epidemiological studies have noted an increase in CV deaths during influenza epidemics indicating that CV complications of influenza infection, including acute ischaemic heart disease and, less often, stroke, are important contributors to morbidity and mortality during influenza infection.

The risk of AMI or stroke is more than four times higher after a respiratory tract infection, with the highest risk in the first 3 days after diagnosis.[271] Preventing influenza, particularly by means of vaccination, could prevent influenza-triggered AMI.[272]

Studies have linked periodontal disease to both atherosclerosis and CVD,[273-275] and serological studies have linked elevated antibody titres of periodontal bacteria to atherosclerotic disease.[276] Nevertheless, if active treatment or prevention of periodontitis improves, clinical prognosis requires further studies despite preliminary evidence.[277-279]

Gaps in evidence

- Large-scale studies to assess the efficacy of influenza vaccination or periodontitis treatment in preventing CVD.
- The association of infection with HIV and total CVD risk.

3.4.8. Migraine

Key messages

- Migraine, and particularly migraine with aura, is an independent risk factor for stroke and ischaemic cardiac disease.
- The risk of ischaemic stroke in subjects with migraine with aura is magnified by the use of combined hormonal contraceptives and by cigarette smoking.

Migraine is a highly prevalent condition affecting around 15% of the general population.[280] There are two main types of migraine − migraine without aura, which is the most common subtype, and migraine with aura, which accounts for about one-third of all migraines; in many patients the two forms coexist.

Available data indicate that migraine overall is associated with a 2-fold increased risk of ischaemic stroke and with 1.5-fold increase in the risk of cardiac ischaemic disease.[183-185, 281, 282] The associations are more evident for migraine with aura.[183, 184, 282] Given the young mean age of 2 the population affected by migraine, the absolute increase in risk is small at the individual level but high at the population level because of the high migraine prevalence.[283]

Several lines of evidence also indicate that the vascular risk of subjects with migraine may be magnified by cigarette smoking[186] and by the use of combined hormonal contraceptives.[187, 283-285] Contraception using combined hormonal contraceptives should be avoided in women with migraine.[285, 286] However, further information is needed as good-quality studies assessing risk of stroke associated with low dose oestrogen use in women with migraine are lacking.

Gaps in evidence

- There are no data that allow reliable identification of subgroups of migraineurs at particular high risk (e.g. active migraine, high frequency auras, young subjects, women).
- The role of comorbid factors (e.g. patent foramen ovale, thrombophilic factors) is unclear, and at the moment there is no indication to screen or to manage for those factors.

3.4.9. Sleep disorders and obstructive sleep apnoea syndrome

Key message

- Non-restorative sleep and a sleep duration that varies significantly up or down from the optimum of 7 hours are associated with increased CV risk.

Sleep disturbances or abnormal sleep durations are associated with increased ASCVD risk.[287-289] Regarding sleep duration, 7 hours seems to be optimal for CV health.[290]

In the general population, the prevalence of general sleep disturbances is around 32.1%: 8.2% for insomnia, 6.1% for parasomnia, 5.9% for hypersomnolence, 12.5% for restless legs disorder and limb movements during sleep, 7.1% for sleep-related breathing disorder (e.g. obstructive sleep apnoea).[291] All sleep disturbances are strongly associated with mental disorders and share hyperarousal as an underlying mechanism.[292, 293]

The most important sleep-related breathing disorder is obstructive sleep apnoea (OSA), which is characterized by repetitive episodes of apnoea each exceeding 10 seconds. Despite the strong associations of OSA with CVD, including hypertension, stroke, heart failure, CAD, and atrial fibrillation, treatment of OSA by positive airway pressure (PAP) has failed to improve hard CV outcomes in patients with established CVD.[294-296] Therefore, interventions that include behaviour change (reduction of obesity, alcohol abstinence), sleep hygiene, and stress reduction in addition to PAP are needed.[293, 297] Regarding hypertension and OSA, there are modest effects of PAP on BP

levels, but only in patients with ambulatory blood pressure monitoring (ABPM)-confirmed resistant hypertension who use PAP for more than 5.8 h/night.[298]

Gaps in evidence

- There is lack of evidence that the inclusion of sleep improves risk prediction.
- Trials are needed that target the complex pathways linking sleep disturbances with CVD.

3.4.10. Mental disorders

Key messages

- Mental disorders are common in the general population (12-month prevalence of 27%) and are associated with excess mortality.
- The onset of CVD increases the risk of mental disorders by the 2.2-fold, leading to a worse prognosis.
- Some mental disorders and even symptoms of anxiety and depression are associated with the development of CVD and with a worse prognosis in those with existing CVD (CHD, AH, AF, HF)
- Excess mortality is mainly caused by behaviour-dependent risk factors (e.g. smoking addiction) and an impaired capacity for self-care (e.g. treatment adherence).

The 12-month prevalence of mental disorders or mental health disorders in the general European population is around 27%.[299] All mental disorders (e.g. anxiety disorders, somatoform disorders, substance disorders, personality disorders, mood disorders and psychotic disorders) are associated with the development of CVD and reduced life expectancy in both genders.[300-303] The risk increases with the severity of the mental disturbance and vigilance for (often non-specific) symptoms is crucial.[304] The onset of CVD has a 2.2-fold increased risk of mental disorders compared with that in the healthy population.[118, 305] In this context screening should be performed at every consultation (or 2-4 times/year). The 12-month prevalence of mental disorders in CVD patients is around 40%, leading to significantly worse prognosis.[103, 111, 306, 307]The onset of CVD increases the risk of committing suicide.[308] In this context awareness of anxiety and depression symptoms should be increased.

The precise mechanism by which mental disorders increase CVD remains uncertain. The detrimental effects are potentially caused by unhealthy lifestyle, increased exposure to socioeconomic stressors, and cardiometabolic side-effects of some medications,[116] but also by direct effects of the amygdala-based fear-defence system and other direct pathophysiological pathways.[306] Abuse of psychostimulants (e.g. cocaine) is a powerful trigger of myocardial ischaemia.[309] Further, the capacity of these patients to adaptively use the healthcare systems is impaired due to their mental condition (e.g. not being able to trust other people and seek help, impaired capacity to be adherent).[103] Barriers on the part of healthcare providers are stigmatizing attitudes, insufficient mental health literacy, and lack of confidence in mental healthcare.[310-312] Although patients with mental disorders have an increased ASCVD risk, they receive a lower rate of recognition and treatment of traditional ASCVD risk factors.[313] Preliminary evidence suggests that taking mental disorders into account improves classical CVD risk models.[314, 315]

Certain categories of patients with learning difficulties and associated disorders (such as Down's syndrome) are at increased risk of CVD disease, but perhaps not specifically ASCVD. However, health inequalities and the prevalence of cardiovascular risk factors may be greater in these populations although epidemiology research is scarce.

Gaps in evidence

- The precise mechanism by which mental disorders increase CVD remains uncertain
- How the consideration of mental disorders improves CV risk models.

3.4.11. Non-alcoholic fatty liver disease

Key messages

- Non-alcoholic fatty liver disease (NAFLD) is associated with other cardiometabolic risk factors.
- Patients with NAFLD should be evaluated for other cardiometabolic risk factors.

NAFLD has been associated with an increased risk of myocardial infarction and stroke. NAFLD represents accumulation of ectopic fat; persons with NAFLD are often overweight or obese, and not uncommonly have abnormal BP, glucose, and lipid levels. A recent study investigating whether NAFLD increases CV risk beyond traditional risk factors[316] shows that after adjusting for established risk factors, the associations did not persist. Nevertheless, patients with NAFLD should have their ASCVD risk calculated, be screened for diabetes, and be recommended a healthy lifestyle with a reduction of alcohol intake.

Gaps in evidence

- Whether NAFLD increases CV risk beyond traditional risk factors.

3.4.12. Sex-specific conditions

Key messages

- Pre-eclampsia and pregnancy-related hypertension, are associated with a higher risk of CVD.
- Polycystic ovary syndrome confers a significant risk for future development of DM.

3.4.1.1 Obstetric conditions

Pre-eclampsia (defined as pregnancy-related hypertension accompanied by proteinuria) occurs in 1–2% of all pregnancies and is associated with an increase in CV risk by a factor 1.5–2.7 compared with all women,[189, 190, 317] while the relative risk (RR) of developing hypertension is and DM is 3[191] and DM is 2.[188, 189] It has not been established whether the increased CV risk after pre-eclampsia occurs independent of CV risk factors. The rationale for screening these women for the occurrence of hypertension and DM is, however, quite strong. At present, no separate risk model for women with history of hypertensive disorders of pregnancy seems necessary, despite their higher baseline risk.[318]

Pregnancy-related hypertension affects 10–15% of all pregnancies. The associated risk of later CVD is lower than for preeclampsia but is still elevated (RR 1.7–2.5).[197, 317, 319, 320] Also, the risk for sustained or future hypertension is elevated (RRs vary, from 2.0 to 7.2 or even higher).[191, 321] Again, however, there was incomplete adjustment for conventional risk factors. The risk of developing DM is also elevated in these women (RR 1.6–2.0).[317, 322] Both preterm (RR 1.6) and stillbirth (RR 1.5) were associated with a moderate increase in risk of CVD.

Finally, gestational diabetes confers a sharply elevated risk of future DM, with up to 50% of affected women developing DM within 5 years after pregnancy, and an up to twofold increased risk of CVD in the future.[192, 323]

Screening by fasting glucose or glycated haemoglobin (HbA1c) may be preferable to oral glucose tolerance testing.[195, 324]

3.4.1.1 Non-obstetric conditions

Polycystic ovary syndrome (PCOS) affects 5% of all women in their fertile years. It has been associated with an increased risk of CVD.[317] The risk of developing hypertension is probably increased, but data are conflicting.[325] PCOS is associated with a higher risk of developing DM (RR 2–4),[193, 194] suggesting that periodic screening for DM is appropriate.

Premature menopause occurs in roughly 1% of women ≤40 years of age. Up to 10% of women experience an early menopause, defined as that occurring by 45 years of age.[317, 326] Early menopause is associated with an increased risk of CVD (RR 1.5).[327-329] A linear inverse relationship between earlier menopause and CHD risk was found, whereby each 1-year decrease in age at menopause portended a 2% increased risk of CHD.

Gaps in evidence

- The degree to which increased CVD risk associated with several of the female-specific conditions occurs independent of conventional CVD risk factors, although data in women are still underpowered as compared to those in men.
- Information on whether female-specific conditions improve risk classification.
- There are insufficient data to draw conclusions on a possible increased risk of hypertension or DM with premature menopause.
- Studies on the specificities of CVD disease in the transgender population are scarce

3.4.1.1 Erectile dysfunction

Key messages

- Erectile dysfunction (ED) is associated with future CV events and mortality in men.
- CVD risk should be assessed in men with ED.
- Asking about ED should be a standard procedure in routine CV risk assessment in men.

ED, defined as the consistent inability to reach and maintain an erection satisfactory for sexual activity, has a multifactorial cause. It affects almost 40% and more than 50% of men over 40 years and 60 years of age, respectively.[330, 331] Men with ED have an increased risk of all-cause mortality (odds ratio [OR] 1.26, 95% CI 1.01−1.57) and CVD mortality (OR 1.43, 95% CI 1.00−2.05). ED and CVD

share common risk factors (hypercholesterolaemia, hypertension, insulin resistance and DM, smoking, obesity, metabolic syndrome, sedentary lifestyle, and depression) and a common pathophysiological basis of aetiology and progression.[332, 333]

Medication used to prevent CVD, such as aldosterone receptor antagonists, some beta-blockers, and thiazide diuretics, can cause ED.[330, 332-335] ED is associated with subclinical vascular disease[336] and precedes CAD, stroke, and PAD by a period that usually ranges from 2−5 years (average 3 years). Men with ED have a 44−59% higher risk for total CV events, 62% for AMI, 39% for stroke, and 24−33% for all-cause mortality, with a higher risk in those with severe ED.[337-341]

There is strong evidence that CVD risk assessment is needed in men presenting with ED.[336, 342] In men with ED and low-to-intermediate CV risk, detailed risk profiling by, for example, CAC score is suggested, but so far not supported by evidence.[338, 341] Assessment of ED severity and physical examination should be part of the first-line CV risk assessment in men.[333, 341] Lifestyle changes are effective in improving sexual function in men: these include vigorous physical exercise,[334, 343] improved nutrition, weight control, and smoking cessation.[343-345]

Gap in evidence

- The benefit of routine screening for ED and the most effective tool to assess it are still unclear.
- The benefit of assessment of subclinical vascular disease in men with ED and low-to-intermediate CVD risk is unclear.

4. Risk Factors and interventions at the individual level

4.1. Treatment recommendations: classes, grades, and freedom of choice

Clear communication about risks and benefits is crucial before any treatment is initiated. Risk communication is discussed in chapter 3, and benefits of individual treatment are the topic of this chapter. In all scenarios where recommendations for individual interventions to reduce risk are "strong" (class I or IIa), it is important to realize that many patients who have received appropriate risk information often (in up to 50% of cases, some studies suggest) consciously opt to forego the proposed intervention. This applies to lifestyle measures but also to drug interventions. Apparently, what professionals feel is sufficient risk reduction for a reasonable effort or initiation of a drug with few side-effects does not always correspond to patients' views. The reverse is also true: not only may some patients at (very) high risk forego interventions, some patients with low to moderate risk may be highly motivated to decrease their risk even further. Hence, treatment recommendations are never 'imperative' for (very) high risk patients, nor are interventions ever 'prohibited' for patients at low to moderate risk. There is evidence that a higher proportion of women, as compared to men, who have a low awareness of their risk CVD and the need for therapeutic interventions warranting efforts to improve awareness, risk assessment and treatment in women.[52, 346-351]

4.2. Optimizing cardiovascular risk management

4.2.1. Goals of clinician–patient communication

Clinicians should provide a personalized presentation of guidelines to improve understanding, encourage lifestyle changes, and support adherence to drug therapy. Applying this in daily practice faces different barriers.[352] Patients' ability to adopt a healthy lifestyle depends on cognitive and emotional factors, the impact of a diagnosis or symptoms, socioeconomic factors, educational level, and mental health. Perceived susceptibility to illness and the anticipated severity of the consequences are also prominent components of patients' motivation.[353]

4.2.2. How to improve motivation?

Communication strategies such as motivational interviewing are useful.[354] Consultation sessions may include a family member or friend, especially in elderly patients. Connection is paramount: focus before greeting; listen intently; agree on what matters most; connect with the person's story; and explore emotions.[355] The OARS principle (Open-ended questions, Affirmation, Reflective listening, and Summarizing) helps patients to present their perceptions, and clinicians to summarize. The SMART principle (Specific, Measurable, Achievable, Realistic, Timely) may help setting goals for behavioural change.[353, 356] Healthcare professionals must consider capability, opportunity (physical, social, or environmental) and motivation for behavioural change.[357] Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended.[358]

4.2.3. Optimizing drug adherence

Medication adherence ranges from 50% for primary ASCVD prevention to 66% for secondary prevention.[359] Physicians should consider non-adherence in every patient and inquire non-judgmentally about it.[360] Approximately 9% of cases of ASCVD in the EU can be attributed to poor medication adherence.[361] Contributors to non-adherence include polypharmacy, complexity of drug/dose regimes, poor doctor–patient relationship, lack of disease acceptance, beliefs about consequences and side-effects, intellectual/cognitive abilities, mental disorders, physical limitations, financial aspects, and living alone.[360, 362-364] Importantly, only substantial risk reduction motivates patients for preventive drug treatment, which obviates the need for appropriate risk communication.[365, 366] Depression is another important factor, and adequate treatment thereof improves adherence.[367, 368]

Mobile phone applications may improve adherence to both medication and behavioural changes.[369] Their use is easy and probably cost-effective.[370]

4.2.4. Treatment goals

In the subsequent sections of this chapter, different domains of individual treatment are discussed. *Table 4* summarises the treatment goals and some key interventions for different categories of patients. For additional information on risk categories and the principle of a stepwise approach to treatment targets, please refer to *section 3.2.2*. For details on treatment goals, how to achieve them, strengths of recommendations and levels of supporting evidence, please go to the relevant sections in this chapter.

2023 **Table 4 Treatment goals for different patient categories**

2024

Patient category	Prevention goals (STEP 1)	Intensified/additional prevention goals[a] (STEP 2)
Apparently healthy persons	For BP and lipids: initiation of drug treatment based on CVD risk assessment (*Table 2*) or SBP >160 mmHg	
<50 years	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <2.6 mmol/L (<100 mg/dL)	SBP <130 mmHg if tolerated[b] LDL-C <1.8 mmol/L (<70 mg/dL) and >50% reduction in high risk LDL-C <1.4 mmol/L (<55 mg/dL)and >50% reduction in very high-risk
50–70 years	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <2.6 mmol/L (<100 mg/dL)	SBP <130 mmHg if tolerated[b] LDL-C <1.8 mmol/L (<70 mg/dL) and >50% reduction in high risk LDL-C <1.4 mmol/L (<55 mg/dL) and >50% reduction in very high-risk
>70 years	Stop smoking and lifestyle optimisation SBP <140 mmHg if tolerated[a,b] LDL-C <2.6 mmol/L (<100 mg/dL)	For specific risk factor management in patients >70 years old please see relevant sections in *chapter 4*.
Patients with CKD	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <2.6 mmol/L (<100 mg/dL) and ≥50% LDL-C reduction Otherwise according to ASCVD and diabetes history	LDL-C <1.8 mmol/L (<70 mg/dL) in *high risk* and <1.4 mmol/L (<55 mg/dL) in *very-high risk* (see table 3)
Familial Hypercholesterolemia	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <2.6 mmol/L (<100 mg/dL) and ≥50% LDL-C reduction Otherwise according to ASCVD and diabetes history	LDL-C <1.8 mmol/L (<70 mg/dL) in *high risk* and <1.4 mmol/L (<55 mg/dL) in *very-high risk* (see table 3)
People with type 2 diabetes mellitus		

Well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Stop smoking and lifestyle optimisation	
Without established ASCVD or severe target organ damage (see *Table 3* for definitions)	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <2.6 mmol/L (<100 mg/dL) HbA1c <53 mmol/mol (<7.0%)	SBP <130 mmHg if tolerated[b] LDL-C <1.8 mmol/L (<70 mg/dL) and >50% reduction SGLT2 inhibitor or GLP1-RA
With established ASCVD and/or severe target organ damage (see *3.2* for definitions)	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] LDL-C <1.8 mmol/L (<70 mg/dL) HbA1c <64 mmol/mol (<8.0%) SGLT2 inhibitor or GLP1-RA *CVD:* antiplatelet therapy	SBP <130 mmHg if tolerated[b] LDL-C <1.4 mmol/L (<55 mg/dL) and >50% reduction SGLT2 inhibitor or GLP1-RA if not already on *May additionally consider novel upcoming treatments: dual antiplatelet therapy, dual pathway inhibition,[a] colchicine, EPA.*
Patients with established ASCVD	Stop smoking and lifestyle optimisation SBP <140 down to 130 mmHg if tolerated[b] Intensive oral lipid-lowering therapy aiming at ≥50% LDL-C reduction and LDL-C <1.8 mmol/L (<70 mg/dL) Antiplatelet therapy	SBP <130 mmHg if tolerated[b] LDL-C <1.4 mmol/L (<55 mg/dL) *May additionally consider novel upcoming treatments: Dual antiplatelet therapy, dual pathway inhibition, colchicine, EPA, etc.*

BP = blood pressure; CKD = chronic kidney disease; ASCVD = atherosclerotic cardiovascular disease; DAPT = dual antiplatelet therapy; DBP = diastolic blood pressure; DM = diabetes mellitus; EPA = icosapent ethyl; GLP-1RA = glucagon-like peptide-1-receptor agonist; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure (office); SGLT2 = sodium-glucose cotransporter 2.

[a] Depending on 10-year (residual) risk AND/OR estimated lifetime benefit (see *Table 3* for details), comorbidities, and patient preference. Levels of Evidence of intensified goals vary, see recommendation tables in sections 4.6 and 4.7. For CKD and Familial Hypercholesterolemia, LDL targets are taken form the 2020 ESC guidelines for the treatment of dyslipidaemia.[62]

[b] Office DBP treatment target range <80 mmHg.

4.3. Optimising lifestyle

4.3.1. Physical activity and exercise

Key messages

- Regular physical activity (PA) is a mainstay of ASCVD prevention.
- Aerobic PA in combination with resistance exercise and the reduction of sedentary time are recommended for all adults.

Recommendations for physical activity

Recommendations	Class[a]	Level[b]
It is recommended for adults of all ages to strive for at least 150–300 min a week of moderate-intensity or 75–150 min a week of vigorous-intensity aerobic physical activity, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity.[371, 372]	I	A
It is recommended that adults who cannot perform 150 min of moderate-intensity physical activity a week should stay as active as their abilities and health condition allow.[373, 374]	I	B
It is recommended to reduce sedentary time to engage in at least light activity throughout the day to reduce all-cause and CV mortality and morbidity.[375-377]	I	B
Performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce all-cause mortality.[378, 379]	I	B
Lifestyle interventions, such as group or individual education, behaviour-change techniques, telephone counselling, and use of consumer-based wearable activity trackers, should be considered to increase physical activity participation.[380-382]	IIa	B

CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease.

[a] Class of recommendation.

[b] Level of evidence.

PA reduces the risk of many adverse health outcomes and risk factors in all ages and both sexes. There is an inverse relationship between moderate-to-vigorous PA and all-cause mortality, CV morbidity and mortality, as well as incidence of type 2 DM.[371-373, 383-387] The reduction in risk continues across the full range of PA volumes, and the slope of risk decline is steepest for the least active individuals.[371-374, 386, 387] More information on PA prescription can be found in recent ESC guideline.[388]

4.3.1.1 Physical activity prescription

PA should be individually assessed and prescribed in terms of frequency, intensity, time (duration), type, and progression.[389] Recommendations regarding pre-participation screening are found in

previous ESC guidelines.[388] Interventions shown to increase PA level or reduce sedentary behaviour include behaviour theory-based interventions, such as goal-setting, re-evaluation of goals, self-monitoring, and feedback.[372, 380, 381] Using a wearable activity tracker may help increase PA.[382] Most important is to encourage activity that people enjoy and/or can include in their daily routines, as such activities are more likely to be sustainable.

4.3.1.1 Aerobic physical activity

Examples of aerobic PA include walking, jogging, cycling, etc.[389] Adults are recommended to perform at least 150−300 min a week of moderate-intensity PA, or 75−150 min of vigorous-intensity PA, or an equivalent combination of both, spread throughout the week.[371, 372] Additional benefits are gained with even more PA. Practising PA should still be encouraged in individuals unable to meet the minimum. In sedentary individuals, a gradual increase in activity level is recommended. When older adults or individuals with chronic conditions cannot achieve 150 min of moderate-intensity PA a week, they should be as active as their abilities and conditions allow.[371-375, 384, 385] PA accumulated in bouts of even <10 minutes is associated with favourable outcomes, including mortality.[371, 390]

PA can be expressed in absolute or relative terms.[389] Absolute intensity is the amount of energy expended per minute of activity, assessed by oxygen uptake per unit of time (mL/min or L/min) or by metabolic equivalent of task (MET). A compendium of the energy cost in MET values for various activities is available.[391] An absolute measure does not consider individual factors such as body weight, sex, and fitness level.[389]

Relative intensity is determined based on individual's maximum (peak) effort, e.g. percentage of cardiorespiratory fitness (%$\dot{V}O_{2max}$), percentage of maximum (peak) HR (%HR_{max}) or using rating of perceived exertion according to the Borg scale. Less fit individuals generally require a higher level of effort than fitter people to perform the same activity. A relative intensity measure is necessary to provide an individualized PA prescription.[389]

Classification for both absolute and relative intensity and examples are presented in *Table 5*.

Table 5 Classification of physical activity intensity and examples of absolute and relative intensity levels. Modified from Howley.[392]

Absolute intensity			Relative intensity		
Intensity	**MET**	**Examples**	**%HR_{max}**	**RPE (Borg scale score)**	**Talk test**
Light	1.1–2.9	Walking <4.7 km/h, light household work	57–63	10–11	
Moderate	3–5.9	Walking with moderate or brisk pace (4.1–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling	64–76	12–13	Breathing is faster but compatible with speaking full sentences

		clubs in trolley), tennis (doubles), ballroom dancing, water aerobics			
Vigorous	≥6	Race-walking, jogging or running, cycling >15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (single)	77–95	14–17	Breathing very hard, incompatible with carrying on a conversation comfortably

%HR_{max} = percentage of measured or estimated maximum heart rate (220-age); MET = metabolic equivalent; O_2 = oxygen; PA = physical activity; RPE = rating of perceived exertion (Borg-scale 6-20); VO_2 = oxygen consumption.

[a] MET is estimated as the energy cost of a given activity divided by resting energy expenditure: 1 MET = 3.5 mL O_2 kg^{-1} min^{-1} VO_2.

4.3.1.1 Resistance exercise

Resistance exercise in addition to aerobic PA is associated with lower risks of total CV events and all-cause mortality.[378, 379, 393-395] The suggested prescription is one to three sets of 8–12 repetitions at the intensity of 60–80% of the individual's 1 repetition maximum (RM) at a frequency of least 2 days a week in a variety of 8–10 different exercises involving each major muscle group. For older adults or deconditioned individuals, it is suggested to start with one set of 10–15 repetitions at 40–50% of 1RM.[389] In addition, older adults are recommended to perform multicomponent PA that combines aerobic, muscle-strengthening, and balance exercises to prevent falls.[372]

4.3.1.1 Sedentary behaviour

Sedentary time is associated with greater risk for several major chronic diseases and mortality.[371, 372, 375-377, 396-399] For physically inactive adults, light-intensity PA, even as little as 15 minutes a day, is likely to produce benefits. There is mixed evidence to suggest how bout breaks in sedentary behaviour are associated with health outcomes.[375, 398, 400]

Gaps in evidence

- Knowledge on the relative importance of the various characteristics of aerobic PA and resistance exercise, or their combination, on all-cause mortality, CV incidence and mortality.
- Understanding how sex, age, weight, race/ethnicity, occupation, and socioeconomic status may modify associations between PA and health outcomes.
- Implementation of strategies to achieve long-term adherence to PA.
- Evaluation of the effects of eHealth tools in promoting PA.

4.3.2. Nutrition and alcohol

Key messages

- A healthy diet lowers the risk of ASCVD and other chronic diseases.
- A shift from a more animal- to plant-based food pattern may reduce ASCVD.

Recommendations for nutrition and alcohol

Recommendations	Class[a]	Level[b]
A healthy diet is recommended as a cornerstone of ASCVD prevention in all individuals.[401, 402]	I	A
It is recommended to adopt a Mediterranean or similar diet to lower risk of ASCVD.[403, 404]	I	A
It is recommended to replace saturated with unsaturated fats to lower the risk of ASCVD.[405-409]	I	A
It is recommended to reduce salt intake to lower BP and risk of ASCVD.[410]	I	A
It is recommended to choose a more plant-based food pattern, rich in fibre that includes whole grains, fruits, vegetables, pulses, and nuts.[411, 412]	I	B
It is recommended to restrict alcohol consumption to a maximum of 100 grams per week.[413-415]	I	B
It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.[406, 416-418]	I	B
It is recommended to restrict free sugar consumption, in particular sugar-sweetened beverages, to a maximum of 10% of energy intake.[419, 420]	I	B

BP = blood pressure; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease;

[a] Class of recommendation.

[b] Level of evidence.

Dietary habits influence CV risk, mainly through risk factors such as lipids, BP, body weight, and DM.[401, 402] *Table 6* summarizes characteristics of a healthy diet. Although recommendations about nutrients and foods remain important for CV health, there is a growing concern about environmental sustainability, supporting a shift from an animal- to a more plant-based food pattern.[411, 412]

Table 6 Healthy diet characteristics

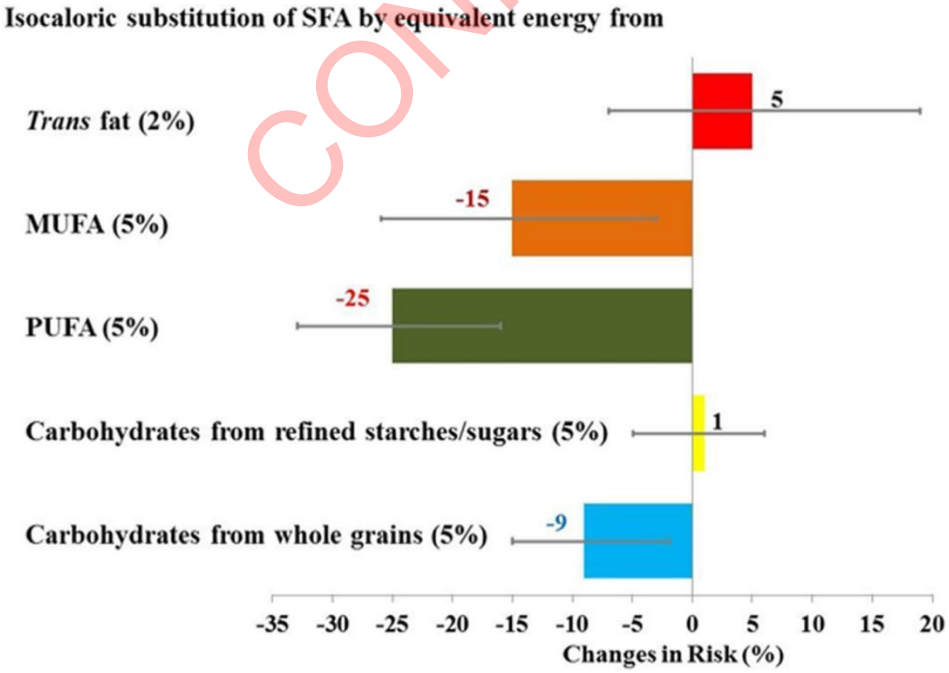
Healthy diet characteristics
Adopt a more plant- and less animal-based food pattern
Saturated fatty acids should account for <10% of total energy intake, through replacement by PUFAs, MUFAs, and carbohydrates from whole grains
Trans unsaturated fatty acids should be minimized as far as possible, with none from processed foods

<5 g total salt intake per day
30–45 g of fibre of per day, preferably from wholegrains
≥200 g of fruit per day (≥2–3 servings)
≥200 g of vegetables per day (≥2–3 servings)
Red meat should be reduced to a maximum of 350−500 g a week, in particular processed meat should be minimized
Fish is recommended 1–2 times per week, in particular fatty fish
30 g unsalted nuts per day
Consumption of alcohol should be limited to a maximum of 100 grams per week
Sugar-sweetened beverages, such as soft drinks and fruit juices, must be discouraged
MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

4.3.1.1 Fatty acids

Risk of CHD is reduced when dietary saturated fats are replaced appropriately (*Figure 9*). This is also the case when replacing meat and dairy foods.[406, 407] Polyunsaturated fats (−25%), monounsaturated fats (−15%), and to a lesser extent carbohydrates from whole grains (−9%), were all associated with reduced CHD risk when isocalorically substituted for dietary saturated fat.[408, 409]

Figure 9 Estimated percent change in risk of coronary heart disease associated with isocaloric substitutions of saturated fat for other types of fat or carbohydrates. Reproduced from Sacks et al.[409]



MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid; SFA: saturated fatty acid.

Reducing saturated fatty acid intake to less than 10% of energy may have additional benefits.[405] However, the LDL-C-lowering effect of substituting PUFAs for saturated fatty acids may be less in obese (5.3%) than in normal-weight persons (9.7%).[421]

Trans fatty acids formed during industrial processing of fats, have unfavourable effects on total cholesterol (increase) and HDL-C (decrease). On average, a 2% increase in energy intake from trans fatty acids is associated with a 23% higher CHD risk.[422] A regulation of the EU Commission has set the upper limits to 2 g per 100 g of fat (April2019) (https://ec.europa.eu/food/safety/labelling_nutrition/trans-fat-food_en).

When guidelines are followed to lower saturated fat intake, reductions in dietary cholesterol intake follow.

4.3.1.1 Minerals and vitamins

A reduction in sodium intake may reduce SBP by, on average, 5.8 mmHg in hypertensive, and 1.9 mmHg in normotensive patients.[410] The DASH trial showed a dose–response relation between sodium reduction and BP reduction. [423] In a meta-analysis, salt reduction of 2.5 g/d resulted in a 20% reduction of ASCVD events (RR 0.80).[410] A U- or J-shaped relation between a low salt intake and ASCVD is debated.[424] Underlying illness and malnutrition may explain both low food and salt intakes as well as increased ASCVD.[410, 425, 426] The totality of evidence warrants salt reduction to prevent CHD and stroke.

In most Western countries, salt intake is high (≈9–10 g/d), whereas the recommended maximum intake is 5 g/d. Optimal intake might be as low as ≈3 g/d. Salt reduction can be achieved by dietary choices (fewer processed foods) and the reformulation of foods by lowering their salt content (see *section 5.2.2*).

Potassium (e.g. in fruits and vegetables) has favourable effects on BP and risk of stroke (RR 0.76).[427]

As for vitamins, observational studies have found inverse associations between vitamins A and E and risk of ASCVD. However, intervention trials have failed to confirm these findings. Also, trials of supplementation with B vitamins (B6, folic acid, and B12), and vitamins C and D have not shown beneficial effects.[428, 429]

4.3.1.1 Fibre

Each 7 g/d higher intake of total fibre is associated with a 9% lower risk of CAD (RR 0.91).[430] A 10 g/d higher fibre intake was associated with a 16% lower risk of stroke (RR 0.84) and a 6% lower risk of type 2DM (RR 0.94,).[431, 432] A high fibre intake may reduce postprandial glucose responses after carbohydrate-rich meals and also lower triglyceride levels.[433]

4.3.1.1 Specific foods and food groups

4.3.2.4.1. Fruits, vegetables, and pulses

A meta-analysis reported a 4% lower risk in CV mortality for each additional serving of fruits (equivalent to 77 g) and vegetables (equivalent to 80 g) per day, while all-cause mortality was not reduced further with intakes of more than five servings.[434] A meta-analysis reported an 11% lower risk for stroke associated with three to five daily servings of fruits and vegetables and of 26% with

five servings a day compared with fewer than three servings.[435, 436] A single portion of pulses (legumes) a day lowers LDL-C by 0.2 mmol/L and is associated with a lower risk of CHD.[437, 438]

4.3.2.4.2. Nuts

A meta-analysis of prospective cohort studies suggested that daily consumption of 30 g of (mixed) nuts was associated with a ≈30% lower risk of ASCVD. [437] Both pulses and nuts contain fibre and other bioactive components.[438]

4.3.2.4.3. Meat

From both a health and an environmental point of view, a lower consumption of meat, especially processed meat, is recommended.[411] A restriction of red meat may have little or no effect on major cardiometabolic outcomes.[416] However, substituting red meat with high-quality plant foods (i.e. nuts, soy, and legumes) does improve LDL-C concentrations.[406] A recent analysis showed that higher intake of processed meat and unprocessed red meat is associated with a 7% and 3%, respectively, increased risk of ASCVD.[417]

By reducing processed meats, salt intake will also be reduced. The World Cancer Research Fund recommends limiting red meat consumption to 350–500 g per week.[439]

4.3.2.4.4. Fish and fish oil supplements

Studies indicate that eating fish, particularly fish rich in n-3 PUFA, at least once a week is associated with a 16% lower risk of CAD,[418] and eating fish two to four times a week is associated with a 6% lower risk of stroke.[440] The highest risk was observed in the range of no or very low intakes.

Several meta-analyses and a recent Cochrane review showed no benefits of fish oils on CV outcomes and/or mortality,[441-443] although a 7% lower risk of CHD events was observed. A meta-analysis of 13 RCTs included the results of VITAL, ASCEND, and REDUCE-IT. In the analysis excluding REDUCE-IT, fish oil reduced total ASCVD (RR 0.97) and CHD death (RR 0.92).[444] Including REDUCE-IT (a study done in participants with high triglycerides, comparing very high EPA doses vs. mineral oil placebo) strengthened the results.[444] However, this is the only study that tested a high EPA dose and questions have been raised regarding the choice of placebo. Very recently, the STRENGTH trial failed to demonstrate benefit of a combined EPA and DHA preparation.[445]

4.3.2.4.5. Alcoholic beverages

The upper safe limit of drinking alcoholic beverages is about 100 g of pure alcohol per week. How this translates into number of drinks depends on portion size, the standards of which differ per country, mostly between 8 and 14 grams per drink. This limit is similar for men and women.[446] Drinking above this limit lowers life expectancy.

Results from epidemiological studies have suggested that whereas higher alcohol consumption is roughly linearly associated with a higher risk of all stroke subtypes, coronary disease, heart failure, and several less common CVD subtypes appeared approximately log-linearly associated with a lower risk of myocardial infarction.[413] Moreover, Mendelian Randomization studies do not support the apparently protective effects of moderate amounts versus no alcohol against ASCVD, suggesting that the lowest risks for CVDs outcomes are in abstainers and that any amount of alcohol uniformly

increases BP and BMI.[414, 415] These data challenge the concept that moderate alcohol consumption is universally associated with lower CVD risk.

4.3.2.4.6. Soft drinks and sugar

Regular consumption of sugar-sweetened beverages (i.e. two servings per day compared with one serving per month) was associated with a 35% higher risk of CAD in women in the Nurses' Health Study, whereas artificially sweetened beverages were not associated with CAD. In the EPIC cohort, both artificially and sugar-sweetened soft drinks were associated with all-cause mortality, while only the former was associated with circulatory diseases.[419] The WHO guideline recommends a maximum intake of 10% of energy from free sugars (mono- and disaccharides), which includes added sugars as well as sugars present in fruit juices.[420]

4.3.2.4.7. Coffee

Non-filtered coffee contains LDL-cholesterol raising cafestol and kahweol, and may be associated with an up to 25% increased risk of ASCVD mortality by consumption of 9 or more drinks a day.[447] Non-filtered coffee includes boiled, Greek and Turkish coffee and some espresso coffees. Moderate coffee consumption (3-4 cups per day) is probably not harmful, perhaps even moderately beneficial.[448]

4.3.2.4.8. Functional foods

Functional foods containing phytosterols (plant sterols and stanols) are effective in lowering LDL-C levels by an average of 10% when consumed in amounts of 2 g/d.[449] The effect is in addition to that obtained with a low-fat diet or use of statins. No studies with clinical endpoints have been performed yet.

Red yeast rice supplements are not recommended and may even cause side-effects.[450]

4.3.2.4.9. Dietary patterns

Studying the impact of a total dietary pattern shows the full preventive potential of diet. The Mediterranean diet, including high intakes of fruits, vegetables, pulses, wholegrain products, fish, and olive oil, moderate consumption of alcohol, and low consumption of (red) meat, dairy products, and saturated fatty acids. Greater adherence to a Mediterranean diet is associated with a 10% reduction in CV incidence or mortality and an 8% reduction in all-cause mortality.[403] Following a Mediterranean diet enriched with nuts over a 5-year period, compared with a control diet, lowered risk of ASCVD by 28% and by 31% with a diet enriched with extra-virgin olive oil.[404]

Also, a shift from a more animal-based to a plant-based food pattern may reduce ASCVD.[411]

Gaps in evidence

- Effective strategies to encourage people to change their diet and to enjoy and maintain a healthy diet.

4.3.3. Body weight and composition

Key messages

- Achieving and maintaining a healthy weight through lifestyle change has favourable effects on risk factors (BP, lipids, glucose metabolism) and lowers ASCVD risk.
- When changes in diet and PA, as well as other conventional, non-invasive interventions are unsuccessful, bariatric surgery should be considered for high-risk individuals.
- Anti-obesity medications with protective ASCVD effects may also be considered.

Recommendations for body weight

Recommendations	Class[a]	Level[b]
It is recommended that overweight and obese people aim for a reduction in weight to reduce BP, dyslipidaemia, and risk of type 2 DM, and thus improve their ASCVD risk profile.[451, 452]	I	A
While a range of diets are effective for weight loss, it is recommended that a healthy diet in regard to ASCVD risk is maintained over time.[453-455]	I	A
Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.[456]	IIa	B

BP = blood pressure; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus.

[a] Class of recommendation.

[b] Level of evidence.

4.3.1.1 Treatment goals and modalities

Although diet, exercise, and behaviour modification are the main therapies for overweight and obesity, they are often unsuccessful in the long term. Yet, maintaining even a moderate weight loss of 5−10% of baseline has salutary effects on risk factors including BP, lipids, and glycaemic control[451, 452] , as well as on premature all-cause mortality.[457] Weight loss is associated with lower morbidity but higher mortality in (biologically) older adults (the “obesity paradox”). In this group, emphasis should be less on weight loss and more on maintaining muscle mass and good nutrition.

4.3.1.1 Diets for weight loss

Energy restriction is the cornerstone of management. PA is essential to maintain weight loss and prevent rebound weight gain, but is not reviewed here. Hypocaloric diets may be categorized as:

1. Diets that aim to reduce ASCVD, including plant-based[458, 459] and hypocaloric Mediterranean diets[459, 460] with modifications to suit local food availability and preferences;
2. Changes to the fat and carbohydrate macronutrient composition of the diet, including low- or very-low carbohydrate diets (with 50−130 g and 20−49 g carbohydrates/day, respectively),

moderate carbohydrate diets (>130–225 g carbohydrates/day), and low-fat diets (<30% of energy from fat);
3. High-protein diets to preserve lean muscle mass and enhance satiety;
4. Diets focusing on specific food groups (e.g. increasing fruit and vegetables or avoiding refined sugars);
5. Diets that restrict energy intake for specified time periods, for example on 2 days a week or alternate days (intermittent fasting) or during certain hours of the day (time-restricted eating).

These diets give broadly similar short-term weight loss.[453-455] By 12 months, the effects tend to diminish.[454] Those of the Mediterranean diet, however, tend to persist. The quality of nutrients in a diet, for example substituting unsaturated for saturated fats (see *section 4.2.2*) and including fibre-rich carbohydrates[461] determines whether a diet is healthy in the long term.

Low or very-low carbohydrate diets may have advantages regarding appetite control, lowering triglycerides, and reducing medications for type 2 diabetes.[462] Such diets may be ketogenic and need medical or at least dietetic supervision. Studies beyond 2 years are scarce. Extreme carbohydrate intakes should be avoided in the long term and plant substitutions of fat and protein for carbohydrates are advantageous over animal ones.[463]

Intermittent fasting diets produce equivalent weight loss to continuous energy restriction when matched for energy intake.[464]

Medications approved in Europe as aids to weight loss (orlistat, naltrexone/bupropion, high-dose liraglutide) may supplement lifestyle change to achieve weight loss and maintenance, though sometimes at the expense of side-effects. Meta-analysis of medication-assisted weight loss found favourable effects on BP, glycaemic control, and ASCVD mortality.[465]

A very effective treatment option for extreme obesity or obesity with comorbidities is bariatric surgery. A meta-analysis indicated that patients undergoing bariatric surgery had over 50% lower risks of total, ASCVD, and cancer mortality compared with people of similar weight who did not have surgery.[456]

Gaps in evidence

- Knowledge and implementation of effective lifestyle and medication-assisted strategies to achieve weight loss and maintain a long-term healthy weight.

4.4. Mental healthcare and psychosocial interventions

Key messages

- Patients with mental disorders have sharply increased lifestyle risks that need recognition and treatment.
- Mental healthcare improves stress symptoms and quality of life, reduces the risk of suicide, and may improve CV outcomes.
- The treatment of ASCVD patients with mental disorders requires interdisciplinary cooperation and communication.

Recommendations for mental healthcare and psychosocial interventions at the individual level

Recommendations	Class[a]	Level[b]
Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and adherence to drug treatment.[3, 466]	I	C
In ASCVD patients with mental disorders, evidence-based mental healthcare and interdisciplinary cooperation are recommended.[103, 116, 467]	I	B
ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CV outcomes and reduce stress symptoms.[468-470]	IIa	B
Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.[471, 472]	IIa	B
In patients with HF and major depression, SSRIs, SNRIs, and tricyclic antidepressants are not recommended.[473, 474 c]	III	B

CHD = coronary heart disease; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; HF = heart failure; SNRI = selective serotonin noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

[a] Class of recommendation.

[b] Level of evidence.

[C] Details explaining this recommendation are provided in the supplementary material.

Treatment of unhealthy lifestyle will reduce ASCVD risk as well as improve mental health. Smoking cessation, for instance, has a positive effect on depression outcomes,[475, 476] as do exercise therapy[116, 477] and healthful dietary practices.[478] Evidence-based interventions for smoking cessation, and improving PA and diet, are considered useful and applicable for persons with mental disorders.[466, 479-481]

Mental disorders are associated with an increased risk of ASCVD and a worse prognosis in patients with ASCVD, due to ASCVD events or other death causes, including suicide.[103, 116, 308] Mental-health treatments effectively reduce stress symptoms and improve quality of life. Several observational studies indicate that treatment or remission of depression reduces ASCVD risk.[116, 482-485] Psychological interventions in patients with CHD reduce cardiac mortality (RR 0.79) and alleviate psychological symptoms.[467]. Psychotherapy focusing on stress management in ASCVD patients improves ASCVD outcomes. In the SUPRIM trial, patients in the intervention group had a 41% lower rate of fatal and non-fatal first recurrent ASCVD events (HR 0.59) and fewer recurrent AMIs (HR 0.55).[468] In the SWITCHD trial, the intervention yielded a substantial reduction in all-cause mortality (OR 0.33).[469] A recent RCT reported that CV rehabilitation (CR) enhanced by stress management produced

significant reductions in ASCVD events compared with standard CR alone (HR 0.49).[470] Concerning psychopharmacotherapy of patients with CHD and depression, SSRI lower rates of CHD readmission (risk ratio 0.63) and all-cause mortality (risk ratio 0.56).[471] A recent RCT reported that in patients with ACS and depression, treatment with the SSRI escitalopram resulted in a lower rate of the composite endpoint of all-cause mortality, myocardial infarction, or PCI (HR 0.69).[472] Collaborative care for patients with CHD and depression has small beneficial effects on depression but significantly reduces short-term major cardiac events.[486]

Concerning side-effects of psychopharmacological treatments, many psychiatric drugs are associated with an increased risk of sudden cardiac death.[487] In patient with HF, antidepressants are associated with increased risk of cardiac and all-cause mortality (HR 1.27; for details see supplemental text).[473] Therefore, ASCVD patients with complex mental disorders, and particularly those needing psychiatric drug treatment, require interdisciplinary cooperation.

Gaps in evidence

- The effectiveness of mental healthcare for the prevention of major ASCVD events.
- How to implement effective ASCVD prevention measures in this high-risk population of patients with mental disorders.

4.5. Smoking intervention

Key messages

- Stopping smoking rapidly reduces ASCVD risk and is the most cost-effective strategy for ASCVD prevention.
- There is strong evidence for medication-assisted interventions: nicotine-replacement therapy (NRT), bupropion, varenicline, and drugs in combination. The most effective are assistance using drug therapy and follow-up support.

Recommendations for smoking-intervention strategies

Recommendations	Class[a]	Level[b]
All smoking of tobacco should be stopped, as tobacco use is strongly and independently causal of ASCVD.[488, 489]	I	A
In smokers, offering follow-up support, nicotine replacement therapy, varenicline, and bupropion individually or in combination should be considered.[490-495]	IIa	A
Smoking cessation is recommended regardless of weight gain, as weight gain does not mitigate the ASCVD benefits of cessation.[496]	I	B

ASCVD = atherosclerotic cardiovascular disease.

[a] Class of recommendation.

[b] Level of evidence.

4.5.1. Smoking cessation

Stopping smoking is potentially the most effective of all preventive measures, with substantial reductions in (repeat) myocardial infarctions or death.[488, 489] Lifetime gains in ASCVD-free years are substantial at all ages, and benefits are obviously even more substantial if other complications from smoking would be accounted for. From age 45, gains of 3–5 years persist in men to age 65 and in women to age 75 (*Figure 10*). Even in heavy (≥20 cigarettes/day) smokers, cessation lowers ASCVD risk within 5 years, though it remains elevated beyond 5 years. Total health benefits will be even larger because of gain in non-CVD health.

Figure 10 Lifetime ASCVD benefit from smoking cessation for apparently healthy persons, based on the following risk factors: age, sex, current smoking, systolic blood pressure, low-density lipoprotein cholesterol. The model is currently validated for low and moderate risk countries.

The lifetime benefit is expressed as "years of median life expectancy free from myocardial infarction or stroke" gained from smoking cessation. The lifetime benefit is calculated by estimating lifetime ASCVD risk with the LIFE-CVD model[74] multiplied by the HR compared to sustained smoking (0.60) from a meta-analysis of studies on the ASCVD risk of smoking[497] and multiplied by the HR (0.73) for non-CVD competing mortality.[498] For individualized estimations of lifetime benefit, this table can be used or the electronic version of LIFE-CVD, assessable via the ESC CVD risk app or http://www.U-Prevent.com.

OUP to match abbreviations in figure.

BP = blood pressure; ASCVD = atherosclerotic cardiovascular disease; DIAL = Diabetes Lifetime-perspective prediction; ESC = European Society of Cardiology; DM = diabetes mellitus; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; MI = myocardial infarction; REACH = Reduction of Atherothrombosis for Continued Health; SBP = systolic blood pressure; SMART = Secondary Manifestations of Arterial Disease.

LIFE-CVD model

CVD-free lifetime gain from smoking cessation (in years)

- < 0.5 years
- 0.5 - 0.9 years
- 1.0 - 1.4 years
- 1.5 - 2.0 years
- ≥ 2.0 years

Systolic BP (mmHg)	Women				Age	Men			
160-179	0.8	0.8	0.9	0.9	90+	0.5	0.5	0.5	0.6
140-159	0.8	0.8	0.8	0.8		0.5	0.5	0.6	0.6
120-139	0.8	0.8	0.8	0.8		0.5	0.6	0.6	0.7
100-119	0.8	0.8	0.8	0.8		0.5	0.7	0.7	0.7
160-179	1.6	1.7	1.9	1.9	85 - 89	0.7	0.9	0.9	1.0
140-159	1.7	1.8	1.9	1.9		0.8	0.9	1.0	1.0
120-139	1.8	1.8	1.8	1.8		0.8	0.9	1.0	1.1
100-119	1.7	1.7	1.8	1.8		0.8	1.0	1.0	1.1
160-179	2.0	2.3	2.4	2.4	80 - 84	1.2	1.3	1.4	1.4
140-159	2.2	2.3	2.4	2.5		1.2	1.3	1.4	1.4
120-139	2.2	2.3	2.5	2.5		1.2	1.3	1.4	1.5
100-119	2.2	2.4	2.5	2.5		1.2	1.3	1.4	1.5
160-179	2.6	2.8	2.8	2.9	75 - 79	1.6	1.7	1.9	1.9
140-159	2.6	2.7	2.9	3.0		1.7	1.8	1.9	1.9
120-139	2.6	2.7	2.9	3.0		1.6	1.8	1.9	2.0
100-119	2.6	2.7	2.9	3.0		1.7	1.8	1.9	1.9
160-179	3.0	3.2	3.4	3.4	70 - 74	2.1	2.3	2.4	2.5
140-159	3.1	3.2	3.3	3.4		2.1	2.2	2.4	2.4
120-139	3.0	3.1	3.3	3.4		2.0	2.2	2.3	2.4
100-119	3.0	3.1	3.2	3.3		2.1	2.2	2.3	2.3
160-179	3.4	3.6	3.8	3.9	65 - 69	2.6	2.7	2.9	2.9
140-159	3.4	3.6	3.7	3.8		2.5	2.7	2.8	2.8
120-139	3.3	3.5	3.6	3.7		2.4	2.6	2.7	2.7
100-119	3.6	3.6	3.8	3.9		2.7	2.7	2.9	2.9
160-179	3.7	4.0	4.1	4.3	60 - 64	3.0	3.1	3.3	3.4
140-159	3.7	3.9	4.1	4.2		2.9	3.0	3.2	3.3
120-139	3.6	3.7	4.0	4.0		2.8	2.9	3.0	3.1
100-119	3.6	3.6	3.8	3.9		2.7	2.7	2.9	2.9
160-179	4.1	4.3	4.5	4.6	55 - 59	3.3	3.5	3.7	3.8
140-159	4.0	4.2	4.4	4.5		3.1	3.2	3.5	3.6
120-139	3.9	4.0	4.3	4.3		2.9	3.1	3.3	3.4
100-119	3.8	3.9	4.0	4.1		2.8	3.0	3.1	3.2
160-179	4.3	4.5	4.8	4.9	50 - 54	3.5	3.7	3.9	4.2
140-159	4.2	4.4	4.6	4.7		3.3	3.5	3.7	3.9
120-139	4.1	4.3	4.4	4.5		3.1	3.3	3.4	3.6
100-119	3.9	4.0	4.2	4.3		2.9	3.1	3.2	3.3
160-179	4.5	4.7	5.0	5.1	45 - 49	3.7	3.9	4.2	4.4
140-159	4.4	4.5	4.8	4.9		3.4	3.7	3.9	4.1
120-139	4.2	4.4	4.6	4.7		3.3	3.4	3.6	3.7
100-119	4.1	4.2	4.4	4.5		3.1	3.2	3.3	3.5
160-179	4.5	4.8	5.1	5.2	40 - 44	3.7	4.0	4.3	4.5
140-159	4.4	4.6	4.9	5.0		3.5	3.7	4.0	4.2
120-139	4.3	4.5	4.6	4.8		3.3	3.5	3.7	3.9
100-119	4.1	4.3	4.5	4.5		3.2	3.3	3.4	3.6
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250 mg/dL

Quitting must be encouraged in all smokers, and passive smoking should be avoided as much as possible. Very brief advice may be advantageous when time is limited (*Table 7*). A major impetus for cessation occurs at the time of diagnosing or treatment of CVD. Prompting a person to try to quit, brief reiteration of CV and other benefits of quitting and agreeing on a specific plan with a follow-up arrangement are evidence-based interventions.

Table 7 "Very brief advice" for smoking cessation

"Very brief advice" on smoking is a proven 30-second clinical intervention, developed in the UK, which identifies smokers, advises them on the best method of quitting, and supports subsequent quit attempts. There are three elements to very brief advice:
• ASK – establishing and recording smoking status
• ADVISE – advising on the best ways of stopping
• ACT – offering help

Smokers who quit may expect an average weight gain of 5 kg, but the health benefits of tobacco cessation outweigh risks from weight gain.[3] Persistent or reuptake of smoking is common in patients with CHD, in particular in those with severe depression and environmental exposures.[499] Mood-management therapies may improve outcomes in patients with current or past depression.[500]

4.5.2. Evidence-based drug interventions

Drug support for stopping smoking should be considered in all smokers who are ready to undertake this action. Evidence-based drug interventions include NRT, bupropion, varenicline, and cytisine (not widely available).[490-492] All forms of NRT (chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets) are effective. Combination versus single-form NRT and 4 mg versus 2 mg gum can increase success.[493] NRT shows no adverse effects in patients with ASCVD,[494] but evidence of efficacy in this group is inconclusive.[495] In patients with ASCVD, varenicline (RR 2.6), bupropion (RR 1.4), telephone therapy (RR 1.5), and individual counselling (RR 1.6) all increase success rates.[495] The antidepressant bupropion aids long-term smoking cessation with similar efficacy to NRT.[491]

Varenicline 1 mg *b.i.d.* increases quitting rates more than twofold compared with placebo.[492] The RR for abstinence versus NRT was 1.25 and versus bupropion 1.4. Lower or variable doses are also effective and reduce side-effects. Varenicline beyond the 12-week standard regimen is well-tolerated. Varenicline initiated in-hospital following ACS is efficacious and safe.[501]

The main side-effect of varenicline is nausea, but this usually subsides. A causal link between varenicline and neuropsychiatric adverse events is unlikely.[502] Varenicline, bupropion, and NRT do not increase serious CV adverse event risks during or after treatment.[503]

Cytisine is effective for smoking cessation but evidence to date is limited.[492]

4.5.1.1 Electronic cigarettes

Electronic cigarettes (e-cigarettes) simulate combustible cigarettes by heating nicotine and other chemicals into a vapour. E-cigarettes deliver nicotine without most of the tobacco chemicals, and are probably less harmful than tobacco.

Recent evidence suggests that e-cigarettes are probably more effective than NRT in terms of smoking cessation.[504-506] The long-term effects of e-cigarettes on cardiovascular and pulmonary health, however, require more research.[507] Dual use with cigarettes should be avoided. Furthermore, as e-cigarettes are addictive, their use should be subject to similar marketing controls as standard cigarettes, especially the flavoured varieties that appeal to children.[508] Despite being lower in toxicants than regular cigarettes, 'heat-not-burn' cigarettes do contain tobacco and should be discouraged.

Gaps in evidence

- A better understanding of how to incorporate effective smoking cessation into clinical practice.

4.6. Lipids

Key messages

- Lower is better: the effect of LDL-C on the risk of ASCVD appears to be determined by both the baseline level and the total duration of exposure to LDL-C.
- Lowering LDL-C with statins, ezetimibe, and – if needed and cost-effective – proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, decreases the risk of ASCVD proportionally to the absolute achieved reduction in LDL-C.
- When LDL-C goals according to level of risk cannot be attained, aim at reducing LDL-C by at least 50% and then strive to reduce other risk factors as part of a shared decision-making process with the patient.

This section covers recommendations for the diagnosis and treatment of unfavourable blood-lipid levels. More detail and guidance for complex cases/tertiary care, including genetic lipid disorders, are available in the 2019 ESC/EAS Guidelines for the management of dyslipidaemias.[3]

Recent evidence has confirmed that the key initiating event in atherogenesis is the retention of LDL and other cholesterol-rich lipoproteins within the arterial wall. The causal role of LDL-C, and other apo-B-containing lipoproteins, in the development of ASCVD is demonstrated beyond any doubt by genetic, observational, and interventional studies.[20] Meta-analysis of clinical trials has indicated that the relative reduction in ASCVD risk is proportional to the absolute reduction of LDL-C, irrespective of the drug(s) used to achieve such change, with no evidence of a lower limit for LDL-C values or "J-curve" effect.[21] The absolute benefit of lowering LDL-C depends on the absolute risk of ASCVD and the absolute reduction in LDL-C, so even a small absolute reduction in LDL-C may translate to significant absolute risk reduction in a high- or very high-risk patient.[509] A recent LDL-C target-driven RCT in patients after ischaemic stroke or TIA demonstrated a target LDL-C level of <1.8 mmol/L (70 mg/dL) with the use of statin and, if required, ezetimibe, was associated with a lower ASCVD risk than those who had a target range of 2.3–2.8 mmol/L (90–110 mg/dL).[510] Studies on the clinical

safety of (very) low achieved LDL-C values have not caused particular concerns, although monitoring for longer periods is required.

4.6.1. Measurement of lipids and lipoproteins

4.6.1.1 Fasting versus non-fasting measurements

Non-fasting sampling of lipid parameters is recommended for general risk screening, since it has the same prognostic value as fasting samples.[511, 512] In patients with metabolic syndrome, DM, or hypertriglyceridaemia, calculated LDL-C from non-fasting samples should be interpreted with care.

4.6.1.1 LDL-C measurement

LDL-C can be measured directly, but in most studies and many laboratories LDL-C is calculated using the Friedewald formula:

- In mmol/L: LDL-C = total cholesterol – HDL-C – (0.45 × triglycerides)
- In mg/dL: LDL-C = total cholesterol – HDL-C – (0.2 × triglycerides)

The calculation is valid only when the concentration of triglycerides is <4.5 mmol/L (~400 mg/dL), and not precise when LDL-C is very low (<1.3 mmol/L [50 mg/dL]). In patients with low LDL-C levels, and/or hypertriglyceridaemia (≤800 mg/dL), alternative formulas are available[513, 514] or LDL can be measured directly.

4.6.1.1 Non–high-density lipoprotein cholesterol

The non–HDL-C value is calculated by subtracting HDL-C from total cholesterol. Non–HDL-C, unlike LDL-C, does not require the triglyceride concentration to be <4.5 mmol/L (400 mg/dL). It also has an advantage in that it is accurate in a non-fasting setting, and it may be more accurate in patients with DM. There is evidence for a role of non–HDL-C as a treatment target as it captures the information regarding all apolipoprotein-B–containing lipoproteins.[515] We suggest it as a reasonable alternative treatment goal for all patients, particularly for those with hypertriglyceridaemia or DM. How non–HDL-C levels correspond to commonly used LDL-C goals is shown in *Table 8.*

4.6.1.1 Apolipoprotein B

Apolipoprotein B provides a direct estimate of the total concentration of atherogenic lipid particles, particularly in patients with elevated triglycerides. However, on average, the information conferred by apolipoprotein B is similar to that of calculated LDL-C.[516] How apolipoprotein B levels correspond to commonly used LDL-C goals is shown in *Table 8*.

Table 8 Corresponding non–high-density lipoprotein cholesterol and apolipoprotein B levels for commonly used low-density lipoprotein cholesterol goals

LDL-C	Non–HDL-C	Apolipoprotein B
2.6 mmol/L (100 mg/dL)	3.4 mmol/L (131 mg/dL)	100 mg/dL

1.8 mmol/L (70 mg/dL)	2.6 mmol/L (100 mg/dL)	80 mg/dL
1.4 mmol/L (55 mg/dL)	2.2 mmol/L (85 mg/dL)	65 mg/dL
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.		

4.6.2. Defining lipid goals

4.6.1.1 Low-density lipoprotein cholesterol goals

Recommendation on low-density lipoprotein cholesterol goals[a]

Recommendation	Class[b]	Level[c]
A stepwise treatment-intensification approach is recommended for apparently healthy people at high or very high ASCVD risk, as well as patients with established ASCVD and/or DM with consideration of ASCVD risk, treatment benefit, risk modifiers, comorbidities and patient preferences.	I	C

ASCVD = atherosclerotic cardiovascular disease; DM = diabetes; LDL-C = low-density lipoprotein cholesterol.

[a] Recommendation from *section 3.*2.

[b] Class of recommendation.

[c] Level of evidence.

LDL-C goals are summarized in the recommendations below. Because not all drugs are tolerated or available/affordable, treatment should focus on achieving LDL-C levels as close as possible to the given goals. Treatment should be a shared decision-making process between physicians and the patient**.**

As explained earlier in these Guidelines (*chapter 3.2.2*), we propose a stepwise approach to treatment goals, also for LDL-C (*Figures 4–6*). This approach may seem novel but, in reality, resembles clinical practice, where treatment intensification is considered based on anticipated benefit, side effects and, importantly, patient preferences. The ultimate lipid goals are the same as in the 2019 ESC dyslipidaemia Guidelines.[62] Evidence from glucose lowering studies treatment indicates that stepwise treatment does not compromise goal attainment, and is associated with fewer side effects and higher patient satisfaction.[64, 65] In specific cases (at very high risk), the physician may opt to merge both steps and proceed directly to the low LDL-C target level of step 2. In apparently healthy people, lifetime treatment benefit of LDL-C reduction may play a role in shared decision-making together with risk modifiers, comorbidities, patient preference, frailty. *Figure 11* may support decision-making, as it shows the estimated lifetime benefits in years-free-of-ASCVD in relation to the total ASCVD risk profile, calibrated in low-to-moderate ASCVD risk countries. Similar calculations can be made for patients with DM or established ASCVD (see *chapter 3*).

After step 1, treatment intensification with step 2 must be considered in all patients. Given that *lower is better*, we encourage liberal intensification of treatment, particularly if submaximal doses of (low-cost) generic statins are used and side-effects are not apparent.

The treatment goal of LDL-C <1.4 mmol/L (55 mg/dL) in step 2, in patients with established ASCVD or without ASCVD but at very high risk, is lower than the lowest LDL-C goal of 1.8 mmol/L (70 mg/dL) in the 2016 ESC Joint Task Force prevention guidelines. This low goal was established based on data from recent mendelian randomization studies,[517] meta-analyses from the Cholesterol Treatment Trialists' (CTT) Collaboration,[21] RCTs such as IMPROVE-IT,[518] and more recently PCSK9 inhibitor clinical outcome studies.[519-521] The class and level of evidence supporting this LDL-C target of <1.4 mmol/L (55 mg/dL) for patients with ASCVD is identical to that in the recent ESC Dyslipidaemia guidelines.[62] For primary prevention in very-high risk patients, however, the class of recommendation is lower (class I in the dyslipidaemia guideline, class IIa in the current guidelines), because the Task Force was less unanimous with regards to this low LDL-C target in the primary prevention context.

For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first) while taking maximum tolerated statin-based therapy, an even lower LDL-C goal of <1.0 mmol/L (40 mg/dL) may be considered. Importantly, there are no differences in the RR reductions between men and women and between younger and older patients (at least up to age 75), or between those with and without DM.[3]

Figure 11 Average years-free-of- cardiovascular disease gained per 1 mmol/L (40 mg/dL) low-density lipoprotein cholesterol reduction in apparently healthy persons. The model is currently validated for low and moderate risk countries.

Lifetime benefit of 1 mmol/L LDL-C lowering for apparently healthy persons, based on the following risk factors: age, sex, current smoking, SBP, and DL-C. The lifetime benefit is expressed as “years of median life expectancy free from myocardial infarction or stroke” gained from 1 mmol/L LDL-C lowering. For 2 mmol/l LDL-c lowering, the average effect is almost twice as large, etc. The lifetime benefit is calculated by estimating lifetime ASCVD risk with the LIFE-CVD model[74] multiplied by the HR (0.78) from a meta-analysis of the effect of lipid-lowering.[22] For individualized estimations of lifetime benefit, this table can be used or the electronic version of LIFE-CVD, assessable via the ESC CVD risk app or http://www.U-Prevent.com.

BP = blood pressure; ASCVD = atherosclerotic cardiovascular disease; DIAL = Diabetes Lifetime-perspective prediction; ESC = European Society of Cardiology; DM = diabetes mellitus; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; MI = myocardial infarction; REACH = Reduction of Atherothrombosis for Continued Health; SBP = systolic blood pressure; SMART = Secondary Manifestations of Arterial Disease. OUP to match abbreviations with figure.

LIFE-CVD model

CVD-free lifetime gain from 1 mmol/L LDL-C reduction (in years)

< 0.5 years
0.5 - 0.9 years
1.0 - 1.4 years
1.5 - 2.0 years
≥ 2.0 years

	Women									Men							
	Non-smoking				Smoking				*Age*	Non-smoking				Smoking			
160-179	0.3	0.4	0.4	0.4	0.1	0.1	0.2	0.2		0.2	0.3	0.3	0.3	0.1	0.0	0.1	0.1
140-159	0.3	0.3	0.4	0.4	0.1	0.1	0.1	0.1		0.2	0.2	0.2	0.3	0.0	0.0	0.0	0.0
120-139	0.2	0.3	0.3	0.3	0.1	0.1	0.1	0.1	90+	0.1	0.1	0.2	0.2	0.1	0.0	0.0	0.1
100-119	0.2	0.2	0.2	0.2	0.0	0.0	0.1	0.1		0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.1
160-179	0.8	0.8	0.9	0.9	0.2	0.2	0.3	0.4		0.4	0.5	0.5	0.5	0.1	0.1	0.1	0.2
140-159	0.6	0.7	0.8	0.8	0.1	0.2	0.2	0.3	85 - 89	0.3	0.4	0.5	0.5	0.1	0.1	0.1	0.1
120-139	0.5	0.6	0.7	0.7	0.1	0.2	0.2	0.2		0.3	0.4	0.4	0.4	0.0	0.0	0.1	0.1
100-119	0.4	0.4	0.5	0.6	0.0	0.1	0.1	0.1		0.2	0.2	0.3	0.3	0.0	0.0	0.0	0.1
160-179	1.0	1.1	1.2	1.3	0.2	0.4	0.4	0.5		0.5	0.6	0.7	0.7	0.1	0.2	0.2	0.2
140-159	0.9	1.0	1.1	1.1	0.2	0.3	0.3	0.4	80 - 84	0.4	0.5	0.6	0.7	0.1	0.1	0.2	0.1
120-139	0.7	0.8	0.9	1.0	0.2	0.2	0.3	0.2		0.4	0.4	0.5	0.5	0.0	0.1	0.1	0.1
100-119	0.5	0.6	0.7	0.8	0.1	0.1	0.2	0.2		0.2	0.3	0.4	0.4	0.0	0.0	0.0	0.1
160-179	1.2	1.3	1.4	1.4	0.4	0.5	0.5	0.6		0.7	0.8	0.9	1.0	0.2	0.2	0.3	0.3
140-159	1.0	1.2	1.3	1.4	0.2	0.3	0.5	0.5	75 - 79	0.6	0.6	0.7	0.9	0.2	0.2	0.3	0.3
120-139	0.8	1.0	1.1	1.2	0.2	0.2	0.3	0.4		0.4	0.5	0.6	0.7	0.1	0.2	0.2	0.2
100-119	0.6	0.8	0.9	1.0	0.2	0.2	0.2	0.3		0.3	0.4	0.5	0.6	0.1	0.1	0.2	0.1
160-179	1.3	1.4	1.5	1.6	0.5	0.6	0.7	0.8		0.8	0.9	1.1	1.1	0.3	0.4	0.5	0.5
140-159	1.1	1.3	1.4	1.5	0.4	0.5	0.6	0.6	70 - 74	0.7	0.8	1.0	1.0	0.2	0.3	0.4	0.4
120-139	0.9	1.1	1.3	1.3	0.2	0.3	0.5	0.5		0.5	0.6	0.7	0.9	0.2	0.2	0.3	0.4
100-119	0.7	0.9	1.0	1.1	0.2	0.3	0.3	0.3		0.4	0.5	0.6	0.6	0.1	0.2	0.3	0.2
160-179	1.3	1.5	1.6	1.7	0.6	0.7	0.9	0.9		0.9	1.1	1.2	1.3	0.5	0.5	0.7	0.7
140-159	1.2	1.4	1.5	1.6	0.5	0.6	0.7	0.7	65 - 69	0.8	1.0	1.0	1.1	0.4	0.5	0.5	0.6
120-139	1.0	1.2	1.4	1.5	0.3	0.5	0.5	0.6		0.6	0.8	0.8	1.0	0.3	0.4	0.4	0.4
100-119	0.9	1.0	1.2	1.3	0.3	0.4	0.4	0.6		0.5	0.7	0.7	0.8	0.3	0.4	0.5	0.4
160-179	1.4	1.6	1.7	1.8	0.6	0.8	0.9	1.1		1.1	1.2	1.4	1.4	0.6	0.7	0.9	0.9
140-159	1.3	1.4	1.6	1.7	0.5	0.7	0.8	0.9	60 - 64	0.8	1.0	1.2	1.2	0.5	0.6	0.7	0.8
120-139	1.1	1.3	1.5	1.6	0.4	0.5	0.7	0.7		0.7	0.8	1.0	1.1	0.4	0.5	0.6	0.6
100-119	0.9	1.0	1.2	1.3	0.3	0.4	0.4	0.6		0.5	0.7	0.7	0.8	0.3	0.4	0.5	0.4
160-179	1.5	1.7	1.8	1.9	0.8	1.0	1.1	1.2		1.1	1.3	1.4	1.6	0.8	0.9	1.0	1.1
140-159	1.3	1.6	1.7	1.8	0.6	0.8	0.9	1.1	55 - 59	0.9	1.1	1.3	1.4	0.6	0.7	0.8	0.9
120-139	1.1	1.3	1.5	1.6	0.5	0.6	0.8	0.8		0.7	0.9	1.1	1.2	0.4	0.6	0.7	0.8
100-119	0.9	1.1	1.3	1.4	0.4	0.4	0.6	0.6		0.6	0.6	0.8	0.9	0.3	0.5	0.5	0.6
160-179	1.5	1.7	1.8	1.9	0.9	1.0	1.3	1.4		1.2	1.4	1.5	1.6	0.9	1.0	1.2	1.3
140-159	1.4	1.5	1.8	1.9	0.7	0.9	1.1	1.1	50 - 54	1.0	1.2	1.3	1.5	0.7	0.8	0.9	1.1
120-139	1.2	1.4	1.6	1.7	0.6	0.7	0.8	0.9		0.8	1.0	1.1	1.2	0.6	0.7	0.7	0.8
100-119	0.9	1.1	1.3	1.5	0.4	0.5	0.6	0.7		0.6	0.7	0.9	1.0	0.4	0.5	0.6	0.6
160-179	1.5	1.7	1.9	2.0	0.9	1.1	1.3	1.4		1.2	1.4	1.6	1.6	0.9	1.1	1.3	1.4
140-159	1.4	1.5	1.7	1.8	0.8	0.9	1.1	1.2	45 - 49	1.0	1.2	1.4	1.5	0.7	0.9	1.1	1.2
120-139	1.2	1.4	1.6	1.7	0.6	0.7	0.9	0.9		0.8	1.0	1.1	1.3	0.6	0.7	0.9	0.9
100-119	0.9	1.2	1.4	1.5	0.5	0.6	0.7	0.8		0.6	0.8	0.9	1.0	0.5	0.6	0.6	0.8
160-179	1.6	1.7	1.9	2.0	0.9	1.1	1.3	1.4		1.3	1.4	1.6	1.7	0.9	1.2	1.4	1.5
140-159	1.4	1.5	1.7	1.8	0.8	0.9	1.1	1.2	40 - 44	1.0	1.2	1.4	1.5	0.8	0.9	1.1	1.3
120-139	1.2	1.4	1.6	1.7	0.6	0.8	0.9	1.0		0.8	1.0	1.1	1.3	0.6	0.8	0.9	1.0
100-119	1.0	1.2	1.4	1.5	0.5	0.6	0.7	0.8		0.6	0.8	0.9	1.0	0.5	0.6	0.7	0.8
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250
mg/dL

4.6.1.1 Triglyceride-rich lipoproteins and their remnants

There are no treatment goals for triglycerides, but <1.7 mmol/L (150 mg/dL) is considered to indicate lower risk whereas higher levels indicate a need to look for other risk factors.

4.6.1.1 High-density lipoprotein cholesterol

To date, no specific goals for HDL-C levels have been determined in clinical trials, although low HDL-C is associated with (residual) risk in ASACVD patients. Physical activity and other lifestyle factors, rather than drug treatment, remain important means of increasing HDL-C levels.

4.6.3. Strategies to control dyslipidaemia

The presence of dyslipidaemias secondary to other conditions must be excluded before beginning treatment, as treatment of underlying disease may improve hyperlipidaemia without requiring lipid-lowering therapy. This is particularly true for hypothyroidism. Secondary dyslipidaemias can also be caused by alcohol abuse, DM, Cushing's syndrome, diseases of the liver and kidneys, as well as by drugs (e.g. corticosteroids). In addition, lifestyle optimisation is crucial in all patients with higher than optimal lipid levels.

4.6.1.1 Strategies to control low-density lipoprotein cholesterol

Diet and lifestyle modifications

Dietary factors influence the development of ASCVD either directly or through their action on traditional risk factors, such as plasma lipids, BP, or glucose levels. Consistent evidence from epidemiological studies indicate that higher consumption of fruit, non-starchy vegetables, nuts, legumes, fish, vegetable oils, yoghurt, and wholegrains, along with a lower intake of red and processed meats, foods higher in refined carbohydrates, and salt, is associated with a lower incidence of CV events.[522] Moreover, the replacement of animal fats, including dairy fat, with vegetable sources of fats and polyunsaturated fatty acids (PUFAs) may decrease the risk of ASCVD.[407] More detail on lifestyle recommendations is found earlier in this chapter.[62]

Drugs for treatment of dyslipidaemias

The currently available lipid-lowering drugs include inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins), fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (e.g. ezetimibe), and, more recently, PCSK9 inhibitors. Additionally, bempedoic acid, an oral cholesterol synthesis inhibitor, has recently been approved in several countries. Usage is mainly intended in combination with ezetimibe in patients with statin intolerance. ASCVD outcome trials are not expected before the end of 2022.

The expected LDL-C reductions in response to therapy are shown in *Figure 12*, and may vary widely among individuals. Therefore, monitoring the effect on LDL-C levels is recommended, with assessment of LDL-C levels 4–6 weeks after any treatment strategy initiation or change.

Figure 12 Expected low-density lipoprotein cholesterol reductions for combination therapies.

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Adapted from Mach et al.[3]

Intensity of lipid lowering treatment

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables). Adapted from Mach et al.[3]

Recommendations	Class[a]	Level[b]
It is recommended that a high-intensity statin is prescribed up to the highest-tolerated dose to reach the LDL-C goals set for the specific risk group.[21, 523, 524]	I	A
An ultimate[c] LDL-C goal of <1.4 mmol/L (55 mg/dL) and LDL-C reduction of >50% from baseline should be considered in apparently healthy persons ≤70 years at very high risk.[21, 22, 525]	IIa	C
An ultimate[c] LDL-C goal of <1.8 mmol/L (70 mg/dL) and LDL-C reduction of >50% from baseline should be considered in apparently healthy persons ≤70 years at high risk.[509, 526, 527]	IIa	C
In patients with established ASCVD, lipid-lowering treatment with an ultimate[c] LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C versus baseline is recommended.[21, 510, 518-520, 525]	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[518]	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.	IIb	C

For secondary prevention patients not achieving their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.[519, 520]	I	A
For very high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goals on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.[518, 528-530]	IIa	B
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may be considered.[528, 529, 531]	IIb	C
If the goal is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C
Statin therapy is not recommended in premenopausal female patients who are considering pregnancy or are not using adequate contraception.	III	C

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

[a] Class of recommendation.

[b] Level of evidence.

[C] A two-step approach to LDL-C targets is recommended; see section 3.2.3 and Figures 4, 5.

4.6.3.1.1. Statins

Statins decrease LDL-C, thereby reducing ASCVD morbidity and mortality as well as the need for coronary artery interventions. Statins also lower triglycerides, and may reduce pancreatitis risk. Therefore, they are the drug of first choice in patients at increased risk of ASCVD.[3]

4.6.3.1.1.1. Adverse effects, interactions, and adherence to statin therapy

The main adverse effect of statin therapy is myopathy, but this is rare. A meta-analysis ruled out any contribution to an increase in non-CV mortality.[525] Increased blood sugar and glycated haemoglobin (HbA1c) levels (i.e. increased risk of type 2 DM) can occur after treatment initiation and are dose dependent, in part linked to slight weight gain, but the benefits of statins outweigh the risks for the majority of patients.[532] Adhering to lifestyle changes when prescribed a statin should lessen risk of DM. Increased levels of liver enzymes may occur during statin therapy, and are usually reversible. Routine monitoring of liver enzyme values is not indicated.

Although 5–10% of patients receiving statins complain of myalgia, in most cases it is not attributable to statins.[3] The risk of myopathy (severe muscular symptoms) can be minimized by identifying vulnerable patients and/or by avoiding statin interactions with specific drugs. Rhabdomyolysis is extremely rare. Because statins are prescribed on a long-term basis, possible interactions with other

drugs deserve particular and continuous attention, as many patients will receive pharmacological therapy for concomitant conditions. In practice, management of a patient with myalgia but without a major increase in creatine kinase is based on trial and error, and usually involves switching to a different statin or use of a very low dosage several days a week, with a gradual increase in frequency and dosage. A management algorithm may help to manage these patients.[3]

4.6.3.1.2. Cholesterol absorption inhibitors (ezetimibe)

The combination of statin with ezetimibe brings a benefit that is in line with meta-analyses showing that LDL-C reduction has benefits independent of the approach used.[3, 21] The beneficial effect of ezetimibe is also supported by genetic studies.[533] Together, these data support the position that ezetimibe should be considered as second-line therapy, either on top of statins when the therapeutic goal is not achieved, or when a statin cannot be prescribed.

4.6.3.1.3. Proprotein convertase subtilisin/kexin type 9 inhibitors

PCSK9 inhibitors (monoclonal antibodies to PCSK9) decrease LDL-C by up to 60%, either as monotherapy or in addition to the maximum tolerated dose of statin and/or other lipid-lowering therapies, such as ezetimibe. Their efficacy appears to be largely independent of background therapy. In combination with high-intensity or maximum tolerated statins, alirocumab and evolocumab reduced LDL-C by 46−73% more than placebo, and by 30% more than ezetimibe.[519, 520] Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe.[534] Both alirocumab and evolocumab effectively lower LDL-C levels in patients who are at high or very high ASCVD risk, including those with DM, with a large reduction in future ASCVD events.[519, 520] PCSK9 inhibitors also lower triglycerides, raise HDL-C and apolipoprotein A-I, and lower lipoprotein(a), although the relative contributions of these lipid modifications remain unknown. PCSK9 inhibitors are costly, and their cost-effectiveness, long-term safety, and effect in primary prevention are as yet unknown. We recommend considering cost-effectiveness in a loco-regional context before implementing recommendations which involve their use. Recommendations for the use of PCSK9 inhibitors are described in the Recommendations for pharmacological LDL-C lowering.

4.6.1.1 Strategies to control plasma triglycerides

Although ASCVD risk is increased when fasting triglycerides are >1.7 mmol/L (150 mg/dL),[535] the use of drugs to lower triglycerides levels may only be considered in high-risk patients when triglycerides are >2.3 mmol/L (200 mg/dL) and triglycerides cannot be lowered by lifestyle measures. The available pharmacological interventions include statins, fibrates, PCSK9 inhibitors, and n-3 PUFAs (in particular icosapent ethyl in doses of 2–4 g/d; see 4.3.2.4.4.).

Recommendations for the treatment of hypertriglyceridaemia are shown in the Recommendations below.

4.6.3.2.1. Fibrates

Fibrates are used primarily for triglyceride lowering and, occasionally, for increasing HDL-C. Evidence supporting the use of these drugs for ASCVD event reduction is limited, and given the strong evidence favouring statins, routine use of these drugs in ASCVD prevention is not recommended.[3] To prevent pancreatitis, when triglycerides are >10 mmol/L (900 mg/dL), they must be reduced not only

by drugs but also by restriction of alcohol, treatment of DM, withdrawal of oestrogen therapy, etc. In those patients with severe primary hypertriglyceridaemia, referral to a specialist must be considered.

Recommendations for drug treatments of patients with hypertriglyceridaemia. Adapted from Mach et al.[3]

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing ASCVD risk in high-risk individuals with hypertriglyceridaemia (triglycerides >2.3 mmol/L [200 mg/dL]).[536]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[537-539]	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/d) may be considered in combination with a statin.[540]	IIb	B

ASCVD = atherosclerotic cardiovascular disease; EPA = icosapent ethyl; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.

[a] Class of recommendation.

[b] Level of evidence.

4.6.4. Important groups

4.6.1.1 Women

The proportional reductions per mmol/L reduction in LDL-C in major vascular events, major coronary events, coronary revascularization, and stroke are similar in women and men. In addition, the relative effects of non-statin drugs that lower LDL-C (ezetimibe and PCSK9 inhibitors, on top of high-intensity statin therapy) are also similar in both women and men.[3]

4.6.1.1 Older patients (>70 years)

Compared to the 2019 ESC dyslipidemia guidelines[62], we provide a single cut-off for identifying 'older persons' as those above 70 years of age, as opposed to 75 years, for reasons of consistency with other parts of the current guidelines.. As a result, Class and LOE have been modified some age groups, in particular the category of patients between 70 and 75 years. Although a single age cut-off is now used, it is important to stress that all such age cut-offs are relatively arbitrary, and biological age influences this threshold in clinical practice. For example, a very fit 75-year old person may

qualify for a treatment normally reserved for those <70 and, conversely, a very frail 65-year old person should sometimes be considered 'older'. General recommendations for lipid-lowering treatment in older patients are summarized below.

Recent evidence has strengthened the role of LDL-c as an ASCVD risk factor in older patients.[541] Evidence from trials indicates that statins and other lipid-lowering drugs produce significant reductions in major vascular events irrespective of age.[542, 543] However, there is less direct evidence of statin benefit in those without evidence of ASCVD. Under the age of 70 years, statins are recommended for primary prevention depending on the level of risk. Above that age, initiation of statin treatment for primary prevention may be considered when at (very) high risk, but we explicitly recommend also taking other arguments into account such as risk modifiers, frailty, estimated life-time benefit, comorbidities and patient preferences (see 3.2.2.2 and figure 11). In case of renal function impairment or risk for drug interactions, statin dose should be up-titrated carefully. In terms of LDL-C targets, there is insufficient evidence to support targets for primary prevention in older patients. Although the conventional LDL-C target of <2.6 mmol/L (100 mg/dL) may seem reasonable, the results of ongoing primary prevention trials in older patients must be awaited (STAREE trial; clinicatrials.gov registration: NCT02099123). Frailty, polypharmacy and muscle symptoms remain relevant factors to consider in older patients.

Recommendations for the treatment of dyslipidaemias in older people (>70 years). Adapted from Mach et al.[3]

Recommendations	Class[a]	Level[b]
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[543, 544]	I	A
Initiation of statin treatment for primary prevention in older people aged >70 may be considered, if at high risk or above.[543, 544]	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions.	I	C

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

[a] Class of recommendation.

[b] Level of evidence.

4.6.1.1 Diabetes mellitus

Lowering of LDL-C in patients with DM is consistently associated with lower ASCVD risk. Similar to prevention in apparently healthy individuals, we propose a stepwise approach to lipid control, dependent of risk, estimated lifetime benefit, comorbidities, and patient preferences (*Figure 7*). PCSK9 inhibitors can also be applied in patients with diabetes not reaching their LDL-C targets with

statins and/or ezetimibe. However, the cost-effectiveness notification for the use of PCSK9-inhibitors apply to patients with DM just as well as for patients without diabetes.

Recommendations for the treatment of dyslipidaemias in diabetes mellitus. Adapted from Mach et al.[3]

Recommendations	Class[a]	Level[b]
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe target organ damage[c]) intensive lipid-lowering therapy, ultimately[d] aiming at ≥50% LDL-C reduction *and* an LDL-C of <1.4 mmol/L (55 mg/dL) is recommended.[21, 22, 525, 545, 546]	I	A
In patients with type 2 DM >40 years at high risk, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% LDL-C reduction and an LDL-C of <1.8 mmol/L (70 mg/dL) is recommended.[545, 546]	I	A
Statin therapy may be considered in persons aged ≤40 years with type 1 or type 2 DM with evidence of end-organ damage and/or an LDL-C level >2.6 mmol/L (100 mg/dL), as long as pregnancy is not being planned.	IIb	C
If the LDL-C goal is not reached, statin combination with ezetimibe should be considered.[518, 547]	IIa	B

ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; LDL-C = low-density lipoprotein cholesterol.

[a] Class of recommendation.

[b] Level of evidence.

[C] Severe Target Organ Damage in this specific context includes eGFR <45 ml/min/1.73m^2; eGFR 46-79 ml/min/1.73m^2 plus microalbuminuria; proteinuria; presence of microvascular disease in at least 3 different sites (e.g. albuminuria plus retinopathy plus neuropathy). See section 3.2 for details

[d] A two-step approach to LDL-c targets is recommended; see section 3.2.2 and Figure 7.

4.6.1.1 Chronic kidney disease

Patients with CKD are at high or very-high risk of ASCVD, and have a characteristic mixed dyslipidaemia (high triglycerides, normal LDL-C and low HDL-C). Statin therapy or statin therapy in combination with ezetimibe (which allows larger LDL-C reductions without increasing the statin dose) has a beneficial effect on ASCVD outcomes in CKD.[548] For patients with end-stage renal disease, however, we recommend that hypolipidaemic therapy should not be initiated (see recommendations below). If patients with CKD already on a hypolipidaemic therapy enter end stage renal disease, the therapy may be maintained.

Recommendations for lipid management in patients with moderate-to-severe chronic kidney disease (Kidney disease Outcomes Quality Initiative stages 3–5). Adapted from Mach et al.[3]

Recommendations	Class[a]	Level[b]
The use of statins or statin/ezetimibe combination is recommended in patients with non–dialysis-dependent, stage 3–5 CKD.[530, 549, 550]	I	A
In patients already on statins, ezetimibe, or a statin/ ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.[551, 552]	III	A

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease.

[a] Class of recommendation.

[b] Level of evidence.

4.6.1.1 Familial hypercholesterolaemia

Patients who could have genetic dyslipidaemias, such as heterozygous FH, can be identified by extreme lipid abnormalities and/or family history (table 8). An LDL-C >4.9 mmol/L (190 mg/dL) in therapy-naive patients requires careful evaluation for possible FH. However, in the presence of premature ASCVD or family history, possible FH should be considered at lower LDL-C levels. Beside genetic testing (not always affordable), use of the Dutch Clinical Lipid Network criteria (*Table 9*) is recommended to identify possible FH. Homozygous FH is rare and should always be placed under the care of lipid experts.

Treatment guidelines for people with FH can be found in the 2019 ESC/EAS dyslipidaemia guidelines.[3]

Table 9 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

Criteria	Points
1) Family history	
First-degree relative with known premature (men aged <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 aged <18 years with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men aged <55 years; women <60 years) CAD	2

Patient with premature (men aged <55 years; women <60 years) cerebral or peripheral vascular disease	1
3) Physical examination[a]	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥8.5 mmol/L (≥325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1
5) DNA analysis	
Functional mutation in the *LDLR*, *apolipoprotein B,* or *PCSK9* genes	8
Choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

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

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

Gaps in evidence

- Cost-effectiveness requires evidence for effects of interventions on health and healthcare over a long period; modelling techniques fill gaps.
- The feasibility and effects of reaching LDL-C levels below 1.4 mmol/L (55 mg/dL) needs further investigation, especially in primary care.
- Particularly among people at low-to-moderate ASCVD risk, older people, and for newer interventions, more evidence of the effects of lipid-modifying treatments on overall mortality is needed in the form of long-term post-trial follow-up in RCTs.
- The cost-effectiveness of using lifetime ASCVD risk and more precise ASCVD risk scores to target interventions needs further investigation.
- The value of triglycerides or HDL-C values as a target for therapy.
- Whether lipoprotein(a) lowering against background statin therapy can reduce the risk of ASCVD.
- Whether functional foods and food supplements with a lipid-lowering effect can safely reduce the risk of ASCVD.

4.7. Blood pressure

Key messages

- When hypertension is suspected, the diagnosis should be confirmed by repeated office BP measurement at different visits, or ambulatory BP or home BP monitoring.
- Lifestyle interventions are indicated for all patients with hypertension and can delay the need for drug treatment or complement the BP-lowering effect of drug treatment.
- BP-lowering drug treatment is recommended in many adults when office BP is ≥140/90 mmHg and in all adults when BP is ≥160/100.
- BP-treatment goals are lower than in the previous ESC CVD prevention Guidelines for all patient groups, including independent older patients.
- BP treatment should be initiated with two drugs (ideally as a single pill) for the majority of patients because monotherapy is often inadequate.
- Wider use of single-pill combination therapy is recommended to reduce poor adherence to BP treatment.
- A simple drug-treatment algorithm should be used to treat most patients, based on combinations of a renin-angiotensin system (RAS) blocker with a calcium channel blocker (CCB) or thiazide/thiazide-like diuretic, or all three. Beta-blockers may also be used where there is a guideline-directed indication.
- Many patients with hypertension will be at sufficient risk to benefit from statin therapy for primary prevention. Antiplatelet therapy is indicated for secondary prevention.

Summary of recommendations for the clinical management of hypertension

Recommendations	Class[a]	Level[b]
Classification of BP		
It is recommended that BP should be classified as optimal, normal, high-normal, or grades 1–3 hypertension, according to office BP.	I	C
Diagnosis of hypertension		
It is recommended to base the diagnosis of hypertension on: • Repeated office BP measurements, on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). Or • Out-of-office BP measurement with ABPM and/or HBPM when feasible.	I I	C C

Assessment of HMOD		
To evaluate for the presence of HMOD, measurement of serum creatinine, eGFR, electrolytes, and albumin: creatinine ratio is recommended for all patients. A 12-lead ECG is recommended for all patients, and echocardiography is recommended for those with ECG abnormalities or signs/symptoms of LV dysfunction. Fundoscopy or retinal imaging is recommended for patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes.[553-556]	I	B
Thresholds for initiation of drug treatment of hypertension		
For grade I hypertension, treatment initiation based on absolute ASCVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.[557, 558]	I	C
For patients with grade 2 hypertension or higher, drug treatment is recommended.[4, 557]	I	A
Office BP treatment targets		
It is recommended that the first objective of treatment is to lower BP to <140/90 mmHg in all patients, and that subsequent BP targets are tailored to age and specific co-morbidities.[557, 559]	I	A
In treated patients aged 18-70 years, it is recommended that SBP should ultimately be lowered to a target range of 120–130 mmHg in most patients.[557, 559-561]	I	A
In treated patients aged over 70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.[557, 559, 562]	I	A
In all treated patients, DBP is recommended to be lowered to <80 mmHg[563-565]	I	A
Treatment of hypertension: lifestyle interventions		
Lifestyle interventions are recommended for people with high-normal blood pressure or higher.[c]	I	A
Treatment of hypertension: drug treatment		
It is recommended to initiate antihypertensive treatment with a two-drug combination in most patients, preferably as a single-pill combination. Exceptions are frail older patients and those with low-risk, grade 1 hypertension (particularly if SBP <150 mmHg).[566-571]	I	B
It is recommended that the preferred combinations include a RAS blocker (i.e. an ACE inhibitor or ARB) with a CCB or diuretic, but other combinations of the five major classes can be used (ACE inhibitor, ARB, beta-blocker, CCB, thiazide/thiazide-like diuretic).[572-575]	I	A
It is recommended, if BP remains uncontrolled with a two-drug combination, that treatment be increased to a three-drug combination, usually a RAS	I	A

blocker with a CCB and a diuretic, preferably as a single-pill combination.[570, 576, 577]		
It is recommended, if BP is not controlled by a three-drug combination, treatment should be increased by the addition of spironolactone, or if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, an alpha-blocker or beta-blocker, or clonidine.[564, 578-580]	I	B
The combination of two RAS blockers is not recommended.[581, 582]	III	A
Management of ASCVD risk in hypertensive patients		
Statin therapy is recommended for many patients with hypertension.[d]	Ch 4.6	
Antiplatelet therapy is indicated for secondary prevention in patients with hypertension.[e]	Ch 4.9	

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BP = blood pressure; CCB = calcium channel blocker; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; LV = left ventricular; RAS = renin-angiotensin system; SBP = systolic blood pressure.

[a] Class of recommendation.

[b] Level of evidence.

[c] See *section 4.2* for details.

[d] See *section 4.6* for details.

[e] See *sections 4.6* and *4.9* for details.

Hypertension is one of the most important preventable causes of premature morbidity and mortality. It affects more than 150 million people across Europe, over 1 billion globally, with a prevalence of ~30-45% in adults, increasing with age to more than 60% in people aged >60 years, and accounting for ~10 million deaths globally per annum.[583] Despite extensive evidence for the effectiveness of BP-lowering treatments at reducing ASCVD risk and death, the detection, treatment, and control of BP in Europe and globally remains suboptimal.[584]

This section covers recommendations for the diagnosis and treatment of hypertension to be applied in routine primary and secondary care. More detail and guidance for complex cases/tertiary care are available in the 2018 ESC/ESH Guidelines for the management of arterial hypertension.[4]

4.7.1. Definition and classification of hypertension

BP is classified according to seated office BP (*Table 10*), with approximately corresponding values according to ambulatory BP monitoring (ABPM) or home BP average values in *Table 11*.

Table 10 Categories for conventionally measured seated office blood pressure

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High-normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a] BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.

[b] Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.

Table 11 Definitions of hypertension according to office, ambulatory and home BP

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24-h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a] Refers to conventional office BP rather than unattended office BP.

4.7.2. Blood pressure measurement

4.7.1.1 Office blood pressure measurement

Office BP should be measured in standardized conditions using validated auscultatory or (semi)automatic devices, as described in *Table 12*.

Table 12 Considerations in blood pressure measurement

Patients should be seated comfortably in a quiet environment for 5 min before BP measurements.
Three BP measurements should be recorded, 1–2 min apart, and additional measurements if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings.
Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patents with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in AF.
Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but use larger and smaller cuffs for larger (arm circumference >32 cm) and smaller (arm circumference <26 cm) arms, respectively.
The cuff should be positioned at the level of the heart with the back and arm supported, to avoid muscle contraction and isometric-exercise–dependant increases in BP.
When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.
Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
Measure BP 1 min and 3 min after standing from the seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, in people with DM, and in other conditions in which orthostatic hypotension may frequently occur. Initial orthostatic hypotension (IOH) may occur even <1 minute after standing and may be difficult to detect with conventional measurement techniques.
Record heart rate and use pulse palpation to exclude arrhythmia.

AF = atrial fibrillation; BP = blood pressure; DBP = diastolic blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure.

4.7.1.1 Unattended automated office blood pressure measurement

Repeated automated office BP readings may improve the reproducibility of BP measurement. If the patient is seated alone and unobserved, unattended automated office BP measurement may reduce or eliminate the “white coat” effect, and unattended automated office BP measurements are usually lower than conventional office BP measurements, and more similar to ambulatory daytime BP or home BP values. There is limited information on the prognostic value of unattended automated office BP measurements.[4]

4.7.1.1 Ambulatory blood pressure monitoring

ABPM is the average of repeated automated measurements of BP during the daytime, night-time, and over 24 h. ABPM is a better predictor of hypertension-mediated organ damage (HMOD) and clinical outcomes than office BP, and identifies "white coat" hypertension and masked hypertension (see below). Diagnostic thresholds for hypertension are lower with ABPM than office BP (*Table 10*).[4]

4.7.1.1 Home blood pressure monitoring

Home BP is the average of all BP readings performed with a validated semiautomatic monitor, for at least 3 consecutive days (ideally 6–7 days), with readings in the morning and evening, taken seated in a quiet room after 5 min of rest. Home BP monitoring (HBPM) thresholds for the diagnosis of hypertension are lower than those for office BP (*Table 10*). Patient self-monitoring may have a beneficial effect on medication adherence and BP control.[4]

Clinical indications for ambulatory or home monitoring are shown in *Table 13*.

Table 13 Indications for home blood pressure monitoring or ambulatory blood pressure monitoring

Conditions in which white-coat hypertension is more common, for example: • Grade I hypertension on office BP measurement • Marked office BP elevation without HMOD
Conditions in which masked hypertension is more common, for example: • High-normal office BP • Normal office BP in individuals with HMOD or at high total CV risk
Postural and post-prandial hypotension in untreated and treated patients
Evaluation of resistant hypertension
Evaluation of BP control, especially in treated higher-risk patients Exaggerated BP response to exercise
When there is considerable variability in the office BP
Evaluating symptoms consistent with hypotension during treatment
Specific indications for ABPM rather than HBPM:

- Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, DM, endocrine hypertension, or autonomic dysfunction)

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage.

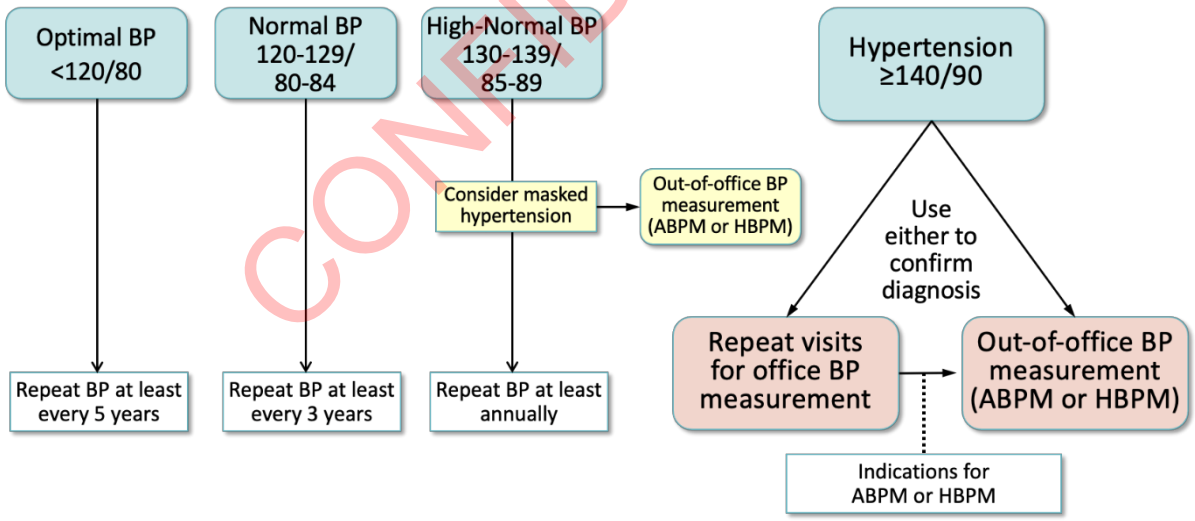
4.7.3. Screening and diagnosis of hypertension

Ideally, all adults should be screened for the presence of hypertension,[584, 585] but most countries lack the required resources and infrastructure. Formally, these Guidelines recommend opportunistic screening at least in susceptible individuals, such as those who are overweight or have a family history for hypertension (see *section 3.1*).

When hypertension is suspected, the diagnosis of hypertension should be confirmed, either by repeated office BP measurements over a number of visits, or by 24 h ABPM or HBPM (*Figure 13*).

Figure 13 Screening and diagnosis of hypertension.

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.



4.7.1.1 White coat and masked hypertension

White-coat hypertension refers to BP that is elevated in the office but normal when measured by ABPM or HBPM. It occurs in up to 30–40% of patients. The risk associated with white-coat hypertension is lower than sustained hypertension but may be higher than normotension. People with white-coat hypertension should receive lifestyle advice to reduce their CV risk and be offered BP

measurement at least every 2 years by ABPM or HBPM because of high rates of transition to sustained hypertension. Routine drug treatment for white-coat hypertension is not indicated.

Masked hypertension refers to patients with a normal office BP but an elevated BP on ABPM or HBPM. These patients often have HMOD and are at a CV risk level at least equivalent to sustained hypertension. It is more common in younger people and in those with high-normal office BP. In masked hypertension, lifestyle changes are recommended, and drug treatment should be considered to control "out of office" BP, with periodic monitoring of BP, usually with HBPM.

4.7.4. Clinical evaluation and risk stratification in hypertensive patients

The routine work-up for hypertensive patients is shown in *Table 14*. Alongside clinical examination, this is designed to:

- Assess risk factors for ASCVD (see *section 3.2*), or the presence of cardiac, vascular, or renal disease.
- Detect evidence of HMOD, e.g. left ventricular hypertrophy, renal disease, or retinopathy; and
- Consider potential secondary causes of hypertension, e.g. renovascular disease, hyperaldosteronism, or pheochromocytoma (see *Table 15*). Also carefully evaluate substance abuse (e.g. cocaine), drugs that may increase blood pressure (e.g. cyclosporine, sympaticomimetics), liquorice, etc… More detail on work-up of suspected secondary hypertension is provided elsewhere.[63]

Echocardiography is recommended in patients with ECG abnormalities, and should be considered when the result will influence clinical decision-making. Fundoscopy is recommended in grade 2 or 3 hypertension and in all patients with diabetes. The routine measurement of other biomarkers or and/use of vascular imaging is not recommended.[553-556]

Table 14 Routine tests for patients with hypertension

Routine laboratory tests
Haemoglobin and/or haematocrit
Fasting blood glucose and/or HbA_{1c}
Blood lipids: total cholesterol, LDL-C, HDL-C, triglycerides
Blood potassium and sodium
Blood uric acid
Blood creatinine and eGFR
Blood liver function tests

Urine analysis: microscopic; urinary protein by dipstick, or, ideally, albumin:creatinine ratio
12-lead ECG

ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

Table 15 Patient characteristics that should raise the suspicion of secondary hypertension. For details, see [4]

Characteristics
Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
Acute worsening hypertension in patients with previously documented chronically stable normotension
Resistant hypertension (BP uncontrolled despite treatment with optimal or best tolerated doses of three or more drugs including a diuretic, and confirmed by ABPM or HBPM)
Severe (grade 3) hypertension or a hypertension emergency
Presence of extensive HMOD
Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD
Clinical features suggestive of OSA
Symptoms suggestive of pheochromocytoma or family history of pheochromocytoma

BP = blood pressure; CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage; OSA = obstructive sleep apnoea.

4.7.5. Treatment of hypertension

The treatment of hypertension involves lifestyle interventions for all patients and drug therapy for most patients.

4.7.1.1 Lifestyle Interventions to lower blood pressure and/or reduce cardiovascular risk

Lifestyle interventions are indicated for all patients with high-normal blood pressure or hypertension, because they can delay the need for drug treatment or complement the BP-lowering effect of drug treatment. Moreover, most lifestyle interventions have health benefits beyond their effect on BP. Lifestyle are discussed extensively in *section 4.3*.

4.7.1.1 Initiation of drug treatment

Drug-treatment decisions in ASCVD prevention are mostly based on absolute ASCVD risk, risk modifiers, comorbidities, estimated benefit of treatment, frailty and patient preferences. The same is true for hypertension. Drug treatment of grade I hypertension (SBP 140−159 mmHg) has level A evidence for reducing ASCVD risk. In younger patients, however, the absolute 10-year ASCVD risk is often low, and lifetime benefit of treatment should be considered and communicated before instituting treatment (*Figure 5* and *section* 3.2). In many such cases, the absolute lifetime benefit per 10 mmHg reduction in SBP is at least moderate to high (*Figure 14*: lifetime benefit for 10 mmHg BP, calibrated in low- to moderate ASCVD risk countries). Also, the presence of HMOD mandates treatment of grade I hypertension. For grade II hypertension or higher (SBP >160 mmHg), treatment is recommended, because not only is the lifetime benefit of reducing BP almost universally high in such patients, there is also the importance of reducing risk of HMOD resulting in other morbidities such as renal disease, haemorrhagic cerebrovascular disease, and HF.

Figure 14 Lifetime benefit from lowering systolic blood pressure by 10 mmHg for apparently healthy persons, based on the following risk factors: age, sex, current smoking, systolic blood pressure, low-density lipoprotein cholesterol. The model is currently validated for low and moderate risk countries.

The lifetime benefit is expressed as “years of median life expectancy free from myocardial infarction or stroke” gained from 10 mmHg SBP lowering. The lifetime benefit is calculated by estimating lifetime ASCVD risk with the LIFE-CVD model multiplied by the HR (0.80) from a meta-analysis of the effect of BP lowering. For 20 mmHg SBP lowering, the average effect is almost twice as large, etc. For individualized estimations of lifetime benefit, this table can be used or the electronic version of LIFE-CVD, assessable via the ESC CVD risk app or http://www.U-Prevent.com.

ASCVD = atherosclerotic cardiovascular disease; DIAL = Diabetes Lifetime-perspective prediction; DM = diabetes mellitus; ESC = European Society of Cardiology; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; MI = myocardial infarction; REACH = Reduction of Atherothrombosis for Continued Health; SBP = systolic blood pressure; SMART = Secondary Manifestations of Arterial Disease. [OUP: To match abbreviations in figure and change , to .]

LIFE-CVD model

CVD-free lifetime gain from 10 mmHg Systolic Blood Pressure reduction (in years)

< 0.5 years
0.5 - 0.9 years
1.0 - 1.4 years
1.5 - 2.0 years
≥ 2.0 years

	Women								Age	Men							
	Non-smoking				Smoking					Non-smoking				Smoking			
160-179	0.3	0.3	0.4	0.4	0.1	0.1	0.2	0.2		0.2	0.2	0.3	0.3	0.1	0.0	0.0	0.1
140-159	0.3	0.3	0.3	0.3	0.1	0.1	0.1	0.1	90+	0.2	0.2	0.2	0.2	0.0	0.0	0.0	0.0
120-139	0.2	0.2	0.3	0.3	0.0	0.1	0.1	0.1		0.1	0.1	0.2	0.2	0.0	0.0	0.0	0.1
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	0.7	0.8	0.8	0.8	0.2	0.2	0.3	0.3		0.3	0.4	0.5	0.5	0.1	0.1	0.1	0.2
140-159	0.6	0.6	0.7	0.8	0.1	0.2	0.2	0.3	85 - 89	0.3	0.3	0.4	0.5	0.1	0.1	0.1	0.1
120-139	0.4	0.5	0.6	0.6	0.1	0.2	0.2	0.2		0.3	0.3	0.3	0.4	0.0	0.0	0.1	0.1
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	0.9	1.0	1.1	1.2	0.2	0.3	0.4	0.4		0.5	0.5	0.6	0.7	0.1	0.2	0.2	0.2
140-159	0.8	0.9	1.0	1.0	0.2	0.3	0.3	0.4	80 - 84	0.4	0.5	0.6	0.6	0.1	0.1	0.2	0.1
120-139	0.6	0.7	0.8	0.9	0.2	0.1	0.2	0.2		0.3	0.4	0.4	0.5	0.0	0.1	0.1	0.1
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.1	1.2	1.3	1.3	0.3	0.5	0.5	0.5		0.6	0.7	0.8	0.9	0.2	0.2	0.3	0.3
140-159	0.9	1.1	1.2	1.2	0.2	0.3	0.4	0.5	75 - 79	0.5	0.6	0.7	0.8	0.2	0.2	0.3	0.3
120-139	0.7	0.9	1.0	1.1	0.2	0.2	0.3	0.4		0.4	0.5	0.6	0.6	0.1	0.2	0.2	0.2
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.2	1.3	1.4	1.5	0.4	0.5	0.7	0.7		0.7	0.8	1.0	1.0	0.3	0.4	0.5	0.5
140-159	1.0	1.2	1.3	1.4	0.4	0.4	0.5	0.6	70 - 74	0.6	0.7	0.9	0.9	0.2	0.3	0.4	0.4
120-139	0.8	1.0	1.1	1.2	0.2	0.3	0.4	0.5		0.4	0.6	0.7	0.8	0.1	0.2	0.3	0.3
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.2	1.3	1.5	1.5	0.5	0.7	0.8	0.9		0.8	1.0	1.1	1.1	0.5	0.5	0.7	0.6
140-159	1.0	1.3	1.4	1.5	0.4	0.5	0.6	0.7	65 - 69	0.7	0.9	0.9	1.0	0.3	0.5	0.5	0.5
120-139	0.9	1.1	1.2	1.3	0.3	0.4	0.5	0.5		0.5	0.7	0.8	0.9	0.2	0.4	0.4	0.4
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.3	1.4	1.5	1.6	0.6	0.7	0.9	1.0		1.0	1.1	1.2	1.3	0.6	0.7	0.8	0.8
140-159	1.2	1.3	1.4	1.5	0.5	0.6	0.7	0.8	60 - 64	0.8	0.9	1.1	1.1	0.5	0.5	0.7	0.7
120-139	1.0	1.1	1.3	1.4	0.4	0.4	0.6	0.6		0.7	0.7	0.9	1.0	0.4	0.4	0.5	0.5
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.3	1.5	1.6	1.7	0.7	0.9	1.0	1.1		1.0	1.2	1.3	1.4	0.7	0.9	0.9	1.0
140-159	1.1	1.4	1.6	1.6	0.6	0.7	0.8	1.0	55 - 59	0.8	1.0	1.2	1.2	0.5	0.6	0.8	0.9
120-139	1.0	1.2	1.4	1.5	0.4	0.5	0.7	0.7		0.7	0.8	1.0	1.0	0.4	0.5	0.6	0.7
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.3	1.5	1.7	1.7	0.8	1.0	1.1	1.2		1.0	1.3	1.4	1.5	0.8	0.9	1.0	1.2
140-159	1.3	1.4	1.6	1.7	0.6	0.8	1.0	1.0	50 - 54	0.9	1.1	1.2	1.3	0.7	0.7	0.8	1.0
120-139	1.1	1.2	1.4	1.5	0.5	0.6	0.7	0.8		0.7	0.9	1.0	1.1	0.5	0.6	0.7	0.7
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.3	1.6	1.7	1.8	0.8	1.0	1.2	1.3		1.1	1.3	1.5	1.5	0.8	1.0	1.2	1.3
140-159	1.3	1.4	1.6	1.6	0.7	0.8	1.0	1.1	45 - 49	0.9	1.1	1.3	1.3	0.7	0.8	1.0	1.1
120-139	1.1	1.2	1.4	1.5	0.5	0.7	0.8	0.8		0.8	0.9	1.0	1.2	0.6	0.7	0.8	0.8
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
160-179	1.4	1.6	1.7	1.8	0.8	1.0	1.2	1.3		1.1	1.3	1.4	1.6	0.9	1.1	1.3	1.4
140-159	1.3	1.4	1.6	1.7	0.7	0.8	1.0	1.1	40 - 44	0.9	1.1	1.3	1.4	0.7	0.9	1.0	1.2
120-139	1.1	1.3	1.4	1.5	0.6	0.7	0.8	0.9		0.7	0.9	1.0	1.2	0.6	0.7	0.8	0.9
100-119	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9		3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9

Non-HDL cholesterol (mmol/L)

150 200 250 mg/dL

2981

4.7.1.1 Blood pressure treatment targets

When drug treatment is used, the aim is to control BP to target within 3 months. Evidence now suggests that the BP targets in the previous iteration of this guideline were too conservative, especially for older patients. In line with the 2-step approach (chapter 3), it is now recommended that the first step in all treated patients should achieve a treated SBP <140 mmHg and diastolic BP <80 mmHg.[557, 559] The recommended ultimate SBP treatment target range for younger patients (18-70 years) is 120–130 mmHg, although some patients may safely achieve lower treated SBP levels than this and, if they are well tolerated, there is no need to back-titrate treatment.[557, 559-561] The ultimate target SBP for patients aged over 70 years is <140 mmHg and down to 130 mmHg if tolerated.[557, 559, 562, 586] This change in the BP target range for older people compared with the 2016 ESC Prevention Guidelines is supported by evidence that these treatment targets are safely achieved in many older patients and are associated with significant reductions in the risk of major stroke, HF, and CV death.[562, 586] It also takes into account that the even lower SBP in the intensively treated group in the Systolic Blood Pressure Intervention Trial (SPRINT) trial (mean 124 mmHg) probably reflects a conventional office SBP range of 130–139 mmHg.[560] It is recognised, however, that the evidence supporting more strict targets is less strong for very old people (>80 years) and those who are frail. Also, in these older and especially frail patients, it may be difficult to achieve the recommended target BP range due to poor tolerability or adverse effects, and high-quality measurement and monitoring for tolerability and adverse effects is especially important in these groups.[586]

Compared to previous ESC/ESH hypertension guidelines, we changed the cut-off for identifying who is 'older' from 65 to 70 years for reasons of consistency with other parts of the current guidelines. Although a single age cut-off is provided, it is important to stress that biological age influences this threshold in clinical practice. For example, a very fit 75-year old person may qualify for a treatment policy normally reserved for those <70 and, vice versa, a very frail 65-year old person should sometimes be considered 'older'.

BP targets for patient subgroups with various comorbidities are shown in *Table 16*.

BP targets according to ABPM and HBPM: there are no outcome-based trials that have used ABPM or HBPM to guide treatment. Therefore, ABPM and HBPM BP targets are extrapolated from observational data. A treated office SBP of 130 mmHg likely corresponds to a 24-h SBP of 125 mmHg and home SBP <130 mmHg.[4]

Table 16 Recommended office blood pressure target ranges. The first step in all groups is a reduction to SBP <140. The subsequent optimal goals are listed below.

Age group	Office SBP treatment target ranges (mmHg)				
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/ TIA

18–70 years	**120 – 130**	**120 – 130**	**<140 – 130**	**120 - 130**	**120 - 130**
	lower SBP acceptable if tolerated				
>70 years	**<140, down to 130 if tolerated** *lower SBP acceptable if tolerated*				
DBP treatment target **(mmHg)**	<80 for all treated patients				

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; DM = diabetes mellitus; SBP = systolic blood pressure; TIA = transient ischaemic attack.

4.7.1.1 Drug treatment of hypertension

The most important driver of benefit is the magnitude of BP lowering. Single-drug therapy will rarely achieve optimal BP control.

Initial therapy with a combination of two drugs should be considered usual care for hypertension.[566, 568-570, 587, 588] The only exception would be a baseline BP close to the recommended target, who might achieve that target with a single drug, or in very old (>80 years) or frail patients who may better tolerate more gentle reduction of BP. Initial combination therapy, even low-dose combination therapy, is more effective at lowering BP than monotherapy,[566, 568, 587] and will reduce BP faster and reduce heterogeneity in response.[566, 587] Moreover, initial combination therapy does not increase risk of adverse effects.[566, 568-570, 587] Initiating therapy with two drugs will also help overcome treatment inertia where patients remain on one drug long term despite inadequate BP control.[569]

Single-pill strategy to treat hypertension: poor adherence to BP-lowering medication is a major cause of poor BP control rates, and is directly related to the number of pills.[588] Single-pill combination therapy (if available) is the preferred strategy. This strategy will control BP in most patients.[566, 568-571, 587]

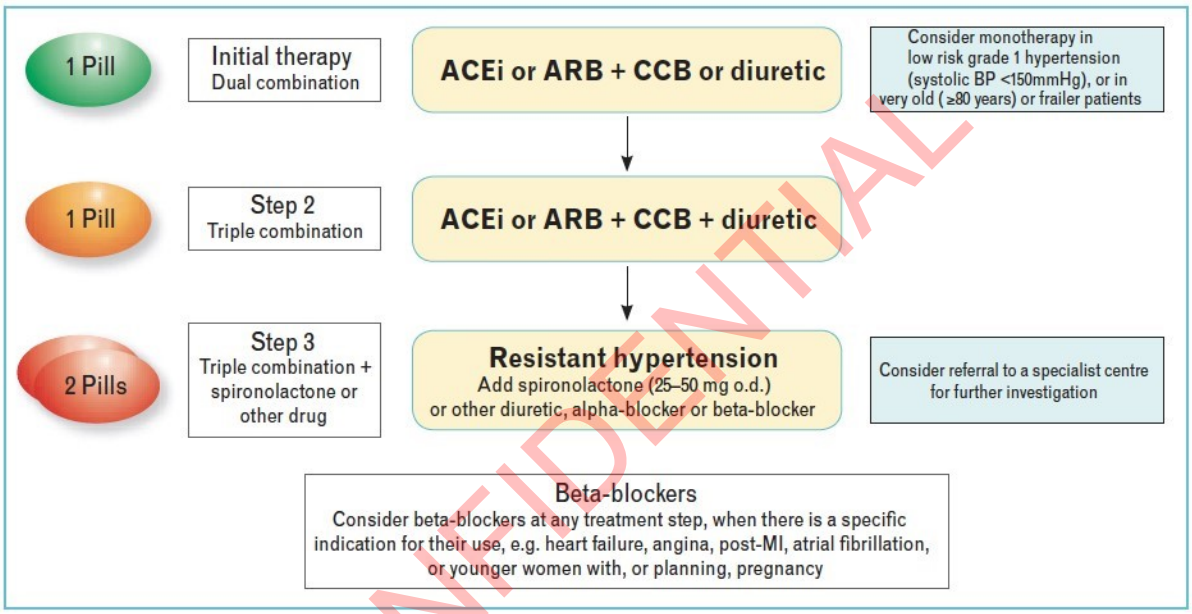
Recommended drug therapy and treatment algorithm: five major classes of BP-lowering drug therapy have shown benefit in reducing CV events; ACE inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, CCBs, and thiazide or thiazide-like diuretics.[589] A recommended treatment algorithm based on best available evidence, pragmatic considerations (e.g. combination pill availability) and pathophysiological reasoning is shown in *Figure 15.*[63] A combination of an ACE inhibitor or ARB with a CCB or thiazide/thiazide-like diuretic is the preferred initial therapy for most patients with hypertension.[572-575] For those in whom treatment requires escalation to three drugs, a combination of an ACE inhibitor or ARB with a CCB and a thiazide/thiazide-like diuretic should be used.[570, 576, 577] Beta-blockers should be used when there is a specific indication (e.g. angina, post myocardial infarction, HFrEF, or as an alternative to an ACE inhibitor or ARB in women of child-

bearing potential).[589] Combinations of ACE inhibitor and ARB are not recommended because of no added benefit on outcomes and increased risk of harm.[581, 582]

Specific modifications of the treatment algorithm are recommended for patients with CHD, CKD, HF, and AF.[4]

Figure 15 Core drug treatment strategy for hypertension. This algorithm is appropriate for most patient with hypertension-mediated organ damage, diabetes mellitus, cerebrovascular disease, and peripheral artery disease.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; CCB = calcium channel blocker; MI = myocardial infarction; *o.d.* = *omni die* (once a day).



4.7.6. Resistant hypertension

Resistant hypertension is defined as BP being uncontrolled despite treatment with optimal or best tolerated doses of three or more drugs including a diuretic, and confirmed by ABPM or HBPM. The prevalence of resistant hypertension is likely to be <10% of treated hypertensive patients. Spironolactone is the most effective drug for lowering BP in resistant hypertension when added to existing treatment; however, the risk of hyperkalaemia is increased in patients with CKD and eGFR <45 mL/min/m^2 and blood potassium levels >4.5 mmol/L.[564, 578] Potassium-binding drugs reduce the risk of hyperkalaemia.[579] When spironolactone is not tolerated, amiloride, alpha-blockers, beta-blockers, or centrally acting drugs, such as clonidine have evidence supporting their use.[564, 578, 580] Renal denervation and device -based therapy may be considered for specific cases, and are discussed in the 2018 ESC/ESH hypertension guidelines.[4]

4.7.7. Management of hypertension in women

The diagnosis and treatment of hypertension in women is similar to that in men except, expect for women of child bearing potential or in pregnancy, because of potential adverse effects of some drugs on the foetus, especially in the first trimester. In addition, the effect of oral contraceptive pills of the risk of developing or worsening hypertension should be considered.[4]

4.7.8. Duration of treatment and follow-up

Treatment of hypertension is usually maintained indefinitely because cessation of treatment usually results in a return of BP to pretreatment levels. In some patients with successful lifestyle changes, it may be possible to gradually reduce the dose or number of drugs. After BP is stable and controlled, visits should be scheduled at least annually, and include the control of other risk factors, renal function and HMOD, as well as reinforce lifestyle advice. When there is a loss of BP control in a previously well-controlled patient, non-compliance with therapy should be considered. Self-measurement of BP using HBPM helps engage the patient in their own management and can improve BP control. HBPM is essential to monitor BP control in patients with a significant "white-coat effect" or masked hypertension. Supervision of patient follow-up increasingly involves nurses and pharmacists and is likely to become increasingly supported by telemedicine and app-based technologies.

Gaps in evidence

- What is the incremental benefit, over ASCVD risk calculators, of measures of HMOD in reclassifying the cardiovascular risk of patients with hypertension?
- What are the benefits of BP treatment for patients with BP in the high-normal range?
- More data on the benefits of BP treatment in very old people and the influence of frailty
- Effect of single pill versus multidrug treatment strategies on adherence to treatment, BP control, and clinical outcomes
- Effectiveness of antihypertensive treatment in preventing cognitive dysfunction or dementia
- Efficacy and cost-effectiveness of invasive procedures and devices for treatment of hypertension

4.8. Diabetes mellitus

Key messages

- The multifactorial approach, including lifestyle changes, is critical in persons with type 2 DM.
- Management of hyperglycaemia reduces the risk of microvascular complications and, to a lesser extent, the risk of ASCVD. Glycaemic targets should be relaxed in old adults and frail individuals.
- New antihyperglycemic drugs are particularly important for persons with type 2 DM with existing ASCVD and (heightened risk of) HF or renal disease, broadly irrespective of glycaemia levels.

Recommendations for treatment of diabetes mellitus

Recommendations	Class[a]	Level[b]
Screening		

When screening for DM in individuals with or without ASCVD, assessment of HbA1c (which can be done non-fasting) or fasting blood glucose should be considered.[590]	**IIa**	**A**
Lifestyle		
Lifestyle changes including smoking cessation, low saturated fat, high-fibre diet, aerobic PA, and strength training are recommended.[591]	**I**	**A**
Reduction in energy intake is recommended to patients, to help achieve lower body weight or prevent or slow weight gain.[591]	**I**	**B**
For those motivated to try, considerable weight loss with use of low-calorie diets followed by food reintroduction and weight-maintenance phases early after diagnosis can lead to diabetes remission and should be considered.[592, 593]	**IIa**	**A**
Glycemia targets		
A target HbA1c for the reduction in risk of ASCVD and microvascular complications in DM of <7.0% (<53 mmol/mol) is recommended for the majority of adults with either type 1 or type 2 DM.[594, 595]	**I**	**A**
For patients with a long duration of DM and in old or frail adults, a relaxing of the HbA1c targets (i.e. less stringent) should be considered.[595]	**IIa**	**B**
A target HbA1c of ≤6.5% (48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in persons who are not frail and do not have ASCVD.[594, 595]	**IIa**	**B**
Treatment of glycemia and ASCVD/cardiorenal risks		
Metformin is recommended as first-line therapy, following evaluation of renal function in the majority of patients without previous ASCVD, CKD, or HF.[596]	**I**	**B**
Avoidance of hypoglycaemia and excessive weight gain should be considered.[595, 597, 598]	**IIa**	**B**
In persons with type 2 DM and ASCVD, the use of a GLP-1RA or SGLT2 inhibitor with proven outcome benefits is recommended to reduce CV and/or cardiorenal outcomes, without necessarily having to first commence metformin.[599-601]	**I**	**B**
In patients with type 2 DM and target organ damage[c], the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits should be considered to reduce future CV and total mortality.[602-605]	**IIa**	B
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.[606,607]	I	A

In patients with type 2 DM and HF with reduced ejection fraction, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.[608 609]	I	A
In patients with type 2 DM but without ASCVD, HF, or CKD, use of an SGLT2 inhibitor or GLP-1RA should be considered based on estimated future risks (e.g. with the ADVANCE risk score or DIAL model) for adverse ASCVD or cardiorenal outcomes from risk factor profiles.[610]	IIa	B
ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon like peptide-1 receptor agonist; HbA1c = glycated haemoglobin; HF = heart failure; PA = physical activity; SGLT2 = sodium-glucose cotransporter 2.		

[a] Class of recommendation.

[b] Level of evidence.

[C] Target Organ Damage in this specific context includes:

- eGFR <45 ml/min/1.73m^2;
- eGFR 46-79 ml/min/1.73m^2 plus microalbuminuria;
- proteinuria;
- presence of microvascular disease in at least 3 different sites (e.g. albuminuria plus retinopathy plus neuropathy). See section 3.2.2.6 for details

4.8.1. Key risk factor concepts and newer paradigms

Except for glucose management, prevention of ASCVD follows the same principles as for people without type 2 DM. Achieving BP LDL-C targets is particularly important. More recently, trial evidence has shown that drugs in the SGLT2 inhibitor or GLP-1RA classes lower ASCVD, HF, and renal risks independently of baseline HbA1c and whether patients are on metformin. Such benefits are most evident in those with existing ASCVD, HF, or CKD, but appear to extend to groups at elevated risk. This has led to newer treatment algorithms.

4.8.1.1 Lifestyle intervention

Lifestyle management is a first priority for prevention and management of DM. Most persons with DM are obese, so weight control is crucial. Several dietary patterns can be adopted, where the predominance of fruits, vegetables, wholegrain cereals, and low-fat protein sources is more important than the precise proportions of total energy provided by the major macronutrients. Salt intake should be restricted. Specific recommendations include limiting saturated and trans fats and alcohol intake, monitoring carbohydrate consumption, and increasing dietary fibre. A Mediterranean-type diet, where fat sources are derived primarily from monounsaturated oils, is protective against ASCVD. More detail is provided in section 4.3

A combination of aerobic and resistance exercise training is effective in preventing the progression of type 2 DM and for the control of glycaemia. Smokers should be offered cessation support (see *section 4.5*). Lifestyle intervention lowers future microvascular and macrovascular risks as well as mortality in the longer term.[611] Intensive lifestyle changes with low-calorie diets and mean weight

losses in the region of 10 kg leads to remission of type 2 DM in around 46% of cases at 1 year and 36% by 2 years.[592] In those with prediabetes, other ASCVD risk factors should be assessed both before (to incentivize improvements) and after lifestyle changes have taken place.[612]

4.8.1.1 Glycaemic control

The UKPDS established the importance of intensive glucose lowering with respect to ASCVD risk reduction in persons newly diagnosed with DM, with better evidence to support metformin, which correctly remains the first agent of choice for the majority of patients diagnosed with DM. Three trials were conducted to see if CV events could be reduced further with more intensive glycaemia treatment.[595, 597, 598] However, there were unexpected increases in total and ASCVD deaths in the ACCORD trial and a similar trend in the VADT trial. The results prompted concerns about pursuing tight glucose control, particularly in older people with DM and in those with existing ASCVD. Subsequent meta-analyses of relevant trials showed reductions in non-fatal AMI and CAD events, but no effect on stroke or total mortality.[613, 614] The meta-analyses suggested that ASCVD benefits for an average HbA1c reduction of 0.9% over 5 years were less than via treatment of cholesterol and BP. HbA1c targets should be personalized to individual characteristics and preferences.

Four trials of dipeptidyl peptidase-4 inhibitors[615-618] in patients with DM and existing ASCVD or at high risk demonstrated non-inferiority (i.e. safety) but not superiority with respect to ASCVD risk. There was, however, an increase in the rate of hospitalization for HF with saxagliptin in the SAVOR-TIMI 53 trial.[616]

4.8.1.1 Newer diabetes drug classes: cardiovascular disease benefits independent of glycated haemoglobin changes or baseline metformin

Recent trials from two classes of drugs (SGLT2 inhibitors and GLP-1RAs) have shown ASCVD benefits that appear independent of glycemic control and, where examined, of baseline metformin use.[604, 619, 620] Their results have recently been systematically meta-analysed (*Supplementary Figures 1–4*).[599, 600]

For SGLT2 inhibitors, three trials demonstrated the CV benefits of empagliflozin, canagliflozin, and dapagliflozin.[619, 621, 622] MACE were reduced modestly by 14%, with no clear effect on stroke and an unclear effect on myocardial infarction.[599] However, reductions in incident HF hospitalization/CVD death by 24% and renal endpoints by 44% were seen.[599] The MACE benefits were evident only in those with baseline ASCVD, but HF and renal benefits appeared to extend to those with type 2 DM with multiple risk factors. A more recent trial in people with Type 2 diabetes and ASCVD showed ertugliflozin to be non-inferior to placebo with respect to MACE outcomes.[623] Whether the results represent a class effect is therefore not clear. Four further SGLT2 inhibitor trials demonstrated the benefit of canagliflozin[606] and dapagliflozin[607] in patients with CKD (with DAPA-CKD showing similar benefits in people without DM), and dapagliflozin[608] and empagliflozin[609] in patients with HFrEF, with both trials showing similar benefits in those without type 2 DM.

The specific pattern of trial results (e.g. early separation of curves for HF hospitalisation) suggests that benefit of SGLT2 inhibitors may relate more to cardio-renal haemodynamic effects than to atherosclerosis.[624] Other than genitourinary infections, rates of adverse events (including diabetic ketoacidosis) were generally low. One trial showed an excess of amputations and fractures,[621] but

none of the other trials noted imbalances. Patients should be advised on the importance of genitourinary hygiene and sick day rule before being prescribed these medications.

GLP-1RAs reduce MACE, CV death, and all-cause mortality by around 12%, with around a 9% reduction in myocardial infarction and a 16% reduction in stroke.[600] Furthermore, HF is lowered by 9% and a composite renal outcome was lowered by 17%. The results cannot be explained by lowering of glucose levels and, in multiple SGLT2i and GLP-1RA trials, benefits were independent of metformin use.[603-605, 625] Most trials were conducted in patients with existing ASCVD or, in the REWIND trial, with a significant proportion of patients at high-risk for ASCVD.[626] Side-effects of this class include mainly nausea and vomiting, which can lessen with gradual up-titration. Risks of hypoglycaemia can be reduced by lowering doses of sulphonylureas or insulin.

The largely positive results of these two classes of drugs (SGLT2 inhibitors and GLP-1RAs) have led to rapid changes in diabetes algorithms, but with some differences in interpretation.[610] The two main areas of debate remain whether metformin should always be first line in all scenarios; and to which persons with type 2 DM *without* ASCVD, HF, or CKD should these drugs be recommended. Our view is that metformin does not need to be first line in patients with ASCVD, and that a risk score plus cost-effective analyses would be useful to determine which patients free from ASCVD or evidence of target-organ damage may be recommended for these newer drugs. In all the above, there is no evidence of any gender interaction in benefits. Finally, people with type 2 DM should be involved in decision making after explanation of the potential benefits and side effects of drugs.

4.8.2. Type 1 diabetes

Key messages

- Intensive management of hyperglycaemia in DM reduces the risk of macrovascular complications and premature mortality; a target of 6.5–7.5% (48–58 mmol/mol) HbA1c is recommended.
- Metformin is not recommended in type 1 DM to lower ASCVD risk.
- Dapagliflozin has been recommended for use in type 1 DM, although there is an increased risk of diabetic ketoacidosis with such therapies.
- Targeting other risk factors, in particular smoking, BP, and cholesterol levels, remains an important means to lower ASCVD risk in type 1 DM.

The DCCT study established the importance of tight glucose control to lessen the risks of both microvascular and macrovascular disease in both men and women with type 1 DM. A 27-year follow-up of this trial showed that 6.5 years of intensive DM therapy was associated with a modestly lower all-cause mortality rate.[627] A glycaemic target for HbA1c of 6.5–7.5% (48–58 mmol/mol) appears to be a balanced approach for long-term care.

Recently, metformin was shown not to lower progression of carotid IMT in persons with type 1 DM considered to be at elevated ASCVD risk.[628] Its use is not recommended in type 1 DM for this indication. SGLT2 inhibitors improve metabolic control in type 1 DM and may complement insulin therapy in selected patients.

Gaps in evidence

- More work is needed to develop risk scores for both MACE and HF in type 2 DM.
- Whether combined SGLT2 inhibitor and GLP-1RA treatments lower MACE or other outcomes beyond either drug alone requires testing.
- Longer-term safety of newer classes of drug is required.

4.9. Antithrombotic therapy

Key message

- All patients with established ASCVD require some form of antithrombotic therapy.

Recommendations for antithrombotic therapy

Recommendations	Class[a]	Level[b]
Aspirin 75–100 mg daily is recommended for secondary prevention of ASCVD.[629]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.[630]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.[630, 631]	IIb	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.[632, 633]	I	A
In patients with DM at high or very high CV risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.[634-636]	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.[634, 637-641]	III	A

CV = cardiovascular; ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus.

[a] Class of recommendation.

[b] Level of evidence.

4.9.1. Antithrombotic therapy in individuals without atherosclerotic disease

In 2009, a meta-analysis in patients with low ASCVD risk reported a 12% reduction in ASCVD with aspirin but a significant increase in major bleeding.[629] CVD risk reduction and bleeding risks were

similar in men and women.[642] More contemporary primary prevention trials reported no or little benefit in patients without ASCVD and a consistent increase in bleeding.[634, 637, 638] An updated meta-analysis did not show a reduction in all-cause or CV mortality with aspirin, but did show a lower risk of non-fatal myocardial infarction (RR 0.82) and ischaemic stroke (RR 0.87).[639] Conversely, aspirin was associated with a higher risk of major bleeding (RR 1.5), intracranial bleeding (RR 1.32), and major gastrointestinal bleeding (RR 1.52), with no difference in the risk of fatal bleeding (RR 1.09). Bleeding risks were particularly increased in older persons. Other recent meta-analyses found very similar results.[640, 641] Overall, although aspirin should not be given routinely to patients without established ASCVD, we cannot exclude that in some patients at high or very high ASCVD risk, the benefits outweigh the risks.[643, 644] In patients with DM and no evident ASCVD, the ASCEND study reported a 12% risk reduction and a significant increase in major bleeding, but not in fatal or intracranial bleeding.[634] A meta-analysis of aspirin for primary prevention in diabetes found a number needed to treat of 95 to prevent one major adverse ischaemic event in 5 years.[636] Hence, as in patients without DM, aspirin may be considered if ASCVD risk is exceptionally high. Only one in four patients in the ASCEND trial were being treated with a proton pump inhibitor. Wider use than this could potentially amplify the benefit of aspirin in primary prevention for patients at higher atherosclerotic risk.

In apparently healthy persons <70 years of age with (very) high ASCVD risk, further studies are needed. Until then, decisions in these high risk persons should be made on a case by case basis, taking both ischemic risk and bleeding risk into consideration.

4.9.2. Antithrombotic therapy in individuals with established atherosclerotic disease

In established atherosclerotic disease, aspirin is associated with significant reductions in serious vascular events, including stroke and coronary events, and a 10% reduction in total mortality.[629] These benefits outweigh the bleeding hazards.

In patients with previous myocardial infarction, stroke, or LEAD, clopidogrel showed a slight superiority for ischaemic events with respect to aspirin, with a similar safety profile.[630] Subgroup analysis suggested a greater benefit of clopidogrel in patients with LEAD. A meta-analysis showed a clinically modest risk reduction with $P2Y_{12}$ inhibitor monotherapy (number needed to treat: 244), and no effect on all-cause or vascular mortality and major bleeding.[631] More guidance on antithrombotic treatment in the specific settings of CAD, cerebrovascular disease, and LEAD, including possible indications for dual pathway inhibition in patients with LEAD, is given in *Chapter 6*.

4.9.3. Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet drugs and may be a useful adjunctive therapy to improve safety.[645, 646] Proton pump inhibitors that specifically inhibit CYP2C19 (omeprazole or ezomeprazole) may reduce the pharmacodynamic response to clopidogrel. Although this interaction has not been shown to affect

the risk of ischaemic events, coadministration of the proton pump inhibitors omeprazole or esomeprazole with clopidrogel is not recommended.[632]

Gap in knowledge

- The role of antithrombotic therapy in primary prevention in (very) high-risk individuals remains to be established.

4.10. Anti-inflammatory therapy

Key points

- Anti-inflammatory therapy is a promising strategy in ASCVD prevention

Low-dose colchicine (0.5 mg qd) may be considered in secondary prevention of ASCVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[83, 84]	IIb	A

Acknowledging that the process of atherosclerosis has inflammatory components has led to the investigation of various anti-inflammatory therapies in recent years. The first study to examine the effects of reducing inflammation without impacting lipid levels was CANTOS, in which the monoclonal antibody canakinumab provided proof-of-concept for anti-inflammatory therapy in high risk patients.[647] This particular drug was, however, not further developed for this indication because of the risk of fatal infections and high costs. Methotrexate was the second anti-inflammatory drug studied for this purpose, but was not proven effective in reducing CVD outcomes.[648]

In 2019, the COLCOT study reported a significant reduction (HR 0.77) in CVD outcomes with low-dose colchicine (0.5 mg qd) in patients with a recent AMI. The more recent LoDoCo2 study reinforced these results in patients with chronic CAD (HR 0.69). This study observed a trend towards increased non-cardiovascular mortality, which requires further attention.

The use of colchicine in daily practice remains to be established based on further clinical study data and experiences in daily practice. Nonetheless, the encouraging results justify consideration of low-dose colchicine in selected, high-risk patients.

4.11. Cardiovascular rehabilitation and prevention programmes

Recommendations for cardiovascular rehabilitation

Recommendations	Class[a]	Level[b]
Participation in a medically supervised, structured, comprehensive, multidisciplinary EBCR and prevention programme for patients after ASCVD	I	A

events and/or revascularization, and for patients with HF (mainly HFrEF), is recommended to improve patient outcomes.[649-653]		
Methods to increase CR and prevention referral and uptake should be considered (i.e. electronic prompts or automatic referrals, referral and liaison visits, structured follow-up by nurses or health professionals, and early programme initiation after discharge).[654-657]	**IIa**	**B**
Home-based CR, telehealth, and mHealth interventions may be considered to increase patient participation and long-term adherence to healthy behaviours.[658, 659]	**IIb**	**B**

CR = cardiovascular rehabilitation; EBCR = exercise-based cardiovascular rehabilitation; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; mHealth = mobile device-based healthcare.

[a] Class of recommendation.

[b] Level of evidence.

Key messages

- Patients after ACS and/or CABG/PCI, or with chronic HFrEF, should participate as early as possible in structured, multidisciplinary exercise-based cardiovascular rehabilitation (EBCR) and prevention programmes.
- EBCR and prevention programmes must comply with certain quality standards and be individualized to each patient's profile.
- Participation and long-term adherence to these programmes has to be encouraged and enhanced. Telerehabilitation and mobile device-based healthcare (mHealth) may help towards achieving this target.

CR is a comprehensive, multidisciplinary intervention not just including exercise training and PA counselling, but also education, risk factor modification, diet/nutritional counselling, vocational and psychosocial support.[358] Prevention and rehabilitation programs after ASCVD events or revascularization reduce CV hospitalisations, myocardial infarction, cardiovascular mortality and in some programs all-cause mortality.[649, 651-653] They may also reduce depressive/anxiety symptoms.[660] In patients with chronic HF (mainly HFrEF), EBCR may improve all-cause mortality, reduce hospital admissions, and improve exercise capacity and quality of life.[650, 661] CR is generally cost-effective.[662]

Clinical trials and registries are highly heterogeneous, which influences national guidelines, legislation, and reimbursement.[663, 664] The results of recent reviews provide clinicians with minimal requirements for successful CR after ACS or CABG:

- CR is a comprehensive multidisciplinary intervention.[467, 660, 665, 666]
- CR is supervised and carried out by adequately trained health professionals, including cardiologists.[660]
- CR starts as soon as possible after the initial CV event.[660]

- EBCR includes aerobic and muscular resistance exercise, which should be individually prescribed based on pre-exercise screening and exercise testing.[667]
- The dose of EBCR (number of weeks of exercise training × average number of sessions/week × average duration of session in minutes) exceeds 1000.[649]
- The number of EBCR sessions needs to exceed 36.[652]
- During CR, all individually recognised CV risk factors need to be addressed and treated.[653]

Recently, the EAPC proposed minimal and optimal standards for improvement of secondary prevention through CR programmes in Europe.[668]

Although exercise training prescription should adopt the FITT model (frequency, intensity, time duration, and type of exercise) inter-clinician variance and disagreement exists.[669] To optimize exercise training, the EAPC has introduced a digital, interactive decision support tool; the EXPERT Tool (https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/expert-tool).[670] No single exercise component is a significant predictor of mortality; only adherence to the full intervention improves outcome.[671]

Despite proven benefits, rates of referral, participation, and implementation are low.[664, 671, 672] [671] Uptake seems lower in women, but a variety of other intrapersonal, interpersonal, clinical, logistical, health system, and CR program related factors affect participation and adherence.[673] CR enrolment is higher if trained nurses or allied healthcare providers intervene face-to-face, whereas adherence may be higher when remote interventions are implemented (i.e. home-based).[654] Nurse-coordinated programs can increase effectiveness.[655-657] Home-based CR with or without telemonitoring may increase participation and appear similarly effective as centra-based CR.[658] Telehealth interventions are more effective than no intervention,[659] but may also complement conventional CR. Also, mHealth delivery through smartphones may be as effective as traditional centre-based CR, showing significant improvements in health-related quality of life.[674] These novel interventions may support the patient to maintain long-term healthy behaviours after specialized CR programmes.[675]

Gaps in evidence

- The effect and the optimal delivery of EBCR in women, older/frail patients, patients with cardiac implantable electronic devices, after heart transplantation or valve replacement, and in patients with AF, stroke, HFpEF, LEAD, or multiple comorbidities.
- Alternative and cost-effective models of CR need to ensure participation globally, including low- and middle-income countries.
- Large RCTs investigating the long-term effects of home-based telerehabilitation and mHealth are needed.

5. Policy interventions at the population level

Recommendations for policy interventions at the population level

Recommendations	Class[a]	Level[b]
Policies and population approaches to ***PA, diet, smoking and tobacco use, and alcohol*** in governmental restrictions and mandates, media and education,		

labelling and information, economic incentives, schools, worksites, and community setting follow different levels of recommendations (see specific tables in the supplementary material).		
Putting in place measures to reduce air pollution, including reducing particulate matter emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions, is recommended, to reduce CVD mortality and morbidity.	I	C

CVD = cardiovascular disease; PA = physical activity.

[a] Class of recommendation.

[b] Level of evidence.

[c] Level of evidence applies less well to policy interventions, and the type of empirical evidence varies widely across the separate approaches suggested.

5.1. Population-level approaches to the prevention of cardiovascular disease

Population level approaches to CVD prevention centre around upstream measures requiring broad public-health interventions targeting lifestyle and promoting monitoring of CVD. These measures are designed to address populations and are intended to shift the population attributable risk (PAR). This is based on a prevention paradox described by Geoffrey Rose in 1981. The PAR depends on the relative risk and on the prevalence of a risk factor in the general population. If the prevalence of a significant relative risk factor is low, then the PAR may be modest. Conversely, if a low-impact relative risk factor is common, the PAR may be high. This prevention approach following the Geoffrey Rose paradigm[676] states that small shifts in the risk of disease across a whole population consistently lead to greater reductions in disease burden than does a large shift in high-risk individuals only.[677, 678] In other words many people exposed to a small risk may generate more disease than a few exposed to a conspicuous risk. This population-wide approach – as opposed to strategies targeting high-risk individuals – has major advantages at the population level whilst sometimes having only a modest benefit at the individual level, because it addresses the CV health of a large number of individuals over the entire life course. They also contribute to reducing health inequalities. It should be noted that high-risk and population-level prevention strategies are not mutually exclusive and must therefore coexist.

Incidence rates of CVD vary across countries, many of their underlying causes are known, and are closely related to dietary habit, PA, smoking, alcohol, employment, social deprivation and the environment. The objective of population approaches to prevention of CVD is to control the underlying determinants of cardiovascular health and in this way reduce population incidence rates.

Individual behaviour is enacted in an environment with hierarchical levels, which encompass individual choice, family influence, cultural and ethnic grouping, workplace, healthcare, and policy at the regional, state and global levels (e.g. EU policies and international trade agreements). The aim of this section of the Guidelines is to provide evidence-based suggestions for the most effective interventions to reduce CVD risk at the population level, improve CVD health and promote healthy

choices at the community, regional, and global level. Health challenges cannot be solved by the health care systems alone and require political support. To advance this cause the WHO has been organizing since 1990 Global Conferences on Health promotion.

5.2. Specific risk factor interventions at the population level (supplementary material)

Population-level interventions aim to alter the societal environment, modify certain social determinants of health and provide incentives to encourage changes in individual behaviour and exposure to risk factors. Social determinants of health include socioeconomic status (education, occupation, and income), wealth inequalities, neighbourhood and urban design, and social networks, to name but a few. Healthcare professionals play an important role in advocating evidence-based population-level interventions. By modifying the general context, one can induce healthy decisions as a default in entire populations (all age groups and particularly vulnerable ones). The task for both national and local authorities is to create social environments that provide healthier defaults, taking into account health literacy.[679, 680] The evidence presented here builds on recent comprehensive reviews and individual studies, noting that it is rarely feasible to use an RCT to evaluate population-level interventions (in contrast to individual-level interventions).[681, 682] The importance of heart disease in women has become apparent and gender differences in CVD prevention have prompted gender-specific awareness campaigns with the aim of reducing gender disparities in research and clinical care. While interpreting this section it is important to recognize that there are often vested interests which may influence policy decisions on health promotion.

This section presents evidence for population level strategies dealing with specific risk factor interventions for physical activity (5.2.1) , diet (5.2.2), smoking and tobacco use (5.2.3), and alcohol consumption (5.2.4) (published in the supplementary material). Lifestyle changes at the population level take time, may be expensive, need to be sustained over time; furthermore the benefits may be slowly manifest, however they persist over the long term.

5.2.1 Physical activity

Key messages

- A significant percentage of worldwide population, in particular the European population, shows high levels of sedentary behaviour and physical inactivity.
- The percentage of those exercising at a regular level is greater in men than in women.
- Global progress to increase physical activity has been slow, largely due to lack of awareness and investment.
- The optimal dose of different types of PA for CVD and general prevention is still controversial and subjected to frequent updates. Increasing moderate to vigorous PA and reducing sitting time however is beneficial and any level of PA is considered better than none.
- PA for health promotion should be implemented by physicians in the same way as drug prescription and should also be promoted by other healthcare professionals.

- Population-based interventions are effective in promoting PA for groups based on age, sex, and race, for high-, middle-, and low-income populations, and for different environments (e.g. kindergarten, school, gyms, companies, and worksites in general).
- Daily PA at school should be practised at least 3 hours per week, and preferably for 60 minutes per day.
- Population based approaches are complementary to individual centred interventions.

5.2.2 Diet

Key messages

- Structural measures such as product reformulation, limitations on (digital) marketing to children, taxes on unhealthy foods/nutrients, and consumer-friendly nutrition labelling will improve healthy food choices.
- Healthy environments in the community, on public transport, at schools, and in workplaces will stimulate a healthier lifestyle.
- The WHO - Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020 extended to 2025 recommends to develop goals, in global, regional and national agendas; within the 10 voluntary targets to reach in 2025, a 30% relative reduction in mean population intake of sodium/salt.

5.2.3 Smoking and tobacco use

Key messages

- Adolescence is the most vulnerable period for the uptake of smoking, with lifelong consequences.
- Previous prevention campaigns reduced tobacco use in girls much less than in boys.
- Teenagers should be informed that smoking is not helpful in weight control.
- High taxes on all tobacco products is the most effective policy measure to reduce smoking uptake by the young.
- Restrictions on smokeless tobacco due to strong evidence of harm.
- Restrictions on e-cigarettes due to evidence of harm.
- Plain packaging is effective in reducing the attractiveness of tobacco products.
- Restrictions on advertising, promotion, and sponsorship by the tobacco industry.
- A goal would be to make a common European decision to achieve a smoking-free Europe by 2030.

5.2.4 Alcohol

Key messages

- Alcohol intake is associated with increased CV mortality, and alcohol use is the leading risk factor for premature death and disability among people aged 15–49 years.
- The interventions for addressing the harmful use of alcohol are cost effective, with a good return (i.e. increasing alcoholic beverage minimum unit pricing and excise taxes, restricting access to alcoholic beverages, and implementing comprehensive restrictions and bans on advertising and the promotion of alcoholic beverages).
- Health care providers may inquire about alcohol intake in every medical evaluation and should inform that alcohol is energy-dense: it provides 7kcal/g and no nutrients.

5.3. Environment, air pollution, and climate change

Key points

- Air pollution contributes to mortality and morbidity, and specifically increases the risk of respiratory and CV diseases.
- Environmental exposure has taken on new urgency, as air pollution, in addition to its health effects, has also been ascribed as a major contributor to climatic changes, notably through the burning of fossil fuels leading to increasing emissions of carbon dioxide.

Air pollution contributes to mortality and morbidity. It specifically increases the risk of respiratory and CV diseases, notably CAD, HF, cardiac arrhythmias and arrest, cerebrovascular disease, and venous thromboembolism.[162, 683, 684] Loss of life-expectancy due to ambient air pollution has been estimated at 2.9 years, accounting for an estimated global excess mortality of 8.8 million/year.[163] Plausible mechanisms by which air pollution is linked to CVD include promoting atherosclerosis, inflammation, thrombosis, systemic vascular dysfunction, myocardial fibrosis, epigenetic changes, and interactions with traditional risk factors.[162]

Important sources of fine particles are road traffic, power plants, and industrial and residential heating using oil, coal, and wood. Main components of outdoor air pollution include airborne particulate matter (PM; ranging in size from coarse particles <10-2.5 µm, fine particles <2.5 µm ($PM_{2.5}$), and ultrafine particles <0.1 µm in diameter) and gaseous pollutants such as ozone, nitrogen dioxide, volatile organic compounds, carbon monoxide, and sulphur dioxide, produced primarily by fossil fuel combustion.[162, 685] Up to one-third of Europeans living in urban areas are exposed to levels exceeding EU air-quality standards. The EU Commission released a policy package to be implemented by 2030, with measures to reduce harmful emissions from traffic, energy plants, and agriculture.

Indoor air pollution and exposure to noise must also be highlighted. Household air pollution, such as that produced from burning biomass, accounts for over 3 million deaths worldwide.[38] It is estimated by the WHO that 30% of the European population is exposed to nightly levels of noise exceeding 55 dB.[165] These levels have been associated with hypertension, arteriosclerosis, CAD, CV mortality, and stroke. It should be noted that mitigating efforts to reduce noise exposure have not as yet proven to have a beneficial health effect.[165]

The extent to which environmental exposures in soil and water contribute to CVD has also been established. Interventions to reduce this pollution are required, including factory regulations and drinking water controls.[161]

Patient organizations and health professionals have an important role in supporting education and policy initiatives. Information on patients' behaviour during smog peaks is needed. Economic incentives such as reduced taxes on electric and hybrid cars can contribute to the improvement of air quality as well as incentives encouraging the use of public transportation. Urban design promoting the construction of new houses and schools in areas remote from highways and polluting industries needs to be urged.

"Clean air" legislation aimed at promoting decreased particle emissions, and promotion of public transportation should also be encouraged. The urgency of accepting what might appear as "comfort sacrifices" for distant health benefits, and the transitory high costs of reorganizing entire sections of industry, probably remain a major dilemma to the population-based approach.

Climate Change

Climate change resulting from the increasing use of fossil fuels, as a major source of both air pollution and "greenhouse" gases, is becoming a major public health and environmental concern. Societal measures to reduce such fuels, and transfer towards renewable sources are becoming urgent to reduce air pollution and climate change.[686] The impact of diet, notably long-term non sustainable meat based food production chains as well as the impact of sedentary lifestyles on climate altering variables will also need to be addressed by policy makers.

Gaps in evidence

- Individual-level exposure studies are needed to better specify the effect of mitigating measures.

5.4. Implications for public health policy and advocacy at the governmental and non-governmental level (supplementary material)

6. Risk management of disease-specific cardiovascular disease

This section addresses ASCVD prevention in specific clinical contexts. A significant number of patients already have such comorbidities, which put them at additional risk. The general principles of lifestyle modification and treatment of major risk factors are outlined in chapter 4. In this chapter, only disease-specific aspects are added.

6.1. Coronary artery disease

Key message

- Multidimensional prevention is crucial for short- and long-term outcomes in CAD.

Disease-specific acute management of coronary syndromes is covered in detail in recent guidelines.[687-690]

As for antithrombotic therapy, dual antiplatelet therapy (DAPT) for 12 months, preferably with prasugrel or ticagrelor, is the standard antithrombotic treatment after ACS.[691-693] There are

conflicting data as to whether prasugrel is preferable to ticagrelor.[694 695] A 6-month duration of DAPT after ACS is generally too short[696] but may be considered in selected patients at high bleeding risk.

In patients with CCS undergoing elective PCI, the standard duration of DAPT is 6 months, but shortening to 1–3 months is an option when bleeding risk is very high.[632] Clopidogrel is the $P2Y_{12}$ inhibitor of choice, but prasugrel and ticagrelor may be considered after complex interventions.[632]

Prolonged DAPT (>12 months) following PCI for either ACS or CCS is an option for patients who tolerate DAPT well and have features of high ischaemic risk.[697 698] In patients with stable CAD, dual-pathway inhibition with low-dose rivaroxaban (2.5 mg *b.i.d.*) and aspirin improved CV outcomes at the price of more major bleeding events than aspirin alone.[81]

Based on the above and in line with the CCS guidelines, adding a second antithrombotic drug ($P2Y_{12}$ inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered for patients who are at high ischaemic risk and do not have a high risk of bleeding. It may also be considered in patients who are at moderate ischaemic risk and without a high risk of bleeding, but the benefits are lower.[632] More details on antithrombotic treatment options are found in the ESC guidelines for CCS.[699]

The management of dyslipidemia and hypertension in patients with CAD is discussed in sections 4.6 and 4.7. For ACE inhibitors (or ARBs) and beta-blockers see also the 2019 ESC Guidelines for diagnosis and management of CCS.[632]

Recommendations for coronary artery disease

Recommendations	Class[a]	Level[b]
Aspirin 75–100 mg daily is recommended for patients with a previous myocardial infarction or revascularization.[629]	I	A
Aspirin 75–100 mg daily may be considered in patients without a history of myocardial infarction or revascularization, but with definitive evidence of CAD on imaging.[632]	IIb	C
In ACS, DAPT with a $P2Y_{12}$ inhibitor in addition to aspirin is recommended for 12 months, unless there are contraindications such as excessive risk of bleeding.[691-693]	I	A
In patients with CCS, clopidogrel 75 mg daily is recommended, in addition to aspirin, for 6 months following coronary stenting, irrespective of stent type, unless a shorter duration (1–3 months) is indicated due to risk or the occurrence of life-threatening bleeding.[632]	I	A
Adding a second antithrombotic drug (a $P2Y_{12}$ inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk.[81, 632, 697, 698, 700]	IIa	A

Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with a moderate risk of ischaemic events and without a high bleeding risk.[81, 632, 697, 698, 700]	IIb	A
ACE inhibitors (or ARB) are recommended if a patient has other conditions (e.g. HF, hypertension, or DM).[632]	I	A
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.[632]	I	A
In patients with established ASCVD, oral lipid-lowering treatment with an ultimate LDL-C goal of <1.4 mmol/L (55 mg/dL) and a ≥50% reduction in LDL-C versus baseline is recommended.	I	A

ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin-receptor blocker; CAD = coronary artery disease; CV = cardiovascular; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HF = heart failure; LV = left ventricular.

[a] Class of recommendation.

[b] Level of evidence.

Gaps in evidence

- The efficacy and safety of aspirin or other antithrombotic therapy in patients without clinical manifestations of CAD but with atherosclerotic disease identified on imaging, such as CCTA, requires further assessment.
- The optimal long-term antithrombotic therapy in patients at high risk of ischaemic events is uncertain. Clinical studies comparing the efficacy and safety of $P2Y_{12}$ inhibitor versus low-dose rivaroxaban or other Xa inhibitors, in combination with aspirin, are warranted to determine which subgroups will derive greater clinical benefit with each strategy.

6.2. Heart failure

Key messages

- Patients with HF benefit from multidisciplinary care management programmes.
- Several neurohormonal antagonists, as well as novel molecules improve clinical outcomes in symptomatic patients with HFrEF.

The management of HF aims to improve mortality, hospitalizations rate, and quality of life.[701] To achieve this, multidisciplinary management programmes and structured follow-up with patient education, optimization of medical treatment, using telehealth facilities, lifestyle changes, psychosocial support, and improved access to care are fundamental.[702-705]

Regarding the management of CVD risk factors, similar basic rules apply for those with and without HF. However, in HF, low cholesterol levels[706, 707] and low body weight are associated with increased mortality.[708, 709] Initiation of lipid-lowering therapy is not recommended in patients with HF without

compelling indications for their use.[3] Whereas unintentional weight loss is associated with a worse prognosis regardless of baseline BMI, the effects of intentional weight loss remain unclear.

Conversely, regular exercise training (particularly combined aerobic and resistance exercises) improves clinical status in all patients with HF[661, 710, 711] and improves CVD burden and prognosis in HFrEF.[711, 712]

it is recommended to screen all patients with HF for both CV and non-CV comorbidities; if present, they should be treated.[701] These diseases include CAD, hypertension, lipid disorders, DM, obesity, cachexia and sarcopenia, thyroid disorders, CKD, anaemia, iron deficiency, and sleep apnoea.[701]

For patients with symptomatic HFrEF, neurohormonal antagonists (ACE inhibitors,[713-716] ARBs,[717] ARNIs,[718-721] beta-blockers,[722-728] and MRAs[729, 730]) improve survival and reduce the risk of HF hospitalizations.[701] These drugs also reduce the risk of CV events in patients with symptomatic HFrEF.[713-730] Importantly, these drugs should be up-titrated to the maximum tolerated doses, particularly in patients recently discharged after HF hospitalization.[701, 731]

SGLT2 inhibitors (currently dapagliflozin and empagliflozin) added on top of neurohormonal blockade reduces the risk of CV death and worsening HF in patients with symptomatic HFrEF, with or without diabetes,[608, 609] and are recommended for all patients with symptomatic HFrEF already treated with an ACE inhibitor (or ARNI), a beta-blocker, and an MRA.

Recently, an oral soluble guanylate cyclase receptor stimulator (vericiguat), administered along with standard neurohormonal blockade in symptomatic patients with HFrEF with recent HF hospitalization, reduced the composite of death from any cause or HF hospitalization.[732]

Other drugs bring additional moderate benefits for selected patients with symptomatic HFrEF. Diuretics,[733, 734] ivabradine,[735, 736] and hydralazine[737, 738] should be considered, and digoxin[739] may be considered as complementary therapies in specific patients with symptomatic HFrEF. Some of these therapies reduce CV morbidity and mortality (e.g. ivabradine).

Additionally, for selected patients with symptomatic HFrEF, there are indications for an implantation of ICD to reduce the risk of sudden death and all-cause mortality, and for cardiac resynchronization therapy in to reduce morbidity and mortality (for details see respective Guidelines).[701]

Gaps in evidence

- For patients with HFpEF, no specific pharmacotherapy or device implantation has been shown to modify the risk of any CV outcome.

Recommendations regarding pharmacological and non-pharmacological interventions for patients with symptomatic (New York Heart Association class II–IV) heart failure with reduced ejection fraction (left ventricular ejection fraction <40%) with proven benefits on clinical outcomes, including cardiovascular morbidity and mortality. For implantable cardioverter-defibrillator and cardiac resynchronization recommendations, see [740]

Recommendations	Class[a]	Level[b]

It is recommended that patients with HF are enrolled in a comprehensive cardiac rehabilitation programme to reduce the risk of HF hospitalization and death.[c 702-705]	I	A
Exercise-based cardiac rehabilitation is recommended in stable symptomatic patients with HFrEF to reduce the risk of HF hospitalization.[711, 712]	I	A
It is recommended to screen patients with HF for both CV and non-CV comorbidities, which, if present, should be treated provided safe and effective interventions exist, not only to alleviate symptoms but also to improve prognosis.[c]	I	A
An ACE inhibitor is recommended, in addition to a beta-blocker and a MRA, for patients with symptomatic HFrEF to reduce the risk of HF hospitalization and death.[713-716]	I	A
A beta-blocker is recommended, in addition to an ACE inhibitor (or an ARNI) and a MRA, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.[722-728]	I	A
An MRA is recommended for patients with HFrEF already treated with an ACE inhibitor (or an ARNI) and a beta-blocker, to reduce the risk of HF hospitalization and death.[729, 730]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I to reduce the risk of HF hospitalization and death in patients with HFrEF.[718, 741]	I	B
ARB is recommended to reduce the risk of HF hospitalization or CV death in symptomatic patients with HFrEF who are unable to tolerate an ACE inhibitor and/or ARNI (patients should also receive a beta-blocker and an MRA).[717]	I	B
Dapagliflozin or empagliflozin are recommended, in addition to optimal treatment of a-n ACE-I (or ARNI), a beta-blocker and an MRA, for patients with HFrEF to reduce the risk of HF hospitalization and death.[608, 609, 741]	I	A
Vericiguat should be considered in patients with symptomatic HFrEF who have experienced HF worsening despite treatment with an ACE inhibitor (or an ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization or CV death.[732]	IIa	B
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to reduce the risk of HF hospitalization.[733, 734]	I	C
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in sinus rhythm, and with a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), an ACE inhibitor (or an ARNI), and an MRA, to reduce the risk of HF hospitalization or CV death.[735]	IIa	B

Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contraindications for a beta-blocker to reduce the risk of HF hospitalization or CV death. Patients should also receive an ACE inhibitor (or ARNI) and an MRA.[736]	IIa	C
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with LVEF <45% combined with a dilated LV in NYHA class III–IV despite treatment with an ACE inhibitor (or ARNI), a beta-blocker, and an MRA, to reduce the risk of HF hospitalization and death.[742]	IIa	B
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who can tolerate neither an ACE inhibitor, an ARB, or an ARNI (or if they are contraindicated), to reduce the risk of death.[743]	IIb	B
Digoxin may be considered in patients with symptomatic HFrEF in sinus rhythm despite treatment with an ACE inhibitor (or ARNI), a beta-blocker, and an MRA, to reduce the risk of hospitalization (both all-cause and HF hospitalizations).[744]	IIb	B

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; bpm = beats per minute; CR = cardiac rehabilitation; CV = cardiovascular; EBCR = exercise-based cardiac rehabilitation; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acid.

[a] Class of recommendation.

[b] Level of evidence.

[c] Applies to all patients with HF, regardless of LVEF.

6.3. Cerebrovascular diseases

Key messages

- Ischaemic events are mainly caused by atherothrombosis, cardioembolism, or small vessel disease, whereas intracerebral haemorrhage is mostly caused by hypertensive angiopathy or cerebral amyloid angiopathy.
- Platelet inhibitors are recommended for non-cardioembolic events and anticoagulants for cardioembolic events.
- In patients with a previous stroke or TIA and high BP, BP lowering reduces the recurrence risk.
- In patients with stroke or TIA, statins prevent ASCVD and cerebrovascular events.

Interventions for cerebrovascular disease depend on the type of event, ischaemic or haemorrhagic.[745, 746] Ischaemic events are mainly caused by atherothrombosis, cardiac embolism, or small vessel disease.[747] Other mechanisms (e.g. arterial dissection, patent foramen ovale, thrombophilia, inherited diseases) are relatively rare. Intracerebral haemorrhage is mostly caused by hypertensive angiopathy and/or cerebral amyloid angiopathy.[748] Bleeding can be precipitated by surges in BP values, use of anticoagulants, or diseases impairing coagulation.[746, 748]

In patients with ischaemic stroke or TIA, antithrombotics prevent further vascular events. Cardioembolic ischemia, which occurs mainly in AF, requires anticoagulation (*sections 3.4.3* and *6.6*).[749-755] In non-cardioembolic mechanism, platelet inhibitors are recommended.[629, 630, 756-766]

In non-cardioembolic ischaemic stroke, aspirin is the most studied antithrombotic drug. Aspirin 75-150 mg/day reduces the risk of recurrent ischaemic stroke and serious vascular events.[629 756] Clopidogrel shows slight superiority to aspirin.[630] In patients with ischemic stroke or transient ischemic attack and ipsilateral carotid stenosis, ticagrelor added to aspirin compared to aspirin alone reduced the risk of stroke or death at one month, without increase of severe bleeding.[767] Adding aspirin to clopidogrel was associated with a non-significant reduction in major vascular events and an increased long-term bleeding risk.[760-762] However, in patients with minor ischaemic stroke or TIA, a short course of DAPT with aspirin and clopidogrel is beneficial.[763, 764] Similarly, ticagrelor and aspirin versus aspirin alone reduces stroke or death at 30-day after mild-to-moderate ischaemic stroke or TIA not treated with thrombolysis or thrombectomy. However, DAPT with ticagrelor and aspirin did not improve the incidence of disability and contributed to severe bleeding.[768] DAPT with dipyridamole plus aspirin also showed superiority over aspirin alone.[757] In patients with ischaemic stroke, however, dipyridamole plus aspirin versus clopidogrel alone showed similar rates of recurrent stroke, including haemorrhagic stroke[758] but more major haemorrhagic events. In patients with non-cardioembolic ischaemic stroke, oral vitamin K antagonists are not superior to aspirin and carry a higher bleeding risk.[765, 766] In the absence of a definite cause of ischaemia and a presumed occult cardioembolic source (e.g. embolic stroke of undetermined cause), neither dabigatran nor rivaroxaban are better than aspirin.[769, 770]

Recommendations for blood pressure and lipid management are congruent to the general recommendations outlined in sections 4.6 and 4.7. In patients with either ischaemic or haemorrhagic cerebrovascular disease who have a BP of 140/90 mm Hg or higher, lowering BP reduces the risk of recurrent stroke.[771, 772] Optimal BP targets in these patients are uncertain, as is the optimal drug regimen.[773] Most evidence is available for ACE inhibitors, ARBs, and diuretics. Comorbidities may guide the choice of antihypertensive agent. In patients with recent lacunar stroke, the target SBP is <130 mmHg.[774]

In patients with stroke (ischaemic or haemorrhagic) or TIA with an LDL-C level of 100−190 mg/dL, atorvastatin 80 mg/d reduced the overall incidence of strokes and of CV events.[775] A recent trial supported an LDL-C target of < 1.8 mmol/L (<70 mg/dL).[510]

Evidence of cerebrovascular lesions (e.g. white matter hyperintensities, lacunes, non-lacunar ischaemia) in the absence of any stroke history is a relatively common finding at neuroimaging, especially in older patients. Silent cerebrovascular disease is a marker of increased risk of stroke.[776, 777] Arterial hypertension, diabetes, and cigarette smoking contribute to these lesions and should be attended to. There are no studies addressing the best treatment options for silent cerebral ischaemia.[778]

Gaps in evidence

- The optimal selection of patient for a short course of DAPT.
- The optimal antihypertensive regimen and target BP.
- The optimal target level of LDL-C.
- Optimal treatment for patients with silent cerebrovascular disease.

Recommendations for patients with cerebrovascular disease

Recommendations	Class[a]	Level[b]
In patients with a cerebrovascular event, improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.[745, 746, 754]	I	A
In patients with ischaemic stroke or TIA, prevention with antithrombotics is recommended; choice of antithrombotic depends on the mechanism of event. Use of antiplatelet is recommended for patients with non-cardioembolic ischaemic stroke or TIA, and use of anticoagulant is recommended in patients with cardioembolic ischaemic stroke or TIA.[745, 754]	I	A
In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin, or clopidogrel alone is recommended.[630, 756-758]	I	A
In patients with minor ischaemic stroke[c] or TIA, DAPT with aspirin and clopidogrel or with aspirin and ticagrelor, for 3 weeks after the acute event should be considered.[763, 764, 768]	IIa	A
In patients with stroke or TIA who have BP of 140/90 mmHg or higher, BP lowering is recommended.[779, 780]	I	A

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; DAPT = dual antiplatelet therapy; LDL-C = low-density lipoprotein cholesterol; TIA = transient ischaemic attack.

[a] Class of recommendation.

[b] Level of evidence.

[c] Minor ischaemic stroke defined as score at National Institutes of Health Stroke Scale ≤3, or ≤5 depending on the trial.

6.4. Lower extremity artery disease

Key messages

- LEAD is associated with an increased ASCVD risk.
- Antiplatelet therapy (alone or in combination with low-dose oral anticoagulation) reduces the risk of adverse limb events and overall ASCVD risk in patients with LEAD.
- Smoking cessation and control of other ASCVD risk factors improve prognosis.

Symptomatic or asymptomatic LEAD (ABI ≤0.90) is associated with a doubling of the 10-year rate of coronary events, CV mortality, and total mortality.[129] Within 5 years of LEAD diagnosis, 20% develop AMI or stroke, and mortality is 10–15%.[781]

All LEAD patients require lifestyle improvement and pharmacological therapy. Smoking cessation increases walking distance and lowers amputation risk.[2] In patient with diabetes, glycaemic control improves limb outcomes.[782] Statins provide modest improvements iCn walking distance, and lower the risk of adverse limb events.[783, 784] Combining a statin with ezetimibe[785] or a PCSK9 inhibitor also has beneficial effects.[786]

Platelet inhibitors are used to prevent limb-related and general CV events. The optimal antiplatelet strategy remains unclear.[787] DAPT is currently recommended only after intervention (irrespective of the stent type) for at least 1 month.

In the COMPASS trial, low-dose rivaroxaban added to aspirin in CVD patients with an ABI <0.90 reduced not only ASCVD events, but also major adverse limb events, including amputation (HR 0.54), albeit at the cost of higher major bleeding risk.[788] These results, combined with similar benefits of rivaroxaban versus aspirin monotherapy, suggest a benefit of anticoagulants in LEAD. However, further studies are needed. Optimal antithrombotic therapy is addressed in more detail in the 2017 ESC/ESVS Guidelines.[789] Importantly, in patients with isolated asymptomatic LEAD (e.g. low ABI), antiplatelet treatment is not recommended.[790]

Recommendations for blood pressure and lipid management are congruent to the general recommendations outlined in sections 4.6 and 4.7. Hypertension targets are based mainly on the INVEST study.[791] A SBP below 110–120 mmHg may increase CV events in patients with LEAD.[791] ACE inhibitors and ARBs reduce CV events in patients with LEAD [581, 792] and are preferred (as monotherapy or as part of a combination drug regimen).[793] Beta-blockers are not contraindicated in mild-to-moderate LEAD as they do not affect walking capacity or adverse limb events[794], and significantly reduce coronary events.[795] Nevertheless, beta-blockers should be carefully considered in critical limb-threatening ischaemia.

Gaps in evidence

- The optimal type and potency of antithrombotic therapy in patients with different manifestations of symptomatic or asymptomatic LEAD are partly unclear.

Recommendations for patients with lower extremity artery disease: best medical therapy

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with LEAD.[29, 796]	I	B

Healthy diet and PA are recommended for all patients with LEAD.	I	C
In patients with intermittent claudication: - supervised exercise training is recommended[797-799] - non-supervised exercise training is recommended when supervised exercise training is not feasible or available	 I I	 A C
Antiplatelet therapy is recommended in patients with symptomatic LEAD.[c]	I	C
In patients with LEAD and hypertension, it is recommended to control BP at <140/90 mmHg.[791, 800, 801]	I	A
In patients with LEAD and diabetes, strict glycemic control is recommended.[782]	I	A
ACE inhibitors or ARBs should be considered as first-line therapy in patients with PAD and hypertension.[d] [581, 802]	IIa	B
In patients with DM and chronic symptomatic LEAD without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg *b.i.d.*) and aspirin (100 mg *o.d.*) may be considered.[788]	IIb	B

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; *b.i.d.* = *bis in die* (twice a day); BP = blood pressure; DM = diabetes mellitus; LEAD = lower extremity artery disease; *o.d.* = *omni die* (once a day); PA = physical activity; PAD = peripheral artery disease.

[a] Class of recommendation.

[b] Level of evidence.

[c] Evidence is not available for all sites. When evidence is available, recommendations specific for the vascular site are presented in corresponding sections.

[d] Calcium channel blockers should be proposed in black individuals.

6.5. Chronic kidney disease

Key messages

- Hypertension, dyslipidaemia, and DM are prevalent among individuals with CKD and require a high-risk treatment strategy approach.
- Risk management includes lifestyle, smoking cessation, nutrition, sufficient RAAS blockade, target BP control, lipid management, and in established CVD aspirin.
- A high value is placed on self-management education programmes and team-based integrated care in patients with DM, CKD, and CVD.

Severe CKD is associated with a very high risk of CVD and is considered a CAD risk equivalent (see section 3.2). As GFR declines, non-traditional risk factors emerge and nonatherosclerotic CVD event risk increases.[208] Trials often exclude patients with eGFR <30 mL/min/1.73 m^2. In patients on dialysis, coronary syndromes may present atypically, and angina equivalents such as shortness of breath or

fatigue are frequent.[803] Standard ASCVD risk management is effective in patients on dialysis, but unique haemodialysis-specific syndromes (i.e. intradialytic hypotension and myocardial stunning) associated with mortality complicate treatment and modify outcomes.

Risk classification of patients with various degrees of CKD is summarized in table 3. Treatment with a statin or statin/ezetimibe combination is recommended in CKD patients with sufficiently high ASCVD risk, but not in those treated with kidney replacement therapy. This recommendation is built on evidence from the SHARP study, which demonstrated a reduction of major atherosclerotic events.[530] Statins should be dosed according to a moderate-intensity regimen based on limited experience and risks associated with high-intensity regimens.[548] Subgroup analysis of a recent study with a PCSK9 inhibitor has shown that the benefits may extend to those with earlier CKD stages (60−90 as well as 30−60 mL/min/1.73 m^2).[804]

Treatment with an ACE inhibitor or an ARB is recommended in patients with DM, hypertension, and albuminuria. These medications should be titrated to the maximum tolerated dose (Kidney Disease Improving Global Outcomes grading 1B). Combination treatment is not recommended.

Individualized HbA1c targets, ranging from 6.5% to <8.0% in patients with diabetes and non−dialysis-dependent CKD (1C), are recommended in parallel. The role of SGLT2 inhibitors and GLP-1 RA's in CKD associated with diabetes is addressed in section 4.8. Dapagliflozin has shown promising reno- and cardio-protective effects[607], and more studies investigating SGLT2 inhibitors in CKD patients without diabetes are ongoing.[805]

Overall, the management of CAD in CKD patients must be informed by the modification of its clinical presentation in CKD, as well as comorbidity and risks of treatment side-effects. Treatment of established risk factors is often suboptimal in patients with CKD.

Gaps in evidence

- Few CVD trials have a focus on patients with CKD, particularly those with advanced CKD.
- Additional prospective studies focusing on diagnosis, prevention, and treatment of CAD and CVD are needed in CKD.

Recommendations in patients with chronic kidney disease: best medical therapy.
Recommendations on CKD management in patients with DM are found in section 4.8.

Recommendations	Class[a]	Level[b]
Treatment with an ACE inhibitor or an ARB is recommended in patients with DM, hypertension, and albuminuria. These medications should be titrated to the highest approved dose that is tolerated.	I	B
An SGLT2 inhibitor with proven outcome benefits should be considered for the prevention of renal deterioration and mortality in patients with CKD.[607]	IIa	B
Combination treatment with ACE inhibitors and ARBs is not recommended.	III	C

- ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; Hb1Ac = glycosylated haemoglobin
- [a] Class of recommendation.
- [b] Level of evidence.

6.6. Atrial fibrillation

Key messages

- Holistic management of patients with AF improves prognosis and reduces health-related costs.
- Comprehensive risk factor modification and targeting underlying conditions reduce AF burden and recurrence.

The simple "Atrial fibrillation Better Care" (ABC) holistic pathway ("A" Anticoagulation/Avoid stroke; "B" Better symptom management; "C" Cardiovascular and Comorbidity optimization) streamlines integrated care of patients with AF.[218] The ABC pathway lowers risk of all-cause death and the composite of stroke, major bleeding, CV death, or first hospitalization,[806] and lowers rates of CV events[807, 808] and health-related costs.[809]

The "C" component of the ABC pathway refers to identification and management of concomitant diseases, cardiometabolic risk factors, and unhealthy lifestyle factors. Therapy of underlying conditions improves rhythm control in persistent AF and HF.[219] In obese patients, weight reduction prevents AF recurrences and symptoms.[810-817] Given that hypertension precipitates AF, treatment of hypertension is mandatory. Alcohol excess is a risk factor for incident AF,[818, 819] and abstinence reduced AF recurrences in regular drinkers.[813] Many studies have demonstrated beneficial effects of moderate exercise/PA.[820-822] The incidence of AF appears, however, to be increased in elite athletes, mainly related to endurance sports.[823-826] Patients should be encouraged to practise moderate-intensity exercise and remain physically active to prevent AF incidence or recurrence, but avoid excessive endurance exercise. CR is recommended universally program for patients with ACS and/or revascularization, and for patients with HF.[650, 651, 666] The benefits of exercise-based CR are more uncertain in patients with AF, but CR remains recommended in patients with the afore-mentioned indications.[827] Continuous positive airway pressure (CPAP) may improve rhythm control and attenuate AF recurrences in OSA patients. [828-831] Intensive glycaemic control does not affect the rate of new-onset AF.[832] Optimal glycaemic control during the 12 months before AF ablation does, however, reduce AF recurrence after ablation.[833] All patients with HF and AF should receive guideline-adherent HF therapy.[834]

Gaps in evidence

- The effects of various CV risk factors and comorbidities in AF.
- Optimal treatment of OSA and its effect on AF progression and symptoms.

Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with atrial fibrillation[218]

Recommendations	Class[a]	Level[b]
Identification and management of risk factors and concomitant diseases are recommended to be considered an integral part of treatment.[810]	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.[219, 810-817]	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.[815, 816]	I	B
In obese patients with AF, weight loss together with management of other risk factors should be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.[810-812]	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for oral anticoagulant therapy.[813, 818, 819]	IIa	B
PA should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.[820-827]	IIa	C
Optimal management of OSA may be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.[828-831]	IIb	C

AF = atrial fibrillation; BP = blood pressure; ESC = European Society of Cardiology; OSA = obstructive sleep apnoea; PA = physical activity.

[a] Class of recommendation.

[b] Level of evidence.

6.7. Multimorbidity

Key messages

- The number of patients with multiple CV and non-CV comorbidities is rapidly increasing.
- Therapeutic competition should be considered in multimorbid patients, as the treatment of one condition might worsen a coexisting condition.
- A paradigm shift from disease-focused to patient-centred care for multimorbid CVD patients is recommended.

The older adult population is growing fast and survival after acute CVD has improved,[835] leading to a increasing number of older patients with CVD and multimorbidity.[836, 837] This development is associated with high healthcare costs,[838, 839] worse outcome measures, higher readmission rates,[840] and mortality.[841]

Up to 70% of patients aged 70 years or more have one or more CVD(s) and two-thirds also develop non-CVD comorbidities. Multimorbidity is important in patients with CVD.[838]

The prevailing CV conditions in patients >60 years are hypertension, hyperlipidaemia, ischaemic heart disease, arrhythmia, DM, and CAD.[838] Other frequent comorbidities include anaemia and arthritis. Low vision, DM, back and neck problems, osteoarthritis, COPD, and cancer are the most common non-CV comorbidities in CVD patients. Most studies found no gender differences in the number of comorbidities. However, in men more CVD comorbidities and in women more non-CVD comorbidities (in particular more depression) were found.[837, 841 842]

So far, guidance for treatment of CVD has focused mainly on single CVDs. In multimorbid patients, application of a single guideline for one CVD is often not feasible as therapeutic competition is highly prevalent (22.6%)[835]; treatment for one condition can worsen a coexisting condition. The challenges for managing CVD and multimorbidity are disease−disease, disease−drug, and drug−drug interactions.[835] Further, pharmacokinetics can be different in patients with comorbidities, and life expectancy has to be taken into account when starting a new medication. A value-based approach should always be discussed and proposed when possible.[835] The incremental benefit of medication when added to an already complex regimen is often uncertain.[843] Moreover, care for multimorbid CVD patients is often fragmented and given by multiple providers, complicating decision making and adherence to recommended treatment.[835]

Multimorbid CVD patients have been underrepresented in most clinical trials that underlie the guidelines. Trials including patients with multimorbidity and endpoints that matter to patients, pragmatic trials, and the use of registries and big data could help elucidate how to optimize treatment and care for patients with CVD and multimorbidity.[835]

There is a plea for a paradigm shift from disease-focused to patient-centred care for multimorbid CVD patients, with a central place for patients' overarching goals of care.[843] "What matters to you" should be the central question, instead of "what is the matter"?

Patient-centred care should include assessment of patients' preferences, interpretation of the evidence and its application to the specific patient, consideration of overall prognosis, including life expectancy, functional status, and quality of life, and clinical feasibility. Adherence to treatment, adverse drug events, economic burden, and stress of caregivers should be taken into account, optimizing therapies and care plans where adherence to essential medication is emphasized and non-essential drugs are stopped.[843] Furthermore, advanced care planning should be initiated early. Multidisciplinary teams and close collaboration between primary care workers and specialists is needed. Finally, automated decision support systems for multimorbidity and CVD could help in aligning the relevant evidence and making adequate decisions.[844]

Gaps in evidence

- The effect of different clusters or combinations of CV and non-CV comorbidities on CV outcomes.
- Optimal, pragmatic treatment strategies in patients with CV and non-CV comorbidities, with particular focus on treatment adherence and therapeutic competition.

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JOINT GUIDELINES

2021 EUROPEAN GUIDELINES ON CARDIOVASCULAR DISEASE PREVENTION IN CLINICAL PRACTICE

Supplementary data

Contents

List of Tables

List of Figures

3. Risk factors and clinical conditions

3.2.2.1 Risk estimation in apparently healthy people between 50–70 years of age

Supplementary Table 1: *Cardiovascular mortality risk in European countries*

Countries	ASDR per 100 000 – total deaths, ICD chapter 9	Collected in
France	71	2014
Spain	89	2015
Netherlands	90	2016
Switzerland	90	2015
Denmark	90	2015
Norway	91	2015
Luxembourg	93	2015
Belgium	99	2015
United Kingdom	100	2015
Iceland	101	2016
Portugal	108	2014
Sweden	109	2016
Italy	110	2015
Cyprus	112	2016
Ireland	112	2014
Finland	129	2015
Austria	131	2016
Greece	139	2015
Germany	139	2015
Slovenia	143	2015
Albania	185	2010
Czech Republic	195	2016
Turkey	200	2015
Croatia	215	2016
Poland	224	2015
Estonia	235	2015
Slovakia	239	2014
Hungary	274	2016
Bosnia and Herzegovina	279	2014
Armenia	306	2016
Lithuania	309	2016
Georgia	310	2015
Latvia	327	2015
Serbia	329	2015
Romania	331	2016
Montenegro	348	2009
Russian Federation	369	2015
TFYR Macedonia	388	2013
Belarus	395	2014

Bulgaria	421	2014
Republic of Moldova	442	2016
Ukraine	477	2015

ASDR = age-standardized death rate; ICD = International Classification of Diseases.

3.3. Potential risk modifiers

3.3.1. Psychosocial factors

Supplementary Table 2: *Examples of common stress symptoms and psychosocial stressors associated with conventional cardiovascular risk factors or cardiovascular disease endpoints*

Psychosocial risk modifier[a]	Population	Endpoint	Adjusted risk estimates[b] (95% CI)
Insomnia[1]	Population free of CVD	CV events	1.45 (1.29–1.62)
Vital exhaustion[2]	CHD patients	Recurrent CHD events	2.03 (1.54–2.68)
Vital exhaustion[2]	Healthy persons from the general population	CHD events	1.50 (1.22–1.85)
Depression[3]	CVD patients	All-cause mortality/fatal CHD	1.53 (1.11–2.10)
Depression[3]	Participants free of CVD	Incident myocardial infarction	1.90 (1.49–2.42)
Anxiety[4]	General population	CV mortality	1.41 (1.13–1.76)
Anger/hostility[5]	Participants free of CVD	CHD events	1.19 (1.05–1.35)
Anger/hostility[5]	CHD population	CHD events	1.24 (1.08–1.42)
Social isolation/loneliness[6]	General population	Incident CHD	1.29 (1.04–1.59)
Optimism[7]	General population and ambulatory patients	CV events	0.65 (0.51–0.78)
Psychological distress[8]	Participants free of CVD and cancer	CV death	1.22 (1.14–1.31)
Adverse childhood experiences[9]	General population	CV events	2.07 (1.66–2.59)
Adverse childhood experiences[9]	General population	Smoking	2.70 (2.34–3.11)
Adverse childhood experiences[9]	General population	Incidence of diabetes	1.38 (1.20–1.60)

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease.

- [a]Definitions: Insomnia: difficulty initiating or maintaining sleep or the presence of restless, disturbed nights. Sleep disturbances are the most common stress symptoms reflecting hyperarousal.
- Vital exhaustion: pervasive fatigue, irritability, and demoralization.
- Depression: subthreshold depressive symptoms (feeling down, tired, joyless) and depressive disorders.
- Anxiety: symptoms of anxiety and phobic avoidance.

- Psychological distress: symptoms of anxiety, depression, social dysfunction, and loss of confidence as measured by questionnaires.
- Anger and hostility: dysregulated anger such as rage outbursts, yelling, intimidation, and a negative attitude toward others represent common symptoms of personality disorders.
- Social isolation and loneliness: lack of interactions with significant others and the feeling of the absence of an intimate companion.
- Optimism: tendency to think good things will happen in the future.
- Adverse childhood experiences: none versus four or more of the following stressors: physical abuse; emotional abuse; sexual abuse; neglect; separation, loss, or divorce of parents; exposure to domestic violence, household substance abuse, criminality; serious childhood illness; financial problems.
- [b]The risk estimates range from temporally adjusted hazard ratios to specific odds and/or relative risks.

Supplementary Table 3*: Screening for psychological stress in patients with cardiovascular disease*

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3
5. Trouble falling or staying asleep, or sleeping too much	0	1	2	3

GAD-2 = Generalized Anxiety Disorder 2-item; PHQ-2 = Patient Health Questionnaire-2.

Anxiety (GAD-2) = sum of items 1 and 2, scores of 3 and above are clinically significant.
Depression (PHQ-2) = sum of items 3 and 4, scores of 3 and above are clinically significant.
Sleep disturbances = item 5, scores of 1 or above indicate clinically significant sleep disturbances.

3.3.10. **Body composition**

3.3.10.1. Which index of obesity is the best predictor of cardiovascular risk?

Supplementary Table 4*: World Health Organization classification of body weight according to body mass index in adults*

Adults (>18 years of age)	**Body mass index (kg/m^2)**
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9

Obese	≥30.0
Class 1	30.0–34.9
Class 2	35.0–39.9
Class 3	≥40.0

4. Risk Factors and interventions at the individual level

4.4. Mental healthcare and psychosocial interventions

Supplementary text for explaining the recommendation "In patients with HF and major depression, SSRI, SNRI, and tricyclic antidepressants are not recommended".

Depression is a common comorbidity in patients with heart failure. Antidepressants are not recommended for treating major depression in heart failure patients because previous trials have failed to show their efficacy and extensive meta-analysis revealed that the intake of antidepressants is associated with harmful effects such as an increased risk of all-cause death. Psychotherapy, exercise therapy, and collaborative care are fist line treatments for patients with depression and HF.[10]

Until now, there are four RCTs on the treatment of major depression in HF patients with serotonin reuptake inhibitors (SSRI). The first small RCT evaluated the SSRI paroxetine in 28 HF patients randomized 1:1 to either paroxetine or placebo.[11] At the 12 week-follow-up, therapy with paroxetine resulted in significant reductions in depression versus placebo. The second trial evaluated the SSRI citalopram. N = 72 HF patients with depression were enrolled. The study was stopped after an interim analysis of 37 patients because of a high rate of placebo response. The authors concluded that citalopram treatment of major depressin in older patients with heart failure was not effective and that the weekly psychiatric follow-up visits, including counseling, may have contributed to the improvement of depression in this population.[12] The following two large RCTs, revealed that the same class of antidepressants did not reduce depression or mortality or improve cardiovascular outcomes. SADHART-CHF randomized n = 469 HF patients to either sertraline in a dosage of 50 to 200 mg/day versus placebo for 12 weeks. Treatment with sertraline compared with placebo did not reduce depression or improve cardiovascular status.[13] In Mood-HF, n = 372 HF-patients were randomized 1:1 to receive escitalopram (10-20mg) or placebo in addition to optimal heart failure therapy.[14] The trial was terminated early based on futility. Treatment with escitalopram over 18 months did not significantly reduce all-cause mortality or hospitalization or improve depression as compared with placebo. Therefore, the current state of the research is that SSRIs are not effective for treating depression in HF patients (as opposed to SSRI treatment of depression in CAD patients).

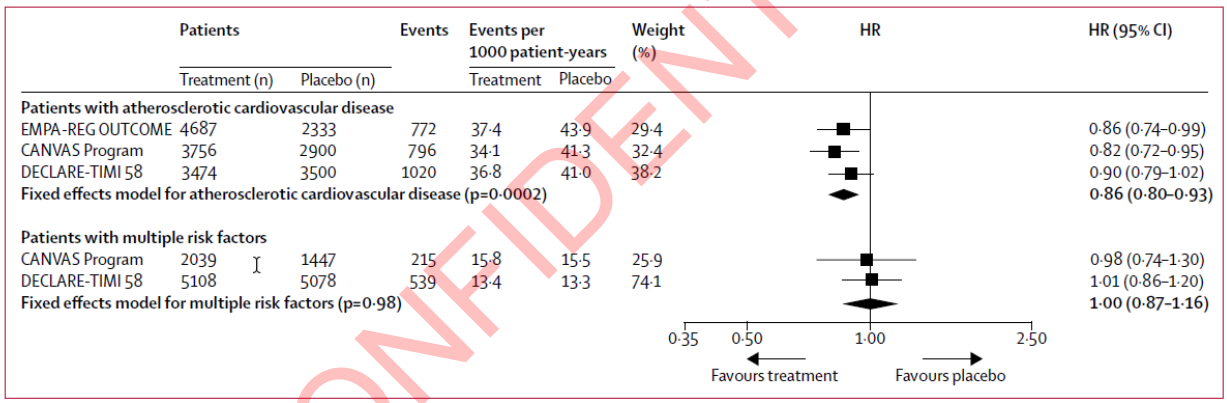
Concerning the safety of antidepressants for HF patients a recent extensive meta-analysis on the effect of antidepressants on death in patients with heart failure reported that all antidepressants were associated with an increased risk of death in HF patients.[15] Depressed HF-patients taking antidepressants had an increased risks of all-cause death (RR = 1.21; 95% CI, 1.16-1.27) and cardiovascular death (RR = 1.21; 95% CI, 1.13–1.30). Compared with nonusers, intake of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCA), and serotonin–norepinephrine reuptake inhibitors (SNRIs) increased the rate of all-cause death (SSRIs: RR = 1.26; 95% CI, 1.19–1.32), TCAs (RR = 1.30; 95% CI, 1.16–1.46), and SNRIs (RR = 1.17; 95% CI, 1.08–1.26)). Further, there

is evidence from a large case-control study of patients aged 65 years and older, that the intake of SSRIs was associated with an increased risk of cardiovascular events with an odds ratio of 1.25 (95% confidence interval, 1.21-1.29).[16]

To sum up, unlike SSRI treatment of depression in patients with CAD, treatment with antidepressants is not evidence-based in HF patients. Firstly, there is evidence that antidepressants are not useful in patients with heart failure (regarding the reduction of depression or cardiovascular events). Secondly, there is evidence that antidepressants are harmful to HF patients. Therefore, the Class III recommendation is fully justified with a B level of evidence. We hope that this new recommendation will convince providers to stop initiating SSRI treatment to affect cardiovascular outcomes in HF patients with depression and choose other treatment options such as exercise therapy, psychotherapy, and collaborative care instead.

4.8. Diabetes Mellitus

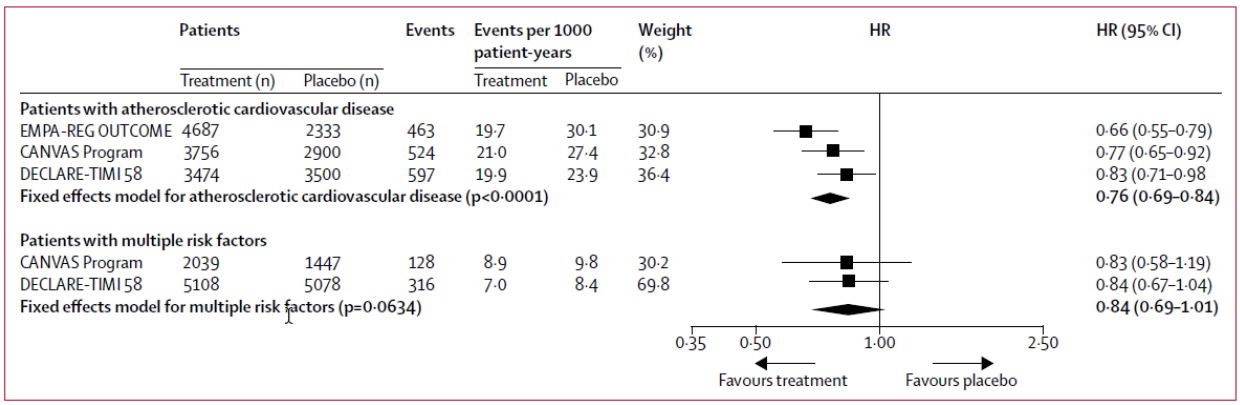
4.8.1.3 Newer diabetes drug classes: cardiovascular disease benefits independent of glycated haemoglobin changes or baseline metformin



Supplementary Figure 1: *Meta-analysis of sodium-glucose cotransporter 2 inhibitor trials on the composite of myocardial infarction, stroke, or cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease.*

A 14% relative reduction of major adverse CV events was found in patients with diabetes and ASCVD. Figure reproduced from Zelniker et al.[17]

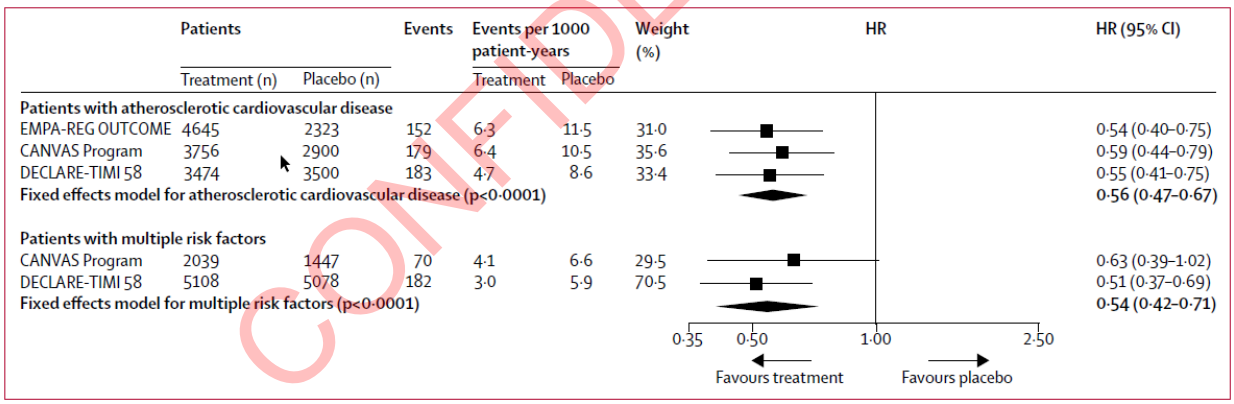
ASCVD = atherosclerotic cardiovascular disease; CANVAS = CANagliflozin cardioVascular Assessment Study; CI = confidence interval; CV = cardiovascular; DECLARE-TIMI 58 = Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR = hazard ratio.



Supplementary Figure 2: *Meta-analysis of sodium-glucose cotransporter 2 inhibitor trials on hospitalization for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease.*

A 24% relative risk reduction was found in patients with diabetes and ASCVD. Figure reproduced from Zelniker et al.[17]

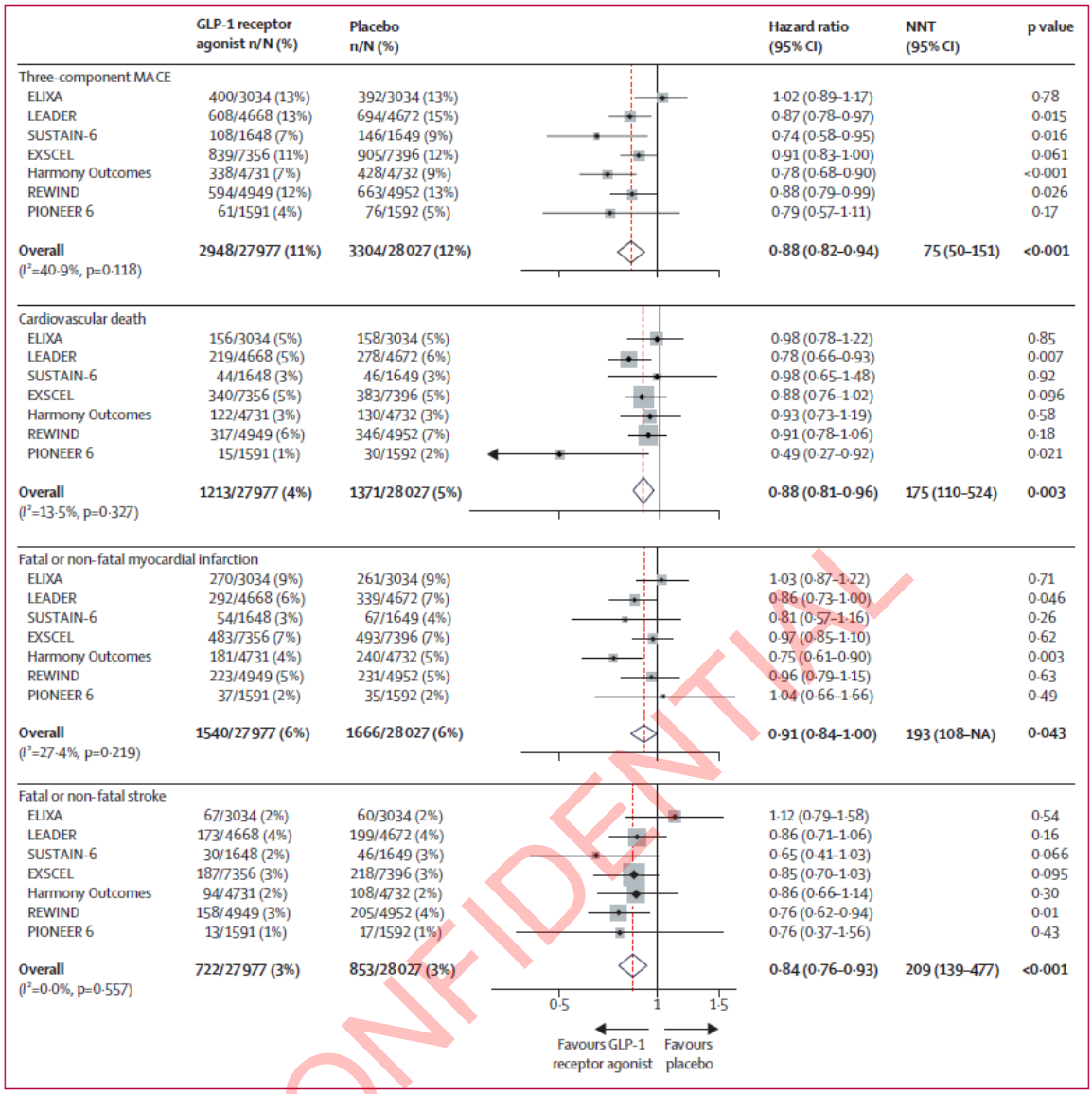
ASCVD = atherosclerotic cardiovascular disease; CANVAS = CANagliflozin cardioVascular Assessment Study; CI = confidence interval; DECLARE-TIMI 58 = Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR = hazard ratio.



Supplementary Figure 3: *Meta-analysis of sodium-glucose cotransporter 2 inhibitor trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease.*

A 44% relative reduction was found in patients with diabetes and ASCVD. Figure reproduced from Zelniker et al.[17]

ASCVD = atherosclerotic cardiovascular disease; CANVAS = CANagliflozin cardioVascular Assessment Study; CI = confidence interval; DECLARE-TIMI 58 = Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME = BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; HR = hazard ratio.



Supplementary Figure 4: *Risk of major adverse cardiovascular events and each of its components in a meta-analysis of glucagon-like peptide-1 receptor agonist trials.*

Figure reproduced from Kristensen et al.18

CI = confidence interval; ELIXA = Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); EXSCEL = Exenatide Study of Cardiovascular Event Lowering Trial; GLP-1 = glucagon-like peptide-1; Harmony Outcomes = Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE = major adverse cardiovascular events; NNT = number needed to treat; PIONEER 6 = A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

5. Policy interventions at the population level

5.2.1 Physical activity

Physical inactivity is the fourth leading cause of death in the world, according to the WHO. Nonetheless, sedentary lifestyle and physical inactivity affect a sizeable part of the population worldwide, and the level of adherence of the general population to recommended levels of PA remains unacceptably low,[19] although one third of general population are aware that they lack adequate physical activity.[20] Alarmingly, indeed, only 10% of the general population meets the minimum recommended level of PA using objective assessments. Worldwide 1 in 4 adults and 3 in 4 adolescents (aged 11-17 years) do not currently meet the global recommendations of physical activity set by WHO. The target of the new Global Action Plan of Physical Activity 2018-2030 is a 15% relative reduction in the global prevalence of physical inactivity in adults and adolescents.[21] Various reasons may explain this habit: perceived limitations in PA and effort; lack of time, fun, and motivation; economic problems; misconceptions of the minimal volume of PA necessary for CV health benefits; and unfavorable environments (lack of sports facilities, lack of walking or cycling lanes, dangerous boroughs because of crime, etc.).[22] Considering these difficulties, more attention has recently been paid to sedentary behaviour (more than physical inactivity), which has been defined as an energy expenditure ≤1.5 METs, while in seated, reclined, or lying posture for several hours a day.[23] A recent American Heart Association report highly encouraged further research that would inform on future quantitative public health guidelines and novel strategies that can influence legislative initiatives.[24] For instance, “active cities” could be achieved, by creating new architectural models with bicycle lanes and walking paths, or by encouraging the use of stairs.[25] Focused media and educational campaigns can also initiate PA in the general population and in subgroups of patients with diseases, such as cancers[26], cardiac diseases (http://www.takeheartproject.eu), and type 2 DM. Recent campaigns from sports medicine societies have endorsed PA prescriptions from general practitioners (http://www.efsma.net), as do the recent ESC Guidelines on sports Cardiology.[27]

Adults should engage 150 minutes per week of accumulated moderate-intensity PA or 75 minutes per week of vigorous-intensity physical activity. For additional benefits in healthy adults a gradual increase of aerobic activity to 300 minutes a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic activity or an equivalent should be considered. The recommendations for physical exercise and exercise training in the 6886 management of cardiovascular health in individuals with cardiovascular risk factors were published several years ago but they are obviously not followed.[28]

Schools are considered ideal settings for the promotion of children’s PA (http:// www.actionforhealthykids.org), which should be started in kindergarten and continued throughout primary and secondary education.[25] Multiple physical and mental health benefits are obtained when children participate in 60 minutes per day of moderate-to-vigorous PA.[29] A review of 11 studies concluded that PA lessons may have a positive effect on PA

improvement, without having an effect on learning or academic-related outcomes.[30] Despite these benefits, population-based studies have reported that over 50% of children are not meeting these recommendations.[31, 32] An international study on health literacy among European citizens has shown that 47% of Europeans lack health literacy.[33] Furthermore it appears that participation in physical activity is associated with health literacy and that those who lack this are less engaged in physical activity.[34]

Worksites can offer many opportunities for PA promotion.[35] Some larger companies offer a corporate wellness programme and/or a fitness centre without fees for employees with varying results.[25, 36, 37] Adherence of the company population to these initiatives remains generally low, with great difficulty in involving inactive individuals (although a "drag effect" has been documented recently from the most active individuals to the sedentary).[38]

Wearable PA monitoring devices and mobile phone applications are thought to increase PA and help maintain the healthy benefits gained life-long.[39, 40] A systematic review[41] and an RCT[42] showed that wearables with PA prescription significantly improved cardiorespiratory fitness in the cardiac population to a greater extent than without devices.

Improved accessibility to recreation and exercise facilities with increasing operating hours may increase regular PA in all age groups (ex. Adaptive Physical Activity (A.P.A.) models) and reduce socioeconomic inequality of access.[43, 44] Finally, an increase in fuel prices may reduce car driving and increase active commuting (with improved safety and public transportation) for those who live within a reasonable walking or cycling distance, with the exception of people with limiting diseases or disabilities.[45]

Gaps in evidence

- Sustainability and long-term outcomes of population-based actions to promote PA.
- How to improve physician implication in PA prescription for health promotion.
- The effect of future implementations in wearable PA monitoring devices.
- Community based exercise program for elderly people: the Adaptive Physical Activity (A.P.A.)

Policy suggestions for physical activity

	Level	Actions	Class[a]	Level[b]
Methods	**Governmental restrictions and mandates**	Consideration of PA when planning new landscaping/building is recommended including increasing cycling and pedestrian lanes and reduced speed trafficking.[46]	I	C
		Sustained, focused, media and educational campaigns, using multiple	IIb	C

	Media and education	media modes (e.g. apps, poster, flyers, and signage) may be considered to promote PA.[45]		
		Short-term community-based educational programmes and wearable devices promoting healthy behaviours, such as walking, should be considered.[39-42, 47]	IIa	C
	Labelling and information	Point-of-decision prompts should be considered to encourage the use of stairs.[47]	IIa	B
		Exercise prescription for health promotion by physicians, especially general practitioners, similar to drug prescription, should be considered.	IIa	C
	Economic incentives	Increased fuel taxes should be considered to increase active transport.[46, 48]	IIa	C
		Tax-reduction incentives for individuals to purchase exercise equipment or health club/fitness membership may be considered.[46, 48]	IIb	C
		Sustained individual financial incentives may be considered for increased activity/fitness or weight loss.[46, 48]	IIb	C
		Tax-reduction incentives to employers to offer comprehensive corporate wellness programmes with nutrition, PA, and tobacco cessation/prevention components may be considered.[46, 48]	IIb	C
Settings	**Schools**	Increased availability and types of school playground spaces and equipment for exercise activity and sports are recommended.[46]	I	C
		Regular classroom PA breaks during academic lessons should be considered.[29, 30]	IIa	B
		Increasing active commuting to school should be considered, e.g. walking school bus programme with supervised	IIa	C

		(for safety) walking routes to and from school.[31, 46]		
		Increasing number and duration of PA classes, with revised PA curricula to implement moderate activity and trained teachers in exercise and sports may be considered.[29]	IIb	B
	Worksites	Comprehensive corporate wellness programmes should be considered with nutrition and PA components, possibly with medical supervision and governance.[35-38]	IIa	B
		Structured corporate wellness programmes that encourage PA also during work hours. Improving stairway access and appeal, potentially in combination with elevators that skip some floors, should be considered.[46, 47]	IIa	C
		Promoting worksite fitness centres/gyms should be considered.	IIa	C
	Community setting	Healthcare providers should consider inquiring about PA in every medical evaluation and promoting it.	IIa	C
		Improving accessibility of recreation and PA spaces and facilities, and improved walkability, should be considered.	IIa	C
		Improved neighbourhood aesthetics to increase activity in adults should be considered.	IIa	C

GP = general practitioner; PA = physical activity.

[a] Class of recommendation.

[b] Level of evidence.

5.2.2 Diet

Diet is a powerful determinant of obesity, hypertension, dyslipidaemia, DM. Important reductions in CV events can be seen after changes in diet at the population level.[49, 50]

Stakeholders, including healthcare professionals, have a shared responsibility for population-based approaches and can help to promote healthy diets and environments.[51-53] On a general note, educational campaigns seem to be more efficient for the higher educated and health literate, whereas taxation and reformulation are measures that tend to work best for less educated groups.

Health benefits include reducing the energy density, and salt and refined sugar content in foods and drinks, as well as the replacement of trans and saturated fats by unsaturated fat.[45, 51-53] These changes have led to successful reductions in trans fats and salt[53-59], the latter likely leading to decreases in BP. Mandatory upper limits harmonized across the EU will ensure that all EU consumers are equally protected.[60] For trans fats, upper limits have been set by a regulation of the European Commission (April 2019).[60]

Governments can facilitate nationwide cooperation between (local) governments, non-governmental organizations, the food industry, retail, catering, schools, workplaces, and other stakeholders.[61-63] Governments also can intervene in the media (e.g. limiting children's exposure to advertising of unhealthy foods) and regulate digital marketing, taking into account the rights of children.[49, 51, 52, 64, 65] A nationwide cooperation including, among other partners, the food industry is recommended with consideration of vested interests of corporations.

Consumer-awareness campaigns on healthy foods as well as nutrition labelling and calories on meals in restaurants and fast-food outlets can be effective in making healthy choices, and have a positive effect on sales and stimulate the reformulation of foods.[66-68] Following the advent of front-of-pack logos, such as the multiple traffic lights and the Swedish keyhole, the Nutri-score logo was launched in 2017. So far, this logo has been introduced in France and the surrounding countries.[69]

Pricing strategies above a certain threshold can lead to a decline in the sales of unhealthy foods and an increase in the sales of fruits and vegetables.[56, 70] Modelling studies have demonstrated that food taxes could improve energy and nutrient intake, BMI, and health.[53, 71, 72] An increasing number of countries have introduced taxes on unhealthy foods and drinks.[66, 73] As healthy diet recommendations tend to be more expensive, subsidising the costs of healthier food might also be considered and have an impact on individuals' choice. Studies on health and cost impacts of various food taxes and subsidies are scarce but in a modelling study tax on sugar and fruit and vegetable subsidies produced the greatest health gain span.[74]

Every school and workplace should have a policy to promote a healthy environment and provide healthy foods and meals.[53, 61, 63, 75] Education on healthy lifestyle must be a part of the school curriculum. In the community, planning the location and density of fast-food outlets and providing good access to supermarkets is needed, especially in deprived areas.[45, 53, 76] Comprehensive strategies involving multiple components are most successful.[49, 56]

At the governmental level, agricultural policies aimed at providing safe, healthy and sustainable foods, and favoring national food security (i.e. aiming at self-sufficiency regarding food production) should be promoted. Furthermore, there is a need of

national food consumption and health surveys to monitor lifestyles and risk factor profiles at the population level; these should be organized at regular intervals and harmonized.

Gaps in evidence

- Cost-effectiveness studies and scientific evidence of the effect of food and nutrition policy instruments on outcome measures such as food intake and CV health are largely lacking.

Policy suggestions for population-based approaches to diet

	Level	Actions	Classa	Levelb
Methods	Governmental restrictions and mandates	Legislation on the composition of foods and beverages, to reduce energy density, salt and saturated fat, and (added) sugar content, and to limit portion sizes, is recommended.[53, 55]	I	B
		Implementation of the regulation on the upper limit of industrially produced trans fats or their ban is recommended.[53]	I	A
		Facilitating an integrated and coherent policy and activities of (local) governments, non-governmental organizations, the food industry, retail, catering, schools, workplaces, and other stakeholders to promote a healthy diet and prevent overweight is recommended.[62, 63]	I	C
		Legislation restricting marketing aimed at children of foods that are high in fats, sugar and/or salt, less healthy options, junk foods, drinks with alcohol and non-alcoholic beverages rich in sugar (e.g. on television, the internet, social media, and on food packages) is recommended.[53, 65, 66]	I	C
	Media and education	Reformulation of foods, accompanied by educational information campaigns, should be considered to create awareness among consumers on the nutrition quality of foods.[68]	IIa	C
	Labelling and information	Mandatory and harmonized front-of-pack nutrition labelling is recommended.[45]	I	C
		Independently and coherently formulated criteria for nutrients should be considered in support of health and nutrition claims and front-of-pack logos (e.g. lights, healthy choices, keyholes, Nutri-score).[69]	IIa	C

		Mandatory nutrition labelling for non-prepackaged foods, including in restaurants, hospitals, and workplaces, should be considered.	IIa	C
	Economic incentives	Pricing and subsidy strategies are recommended to promote healthier food and beverage choices.[53, 56, 70-72]	I	B
		Taxes on foods and beverages rich in sugar and saturated fat, and on alcoholic drinks, are recommended.[71, 72]	I	B
Settings	Schools	At all schools, preschools, and day-care centres, a multicomponent, comprehensive and coherent policy is recommended to promote a healthy diet.[63, 66]	I	B
		Availability of fresh drinking water and healthy foods in schools, and in vending machines, is recommended.[63, 66]	I	B
	Worksites	At all companies, a coherent and comprehensive health policy and nutritional education are recommended to stimulate the health awareness of employees.[45, 75]	I	B
		Increased availability of fresh drinking water and improved nutritional quality of food served and/or sold in the workplace, and in vending machines, should be considered.	IIa	C
	Community setting	Regulation of the location and density of fast food and alcohol purchasing outlets and other catering establishments should be considered.	IIa	C

[a] Class of recommendation.

[b] Level of evidence.

5.2.3 Smoking and tobacco use

Policy suggestions for population-based approaches to smoking and other tobacco use

	Level	Actions	Class[a]	Level[b]
Methods	**Governmental restrictions and mandates**	Banning smoking in public places is recommended to prevent smoking and promote smoking cessation.[53]	I	A
		Banning smoking in public places, outside public entrances, and in workplaces, restaurants, and bars is recommended to protect people from passive smoking.[45]	I	A

		Prohibiting sales of tobacco products to adolescents is recommended.[53]	I	A
		Banning of tobacco vending machines is recommended.[53]	I	A
		Restrictions on advertising, marketing, and sale of smokeless tobacco are recommended.	I	A
		Complete ban on advertising and promotion of tobacco products is recommended.[45]	I	B
		Reduced density of retail tobacco outlets in residential areas and near schools and hospitals is recommended.[45]	I	B
		Harmonization of border sales and tax-free sales of all tobacco products is recommended.[53]	I	B
		Restrictions on advertising, marketing, and sale of electronic cigarettes should be considered.	IIa	A
	Media and education	Telephone and internet-based lines for cessation counselling and support services are recommended.[45]	I	A
		Media and educational campaigns as part of multicomponent strategies to reduce smoking and increase quit rates, reduce passive smoking and use of smokeless tobacco are recommended.[45]	I	A
		Media and educational campaigns concentrating solely on reducing smoking, increasing quit rates, reducing passive smoking and the use of smokeless tobacco should be considered.[45, 53]	IIa	B
	Labelling and information	Cigarette package pictorial and text warnings are recommended.[45, 53]	I	B
		Plain packaging is recommended.[45, 53]	I	B
	Economic incentives	Differential taxes on nicotine-yielding products on the basis of degree of risk is recommended.[77]	I	B
Settings	**Schools**	Banning smoking in schools, preschools, and in childcare facilities to protect from passive smoking is recommended.[53]	I	A

		Promotion and teaching of a healthy lifestyle, including tobacco-free life, should be considered in all schools.[45, 53]	IIa	B
	Worksites	Workplace specific bans on smoking to reduce passive smoking and increase quit rates are recommended.[53]	I	A
		Workplace policy on tobacco cessation/prevention is recommended.[45]	I	A
	Community setting	It is recommended that health personnel, caregivers, and school personnel set an example by not smoking or using tobacco products at work.[45, 53]	I	A
		It is recommended to advise parents to be tobacco-free when children are present.[45, 53]	I	A
		It is recommended to advise pregnant women to be tobacco-free during pregnancy.	I	A
		It is recommended to advise parents to never smoke in cars and private homes.[45, 53]	I	A
		Residence-specific restrictions on smoking should be considered.	IIa	B

[a] Class of recommendation.

[b] Level of evidence.

The WHO Framework Convention on Tobacco Control recommends smoke-free laws: protecting people from tobacco smoke and banning smoking in public places, warning about the dangers of tobacco, raising taxes on tobacco, and enforcing advertising bans. Children and low socio-economic groups are sensitive to population-based tobacco interventions. Passive smoking increases CVD risk[45, 53], more so in women than in men in particular with regards to ASCVD.[78] All smoking, including smoking a water pipe, is deleterious. Nicotine is a powerful vasoconstrictor and therefore particularly deleterious in the context of atherosclerotic vascular diseases. Smokeless tobacco (in Europe usually snus, a moist powder tobacco placed under the upper lip) does not show associations with development of AMI or ischaemic heart disease[79, 80], in contrast to some other types of smokeless tobacco used in other parts of the world. However, there could be a relation to fatal events.[80, 81] Many smokers use e-cigarettes and Electronic Nicotine Delivery Systems (heated tobacco products) to quit. There are still however unanswered questions about their safety and effect on public health and caution should be urged in their use before evidence of lack of harm is available.[82] International legislation should be harmonized to prevent a new tobacco epidemic.[45, 53]

Higher taxes reduce tobacco consumption and encourage quitting, particularly among young and lower socioeconomic groups.[53] Implementing differential taxes on nicotine-yielding products on the basis of degree of risk could substantially expedite the move away from cigarette smoking.[77]

School-based smoking bans should be implemented.[45] Smoking bans at workplaces reduce exposure to passive smoking, decrease smoking, and increase quitting rates.[53] The deleterious and harmful effects of passive smoking need to be taken into account in policies. Tobacco outlet density near homes, hospitals, and schools should be reduced. Pregnant women should avoid tobacco, and parents should be tobacco-free when children are present. Health personnel, caregivers, and teachers must set an example by not using tobacco products at work.

Gaps in evidence

- Health effects of Electronic Nicotine Delivery Systems and e-cigarettes.

5.2.4 Alcohol

At the population level, alcohol consumption is associated with multiple health risks. In 2016, about 2.8 million deaths were attributed to alcohol use, corresponding to 2.2% of total age-standardized deaths among females and 6.8% among males. Globally, alcohol use was ranked as the seventh leading risk factor for premature death and disability in the overall adult population, and the leading risk factor among the population aged 15–49 years, causing 8.9% of attributable disability adjusted life-years for men and 2.3% for women.[83]

Recent research, which has used methodologies such as mendelian randomization, and pooling large-scale cohort studies, has consistently shown either a non-significant or no protective effect of drinking on CV outcomes.[84, 85] Taken together, these findings emphasize that alcohol use, regardless of amount, leads to loss of health across populations.

In reducing population-level alcohol use, governments should consider how these recommendations can be implemented within their local contexts and broader policy platforms, including excise taxes on alcohol, controlling the physical availability of alcohol and the hours of sale, and controlling alcohol advertising. Any of these policy actions would contribute to reductions in population-level consumption − an important step toward decreasing the loss of health associated with alcohol use.[86, 87]

The following strategies and interventions have the highest level of effectiveness: taxation of alcohol and minimum unit pricing[88, 89]; age limits for sale and serving; drink-driving strategies[90]; government retail monopolies on the sale of alcohol and reducing the hours of sale[91]; and banning alcohol advertising, promotion, and sponsorship of events.[86]

In the absence of other population-level measures, such as taxation and advertising restrictions, labelling alcohol with information on caloric content and health warning messages of the harmful effects of alcohol has a limited effect.[86, 92] Alcohol regulations in the

policies of workplaces, educational centres, and schools are effective. Brief intervention in primary care to prevent alcohol abuse has been shown to be effective.[93]

Gap in evidence

- Better quality evidence is needed regarding potential confounding in studies on the effects of alcohol consumption.
- Gender differences with regard to the impact of alcohol consumption on different forms of CVDs.

Policy suggestions for population-based approaches to alcohol abuse

	Level	Actions	Class	Level
Methods	Governmental restrictions and mandates	Regulating physical availability of alcoholic beverages is recommended, including minimum legal purchase age, restrictions on outlet density and time and place of sales, public health-orientated licensing systems, and governmental monopolies of retail sales.	I	B
		Drink-driving countermeasures are recommended such as lowered blood-alcohol concentration limits and "zero tolerance", random breath testing, and sobriety check points.	I	B
		Implementing comprehensive restrictions and bans on advertising and promotion of alcoholic beverages is recommended.	I	C
	Media and education	Educational information campaigns may be considered to create awareness on the hazardous effects of alcohol.	IIb	B
	Labelling and information	Labelling alcohol with information on caloric content and health warning messages of the harmful effects of alcohol may be considered.	IIb	B
	Economic incentives	Taxes and mimimun prices on alcoholic beverages are recommended.	I	B
Settings	Schools	At every school, preschool, and day-care centre, a multicomponent, comprehensive, and coherent education may be considered to prevent alcohol abuse.	IIb	B
	Worksites	At every company, a coherent and comprehensive health policy and nutritional education on stimulating the health of employees, including limiting excessive alcohol intake, are recommended.	I	B

	Community setting	Measures to support and empower primary care to adopt effective approaches to prevent and reduce harmful use of alcohol are recommended.	I	B
		Enacting management policies relating to responsible serving of alcoholic beverages should be considered to reduce the negative consequences of drinking.	IIa	B
		Planning of location and density of alcohol-purchasing outlets and other catering establishments should be considered.	IIa	C

[a] Class of recommendation.

[b] Level of evidence.

5.4. Implications for public health policy and advocacy at the governmental and non-governmental level

5.4.1. Government and public health

Recommendations for population-based interventions to promote CV health are described in *section 5.1*. Different clusters of stakeholders are concerned and are responsible for the interventions.[53]

- International level – WHO, World Trade Organization, EU, international scientific societies
- National level – government departments, health authorities, health-promoting agencies, consumer organizations, health NGOs, industries, health insurance companies.
- Regional and local level – local governmental departments, communities, schools and universities, health professionals, catering sector, retailers, NGOs.

Legislation should be developed regarding the nutritional composition of food; nutrition labelling; fruit and vegetable subsidies, saturated fat, sugar and salt taxes and "junk food" taxes (on non-essential, energy dense food[74]), restriction or marketing of unhealthy foods, alcohol and tobacco products, smoke-free policies and environments; and promoting environments that encourage PA in everyday life.[94] Also, policy measures to reduce air pollution should be developed. Government, industry, and business should join a common effort to ensure availability and accessibility to PA opportunity. To this aim, the 10-year strategy Europe 2020, including Horizon 2020 framework programme, represents the main EU initiative for smart, sustainable, and inclusive growth, and it sets up a new partnership between the EU institutions, national and regional governments, and EU stakeholders.[59, 95]

5.4.2 Non-governmental organizations

NGOs are important stakeholders in advocating the development and maintenance of public health policies and are important partners with healthcare workers in promoting CV prevention. They engage in regular dialogue with public authorities with a view to ensuring better implementation of EU initiatives and policies in the EU countries. NGOs such as the

International Union for Health promotion and Education (IUHPE) and its collaborating networks such as Global Advocacy for PA (GAPA) can play a central role in promoting PA and overcoming barriers to action in countries and regions at varying levels of economic development. Several NGOs, including the European Heart Network (EHN), health and medical professional societies (ESC, European Chronic Disease Alliance, International Society for Physical Activity and Health, World Heart Federation), and consumer organizations (e.g. Bureau Européen des Unions de Consommateurs) improve the CV health of the public and patients, providing and delivering enabling policies, services, environments, and programmes via advocacy strategies, global communication, network development, and partnerships. The "EU Platform for action on Diet, PA and Health" is one of the main tools of the European strategy to fight against obesity and overweight-related problems[96], despite the recent intention of some NGOs resignation from the platform because of the supposed diminution of EU action[97], despite their persistent high prevalence.[98, 99] In creating healthy and active environments, especially in schools and universities, workplaces, and the community, teachers and parent organizations, employer organizations, the catering sector, sports clubs and fitness centres, and public transport can play a major role.[63, 66] It is important to note that it is not sufficient to launch cardiovascular prevention programs without anticipating adequate surveillance of their impact as measured by specific outcome indices. This requires dedicated personnel and funds, promotional campaigns, cooperation among healthcare professionals, stakeholders, communities, institutions, non-profit organizations and sustainability over time.

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