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2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies

With the special contribution of the European Association of Preventive Cardiology (EAPC)

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Abbreviations and acronyms

$\%HR_{max}$	Percentage of maximum heart rate
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 syndromes
ADA	American Diabetes Association
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
b.p.m.	Beats per minute
CAC	Coronary artery calcium
CAD	Coronary artery disease
CANTOS	Canakinumab Antiinflammatory Thrombosis Outcome Study
CCB	Calcium channel blocker
CCS	Chronic coronary syndromes

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CCTA	Contrast computed tomography angiography
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology
COLCOT	Colchicine Cardiovascular Outcomes Trial
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
COPD	Chronic obstructive pulmonary disease
CR	Cardiac rehabilitation
CTA	Computed tomography angiography
CV	Cardiovascular
CVD	Cardiovascular disease
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
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
EAPC	European Association of Preventive Cardiology
EAS	European Atherosclerosis Society
EASD	European Association for the Study of Diabetes
EBCR	Exercise-based cardiac rehabilitation
ECG	Electrocardiographic/electrocardiogram
ED	Erectile dysfunction
eGFR	Estimated glomerular filtration rate
EORP	EURObservational Research Programme
EPIC	European Prospective Investigation into Cancer and Nutrition
ESC	European Society of Cardiology
ESH	European Society of Hypertension
ESVS	European Society for Vascular Surgery
EU	European Union
EUROASPIRE	European Action on Secondary and Primary Prevention by Intervention to Reduce Events
EuroHeart	European Unified Registries On Heart Care Evaluation and Randomized Trials
EXPERT	EXercise Prescription in Everyday practice & Rehabilitation Training
FEV1	Forced expiratory volume in 1 second
FH	Familial hypercholesterolaemia
FITT	Frequency, intensity, time duration, and type of exercise
GFR	Glomerular filtration rate
GLP-1RA	Glucagon-like peptide-1 receptor agonist
HbA1c	Glycated haemoglobin
HBPM	Home blood pressure monitoring
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
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
IL	Interleukin
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IMT	Intima-media thickness
INVEST	INternational VErapamil-SR/Trandolapril STudy
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LEAD	Lower extremity artery disease
LIFE-CVD	LIFEtime-perspective CardioVascular Disease
LoDoCo	Low-dose colchicine
LV	Left ventricular/ventricle
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MET	Metabolic equivalent of task
mHealth	Mobile device-based healthcare
MRA	Mineralocorticoid receptor antagonist
MUFA	Monounsaturated fatty acid
N/A	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NRT	Nicotine-replacement therapy
NYHA	New York Heart Association
o.d.	*Omni die* (once a day)
OARS	Open-ended questions, Affirmation, Reflecting listening, and Summarizing
OR	Odds ratio
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
PM	Particulate matter
$PM_{2.5}$	Particulate matter <2.5 μm
PUFA	Polyunsaturated fatty acid
QI	Quality indicator
RAAS	Renin-angiotensin-aldosterone system
RAS	Renin-angiotensin system
RCT	Randomized controlled trial
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl—Intervention Trial
REWIND	Researching Cardiovascular Events With a Weekly Incretin in Diabetes
RPE	Rating of perceived exertion
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
SCORE2	Systemic Coronary Risk Estimation 2
SCORE2-OP	Systematic Coronary Risk Estimation 2-Older Persons
SCOT-HEART	Scottish Computed Tomography of the Heart
SGLT2	Sodium-glucose cotransporter 2

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SHARP	Study of Heart and Renal Protection
SMART	Secondary Manifestations of Arterial Disease
SMART	Specific, Measurable, Achievable, Realistic, Timely
SMART-REACH	Secondary Manifestations of Arterial Disease-Reduction of Atherothrombosis for Continued Health
SNRI	Serotonin-noradrenaline reuptake inhibitor
SPRINT	Systolic Blood Pressure Intervention Trial
SSRI	Selective serotonin reuptake inhibitor
STAREE	STAtin Therapy for Reducing Events in the Elderly
STRENGTH	Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia
SUPRIM	Secondary Prevention in Uppsala Primary Health Care project
SWITCHD	Stockholm Women's Intervention Trial for Coronary Heart Disease
TIA	Transient ischaemic attack
TNF	Tumour necrosis factor
TOD	Target organ damage
UK	United Kingdom
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

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in proposing the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

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

In addition to the publication of Clinical Practice Guidelines, the ESC carries out the EURObservational Research Programme of international registries of cardiovascular diseases and interventions which are essential to assess diagnostic/therapeutic processes, use of resources and adherence to guidelines. These registries aim at providing a better understanding of medical practice in Europe and around the world, based on high-quality data collected during routine clinical practice.

Furthermore, the ESC has developed and embedded in this document a set of quality indicators (QIs), which are tools to evaluate the level of implementation of the guidelines and may be used by the ESC, hospitals, healthcare providers and professionals to measure clinical practice as well as used in educational programmes, alongside the key messages from the guidelines, to improve quality of care and clinical outcomes.

The Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Clinical Practice Guidelines Committee (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined below.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/guidelines)and have been compiled in a report and published in a supplementary document simultaneously to the guidelines.

This process ensures transparency and prevents potential biases in the development and review processes. Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new guidelines. The Committee is also responsible for the endorsement process of these guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the guidelines are signed-off by all the experts involved in the Task Force. The finalized document is signed-off by the CPG for publication in the European Heart Journal. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, for more detailed information, the user should always access to the full text version of the guidelines, which is freely available via the ESC website and hosted on the EHJ website. The National Cardiac Societies of the ESC are encouraged to endorse, adopt, translate and implement all ESC Guidelines. Implementation

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Table 1 Classes of recommendations

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

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Table 2 Levels of evidence

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

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programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

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

2. Introduction

Atherosclerotic cardiovascular (CV) disease (ASCVD) incidence and mortality rates are declining in many countries in Europe, but it is still a major cause of morbidity and mortality. Over the past few decades, major ASCVD risk factors have been identified. The most

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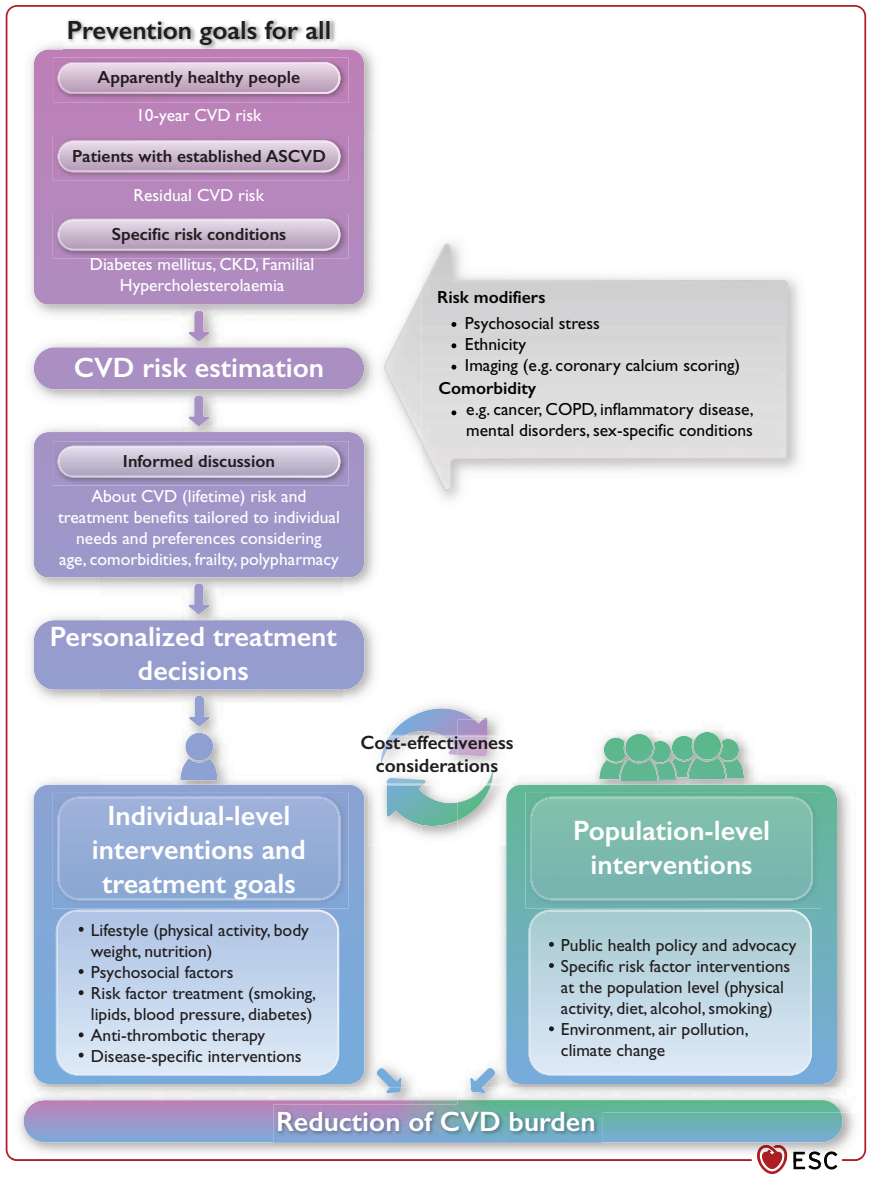

Figure 1 Central Illustration. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease

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) CVD risk.[1] Prevention of CV events by reducing CVD 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 CVD prevention in clinical practice were published in 2016.[2] Recent developments in prediction of cardiovascular disease (CVD) risk and treatment benefit, as well as novel treatments and treatment goals, necessitated new, up-to-date guidelines. The current guidelines on CVD 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 have been given to differences in age, sex and gender, life expectancy, risk factor profiles, ethnic, and geographic differences. Estimating CVD risk not only in apparently healthy subjects, but also in older persons and in patients with established ASCVD or diabetes mellitus (DM), provides information for tailored intervention on an individual level. Treatment goals can be individualized in a stepwise approach. 'Residual' CVD risk is defined as the risk

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estimated after initial lifestyle changes and risk factor treatment, and is mostly used in patients with established ASCVD. For younger apparently healthy subjects, lifetime CVD 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 CVD risk score that takes competing non-CVD 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 CVD 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, BP, and glycaemic control in patients with DM, goals and targets remain as recommended in recent European Society of Cardiology (ESC) Guidelines.[3–5] These prevention 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-specific aspects are included.

ASCVD 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).

2.2. Development

The Task Force chairs and members were appointed by the ESC Clinical Practice Guidelines Committee (CPG). 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 budgets 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 interventions (e.g. expensive drugs, such as novel lipid-lowering or 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 3*.

3. Risk factors and clinical conditions

3.1. Target population for assessing cardiovascular disease risk

CVD risk assessment or screening can be done opportunistically or systematically. Opportunistic screening, which means screening without a predefined strategy, 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 DM, or family history of premature CVD. Systematic screening results in improvements in risk factors, but has no effect on CVD outcomes.[6–9] Opportunistic screening for ASCVD risk factors, such as BP or lipids, is effective at increasing detection rates and is recommended, although a beneficial effect on clinical outcome is uncertain.[10]

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

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

Systematic CVD risk assessment 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.

3.2. Risk factors and risk classification

3.2.1. Risk factors

The main causal and modifiable ASCVD risk factors are blood apolipoprotein-B-containing lipoproteins [of which low-density lipoprotein (LDL) is most abundant], high BP, cigarette smoking, and DM.

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Table 3 What is new

New or revised	Recommendations in 2013 version	Class	Recommendations in 2021 version	Class
Risk factors and clinical conditions – section 3				
New			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 nonfatal CVD risk with SCORE2 is recommended.	I
New			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 nonfatal CVD risk with SCORE2-OP is recommended.	I
New			Patients with established ASCVD 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.	I
New			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.	I
New			Treatment of ASCVD risk factors is recommended in apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at very high CVD risk (SCORE2 ≥7.5% for age under 50; SCORE2 ≥10% for age 50–69; SCORE2-OP ≥15% for age ≥70).	I
New			An informed discussion about CVD risk and treatment benefits tailored to the needs of a patient is recommended.	I
New			It is recommended that mental disorders with either significant functional impairment or decreased use of healthcare systems be considered as influencing	I
New			Treatment of ASCVD risk factors should be considered in apparently healthy people without DM, CKD, genetic/rarer lipid, or BP disorders who are at high CVD risk (SCORE2 2.5 to <7.5% for age under 50; SCORE2 5 to <10% for age 50–69; SCORE2-OP 7.5 to <15% for age ≥70 years), taking ASCVD risk modifiers, lifetime risk and treatment benefit, and patient preferences into account.	IIa
New			In apparently healthy people, after estimation of 10-year fatal and non-fatal CVD risk, lifetime risk and treatment benefit, risk modifiers, frailty, polypharmacy, and patient preferences should be considered.	IIa
New			Presence of migraine with aura should be considered in CVD risk assessment.	IIa
New			Assessment of CVD risk should be considered in men with ED.	IIa
New			In women with a history of premature or stillbirth, periodic screening for hypertension and DM may be considered.	IIb
New			Assessment of total CVD risk may be considered in adults with chronic inflammatory conditions.	IIb
New			Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.	IIb
Risk factors and interventions at the individual level – section 4				
New			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.	I

Continued

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Table 3 *Continued*

New or revised	Recommendations in 2013 version	Class	Recommendations in 2021 version	Class
New			It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.	I
New			It is recommended to restrict alcohol consumption to a maximum of 100 g per week.	I
New			It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.	I
New			Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.	I
New			Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.	I
New			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 vs. baseline is recommended.	I
New			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.	I
New			In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD), 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.	I
New			In patients with type 2 DM >40 years of age 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.	I
New			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 comorbidities.	I
New			In treated patients aged 18–69 years, it is recommended that SBP should ultimately be lowered to a target range of 120–130 mmHg in most patients.	I
New			In treated patients aged ≥70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.	I
New			In all treated patients, DBP is recommended to be lowered to <80 mmHg.	I
New			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.	I
New			In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve CVD and/or cardiorenal outcomes.	I
New			In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.	I
New			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.	I

Continued

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Table 3 *Continued*

New or revised	Recommendations in 2013 version	Class	Recommendations in 2021 version	Class
New			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 PA participation.	IIa
New			Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.	IIa
New			ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CVD outcomes and reduce stress symptoms.	IIa
New			Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.	IIa
New			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.	IIa
New			An ultimate 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.	IIa
New			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 DM remission and should be considered.	IIa
New			In patients with type 2 DM and TOD, the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits may be considered to reduce future CVD and total mortality.	IIb
New			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
New			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/day) may be considered in combination with a statin.	IIb
New			Initiation of statin treatment for primary prevention in older people aged ≥70 may be considered, if at high risk or above.	IIb
New			Statin therapy may be considered in persons aged ≤40 years with type 1 or type 2 DM with evidence of TOD and/or an LDL-C level >2.6 mmol/L (100 mg/dL), as long as pregnancy is not being planned.	IIb
New			In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.	IIb
New			Home-based CR, telehealth, and mHealth interventions may be considered to increase patient participation and long-term adherence to healthy behaviours.	IIb
New			In patients with HF and major depression, SSRIs, SNRIs, and tricyclic antidepressants are not recommended.	III
New			In patients with dialysis-dependent CKD who are free of ASCVD, commencing statin therapy is not recommended.	III

Continued

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Table 3 *Continued*

New or revised	Recommendations in 2013 version	Class	Recommendations in 2021 version	Class
Policy interventions at the population level – section 5				
New			Putting in place measures to reduce air pollution, including reducing PM emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions, are recommended to reduce CVD mortality and morbidity.	I
Risk management of disease-specific cardiovascular disease – section 6				
New			It is recommended that patients with HF are enrolled in a comprehensive CR programme to reduce the risk of HF hospitalization and death.	I
New			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.	I
New			In patients with a cerebrovascular event, improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.	I
New			Identification and management of risk factors and concomitant diseases are recommended to be an integral part of treatment in patients with AF.	I
New			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.	IIa
New			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.	IIb
			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.	IIb
Risk factors and clinical conditions – section 3				
Revised	ABI may be considered as a risk modifier in CVD risk assessment.	IIb	The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended.	III
Risk factors and interventions at the individual level – section 4				
Revised	Drug treatment should be considered in patients with grade 1 or 2 hypertension who are at high CVD risk.	IIa	For grade 1 hypertension, treatment initiation based on absolute CVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.	I
Revised	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 CVD and total mortality.	IIa	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.	I

ABI = ankle brachial index; AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; *b.i.d.* = *bis in die* (twice a day); BP = blood pressure; CAC = coronary artery calcium; CHD = coronary heart disease; CKD = chronic kidney disease; CR = cardiac rehabilitation; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; EBCR = exercise-based cardiac rehabilitation; ED = erectile dysfunction; 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; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; mHealth = mobile device-based healthcare; *o.d.* = *omni die* (once a day); PA = physical activity; PCSK9 = proprotein convertase subtilisin/kexin type 9; PM = particulate matter; PUFA = polyunsaturated fatty acid; SBP = systolic blood pressure; SCORE2 = Systematic Coronary Risk Estimation 2; SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons; SGLT2 = sodium-glucose cotransporter 2; SNRI = serotonin-noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TOD = target organ damage.

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New sections
Section 3
3.2.2 Sex and gender and their impact on health
3.2.3 Atherosclerotic cardiovascular disease risk classification
3.2.3.1 A stepwise approach to risk factor treatment and treatment intensification
3.2.3.2 Risk estimation in apparently healthy people
3.2.3.3 Translating atherosclerotic cardiovascular disease risk to treatment thresholds
3.2.3.4 Risk estimation and risk factor treatment in apparently healthy people 50–69 years of age
3.2.3.5 Risk estimation and risk factor treatment estimation in apparently healthy people ≥70 years of age
3.2.3.6 Risk estimation and risk factor treatment in apparently healthy people <50 years of age
3.2.3.7 Risk estimation and risk factor treatment in patients with established atherosclerotic 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
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
New /revised concepts
Section 3
• SCORE2 and SCORE2-OP risk charts for fatal and non-fatal (myocardial infarction, stroke) ASCVD
• Estimating 10-year total CVD risk in apparently healthy people 50–69 years of age
• Estimating lifetime risk in apparently healthy people <50 years of age
• Estimating 10-year total CVD risk in apparently healthy people ≥70 years of age
• Cut-offs of 10-year CVD risk, based on SCORE2/SCORE2-OP, to define low–moderate risk, high risk, and very high risk for apparently healthy people in different age groups (<50, 50–69, and ≥70 years)
• Estimating 10-year CVD risk in patients with established CVD and/or DM
• Lifetime benefit of stopping smoking, reducing LDL-C, or lowering SBP (*sections 3* and *4*)
• A stepwise approach to attaining ultimate treatment goals (*sections 3* and *4*)
• Communication of CVD risk and benefit of treatment to patients in an understandable way
• 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 4.6.1.1*)
• A stepwise 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 CVD. This section addresses CVD prevention when certain underlying diseases are present and aims to provide 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

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DM =diabetes mellitus; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood-pressure; SCORE2 = Systematic Coronary Risk Estimation 2; SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons.

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Recommendations for CVD risk assessment

Recommendations	Class[a]	Level[b]
Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, FH, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD 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 individuals who have undergone CVD risk assessment in the context of 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 CVD 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

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ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia.
[a]Class of recommendation.
[b]Level of evidence.

Another important risk factor is adiposity, which increases CVD 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 (*sections 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 randomized controlled trials (RCTs) indicate that lowering LDL-C safely reduces CVD risk even at low LDL-C levels [e.g. LDL-C <1.4 mmol/L (55 mg/dL)].[20]
- The relative reduction in CVD 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-high-density lipoprotein cholesterol (HDL-C) encompasses all atherogenic (apo-B-containing) lipoproteins, and is calculated as: total cholesterol − HDL-C = non-HDL-C. The relationship between non-HDL-C and CV risk is at least as strong as 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] Non-HDL-C is used as an input in the Systemic Coronary Risk Estimation 2 (SCORE2) and SCORE2-Older Persons (SCORE2-OP) risk algorithms.

HDL-C is inversely associated with CVD risk. Very high HDL-C levels may signal an increased CVD 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 CVD risk.[25–28] HDL-C is nonetheless a useful biomarker to refine risk estimation using the SCORE2 algorithms. The SCORE2 algorithm cannot be used for patients with a genetic lipid disorder, such as familial hypercholesterolaemia (FH). Specific LDL-C thresholds and targets are recommended irrespective of estimated CV risk for patients with FH or other rare/genetic lipid disorders.

3.2.1.2 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 coronary artery disease (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 systolic BP (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 BP evolution differs in women 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.

3.2.1.3 Cigarette smoking

Cigarette smoking is responsible for 50% of all avoidable deaths in smokers, with 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 CVD risk in smokers <50 years of age is five-fold 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]

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3.2.1.4 Diabetes mellitus

Type 1 DM, type 2 DM, and prediabetes are independent risk factors for ASCVD, increasing risk of ASCVD by about two-fold, 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.

3.2.1.5 Adiposity

Over recent decades, body mass index (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^2 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 interrelationship between these concepts and CV, as well as psychological, health. There is, at present, no official ESC position on the specific terminology to be used. According to the World Health Organization (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 in these guidelines.[50] The influence of gender on an 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 can also be determinants of health access, healthcare utilization, disease perception, decision-making, and perhaps therapeutic response,[50] including in the field of CVD and ASCVD prevention. Research is ongoing, but gaps in evidence remain 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 (LV) ejection fraction (LVEF), adverse drug reactions, trends in ASCVD risk factors and awareness, sex disparities in the management of and outcomes after acute coronary syndromes (ACS).[51−58] Furthermore, CVD health after menopause transition, pregnancy disorders, and gynaecologic conditions have recently been reviewed.[59]

3.2.3. Cardiovascular disease risk classification

The current guidelines on CVD prevention in clinical practice concentrate principally, but not exclusively, on risk and prevention of 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 CVD 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 CVD 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 CVD risk. Women below 50 years and men below 40 years of age are almost invariably at low 10-year CVD risk, but may have unfavourable modifiable risk factors that sharply increase their longer-term CVD risk. Conversely, men over 65 years and women over 75 years of age are almost always at high 10-year CVD risk. Only between the ages of 55 and 75 years in women and 40 and 65 years in men does the 10-year CVD risk vary around commonly used thresholds for intervention. The age categories <50, 50−69, and ≥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.

CVD risk can also be assessed in patients with type 2 DM and in patients with established ASCVD. The populations or patient groups in whom CVD risk needs to be considered are summarized and presented in *Table 4*. Lifetime CVD risk estimation is available for various groups of patients, and enables estimation of lifetime benefit from preventive interventions such as smoking cessation (see *section 4.5.1*), lipid-lowering (see *section 4.6.2.1*), and BP treatment (see *section 4.7.5.2*). Lifetime risk and benefit estimation may be used for communication in the shared decision-making process, together with consideration of comorbidities, frailty, patient preferences for initiating (STEP 1) and intensifying (STEP 2) risk factor treatment (*Figure 2*).

3.2.3.1 A stepwise approach to risk factor treatment and treatment intensification

As explained before, targets and goals for LDL-C, BP, and glycaemic control in DM remain as recommended in recent ESC Guidelines.[3−5] These guidelines propose a stepwise approach to treatment intensification as a tool to help physicians and patients pursue these targets in a way that fits patient profiles and preferences. This principle (outlined in *Figure 2*, using the example of a stepwise 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 healthcare professionals and patients.

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Table 4 Patient categories and associated cardiovascular disease 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 CVD 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 CVD risk and treatment benefits.
	50-69 years	Low- to very high-risk	10-year CVD 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 CVD 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 mL/min/1.73 m^2 and ACR <30 **or** eGFR 45−59 mL/min/1.73 m^2 and ACR 30−300 **or** eGFR ≥60 mL/min/1.73 m^2 and ACR >300)	High-risk	N/A
	Severe CKD (eGFR<30 mL/min/1.73 m^2 **or** eGFR 30−44 mL/min/1.73 m^2 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 CVD risk estimation after general prevention goals (e.g. with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
	Patients with DM with established ASCVD and/or severe TOD:[87,93-95] • eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria • eGFR 45-59 mL/min/1.73 m^2 and microalbuminuria (ACR 30 -300 mg/g) • Proteinuria (ACR >300 mg/g) • Presence of microvascular disease in at least 3 different sites (e.g. microalbuminuria plus retinopathy plus neuropathy)	Very high-risk	Residual 10-year CVD 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 CVD risk and benefit estimation of risk factor treatment (e.g. DIAL model).
Patients with established ASCVD			
Documented ASCVD, clinical or unequivocal on imaging. Documented clinical ASCVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography or carotid ultrasound or on CTA. 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 CVD risk estimation after general prevention goals (e.g. 10-year risk with the SMART risk score for patients with established CVD or 1- or 2-year risk with EUROASPIRE risk score for patients with CHD). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g. SMART-REACH model; or DIAL model if diabetes).

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ACR = albumin-to-creatinine ratio: (to convert mg/g to mg/mmol: divide by 10); ACS = acute coronary syndromes; ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; AMI = acute myocardial infarction; ASCVD = atherosclerotic cardiovascular disease; 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; 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.

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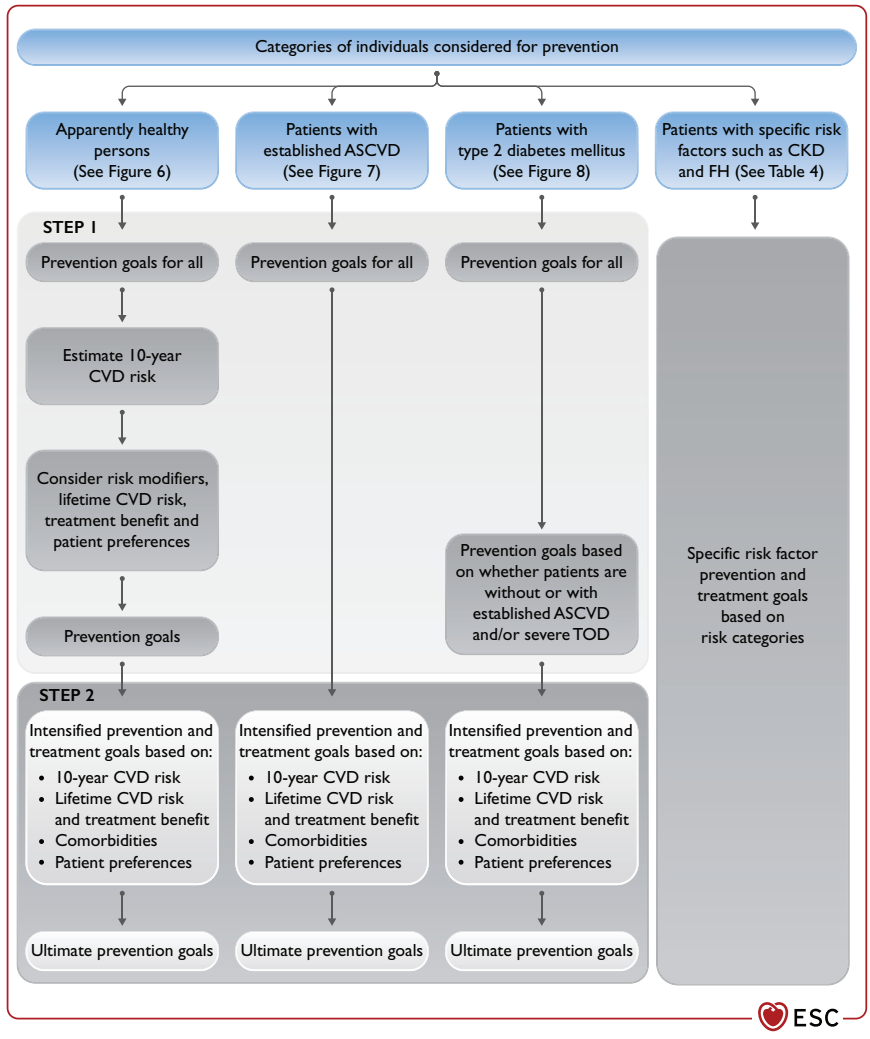

Figure 2 Examples of a stepwise approach to risk stratification and treatment options. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; DM = diabetes mellitus; FH = familial hypercholesterolaemia; TOD = target organ damage.

A stepwise approach starts with prevention goals for all, regardless of CVD risk. This is followed by CVD 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, comorbidities, and frailty, all of which converge with patient preferences in a shared decision-making process.

In the field of DM, 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 such an approach.[66,67] 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 CVD risk reduction and are to be considered in all patients.

3.2.3.2 Risk estimation in apparently healthy people

Apparently healthy people are those without established ASCVD, type 2 DM, or severe comorbidities. In the 2016 ESC prevention guidelines,[2] the Systemic Coronary Risk Estimation (SCORE) algorithm was used to estimate 10-year risk of CVD death. However, CVD morbidity (non-fatal myocardial infarction, non-fatal stroke) combined with CVD mortality better reflects the total burden of ASCVD. The updated SCORE algorithm—SCORE2—used in these guidelines (see *Figure 3*), estimates an individual's 10-year risk of *fatal and non-fatal* CVD events (myocardial infarction, stroke) in apparently healthy people aged 40–69 years with risk factors that are untreated or have been stable for several years.[68]

Several specific considerations apply to CVD risk estimation in older people. First, the gradient of the relationship between classical risk factors, such as lipids and BP, with CVD risk attenuates with age.[69] Second, CVD-free survival dissociates from overall survival progressively with increasing age, because risk for non-CVD mortality increases ('competing risk').[70] For these reasons, traditional risk

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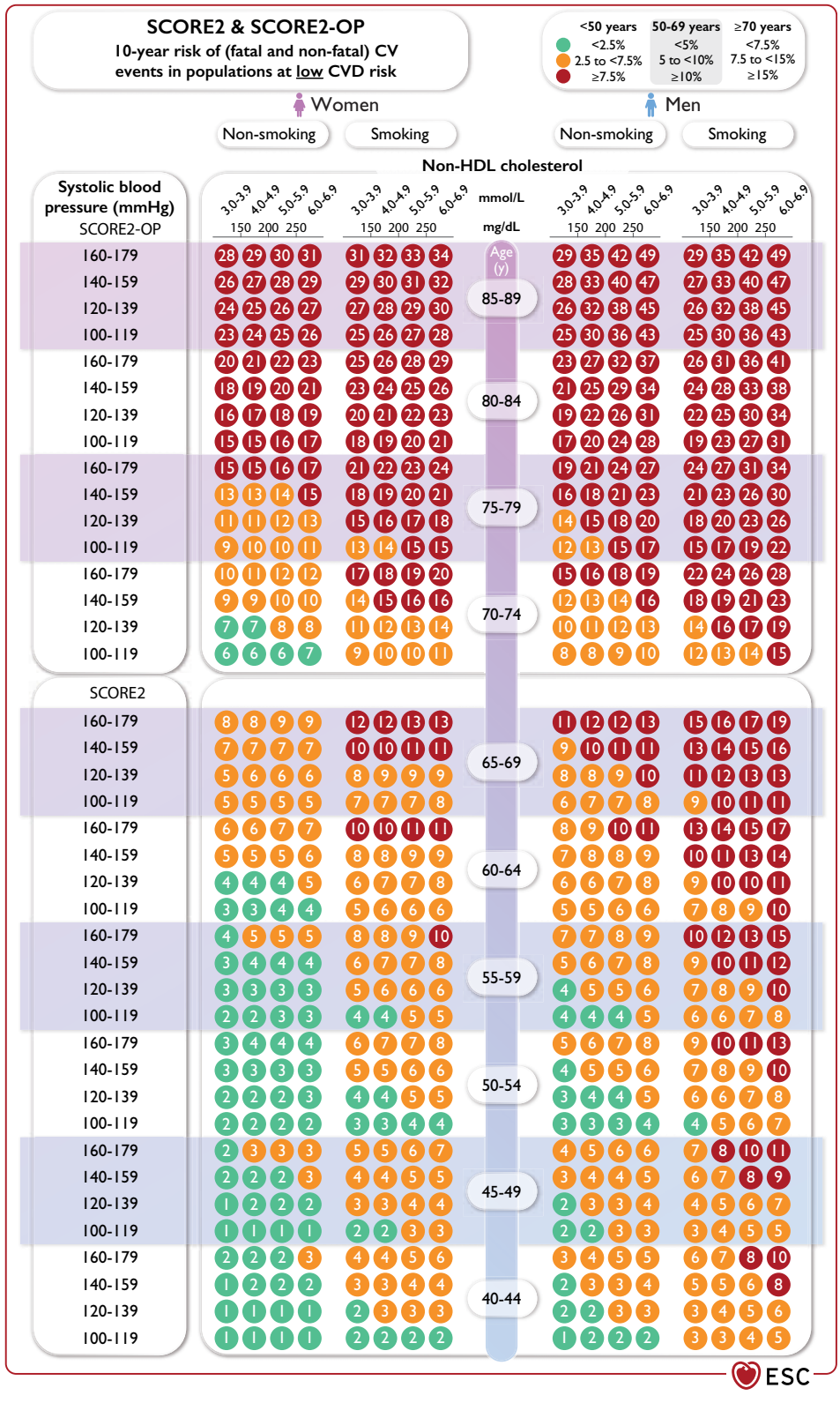

Figure 3 Systematic Coronary Risk Estimation 2 and Systematic Coronary Risk Estimation 2-Older Persons risk charts for fatal and non-fatal (myocardial infarction, stroke) cardiovascular disease.[68,72] ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; SBP = systolic blood pressure; HDL-C = high-density lipoprotein cholesterol; SCORE2 = Systematic Coronary Risk Estimation 2; SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons; TFYR = The Former Yugoslav Republic; UK = United Kingdom. For apparently healthy people aged 40–69 years, the SCORE2 algorithm[68] is used to estimate 10-year risk of fatal and non-fatal (myocardial infarction, stroke) CVD. For apparently healthy people ≥70 years of age, the SCORE2-OP is used.[72]. **Low-risk countries**: Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the UK. **Moderate-risk countries**: Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden. **High-risk countries**: Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey. **Very-high-risk countries**: Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, TFYR (Macedonia), Tunisia, Ukraine, and Uzbekistan.

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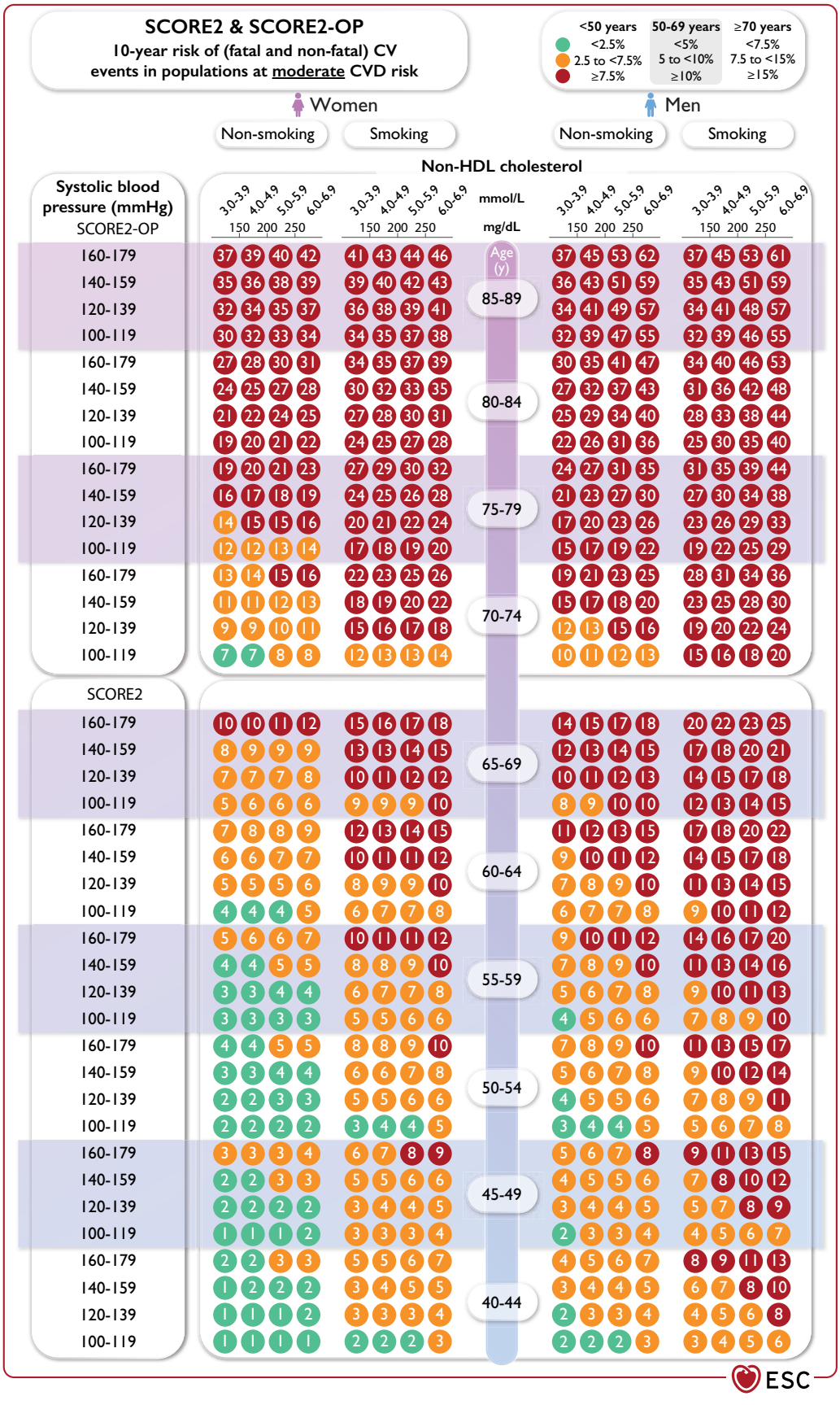

Figure 3 Continued.

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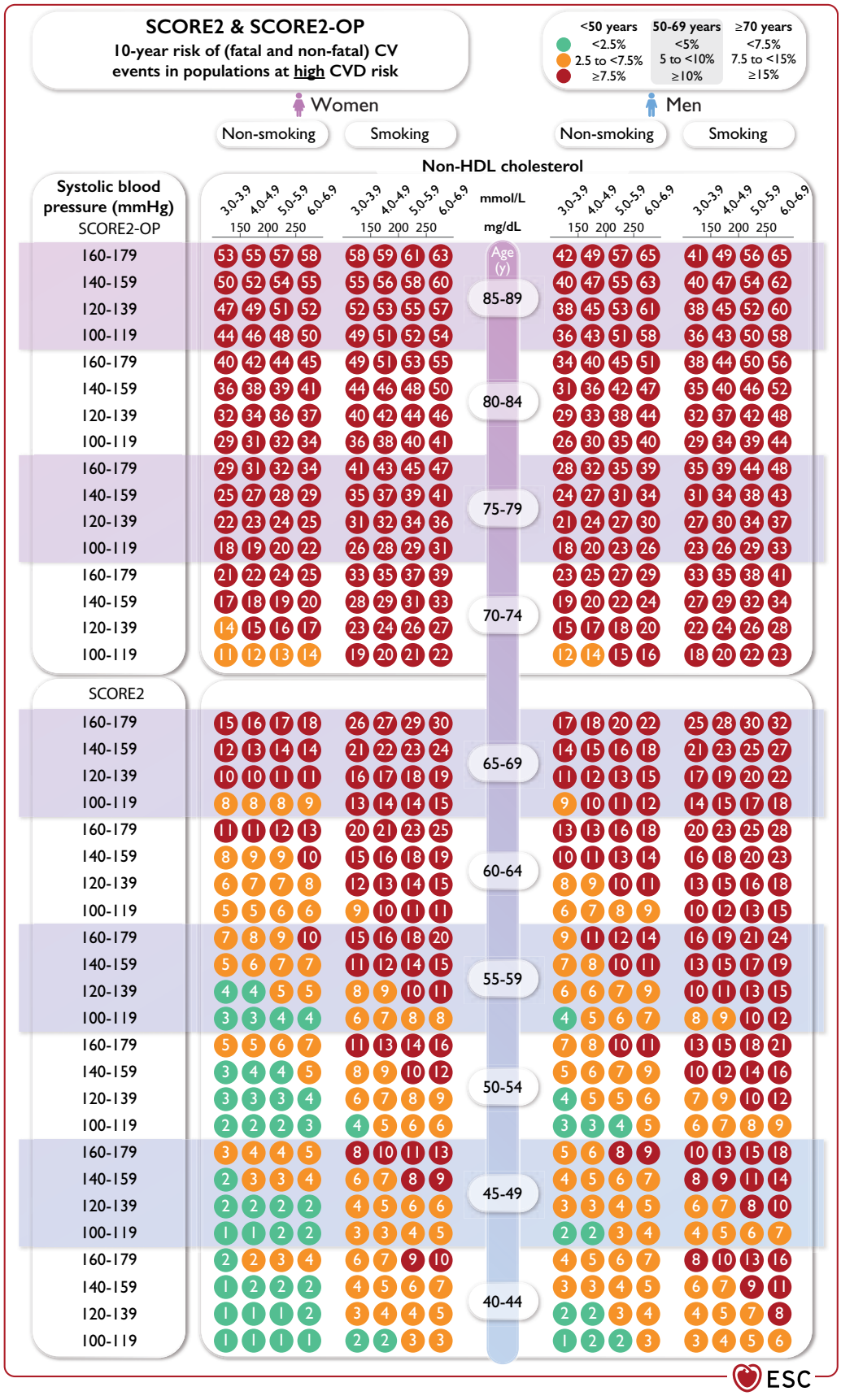

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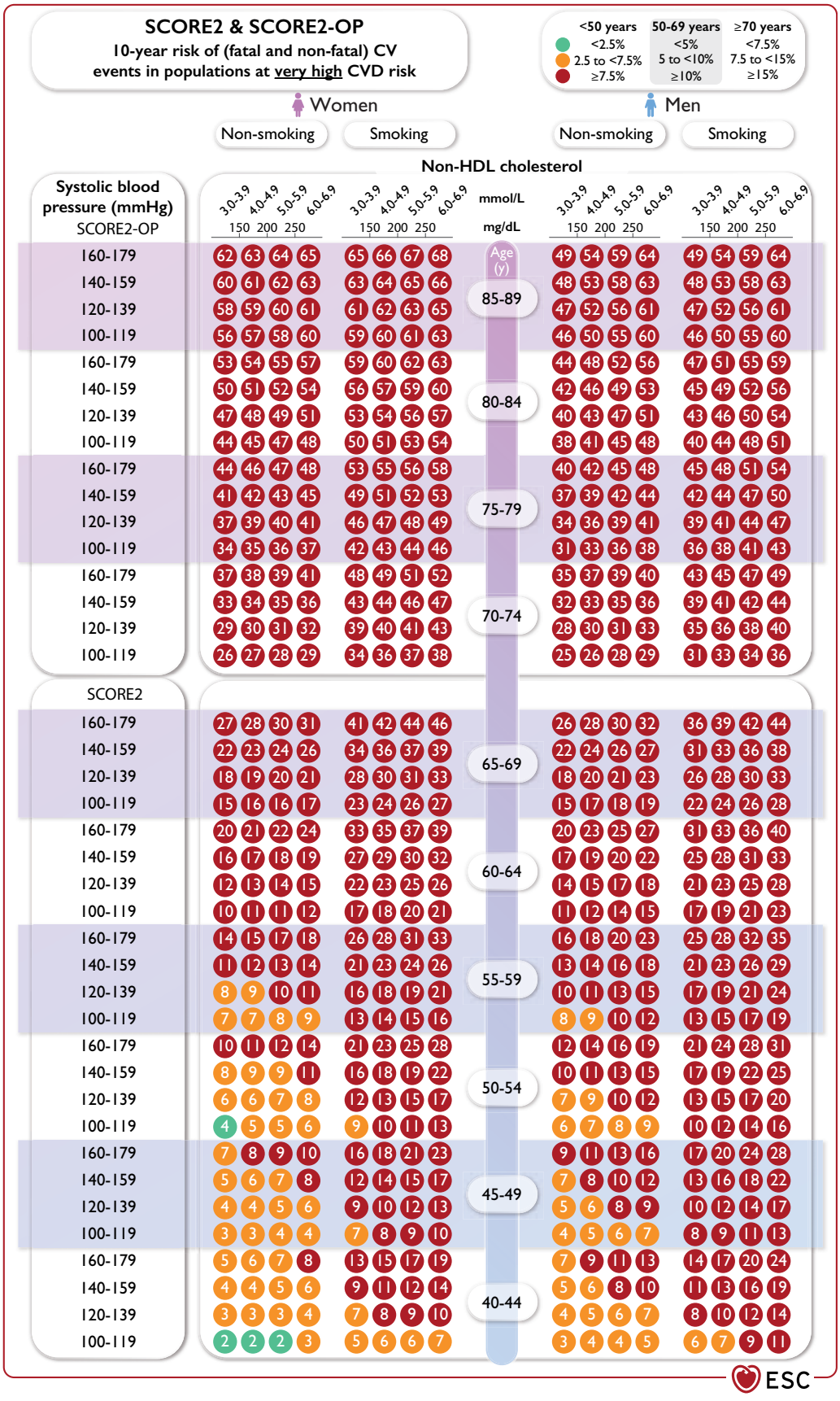

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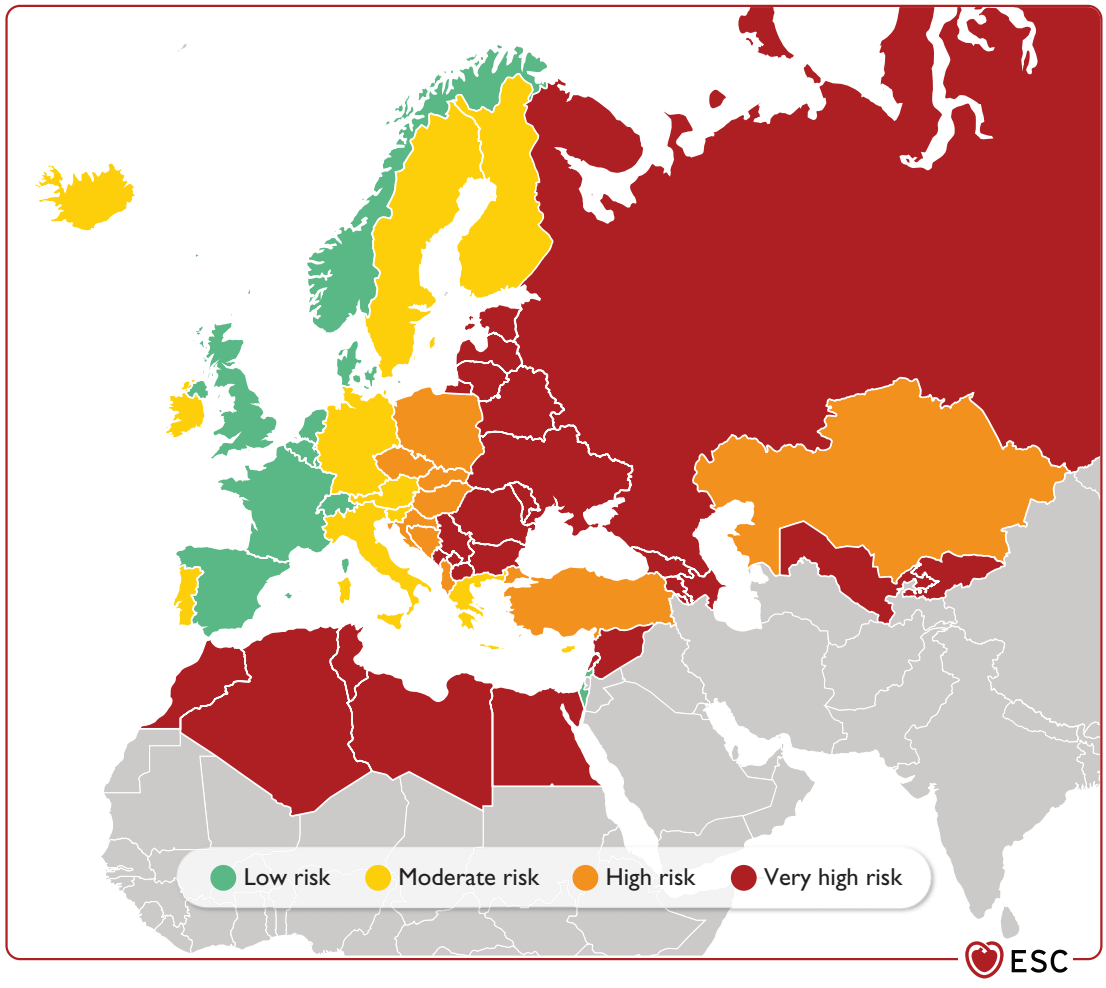

Figure 4 Risk regions based on World Health Organization cardiovascular mortality rates.[68,72,73]

models that do not take into account the competing risk of non-CVD mortality, tend to overestimate the actual 10-year risk of CVD, and hence overestimate the potential benefit of treatment.[71] The SCORE2-OP algorithm estimates 5-year and 10-year fatal and non-fatal CVD events (myocardial infarction, stroke) adjusted for competing risks in apparently healthy people aged ≥70 years.[72]

SCORE2 and SCORE2-OP are calibrated to four clusters of countries (low, moderate, high, and very high CVD risk) that are grouped based on national CVD mortality rates published by the WHO (*Supplementary Table 3* and *Figure 4*).[73] **Low-risk countries:** Belgium, Denmark, France, Israel, Luxembourg, Norway, Spain, Switzerland, the Netherlands, and the United Kingdom (UK). **Moderate-risk countries:** Austria, Cyprus, Finland, Germany, Greece, Iceland, Ireland, Italy, Malta, Portugal, San Marino, Slovenia, and Sweden. **High-risk countries:** Albania, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Kazakhstan, Poland, Slovakia, and Turkey. **Very high-risk countries:** Algeria, Armenia, Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Republic of Moldova, Romania, Russian Federation, Serbia, Syria, The Former Yugoslav Republic (Macedonia), Tunisia, Ukraine, and Uzbekistan. A multiplier approach has been used for converting CVD mortality rates to fatal and non-fatal CVD events.[74] 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 4*). 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 BP disorders, CKD, and in pregnant women.

To estimate a person's 10-year risk of total CVD 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-C. Risk estimates then need to be adjusted upwards as the person approaches the next age category.

3.2.3.3 Translating cardiovascular disease risk to treatment thresholds

While no risk threshold is universally applicable, the intensity of treatment should increase with increasing CVD risk. In individual cases, however, no lower threshold of total CVD risk precludes treatment of risk factors. Conversely, no high threshold for total CVD risk implies 'mandatory' treatment. Across the entire range of CVD 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

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Table 5 Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

	<50 years	50–69 years	≥70 years[a]
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended[a]	≥7.5%	≥10%	≥15%

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CVD = cardiovascular disease.

[a]In apparently healthy people ≥70 years old, the treatment recommendation for lipid-lowering drugs is Class IIb ('may be considered').

The division of the population into three distinct age groups (<50, 50–69, 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 cut-off. *Figure 5* illustrates how a continuous increase in age relates to increasing risk thresholds, and may be used as a guide for daily practice.

categories of CVD 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. As age is a major driver of CVD risk, but lifelong risk factor treatment benefit is higher in younger people, the risk thresholds for considering treatment are lower for younger people (*Table 5*).

Risk categories do not 'automatically' translate into recommendations for starting drug treatment. In all age groups, consideration of risk modifiers, lifetime CVD risk, treatment benefit, comorbidities, 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 50–69-year age range, a 10-year CVD mortality risk threshold of 5% estimated with the previously used SCORE algorithm corresponds, on average, to a 10-year fatal and non-fatal CVD risk threshold of 10% estimated with SCORE2, as approximately the same number of people are above the risk threshold and would qualify for treatment.[68]

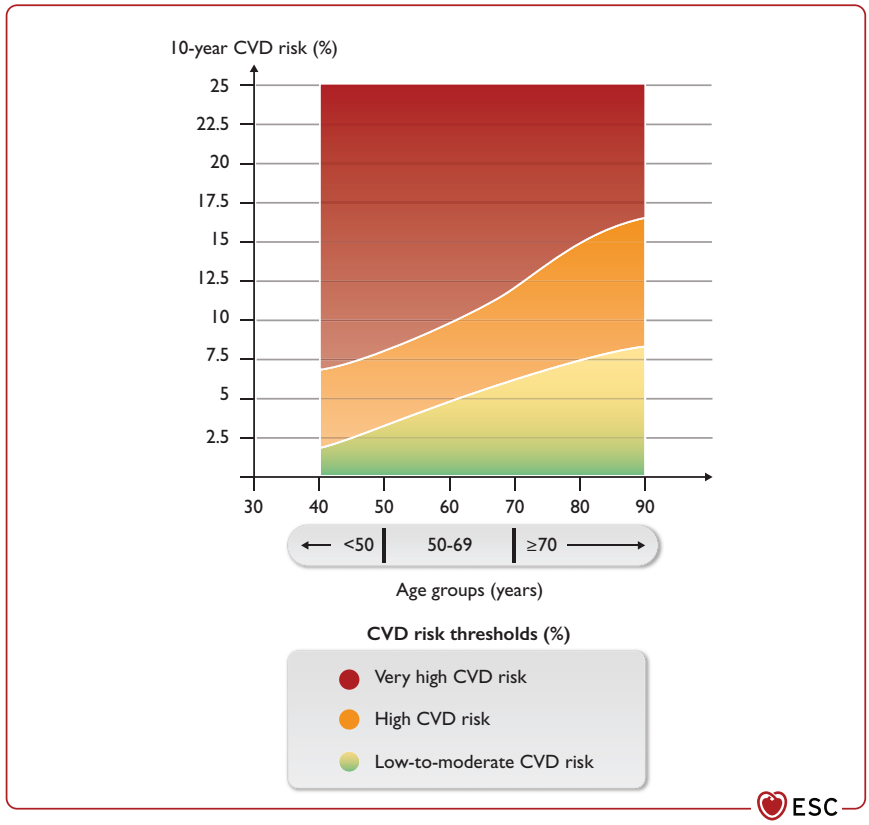

Figure 5 Schematic representation of increasing 10-year cardiovascular disease risk thresholds across age groups. CVD = atherosclerotic cardiovascular disease.

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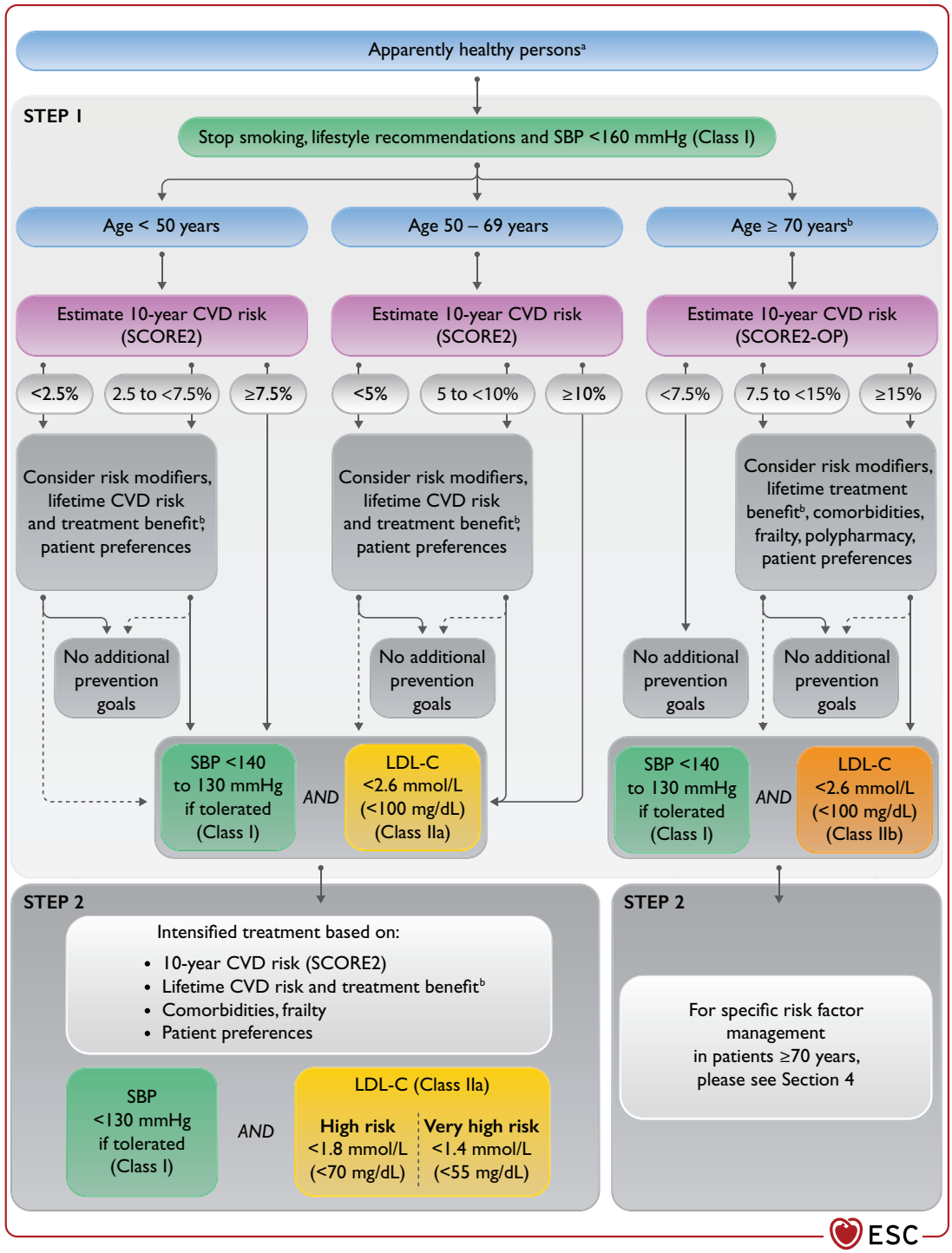

Figure 6 Flow chart of cardiovascular disease risk and risk factor treatment in apparently healthy persons. ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; ESC = European Society of Cardiology; FH = familial hypercholesterolaemia; 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 SBP (<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. 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 https://www.u-prevent.com. [a]Does not include patients with CVD, DM, CKD, or FH. [b]The LIFE-CVD model for estimating lifetime CVD risk and treatment benefit is calibrated for low- and moderate-risk regions (see *Box 1*).

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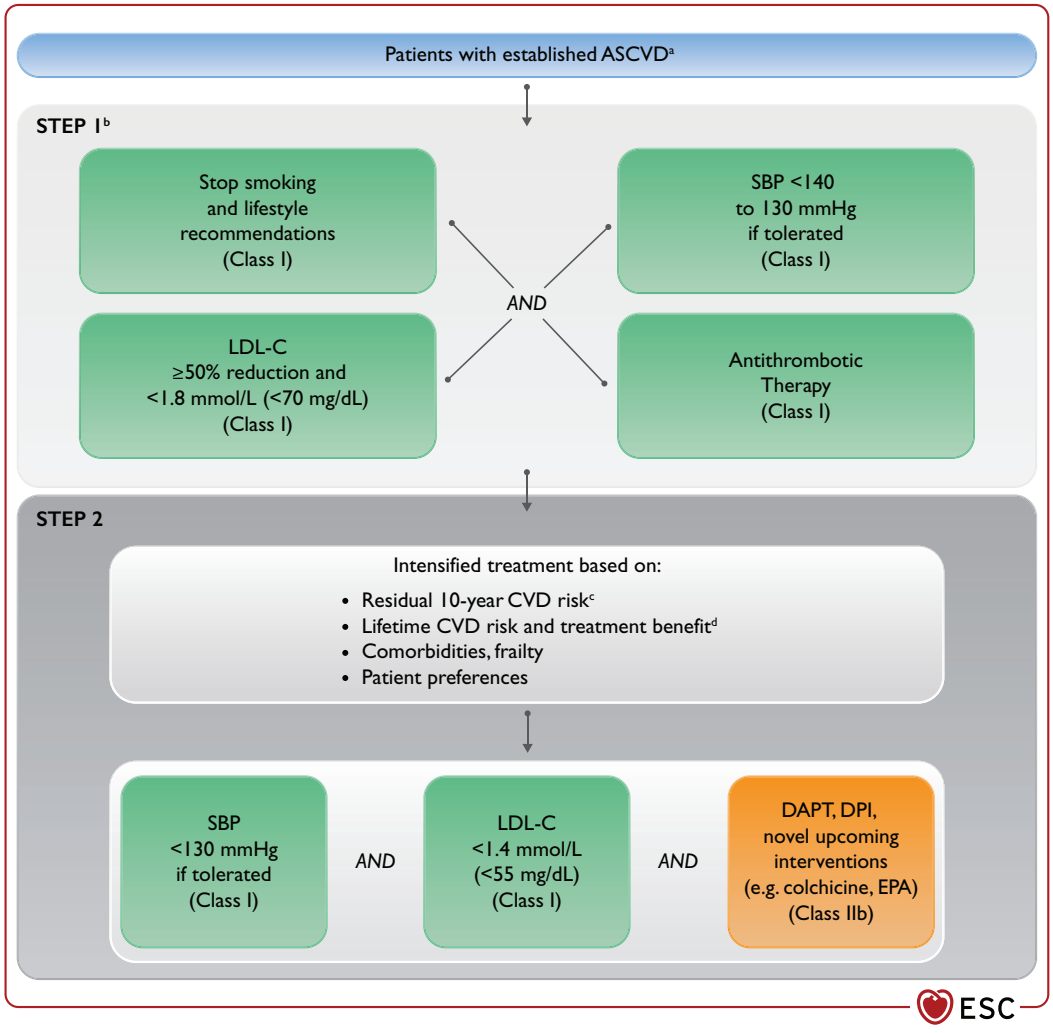

Figure 7 Flow chart of cardiovascular risk and risk factor treatment in patients with established atherosclerotic cardiovascular disease. Ultimate treatment goals for SBP (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines[3,4] are to be pursued as indicated. 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 syndromes; ASCVD = atherosclerotic cardiovascular disease; CR = cardiac rehabilitation; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; ESC = European Society of Cardiology; EUROASPIRE = European Action on Secondary and Primary Prevention by Intervention to Reduce Events; LDL-C = low-density lipoprotein cholesterol; 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 https://www.u-prevent.com. [a]For patients with DM see DM flow chart (*Figure 8*). [b]For patients with recent ACS, these prevention goals are part of participation in CR (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.

As the 10-year CVD 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.

3.2.3.4 Risk estimation and risk factor treatment in apparently healthy people 50–69 years of age

Stopping smoking, lifestyle recommendations, and SBP <160 mmHg are recommended for all (*Figure 6*). A 10-year CVD risk (fatal and non-fatal ASCVD events) ≥10% is generally considered 'very high risk', and treatment of CVD risk factors is recommended. A 10-year CVD risk of 5 to <10% is considered 'high risk', and treatment of risk factors should be considered, taking CVD risk modifiers, lifetime risk and treatment benefit (in low- and moderate-risk regions, *Box 1*), and patient preferences into account. A 10-year CVD risk <5% is considered 'low-to-moderate risk', and would generally not qualify for risk factor treatment unless one or several risk modifiers (see *section 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 6*). Age is the dominant driver of CVD

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risk, and estimated 10-year CVD risk of almost all individuals ≥70 years exceeds conventional risk thresholds. Also, lifetime benefit of treatment in terms of time gained free of CVD is lower in older people. Therefore, the CVD risk thresholds for risk factor treatment are higher in apparently healthy people ≥70 years. A 10-year CVD 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 CVD risk of 7.5 to <15% is considered 'high risk', and treatment of risk factors should be considered taking CVD risk modifiers, frailty, lifetime treatment benefit (in low and moderate risk regions, *Box 1*), comorbidities, 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 CVD risk <7.5% is considered 'low-to-moderate risk', and would generally not qualify for risk factor treatment unless one or several risk modifiers (*section 3.3*) increase risk or the estimated lifetime risk and treatment benefit is considered substantial.[75–79]

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

Stopping smoking, lifestyle recommendations, and SBP <160 mmHg are recommended for all (*Figure 6*). The 10-year CVD risk in relatively young, apparently healthy people is on average low, even in the presence of high risk factor levels, but the lifetime CVD risk is in these circumstances very high. In apparently healthy people <50 years of age, a 10-year CVD 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 CVD risk of 2.5 to <7.5% is considered 'high risk', and treatment of risk factors should be considered, taking CVD risk modifiers, lifetime risk and treatment benefit (in low- and moderate-risk regions), and patient preferences into account. A 10-year CVD risk <2.5% is considered 'low-to-moderate risk', and would generally not qualify for risk factor treatment unless one or several risk modifiers (see *section 3.3*) increase risk or the estimated lifetime risk and treatment benefit is considered substantial (see *Box 1*) (*Figure 6*).[75–78]

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

CVD 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 BP-lowering drug treatment are not usually considered, except for patients with FH or specific BP 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 CVD risk over a lifespan.[80]

3.2.3.7 Risk estimation and risk factor treatment in patients with established atherosclerotic cardiovascular disease

Patients with clinically established ASCVD are, on average, at very high risk of recurrent CVD 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 CVD risk, comorbidities, lifetime risk and treatment benefit (*Box 1*), frailty, and patient preferences into account in a shared decision-making process (*Figure 7*).

After initial risk factor treatment and the achievement of risk factor treatment goals, the individual *residual* risk for recurrent

Box 1. Lifetime CVD risk and treatment benefit estimation

Prevention of CVD by treating risk factors is usually done with a lifetime perspective. Lifetime CVD 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 ASCVD, and persons with type 2 DM with specific lifetime CVD risk scores.[75–77] 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 11*), lipid lowering (see also *Figure 12*), and BP lowering (see also *Figure 15*) on an individual patient level expressed as extra CVD-free life-years.[78] 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 a CVD 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 a CVD 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.

BP = blood pressure; CVD = cardiovascular disease; DM = diabetes mellitus; ESC = European Society of Cardiology; HR = hazard ratio; RCT = randomized controlled trial.

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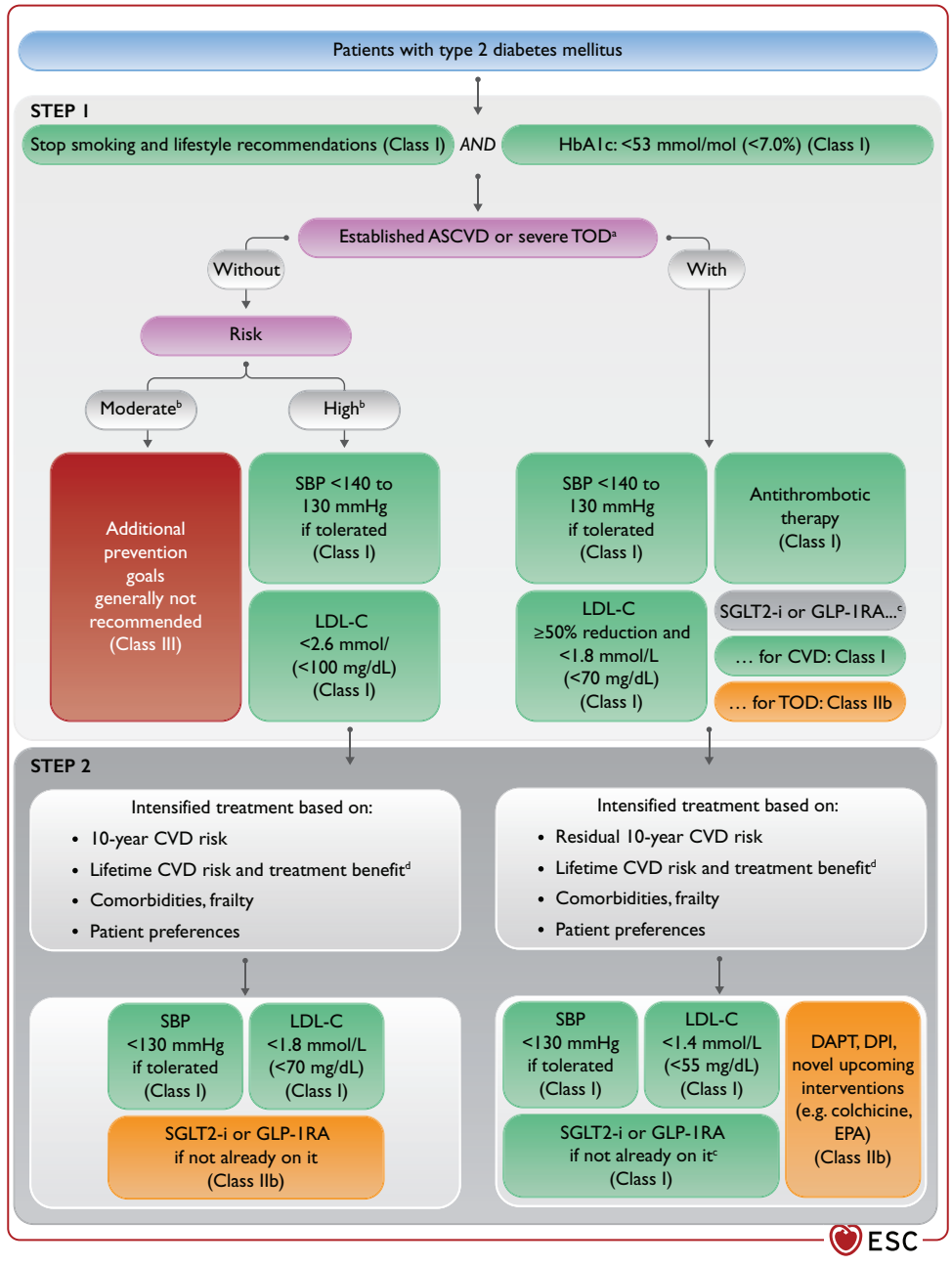

Figure 8 Flow chart of cardiovascular risk and risk factor treatment in patients with type 2 diabetes mellitus. Ultimate treatment goals for SBP (<130 mmHg) and LDL-C (according to level of risk) according to the respective ESC Guidelines[3,4] are to be pursued as indicated. The stepwise approach has to be applied as a whole: after STEP 1, considering proceeding to the intensified goals of STEP 2 is mandatory. 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 https://www.u-prevent.com. ACR = albumin-to-creatinine ratio; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated haemoglobin; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; SGLT2 = sodium-glucose cotransporter 2; TOD = target organ damage (retinopathy, nephropathy, neuropathy). [a]Severe TOD is defined as at least one of: eGFR <45 mL/min/1.73 m^2 irrespective of the presence or absence of albuminuria; eGFR 46–59 mL/min/1.73 m^2 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 three different sites (e.g. microalbuminuria plus retinopathy plus neuropathy). [b]See *Table 4* for CVD risk groups. [c]Patients with prevalent HF or CKD are recommended for SGLT2 inhibitor, and patients post stroke are recommended for GLP-1RA treatment. [d]Lifetime treatment benefit is expressed as extra CVD-free life gained from a certain intervention or treatment intensification. See *Box 1*.

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CVD varies widely and should be considered.[81] It is evident that patients with a recent ACS or progressive vascular disease, and patients with DM and vascular disease, are all at exceptionally high risk for recurrent CVD 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 CVD risk with a calculator.

The risk of recurrent CVD is influenced mainly by classical risk factors, vascular disease site, and kidney function. Risk stratification tools for secondary prevention include the SMART (Secondary Manifestations of Arterial Disease) risk score (available in the ESC CVD Risk app) for estimating 10-year residual CVD risk in patients with stable ASCVD, defined as CAD, PAD, or cerebrovascular disease,[81] and the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) risk model, which estimates 2-year risk of recurrent CVD in patients with stable CAD.[82]

Occasionally, recurrent CVD 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,[83] icosapent ethyl,[84] or anti-inflammatory therapy with colchicine (see *section 4.10*)[85,86] may be considered.

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

Most adults with type 2 DM are at high or very high risk for future CVD, 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 target organ damage (TOD). Type 2 DM also increases the risk for cardiorenal outcomes, in particular HF and CKD. Relative risks (RRs) for CVD in type 2 DM are higher at younger ages of onset and are modestly higher in women compared with men.[87] 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 DM, 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.[88]

Persons with DM with severe TOD (for definition: see *Table 4*) can be considered to be at very high CVD risk, similar to people with established CVD (see *Table 4*). Most others with DM are considered to be at high ASCVD risk.[64] However, an exception can be made for patients with well-controlled short-standing DM (e.g. <10 years), no evidence of TOD, and no additional ASCVD risk factors, who may be considered as being at moderate CVD risk.

In addition to the semi-quantitative division into three risk categories described above, DM-specific risk models may refine risk estimates and illustrate the impact of treatments. These models generally include duration of DM, glycated haemoglobin (HbA1c) level, and presence of TOD. Examples are the ADVANCE (Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation) risk score, which predicts 10-year CVD risk, and the UKPDS (UK Prospective Diabetes Study) risk engine, which predicts fatal and non-fatal CVD risk and is available for use in the UK. However, we recommend cautious use of these calculators, since both are based on older cohort data[89,90] (*Figure 8*).

Recommendations for CVD risk estimation

Recommendations	Class[a]	Level[b]
In apparently healthy people <70 years without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and non-fatal CVD risk with SCORE2 is recommended.[68]	I	B
In apparently healthy people ≥70 years without established ASCVD, DM, CKD, genetic/rarer lipid or BP disorders, estimation of 10-year fatal and non-fatal CVD risk with SCORE2-OP is recommended.[72]	I	B
In apparently healthy people, after estimation of 10-year fatal and non-fatal CVD risk, lifetime risk and treatment benefit, risk modifiers, frailty, polypharmacy, and patient preferences should be considered.	IIa	C
Patients with established ASCVD 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.[75,77,81,88–90]	I	A
A stepwise treatment-intensification approach aiming at intensive risk factor treatment is recommended for apparently healthy people at high or very high CVD 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.[66,67]	I	B
Treatment of ASCVD risk factors is recommended in apparently healthy people without DM, CKD, genetic/rarer lipid, or BP disorders who are at very high CVD risk (SCORE2 ≥7.5% for age under 50; SCORE2 ≥10% for age 50–69; SCORE2-OP ≥15% for age ≥70 years).[68,72]	I	C
Treatment of ASCVD risk factors should be considered in apparently healthy people without DM, CKD, genetic/rarer lipid, or BP disorders who are at high CVD risk (SCORE2 2.5 to <7.5% for age under 50; SCORE2 5 to <10% for age 50–69; SCORE2-OP 7.5 to <15% for age ≥70 years), taking CVD 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 4*); DM = diabetes mellitus; SCORE2 = Systemic Coronary Risk Estimation 2; SCORE2-OP = Systemic Coronary Risk Estimation 2-Older Persons.
[a]Class of recommendation.
[b]Level of evidence.

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Intensification of risk factor treatment in STEP 2 must be considered in all patients, taking into account 10-year CVD risk, comorbidities, lifetime risk and treatment benefit (*Box 1*), frailty, and patient preferences in a shared decision-making process.[75]

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 CVD risk, and earlier manifestation of type 1 DM relates to more life-years lost in women than men, mostly due to CVD.[91] RRs of CVD are, on average, higher in type 1 vs. 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.[92] CVD risks have declined over time, commensurate with improvements in life expectancy.[93] Lifetime CVD risks in type 1 DM are higher with poorer glycaemic control, lower social class, and younger age of onset. The absolute risk of CVD events or CVD mortality is highest among those with any evidence of microvascular disease, particularly renal complications, and is strongly influenced by age. CVD risk stratification in persons with type 1 DM may be based on the same risk classification as for type 2 DM, summarized in *Table 4*, although the level of evidence for type 1 DM is weaker.

3.2.4. Communication of cardiovascular disease risk

Reducing CVD risk at the individual level begins with appropriate assessment of individual risk and effective communication of risk and anticipated risk reduction by risk factor treatment. Patient-doctor interactions are complex and communicating risk is challenging.[94,95] There is no single 'correct' approach; rather, it will depend on the individual's preferences and understanding, which may differ with education status and numeracy. Risk perception is also strongly affected by emotional factors such as fear, optimism, etc. ('patients don't think risk, they feel risk').[96]

It is important to explore whether patients understand their risk, the anticipated risk reduction, and 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 their 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 RR (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 a CVD 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 https://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 mortality into account.[78] Direct translation of RRs to treatment decisions is not recommended, as absolute risk remains the key criterion for starting treatment.

Recommendation for CVD risk communication

Recommendation	Class[a]	Level[b]
An informed discussion about CVD risk and treatment benefits tailored to the needs of a patient is recommended.[96]	I	C

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CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.

Recommendations for CVD risk modifiers

Recommendations	Class[a]	Level[b]
Stress symptoms and psychosocial stressors modify CVD risk. Assessment of these stressors should be considered.[100–102]	IIa	B
CAC 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.[103,104]	IIb	B
Multiplication of calculated risk by RR for specific ethnic subgroups should be considered.[105]	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 CAC scoring or carotid ultrasound for plaque determination), is not recommended.	III	B

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CVD = cardiovascular disease; CAC = coronary artery calcium; RR = relative risk.
[a]Class of recommendation.
[b]Level of evidence.

An alternative way of expressing individual risk is to calculate a person's 'risk age'.[96] 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 RR of CVD will be exposed to if preventive measures are not adopted. Risk age is also automatically calculated as part of HeartScore (http://www.heartscore.org/).[97–99]

CVD risk may also be expressed with a lifetime rather than a 10-year horizon, for example, the LIFE-CVD (LIFEtime-perspective CardioVascular Disease) calculator (ESC CVD Risk Calculation app or https://www.u-prevent.com) (also see *Box 1*).[78] Lifetime CVD 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

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interventions.[78] Lifetime benefit of preventive interventions can be expressed as gain in CVD-free life (years), which is easier to communicate to a patient and may support the shared decision-making process.

3.3. Potential risk modifiers

Apart from the conventional CVD 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)
- 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.[106] 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. In low-risk or very-high-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 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) RRs reported for these modifiers in the literature.[107]

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

3.3.1. Psychosocial factors

Psychosocial stress is associated, in a dose-response pattern, with the development and progression of ASCVD, independently of conventional risk factors and sex. Psychosocial stress includes stress symptoms (i.e. symptoms of mental disorders), as well as stressors such as loneliness and critical life events. The RRs of psychosocial stress are commonly between 1.2 and 2.0[108,109] (*Supplementary Table 4*). Conversely, indicators of mental health, such as optimism and a strong sense of purpose, are associated with lower risk.[109] Psychosocial stress has direct biological effects, but is also highly correlated with socioeconomic and behavioural risk factors (e.g. smoking, poor adherence).[100,109–113] Although the associations of psychosocial stress with CV health are robust, only 'vital exhaustion' has been proven to improve risk reclassification.[101] Owing to the importance of stress symptoms among ASCVD patients, several guidelines and scientific statements recommend screening of ASCVD patients for psychological stress[113–115] (*Box 2* and *Supplementary Table 5*). 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.[102]

3.3.2. Ethnicity

Europe includes many citizens whose ethnic background originates in countries such as India, China, North Africa, and Pakistan. Given the considerable variability in ASCVD risk factors between immigrant groups, no single CVD risk score performs adequately in all groups. Rather, the use of a multiplying factor would be helpful to take account of CVD 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,[105] although this focuses on a wider range of CVD outcomes and not simply on CVD mortality.

Immigrants from South Asia (notably India and Pakistan) present higher CVD rates independent of other risk factors, whereas adjusted CVD risks appear lower in most other ethnic groups. The reasons for such differences remain inadequately studied, as do the risks associated with other ethnic backgrounds. Based on such data, the following correction factors, based on data from the UK, could be applied when assessing CVD risk using risk calculators.[105] Ideally, country and risk-calculator-specific RRs 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 0.7.

Box 2. Core topics for psychosocial assessment

Simultaneous diagnostic assessment	At least one in five patients carries a diagnosis of a mental disorder, usually presenting 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,[116] see *Supplementary Table 5*).[117,118]
Stressors	There are simple questions to get into a conversation about significant stressors[112]: 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?

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3.3.3. Imaging

3.3.3.1 Coronary artery calcium

Coronary artery calcium (CAC) scoring can reclassify CVD 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.[103,104] Availability and cost-effectiveness of large-scale CAC scanning must, however, be considered in a locoregional context (see *section 2.3* on cost-effectiveness). If CAC 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.

3.3.3.2 Contrast computed tomography coronary angiography

Contrast computed tomography angiography (CCTA) allows identification of coronary stenoses and predicts cardiac events.[119] In the SCOT-HEART (Scottish Computed Tomography of the Heart) study, 5-year rates of coronary death or myocardial infarction were reduced when CCTA was used in patients with stable chest pain.[120] 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.

3.3.3.3 Carotid ultrasound

Systematic use of intima-media thickness (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 CVD events, even in the intermediate-risk group.[121]

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.[122] Although the evidence is less extensive than it is for CAC, carotid artery plaque assessment using ultrasonography probably also reclassifies CVD risk,[104,122] and may be considered as a risk modifier in patients at intermediate risk when a CAC score is not feasible.

3.3.3.4 Arterial stiffness

Arterial stiffness is commonly measured using either aortic pulse wave velocity or arterial augmentation index. Studies suggest that arterial stiffness predicts future CVD risk and improves risk classification.[123] However, measurement difficulties and substantial publication bias[106] argue against widespread use.

3.3.3.5 Ankle brachial index

Estimates are that 12–27% of middle-aged individuals have an ankle brachial index (ABI) <0.9, around 50–89% of whom do not have typical claudication.[124] An individual patient data meta-analysis concluded that the reclassification potential of ABI was limited, perhaps with the exception of women at intermediate risk.[125]

3.3.3.6 Echocardiography

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

3.3.4.Frailty

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 for unfavourable outcomes, including both high CV and non-CV morbidity and mortality.[126,127]

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 can 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 CVD events).[126,127] 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.[126,127] Most of the tools relate to frail features, including slowness, weakness, low physical activity (PA), exhaustion, and shrinking (e.g. Fried scale, Short Physical Performance Battery, Rockwood Clinical Frailty Scale, handgrip strength, gait speed).[126–129] Frailty assessment is important at each stage of an ASCVD trajectory. During an acute CVD 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 CVD risk. The impact of frailty on CVD 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 HF,[126–130] with frailty itself rather than classical CVD risk factors predicting both all-cause and CVD mortality in the very old.[130,131] Importantly, the ability of frailty measures to improve CVD risk prediction has not been formally assessed. Hence, we do not recommend that frailty measures are integrated into formal CVD 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.[126,127,132] 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.[126,127]

3.3.5. Family history

Family history of premature CVD is a simple indicator of CVD risk, reflecting the genetic and environment interplay.[133] In the few studies that simultaneously assessed the effects of family history and genetics, family history remained significantly associated with CVD after adjusting for genetic scores.[134,135] However, family history only marginally improves the prediction of CVD risk beyond conventional ASCVD risk factors.[136–141] Possible explanations are the varying definitions

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of family history applied and that conventional ASCVD risk factors largely explain the impact of family history.

A family history of premature CVD is simple, inexpensive information that can trigger comprehensive risk assessment in individuals with a family history of premature CVD.[136]

3.3.6. Genetics

The aetiology of ASCVD has a genetic component, but this information is not currently used in preventive approaches.[142] Advances on polygenic risk scores for risk stratification could increase the use of genetics in prevention.[143–145] 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 polygenic risk scores.[146] Polygenic risk scoring has shown some potential to improve ASCVD risk prediction for primary prevention,[147–149] but the incremental prediction accuracy is relatively modest and needs further evaluation in both men and women.[150,151] Additional evidence is also needed to evaluate the clinical utility of polygenic risk scores in other clinical settings, such as in patients with pre-existing ASCVD.[152]

3.3.7. Socioeconomic determinants

Low socioeconomic status and work stress are independently associated with ASCVD development and prognosis in both sexes.[153,154] The strongest association has been found between low income and CVD mortality, with a RR of 1.76 [95% confidence interval (CI) 1.45–2.14].[155] 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.[156]

3.3.8. Environmental exposure

Environmental exposures with CVD 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 2.5–10 μm in diameter, to fine (<2.5 μm; $PM_{2.5}$), and ultrafine (<0.1 μm)] and gaseous pollutants (e.g. ozone, nitrogen dioxide, volatile organic compounds, carbon monoxide, sulphur dioxide), produced primarily by combustion of fossil fuels. Soil and water pollutions are also CVD risk modifiers; increased exposure to lead, arsenic, and cadmium is associated with multiple CVD outcomes including hypertension, coronary heart disease (CHD), stroke, and CVD mortality.[157] 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.[158] A recent model estimated that loss of life expectancy due to ambient air pollution is similar to, if not exceeding, that due to tobacco smoking, and accounts for a global excess mortality estimated at 8.8 million/year.[159]

The short-term attributable effects on mortality are linked primarily to exposure to PM, nitrogen dioxide, and ozone, with an average 1.0% increase of all-cause mortality for an increment of 10 $\mu g/m^3$ in exposure to $PM_{2.5}$; the long-term effects are associated mainly with $PM_{2.5}$. The evidence linking exposure to PM and CVD 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.[38,160,161] As 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 CVD may be encouraged to try to avoid long-term exposure to regions with high air pollution.	IIb	C
In regions where people have long-term exposure to high levels of air pollution, (opportunistic) CVD risk screening programmes may be considered.	IIb	C

CVD = cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.

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3.3.9. Biomarkers in blood or urine

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,[2] we recommended against the routine use of biomarkers because most do not improve risk prediction, and publication bias seriously distorts the evidence.[106,162] New studies confirm that C-reactive protein has limited additional value.[103] There is renewed interest in lipoprotein(a), but it too provides limited additional value in terms of reclassification potential.[163,164] Cardiac biomarkers are promising,[165,166] but further work is needed.

3.3.10. Body composition

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 the elderly and the 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.[167,168 169] However, this evidence should be interpreted with caution as reverse causality and other biases may be operating.[45]

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3.3.10.1 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 6*). 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'.[170]

3.3.10.2 Risk reclassification

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

Recommendations for cardiovascular disease assessment in specific clinical conditions

Clinical condition	Recommendations	Class[a]	Level[b]
CKD	In all CKD patients, with or without DM, appropriate screening for ASCVD and kidney disease progression, including monitoring changes in albuminuria is recommended.[172]	I	C
Cancer	It is recommended to monitor cardiac dysfunction using imaging techniques and circulating biomarkers before, periodically during, and after cancer treatment.[173]	I	B
	Cardioprotection in high-risk patients (those receiving high cumulative doses or combined radiotherapy) receiving anthracycline chemotherapy may be considered for prevention of LV dysfunction.[174,175]	IIb	B
	Screening for ASCVD risk factors and optimization of the CVD 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.[176]	IIb	B
	Multiplication of calculated total CVD risk by a factor of 1.5 should be considered in adults with rheumatoid arthritis.[177,178]	IIa	B
Migraine	Presence of migraine with aura should be considered in CVD risk assessment.[179–181]	IIa	B
	Avoidance of combined hormonal contraceptives may be considered in women with migraine with aura.[182,183]	IIb	B
Sleep disorders and OSA	In patients with ASCVD, 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.[184–187]	IIa	B
	In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.[188–191]	IIa	B
	In women with a history of premature or stillbirth, periodic screening for hypertension and DM may be considered.[192,193]	IIb	B
	Assessment of CVD risk should be considered in men with ED.	IIa	C

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ED = erectile dysfunction; LV = left ventricular; OSA = obstructive sleep apnoea.
[a]Class of recommendation.
[b]Level of evidence.

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3.3.10.3 Assess risk factors and cardiovascular disease risk in persons with obesity

Comprehensive CVD 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)[171] and the development of type 2 DM, CVD events, as well as HF and AF.

3.4. Clinical conditions

Individual calculated risks of CVD, 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 CVD risk. These clinical conditions often increase the likelihood of CVD, or are associated with poorer clinical prognosis. The current section 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.

3.4.1. Chronic kidney disease

Worldwide, the total number of individuals with chronic kidney disease (CKD) who are not treated with kidney replacement therapy was approximately 850 million in 2017.[194] This number accounts to a prevalence of 10 - 12% among men and women. CKD is the third fastest growing cause of death globally.[195]

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 DM, are albuminuria [albumin-to-creatinine ratio (ACR) >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 (Chronic Kidney Disease Epidemiology) Collaboration 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/1.73 m^2 is classified as having CKD stage 3a, which represents an advanced kidney function impairment.[172]

Among persons with CKD, CVD is the leading cause of morbidity and death.[196] Even after adjustment for known CAD risk factors, including DM and hypertension, mortality risk progressively increases with worsening CKD.[197] As GFR declines below approximately 60 - 75 mL/min/1.73 m^2, the probability of developing CAD increases linearly,[198] 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 CVD risk. Among persons with CKD, there is a high prevalence of traditional CAD risk factors, such as DM and hypertension. The use of CAC score to risk stratify patients with CKD might be a promising tool.[199–203] Furthermore, persons with CKD are also exposed to other non-traditional ASCVD 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.[204]

3.4.2. Atrial fibrillation

Atrial fibrillation (AF) appears to be associated with an increased risk of death and of CVD and kidney disease.[205] Furthermore, AF appears to be a stronger risk factor for CVD in women than in men.[206]

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 searching for undiagnosed AF, as well as lower CV death.[207] The age-adjusted incidence, prevalence, and lifetime risk of AF are lower in women vs. men and in non-white vs. white cohorts.[208,209] The lifetime AF risk estimate is now 1 in 3 individuals of European ancestry at an index age of 55 years.[210] ASCVD risk factor burden and comorbidities, including lifestyle factors, and age significantly affect the lifetime risk for AF development.[211–213] The observed effect of clinical ASCVD risk factor burden and multiple comorbidities 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% in those with borderline and elevated clinical risk factors, respectively[214]) suggests that early intervention and control of modifiable ASCVD risk factors 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 9*).[215] 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.[216] However, studies addressing isolated management of specific conditions alone (e.g. hypertension) yielded inconsistent findings.[217]

The overall annual risk of ischaemic stroke in patients with AF is 5%, but varies considerably according to comorbidities.[215] Cardioembolic strokes associated with AF are usually more severe, and often recurrent.[218] Furthermore, AF appears to be a stronger predictor of stroke in women than in men.[215] AF is also associated with impaired cognitive function, ranging from mild cognitive impairment to dementia.[219] AF is independently associated with a two-fold increased risk of all-cause mortality in women and a 1.5-fold increased risk in men.[220] 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%.[221] 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.

Regarding PA, both sedentary lifestyles and very high levels of PA 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

Heart failure (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,[222] and HF with preserved ejection fraction (HFpEF)] increases the risk of urgent CV hospitalizations (including hospitalizations due to HF worsening) and CV and all-cause deaths.

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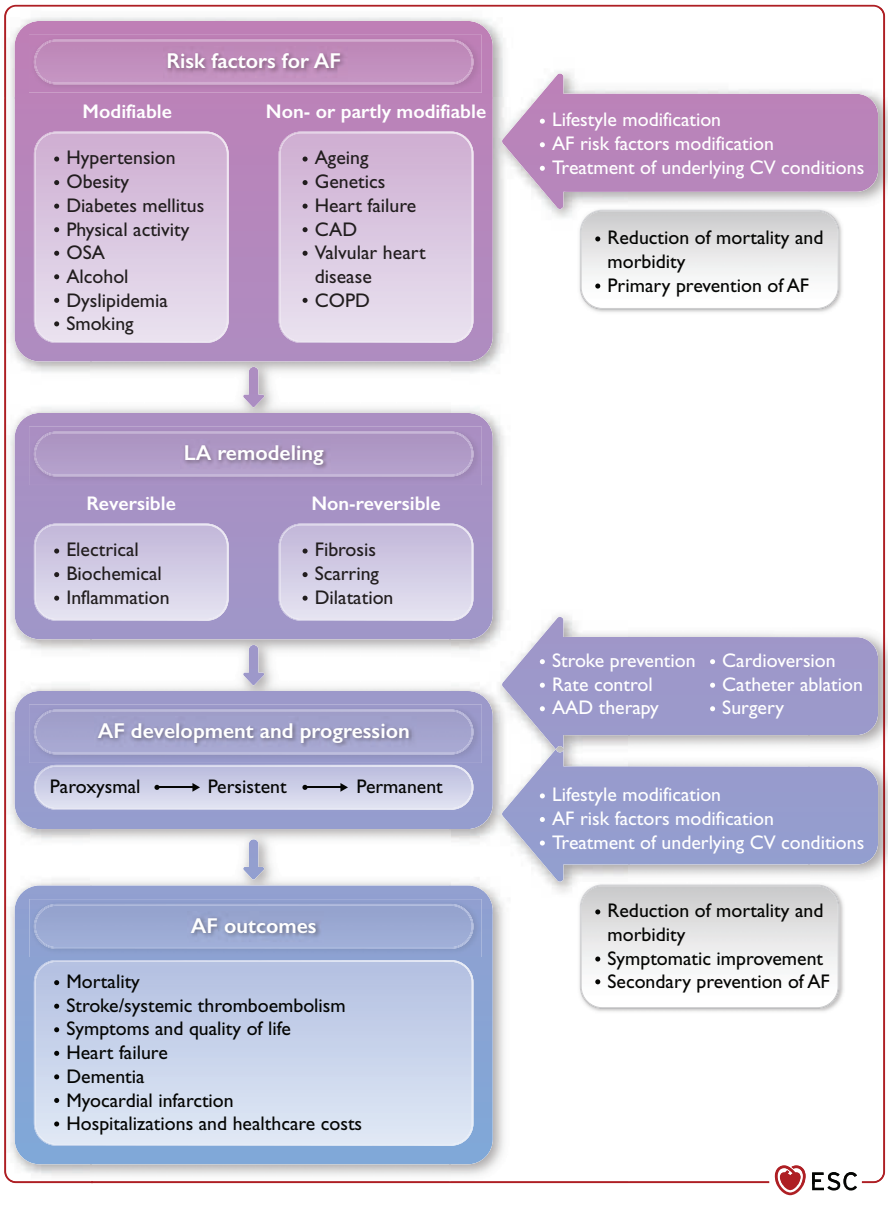

Figure 9 The role of risk factors and comorbidities in atrial fibrillation.[215] AF = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; DM = diabetes mellitus; HF = heart failure; OSA = obstructive sleep apnoea.

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.[223]

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*).

3.4.4. Cancer

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 CVD as well as cancer risk. Moreover, the rates of the extent of CVD risk depend on both the CVD toxicity of treatments and patient-related factors. Owing to recent improvements in clinical outcomes for many patients with cancer, CVD mortality may ultimately exceed those from most forms of cancer recurrence.[224,225]

The rapidly expanding variety of novel anticancer drugs/adjuvant therapies has demonstrated a wide range of both early and late CVD side-effects, including cardiomyopathy, LV dysfunction, HF, hypertension, CAD, arrhythmias, and other injuries. Therefore, effective strategies for the prediction and prevention of CVD 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

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administration of other cardiotoxic drugs, and patient factors (which include, amongst other factors, younger age, traditional risk factors, and history of heart disease).[226,227] Furthermore, radio- and chemotherapy may exert direct vascular effects and increase atherosclerosis-related CVD outcomes.[227,228]

3.4.4.1 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 (such as cardiac troponins and natriuretic peptides) is currently recommended.[173,229] Measures of myocardial strain, particularly systolic global longitudinal strain, may precede a significant decline in LVEF.[230–233]

3.4.4.2 Prevention of cardiotoxicity and cardiovascular risk factors

RCTs of preventive therapy with renin-angiotensin-aldosterone system (RAAS) inhibitors and/or beta-blockers after trastuzumab or anthracyclines have reported contradictory results.[230,234,235] 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.[236] A study showed a 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 ASCVD risk factors.[237] Therefore, aggressive management of ASCVD risk factors in this population is recommended.

3.4.5. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (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 recognized and thoroughly investigated as a CVD comorbidity, its role as an ASCVD risk factor is not well established. Nevertheless, COPD patients have a two- to three- fold increased risk of CVD 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 CVD, stroke, and HF.[238,239] CVD also runs undiagnosed; less than one-third of COPD patients with electrocardiographic (ECG) evidence of myocardial infarction are diagnosed with CVD.[240] CVD mortality increases by 28%, and the frequency of non-fatal coronary events by 20%, for every 10% decrease in the forced expiratory volume in 1 second (FEV1).[241] Acute COPD exacerbations, mainly due to infections, are frequent and are responsible for a four-fold increase of CVD events.[242] The risk of both myocardial infarction and ischaemic stroke is increased during the 3 months after an acute exacerbation.[243]

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.[244] Metabolic syndrome and reduced PA is present in 34% of COPD patients, with its most prevalent components being hypertension (56%), abdominal obesity (39%), and hyperglycaemia (44%).[245] CVD 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.[246] Systemic inflammation is prominent in COPD, with circulating biomarkers in high concentrations and associated with increased mortality.[247] Troponin is elevated during an acute exacerbation of COPD, and 10% of hospitalized patients meet the definition of acute myocardial infarction (AMI).[248] B-natriuretic peptide level, if elevated, increases the mortality risk.[249]

Systemic inflammation and oxidative stress caused by COPD promote vascular remodelling, stiffness, and atherosclerosis, and induce a 'procoagulant' state that affects all vasculature types.[250] 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 seven-fold higher following an acute exacerbation.[251] PAD is present in about 9% of COPD patients,[252] who have an almost doubled risk of developing PAD,[253] as well as an increased prevalence of carotid plaques related to the disease severity.[254] Finally, COPD is positively associated with abdominal aortic aneurysm, regardless of smoking status.[255]

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.[256] AF is frequent, directly associated with FEV1, usually triggered by acute exacerbations of COPD, and an independent predictor of in-hospital COPD mortality.[257,258] COPD is also a risk factor for ventricular tachycardia independent of LVEF,[259] and for sudden cardiac death independent of CVD risk profile.[260]

Unrecognized ventricular dysfunction is common in COPD,[261] although HF is 3.8 times more common in COPD patients than in controls.[262] Patients with frequent acute exacerbations have a high frequency of diastolic dysfunction; HFpEF risk is higher because of a high prevalence of hypertension and DM.[263]

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 medications (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.[264]

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3.4.6. Inflammatory conditions

Inflammatory conditions increase CVD risk both acutely and over time. The best evidence for chronic inflammation increasing CVD risk is available for rheumatoid arthritis, which increases CVD risk by approximately 50% beyond established risk factors.[176] Hence, a low threshold for assessment of total CVD risk is appropriate in adults with rheumatoid arthritis, and one should consider increasing the risk estimate based on the level of disease activity.[176] There is also evidence for an approximately 20% increased CVD risk in patients with active inflammatory bowel disease.[265]

In other chronic inflammatory conditions, such as psoriasis[177] and ankylosing spondylitis,[178] CVD 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 CVD 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, CVD 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.

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

Infection with human immunodeficiency virus (HIV) is associated with a 19% increased risk of LEAD and CAD beyond that explained by traditional atherosclerotic risk factors.[266,267] However, for those with sustained CD4 cell counts <200 cells/mm^3, the risk of incident LEAD events is nearly two-fold 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.[268]

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.[269] Preventing influenza, particularly by means of vaccination, could prevent influenza-triggered AMI.[270]

Studies have linked periodontal disease to both atherosclerosis and CVD,[271–273] and serological studies have linked elevated antibody titres of periodontal bacteria to atherosclerotic disease.[274] Nevertheless, if active treatment or prevention of periodontitis improves, clinical prognosis requires further studies despite preliminary evidence.[275–277]

3.4.8. Migraine

Migraine is a highly prevalent condition affecting around 15% of the general population.[278] 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 two-fold increased risk of ischaemic stroke and a 1.5-fold increase in the risk of cardiac ischaemic disease.[179–181,279,280] The associations are more evident for migraine with aura.[179,180,280] Given the young mean age of 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.[281]

Several lines of evidence also indicate that the vascular risk of subjects with migraine may be magnified by cigarette smoking[182] and by the use of combined hormonal contraceptives.[183,281–283] Contraception using combined hormonal contraceptives should therefore be avoided in women with migraine.[282,283] 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.

3.4.9.Sleep disorders and obstructive sleep apnoea

Sleep disturbances or abnormal sleep durations are associated with increased CVD risk.[284–286] Regarding sleep duration, 7 h seems to be optimal for CV health.[287]

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, and 7.1% for sleep-related breathing disorder [e.g. obstructive sleep apnoea (OSA)].[288] All sleep disturbances are strongly associated with mental disorders and share hyperarousal as an underlying mechanism.[289,290]

The most important sleep-related breathing disorder is OSA, which is characterized by repetitive episodes of apnoea, each exceeding 10 seconds. Despite the strong associations of OSA with CVD, including hypertension, stroke, HF, CAD, and AF, treatment of OSA by positive airway pressure (PAP) has failed to improve hard CV outcomes in patients with established CVD.[291–293] Therefore, interventions that include behaviour change (reduction of obesity, alcohol abstinence), sleep hygiene, and stress reduction in addition to PAP are needed.[290,294] Regarding hypertension and OSA, there are modest effects of PAP on BP levels, but only in patients with ABPM-confirmed resistant hypertension who use PAP for more than 5.8 h/night.[295]

3.4.10. Mental disorders

The 12-month prevalence of mental disorders or mental health disorders in the general European population is between 27% and 38% depending on sources and definitions.[296] 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 sexes.[297–300] The risk increases with the severity of the mental disturbance and vigilance for (often non-specific) symptoms is crucial.[301] The onset of CVD is associated with an approximately 2–3-fold increased risk of mental disorders compared to a healthy population.[115,302] 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.[100,108,303,304] The onset of CVD increases the risk of committing suicide.[305] In this context, awareness of anxiety and depression symptoms should be increased.

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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,[113] but also by direct effects of the amygdala-based fear-defence system and other direct pathophysiological pathways.[303] Abuse of psychostimulants (e.g. cocaine) is a powerful trigger of myocardial ischaemia.[306] 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).[100] Barriers on the part of healthcare providers are stigmatizing attitudes, insufficient mental health literacy, and lack of confidence in mental healthcare.[307–309] Although patients with mental disorders have an increased CVD risk, they receive a lower rate of recognition and treatment of traditional ASCVD risk factors.[310] Preliminary evidence suggests that taking mental disorders into account improves classical CVD risk models.[311,312]

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 CV risk factors may be greater in these populations, although epidemiology research is scarce.

3.4.11. Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (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[313] shows that after adjusting for established risk factors, the associations did not persist. Nevertheless, patients with NAFLD should have their CVD risk calculated, be screened for DM, and be recommended a healthy lifestyle with a reduction of alcohol intake.

3.4.12. Sex-specific conditions

3.4.12.1 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 CVD risk by a factor of 1.5–2.7 compared with all women,[185,186,314] while the RR of developing hypertension is 3[187] and DM is 2.[184,185] It has not been established whether the increased CVD risk after preeclampsia occurs independently 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 a history of hypertensive disorders of pregnancy seems necessary, despite their higher baseline risk.[315]

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).[193,314,316,317] Also, the risk for sustained or future hypertension is elevated (RRs vary, from 2.0 to 7.2 or even higher).[187,318] 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).[314,319] Both preterm (RR 1.6) and stillbirth (RR 1.5) have been associated with a moderate increase in risk of CVD.[316]

Finally, gestational DM 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 two-fold increased risk of CVD in the future.[188,320] Screening by fasting glucose or HbA1c may be preferable to oral glucose tolerance testing.[191,321]

3.4.12.2 Non-obstetric conditions

Polycystic ovary syndrome affects 5% of all women in their fertile years.[322,323] It has been associated with an increased risk of CVD.[314] The risk of developing hypertension is probably increased, but data are conflicting.[324] Polycystic ovary syndrome is associated with a higher risk of developing DM (RR 2–4),[189,190] 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.[314,325] Early menopause is associated with an increased risk of CVD (RR 1.5).[326–328] A linear inverse relationship between earlier menopause and CHD risk has been found, whereby each 1-year decrease in age at menopause portended a 2% increased risk of CHD.[329]

3.4.12.3 Erectile dysfunction

Erectile dysfunction (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 to 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 CVD 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 CVD 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]

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 *section 3.2.4*,

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Table 6 Treatment goals for different patient categories

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 5*) or SBP >160 mmHg	
<50 years	Stop smoking and lifestyle optimization 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 patients LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% reduction in very-high-risk patients
50 - 69 years	Stop smoking and lifestyle optimization 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 patients LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% reduction in very-high-risk patients
≥70 years	Stop smoking and lifestyle optimization SBP <140 mmHg if tolerated[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 *section 4*.
Patients with CKD	Stop smoking and lifestyle optimization 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 DM history	LDL-C <1.8 mmol/L (70 mg/dL) in high-risk patients and <1.4 mmol/L (55 mg/dL) in very-high risk patients (see *Table 4*)
Patients with FH	Stop smoking and lifestyle optimization 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 DM history	LDL-C <1.8 mmol/L (70 mg/dL) in high-risk patients and <1.4 mmol/L (55 mg/dL) in very-high risk patients (see *Table 4*)
People with type 2 DM		
Well-controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	Stop smoking and lifestyle optimization	
Without established ASCVD or severe TOD (see *Table 4* for definitions)	Stop smoking and lifestyle optimization 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 GLP-1RA
With established ASCVD and/or severe TOD (see *Table 4* 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 GLP-1RA if not already on *May additionally consider novel upcoming treatments: DAPT, dual pathway inhibition,a colchicine, icosapent ethyl*
Patients with established ASCVD	Stop smoking and lifestyle optimization 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: DAPT, dual pathway inhibition, colchicine, icosapent ethyl, etc.*

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DBP = diastolic blood pressure; DM = diabetes mellitus; EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolaemia; GLP-1RA = glucagon-like peptide-1receptor agonist; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure (office); SGLT2 = sodium-glucose cotransporter 2; TOD = target organ damage.

[a]Depending on 10-year (residual) risk and/or estimated lifetime benefit (see *Table 4* 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 FH, LDL-C targets are taken form the 2019 ESC/EAS Guidelines for the treatment of dyslipidaemias.[3]

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

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and benefits of individual treatment are the topic of this section. 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 not only 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, compared to men, have a low awareness of their CVD risk and the need for therapeutic interventions. This warrants efforts to improve awareness, risk assessment, and treatment in women.[52,346–351]

4.2. Optimizing cardiovascular risk management

4.2.1. Goals of clinicianpatient 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 for 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 (Open-ended questions, Affirmation, Reflective listening, and Summarizing) principle helps patients to present their perceptions, and clinicians to summarize. The SMART (Specific, Measurable, Achievable, Realistic, Timely) principle may help with 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 Europe 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, different domains of individual treatment are discussed. *Table 6* summarizes 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 3.2.3.1*. For details on treatment goals, how to achieve them, strengths of recommendations and levels of supporting evidence, please go to the relevant subsections.

4.3.Optimizing lifestyle

4.3.1. Physical activity and exercise

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 PA, 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 PA 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 PA participation.[380–382]	IIa	B

CV = cardiovascular; PA = physical activity.
[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

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Table 7 Classification of physical activity intensity and examples of absolute and relative intensity levels.

Absolute intensity			Relative intensity		
Intensity	**MET[a]**	**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 at moderate or brisk pace (4.1–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing, water aerobics	64–76	12–13	Breathing is faster but compatible with speaking full sentences
Vigorous	≥6	Race-walking, jogging, or running, cycling >15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (singles)	77–95	14–17	Breathing very hard, incompatible with carrying on a conversation comfortably

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%HR_{max} = percentage of measured or estimated maximum heart rate (220–age); MET = metabolic equivalent of task; 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 oxygen kg^{-1} min^{-1} VO_2.
Modified from [392]

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 a 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 can be 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.

4.3.1.2 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 min 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 an individual's maximum (peak) effort, e.g. percentage of cardiorespiratory fitness (%VO_2 max), percentage of maximum (peak) heart rate (%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 7*.

4.3.1.3 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 at a frequency of at 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 1 repetition maximum.[389] In addition, older adults are recommended to perform multicomponent PA that combines aerobic, muscle-strengthening, and balance exercises to prevent falls.[372]

4.3.1.4 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 activity bouts that interrupt sedentary behaviour are associated with health outcomes.[375,398,400]

4.3.2. Nutrition and alcohol

Recommendations for nutrition and alcohol

Recommendations	Class[a]	Level[b]
A healthy diet is recommended as a cornerstone of CVD prevention in all individuals.[401,402]	I	A

Continued

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It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.[403,404]	I	A
It is recommended to replace saturated with unsaturated fats to lower the risk of CVD.[405–409]	I	A
It is recommended to reduce salt intake to lower BP and risk of CVD.[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 g 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

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CVD = cardiovascular disease; BP = blood pressure.
[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 8* summarizes the 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]

4.3.2.1 Fatty acids

Risk of CHD is reduced when dietary saturated fats are replaced appropriately (*Figure 10*). 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]

Reducing saturated fatty acid intake to less than 10% of energy may have additional benefits.[405] However, the LDL-C-lowering effect of substituting polyunsaturated fatty acids (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 European Union (EU) Commission has set the upper limit to 2 g per 100 g of fat (April 2019) (https://ec.europa.eu/food/safety/labelling_nutrition/trans-fat-food_en).

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

4.3.2.2 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]

Table 8 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 g per week
Sugar-sweetened beverages, such as soft drinks and fruit juices, must be discouraged

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MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

The DASH (Dietary Approaches to Stop Hypertension) trial showed a dose–response relation between sodium reduction and BP reduction.[423] In a meta-analysis, salt reduction of 2.5 g/day 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/day), whereas the recommended maximum intake is 5 g/day. Optimal intake might be as low as ≈3 g/day. 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]

4.3.2.3 Fibre

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

4.3.2.4 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

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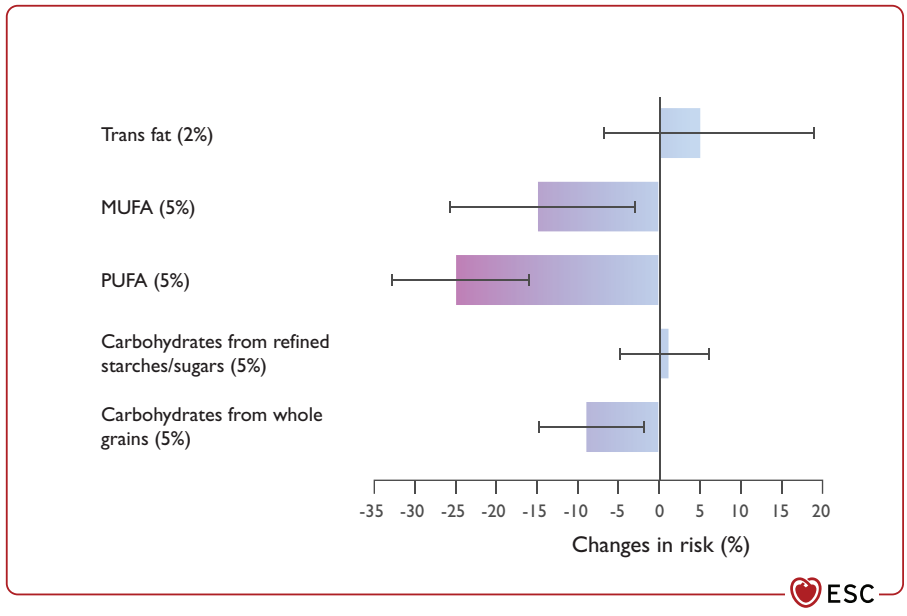

Figure 10 Estimated percentage change in risk of coronary heart disease associated with isocaloric substitutions of saturated fat for other types of fat or carbohydrates. Reproduced from Sacks *et al.*[409] MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

(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 (Vitamin D and Omega-3 Trial), ASCEND (A Study of Cardiovascular Events in Diabetes), and REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial).[444] 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 icosapent ethyl doses vs. mineral oil placebo) strengthened the results.[444] However, this is the only study that tested a high icosapent ethyl dose and questions have been raised regarding the choice of placebo. Very recently, STRENGTH (Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia) failed to demonstrate benefit of a combined eicosapentaenoic acid and docosahexaenoic acid 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 g per drink. This limit is similar for men and women.[413] 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, HF, and several less common CVD subtypes, it 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 vs. no alcohol against ASCVD, suggesting that the lowest risks for CVD 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.

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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 (European Prospective Investigation into Cancer and Nutrition) 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-C-raising cafestol and kahweol, and may be associated with an up to 25% increased risk of ASCVD mortality by consumption of nine or more drinks a day.[446] 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.[447]

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/day.[448] 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.[449]

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 includes 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 the 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]

4.3.3. Body weight and composition

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 CVD risk profile.[450,451]	I	A
While a range of diets are effective for weight loss, it is recommended that a healthy diet in regard to CVD risk is maintained over time.[452–454]	I	A
Bariatric surgery for obese high-risk individuals should be considered when lifestyle change does not result in maintained weight loss.[455]	IIa	B

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CVD = cardiovascular disease; BP = blood pressure; DM = diabetes mellitus.
[a]Class of recommendation.
[b]Level of evidence.

4.3.3.1 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% from baseline has salutary effects on risk factors including BP, lipids, and glycaemic control,[450,451] as well as on premature all-cause mortality.[456] 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.

4.3.3.2 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[457,458] and hypocaloric Mediterranean diets,[458,459] 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.[452–454] By 12 months, the effects tend to diminish.[453] Benefits of the Mediterranean diet, however, tend to persist. The quality of nutrients in a diet, for example substituting unsaturated for saturated fats (see *section 4.3.2.1*) and including fibre-rich carbohydrates[460] 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 DM.[461] 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.[462]

Intermittent fasting diets produce equivalent weight loss to continuous energy restriction when matched for energy intake.[463]

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, although

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sometimes at the expense of side-effects. Meta-analysis of medication-assisted weight loss found favourable effects on BP, glycaemic control, and ASCVD mortality.[464]

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.[455]

4.4. Mental healthcare and psychosocial interventions

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 drug treatment.[3,465]	I	C
In ASCVD patients with mental disorders, evidence-based mental healthcare and interdisciplinary cooperation are recommended.[100,113,466]	I	B
ASCVD patients with stress should be considered for referral to psychotherapeutic stress management to improve CV outcomes and reduce stress symptoms.[467–469]	IIa	B
Patients with CHD and moderate-to-severe major depression should be considered for antidepressive treatment with an SSRI.[470,471]	IIa	B
In patients with HF and major depression, SSRIs, SNRIs, and tricyclic antidepressants are not recommended.[472,473 c]	III	B

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ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CV = cardiovascular; HF = heart failure; SNRI = 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 *section 2.1*.

Treatment of an unhealthy lifestyle will reduce CVD risk as well as improve mental health. Smoking cessation, for instance, has a positive effect on depression outcomes,[474,475] as do exercise therapy[113,476] and healthy dietary practices.[477] Evidence-based interventions for smoking cessation, and improving PA and diet, are considered useful and applicable for persons with mental disorders.[465,478–480]

Mental disorders are associated with an increased risk of CVD and a worse prognosis in patients with ASCVD, due to CVD events or other death causes, including suicide.[100,113,305] Mental-health treatments effectively reduce stress symptoms and improve quality of life. Several observational studies indicate that treatment or remission of depression reduces CVD risk.[113,481–484] Psychological interventions in patients with CHD may reduce cardiac mortality (RR 0.79) and alleviate psychological symptoms.[466] Psychotherapy focusing on stress management in ASCVD patients improves CVD outcomes. In SUPRIM (Secondary Prevention in Uppsala Primary Health Care project), patients in the intervention group had a 41% lower rate of fatal and non-fatal first recurrent ASCVD events [hazard ratio (HR 0.59)] and fewer recurrent AMIs (HR 0.55).[467] In SWITCHD (Stockholm Women's Intervention Trial for Coronary Heart Disease), the intervention yielded a substantial reduction in all-cause mortality (OR 0.33).[468] A recent RCT reported that cardiac rehabilitation (CR) enhanced by stress management produced significant reductions in ASCVD events compared with standard CR alone (HR 0.49).[469] Concerning psychopharmacotherapy of patients with CHD and depression, selective serotonin reuptake inhibitor (SSRI) treatment lowers rates of CHD readmission (risk ratio 0.63) and all-cause mortality (risk ratio 0.56).[470] 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 percutaneous coronary intervention (PCI) (HR 0.69).[471] Collaborative care for patients with CHD and depression has small beneficial effects on depression, but significantly reduces short-term major cardiac events.[485]

Concerning side-effects of psychopharmacological treatments, many psychiatric drugs are associated with an increased risk of sudden cardiac death.[486] In patients with HF, antidepressants are associated with increased risk of cardiac and all-cause mortality (HR 1.27; for details see supplementary material for *section 4.4*).[472] Therefore, ASCVD patients with complex mental disorders, and particularly those needing psychiatric drug treatment, require interdisciplinary cooperation.

4.5. Smoking intervention

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.[487,488]	I	A
In smokers, offering follow-up support, nicotine replacement therapy, varenicline, and bupropion individually or in combination should be considered.[489–494]	IIa	A
Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.[495]	I	B

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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.[487,488] Lifetime gains in CVD-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 years, gains of 3 - 5 years persist in men to age 65 and in women to age 75 years (*Figure 11*). Even in heavy smokers (≥20 cigarettes/day), cessation lowers CVD risk within 5 years, although it remains elevated beyond 5 years. Total health benefits will be even larger because of gain in non-CVD health.

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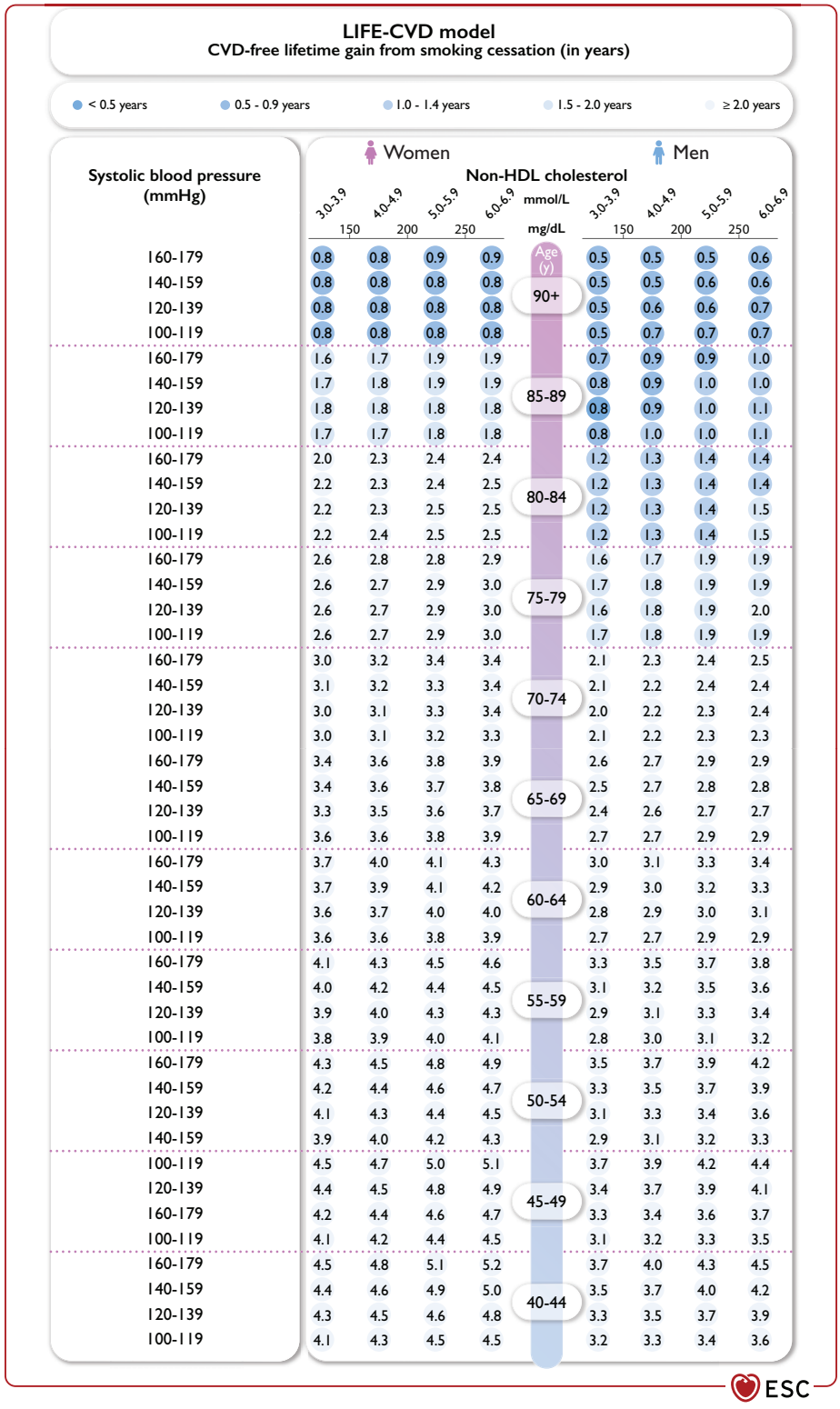

Figure 11 Lifetime atherosclerotic cardiovascular disease benefit from smoking cessation for apparently healthy persons, based on the following risk factors: age, sex, systolic blood pressure, and non-high-density lipoprotein-cholesterol. The model is currently validated for low- and moderate-risk countries. CVD = cardiovascular disease; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; SBP = systolic blood pressure. 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 CVD risk with the LIFE-CVD model[76] multiplied by the HR compared to sustained smoking (0.60) from a meta-analysis of studies on the CVD risk of smoking[496] and multiplied by the HR (0.73) for non-CVD competing mortality.[497] 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 https://u-prevent.com/.

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Table 9 '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

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UK = United Kingdom.

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 9*). A major impetus for cessation occurs at the time of diagnosis 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.

Smokers who quit may expect an average weight gain of 5 kg, but the health benefits of tobacco cessation outweigh risks from weight gain.[495] Persistent or reuptake of smoking is common in patients with CHD, in particular in those with severe depression and environmental exposures.[498] Mood-management therapies may improve outcomes in patients with current or past depression.[499]

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 nicotine-replacement therapy (NRT), bupropion, varenicline, and cytisine (not widely available).[489–491] All forms of NRT (chewing gum, transdermal nicotine patches, nasal spray, inhaler, sublingual tablets) are effective. Combination vs. single-form NRT and 4 mg vs. 2 mg gum can increase success.[492] NRT shows no adverse effects in patients with ASCVD,[493] but evidence of efficacy in this group is inconclusive.[494] 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.[494] The antidepressant, bupropion, aids long-term smoking cessation with similar efficacy to NRT.[490]

Varenicline 1 mg *b.i.d.* (twice a day) increases quitting rates more than two-fold compared with placebo.[491] The RR for abstinence vs. NRT was 1.25 and vs. 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.[500]

The main side-effect of varenicline is nausea, but this usually subsides. A causal link between varenicline and neuropsychiatric adverse events is unlikely.[501] Varenicline, bupropion, and NRT do not increase serious CV adverse event risks during or after treatment.[502]

Cytisine is effective for smoking cessation, but evidence to date is limited.[491]

4.5.2.1 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.[503–505] The long-term effects of e-cigarettes on CV and pulmonary health, however, require more research.[506] 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.[507] Despite being lower in toxicants than regular cigarettes, 'heat-not-burn' cigarettes do contain tobacco and should be discouraged.

4.6. Lipids

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/European Atherosclerosis Society (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 CVD 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.[22] A recent LDL-C target-driven RCT in patients after ischaemic stroke or transient ischaemic attack (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 CVD risk than those who had a target range of 2.3–2.8 mmol/L (90–110 mg/dL).[508] 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 vs. 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.[509,510] In patients with metabolic syndrome, DM, or hypertriglyceridaemia, calculated LDL-C from non-fasting samples should be interpreted with care.

Table 10 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

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

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4.6.1.2 Low-density lipoprotein cholesterol 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 only valid 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 formulae are available[511,512] or LDL-C can be measured directly.

4.6.1.3 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 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.[513] 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 10*.

4.6.1.4 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.[514] How apolipoprotein B levels correspond to commonly used LDL-C goals is shown in *Table 10*.

4.6.2. Defining lipid goals

4.6.2.1 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 CVD risk, as well as patients with established ASCVD and/or DM with consideration of CVD risk, treatment benefit, risk modifiers, comorbidities, and patient preferences.	I	C

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ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus.
[a]Recommendation from *section 3.2*.
[b]Class of recommendation.
[c]Level of evidence.

LDL-C goals are summarized in the recommendations below. As 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 (*section 3.2.3.1*), we propose a stepwise approach to treatment goals, also for LDL-C (*Figures 6–8*). 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/EAS dyslipidaemia Guidelines.[3] Evidence from glucose-lowering treatment studies indicates that stepwise treatment does not compromise goal attainment, and is associated with fewer side-effects and higher patient satisfaction.[66,67] 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, and frailty. *Figure 12* may support decision-making, as it shows the estimated lifetime benefits in years-free-of-CVD in relation to the total CVD risk profile, calibrated in low-to-moderate CVD risk countries.

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 prevention Guidelines.[2] This low goal was established based on data from recent Mendelian randomization studies,[80] meta-analyses from the Cholesterol Treatment Trialists' Collaboration,[21] RCTs such as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial),[515] and—more recently—proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor clinical outcome studies.[516–518] 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/EAS dyslipidaemia guidelines.[3] For primary prevention in very-high-risk patients, however, the class of recommendation is lower (Class I in the dyslipidaemia guidelines, 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 years), or between those with and without DM.[3]

4.6.2.2 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.

4.6.2.3 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 ASCVD patients. PA and other lifestyle factors, rather than drug treatment, remain important means of increasing HDL-C levels.

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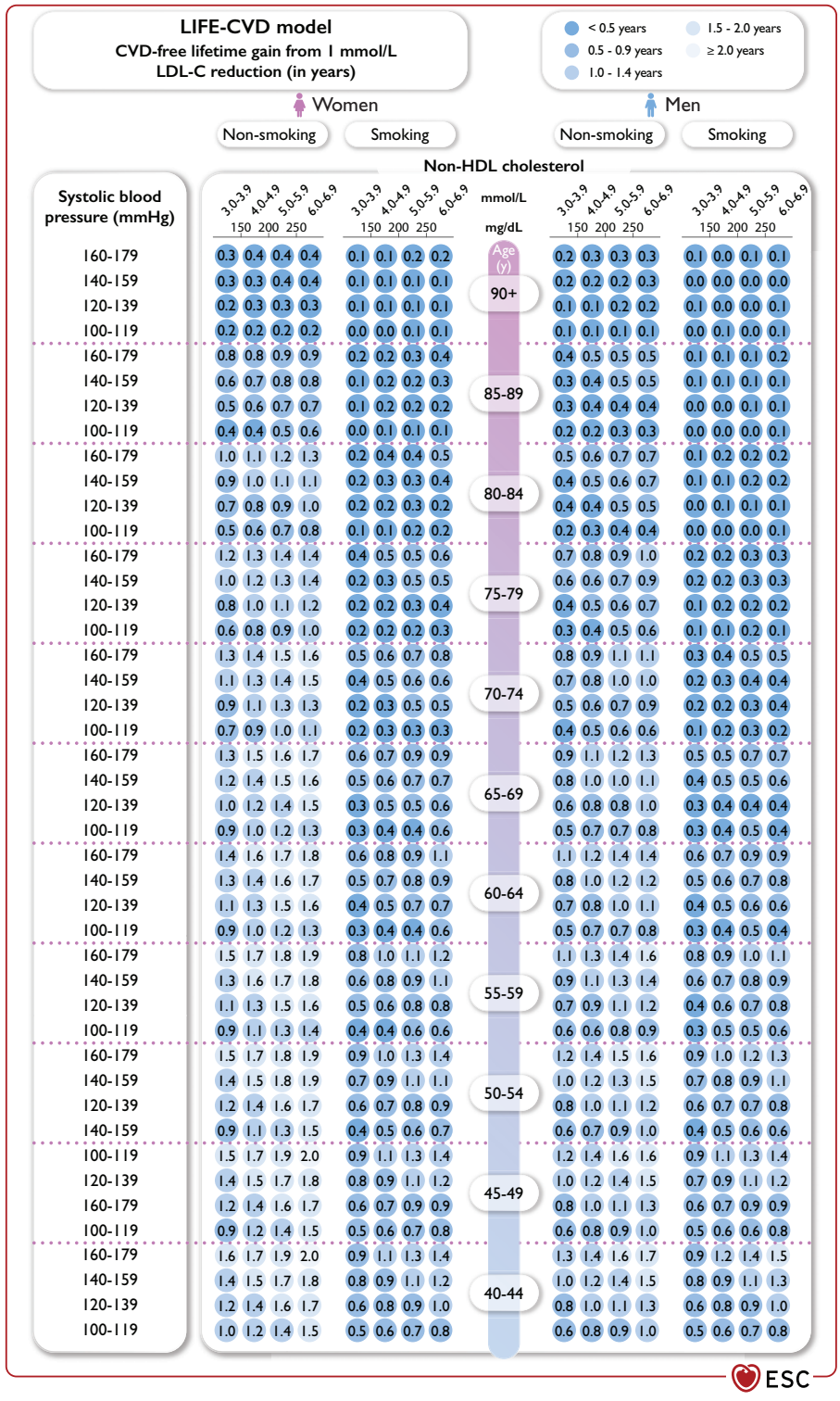

Figure 12 Average years-free-of-cardiovascular disease gained per 1 mmol/L (40 mg/dL) low-density lipoprotein cholesterol reduction in apparently healthy persons. The model is currently validated for low- and moderate-risk countries. Lifetime benefit of 1 mmol/L LDL-C lowering for apparently healthy persons, based on the following risk factors: age, sex, current smoking, SBP, and non-HDL-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, and so on. The lifetime benefit is calculated by estimating lifetime CVD risk with the LIFE-CVD model[76] 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 https://u-prevent.com/. CVD = cardiovascular disease; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; SBP = systolic blood pressure.

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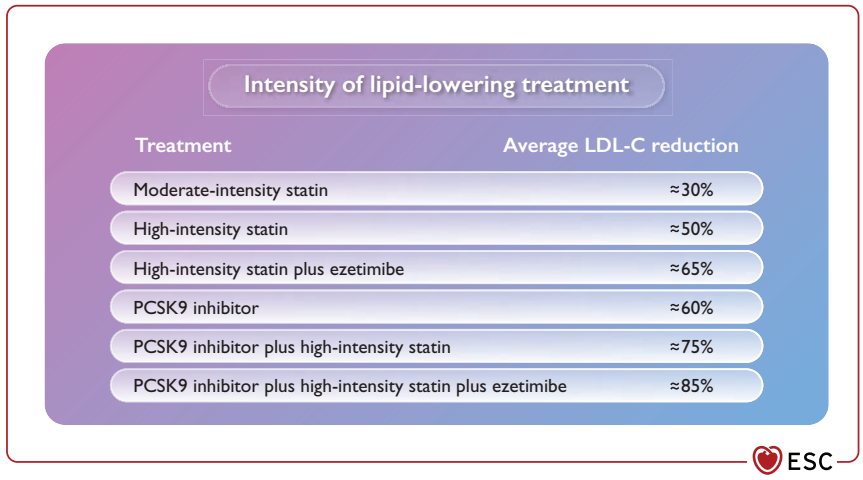

Figure 13 Expected low-density lipoprotein cholesterol reductions for combination therapies. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Adapted from Mach *et al.*[3]

4.6.3. Strategies to control dyslipidaemias

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 optimization is crucial in all patients with higher than optimal lipid levels.

4.6.3.1 Strategies to control low-density lipoprotein cholesterol

4.6.3.1.1. 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 indicates 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.[519] Moreover, the replacement of animal fats, including dairy fat, with vegetable sources of fats and PUFAs may decrease the risk of ASCVD.[407] More detail on lifestyle recommendations can be found earlier in this section.

4.6.3.1.2. 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. 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. Additionally, inclisiran, a new small interfering ribonucleic acid, has shown to reduce LDL-C by 50−55% when applied subcutaneously twice a year. These results were obtained either on top of statin or without other lipid-lowering therapies, and with almost no side-effects. Inclisiran has been approved in several European countries. Results from the ASCVD outcomes trial are expected for 2023.

The expected LDL-C reductions in response to therapy are shown in *Figure 13*, 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.

Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age (for recommendations for persons aged ≥70 years, see respective recommendations tables).

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.[21,520,521]	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.[21,22,522]	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.[21,22,522]	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 vs. baseline is recommended.[21,508,515−517,522]	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.[515]	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

Continued

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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.[516,517]	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.[515,523–525]	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.[523,524,526]	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

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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 stepwise approach to LDL-C targets is recommended; see *section 3.2.3.1* and *Figures 6 and 7*.
Adapted from [3]

4.6.3.1.3. 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]

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

The most frequent 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.[522] Increased blood sugar and 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.[527] Adhering to lifestyle changes when prescribed a statin should lessen the 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. As 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]

4.6.3.1.4. 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.[528] 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.

4.6.3.1.5. 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.[516,517] Among patients in whom statins cannot be prescribed, PCSK9 inhibition reduced LDL-C levels when administered in combination with ezetimibe.[529] Both alirocumab and evolocumab effectively lower LDL-C levels in patients who are at high or very high CVD risk, including those with DM, with a large reduction in future ASCVD events.[516,517] 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 that involve their use. Recommendations for the use of PCSK9 inhibitors are described in the Recommendations for pharmacological LDL-C lowering. Inclisiran is a long-acting hepatic PCSK9 synthesis inhibitor that also lowers LDL-C levels considerably.[530] Its effect on clinical outcomes remains to be established.

4.6.3.2 Strategies to control plasma triglycerides

Although CVD risk is increased when fasting triglycerides are >1.7 mmol/L (150 mg/dL),[531] the use of drugs to lower triglyceride 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/day; see *section 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 CVD event reduction is limited, and given the strong evidence favouring statins, routine use of these drugs in CVD prevention is not recommended.[3] To prevent pancreatitis, when

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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 patients with severe primary hypertriglyceridaemia, referral to a specialist must be considered.

An evidence-based approach to the use of lipid-lowering nutraceuticals could improve the quality of the treatment, including therapy adherence, and achievement of the LDL-C goal in clinical practice. However, it has to be clearly stressed that there are still no outcome studies proving that nutraceuticals can prevent CVD morbidity or mortality.[532]

4.6.4. Important groups

Recommendations for drug treatments of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	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.[534–536]	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/day) may be considered in combination with a statin.[84]	IIb	B

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CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from [3]

4.6.4.1 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]

4.6.4.2 Older patients (≥70 years)

Compared to the 2019 ESC/EAS dyslipidaemia guidelines,[3] we provide a single cut-off for identifying 'older persons' as those ≥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 level of evidence have been modified in 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.[537] Evidence from trials indicates that statins and other lipid-lowering drugs produce significant reductions in major vascular events irrespective of age.[538,539] 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 *section 3.2.3.3* and *Figure 12*). In case of renal function impairment or risk for drug interactions, the 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 (STAtin Therapy for Reducing Events in the Elderly) 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).

Recommendations	Class[a]	Level[b]
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.[538,539]	I	A
Initiation of statin treatment for primary prevention in older people aged ≥70 may be considered, if at high risk or above.[538,539]	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

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ASCVD = atherosclerotic cardiovascular disease.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from [3]

4.6.4.3 Diabetes mellitus

Lowering of LDL-C in patients with DM is consistently associated with lower CVD risk. Similar to prevention in apparently healthy individuals, we propose a stepwise approach to lipid control, dependent on risk, estimated lifetime benefit, comorbidities, and patient preferences (*Figure 8*). PCSK9 inhibitors can also be used in patients with DM not reaching their LDL-C targets with statins and/or ezetimibe.

Recommendations for the treatment of dyslipidaemias in diabetes mellitus.

Recommendations	Class[a]	Level[b]
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD[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.[21,22,522,540,541]	I	A

Continued

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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.[540,541]	I	A
Statin therapy may be considered in persons aged ≤40 years with type 1 or type 2 DM with evidence of TOD 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.[515,542]	IIa	B

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ASCVD = atherosclerotic cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; TOD = target organ damage.
[a]Class of recommendation.
[b]Level of evidence.
[c]Severe TOD in this specific context includes eGFR <45 mL/min/1.73 m^2; eGFR 46–79 mL/min/1.73 m^2 plus microalbuminuria; proteinuria; presence of microvascular disease in at least three different sites (e.g. albuminuria plus retinopathy plus neuropathy). See *Table 4* for details.
[d]A stepwise approach to LDL-C targets is recommended; see *section 3.2.3.1* and *Figure 8*.
Adapted from [3]

4.6.4.4 Chronic kidney disease

Patients with CKD are at high or very high risk of ASCVD, and have a characteristic 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.[543] 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).

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.[525,544,545]	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 who are free of ASCVD, commencing statin therapy is not recommended.[546,547]	III	A

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ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease.
[a]Class of recommendation.
[b]Level of evidence.
Adapted from [3]

Table 11 Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

Criteria (choose only one score per group, the highest applicable; diagnosis is based on the total number of points obtained)	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	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥8.5 mmol/L (326 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
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

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

4.6.4.5 Familial Hypercholesterolaemia

Patients who could have genetic dyslipidaemias, such as heterozygous FH, can be identified by extreme lipid abnormalities and/or family history (*Table 11*). An LDL-C >4.9 mmol/L (190 mg/dL) in therapy-naïve 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. Besides genetic testing (not always affordable), use of the Dutch Clinical Lipid Network criteria (*Table 11*) 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]

4.7. Blood pressure

Hypertension is one of the most important preventable causes of premature morbidity and mortality. It affects more than 150 million

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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)	I	C
or • Out-of-office BP measurement with ABPM and/or HBPM when feasible.	I	C
Assessment of HMOD		
To evaluate for the presence of HMOD, measurement of serum creatinine, eGFR, electrolytes, and ACR 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 DM.[548–551]	I	B
Thresholds for initiation of drug treatment of hypertension		
For grade 1 hypertension, treatment initiation based on absolute CVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.[552,553]	I	C
For patients with grade 2 hypertension or higher, drug treatment is recommended.[4,552]	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 comorbidities.[552,554]	I	A
In treated patients aged 18–69 years, it is recommended that SBP should ultimately be lowered to a target range of 120 - 130 mmHg in most patients.[552,554–556]	I	A
In treated patients aged ≥70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.[552,554,557]	I	A
In all treated patients, DBP is recommended to be lowered to <80 mmHg.[555,558,559]	I	A
Treatment of hypertension: lifestyle interventions		
Lifestyle interventions are recommended for people with high-normal BP 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).[560–565]	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).[566–569]	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 blocker with a CCB and a diuretic, preferably as a single-pill combination.[563,570,571]	I	A
It is recommended, if BP is not controlled by a three-drug combination, that 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.[555,572–574]	I	B
The combination of two RAS blockers is not recommended.[575,576]	III	A
Management of CVD risk in hypertensive patients		
Statin therapy is recommended for many patients with hypertension.[d]	*Section 4.6*	
Antiplatelet therapy is indicated for secondary prevention in patients with hypertension.[e]	*Section 4.9*	

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ACR = albumin-to-creatinine ratio; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CCB = calcium channel blocker; DBP = diastolic blood pressure; 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 4.3* for details.
[d]See *section 4.6* for details.
[e]See *section 4.9* for details.

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.[577] Despite extensive evidence for the effectiveness of BP-lowering treatments at reducing CVD risk and death, the detection, treatment, and control of BP in Europe and globally remains suboptimal.[578]

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/European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension.[4]

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4.7.1. Definition and classification of hypertension

BP is classified according to seated office BP (*Table 12*), with approximately corresponding values according to ABPM or home BP average values in *Table 13*.

4.7.2. Blood pressure measurement

4.7.2.1 Office blood pressure measurement

Office BP should be measured in standardized conditions using validated auscultatory or (semi)automatic devices, as described in *Table 14*.

4.7.2.2 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]

4.7.2.3 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 12*).[4]

4.7.2.4 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 12*). 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 15*.

4.7.3 Screening and diagnosis of hypertension

Ideally, all adults should be screened for the presence of hypertension,[578,579] 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 of hypertension (see *section 3.1*).

Table 12 Categories for conventionally measured seated office blood pressure[a]

Category	SBP (mmHg)		DBP (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.

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Table 13 Definitions of hypertension according to office, ambulatory, and home blood pressure

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.

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Table 14 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 may occur <1 min 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.

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Table 15 Indications for home blood pressure monitoring or ambulatory blood pressure monitoring

Conditions in which white-coat hypertension is more common, for example: ● Grade 1 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.

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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 14*).

4.7.3.1 White-coat and masked hypertension

White-coat hypertension refers to BP that is elevated in the office but is 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 16*. Alongside clinical examination, this is designed to:

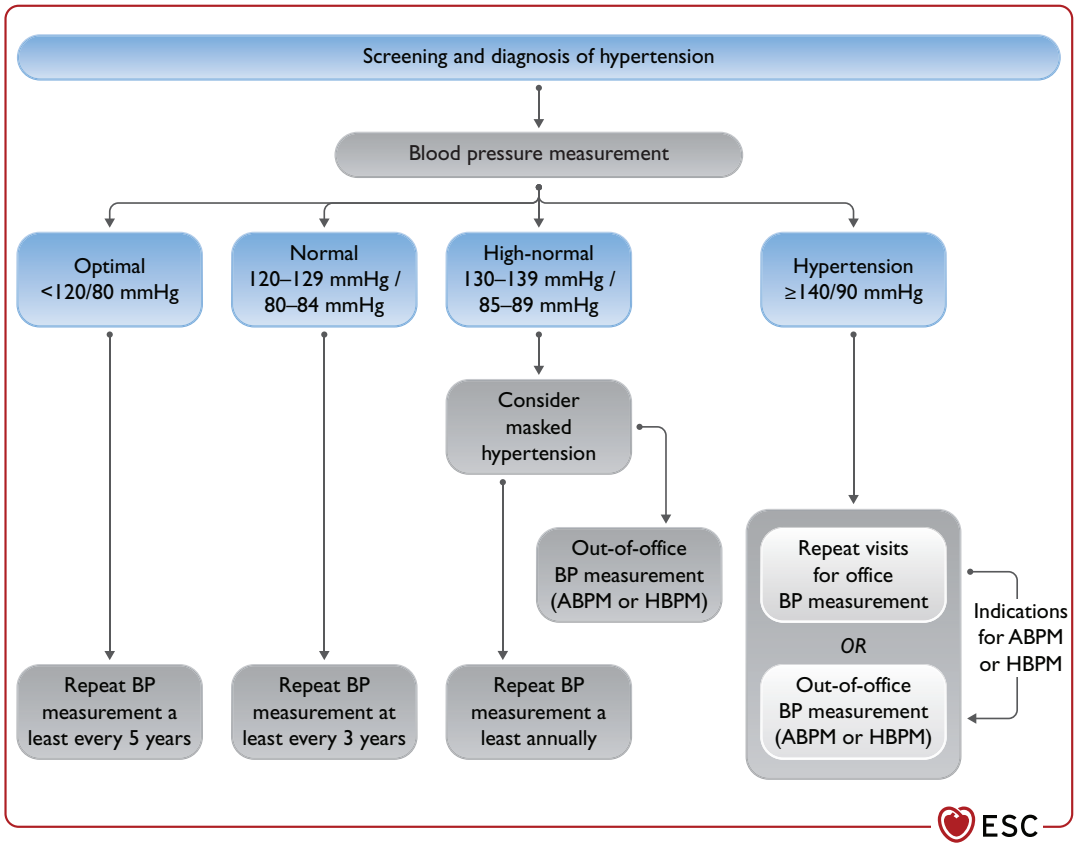

Figure 14 Screening and diagnosis of hypertension. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.

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Table 16 Routine tests for patients with hypertension

Routine tests
Haemoglobin and/or haematocrit
Fasting blood glucose and/or HbA1c
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, ACR
12-lead ECG

ACR = albumin-to-creatinine ratio; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

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- Assess risk factors for ASCVD (see *section 3.2*), or the presence of cardiac, vascular, or renal disease
- Detect evidence of HMOD, e.g. LV hypertrophy, renal disease, or retinopathy
- Consider potential secondary causes of hypertension, e.g. renovascular disease, hyperaldosteronism, or pheochromocytoma (see *Table 17*). Also, carefully evaluate substance abuse (e.g. cocaine), drugs that may increase BP (e.g. cyclosporine, sympathicomimetics), liquorice, etc. More detail on work-up of suspected secondary hypertension is provided elsewhere.[4]

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 DM. The routine measurement of other biomarkers and use of vascular imaging are not recommended.[548–551]

4.7.5. Treatment of hypertension

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

4.7.5.1 Lifestyle interventions to lower blood pressure and/or reduce cardiovascular risk

Lifestyle interventions are indicated for all patients with high-normal BP 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 is discussed extensively in *section 4.3*.

4.7.5.2 Initiation of drug treatment

Drug treatment decisions in CVD prevention are mostly based on absolute CVD risk, risk modifiers, comorbidities, estimated benefit of treatment, frailty, and patient preferences. The same is true for hypertension. Drug treatment of grade 1 hypertension (SBP 140 - 159 mmHg) has level A evidence for reducing CVD risk. In younger patients, however, the absolute 10-year CVD risk is often low, and lifetime benefit of treatment should be considered and communicated before instituting treatment (*Figure 6* and *section 3.2.3.6*). In many such cases, the absolute lifetime benefit per 10-mmHg reduction in SBP is at least moderate to high [*Figure 15* (lifetime benefit calibrated in low-to-moderate CVD risk countries]. Also, the presence of HMOD mandates treatment of grade 1 hypertension. For grade 2 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 the risk of HMOD resulting in other morbidities such as renal disease, haemorrhagic cerebrovascular disease, and HF.

Table 17 Patient characteristics that should raise the suspicion of secondary hypertension.

Characteristics
Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
Acute worsening of 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

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; OSA = obstructive sleep apnoea.
Adapted from [4]

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4.7.5.3 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[2] were too conservative, especially for older patients. In line with the stepwise approach (*section 3.2.3.1*), it is now recommended that the first step in all treated patients should achieve a treated SBP <140 mmHg and diastolic BP (DBP) <80 mmHg.[552,554] The recommended ultimate SBP treatment target range for younger patients (18–69 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.[552,554–556] The ultimate target SBP for patients aged ≥70 years is <140 mmHg and down to 130 mmHg if tolerated.[552,554,557,580] This change in the BP target range for older people compared with the 2016 ESC prevention guidelines[2] 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.[557,580] It also takes into account that the even lower SBP in the intensively treated group in SPRINT (Systolic Blood Pressure Intervention Trial) (mean 124 mmHg) probably reflects a conventional office SBP range of 130–139 mmHg.[555] It is recognized, 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

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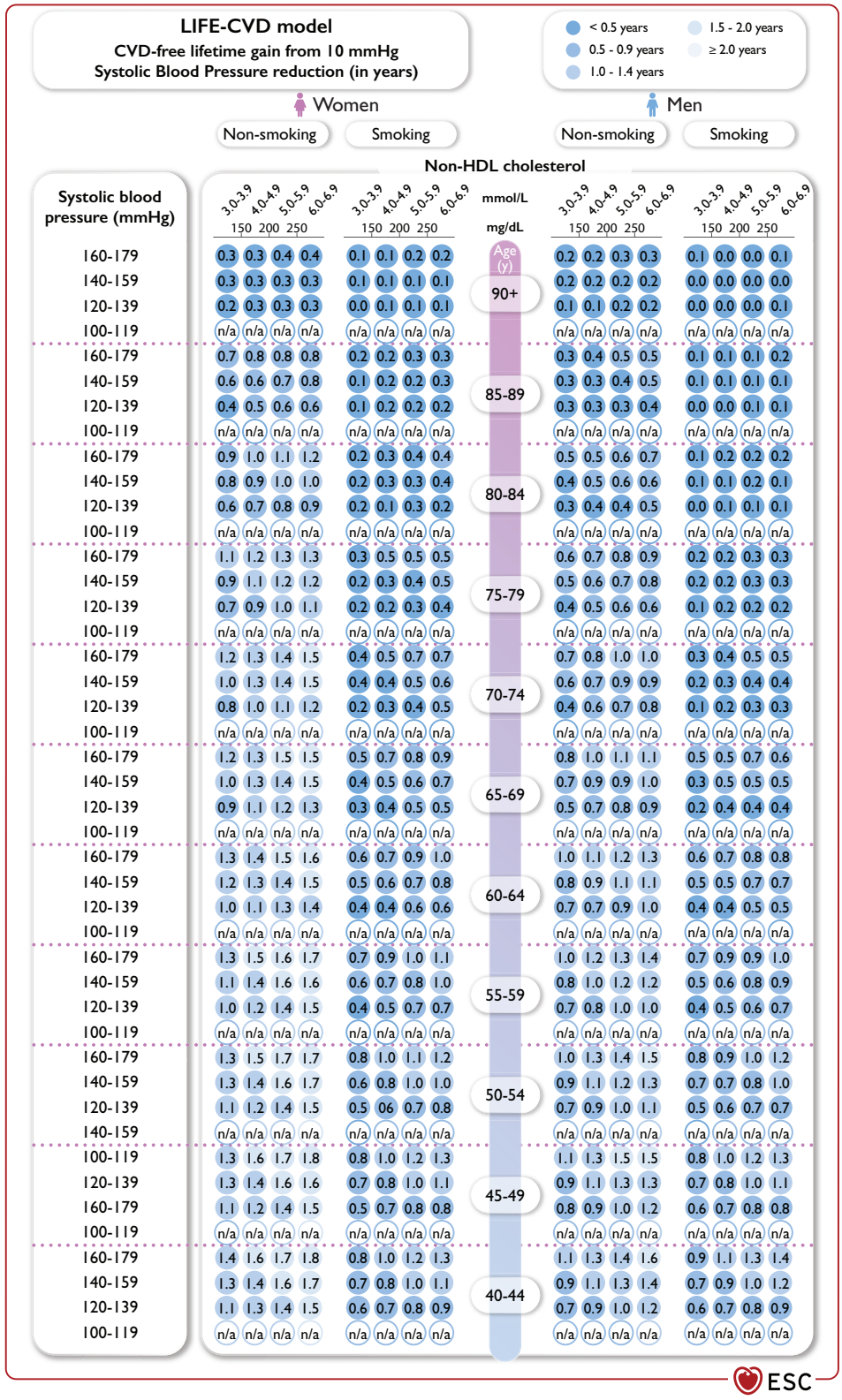

Figure 15 Lifetime benefit from lowering systolic blood pressure by 10 mmHg for apparently healthy persons, based on the following risk factors: age, sex, current smoking, systolic blood pressure, non-high-density lipoprotein cholesterol. The model is currently validated for low- and moderate-risk countries. 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 CVD 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 https://u-prevent.com/. BP = blood pressure; CVD = cardiovascular disease; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LIFE-CVD = LIFEtime-perspective CardioVascular Disease; N/A = not applicable; SBP = systolic blood pressure.

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Table 18 Recommended office blood pressure target ranges. The first step in all groups is a reduction to systolic blood pressure <140 mmHg. The subsequent optimal goals are listed below.

Age group	Office SBP treatment target ranges (mmHg)				
	Hypertension	+ DM	+ CKD	+ CAD	+ Stroke/TIA
18 – 69 years	120–130	120–130	<140–130	120–130	120–130
	Lower SBP acceptable if tolerated				
≥70 years	**<140 mmHg, down to 130 mmHg if tolerated**				
	Lower SBP acceptable if tolerated				
DBP treatment target (mmHg)	<80 for all treated patients				

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

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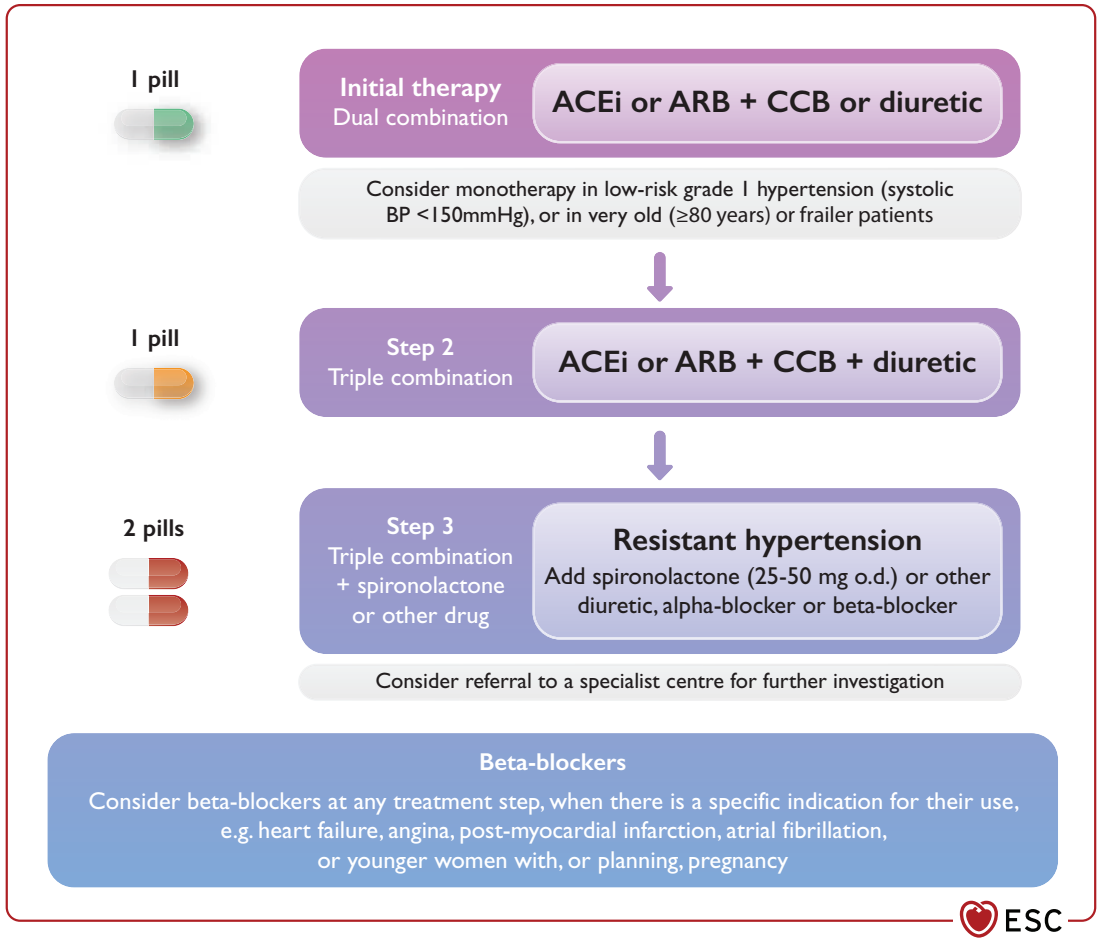

Figure 16 Core drug treatment strategy for hypertension. This algorithm is appropriate for most patients with hypertension-mediated organ damage, diabetes mellitus, cerebrovascular disease, and peripheral artery disease. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; HF = heart failure; *o.d.* = *omni die* (once a day).

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.[580]

Compared to previous ESC/ESH Hypertension Guidelines,[4] 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 18*.

4.7.5.3.1. Blood pressure targets according to ambulatory and home blood pressure monitoring. There are no outcome-based trials that have used ABPM or HBPM to guide treatment. Therefore,

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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]

4.7.5.4 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.[560–563,565,581] The only exceptions would be patients with a baseline BP close to the recommended target, who might achieve that target with a single drug, or very old (>80 years) or frail patients who may better tolerate a more gentle reduction of BP. Initial combination therapy, even low-dose combination therapy, is more effective at lowering BP than monotherapy,[560,561,565] and will reduce BP faster and reduce heterogeneity in response.[560,565] Moreover, initial combination therapy does not increase risk of adverse effects.[560–563,565] Initiating therapy with two drugs will also help overcome treatment inertia where patients remain on one drug long term despite inadequate BP control.[562]

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.[581] Single-pill combination therapy (if available) is the preferred strategy. This strategy will control BP in most patients.[560–565]

Recommended drug therapy and treatment algorithm: five major classes of BP-lowering drug therapy have shown benefit in reducing CV events; angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and thiazide or thiazide-like diuretics.[582] A recommended treatment algorithm based on best available evidence, pragmatic considerations (e.g. combination pill availability), and pathophysiological reasoning is shown in *Figure 16*.[4] 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.[566–569] 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.[563,570,571] Beta-blockers should be used when there is a specific indication (e.g. angina, post myocardial infarction, arrythmia, HFrEF, or as an alternative to an ACE inhibitor or ARB in women of child-bearing potential).[582] Combinations of an ACE inhibitor and an ARB are not recommended because of no added benefit on outcomes and increased risk of harm.[575,576]

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

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.[555,572] Potassium-binding drugs reduce the risk of hyperkalaemia.[573] When spironolactone is not tolerated, amiloride, alpha-blockers, beta-blockers, or centrally acting drugs, such as clonidine, have evidence supporting their use.[555,572,574] 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 for women of child-bearing potential or during 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 on 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.

4.8. Diabetes mellitus

Recommendations for the treatment of patients with 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.[583]	IIa	A
Lifestyle		
Lifestyle changes including smoking cessation, a low saturated fat, high-fibre diet, aerobic PA, and strength training are recommended.[584]	I	A
Reduction in energy intake is recommended to patients, to help achieve lower body weight or prevent or slow weight gain.[584]	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 DM remission and should be considered.[585,586]	IIa	A

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Glycaemia targets		
A target HbA1c for the reduction of CVD risk and microvascular complications of DM of <7.0% (53 mmol/mol) is recommended for the majority of adults with either type 1 or type 2 DM.[587,588]	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.[588]	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.[587,588]	IIa	B
Treatment of hyperglycaemia 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.[589]	I	B
In persons with type 2 DM with ASCVD, metformin should be considered, unless contraindications are present.[5,590–592]	IIa	B
Avoidance of hypoglycaemia and excessive weight gain should be considered.[559,588,593]	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.[590–592]	I	A
In patients with type 2 DM and TOD,[c] the use of an SGLT2 inhibitor or GLP-1RA with proven outcome benefits may be considered to reduce future CV and total mortality.[594–597]	IIb	B
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve ASCVD and/or cardiorenal outcomes.[598,599]	I	A
In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.[600,601]	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 CVD or cardiorenal outcomes from risk factor profiles.[602]	IIa	B

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ACR = albumin-to-creatinine ratio; ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; DIAL = Diabetes lifetime-perspective prediction; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated haemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; PA = physical activity; SGLT2 = sodium-glucose cotransporter 2; TOD = target organ damage.

[a]Class of recommendation.

[b]Level of evidence.

[c]See *Table 4* 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 and LDL-C targets is particularly important. More recently, trial evidence has shown that drugs in the sodium-glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist (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 ASCVD 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 4.3.2*.

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.[603] 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.[585] In those with prediabetes, other ASCVD risk factors should be assessed both before (to incentivize improvements) and after lifestyle changes have taken place.[604]

4.8.1.2 Glycaemic control

The UKPDS[587] established the importance of intensive glucose lowering with respect to CVD 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.[559,588,593] However, there were unexpected increases in total and ASCVD deaths in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial[559] and a similar trend in VADT (Veterans Affairs Diabetes Trial).[593] 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.[605,606] The meta-analyses suggested that CVD 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[607–610] in patients with DM and existing ASCVD or at high risk demonstrated non-inferiority (i.e. safety) but not superiority with respect to CVD risk.

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There was, however, an increase in the rate of hospitalization for HF with saxagliptin in the SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus Thrombolysis in Myocardial Infarction) trial.[608]

4.8.1.3 Newer diabetes mellitus drug classes: cardiovascular disease benefits

Recent trials from two classes of drugs (SGLT2 inhibitors and GLP-1RAs) have shown CVD benefits that appear independent of glycaemic control and, where examined, of baseline metformin use.[596,597,611] Their results have recently been systematically meta-analysed (*Supplementary Figures 1 – 4*).[590,591]

For SGLT2 inhibitors, three trials demonstrated the CV benefits of empagliflozin, canagliflozin, and dapagliflozin.[611–613] Major adverse CV events (MACE) were reduced modestly, by 14%, with no clear effect on stroke and an unclear effect on myocardial infarction.[590] However, reductions in incident HF hospitalization/CVD death by 24% and renal endpoints by 44% were seen.[590] 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. However, a more recent trial in people with type 2 DM and ASCVD showed ertugliflozin to be non-inferior to placebo with respect to MACE outcomes.[614] Whether the results represent a class effect is, therefore, not clear. Four further SGLT2 inhibitor trials demonstrated the benefit of canagliflozin[598] and dapagliflozin[599] in patients with CKD [with DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) showing similar benefits in people without DM], and dapagliflozin[600] and empagliflozin[601] 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 hospitalization) suggests that the benefits of SGLT2 inhibitors may relate more to cardiorenal haemodynamic effects than to atherosclerosis.[600] Other than genitourinary infections, rates of adverse events (including diabetic ketoacidosis) were generally low. One trial showed an excess of amputations and fractures,[612] but none of the other trials noted imbalances. Patients should be advised on the importance of genitourinary hygiene 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.[591] 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 SGLT2 inhibitor and GLP-1RA trials, subgroup analyses suggested that these benefits could be independent of metformin use.[594–597] Most trials were conducted in patients with existing ASCVD or, in the REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes) trial, with a significant proportion of patients at high risk for CVD.[615] Side-effects of this class mainly include 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 DM algorithms, but with some differences in interpretation.[602] Most DM guidelines, including those within the 2020 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report,[592] recommend that metformin should be used as first-line treatment, while the ESC Guidelines[5] recommended in 2019 that SGLT2 inhibitors and GLP-1RAs may be used without metformin in people with DM and CVD or at high risk of CVD, as reviewed.[602] A subset of the writing groups of the ADA/EASD consensus report and the ESC Guidelines[616] was convened as an expert panel. The expert panel emphasized the overall commonalities of approach and the need to ensure that people with type 2 DM, CVD, HF, or CKD are treated appropriately with an SGLT2 inhibitor or GLP-1RA. The panel concluded that this approach should be initiated independent of background therapy, glycaemic control, or individualized treatment goals.[616] The view of the ESC is that metformin should be considered, but is not mandatory first-line treatment in patients with ASCVD or evidence of TOD. Certainly, the initiation of metformin in such patients should not forego or delay the initiation of evidence-based SGLT2 inhibitors or GLP-1RAs. A risk score plus cost-effective analyses would be useful to determine which patients free from ASCVD or evidence of TOD may be recommended for these newer drugs. In all the above, there is no evidence of any sex 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 the drugs.

4.8.2. Type 1 diabetes mellitus

The DCCT (Diabetes Control and Complications Trial) 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.[617] 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.[617] 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 CVD risk.[618] 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.

4.9. Antithrombotic therapy

Recommendations for antithrombotic therapy

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for secondary prevention of CVD.[619]	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.[620]	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in patients with established ASCVD.[620,621]	IIb	A
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.[622,623]	I	A

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In patients with DM at high or very high CVD risk, low-dose aspirin may be considered for primary prevention in the absence of clear contraindications.[5,624,625]	IIb	A
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.[624,626–630]	III	A

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ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; 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 CVD risk reported a 12% reduction in ASCVD with aspirin but a significant increase in major bleeding.[619] CVD risk reduction and bleeding risks were similar in men and women.[631] More contemporary primary prevention trials reported no or little benefit in patients without ASCVD and a consistent increase in bleeding.[624,626,627] 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).[628] Conversely, aspirin was associated with a higher risk of major bleeding (RR 1.50), 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.[629,630] 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 CVD risk, the benefits outweigh the risks.[632,633] 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.[624] A meta-analysis of aspirin for primary prevention in DM found a number needed to treat of 95 to prevent one major adverse ischaemic event in 5 years.[625] Hence, as in patients without DM, aspirin may be considered if CVD risk is exceptionally high. Only one in four patients in the ASCEND study 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 CVD risk, further studies are needed. Until then, decisions in these high-risk persons should be made on a case-by-case basis, taking both ischaemic 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.[619] 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.[620] 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.[621] 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 *section 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.[634,635] Proton pump inhibitors that specifically inhibit CYP2C19 (omeprazole or esomeprazole) may reduce the pharmacodynamic response to clopidogrel. Although this interaction has not been shown to affect the risk of ischaemic events, coadministration of omeprazole or esomeprazole with clopidogrel is not recommended.[622]

4.10. Anti-inflammatory therapy

Recommendation for anti-inflammatory therapy

Recommendation	Class[a]	Level[b]
Low-dose colchicine (0.5 mg *o.d.*) may be considered in secondary prevention of CVD, particularly if other risk factors are insufficiently controlled or if recurrent CVD events occur under optimal therapy.[85,86]	IIb	A

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CVD = cardiovascular; *o.d.* = *omni die* (once a day).
[a]Class of recommendation.
[b]Level of evidence.

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 (Canakinumab Antiinflammatory Thrombosis Outcome Study), in which the monoclonal antibody, canakinumab, provided proof-of-concept for anti-inflammatory therapy in high-risk patients.[636] 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.[637]

In 2019, COLCOT (Colchicine Cardiovascular Outcomes Trial) reported a significant reduction (HR 0.77) in CVD outcomes with low-dose colchicine [0.5 mg *o.d.* (once a day)] in patients with a recent AMI. The more recent LoDoCo2 (second low-dose colchicine) trial reinforced these results in patients with chronic CAD (HR 0.69).[85] This study observed a trend towards increased non-CV 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.

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4.11. Cardiac rehabilitation and prevention programmes

Recommendations for cardiac rehabilitation

Recommendations	Class[a]	Level[b]
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.[638–642]	I	A
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).[643–646]	IIa	B
Home-based CR, telehealth, and mHealth interventions may be considered to increase patient participation and long-term adherence to healthy behaviours.[647,648]	IIb	B

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ASCVD = atherosclerotic cardiovascular disease; CR = cardiac rehabilitation; EBCR = exercise-based cardiac rehabilitation; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; mHealth = mobile device-based healthcare.
[a]Class of recommendation.
[b]Level of evidence.

CR is a comprehensive, multidisciplinary intervention not just including exercise training and PA counselling, but also education, risk factor modification, diet/nutritional counselling, and vocational and psychosocial support.[358] Prevention and rehabilitation programmes after ASCVD events or revascularization reduce CV hospitalizations, myocardial infarction, CV mortality and, in some programmes, all-cause mortality.[638,640–642] They may also reduce depressive/anxiety symptoms.[649] In patients with chronic HF (mainly HFrEF), exercise-based cardiac rehabilitation (EBCR) may improve all-cause mortality, reduce hospital admissions, and improve exercise capacity and quality of life.[639,650] CR is generally cost-effective.[651]

Clinical trials and registries are highly heterogeneous, which influences national guidelines, legislation, and reimbursement.[652,653] The results of recent reviews provide clinicians with minimal requirements for successful CR after ACS or coronary artery bypass graft:

- CR is a comprehensive multidisciplinary intervention[466,649,654,655]
- CR is supervised and carried out by adequately trained health professionals, including cardiologists[649]
- CR starts as soon as possible after the initial CV event[649]
- EBCR includes aerobic and muscular resistance exercise, which should be individually prescribed based on pre-exercise screening and exercise testing[656]
- The dose of EBCR (number of weeks of exercise training × average number of sessions/week × average duration of session in minutes) exceeds 1000[638]
- The number of EBCR sessions needs to exceed 36[641]
- During CR, all individually recognized CV risk factors need to be addressed and treated.[642]

Recently, the European Association of Preventive Cardiology (EAPC) proposed minimal and optimal standards for improvement of secondary prevention through CR programmes in Europe.[657]

Although exercise training prescription should adopt the FITT (frequency, intensity, time duration, and type of exercise) model, inter-clinician variance and disagreement exists.[658] To optimize exercise training, the EAPC has introduced a digital, interactive decision support tool; the EXPERT (EXercise Prescription in Everyday practice & Rehabilitation Training) Tool (https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/expert-tool).[659] No single exercise component is a significant predictor of mortality; only adherence to the full intervention improves outcome.[660]

Despite proven benefits, rates of referral, participation, and implementation are low.[653,660,661] Uptake seems lower in women, but a variety of other intrapersonal, interpersonal, clinical, logistical, health system, and CR programme-related factors affect participation and adherence.[662] 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).[643] Nurse-coordinated programmes can increase effectiveness.[644–646] Home-based CR with or without telemonitoring may increase participation and appear similarly effective as centre-based CR.[647] Telehealth interventions are more effective than no intervention,[648] but may also complement conventional CR. Also, mobile device-based healthcare (mHealth) delivery through smartphones may be as effective as traditional centre-based CR, showing significant improvements in health-related quality of life.[663] These novel interventions may support the patient to maintain long-term healthy behaviours after specialized CR programmes.[664]

5. Policy interventions at the population level

Recommendations for policy interventions at the population level

Recommendations	Class[a]	Level[b,c]
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 settings follow different levels of recommendations (see specific tables in the supplementary material for *section 5*).		
Putting in place measures to reduce air pollution, including reducing PM emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions, are recommended, to reduce CVD mortality and morbidity.	I	C

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CVD = cardiovascular disease; PA = physical activity; PM = particulate matter.
[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.

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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. This is based on a prevention paradox described by Geoffrey Rose in 1981.[665] The population attributable risk depends on the RR and on the prevalence of a risk factor in the general population. If the prevalence of a significant RR factor is low, then the population attributable risk may be modest. Conversely, if a low-impact RR factor is common, the population attributable risk may be high. This prevention approach following the Geoffrey Rose paradigm[665,666] 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.[667,668] 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. It should be noted that high-risk and population-level prevention strategies are not mutually exclusive and must therefore coexist.

Prevalence of high-risk conditions and incidence rates of CVD vary across countries. Many of their underlying causes are known, and they are closely related to dietary habits, 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 CV health and, in this way, reduce population incidence rates. The population approach may bring numerous benefits, such as narrowing the gap in health inequalities, preventing other conditions such as cancer, pulmonary diseases, and type 2 DM, and saving costs from the avoided CV events and early retirement due to health problems.

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 healthcare systems alone and require political support. To advance this cause, the WHO has been organizing Global Conferences on Health promotion since 1990.

5.2. Specific risk factor interventions at the population level

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 health literacy into account.[669,670] 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).[671,672] The importance of heart disease in women has become apparent and sex differences in CVD prevention have prompted sex-specific awareness campaigns with the aim of reducing sex 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.

The supplementary material for this section presents evidence for population-level strategies dealing with specific risk factor interventions for PA (*section 5.2.1*), diet (*section 5.2.2*), smoking and tobacco use (*section 5.2.3*), and alcohol consumption (*section 5.2.4*). Lifestyle changes at the population level take time, may be expensive, and need to be sustained over time. Furthermore, the benefits may be slow to manifest; however, they persist over the long term and improve health-related quality of life and well-being.

5.2.1. Physical activity

Please see the supplementary material *section 3.1*.

5.2.2. Diet

Please see the supplementary material *section 3.2*.

5.2.3. Smoking and tobacco use

Please see the supplementary material *section 3.3*.

5.2.4. Alcohol

Please see the supplementary material *section 3.4*.

5.3. Environment, air pollution, and climate change

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.[158,673,674] 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.[159] 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.[158]

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 PM (ranging in size from coarse particles 2.5−10 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.[158,675] Up to one-third of Europeans living in urban areas

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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 has been estimated by the WHO that 30% of the European population is exposed to nightly levels of noise exceeding 55 dB.[161] 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.[161]

The extent to which environmental exposures in soil and water contribute to CVD has also been established.[157] Interventions to reduce this pollution are required, including factory regulations and drinking water controls.[157]

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 transport. 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 transport 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. An example of such legislation is the European Green Deal, by which the EU aims to be climate neutral by 2050.

5.3.1.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.[676] 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.

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

Please see the supplementary material *section 3.5*.

6. Risk management of disease-specific cardiovascular disease

This section addresses CVD 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 *section 4*. In this section, only disease-specific aspects are added.

6.1.Coronary artery disease

Disease-specific acute management of coronary syndromes is covered in detail in recent guidelines.[677–680]

As for antithrombotic therapy, dual antiplatelet therapy (DAPT) for 12 months, preferably with prasugrel or ticagrelor, is the standard antithrombotic treatment after ACS.[681–683] There are conflicting data as to whether prasugrel is preferable to ticagrelor.[684,685] A 6-month duration of DAPT after ACS is generally too short,[686] but may be considered in selected patients at high bleeding risk.

In patients with chronic coronary syndromes (CCS) undergoing elective PCI, the standard duration of DAPT is 6 months, but shortening this to 1 - 3 months is an option when bleeding risk is very high.[622] Clopidogrel is the $P2Y_{12}$ inhibitor of choice, but prasugrel and ticagrelor may be considered after complex interventions.[622]

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.[687,688] 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.[83]

Based on the above, and in line with the CCS Guidelines,[622] 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.[622] More details on antithrombotic treatment options are found in the ESC Guidelines for CCS.[622]

Recommendations for patients with coronary artery disease

Recommendations	Class[a]	Level[b]
Aspirin 75 - 100 mg daily is recommended for patients with a previous myocardial infarction or revascularization.[619]	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.[622]	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.[681–683]	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 occurrence of life-threatening bleeding.[622]	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.[83,622,687–689]	IIa	A

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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.[83,622,687–689]	IIb	A
ACE inhibitors (or ARB) are recommended if a patient has other conditions (e.g. HF, hypertension, or DM).[622]	I	A
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.[622]	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 vs. baseline is recommended.	I	A

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ACE = angiotensin-converting enzyme; ACS = acute coronary syndromes; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CCS = chronic coronary syndromes; DAPT = dual antiplatelet therapy; DM = diabetes mellitus; HF = heart failure; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular.
[a]Class of recommendation.
[b]Level of evidence.

The management of dyslipidaemia and hypertension in patients with CAD is discussed in *sections 4.6 and 4.7*, respectively. For ACE inhibitors (or ARBs) and beta-blockers, see also the 2019 ESC Guidelines for diagnosis and management of CCS.[622]

6.2. Heart failure

The management of HF aims to improve mortality, hospitalization rate, and quality of life.[690] 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.[691–694]

Regarding the management of CVD risk factors, similar basic rules apply for those with and without HF. However, in HF, low cholesterol levels[695,696] and low body weight are associated with increased mortality.[697,698] 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[650,699,700] and improves CVD burden and prognosis in HFrEF.[700,701]

It is recommended to screen all patients with HF for both CV and non-CV comorbidities; if present, they should be treated.[690] These diseases include CAD, hypertension, lipid disorders, DM, obesity, cachexia and sarcopenia, thyroid disorders, CKD, anaemia, iron deficiency, and sleep apnoea.[690]

For patients with symptomatic HFrEF, neurohormonal antagonists [ACE inhibitors,[702–705] ARBs,[706] angiotensin receptor neprilysin inhibitors (ARNIs),[707–710] beta-blockers,[711–717] and mineralocorticoid receptor antagonists (MRAs)[718,719]] improve survival and reduce the risk of HF hospitalizations.[690] These drugs also reduce the risk of CV events in patients with symptomatic HFrEF.[702–719] Importantly, these drugs should be up-titrated to the maximum tolerated doses, which may be different for men and women, particularly in patients recently discharged after HF hospitalization.[690,720,721]

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 DM,[600,601] 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.[722]

Other drugs bring additional moderate benefits for selected patients with symptomatic HFrEF. Diuretics,[723,724] ivabradine,[725,726] and hydralazine[727,728] should be considered, and digoxin[729] 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 implantable cardioverter defibrillator to reduce the risk of sudden death and all-cause mortality, and for cardiac resynchronization therapy to reduce morbidity and mortality (for details, see 2021 HF Guidelines).[690]

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.

Recommendations	Class[a]	Level[b]
It is recommended that patients with HF are enrolled in a comprehensive CR programme to reduce the risk of HF hospitalization and death.[c] 691-694	I	A
EBCR is recommended in stable symptomatic patients with HFrEF to reduce the risk of HF hospitalization.[700,701]	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 an MRA, for patients with symptomatic HFrEF to reduce the risk of HF hospitalization and death.[702–705]	I	A
A beta-blocker is recommended, in addition to an ACE inhibitor (or an ARNI) and an MRA, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.[711–717]	I	A

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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.[718,719]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE inhibitor to reduce the risk of HF hospitalization and death in patients with HFrEF.[707,730]	I	B
An 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).[706]	I	B
Dapagliflozin or empagliflozin are recommended, in addition to optimal treatment of an ACE inhibitor (or ARNI), a beta-blocker, and an MRA, for patients with HFrEF to reduce the risk of HF hospitalization and death.[600,601,730]	I	A
Vericiguat may 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.[722]	IIb	B
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to reduce the risk of HF hospitalization.[723,724]	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 a 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.[725]	IIa	B
Ivabradine should be considered in symptomatic patients with LVEF ≤35%, in sinus rhythm, and with a resting heart rate ≥70 b.p.m. 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.[726]	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.[731]	IIa	B
Hydralazine and isosorbide dinitrate may be considered in patients with symptomatic HFrEF who cannot tolerate ACE inhibitors, ARBs, or ARNIs (or if they are contraindicated), to reduce the risk of death.[728]	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 hospitalizations (all-cause and HF).[729]	IIb	B

Continued

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ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; b.p.m. = 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 ventricle; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.
[c]Applies to all patients with HF, regardless of LVEF.
For implantable cardioverter-defibrillator and cardiac resynchronization recommendations, see [690]

6.3. Cerebrovascular diseases

Interventions for cerebrovascular diseases depend on the type of event, i.e. ischaemic or haemorrhagic.[732,733] Ischaemic events are mainly caused by atherothrombosis, cardiac embolism, or small vessel disease.[734] 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.[735] Bleeding can be precipitated by surges in BP values, use of anticoagulants, or diseases impairing coagulation.[733,735]

In patients with ischaemic stroke or TIA, antithrombotics prevent further vascular events. Cardioembolic ischaemia, which occurs mainly in AF, requires anticoagulation (see *sections 3.4.3 and 6.6*).[736–742] In non-cardioembolic mechanism, platelet inhibitors are recommended.[619,620,743–753]

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.[619,743] Clopidogrel shows slight superiority to aspirin.[620] In patients with ischaemic stroke or TIA and ipsilateral carotid stenosis, ticagrelor added to aspirin compared to aspirin alone reduced the risk of stroke or death at 1 month, without an increase of severe bleeding.[754] Adding aspirin to clopidogrel was associated with a non-significant reduction in major vascular events and an increased long-term bleeding risk.[747–749] However, in patients with minor ischaemic stroke or TIA, a short course of DAPT with aspirin and clopidogrel is beneficial.[750,751] Similarly, ticagrelor and aspirin vs. aspirin alone reduces stroke or death at 30 days 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.[755] DAPT with dipyridamole plus aspirin also showed superiority over aspirin alone.[744] In patients with ischaemic stroke, however, dipyridamole plus aspirin vs. clopidogrel alone showed similar rates of recurrent stroke, including haemorrhagic stroke,[745] 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.[752,753] In the absence of a definite cause of ischaemia and a presumed occult cardioembolic

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source (e.g. embolic stroke of undetermined cause), neither dabigatran nor rivaroxaban are better than aspirin.[756,757]

Recommendations for BP and lipid management are congruent to the general recommendations outlined in *sections 4.6 and 4.7.4*. In patients with either ischaemic or haemorrhagic cerebrovascular disease who have a BP of 140/90 mmHg or higher, lowering BP reduces the risk of recurrent stroke.[758,759] Optimal BP targets in these patients are uncertain, as is the optimal drug regimen.[760] 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.[761]

In patients with stroke (ischaemic or haemorrhagic) or TIA with an LDL-C level of 100 - 190 mg/dL, atorvastatin 80 mg/day reduced the overall incidence of strokes and CV events.[762] A recent trial supported an LDL-C target of <1.8 mmol/L (70 mg/dL).[508]

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.[763,764] Arterial hypertension, DM, 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.[765]

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.[732,733,741]	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 an antiplatelet is recommended for patients with non-cardioembolic ischaemic stroke or TIA, and use of an anticoagulant is recommended in patients with cardioembolic ischaemic stroke or TIA.[732,741]	I	A
In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin, or clopidogrel alone is recommended.[620,743–745]	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.[750,751,755]	IIa	A
In patients with stroke or TIA who have BP of 140/90 mmHg or higher, BP lowering is recommended.[757,766]	I	A

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BP = blood pressure; DAPT = dual antiplatelet therapy; 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

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.[125] Within 5 years of LEAD diagnosis, 20% develop AMI or stroke, and mortality is 10–15%.[767]

All LEAD patients require lifestyle improvement and pharmacological therapy. Smoking cessation increases walking distance and lowers amputation risk.[2] In patients with DM, glycaemic control improves limb outcomes.[768] Statins provide modest improvements in walking distance, and lower the risk of adverse limb events.[769,770] Combining a statin with ezetimibe[771] or a PCSK9 inhibitor also has beneficial effects.[772]

Platelet inhibitors are used to prevent limb-related and general CV events. The optimal antiplatelet strategy remains unclear.[773] DAPT is currently recommended only after intervention (irrespective of the stent type) for at least 1 month.

In the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) 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),

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.[29,781]	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[782–784]	I	A
• Non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	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.[776,785,786]	I	A
In patients with LEAD and DM, strict glycaemic control is recommended.[768]	I	A
ACE inhibitors or ARBs should be considered as first-line therapy in patients with PAD and hypertension.[d] [575,787]	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.[774]	IIb	B

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ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; *b.i.d.* = *bis in die* (twice a day); BP = blood pressure; CCB = calcium channel blocker; 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]CCBs should be proposed in black individuals.

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albeit at the cost of higher major bleeding risk.[774] These results, combined with similar benefits of rivaroxaban vs. 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/European Society for Vascular Surgery (ESVS) Guidelines.[775] Importantly, in patients with isolated asymptomatic LEAD (e.g. low ABI), antiplatelet treatment is not recommended.[775]

Recommendations for BP and lipid management are congruent to the general recommendations outlined in *sections 4.6 and 4.7*. Hypertension targets are based mainly on INVEST (INternational VErapamil-SR/Trandolapril STudy).[776] An SBP below 110–120 mmHg may increase CV events in patients with LEAD.[776] ACE inhibitors and ARBs reduce CV events in patients with LEAD,[575,777] and are preferred (as monotherapy or as part of a combination drug regimen).[778] Beta-blockers are not contraindicated in mild-to-moderate LEAD as they do not affect walking capacity or adverse limb events,[779] and significantly reduce coronary events.[780] Nevertheless, beta-blockers should be carefully considered in critical limb-threatening ischaemia.

6.5. Chronic kidney disease

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 non-atherosclerotic CVD event risk increases.[204] 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.[788] Standard CVD 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 4*. Treatment with a statin or statin/ezetimibe combination is recommended in CKD patients with sufficiently high CVD risk, but not in those treated with kidney replacement therapy. This recommendation is built on evidence from SHARP (Study of Heart and Renal Protection), which demonstrated a reduction of major atherosclerotic events.[525] Statins should be dosed according to a moderate-intensity regimen based on limited experience and risks associated with high-intensity regimens.[543] 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).[789]

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).

Individualized HbA1c targets, ranging from 6.5% to <8.0% in patients with DM and non-dialysis-dependent CKD, are recommended in parallel. The role of SGLT2 inhibitors and GLP-1RAs in CKD associated with DM is addressed in *section 4.8*. Dapagliflozin has shown promising reno- and cardioprotective effects,[599] and more studies investigating SGLT2 inhibitors in CKD patients without DM are ongoing.[790]

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.

Recommendations in patients with chronic kidney disease: best medical therapy[a]

Recommendations	Class[b]	Level[c]
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.[599]	IIa	B
Combination treatment with ACE inhibitors and ARBs is not recommended.	III	C

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; DM = diabetes mellitus; SGLT2 = sodium-glucose cotransporter 2.
[a]Recommendations on CKD management in patients with DM are found in *section 4.8*.
[b]Class of recommendation.
[c]Level of evidence.

6.6. Atrial fibrillation

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.[215] The ABC pathway lowers risk of all-cause death and the composite of stroke, major bleeding, CV death, or first hospitalization,[791] and lowers rates of CV events[792,793] and health-related costs.[794]

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.[216] In obese patients, weight reduction prevents AF recurrences and symptoms.[795–802] Given that hypertension precipitates AF, treatment of hypertension is mandatory. Alcohol excess is a risk factor for incident AF,[803,804] and abstinence reduced AF recurrences in regular drinkers.[798] Many studies have demonstrated beneficial effects of moderate exercise/PA.[805–807] The incidence of AF appears, however, to be increased in elite athletes, mainly related to endurance sports.[808–811] 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 a universally recommended programme for patients with ACS and/or revascularization, and for patients with HF.[639,640,655] The benefits of EBCR are more uncertain in patients with AF, but CR remains recommended in patients with the aforementioned indications.[812] Continuous PAP may improve rhythm control and attenuate AF recurrences in OSA patients.[813–816] Intensive glycaemic control does not affect the rate of new-onset AF.[817] Optimal glycaemic control during the 12 months before AF ablation does, however, reduce AF recurrence after ablation.[818] All patients with HF and AF should receive guideline-adherent HF therapy.[819]

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Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with atrial fibrillation[215]

Recommendations	Class[a]	Level[b]
Identification and management of risk factors and concomitant diseases are recommended to be an integral part of treatment.[795]	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.[216,795–802]	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.[800,801]	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.[795–797]	IIa	B
Advice and management to avoid alcohol excess should be considered for AF prevention and in AF patients considered for oral anticoagulant therapy.[798,803,804]	IIa	B
PA should be considered to help prevent AF incidence or recurrence, with the exception of excessive endurance exercise, which may promote AF.[805–812]	IIa	C
Optimal management of OSA may be considered to reduce AF incidence, AF progression, AF recurrences, and symptoms.[813–816]	IIb	C

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AF = atrial fibrillation; BP = blood pressure; OSA = obstructive sleep apnoea; PA = physical activity.
[a]Class of recommendation.
[b]Level of evidence.

6.7. Multimorbidity

The older adult population is growing fast and survival after acute CVD has improved,[820] leading to an increasing number of older patients with CVD and multimorbidity.[821,822] This development is associated with high healthcare costs,[823,824] worse outcome measures, higher readmission rates,[825] and mortality.[826]

Up to 70% of patients aged ≥70 years have at least one CVD and two-thirds also develop non-CVD comorbidities. Multimorbidity is important in patients with CVD.[823]

The prevailing CV conditions in patients aged >60 years are hypertension, hyperlipidaemia, ischaemic heart disease, arrhythmia, DM, and CAD.[823] Other frequent comorbidities include anaemia and arthritis. Low vision, back and neck problems, osteoarthritis, COPD, depression, and cancer are the most common non-CV comorbidities in CVD patients. Most studies have found no sex differences in the number of comorbidities. However, men have more CVD comorbidities and women have more non-CVD comorbidities (in particular more depression).[822,826,827]

So far, guidance for the 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%)[820] and 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.[820] 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.[820] The incremental benefit of medication when added to an already complex regimen is often uncertain.[828] Moreover, care for multimorbid CVD patients is often fragmented and given by multiple providers, complicating decision-making and adherence to recommended treatment.[820]

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.[820]

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.[828] '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, the occurrence of adverse drug events, the economic burden, and the stress experienced by caregivers should be taken into account when optimizing therapies and care plans where adherence to essential medication is emphasized and non-essential drugs are stopped.[828] 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.[829]

7. Key messages

Risk factors and risk classification

- The major risk factors for ASCVD are cholesterol, BP, cigarette smoking, DM, and adiposity.
- Risk factors are treated in a stepwise approach to reach the ultimate treatment goals in apparently healthy people, patients with established ASCVD, and patients with DM.
- 10-year CVD risk is estimated in apparently healthy people aged 40–69 years with SCORE2, and in people aged ≥70 years with SCORE2-OP.
- Age-specific 10-year CVD risk thresholds—together with consideration of risk modifiers, frailty, comorbidities, lifetime CVD risk, treatment benefit, polypharmacy, and patient preferences—guide treatment decisions for lipid and BP treatment.
- There are various options of communicating the (residual) CVD risk, and this should be tailored to the individual patient.

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Risk modifiers

- Psychosocial stress is associated with risk of ASCVD.
- Current risk scores may under- or overestimate CVD risk in differing ethnic minority groups.
- CAC scoring is the best-established imaging modality to improve CVD risk stratification.
- Frailty is a functional risk factor of both CV and non-CV morbidity and mortality.
- Frailty assessment is not a method to determine eligibility for any particular treatment, but rather serves to build an individualized care plan with predefined priorities.
- Family history should be enquired about routinely, and a positive family history of premature ASCVD should be followed by comprehensive CVD risk assessment.
- Current data does not support the use of genomic risk scores in CVD risk assessment in primary prevention.
- ASCVD development and prognosis are linked to social gradients.
- Air pollution is strongly associated with ASCVD.
- Additional circulating and urine biomarkers should not be routinely measured.
- Assess CVD risk in persons with obesity.

Clinical conditions

- 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 RAAS inhibition is associated with improved CV and kidney outcomes.
- Similarly, SGLT2 inhibitors are associated with long-term benefits in CV and renal risks.
- AF is associated with an increased risk of death and an increased risk of CVD.
- Ischaemic HF constitutes the most advanced clinical manifestation of atherosclerosis within the myocardium.
- The diagnosis of overt HF, as well as asymptomatic presentation with LV dysfunction, increases the risk of CVD events (myocardial infarction, ischaemic stroke, CV death).
- 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, periodically during, and after treatment.
- Exercise should be strongly advised, in particular aerobic exercise, to prevent cardiotoxicity.
- COPD is a major risk factor for CVD, especially ASCVD, stroke, and HF.
- COPD patients are prone to arrhythmias (AF and ventricular tachycardia) and sudden cardiac death.
- All COPD patients should be investigated for CVD.
- Common COPD medications are usually safe in terms of CV adverse events.
- Chronic inflammatory conditions increase CVD risk.
- Infection with HIV is associated with an increased risk of LEAD and CAD.
- There is an association between influenza and periodontitis infections and ASCVD.
- Migraine, 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 cigarette smoking.
- Non-restorative sleep and a sleep duration that varies significantly up or down from the optimum of 7 h are associated with increased CV risk.
- 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 2.2-fold, leading to a worse prognosis.
- Some mental disorders—even symptoms of anxiety and depression—are associated with the development of CVD and with a worse prognosis in those with existing CVD (CHD, arterial hypertension, 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).
- NAFLD is associated with other cardiometabolic risk factors.
- Patients with NAFLD should be evaluated for other cardiometabolic risk factors.
- Sex-specific conditions:
  - Preeclampsia and pregnancy-related hypertension are associated with a higher risk of CVD.
  - Polycystic ovary syndrome confers a significant risk for future development of DM.
  - 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.

Risk factors and interventions at the individual level

- Regular 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.
- A healthy diet lowers the risk of CVD and other chronic diseases.
- A shift from a more animal- to plant-based food pattern may reduce CVD.
- Achieving and maintaining a healthy weight through lifestyle changes has favourable effects on risk factors (BP, lipids, glucose metabolism) and lowers CVD 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.
- 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.
- Stopping smoking rapidly reduces CVD risk and is the most cost-effective strategy for ASCVD prevention.

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- There is strong evidence for medication-assisted interventions: NRT, bupropion, varenicline, and drugs in combination. The most effective are assistance using drug therapy and follow-up support.
- Lower is better: the effect of LDL-C on the risk of CVD 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—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 to reduce LDL-C by ≥50% and then strive to reduce other risk factors as part of a shared decision-making process with the patient.
- When hypertension is suspected, the diagnosis should be confirmed by repeated office BP measurement at different visits, or ABPM or HBPM.
- 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 mmHg.
- BP treatment goals are lower than in the previous ESC CVD prevention guidelines for all patient groups, including independent older patients.
- 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 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.
- A 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 CVD. Glycaemic targets should be relaxed in older adults and frail individuals.
- New antihyperglycaemic 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.

Type 1 diabetes mellitus

- Intensive management of hyperglycaemia in DM reduces the risk of micro- and 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 CVD 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 CVD risk in type 1 DM.
- All patients with established ASCVD require some form of antithrombotic therapy.
- Anti-inflammatory therapy is a promising strategy in CVD prevention.
- Patients after ACS and/or coronary artery bypass graft/PCI, or with chronic HFrEF, should participate as early as possible in structured, multidisciplinary 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 mHealth may help towards achieving this target.

Population-level approaches to cardiovascular disease prevention

Physical activity

- A significant percentage of the 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 PA 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 for at least 3 h/week, and preferably for 60 minutes per day.
- Population-based approaches are complementary to individual-centred interventions.
- Diet
- Structural measures such as changes in agricultural supply chain and food industry, 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 is a 30% relative reduction in mean population intake of sodium/salt.[830]

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Smoking and tobacco use

- 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.
- There should be restrictions on smokeless tobacco due to strong evidence of harm.
- Also, restrictions on e-cigarettes due to evidence of harm.
- Plain packaging is effective in reducing the attractiveness of tobacco products.
- There should be 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.

Alcohol

- 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).
- Healthcare providers may inquire about alcohol intake in every medical evaluation and should inform patients that alcohol is energy-dense: it provides 7 kcal/g and no nutrients.

Environment, air pollution, and climate change

- 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 climate changes, notably through the burning of fossil fuels leading to increasing emissions of carbon dioxide.

Risk management of disease-specific cardiovascular disease

Coronary artery disease

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

Heart failure

- 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.

Cerebrovascular diseases

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

Chronic kidney disease

- 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.

Atrial fibrillation

- 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.

Multimorbidity

- 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.

8. Gaps in evidence

CVD risk classification

- 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 vs. treatment guided by risk factor level.
- Comparison of the precision of competing risk-adjusted CVD risk models vs. standard CVD risk models.
- Incorporating potential risk markers into conventional risk models, such as socioeconomic status and ethnicity.
- Comparison of treatment benefit-guided strategy vs. risk-guided strategy in reducing risk factor levels and CVD risk.

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- Management of CVD risk in older people (>85 years) with marked fragility, for whom no data currently exist.
- Comparison of different methods for the estimation of lifetime CVD risk and lifetime benefit of risk factor treatment.

Risk modifiers

Psychosocial factors

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

Ethnicity

- Whether recalibration of factors for ethnicity are homogeneous in various European countries.
- Risks associated with other ethnic backgrounds.

Frailty

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

Family history

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

Genetics

- The potential of polygenic risk scores to complement existing risk scores.

Socioeconomic determinants

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

Environmental exposure

- Whether air pollution reclassifies risk in individual patients.

Biomarkers

- Added value of biomarkers in risk classification.

Clinical conditions

Chronic kidney disease

- 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.

Atrial fibrillation

- Evaluate the effect of interventions aimed at reducing outcomes beyond stroke.
- Is AF a causal factor for increased CVD 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.

Heart failure

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

Cancer

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

Chronic obstructive pulmonary disease

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

Inflammatory conditions

- The optimal way of integrating information on chronic inflammatory conditions into CVD risk assessment.
- The effect of modern anti-inflammatory drugs on CV risk [e.g. anti-tumour necrosis factor (TNF), interleukin (IL)-1, IL-17, IL-23 biologics].

Infections

- 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.

Migraine

- 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 these factors.

Sleep disorders

- 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.

Mental disorders

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

Non-alcoholic fatty liver disease

- Whether NAFLD increases CV risk beyond traditional risk factors.

Sex-specific conditions

- The degree to which increased CVD risk associated with several of the female-specific conditions occurs independently of

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conventional CVD risk factors, although data in women are still underpowered compared to 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.

Erectile dysfunction

- 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.

Risk factors and interventions at the individual level

Physical activity and exercise

- Knowledge of 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.

Nutrition

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

Body weight

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

Mental healthcare and psychosocial interventions

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

Smoking intervention

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

Lipids

- Direct empirical evidence for the stepwise approach to treatment intensification from RCTs. The feasibility and effects of reaching LDL-C levels <1.4 mmol/L (55 mg/dL) needs further investigation, especially in primary care.
- Particularly among people at low-to-moderate CVD 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 CVD risk and more precise CVD 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, ezetimibe and PCSK9i therapy can reduce the risk of ASCVD.
- Whether functional foods and food supplements with a lipid-lowering effect can safely reduce the risk of CVD.

Blood pressure

- What is the incremental benefit, over CVD risk calculators, of measures of HMOD in reclassifying the CV risk of patients with hypertension?
- Direct empirical evidence for the stepwise approach to treatment intensification from RCTs.
- 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 vs. 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 the treatment of hypertension.
- Sex-specific BP treatment thresholds for men and women.

Diabetes mellitus

- 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.

Antithrombotic therapy

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

Cardiac rehabilitation and prevention programmes

- 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.

Environment, air pollution, and climate change

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

Risk management of disease-specific cardiovascular disease

Coronary artery disease

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- 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 $P2Y_{12}$ inhibitors vs. low-dose rivaroxaban or other factor Xa inhibitors, in combination with aspirin, are warranted to determine which subgroups will derive greater clinical benefit with each strategy.

Heart failure

- For patients with HFpEF, no specific pharmacotherapy or device implantation has been shown to modify the risk of any CV outcome.
- Lower dosage of HF treatments in women with HFrEF needs to be addressed, since women were underrepresented in many HF trials.

Cerebrovascular disease

- 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.

Lower extremity artery disease

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

Chronic kidney disease

- 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.

Atrial fibrillation

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

Multimorbidity

- 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.

9. 'What to do' and 'what not to do' messages from the guidelines

Recommendations	Class[a]	Level[b]
Recommendations for cardiovascular disease risk assessment		
Systematic global CVD risk assessment is recommended in individuals with any major vascular risk factor (i.e. family history of premature CVD, FH, CVD risk factors such as smoking, arterial hypertension, DM, raised lipid level, obesity, or comorbidities increasing CVD risk).	I	C
Systematic CVD risk assessment in men <40 years of age and women <50 years of age with no known CV risk factors is not recommended.	III	C
Recommendations for cardiovascular disease risk estimation		
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 CVD risk with SCORE2 is recommended.	I	B
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 nonfatal CVD risk with SCORE2-OP is recommended.	I	B
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.	I	A
A stepwise treatment-intensification approach aiming at intensive risk factor treatment is recommended for apparently healthy people at high or very high CVD 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.	I	B
Treatment of ASCVD risk factors is recommended in apparently healthy people without DM, CKD, genetic/rarer lipid or BP disorders who are at very high risk (SCORE2 ≥7.5% for age under 50; SCORE2 ≥10% for age 50–69; SCORE2-OP ≥15% for age ≥70 years).	I	C
Recommendation for cardiovascular disease risk communication		
An informed discussion about CVD risk and treatment benefits tailored to the needs of a patient is recommended.	I	C
Recommendations for risk modifiers		
The routine collection of other potential modifiers, such as genetic risk scores, circulating or urinary biomarkers, or vascular tests or imaging methods (other than CAC scoring or carotid ultrasound for plaque determination), is not recommended.	III	B

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Recommendations for cardiovascular disease risk assessment in specific clinical conditions		
In all CKD patients, with or without DM, appropriate screening for ASCVD and kidney disease progression, including monitoring changes in albuminuria is recommended.	I	C
It is recommended to monitor cardiac dysfunction using imaging techniques and circulating biomarkers before, periodically during, and after cancer treatment.	I	B
Screening for CV risk factors and optimization of the CV risk profile is recommended in patients on treatment for cancer.	I	C
It is recommended that all COPD patients be investigated for ASCVD and ASCVD risk factors.	I	C
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
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
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 PA, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity.	I	A
It is recommended that adults who cannot perform 150 min of moderate-intensity PA a week should stay as active as their abilities and health condition allow.	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.	I	B
Performing resistance exercise, in addition to aerobic activity, is recommended on 2 or more days per week to reduce all-cause mortality.	I	B
Recommendations for nutrition and alcohol		
A healthy diet is recommended as a cornerstone of CVD prevention in all individuals.	I	A
It is recommended to adopt a Mediterranean or similar diet to lower risk of CVD.	I	A
It is recommended to replace saturated with unsaturated fats to lower the risk of CVD.	I	A
It is recommended to reduce salt intake to lower BP and risk of CVD.	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.	I	B
It is recommended to restrict alcohol consumption to a maximum of 100 g per week.	I	B
It is recommended to eat fish, preferably fatty, at least once a week and restrict (processed) meat.	I	B
It is recommended to restrict free sugar consumption, in particular sugar-sweetened beverages, to a maximum of 10% of energy intake.	I	B
Recommendations for body weight		
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 CVD risk profile.	I	A
While a range of diets are effective for weight loss, it is recommended that a healthy diet in regard to CVD risk is maintained over time.	I	A
Recommendations for mental healthcare and psychosocial interventions at the individual level		
Patients with mental disorders need intensified attention and support to improve adherence to lifestyle changes and drug treatment.	I	C
In ASCVD patients with mental disorders, evidence-based mental healthcare and interdisciplinary cooperation are recommended.	I	B
In patients with HF and major depression, SSRIs, SNRIs, and tricyclic antidepressants are not recommended.	III	B
Recommendations for smoking intervention strategies		
All smoking of tobacco should be stopped, as tobacco use is strongly and independently causal of ASCVD.	I	A
Smoking cessation is recommended regardless of weight gain, as weight gain does not lessen the ASCVD benefits of cessation.	I	B
Recommendations on low-density lipoprotein cholesterol goals		
A stepwise treatment-intensification approach is recommended for apparently healthy people at high or very high CVD risk, as well as patients with established ASCVD and/or DM with consideration of CVD risk, treatment benefit, risk modifiers, comorbidities, and patient preferences.	I	C

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Recommendations for pharmacological low-density lipoprotein cholesterol lowering for those <70 years of age		
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.	I	A
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 in LDL-C vs. baseline is recommended.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
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.	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
Statin therapy is not recommended in premenopausal female patients who are considering pregnancy or are not using adequate contraception.	III	C
Recommendation for drug treatments of patients with hypertriglyceridaemia		
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].	I	A
Recommendations for the treatment of dyslipidaemias in older people (≥70 years)		
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions.	I	C
Recommendation for the treatment of dyslipidaemias in diabetes mellitus		
In patients with type 2 DM at very high risk (e.g. with established ASCVD and/or severe TOD) 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.	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.	I	A
Recommendations for lipid management in patients with moderate-to-severe chronic kidney disease (Kidney Disease Outcomes Quality Initiative stages 3–5)		
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent, stage 3–5 CKD.	I	A
In patients with dialysis-dependent CKD who are free of ASCVD, commencing statin therapy is not recommended.	III	A
Recommendations for the clinical management of hypertension		
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	I	C
• Out-of-office BP measurement with ABPM and/or HBPM when feasible.	I	C
Assessment of HMOD		
To evaluate for the presence of HMOD, measurement of serum creatinine, eGFR, electrolytes, and ACR 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 DM.	I	B
Thresholds for initiation of drug treatment of hypertension		
For grade 1 hypertension, treatment initiation based on absolute CVD risk, estimated lifetime benefit, and the presence of HMOD is recommended.	I	C
For patients with grade 2 hypertension or higher, drug treatment is recommended.	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 comorbidities.	I	A

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In treated patients aged 18–69 years, it is recommended that SBP should ultimately be lowered to a target range of 120–130 mmHg in most patients.	I	A
In treated patients aged ≥70 years, it is recommended that SBP should generally be targeted to <140 and down to 130 mmHg if tolerated.	I	A
In all treated patients, DBP is recommended to be lowered to <80 mmHg.	I	A
Treatment of hypertension: lifestyle interventions		
Lifestyle interventions are recommended for people with high-normal BP or higher.	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).	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).	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 blocker with a CCB and a diuretic, preferably as a single-pill combination.	I	A
It is recommended, if BP is not controlled by a three-drug combination, that 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.	I	B
The combination of two RAS blockers is not recommended.	III	A
Recommendations for the treatment of patients with diabetes mellitus		
Lifestyle		
Lifestyle changes including smoking cessation, a low saturated fat, high-fibre diet, aerobic PA, and strength training are recommended.	I	A
Reduction in energy intake is recommended to patients, to help achieve lower body weight or prevent or slow weight gain.	I	A
Glycaemia target		
A target HbA1c for the reduction of CVD risk and microvascular complications of DM of <7.0% (53 mmol/mol) is recommended for the majority of adults with either type 1 or type 2 DM.	I	A
Treatment of hyperglycaemia 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.	I	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.	I	A
In patients with type 2 DM and CKD, the use of an SGLT2 inhibitor is recommended to improve CVD and/or cardiorenal outcomes.	I	A
In patients with type 2 DM and HFrEF, use of an SGLT2 inhibitor with proven outcome benefits is recommended to lessen HF hospitalizations and CV death.	I	A
Recommendations for antithrombotic therapy		
Aspirin 75–100 mg daily is recommended for secondary prevention of CVD.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in secondary prevention in case of aspirin intolerance.	I	B
Concomitant use of a proton pump inhibitor is recommended in patients receiving antiplatelet therapy who are at high risk of gastrointestinal bleeding.	I	B
Antiplatelet therapy is not recommended in individuals with low/moderate CV risk due to the increased risk of major bleeding.	III	A
Recommendations for cardiac rehabilitation		
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.	I	A
Recommendation for policy interventions at the population level		
Putting in place measures to reduce air pollution, including reducing PM emission and gaseous pollutants, reducing the use of fossil fuels, and limiting carbon dioxide emissions, are recommended, to reduce CVD mortality and morbidity.	I	C

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Recommendations for patients with coronary artery disease		
Aspirin 75–100 mg daily is recommended for patients with a previous myocardial infarction or revascularization.	I	A
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.	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.	I	A
ACE inhibitors (or ARB) are recommended if a patient has other conditions (e.g. HF, hypertension, or DM).	I	A
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.	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 vs. baseline is recommended.	I	A
Recommendations regarding pharmacological and nonpharmacological 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		
It is recommended that patients with HF are enrolled in a comprehensive CR programme to reduce the risk of HF hospitalization and death.	I	A
EBCR is recommended in stable symptomatic patients with HFrEF to reduce the risk of HF hospitalization.	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.	I	A
An ACE inhibitor is recommended, in addition to a beta-blocker and an MRA, for patients with symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition to an ACE inhibitor (or an ARNI) and an MRA, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	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.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE inhibitor to reduce the risk of HF hospitalization and death in patients with HFrEF.	I	B
An 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).	I	B
Dapagliflozin or empagliflozin are recommended, in addition to optimal treatment of an ACE inhibitor (or ARNI), a beta-blocker, and an MRA, for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to reduce the risk of HF hospitalization.	I	C
Recommendations for patients with cerebrovascular disease		
In patients with a cerebrovascular event, improvement of lifestyle factors in addition to appropriate pharmacological management is recommended.	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 an antiplatelet is recommended for patients with non-cardioembolic ischaemic stroke or TIA, and use of an anticoagulant is recommended in patients with cardioembolic ischaemic stroke or TIA.	I	A
In patients with non-cardioembolic ischaemic stroke or TIA, prevention with aspirin only, or dipyridamole plus aspirin, or clopidogrel alone is recommended.	I	A
In patients with stroke or TIA who have BP of 140/90 mmHg or higher, BP lowering is recommended.	I	A
Recommendations for patients with lower extremity artery disease: best medical therapy		
Smoking cessation is recommended in all patients with LEAD.	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	I	A
• Non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
Antiplatelet therapy is recommended in patients with symptomatic LEAD.	I	C
In patients with LEAD and hypertension, it is recommended to control BP at <140/90 mmHg.	I	A
In patients with LEAD and DM, strict glycaemic control is recommended.	I	A

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Recommendations in patients with chronic kidney disease: best medical therapy		
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
Combination treatment with ACE inhibitors and ARBs is not recommended.	III	C
Recommendations for lifestyle interventions and management of risk factors and concomitant diseases in patients with atrial fibrillation		
Identification and management of risk factors and concomitant diseases are recommended to be considered an integral part of treatment.	I	B
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity.	I	B
Attention to good BP control is recommended in AF patients with hypertension to reduce AF recurrences and risk of stroke and bleeding.	I	B

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ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ACR = albumin-to-creatinine ratio; ACS = acute coronary syndromes; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CAC = coronary artery calcium; CCB = calcium channel blocker; CCS = chronic coronary syndromes; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CR = cardiac rehabilitation; CV = cardiovascular; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; DBP = diastolic blood pressure; DM = diabetes mellitus; EBCR = exercise-based cardiac rehabilitation; ECG = electrocardiogram; eGRF = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; GLP-1RA = glucagon-like peptide-1 receptor agonist; HbA1c = glycated haemoglobin; HBPM = home blood pressure monitoring; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HMOD = hypertension-mediated organ damage; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; LV = left ventricular; MRA = mineralocorticoid receptor antagonist; PA = physical activity; PCSK9 = proprotein convertase subtilisin/kexin type 9; PM = particulate matter; RAS = renin-angiotensin system; SBP = systolic blood pressure; SCORE2 = Systematic Coronary Risk Estimation 2; SCORE2-OP = Systematic Coronary Risk Estimation 2-Older Persons; SGLT2 = sodium-glucose cotransporter 2; SNRI = serotonin-noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TIA = transient ischaemic attack; TOD = target organ damage.

10. Quality indicators

Quality indicators (QIs) are tools that may be used to evaluate care quality, including that of processes of care and clinical outcomes.[730] They may also serve as a mechanism for enhancing adherence to guideline recommendations, through quality assurance endeavours and benchmarking of care providers.[831] As such, the role of QIs in driving quality improvement is increasingly recognized and attracts interest from healthcare authorities, professional organizations, payers, and the public.[832]

The ESC recognizes the need for measuring and reporting the quality and outcomes of CV care. One aspect of this is the development and implementation of QIs for CVD. The methodology by which the ESC QIs are developed has been published[832] and, to date, a suite of QIs for an initial tranche of CV conditions has been produced.[833,834] To facilitate quality improvement initiatives, the disease-specific ESC QIs are included in corresponding ESC Clinical Practice Guidelines.[215,680] This is further enhanced by way of their integration into the EORP (EURObservational Research Programme) and the EuroHeart (European Unified Registries On Heart Care Evaluation and Randomized Trials) project.[835]

For CVD prevention, QIs are available for specific conditions, such as the management of high BP[836] and secondary lipid prevention.[837] However, a comprehensive set of QIs that encompasses the depth and breadth of CVD prevention is lacking. Such a set may evaluate the adoption of, and adherence to, the guideline recommendations provided in this document, and may be applied retrospectively to assess the delivery of evidence-based care. Thus, and in line with other ESC Clinical Practice Guidelines, the process of developing and defining QIs for CVD prevention has been initiated during the writing of this guideline and the results will be published in a separate document.

11 Supplementary data

Supplementary data with additional Supplementary Figures, Tables, and text complementing the full text are available on the European Heart Journal website and via the ESC website at https://www.escardio.org/guidelines.

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14. References

1. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, Maggioni A, Marques-Vidal P, Jennings C, Abreu A, Aguiar C, Badariene J, Bruthans J, Cifkova R, Davletov K, Dilic M, Dolzhenko M, Gaita D, Gotcheva N, Hasan-Ali H, Jankowski P, Lionis C, Mancas S, Milicic D, Mirrakhimov E, Oganov R, Pogosova N, Reiner Z, Vulic D, Wood D. Primary prevention efforts are poorly developed in people at high cardiovascular risk: A report from the European Society of Cardiology EURObservational Research Programme EUROASPIRE V survey in 16 European countries. *Eur J Prev Cardiol* 2020:2047487320908698.
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corra U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Lochen ML, Lollgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, ESC Scientific Document Group. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;**37**:2315–2381.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
5. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Juni P, Lettino M, Marx N, Mellbin LG, Ostgren CJ, Rocca B, Roffi M, Sattar N, Seferovic PM, Sousa-Uva M, Valensi P, Wheeler DC, ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.
6. Jorgensen T, Jacobsen RK, Toft U, Aadahl M, Glumer C, Pisinger C. Effect of screening and lifestyle counselling on incidence of ischaemic heart disease in general population: Inter99 randomised trial. *BMJ* 2014;**348**:g3617.
7. Ebrahim S, Taylor F, Ward K, Beswick A, Burke M, Davey Smith G. Multiple risk factor interventions for primary prevention of coronary heart disease. *Cochrane Database Syst Rev* 2011:CD001561.
8. Kennedy O, Su F, Pears R, Walmsley E, Roderick P. Evaluating the effectiveness of the NHS Health Check programme in South England: a quasi-randomised controlled trial. *BMJ Open* 2019;**9**:e029420.
9. Krogsboll LT, Jorgensen KJ, Gotzsche PC. General health checks in adults for reducing morbidity and mortality from disease. *Cochrane Database Syst Rev* 2019;**1**:CD009009.
10. Si S, Moss JR, Sullivan TR, Newton SS, Stocks NP. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. *Br J Gen Pract* 2014;**64**:e47-53.
11. Patel R, Barnard S, Thompson K, Lagord C, Clegg E, Worrall R, Evans T, Carter S, Flowers J, Roberts D, Nuttall M, Samani NJ, Robson J, Kearney M, Deanfield J, Waterall J. Evaluation of the uptake and delivery of the NHS Health Check programme in England, using primary care data from 9.5 million people: a cross-sectional study. *BMJ Open* 2020;**10**:e042963.
12. Mehta S, Wells S, Grey C, Riddell T, Kerr A, Marshall R, Ameratunga S, Harrison J, Kenealy T, Bramley D, Chan WC, Thornley S, Sundborn G, Jackson R. Initiation and maintenance of cardiovascular medications following cardiovascular risk assessment in a large primary care cohort: PREDICT CVD-16. *Eur J Prev Cardiol* 2014;**21**:192–202.
13. Chamnan P, Simmons RK, Khaw KT, Wareham NJ, Griffin SJ. Estimating the population impact of screening strategies for identifying and treating people at high risk of cardiovascular disease: modelling study. *BMJ* 2010;**340**:c1693.
14. Lindholt JS, Sogaard R. Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial. *Lancet* 2017;**390**:2256–2265.
15. Christensen B, Engberg M, Lauritzen T. No long-term psychological reaction to information about increased risk of coronary heart disease in general practice. *Eur J Cardiovasc Prev Rehabil* 2004;**11**:239–243.
16. Nielsen AD, Videbech P, Gerke O, Petersen H, Jensen JM, Sand NP, Egstrup K, Larsen ML, Mickley H, Diederichsen AC. Population screening for coronary artery calcification does not increase mental distress and the use of psychoactive medication. *J Thorac Imaging* 2012;**27**:202–206.
17. Lokkegaard T, Andersen JS, Jacobsen RK, Badsberg JH, Jorgensen T, Pisinger C. Psychological consequences of screening for cardiovascular risk factors in an unselected general population: results from the Inter99 randomised intervention study. *Scand J Public Health* 2015;**43**:102–110.
18. Jorgensen T, Ladelund S, Borch-Johnsen K, Pisinger C, Schrader AM, Thomsen T, Glumer C, Ibsen H, Mortensen EL. Screening for risk of cardiovascular disease is not associated with mental distress: the Inter99 study. *Prev Med* 2009;**48**:242–246.
19. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Smith N, Webber E, Perdue LA, Bigler KD, Whitlock EP. *Screening for High Blood Pressure in Adults: A Systematic Evidence Review for the U.S. Preventive Services Task Force*. Rockville (MD); 2014.
20. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Boren J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen MR, Tokgozoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* 2017;**38**:2459–2472.
21. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**:1670–1681.
22. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;**380**:581–590.
23. Pencina KM, Thanassoulis G, Wilkins JT, Vasan RS, Navar AM, Peterson ED, Pencina MJ, Sniderman AD. Trajectories of Non-HDL Cholesterol Across

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Midlife: Implications for Cardiovascular Prevention. *J Am Coll Cardiol* 2019;**74**:70–79.
24. Emerging Risk Factors Collaboration, Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;**302**:1993–2000.
25. Holmes MV, Asselbergs FW, Palmer TM, Drenos F, Lanktree MB, Nelson CP, Dale CE, Padmanabhan S, Finan C, Swerdlow DI, Tragante V, van Iperen EP, Sivapalaratnam S, Shah S, Elbers CC, Shah T, Engmann J, Giambartolomei C, White J, Zabaneh D, Sofat R, McLachlan S, UCLEB consortium, Doevendans PA, Balmforth AJ, Hall AS, North KE, Almoguera B, Hoogeveen RC, Cushman M, Fornage M, Patel SR, Redline S, Siscovick DS, Tsai MY, Karczewski KJ, Hofker MH, Verschuren WM, Bots ML, van der Schouw YT, Melander O, Dominiczak AF, Morris R, Ben-Shlomo Y, Price J, Kumari M, Baumert J, Peters A, Thorand B, Koenig W, Gaunt TR, Humphries SE, Clarke R, Watkins H, Farrall M, Wilson JG, Rich SS, de Bakker PI, Lange LA, Davey Smith G, Reiner AP, Talmud PJ, Kivimaki M, Lawlor DA, Dudbridge F, Samani NJ, Keating BJ, Hingorani AD, Casas JP. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J* 2015;**36**:539–550.
26. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Holm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, Konig IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schafer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* 2012;**380**:572–580.
27. Frikke-Schmidt R, Nordestgaard BG, Stene MC, Sethi AA, Remaley AT, Schnohr P, Grande P, Tybjaerg-Hansen A. Association of loss-of-function mutations in the ABCA1 gene with high-density lipoprotein cholesterol levels and risk of ischemic heart disease. *JAMA* 2008;**299**:2524–2532.
28. HPS3/TIMI55–REVEAL Collaborative Group, Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E, Landray MJ. Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease. *N Engl J Med* 2017;**377**:1217–1227.
29. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, Amann M, Anderson HR, Andrews KG, Aryee M, Atkinson C, Bacchus LJ, Bahalim AN, Balakrishnan K, Balmes J, Barker-Collo S, Baxter A, Bell ML, Blore JD, Blyth F, Bonner C, Borges G, Bourne R, Boussinesq M, Brauer M, Brooks P, Bruce NG, Brunekreef B, Bryan-Hancock C, Bucello C, Buchbinder R, Bull F, Burnett RT, Byers TE, Calabria B, Carapetis J, Carnahan E, Chafe Z, Charlson F, Chen H, Chen JS, Cheng AT, Child JC, Cohen A, Colson KE, Cowie BC, Darby S, Darling S, Davis A, Degenhardt L, Dentener F, Des Jarlais DC, Devries K, Dherani M, Ding EL, Dorsey ER, Driscoll T, Edmond K, Ali SE, Engell RE, Erwin PJ, Fahimi S, Falder G, Farzadfar F, Ferrari A, Finucane MM, Flaxman S, Fowkes FG, Freedman G, Freeman MK, Gakidou E, Ghosh S, Giovannucci E, Gmel G, Graham K, Grainger R, Grant B, Gunnell D, Gutierrez HR, Hall W, Hoek HW, Hogan A, Hosgood HD, 3rd, Hoy D, Hu H, Hubbell BJ, Hutchings SJ, Ibeanusi SE, Jacklyn GL, Jasrasaria R, Jonas JB, Kan H, Kanis JA, Kassebaum N, Kawakami N, Khang YH, Khatibzadeh S, Khoo JP, Kok C, Laden F, Lalloo R, Lan Q, Lathlean T, Leasher JL, Leigh J, Li Y, Lin JK, Lipshultz SE, London S, Lozano R, Lu Y, Mak J, Malekzadeh R, Mallinger L, Marcenes W, March L, Marks R, Martin R, McGale P, McGrath J, Mehta S, Mensah GA, Merriman TR, Micha R, Michaud C, Mishra V, Mohd Hanafiah K, Mokdad AA, Morawska L, Mozaffarian D, Murphy T, Naghavi M, Neal B, Nelson PK, Nolla JM, Norman R, Olives C, Omer SB, Orchard J, Osborne R, Ostro B, Page A, Pandey KD, Parry CD, Passmore E, Patra J, Pearce N, Pelizzari PM, Petzold M, Phillips MR, Pope D, Pope CA, 3rd, Powles J, Rao M, Razavi H, Rehfuess EA, Rehm JT, Ritz B, Rivara FP, Roberts T, Robinson C, Rodriguez-Portales JA, Romieu I, Room R, Rosenfeld LC, Roy A, Rushton L, Salomon JA, Sampson U, Sanchez-Riera L, Sanman E, Sapkota A, Seedat S, Shi P, Shield K, Shivakoti R, Singh GM, Sleet DA, Smith E, Smith KR, Stapelberg NJ, Steenland K, Stockl H, Stovner LJ, Straif K, Straney L, Thurston GD, Tran JH, Van Dingenen R, van Donkelaar A, Veerman JL, Vijayakumar L, Weintraub R, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams W, Wilson N, Woolf AD, Yip P, Zielinski JM, Lopez AD, Murray CJ, Ezzati M, AlMazroa MA, Memish ZA. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2224–2260.
30. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360**:1903–1913.
31. Whelton SP, McEvoy JW, Shaw L, Psaty BM, Lima JAC, Budoff M, Nasir K, Szklo M, Blumenthal RS, Blaha MJ. Association of Normal Systolic Blood Pressure Level With Cardiovascular Disease in the Absence of Risk Factors. *JAMA Cardiol* 2020;**5**:1011–1018.
32. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, Benzeval M, Brunner E, Cooper R, Kivimaki M, Kuh D, Muniz-Terrera G, Hardy R. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. *PLoS Med* 2011;**8**:e1000440.
33. Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, Claggett B, Merz CNB, Cheng S. Sex Differences in Blood Pressure Associations With Cardiovascular Outcomes. *Circulation* 2021;**143**:761–763.
34. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, Cheng S. Sex Differences in Blood Pressure Trajectories Over the Life Course. *JAMA Cardiol* 2020;**5**:19–26.
35. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;**328**:1519.
36. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998;**316**:1043–1047.
37. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet* 2011;**378**:1297–1305.
38. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1923–1994.
39. Lv X, Sun J, Bi Y, Xu M, Lu J, Zhao L, Xu Y. Risk of all-cause mortality and cardiovascular disease associated with secondhand smoke exposure: a systematic review and meta-analysis. *Int J Cardiol* 2015;**199**:106–115.
40. Gupta R, Gupta S, Sharma S, Sinha DN, Mehrotra R. Risk of Coronary Heart Disease Among Smokeless Tobacco Users: Results of Systematic Review and Meta-Analysis of Global Data. *Nicotine Tob Res* 2019;**21**:25–31.
41. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**:2215–2222.
42. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. *Lancet* 2014;**383**:1973–1980.
43. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017;**390**:2627–2642.
44. Sun YQ, Burgess S, Staley JR, Wood AM, Bell S, Kaptoge SK, Guo Q, Bolton TR, Mason AM, Butterworth AS, Di Angelantonio E, Vie GA, Bjorngaard JH, Kinge JM, Chen Y, Mai XM. Body mass index and all cause mortality in HUNT and UK Biobank studies: linear and non-linear mendelian randomisation analyses. *BMJ* 2019;**364**:l1042.
45. Global BMI Mortality Collaboration, Di Angelantonio E, Bhupathiraju Sh N, Wormser D, Gao P, Kaptoge S, Berrington de Gonzalez A, Cairns BJ, Huxley R, Jackson Ch L, Joshy G, Lewington S, Manson JE, Murphy N, Patel AV, Samet JM, Woodward M, Zheng W, Zhou M, Bansal N, Barricarte A, Carter B, Cerhan JR, Smith GD, Fang X, Franco OH, Green J, Halsey J, Hildebrand JS, Jung KJ, Korda RJ, McLerran DF, Moore SC, O'Keeffe LM, Paige E, Ramond A, Reeves GK, Rolland B, Sacerdote C, Sattar N, Sofianopoulou E, Stevens J, Thun M, Ueshima H, Yang L, Yun YD, Willeit P, Banks E, Beral V, Chen Z, Gapstur SM, Gunter MJ, Hartge P, Jee SH, Lam TH, Peto R, Potter JD, Willett WC, Thompson SG, Danesh J, Hu FB. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;**388**:776–786.
46. Aune D, Sen A, Prasad M, Norat T, Janszky I, Tonstad S, Romundstad P, Vatten LJ. BMI and all cause mortality: systematic review and non-linear dose-response

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meta-analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ* 2016;**353**:i2156.
47. Emerging Risk Factors Collaboration, Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011;**377**:1085–1095.
48. World Health Organization. *Gender and health*. https://www.who.int/health-topics/gender#tab=tab_1 (4 June 2021).
49. Global Health 50/50. Gender and global health. https://globalhealth5050.org/gender-and-global-health (4 June 2021).
50. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, De Vries GJ, Epperson CN, Govindan R, Klein SL, Lonardo A, Maki PM, McCullough LD, Regitz-Zagrosek V, Regensteiner JG, Rubin JB, Sandberg K, Suzuki A. Sex and gender: modifiers of health, disease, and medicine. *Lancet* 2020;**396**:565–582.
51. Peters SAE, Muntner P, Woodward M. Sex Differences in the Prevalence of, and Trends in, Cardiovascular Risk Factors, Treatment, and Control in the United States, 2001 to 2016. *Circulation* 2019;**139**:1025–1035.
52. Lee CMY, Mnatzaganian G, Woodward M, Chow CK, Sitas F, Robinson S, Huxley RR. Sex disparities in the management of coronary heart disease in general practices in Australia. *Heart* 2019;**105**:1898–1904.
53. Cushman M, Shay CM, Howard VJ, Jimenez MC, Lewey J, McSweeney JC, Newby LK, Poudel R, Reynolds HR, Rexrode KM, Sims M, Mosca LJ, American Heart Association. Ten-Year Differences in Women's Awareness Related to Coronary Heart Disease: Results of the 2019 American Heart Association National Survey: A Special Report From the American Heart Association. *Circulation* 2021;**143**:e239–e248.
54. Pelletier R, Khan NA, Cox J, Daskalopoulou SS, Eisenberg MJ, Bacon SL, Lavoie KL, Daskupta K, Rabi D, Humphries KH, Norris CM, Thanassoulis G, Behlouli H, Pilote L, GENESIS-PRAXY Investigators. Sex Versus Gender-Related Characteristics: Which Predicts Outcome After Acute Coronary Syndrome in the Young? *J Am Coll Cardiol* 2016;**67**:127–135.
55. Bots SH, Groepenhoff F, Eikendal ALM, Tannenbaum C, Rochon PA, Regitz-Zagrosek V, Miller VM, Day D, Asselbergs FW, den Ruijter HM. Adverse Drug Reactions to Guideline-Recommended Heart Failure Drugs in Women: A Systematic Review of the Literature. *JACC Heart Fail* 2019;**7**:258–266.
56. Regitz-Zagrosek V, Seeland U. Sex and gender differences in clinical medicine. *Handb Exp Pharmacol* 2012:3–22.
57. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, Kirchner HL, Manus JNA, James N, Ayar Z, Gladding P, Good CW, Cleland JGF, Fornwalt BK. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J* 2020;**41**:1249–1257.
58. Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, Canham RM, Levine BD, Drazner MH. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: the Dallas Heart Study. *Circulation* 2006;**113**:1597–1604.
59. Maas A, Rosano G, Cifkova R, Chieffo A, van Dijken D, Hamoda H, Kunadian V, Laan E, Lambrinoudaki I, Maclaran K, Panay N, Stevenson JC, van Trotsenburg M, Collins P. Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists. *Eur Heart J* 2021;**42**:967–984.
60. Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *BMJ* 1995;**311**:1356–1359.
61. Dorresteijn JA, Visseren FL, Ridker PM, Wassink AM, Paynter NP, Steyerberg EW, van der Graaf Y, Cook NR. Estimating treatment effects for individual patients based on the results of randomised clinical trials. *BMJ* 2011;**343**:d5888.
62. Fox CS, Matsushita K, Woodward M, Bilo HJ, Chalmers J, Heerspink HJ, Lee BJ, Perkins RM, Rossing P, Sairenchi T, Tonelli M, Vassalotti JA, Yamagishi K, Coresh J, de Jong PE, Wen CP, Nelson RG, Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet* 2012;**380**:1662–1673.
63. Robbins JM, Strauss G, Aron D, Long J, Kuba J, Kaplan Y. Mortality rates and diabetic foot ulcers: is it time to communicate mortality risk to patients with diabetic foot ulceration? *J Am Podiatr Med Assoc* 2008;**98**:489–493.
64. Brownrigg JR, Hughes CO, Burleigh D, Karthikesalingam A, Patterson BO, Holt PJ, Thompson MM, de Lusignan S, Ray KK, Hinchliffe RJ. Microvascular disease and risk of cardiovascular events among individuals with type 2 diabetes: a population-level cohort study. *Lancet Diabetes Endocrinol* 2016;**4**:588–597.
65. International Society of Nephrology. KDIGO 2020 *Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease*. https://kdigo.org/wp-content/uploads/2020/10/KDIGO-2020-Diabetes-in-CKD-GL.pdf (4 June 2021).
66. Cersosimo E, Johnson EL, Chovanes C, Skolnik N. Initiating therapy in patients newly diagnosed with type 2 diabetes: Combination therapy vs a stepwise approach. *Diabetes Obes Metab* 2018;**20**:497–507.
67. Rodbard HW, Visco VE, Andersen H, Hiort LC, Shu DH. Treatment intensification with stepwise addition of prandial insulin aspart boluses compared with full basal-bolus therapy (FullSTEP Study): a randomised, treat-to-target clinical trial. *Lancet Diabetes Endocrinol* 2014;**2**:30–37.
68. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J* 2021;**42**:2439–2454.
69. Kannel WB. Coronary heart disease risk factors in the elderly. *Am J Geriatr Cardiol* 2002;**11**:101–107.
70. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;**20**:555–561.
71. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc* 2010;**58**:783–787.
72. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. *Eur Heart J* 2021;**42**:2455–2467.
73. World Health Organization. Disease burden and mortality estimates. www.who.int/healthinfo/global_burden_disease/estimates/en (4 June 2021).
74. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, Burgess S, Willeit P, Bolton T, Moons KGM, van der Schouw YT, Selmer R, Khaw KT, Gudnason V, Assmann G, Amouyel P, Salomaa V, Kivimaki M, Nordestgaard BG, Blaha MJ, Kuller LH, Brenner H, Gillum RF, Meisinger C, Ford I, Knuiman MW, Rosengren A, Lawlor DA, Volzke H, Cooper C, Marin Ibanez A, Casiglia E, Kauhanen J, Cooper JA, Rodriguez B, Sundstrom J, Barrett-Connor E, Dankner R, Nietert PJ, Davidson KW, Wallace RB, Blazer DG, Bjorkelund C, Donfrancesco C, Krumholz HM, Nissinen A, Davis BR, Coady S, Whincup PH, Jorgensen T, Ducimetiere P, Trevisan M, Engstrom G, Crespo CJ, Meade TW, Visser M, Kromhout D, Kiechl S, Daimon M, Price JF, Gomez de la Camara A, Wouter Jukema J, Lamarche B, Onat A, Simons LA, Kavousi M, Ben-Shlomo Y, Gallacher J, Dekker JM, Arima H, Shara N, Tipping RW, Roussel R, Brunner EJ, Koenig W, Sakurai M, Pavlovic J, Gansevoort RT, Nagel D, Goldbourt U, Barr ELM, Palmieri L, Njolstad I, Sato S, Monique Verschuren WM, Varghese CV, Graham I, Onuma O, Greenland P, Woodward M, Ezzati M, Psaty BM, Sattar N, Jackson R, Ridker PM, Cook NR, D'Agostino RB, Thompson SG, Danesh J, Di Angelantonio E, Emerging Risk Factors Collaboration. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participant meta-analysis of 86 prospective studies. *Eur Heart J* 2019;**40**:621–631.
75. Berkelmans GFN, Gudbjornsdottir S, Visseren FLJ, Wild SH, Franzen S, Chalmers J, Davis BR, Poulter NR, Spijkerman AM, Woodward M, Pressel SL, Gupta AK, van der Schouw YT, Svensson AM, van der Graaf Y, Read SH, Eliasson B, Dorresteijn JAN. Prediction of individual life-years gained without cardiovascular events from lipid, blood pressure, glucose, and aspirin treatment based on data of more than 500 000 patients with Type 2 diabetes mellitus. *Eur Heart J* 2019;**40**:2899–2906.
76. Jaspers NEM, Blaha MJ, Matsushita K, van der Schouw YT, Wareham NJ, Khaw KT, Geisel MH, Lehmann N, Erbel R, Jockel KH, van der Graaf Y, Verschuren WMM, Boer JMA, Nambi V, Visseren FLJ, Dorresteijn JAN. Prediction of individualized lifetime benefit from cholesterol lowering, blood pressure lowering, antithrombotic therapy, and smoking cessation in apparently healthy people. *Eur Heart J* 2020;**41**:1190–1199.
77. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, Wilson PWF, D'Agostino RB, Sr., Massaro JM, van der Graaf Y, Cramer MJM, Kappelle LJ, de Borst GJ, Steg PG, Visseren FLJ. Estimated Life Expectancy Without Recurrent Cardiovascular Events in Patients With Vascular Disease: The SMART-REACH Model. *J Am Heart Assoc* 2018;**7**:e009217.
78. Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, Cobain M, Piepoli MF, Visseren FL, Dendale P. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). *Eur J Cardiovasc Nurs* 2019;**18**:534–544.
79. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. *Circ Res* 2019;**124**:1045–1060.
80. Ference BA, Bhatt DL, Catapano AL, Packard CJ, Graham I, Kaptoge S, Ference TB, Guo Q, Laufs U, Ruff CT, Cupido A, Hovingh GK, Danesh J, Holmes MV, Smith GD, Ray KK, Nicholls SJ, Sabatine MS. Association of Genetic Variants Related to Combined Exposure to Lower Low-Density Lipoproteins and Lower Systolic Blood Pressure With Lifetime Risk of Cardiovascular Disease. *JAMA* 2019;**322**:1381–1391.

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81. Kaasenbrood L, Boekholdt SM, van der Graaf Y, Ray KK, Peters RJ, Kastelein JJ, Amarenco P, LaRosa JC, Cramer MJ, Westerink J, Kappelle LJ, de Borst GJ, Visseren FL. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. *Circulation* 2016;**134**:1419–1429.
82. De Bacquer D, Ueda P, Reiner Z, De Sutter J, De Smedt D, Lovic D, Gotcheva N, Fras Z, Pogosova N, Mirrakhimov E, Lehto S, Jernberg T, Kotseva K, Ryden L, Wood D, EUROASPIRE IV and V National Coordinators. Prediction of recurrent event in patients with coronary heart disease: the EUROASPIRE Risk Model. *Eur J Prev Cardiol* 2020:[Online ahead of print].
83. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Stork S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S, COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *N Engl J Med* 2017;**377**:1319–1330.
84. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Jr., Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM, REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019;**380**:11–22.
85. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL, LoDoCo2 Trial Investigators. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med* 2020;**383**:1838–1847.
86. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, Lopez-Sendon J, Ostadal P, Koenig W, Angoulvant D, Gregoire JC, Lavoie MA, Dube MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019;**381**:2497–2505.
87. Sattar N, Rawshani A, Franzen S, Rawshani A, Svensson AM, Rosengren A, McGuire DK, Eliasson B, Gudbjornsdottir S. Age at Diagnosis of Type 2 Diabetes Mellitus and Associations With Cardiovascular and Mortality Risks. *Circulation* 2019;**139**:2228–2237.
88. Kaasenbrood L, Poulter NR, Sever PS, Colhoun HM, Livingstone SJ, Boekholdt SM, Pressel SL, Davis BR, van der Graaf Y, Visseren FL, CARDS, ALLHAT, and ASCOT Investigators. Development and Validation of a Model to Predict Absolute Vascular Risk Reduction by Moderate-Intensity Statin Therapy in Individual Patients With Type 2 Diabetes Mellitus: The Anglo Scandinavian Cardiac Outcomes Trial, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, and Collaborative Atorvastatin Diabetes Study. *Circ Cardiovasc Qual Outcomes* 2016;**9**:213–221.
89. Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, Chalmers J, Colagiuri S, Grobbee DE, Hamet P, Heller S, Neal B, Woodward M, ADVANCE Collaborative Group. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:393–398.
90. Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001;**101**:671–679.
91. Rawshani A, Sattar N, Franzen S, Rawshani A, Hattersley AT, Svensson AM, Eliasson B, Gudbjornsdottir S. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet* 2018;**392**:477–486.
92. Rawshani A, Rawshani A, Sattar N, Franzen S, McGuire DK, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, Rosengren A, Gudbjornsdottir S. Relative Prognostic Importance and Optimal Levels of Risk Factors for Mortality and Cardiovascular Outcomes in Type 1 Diabetes Mellitus. *Circulation* 2019;**139**:1900–1912.
93. Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J, Cleland S, Leese GP, McKnight J, Morris AD, Pearson DW, Peden NR, Petrie JR, Philip S, Sattar N, Sullivan F, Colhoun HM. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. *PLoS Med* 2012;**9**:e1001321.
94. Spiegelhalter D, Pearson M, Short I. Visualizing uncertainty about the future. *Science* 2011;**333**:1393–1400.
95. Zipkin DA, Umscheid CA, Keating NL, Allen E, Aung K, Beyth R, Kaatz S, Mann DM, Sussman JB, Korenstein D, Schardt C, Nagi A, Sloane R, Feldstein DA. Evidence-based risk communication: a systematic review. *Ann Intern Med* 2014;**161**:270–280.
96. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2017;**3**:CD006887.
97. Damman OC, Vonk SI, van den Haak MJ, van Hooijdonk CMJ, Timmermans DRM. The effects of infographics and several quantitative versus qualitative formats for cardiovascular disease risk, including heart age, on people's risk understanding. *Patient Educ Couns* 2018;**101**:1410–1418.
98. Cooney MT, Vartiainen E, Laatikainen T, De Bacquer D, McGorrian C, Dudina A, Graham I, SCORE and FINRISK investigators. Cardiovascular risk age: concepts and practicalities. *Heart* 2012;**98**:941–946.
99. Cuende JI, Cuende N, Calaveras-Lagartos J. How to calculate vascular age with the SCORE project scales: a new method of cardiovascular risk evaluation. *Eur Heart J* 2010;**31**:2351–2358.
100. Albus C, Waller C, Fritzsche K, Gunold H, Haass M, Hamann B, Kindermann I, Kollner V, Leithauser B, Marx N, Meesmann M, Michal M, Ronel J, Scherer M, Schrader V, Schwaab B, Weber CS, Herrmann-Lingen C. Significance of psychosocial factors in cardiology: update 2018 : Position paper of the German Cardiac Society. *Clin Res Cardiol* 2019;**108**:1175–1196.
101. Schnohr P, Marott JL, Kristensen TS, Gyntelberg F, Gronbaek M, Lange P, Jensen MT, Jensen GB, Prescott E. Ranking of psychosocial and traditional risk factors by importance for coronary heart disease: the Copenhagen City Heart Study. *Eur Heart J* 2015;**36**:1385–1393.
102. Kim JM, Stewart R, Kang HJ, Kim SY, Kim JW, Lee HJ, Lee JY, Kim SW, Shin IS, Kim MC, Shin HY, Hong YJ, Ahn Y, Jeong MH, Yoon JS. Long-term cardiac outcomes of depression screening, diagnosis and treatment in patients with acute coronary syndrome: the DEPACS study. *Psychol Med* 2020:1–11.
103. Lin JS, Evans CV, Johnson E, Redmond N, Coppola EL, Smith N. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2018;**320**:281–297.
104. Peters SA, den Ruijter HM, Bots ML, Moons KG. Improvements in risk stratification for the occurrence of cardiovascular disease by imaging subclinical atherosclerosis: a systematic review. *Heart* 2012;**98**:177–184.
105. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;**357**:j2099.
106. Tzoulaki I, Siontis KC, Evangelou E, Ioannidis JP. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med* 2013;**173**:664–671.
107. Kooter AJ, Kostense PJ, Groenewold J, Thijs A, Sattar N, Smulders YM. Integrating information from novel risk factors with calculated risks: the critical impact of risk factor prevalence. *Circulation* 2011;**124**:741–745.
108. Kivimaki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol* 2018;**15**:215–229.
109. Rozanski A. Behavioral cardiology: current advances and future directions. *J Am Coll Cardiol* 2014;**64**:100–110.
110. Crawshaw J, Auyeung V, Norton S, Weinman J. Identifying psychosocial predictors of medication non-adherence following acute coronary syndrome: A systematic review and meta-analysis. *J Psychosom Res* 2016;**90**:10–32.
111. Steinberg ML, Williams JM, Li Y. Poor Mental Health and Reduced Decline in Smoking Prevalence. *Am J Prev Med* 2015;**49**:362–369.
112. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sitthi-amorn C, Sato H, Yusuf S, INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**:953–962.
113. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Koller A, Manfrini O, Milicic D, Padro T, Pries AR, Quyyumi AA, Tousoulis D, Trifunovic D, Vasiljevic Z, de Wit C, Bugiardini R, ESC Scientific Document Group Reviewers. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *Eur Heart J* 2020;**41**:1687–1696.
114. Albus C, Barkhausen J, Fleck E, Haasenritter J, Lindner O, Silber S. The Diagnosis of Chronic Coronary Heart Disease. *Dtsch Arztebl Int* 2017;**114**:712–719.
115. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and Management of Depression in Patients With Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;**73**:1827–1845.
116. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999;**282**:1737–1744.
117. Celano CM, Suarez L, Mastromauro C, Januzzi JL, Huffman JC. Feasibility and utility of screening for depression and anxiety disorders in patients with cardiovascular disease. *Circ Cardiovasc Qual Outcomes* 2013;**6**:498–504.
118. MacGregor KL, Funderburk JS, Pigeon W, Maisto SA. Evaluation of the PHQ-9 Item 3 as a screen for sleep disturbance in primary care. *J Gen Intern Med* 2012;**27**:339–344.

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119. Hadamitzky M, Freissmuth B, Meyer T, Hein F, Kastrati A, Martinoff S, Schomig A, Hausleiter J. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. *JACC Cardiovasc Imaging* 2009;**2**:404–411.
120. SCOT-HEART Investigators, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M, Forbes J, Hunter A, Lewis S, MacLean S, Mills NL, Norrie J, Roditi G, Shah ASV, Timmis AD, van Beek EJR, Williams MC. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. *N Engl J Med* 2018;**379**:924–933.
121. Den Ruijter HM, Peters SA, Anderson TJ, Britton AR, Dekker JM, Eijkemans MJ, Engstrom G, Evans GW, de Graaf J, Grobbee DE, Hedblad B, Hofman A, Holewijn S, Ikeda A, Kavousi M, Kitagawa K, Kitamura A, Koffijberg H, Lonn EM, Lorenz MW, Mathiesen EB, Nijpels G, Okazaki S, O'Leary DH, Polak JF, Price JF, Robertson C, Rembold CM, Rosvall M, Rundek T, Salonen JT, Sitzer M, Stehouwer CD, Witteman JC, Moons KG, Bots ML. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA* 2012;**308**:796–803.
122. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS, American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;**21**:93–111; quiz 189-190.
123. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol* 2010;**55**:1318–1327.
124. McDermott MM, Greenland P, Liu K, Guralnik JM, Celic L, Criqui MH, Chan C, Martin GJ, Schneider J, Pearce WH, Taylor LM, Clark E. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. *Ann Intern Med* 2002;**136**:873–883.
125. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, Folsom AR, Hirsch AT, Dramaix M, deBacker G, Wautrecht JC, Kornitzer M, Newman AB, Cushman M, Sutton-Tyrrell K, Fowkes FG, Lee AJ, Price JF, d'Agostino RB, Murabito JM, Norman PE, Jamrozik K, Curb JD, Masaki KH, Rodriguez BL, Dekker JM, Bouter LM, Heine RJ, Nijpels G, Stehouwer CD, Ferrucci L, McDermott MM, Stoffers HE, Hooi JD, Knottnerus JA, Ogren M, Hedblad B, Witteman JC, Breteler MM, Hunink MG, Hofman A, Criqui MH, Langer RD, Fronek A, Hiatt WR, Hamman R, Resnick HE, Guralnik J, McDermott MM. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
126. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014;**63**:747–762.
127. Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J* 2014;**35**:1726–1731.
128. Tamura Y, Ishikawa J, Fujiwara Y, Tanaka M, Kanazawa N, Chiba Y, Iizuka A, Kaito S, Tanaka J, Sugie M, Nishimura T, Kanemaru A, Shimoji K, Hirano H, Furuta K, Kitamura A, Seino S, Shinkai S, Harada K, Kyo S, Ito H, Araki A. Prevalence of frailty, cognitive impairment, and sarcopenia in outpatients with cardiometabolic disease in a frailty clinic. *BMC Geriatr* 2018;**18**:264.
129. Chainani V, Shaharyar S, Dave K, Choksi V, Ravindranathan S, Hanno R, Jamal O, Abdo A, Abi Rafeh N. Objective measures of the frailty syndrome (hand grip strength and gait speed) and cardiovascular mortality: A systematic review. *Int J Cardiol* 2016;**215**:487–493.
130. Higueras-Fresnillo S, Cabanas-Sanchez V, Lopez-Garcia E, Esteban-Cornejo I, Banegas JR, Sadarangani KP, Rodriguez-Artalejo F, Martinez-Gomez D. Physical Activity and Association Between Frailty and All-Cause and Cardiovascular Mortality in Older Adults: Population-Based Prospective Cohort Study. *J Am Geriatr Soc* 2018;**66**:2097–2103.
131. Vaes B, Depoortere D, Van Pottelbergh G, Mathei C, Neto J, Degryse J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. *BMC Geriatr* 2017;**17**:234.
132. Vigorito C, Abreu A, Ambrosetti M, Belardinelli R, Corra U, Cupples M, Davos CH, Hoefer S, Iliou MC, Schmid JP, Voeller H, Doherty P. Frailty and cardiac rehabilitation: A call to action from the EAPC Cardiac Rehabilitation Section. *Eur J Prev Cardiol* 2017;**24**:577–590.
133. Bachmann JM, Willis BL, Ayers CR, Khera A, Berry JD. Association between family history and coronary heart disease death across long-term follow-up in men: the Cooper Center Longitudinal Study. *Circulation* 2012;**125**:3092–3098.
134. Tikkanen E, Havulinna AS, Palotie A, Salomaa V, Ripatti S. Genetic risk prediction and a 2-stage risk screening strategy for coronary heart disease. *Arterioscler Thromb Vasc Biol* 2013;**33**:2261–2266.
135. Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, Guiducci C, Perola M, Jula A, Sinisalo J, Lokki ML, Nieminen MS, Melander O, Salomaa V, Peltonen L, Kathiresan S. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet* 2010;**376**:1393–1400.
136. Sivapalaratnam S, Boekholdt SM, Trip MD, Sandhu MS, Luben R, Kastelein JJ, Wareham NJ, Khaw KT. Family history of premature coronary heart disease and risk prediction in the EPIC-Norfolk prospective population study. *Heart* 2010;**96**:1985–1989.
137. Veronesi G, Gianfagna F, Giampaoli S, Chambless LE, Mancia G, Cesana G, Ferrario MM. Improving long-term prediction of first cardiovascular event: the contribution of family history of coronary heart disease and social status. *Prev Med* 2014;**64**:75–80.
138. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;**308**:788–795.
139. Antiochos P, Marques-Vidal P, McDaid A, Waeber G, Vollenweider P. Association between parental history and genetic risk scores for coronary heart disease prediction: The population-based CoLaus study. *Atherosclerosis* 2016;**244**:59–65.
140. van Dis I, Geleijnse JM, Kromhout D, Boer J, Boshuizen H, Verschuren WM. Do obesity and parental history of myocardial infarction improve cardiovascular risk prediction? *Eur J Prev Cardiol* 2013;**20**:793–799.
141. Merry AH, Boer JM, Schouten LJ, Ambergen T, Steyerberg EW, Feskens EJ, Verschuren WM, Gorgels AP, van den Brandt PA. Risk prediction of incident coronary heart disease in The Netherlands: re-estimation and improvement of the SCORE risk function. *Eur J Prev Cardiol* 2012;**19**:840–848.
142. Musunuru K, Kathiresan S. Genetics of Common, Complex Coronary Artery Disease. *Cell* 2019;**177**:132–145.
143. Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet* 2018;**19**:581–590.
144. Lambert SA, Gil L, Jupp S, Ritchie SC, Xu Y, Buniello A, McMahon A, Abraham G, Chapman M, Parkinson H, Danesh J, MacArthur JAL, Inouye M. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat Genet* 2021;**53**:420–425.
145. Wand H, Lambert SA, Tamburro C, Iacocca MA, O'Sullivan JW, Sillari C, Kullo IJ, Rowley R, Dron JS, Brockman D, Venner E, McCarthy MI, Antoniou AC, Easton DF, Hegele RA, Khera AV, Chatterjee N, Kooperberg C, Edwards K, Vlessis K, Kinnear K, Danesh JN, Parkinson H, Ramos EM, Roberts MC, Ormond KE, Khoury MJ, Janssens A, Goddard KAB, Kraft P, MacArthur JAL, Inouye M, Wojcik GL. Improving reporting standards for polygenic scores in risk prediction studies. *Nature* 2021;**591**:211–219.
146. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. *Hum Mol Genet* 2019;**28**:R133–R142.
147. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, Ye S, Webb TR, Rutter MK, Tzoulaki I, Patel RS, Loos RJF, Keavney B, Hemingway H, Thompson J, Watkins H, Deloukas P, Di Angelantonio E, Butterworth AS, Danesh J, Samani NJ, UK Biobank CardioMetabolic Consortium CHD Working Group. Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults: Implications for Primary Prevention. *J Am Coll Cardiol* 2018;**72**:1883–1893.
148. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, Natarajan P, Lander ES, Lubitz SA, Ellinor PT, Kathiresan S. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet* 2018;**50**:1219–1224.
149. Sun L, Pennells L, Kaptoge S, Nelson CP, Ritchie SC, Abraham G, Arnold M, Bell S, Bolton T, Burgess S, Dudbridge F, Guo Q, Sofianopoulou E, Stevens D, Thompson JR, Butterworth AS, Wood A, Danesh J, Samani NJ, Inouye M, Di Angelantonio E. Polygenic risk scores in cardiovascular risk prediction: A cohort study and modelling analyses. *PLoS Med* 2021;**18**:e1003498.
150. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam M, Evangelou E, Moons KGM, Dehghan A, Muller DC, Elliott P, Tzoulaki I. Predictive Accuracy of a Polygenic Risk Score-Enhanced Prediction Model vs a Clinical Risk Score for Coronary Artery Disease. *JAMA* 2020;**323**:636–645.
151. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, Kundu S, Robinson-Cohen C, Psaty BM, Rich SS, Post WS, Guo X, Rotter JI, Roden DM, Gerszten RE, Wang TJ. Predictive Accuracy of a Polygenic Risk Score Compared With a Clinical Risk Score for Incident Coronary Heart Disease. *JAMA* 2020;**323**:627–635.
152. Levin MG, Rader DJ. Polygenic Risk Scores and Coronary Artery Disease: Ready for Prime Time? *Circulation* 2020;**141**:637–640.
153. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, Quyyumi AA, Taylor HA, Gulati M, Harold JG, Mieres JH, Ferdinand KC, Mensah GA, Sperling LS. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. *Circulation* 2018;**137**:2166–2178.
154. de Mestral C, Stringhini S. Socioeconomic Status and Cardiovascular Disease: an Update. *Curr Cardiol Rep* 2017;**19**:115.

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155. Khaing W, Vallibhakara SA, Attia J, McEvoy M, Thakkinstian A. Effects of education and income on cardiovascular outcomes: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**:1032–1042.
156. Kivimaki M, Pentti J, Ferrie JE, Batty GD, Nyberg ST, Jokela M, Virtanen M, Alfredsson L, Dragano N, Fransson EI, Goldberg M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Luukkonen R, Oksanen T, Rugulies R, Siegrist J, Singh-Manoux A, Suominen S, Theorell T, Vaananen A, Vahtera J, Westerholm PJM, Westerlund H, Zins M, Strandberg T, Steptoe A, Deanfield J, IPD-Work consortium. Work stress and risk of death in men and women with and without cardiometabolic disease: a multicohort study. *Lancet Diabetes Endocrinol* 2018;**6**:705–713.
157. Burroughs Pena MS, Rollins A. Environmental Exposures and Cardiovascular Disease: A Challenge for Health and Development in Low- and Middle-Income Countries. *Cardiol Clin* 2017;**35**:71–86.
158. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, Forastiere F, Franchini M, Franco OH, Graham I, Hoek G, Hoffmann B, Hoylaerts MF, Kunzli N, Mills N, Pekkanen J, Peters A, Piepoli MF, Rajagopalan S, Storey RF, ESC Working Group on Thrombosis, European Association for Cardiovascular Prevention and Rehabilitation, ESC Heart Failure Association. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015;**36**:83–93b.
159. Lelieveld J, Pozzer A, Poschl U, Fnais M, Haines A, Munzel T. Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective. *Cardiovasc Res* 2020;**116**:1910–1917.
160. Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho M, Saldiva PHN, Lavigne E, Matus P, Valdes Ortega N, Osorio Garcia S, Pascal M, Stafoggia M, Scortichini M, Hashizume M, Honda Y, Hurtado-Diaz M, Cruz J, Nunes B, Teixeira JP, Kim H, Tobias A, Iniguez C, Forsberg B, Astrom C, Ragettli MS, Guo YL, Chen BY, Bell ML, Wright CY, Scovronick N, Garland RM, Milojevic A, Kysely J, Urban A, Orru H, Indermitte E, Jaakkola JJK, Ryti NRI, Katsouyanni K, Analitis A, Zanobetti A, Schwartz J, Chen J, Wu T, Cohen A, Gasparrini A, Kan H. Ambient Particulate Air Pollution and Daily Mortality in 652 Cities. *N Engl J Med* 2019;**381**:705–715.
161. Argacha JF, Mizukami T, Bourdrel T, Bind MA. Ecology of the cardiovascular system: Part II - A focus on non-air related pollutants. *Trends Cardiovasc Med* 2019;**29**:274–282.
162. Ioannidis JP, Tzoulaki I. Minimal and null predictive effects for the most popular blood biomarkers of cardiovascular disease. *Circ Res* 2012;**110**:658–662.
163. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, Thompson A, Butterworth AS, Sarwar N, Wormser D, Saleheen D, Ballantyne CM, Psaty BM, Sundstrom J, Ridker PM, Nagel D, Gillum RF, Ford I, Ducimetiere P, Kiechl S, Koenig W, Dullaart RP, Assmann G, D'Agostino RB, Sr., Dagenais GR, Cooper JA, Kromhout D, Onat A, Tipping RW, Gomez-de-la-Camara A, Rosengren A, Sutherland SE, Gallacher J, Fowkes FG, Casiglia E, Hofman A, Salomaa V, Barrett-Connor E, Clarke R, Brunner E, Jukema JW, Simons LA, Sandhu M, Wareham NJ, Khaw KT, Kauhanen J, Salonen JT, Howard WJ, Nordestgaard BG, Wood AM, Thompson SG, Boekholdt SM, Sattar N, Packard C, Gudnason V, Danesh J. Lipid-related markers and cardiovascular disease prediction. *JAMA* 2012;**307**:2499–2506.
164. Kamstrup PR, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and improved cardiovascular risk prediction. *J Am Coll Cardiol* 2013;**61**:1146–1156.
165. Natriuretic Peptides Studies Collaboration, Willeit P, Kaptoge S, Welsh P, Butterworth AS, Chowdhury R, Spackman SA, Pennells L, Gao P, Burgess S, Freitag DF, Sweeting M, Wood AM, Cook NR, Judd S, Trompet S, Nambi V, Olsen MH, Everett BM, Kee F, Arnlov J, Salomaa V, Levy D, Kauhanen J, Laukkanen JA, Kavousi M, Ninomiya T, Casas JP, Daniels LB, Lind L, Kistorp CN, Rosenberg J, Mueller T, Rubattu S, Panagiotakos DB, Franco OH, de Lemos JA, Luchner A, Kizer JR, Kiechl S, Salonen JT, Goya Wannamethee S, de Boer RA, Nordestgaard BG, Andersson J, Jorgensen T, Melander O, Ballantyne Ch M, DeFilippi C, Ridker PM, Cushman M, Rosamond WD, Thompson SG, Gudnason V, Sattar N, Danesh J, Di Angelantonio E. Natriuretic peptides and integrated risk assessment for cardiovascular disease: an individual-participant-data meta-analysis. *Lancet Diabetes Endocrinol* 2016;**4**:840–849.
166. Willeit P, Welsh P, Evans JDW, Tschiderer L, Boachie C, Jukema JW, Ford I, Trompet S, Stott DJ, Kearney PM, Mooijaart SP, Kiechl S, Di Angelantonio E, Sattar N. High-Sensitivity Cardiac Troponin Concentration and Risk of First-Ever Cardiovascular Outcomes in 154,052 Participants. *J Am Coll Cardiol* 2017;**70**:558–568.
167. Lamelas PM, Maheer K, Schwalm JD. Body mass index and mortality after acute coronary syndromes: a systematic review and meta-analysis. *Acta Cardiol* 2017;**72**:655–661.
168. Ma WQ, Sun XJ, Wang Y, Han XQ, Zhu Y, Liu NF. Does body mass index truly affect mortality and cardiovascular outcomes in patients after coronary revascularization with percutaneous coronary intervention or coronary artery bypass graft? A systematic review and network meta-analysis. *Obes Rev* 2018;**19**:1236–1247.
169. Mahajan R, Stokes M, Elliott A, Munawar DA, Khokhar KB, Thiyagarajah A, Hendriks J, Linz D, Gallagher C, Kaye D, Lau D, Sanders P. Complex interaction of obesity, intentional weight loss and heart failure: a systematic review and meta-analysis. *Heart* 2020;**106**:58–68.
170. Bell JA, Hamer M, Sabia S, Singh-Manoux A, Batty GD, Kivimaki M. The natural course of healthy obesity over 20 years. *J Am Coll Cardiol* 2015;**65**:101–102.
171. Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, Klein B, Kronenberg F, Lee BJ, Li Y, Miura K, Navaneethan SD, Roderick PJ, Valdivielso JM, Visseren FLJ, Zhang L, Gansevoort RT, Hallan SI, Levey AS, Matsushita K, Shalev V, Woodward M, CKD Prognosis Consortium (CKD-PC). Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *BMJ* 2019;**364**:k5301.
172. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020;**395**:709–733.
173. Celutkiene J, Pudil R, Lopez-Fernandez T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, Cohen-Solal A, Farmakis D, Tocchetti CG, von Haehling S, Barberis V, Flachskampf FA, Ceponiene I, Haegler-Laube E, Suter T, Lapinskas T, Prasad S, de Boer RA, Wechalekar K, Anker MS, Iakobishvili Z, Bucciarelli-Ducci C, Schulz-Menger J, Cosyns B, Gaemperli O, Belenkov Y, Hulot JS, Galderisi M, Lancellotti P, Bax J, Marwick TH, Chioncel O, Jaarsma T, Mullens W, Piepoli M, Thum T, Heymans S, Mueller C, Moura B, Ruschitzka F, Zamorano JL, Rosano G, Coats AJS, Asteggiano R, Seferovic P, Edvardsen T, Lyon AR. Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:1504–1524.
174. Bosch X, Rovira M, Sitges M, Domenech A, Ortiz-Perez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzo M, Esteve J. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol* 2013;**61**:2355–2362.
175. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. *Eur J Cancer* 2013;**49**:2900–2909.
176. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, Kvien TK, Dougados M, Radner H, Atzeni F, Primdahl J, Sodergren A, Wallberg Jonsson S, van Rompay J, Zabalan C, Pedersen TR, Jacobsson L, de Vlam K, Gonzalez-Gay MA, Semb AG, Kitas GD, Smulders YM, Szekanecz Z, Sattar N, Symmons DP, Nurmohamed MT. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;**76**:17–28.
177. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, Troxel AB, Hennessy S, Kimmel SE, Margolis DJ, Choi H, Mehta NN, Gelfand JM. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;**74**:326–332.
178. Hung YM, Chang WP, Wei JC, Chou P, Wang PY. Midlife Ankylosing Spondylitis Increases the Risk of Cardiovascular Diseases in Males 5 Years Later: A National Population-Based Study. *Medicine (Baltimore)* 2016;**95**:e3596.
179. Adelborg K, Szepligeti SK, Holland-Bill L, Ehrenstein V, Horvath-Puho E, Henderson VW, Sorensen HT. Migraine and risk of cardiovascular diseases: Danish population based matched cohort study. *BMJ* 2018;**360**:k96.
180. Mahmoud AN, Mentias A, Elgendy AY, Qazi A, Barakat AF, Saad M, Mohsen A, Abuzaid A, Mansoor H, Mojadidi MK, Elgendy IY. Migraine and the risk of cardiovascular and cerebrovascular events: a meta-analysis of 16 cohort studies including 1 152 407 subjects. *BMJ Open* 2018;**8**:e020498.
181. Sacco S, Ornello R, Ripa P, Tiseo C, Degan D, Pistoia F, Carolei A. Migraine and risk of ischaemic heart disease: a systematic review and meta-analysis of observational studies. *Eur J Neurol* 2015;**22**:1001–1011.
182. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *BMJ* 1999;**318**:13–18.
183. Champaloux SW, Tepper NK, Monsour M, Curtis KM, Whiteman MK, Marchbanks PA, Jamieson DJ. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. *Am J Obstet Gynecol* 2017;**216**:489 e481–489 e487.
184. Engeland A, Bjorge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, Furu K. Risk of diabetes after gestational diabetes and preeclampsia. A registry-based study of 230,000 women in Norway. *Eur J Epidemiol* 2011;**26**:157–163.

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185. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;**53**:944–951.
186. Skjaerven R, Wilcox AJ, Klungsoyr K, Irgens LM, Vikse BE, Vatten LJ, Lie RT. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. *BMJ* 2012;**345**:e7677.
187. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WC. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003;**326**:845.
188. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009;**373**:1773–1779.
189. Moran LJ, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update* 2010;**16**:347–363.
190. Morgan CL, Jenkins-Jones S, Currie CJ, Rees DA. Evaluation of adverse outcome in young women with polycystic ovary syndrome versus matched, reference controls: a retrospective, observational study. *J Clin Endocrinol Metab* 2012;**97**:3251–3260.
191. Venkataraman H, Sattar N, Saravanan P. Postnatal testing following gestational diabetes: time to replace the oral glucose tolerance test? *Lancet Diabetes Endocrinol* 2015;**3**:754–756.
192. Bonamy AK, Parikh NI, Cnattingius S, Ludvigsson JF, Ingelsson E. Birth characteristics and subsequent risks of maternal cardiovascular disease: effects of gestational age and fetal growth. *Circulation* 2011;**124**:2839–2846.
193. Lykke JA, Paidas MJ, Damm P, Triche EW, Kuczynski E, Langhoff-Roos J. Preterm delivery and risk of subsequent cardiovascular morbidity and type-II diabetes in the mother. *BJOG* 2010;**117**:274–281.
194. Jager KJ, Kovesdy C, Langham R, Rosenberg M, Jha V, Zoccali C. A single number for advocacy and communication-worldwide more than 850 million individuals have kidney diseases. *Nephrol Dial Transplant* 2019;**34**:1803–1805.
195. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;**390**:1151–1210.
196. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, Matsushita K, Wen CP. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 2013;**382**:339–352.
197. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**:2073–2081.
198. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, Sarnak MJ. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol* 2003;**41**:47–55.
199. Dzaye O, Dudum R, Reiter-Brennan C, Kianoush S, Tota-Maharaj R, Cainzos-Achirica M, Blaha MJ. Coronary artery calcium scoring for individualized cardiovascular risk estimation in important patient subpopulations after the 2019 AHA/ACC primary prevention guidelines. *Prog Cardiovasc Dis* 2019;**62**:423–430.
200. Chen J, Budoff MJ, Reilly MP, Yang W, Rosas SE, Rahman M, Zhang X, Roy JA, Lustigova E, Nessel L, Ford V, Raj D, Porter AC, Soliman EZ, Wright JT, Jr., Wolf M, He J, CRIC Investigators. Coronary Artery Calcification and Risk of Cardiovascular Disease and Death Among Patients With Chronic Kidney Disease. *JAMA Cardiol* 2017;**2**:635–643.
201. Matsushita K, Sang Y, Ballew SH, Shlipak M, Katz R, Rosas SE, Peralta CA, Woodward M, Kramer HJ, Jacobs DR, Sarnak MJ, Coresh J. Subclinical atherosclerosis measures for cardiovascular prediction in CKD. *J Am Soc Nephrol* 2015;**26**:439–447.
202. Kramer H, Toto R, Peshock R, Cooper R, Victor R. Association between chronic kidney disease and coronary artery calcification: the Dallas Heart Study. *J Am Soc Nephrol* 2005;**16**:507–513.
203. Budoff MJ, Rader DJ, Reilly MP, Mohler ER, 3rd, Lash J, Yang W, Rosen L, Glenn M, Teal V, Feldman HI, CRIC Study Investigators. Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2011;**58**:519–526.
204. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. *Lancet* 2016;**388**:276–284.
205. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 2016;**354**:i4482.
206. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, Odutayo AA. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* 2016;**532**:h7013.
207. Lane DA, Skjoth F, Lip GYH, Larsen TB, Kotecha D. Temporal Trends in Incidence, Prevalence, and Mortality of Atrial Fibrillation in Primary Care. *J Am Heart Assoc* 2017;**6**:e005155.
208. Ko D, Rahman F, Schnabel RB, Yin X, Benjamin EJ, Christophersen IE. Atrial fibrillation in women: epidemiology, pathophysiology, presentation, and prognosis. *Nat Rev Cardiol* 2016;**13**:321–332.
209. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status: ARIC Study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol* 2018;**11**:e006350.
210. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Njolstad I, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Mathiesen E, Jorgensen T, Soderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB, BiomarCaRE Consortium. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). *Circulation* 2017;**136**:1588–1597.
211. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: does it exist? *J Am Coll Cardiol* 2014;**63**:1715–1723.
212. Allan V, Honarbakhsh S, Casas JP, Wallace J, Hunter R, Schilling R, Perel P, Morley K, Banerjee A, Hemingway H. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost* 2017;**117**:837–850.
213. Feghaly J, Zakka P, London B, MacRae CA, Refaat MM. Genetics of Atrial Fibrillation. *J Am Heart Assoc* 2018;**7**:e009884.
214. Staerk L, Wang B, Preis SR, Larson MG, Lubitz SA, Ellinor PT, McManus DD, Ko D, Weng LC, Lunetta KL, Frost L, Benjamin EJ, Trinquart L. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ* 2018;**361**:k1453.
215. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
216. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, Van Veldhuisen DJ, Crijns H, Van Gelder IC, RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–2996.
217. Parkash R, Wells GA, Sapp JL, Healey JS, Tardif JC, Greiss I, Rivard L, Roux JF, Gula L, Nault I, Novak P, Birnie D, Ha A, Wilton SB, Mangat I, Gray C, Gardner M, Tang ASL. Effect of Aggressive Blood Pressure Control on the Recurrence of Atrial Fibrillation After Catheter Ablation: A Randomized, Open-Label Clinical Trial (SMAC-AF [Substrate Modification With Aggressive Blood Pressure Control]). *Circulation* 2017;**135**:1788–1798.
218. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996;**27**:1760–1764.
219. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 2013;**158**:338–346.
220. Andersson T, Magnuson A, Bryngelsson IL, Frobert O, Henriksson KM, Edvardsson N, Poci D. All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study. *Eur Heart J* 2013;**34**:1061–1067.
221. An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, Esato M, Tsuji H, Wada H, Hasegawa K, Abe M, Lip GYH, Akao M. Causes of death in Japanese patients with atrial fibrillation: The Fushimi Atrial Fibrillation Registry. *Eur Heart J Qual Care Clin Outcomes* 2019;**5**:35–42.
222. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Bohm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the

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European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail* 2021;**23**:352–380.
223. Chew DS, Heikki H, Schmidt G, Kavanagh KM, Dommasch M, Bloch Thomsen PE, Sinnecker D, Raatikainen P, Exner DV. Change in Left Ventricular Ejection Fraction Following First Myocardial Infarction and Outcome. *JACC Clin Electrophysiol* 2018;**4**:672–682.
224. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. *J Clin Oncol* 2005;**23**:8597–8605.
225. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res* 2011;**13**:R64.
226. Darby S, McGale P, Peto R, Granath F, Hall P, Ekbom A. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. *BMJ* 2003;**326**:256–257.
227. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;**368**:987–998.
228. Dahlen T, Edgren G, Lambe M, Hoglund M, Bjorkholm M, Sandin F, Sjalander A, Richter J, Olsson-Stromberg U, Ohm L, Back M, Stenke L, Swedish CML Group, Swedish CML Register Group. Cardiovascular Events Associated With Use of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: A Population-Based Cohort Study. *Ann Intern Med* 2016;**165**:161–166.
229. Pudil R, Mueller C, Celutkiene J, Henriksen PA, Lenihan D, Dent S, Barac A, Stanway S, Moslehi J, Suter TM, Ky B, Sterba M, Cardinale D, Cohen-Solal A, Tocchetti CG, Farmakis D, Bergler-Klein J, Anker MS, Von Haehling S, Belenkov Y, Iakobishvili Z, Maack C, Ciardiello F, Ruschitzka F, Coats AJS, Seferovic P, Lainscak M, Piepoli MF, Chioncel O, Bax J, Hulot JS, Skouri H, Hagler-Laube ES, Asteggiano R, Fernandez TL, de Boer RA, Lyon AR. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1966–1983.
230. Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland A, Storas TH, Hagve TA, Rosjo H, Steine K, Geisler J, Omland T. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 x 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J* 2016;**37**:1671–1680.
231. Narayan HK, French B, Khan AM, Plappert T, Hyman D, Bajulaiye A, Domchek S, DeMichele A, Clark A, Matro J, Bradbury A, Fox K, Carver JR, Ky B. Noninvasive Measures of Ventricular-Arterial Coupling and Circumferential Strain Predict Cancer Therapeutics-Related Cardiac Dysfunction. *JACC Cardiovasc Imaging* 2016;**9**:1131–1141.
232. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol* 2014;**63**:2751–2768.
233. Yu AF, Ky B. Roadmap for biomarkers of cancer therapy cardiotoxicity. *Heart* 2016;**102**:425–430.
234. Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, Los M, Smit WM, Nieboer P, Smorenburg CH, Mandigers CM, van der Wouw AJ, Kessels L, van der Velden AW, Ottevanger PB, Smilde T, de Boer J, van Veldhuisen DJ, Kema IP, de Vries EG, Schellens JH. Angiotensin II-Receptor Inhibition With Candesartan to Prevent Trastuzumab-Related Cardiotoxic Effects in Patients With Early Breast Cancer: A Randomized Clinical Trial. *JAMA Oncol* 2016;**2**:1030–1037.
235. Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Pagano JJ, Chow K, Thompson RB, Vos LJ, Ghosh S, Oudit GY, Ezekowitz JA, Paterson DI. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. *J Clin Oncol* 2017;**35**:870–877.
236. Jones LW, Habel LA, Weltzien E, Castillo A, Gupta D, Kroenke CH, Kwan ML, Quesenberry CP, Jr., Scott J, Sternfeld B, Yu A, Kushi LH, Caan BJ. Exercise and Risk of Cardiovascular Events in Women With Nonmetastatic Breast Cancer. *J Clin Oncol* 2016;**34**:2743–2749.
237. Armenian SH, Xu L, Ky B, Sun C, Farol LT, Pal SK, Douglas PS, Bhatia S, Chao C. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J Clin Oncol* 2016;**34**:1122–1130.
238. Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015;**3**:631–639.
239. Vanfleteren LEGW, Spruit MA, Wouters EFM, Franssen FME. Management of chronic obstructive pulmonary disease beyond the lungs. *Lancet Respir Med* 2016;**4**:911–924.
240. Brekke PH, Omland T, Smith P, Soyseth V. Underdiagnosis of myocardial infarction in COPD - Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med* 2008;**102**:1243–1247.
241. Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;**2**:8–11.
242. Kunisaki KM, Dransfield MT, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, Hartley BF, Martinez FJ, Newby DE, Pragman AA, Vestbo J, Yates JC, Niewoehner DE, SUMMIT Investigators. Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events. A Post Hoc Cohort Analysis from the SUMMIT Randomized Clinical Trial. *Am J Respir Crit Care Med* 2018;**198**:51–57.
243. Rothnie KJ, Connell O, Mullerova H, Smeeth L, Pearce N, Douglas I, Quint JK. Myocardial Infarction and Ischemic Stroke after Exacerbations of Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2018;**15**:935–946.
244. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005;**128**:2640–2646.
245. Cebron Lipovec N, Beijers RJ, van den Borst B, Doehner W, Lainscak M, Schols AM. The Prevalence of Metabolic Syndrome In Chronic Obstructive Pulmonary Disease: A Systematic Review. *COPD* 2016;**13**:399–406.
246. Wang LY, Zhu YN, Cui JJ, Yin KQ, Liu SX, Gao YH. Subclinical atherosclerosis risk markers in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Respir Med* 2017;**123**:18–27.
247. Agusti A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E, Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012;**7**:e37483.
248. MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ. Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. *Lancet Respir Med* 2016;**4**:138–148.
249. Chang CL, Robinson SC, Mills GD, Sullivan GD, Karalus NC, McLachlan JD, Hancox RJ. Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 2011;**66**:764–768.
250. Maclay JD, McAllister DA, Johnston S, Raftis J, McGuinnes C, Deans A, Newby DE, Mills NL, MacNee W. Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax* 2011;**66**:769–774.
251. Lahousse L, Tiemeier H, Ikram MA, Brusselle GG. Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review. *Respir Med* 2015;**109**:1371–1380.
252. Houben-Wilke S, Jorres RA, Bals R, Franssen FM, Glaser S, Holle R, Karch A, Koch A, Magnussen H, Obst A, Schulz H, Spruit MA, Wacker ME, Welte T, Wouters EF, Vogelmeier C, Watz H. Peripheral Artery Disease and Its Clinical Relevance in Patients with Chronic Obstructive Pulmonary Disease in the COPD and Systemic Consequences-Comorbidities Network Study. *Am J Respir Crit Care Med* 2017;**195**:189–197.
253. Terzikhan N, Lahousse L, Verhamme KMC, Franco OH, Ikram AM, Stricker BH, Brusselle GG. COPD is associated with an increased risk of peripheral artery disease and mortality. *ERJ Open Res* 2018;**4**:[eCollection].
254. Ambrosino P, Lupoli R, Cafaro G, Iervolino S, Carone M, Pappone N, Di Minno MND. Subclinical carotid atherosclerosis in patients with chronic obstructive pulmonary disease: a meta-analysis of literature studies. *Ann Med* 2017;**49**:513–524.
255. Xiong J, Wu Z, Chen C, Guo W. Chronic obstructive pulmonary disease effect on the prevalence and postoperative outcome of abdominal aortic aneurysms: A meta-analysis. *Sci Rep* 2016;**6**:25003.
256. Goudis CA, Konstantinidis AK, Ntalas IV, Korantzopoulos P. Electrocardiographic abnormalities and cardiac arrhythmias in chronic obstructive pulmonary disease. *Int J Cardiol* 2015;**199**:264–273.
257. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J* 2003;**21**:1012–1016.
258. Goudis CA. Chronic obstructive pulmonary disease and atrial fibrillation: An unknown relationship. *J Cardiol* 2017;**69**:699–705.
259. Konecny T, Somers KR, Park JY, John A, Orban M, Doshi R, Scanlon PD, Asirvatham SJ, Rihal CS, Brady PA. Chronic obstructive pulmonary disease as a risk factor for ventricular arrhythmias independent of left ventricular function. *Heart Rhythm* 2018;**15**:832–838.
260. van den Berg ME, Stricker BH, Brusselle GG, Lahousse L. Chronic obstructive pulmonary disease and sudden cardiac death: A systematic review. *Trends Cardiovasc Med* 2016;**26**:606–613.

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261. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, Comignani PD, Gimeno G, Arakaki D, Laffaye N, Fuselli JJ, Massolin HP, Gambarte J, Romero M, Tognoni G. Unrecognised ventricular dysfunction in COPD. *Eur Respir J* 2012;**39**:51–58.
262. Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E, Jr., She D. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol* 2006;**16**:63–70.
263. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008;**32**:962–969.
264. Li C, Cheng W, Guo J, Guan W. Relationship of inhaled long-acting bronchodilators with cardiovascular outcomes among patients with stable COPD: a meta-analysis and systematic review of 43 randomized trials. *Int J Chron Obstruct Pulmon Dis* 2019;**14**:799–808.
265. Singh S, Singh H, Loftus EV, Jr., Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014;**12**:382–393 e381; quiz e322.
266. Hsue PY, Waters DD. HIV infection and coronary heart disease: mechanisms and management. *Nat Rev Cardiol* 2019;**16**:745–759.
267. Sinha A, Feinstein MJ. Coronary Artery Disease Manifestations in HIV: What, How, and Why. *Can J Cardiol* 2019;**35**:270–279.
268. Beckman JA, Duncan MS, Alcorn CW, So-Armah K, Butt AA, Goetz MB, Tindle HA, Sico JJ, Tracy RP, Justice AC, Freiberg MS. Association of Human Immunodeficiency Virus Infection and Risk of Peripheral Artery Disease. *Circulation* 2018;**138**:255–265.
269. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;**351**:2611–2618.
270. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, Ciszewski A, Vakili H, Hoffman EB, Farkouh ME, Cannon CP. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA* 2013;**310**:1711–1720.
271. Dietrich T, Jimenez M, Krall Kaye EA, Vokonas PS, Garcia RI. Age-dependent associations between chronic periodontitis/edentulism and risk of coronary heart disease. *Circulation* 2008;**117**:1668–1674.
272. Carrizales-Sepulveda EF, Ordaz-Farias A, Vera-Pineda R, Flores-Ramirez R. Periodontal Disease, Systemic Inflammation and the Risk of Cardiovascular Disease. *Heart Lung Circ* 2018;**27**:1327–1334.
273. Ryden L, Buhlin K, Ekstrand E, de Faire U, Gustafsson A, Holmer J, Kjellstrom B, Lindahl B, Norhammar A, Nygren A, Nasman P, Rathnayake N, Svenungsson E, Klinge B. Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study. *Circulation* 2016;**133**:576–583.
274. Qi J, Zihang Z, Zhang J, Park YM, Shrestha D, Jianling B, Merchant AT. Periodontal Antibodies and All-Cause and Cardiovascular Disease Mortality. *J Dent Res* 2020;**99**:51–59.
275. Lee YL, Hu HY, Chou P, Chu D. Dental prophylaxis decreases the risk of acute myocardial infarction: a nationwide population-based study in Taiwan. *Clin Interv Aging* 2015;**10**:175–182.
276. Holmlund A, Lampa E, Lind L. Poor Response to Periodontal Treatment May Predict Future Cardiovascular Disease. *J Dent Res* 2017;**96**:768–773.
277. Park SY, Kim SH, Kang SH, Yoon CH, Lee HJ, Yun PY, Youn TJ, Chae IH. Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea. *Eur Heart J* 2019;**40**:1138–1145.
278. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basanez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabe E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torne C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fevre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabweijano J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA, 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De Leon FR, Ronfani L, Room R, Rosenfeld LC, Rushton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tamburlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**:2163–2196.
279. Kurth T, Winter AC, Eliassen AH, Dushkes R, Mukamal KJ, Rimm EB, Willett WC, Manson JE, Rexrode KM. Migraine and risk of cardiovascular disease in women: prospective cohort study. *BMJ* 2016;**353**:i2610.
280. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009;**339**:b3914.
281. Sacco S, Kurth T. Migraine and the risk for stroke and cardiovascular disease. *Curr Cardiol Rep* 2014;**16**:524.
282. Sacco S, Merki-Feld GS, KL AE, Bitzer J Canonico M, Kurth T, Lampl C, Lidegaard O, Anne MacGregor E, MaassenVanDenBrink A, Mitsikostas DD, Nappi RE, Ntaios G, Sandset PM, Martelletti p, European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). *J Headache Pain* 2017;**18**:108.
283. Ornello R, Canonico M, Merki-Feld GS, Kurth T, Lidegaard O, MacGregor EA, Lampl C, Nappi RE, Martelletti P, Sacco S. Migraine, low-dose combined hormonal contraceptives, and ischemic stroke in young women: a systematic review and suggestions for future research. *Expert Rev Neurother* 2020;**20**:313–317.
284. Badran M, Yassin BA, Fox N, Laher I, Ayas N. Epidemiology of Sleep Disturbances and Cardiovascular Consequences. *Can J Cardiol* 2015;**31**:873–879.
285. Sofi F, Cesari F, Casini A, Macchi C, Abbate R, Gensini GF. Insomnia and risk of cardiovascular disease: a meta-analysis. *Eur J Prev Cardiol* 2014;**21**:57–64.
286. Ge L, Guyatt G, Tian J, Pan B, Chang Y, Chen Y, Li H, Zhang J, Li Y, Ling J, Yang K. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. *Sleep Med Rev* 2019;**48**:101215.
287. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, Peng X, Peng Z, Yu K, Bao W, Yang W, Chen X, Liu L. Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *J Am Heart Assoc* 2017;**6**:e005947.
288. Kerkhof GA. Epidemiology of sleep and sleep disorders in The Netherlands. *Sleep Med* 2017;**30**:229–239.
289. Remi J, Pollmacher T, Spiegelhalder K, Trenkwalder C, Young P. Sleep-Related Disorders in Neurology and Psychiatry. *Dtsch Arztebl Int* 2019;**116**:681–688.
290. Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR, Roth T, Drake CL. Hyperarousal and sleep reactivity in insomnia: current insights. *Nat Sci Sleep* 2018;**10**:193–201.
291. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, Goldberg AN, Long C, Gerstenfeld EP, Yeghiazarians, Y. Obstructive Sleep

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Apnea in Cardiovascular Disease: A Review of the Literature and Proposed Multidisciplinary Clinical Management Strategy. *J Am Heart Assoc* 2019;**8**:e010440.
292. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, Chen G, Du B, McArdle N, Mukherjee S, Tripathi M, Billot L, Li Q, Lorenzi-Filho G, Barbe F, Redline S, Wang J, Arima H, Neal B, White DP, Grunstein RR, Zhong N, Anderson CS, SAVE Investigators and Coordinators. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med* 2016;**375**:919–931.
293. Collen J, Lettieri C, Wickwire E, Holley A. Obstructive sleep apnea and cardiovascular disease, a story of confounders! *Sleep Breath* 2020;**24**:1299–1313.
294. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S, INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists). Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science. *Circulation* 2017;**136**:1840–1850.
295. Kasiakogias A, Tsioufis C, Thomopoulos C, Tousoulis D. Effects of continuous positive airway pressure on blood pressure in hypertensive patients with obstructive sleep apnoea. *J Hypertens* 2014;**32**:2279–2280.
296. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011;**21**:655–679.
297. Krupchanka D, Mlada K, Winkler P, Khazaal Y, Albanese E. Mortality in people with mental disorders in the Czech Republic: a nationwide, register-based cohort study. *Lancet Public Health* 2018;**3**:e289–e295.
298. Starace F, Mungai F, Baccari F, Galeazzi GM. Excess mortality in people with mental illness: findings from a Northern Italy psychiatric case register. *Soc Psychiatry Psychiatr Epidemiol* 2018;**53**:249–257.
299. John U, Rumpf HJ, Hanke M, Meyer C. Mental disorders and total mortality after 20 years in an adult general population sample. *Eur Psychiatry* 2020;**63**:e30.
300. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ* 2013;**346**:f2539.
301. Scott KM, de Jonge P, Alonso J, Viana MC, Liu Z, O'Neill S, Aguilar-Gaxiola S, Bruffaerts R, Caldas-de-Almeida JM, Stein DJ, de Girolamo G, Florescu SE, Hu C, Taib NI, Lepine JP, Levinson D, Matschinger H, Medina-Mora ME, Piazza M, Posada-Villa JA, Uda H, Wojtyniak BJ, Lim CC, Kessler RC. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. *Int J Cardiol* 2013;**168**:5293–5299.
302. Harter M, Baumeister H, Reuter K, Jacobi F, Hofler M, Bengel J, Wittchen HU. Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychother Psychosom* 2007;**76**:354–360.
303. Dar T, Radfar A, Abohashem S, Pitman RK, Tawakol A, Osborne MT. Psychosocial Stress and Cardiovascular Disease. *Curr Treat Options Cardiovasc Med* 2019;**21**:23.
304. Zhang WY, Nan N, Song XT, Tian JF, Yang XY. Impact of depression on clinical outcomes following percutaneous coronary intervention: a systematic review and meta-analysis. *BMJ Open* 2019;**9**:e026445.
305. Petersen BD, Stenager E, Mogensen CB, Erlangsen A. The association between heart diseases and suicide: a nationwide cohort study. *J Intern Med* 2020;**287**:558–568.
306. Duflou J. Psychostimulant use disorder and the heart. *Addiction* 2020;**115**:175–183.
307. Schnyder N, Panczak R, Groth N, Schultze-Lutter F. Association between mental health-related stigma and active help-seeking: systematic review and meta-analysis. *Br J Psychiatry* 2017;**210**:261–268.
308. Knaak S, Mantler E, Szeto A. Mental illness-related stigma in healthcare: Barriers to access and care and evidence-based solutions. *Healthc Manage Forum* 2017;**30**:111–116.
309. Henderson C, Noblett J, Parke H, Clement S, Caffrey A, Gale-Grant O, Schulze B, Druss B, Thornicroft G. Mental health-related stigma in health care and mental health-care settings. *Lancet Psychiatry* 2014;**1**:467–482.
310. Thornicroft G. Physical health disparities and mental illness: the scandal of premature mortality. *Br J Psychiatry* 2011;**199**:441–442.
311. Cunningham R, Poppe K, Peterson D, Every-Palmer S, Soosay I, Jackson R. Prediction of cardiovascular disease risk among people with severe mental illness: A cohort study. *PLoS One* 2019;**14**:e0221521.
312. Piepoli MF, Abreu A, Albus C, Ambrosetti M, Brotons C, Catapano AL, Corra U, Cosyns B, Deaton C, Graham I, Hoes A, Lochen ML, Matrone B, Redon J, Sattar N, Smulders Y, Tiberi M. Update on cardiovascular prevention in clinical practice: A position paper of the European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Prev Cardiol* 2020;**27**:181–205.
313. Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Avillach P, Egger P, Dhalwani NN, Kendrick S, Celis-Morales C, Waterworth DM, Alazawi W, Sattar N. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. *BMJ* 2019;**367**:l5367.
314. Young L, Cho L. Unique cardiovascular risk factors in women. *Heart* 2019;**105**:1656–1660.
315. Dam V, Onland-Moret NC, Verschuren WMM, Boer JMA, Benschop L, Franx A, Moons KGM, Boersma E, van der Schouw YT, CREW-consortium. Cardiovascular risk model performance in women with and without hypertensive disorders of pregnancy. *Heart* 2019;**105**:330–336.
316. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, Platt RW. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. *Circulation* 2019;**139**:1069–1079.
317. Riise HKR, Sulo G, Tell GS, Igland J, Nygard O, Iversen AC, Daltveit AK. Association Between Gestational Hypertension and Risk of Cardiovascular Disease Among 617 589 Norwegian Women. *J Am Heart Assoc* 2018;**7**:e008337.
318. Grandi SM, Reynier P, Platt RW, Basso O, Filion KB. The timing of onset of hypertensive disorders in pregnancy and the risk of incident hypertension and cardiovascular disease. *Int J Cardiol* 2018;**270**:273–275.
319. Timpka S, Markovitz A, Schyman T, Mogren I, Fraser A, Franks PW, Rich-Edwards JW. Midlife development of type 2 diabetes and hypertension in women by history of hypertensive disorders of pregnancy. *Cardiovasc Diabetol* 2018;**17**:124.
320. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. *Diabetologia* 2019;**62**:905–914.
321. Claesson R, Ignell C, Shaat N, Berntorp K. HbA1c as a predictor of diabetes after gestational diabetes mellitus. *Prim Care Diabetes* 2017;**11**:46–51.
322. Ding T, Hardiman PJ, Petersen I, Wang FF, Qu F, Baio G. The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. *Oncotarget* 2017;**8**:96351–96358.
323. Liu J, Wu Q, Hao Y, Jiao M, Wang X, Jiang S, Han L. Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. *Hum Reprod* 2021;**36**:1108–1119.
324. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, Kelsey SF, Kip KE, Cooper-Dehoff RM, Johnson BD, Vaccarino V, Reis SE, Bittner V, Hodgson TK, Rogers W, Pepine CJ. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab* 2008;**93**:1276–1284.
325. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA Cardiol* 2016;**1**:767–776.
326. Ding DC, Tsai IJ, Wang JH, Lin SZ, Sung FC. Coronary artery disease risk in young women with polycystic ovary syndrome. *Oncotarget* 2018;**9**:8756–8764.
327. Hong JS, Yi SW, Kang HC, Jee SH, Kang HG, Bayasgalan G, Ohrr H. Age at menopause and cause-specific mortality in South Korean women: Kangwha Cohort Study. *Maturitas* 2007;**56**:411–419.
328. Zhao L, Zhu Z, Lou H, Zhu G, Huang W, Zhang S, Liu F. Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): a meta-analysis. *Oncotarget* 2016;**7**:33715–33721.
329. Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis. *Menopause* 2012;**19**:1081–1087.
330. DeLay KJ, Haney N, Hellstrom WJ. Modifying Risk Factors in the Management of Erectile Dysfunction: A Review. *World J Mens Health* 2016;**34**:89–100.
331. Kessler A, Sollie S, Challacombe B, Briggs K, Van Hemelrijck M. The global prevalence of erectile dysfunction: a review. *BJU Int* 2019:[Online ahead of print].
332. Ibrahim A, Ali M, Kiernan TJ, Stack AG. Erectile Dysfunction and Ischaemic Heart Disease. *Eur Cardiol* 2018;**13**:98–103.
333. Miner M, Nehra A, Jackson G, Bhasin S, Billups K, Burnett AL, Buvat J, Carson C, Cunningham G, Ganz P, Goldstein I, Guay A, Hackett G, Kloner RA, Kostis JB, LaFlamme KE, Montorsi P, Ramsey M, Rosen R, Sadovsky R, Seftel A, Shabsigh R, Vlachopoulos C, Wu F. All men with vasculogenic erectile dysfunction require a cardiovascular workup. *Am J Med* 2014;**127**:174–182.
334. Montorsi P, Ravagnani PM, Galli S, Salonia A, Briganti A, Werba JP, Montorsi F. Association between erectile dysfunction and coronary artery disease: Matching the right target with the right test in the right patient. *Eur Urol* 2006;**50**:721–731.

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335. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, Aznaouridis KA, Stefanadis CI. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. *Circ Cardiovasc Qual Outcomes* 2013;**6**:99–109.
336. Zhao B, Zhang W. Does erectile dysfunction independently predict cardiovascular events? It's time to act on the evidence. *Eur J Prev Cardiol* 2018;**25**:1307–1311.
337. Chrysant SG. Antihypertensive therapy causes erectile dysfunction. *Curr Opin Cardiol* 2015;**30**:383–390.
338. Fan Y, Hu B, Man C, Cui F. Erectile dysfunction and risk of cardiovascular and all-cause mortality in the general population: a meta-analysis of cohort studies. *World J Urol* 2018;**36**:1681–1689.
339. Imprialos KP, Stavropoulos K, Doumas M, Tziomalos K, Karagiannis A, Athyros VG. Sexual Dysfunction, Cardiovascular Risk and Effects of Pharmacotherapy. *Curr Vasc Pharmacol* 2018;**16**:130–142.
340. Osondu CU, Vo B, Oni ET, Blaha MJ, Veledar E, Feldman T, Agatston AS, Nasir K, Aneni EC. The relationship of erectile dysfunction and subclinical cardiovascular disease: A systematic review and meta-analysis. *Vasc Med* 2018;**23**:9–20.
341. Raheem OA, Su JJ, Wilson JR, Hsieh TC. The Association of Erectile Dysfunction and Cardiovascular Disease: A Systematic Critical Review. *Am J Mens Health* 2017;**11**:552–563.
342. Gowani Z, Uddin SMI, Mirbolouk M, Ayyaz D, Billups KL, Miner M, Feldman DI, Blaha MJ. Vascular Erectile Dysfunction and Subclinical Cardiovascular Disease. *Curr Sex Health Rep* 2017;**9**:305–312.
343. Shah NP, Cainzos-Achirica M, Feldman DI, Blumenthal RS, Nasir K, Miner MM, Billups KL, Blaha MJ. Cardiovascular Disease Prevention in Men with Vascular Erectile Dysfunction: The View of the Preventive Cardiologist. *Am J Med* 2016;**129**:251–259.
344. Gerbild H, Larsen CM, Graugaard C, Areskoug Josefsson K. Physical Activity to Improve Erectile Function: A Systematic Review of Intervention Studies. *Sex Med* 2018;**6**:75–89.
345. Vlachopoulos C, Jackson G, Stefanadis C, Montorsi P. Erectile dysfunction in the cardiovascular patient. *Eur Heart J* 2013;**34**:2034–2046.
346. Rachamin Y, Grischott T, Rosemann T, Meyer MR. Inferior control of low-density lipoprotein cholesterol in women is the primary sex difference in modifiable cardiovascular risk: A large-scale, cross-sectional study in primary care. *Atherosclerosis* 2021;**324**:141–147.
347. Victor BM, Teal V, Ahedor L, Karalis DG. Gender differences in achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol* 2014;**113**:1611–1615.
348. Virani SS, Woodard LD, Ramsey DJ, Urech TH, Akeroyd JM, Shah T, Deswal A, Bozkurt B, Ballantyne CM, Petersen LA. Gender disparities in evidence-based statin therapy in patients with cardiovascular disease. *Am J Cardiol* 2015;**115**:21–26.
349. Xia S, Du X, Guo L, Du J, Arnott C, Lam CSP, Huffman MD, Arima H, Yuan Y, Zheng Y, Wu S, Guang X, Zhou X, Lin H, Cheng X, Anderson CS, Dong J, Ma C. Sex Differences in Primary and Secondary Prevention of Cardiovascular Disease in China. *Circulation* 2020;**141**:530–539.
350. Hyun KK, Redfern J, Patel A, Peiris D, Brieger D, Sullivan D, Harris M, Usherwood T, MacMahon S, Lyford M, Woodward M. Gender inequalities in cardiovascular risk factor assessment and management in primary healthcare. *Heart* 2017;**103**:492–498.
351. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation* 2011;**124**:2145–2154.
352. Wandell PE, de Waard AM, Holzmann MJ, Gornitzki C, Lionis C, de Wit N, Sondergaard J, Sonderlund AL, Kral N, Seifert B, Korevaar JC, Schellevis FG, Carlsson AC. Barriers and facilitators among health professionals in primary care to prevention of cardiometabolic diseases: A systematic review. *Fam Pract* 2018;**35**:383–398.
353. Astin F, Lucock M, Jennings CS. Heart and mind: behavioural cardiology demystified for the clinician. *Heart* 2019;**105**:881–888.
354. Lee WW, Choi KC, Yum RW, Yu DS, Chair SY. Effectiveness of motivational interviewing on lifestyle modification and health outcomes of clients at risk or diagnosed with cardiovascular diseases: A systematic review. *Int J Nurs Stud* 2016;**53**:331–341.
355. Zulman DM, Haverfield MC, Shaw JG, Brown-Johnson CG, Schwartz R, Tierney AA, Zionts DL, Safaeinili N, Fischer M, Thadaney Israni S, Asch SM, Verghese A. Practices to Foster Physician Presence and Connection With Patients in the Clinical Encounter. *JAMA* 2020;**323**:70–81.
356. Miller WR, Rose GS. Toward a theory of motivational interviewing. *Am Psychol* 2009;**64**:527–537.
357. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;**6**:42.
358. Ambrosetti M, Abreu A, Corra U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2020:2047487320913379.
359. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 2012;**125**:882–887 e881.
360. Brown MT, Bussell J, Dutta S, Davis K, Strong S, Mathew S. Medication Adherence: Truth and Consequences. *Am J Med Sci* 2016;**351**:387–399.
361. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;**34**:2940–2948.
362. Arlt AD, Nestoriuc Y, Rief W. Why current drug adherence programs fail: addressing psychological risk factors of nonadherence. *Curr Opin Psychiatry* 2017;**30**:326–333.
363. Easthall C, Taylor N, Bhattacharya D. Barriers to medication adherence in patients prescribed medicines for the prevention of cardiovascular disease: a conceptual framework. *Int J Pharm Pract* 2019;**27**:223–231.
364. Seabury SA, Dougherty JS, Sullivan J. Medication adherence as a measure of the quality of care provided by physicians. *Am J Manag Care* 2019;**25**:78–83.
365. Schneider APH, Gaedke MA, Garcez A, Barcellos NT, Paniz VMV. Effect of characteristics of pharmacotherapy on non-adherence in chronic cardiovascular disease: A systematic review and meta-analysis of observational studies. *Int J Clin Pract* 2018;**72**:[Epub].
366. Albarqouni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a systematic review. *Heart* 2017;**103**:1578–1586.
367. Hennein R, Hwang SJ, Au R, Levy D, Muntner P, Fox CS, Ma J. Barriers to medication adherence and links to cardiovascular disease risk factor control: the Framingham Heart Study. *Intern Med J* 2018;**48**:414–421.
368. Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication adherence in cardiovascular disease: the perfect challenge for the integrated care team. *Patient Prefer Adherence* 2017;**11**:547–559.
369. Palmer MJ, Barnard S, Perel P, Free C. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. *Cochrane Database Syst Rev* 2018;**6**:CD012675.
370. Guerriero C, Cairns J, Roberts I, Rodgers A, Whittaker R, Free C. The cost-effectiveness of smoking cessation support delivered by mobile phone text messaging: Txt2stop. *Eur J Health Econ* 2013;**14**:789–797.
371. Kraus WE, Powell KE, Haskell WL, Janz KF, Campbell WW, Jakicic JM, Troiano RP, Sprow K, Torres A, Piercy KL, 2018 Physical Activity Guidelines Advisory Committee. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. *Med Sci Sports Exerc* 2019;**51**:1270–1281.
372. Powell KE, King AC, Buchner DM, Campbell WW, DiPietro L, Erickson KI, Hillman CH, Jakicic JM, Janz KF, Katzmarzyk PT, Kraus WE, Macko RF, Marquez DX, McTiernan A, Pate RR, Pescatello LS, Whitt-Glover MC. The Scientific Foundation for the Physical Activity Guidelines for Americans, 2nd Edition. *J Phys Act Health* 2018:1–11.
373. Sattelmair J, Pertman J, Ding EL, Kohl HW, 3rd, Haskell W, Lee IM. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. *Circulation* 2011;**124**:789–795.
374. Hupin D, Roche F, Gremeaux V, Chatard JC, Oriol M, Gaspoz JM, Barthelemy JC, Edouard P. Even a low-dose of moderate-to-vigorous physical activity reduces mortality by 22% in adults aged >/=60 years: a systematic review and meta-analysis. *Br J Sports Med* 2015;**49**:1262–1267.
375. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, Whincup P, Diaz KM, Hooker SP, Chernofsky A, Larson MG, Spartano N, Vasan RS, Dohrn IM, Hagstromer M, Edwardson C, Yates T, Shiroma E, Anderssen SA, Lee IM. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. *BMJ* 2019;**366**:l4570.
376. Patterson R, McNamara E, Tainio M, de Sa TH, Smith AD, Sharp SJ, Edwards P, Woodcock J, Brage S, Wijndaele K. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. *Eur J Epidemiol* 2018;**33**:811–829.
377. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, Alter DA. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Ann Intern Med* 2015;**162**:123–132.

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378. Liu Y, Lee DC, Li Y, Zhu W, Zhang R, Sui X, Lavie CJ, Blair SN. Associations of Resistance Exercise with Cardiovascular Disease Morbidity and Mortality. *Med Sci Sports Exerc* 2019;**51**:499–508.
379. Saeidifard F, Medina-Inojosa JR, West CP, Olson TP, Somers VK, Bonikowske AR, Prokop LJ, Vinciguerra M, Lopez-Jimenez F. The association of resistance training with mortality: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2019;**26**:1647–1665.
380. Cradock KA, OL G, Finucane FM, Gainforth HL, Quinlan LR, Ginis KA. Behaviour change techniques targeting both diet and physical activity in type 2 diabetes: A systematic review and meta-analysis. *Int J Behav Nutr Phys Act* 2017;**14**:18.
381. Howlett N, Trivedi D, Troop NA, Chater AM. Are physical activity interventions for healthy inactive adults effective in promoting behavior change and maintenance, and which behavior change techniques are effective? A systematic review and meta-analysis. *Transl Behav Med* 2019;**9**:147–157.
382. Brickwood KJ, Watson G, O'Brien J, Williams AD. Consumer-Based Wearable Activity Trackers Increase Physical Activity Participation: Systematic Review and Meta-Analysis. *JMIR Mhealth Uhealth* 2019;**7**:e11819.
383. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, Veerman JL, Delwiche K, Iannarone ML, Moyer ML, Cercy K, Vos T, Murray CJ, Forouzanfar MH. Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ* 2016;**354**:i3857.
384. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, Kaur A, Friedemann Smith C, Wilkins E, Rayner M, Roberts N, Scarborough P. Quantifying the Association Between Physical Activity and Cardiovascular Disease and Diabetes: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2016;**5**:e002495.
385. Moore SC, Patel AV, Matthews CE, Berrington de Gonzalez A, Park Y, Katki HA, Linet MS, Weiderpass E, Visvanathan K, Helzlsouer KJ, Thun M, Gapstur SM, Hartge P, Lee IM. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med* 2012;**9**:e1001335.
386. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, Berrington de Gonzalez A, Hartge P, Adami HO, Blair CK, Borch KB, Boyd E, Check DP, Fournier A, Freedman ND, Gunter M, Johannson M, Khaw KT, Linet MS, Orsini N, Park Y, Riboli E, Robien K, Schairer C, Sesso H, Spriggs M, Van Dusen R, Wolk A, Matthews CE, Patel AV. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med* 2016;**176**:816–825.
387. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, Linet MS, Lee IM, Matthews CE. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 2015;**175**:959–967.
388. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M, ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96.
389. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;**43**:1334–1359.
390. Jakicic JM, Kraus WE, Powell KE, Campbell WW, Janz KF, Troiano RP, Sprow K, Torres A, Piercy KL, 2018 Physical Activity Guidelines Advisory Committee. Association between Bout Duration of Physical Activity and Health: Systematic Review. *Med Sci Sports Exerc* 2019;**51**:1213–1219.
391. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;**43**:1575–1581.
392. Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc* 2001;**33**:S364–369; discussion S419-320.
393. Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death: cohort study of one million participants. *BMJ* 2012;**345**:e7279.
394. Ruiz JR, Sui X, Lobelo F, Morrow JR, Jr., Jackson AW, Sjostrom M, Blair SN. Association between muscular strength and mortality in men: prospective cohort study. *BMJ* 2008;**337**:a439.
395. Volaklis KA, Halle M, Meisinger C. Muscular strength as a strong predictor of mortality: A narrative review. *Eur J Intern Med* 2015;**26**:303–310.
396. Chastin SFM, De Craemer M, De Cocker K, Powell L, Van Cauwenberg J, Dall P, Hamer M, Stamatakis E. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. *Br J Sports Med* 2019;**53**:370–376.
397. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012;**380**:219–229.
398. Katzmarzyk PT, Powell KE, Jakicic JM, Troiano RP, Piercy K, Tennant B, 2018 Physical Activity Guidelines Advisory Committee. Sedentary Behavior and Health: Update from the 2018 Physical Activity Guidelines Advisory Committee. *Med Sci Sports Exerc* 2019;**51**:1227–1241.
399. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, Lewis CE, Owen N, Perry CK, Siddique J, Yong CM, Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Functional Genomics and Translational Biology, and Stroke Council. Sedentary Behavior and Cardiovascular Morbidity and Mortality: A Science Advisory From the American Heart Association. *Circulation* 2016;**134**:e262-279.
400. Yates T, Edwardson CL, Celis-Morales C, Biddle SJH, Bodicoat D, Davies MJ, Esliger D, Henson J, Kazi A, Khunti K, Sattar N, Sinclair AJ, Rowlands A, Velayudhan L, Zaccardi F, Gill JMR. Metabolic Effects of Breaking Prolonged Sitting With Standing or Light Walking in Older South Asians and White Europeans: A Randomized Acute Study. *J Gerontol A Biol Sci Med Sci* 2020;**75**:139–146.
401. Eilat-Adar S, Sinai T, Yosefy C, Henkin Y. Nutritional recommendations for cardiovascular disease prevention. *Nutrients* 2013;**5**:3646–3683.
402. European Heart Network. *Transforming European food and drink policies for cardiovascular health*. http://www.ehnheart.org/publications-and-papers/publications/1093:transforming-european-food-and-drinks-policies-for-cardiovascular-health.html (21 July 2020).
403. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010;**92**:1189–1196.
404. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Fito M, Gea A, Hernan MA, Martinez-Gonzalez MA, PREDIMED Study Investigators. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. *N Engl J Med* 2018;**378**:e34.
405. Mensink RP. *Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis* https://apps.who.int/iris/bitstream/handle/10665/246104/9789241565349-eng.pdf?sequence=1 (21 July 2020).
406. Guasch-Ferre M, Satija A, Blondin SA, Janiszewski M, Emlen E, O'Connor LE, Campbell WW, Hu FB, Willett WC, Stampfer MJ. Meta-Analysis of Randomized Controlled Trials of Red Meat Consumption in Comparison With Various Comparison Diets on Cardiovascular Risk Factors. *Circulation* 2019;**139**:1828–1845.
407. Chen M, Li Y, Sun Q, Pan A, Manson JE, Rexrode KM, Willett WC, Rimm EB, Hu FB. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. *Am J Clin Nutr* 2016;**104**:1209–1217.
408. Li Y, Hruby A, Bernstein AM, Ley SH, Wang DD, Chiuve SE, Sampson L, Rexrode KM, Rimm EB, Willett WC, Hu FB. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. *J Am Coll Cardiol* 2015;**66**:1538–1548.
409. Sacks FM, Lichtenstein AH, Wu JHY, Appel LJ, Creager MA, Kris-Etherton PM, Miller M, Rimm EB, Rudel LL, Robinson JG, Stone NJ, Van Horn LV, American Heart Association. Dietary Fats and Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation* 2017;**136**:e1–e23.
410. He FJ, Tan M, Ma Y, MacGregor GA. Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020;**75**:632–647.
411. Willett W, Rockstrom J, Loken B, Springmann M, Lang T, Vermeulen S, Garnett T, Tilman D, DeClerck F, Wood A, Jonell M, Clark M, Gordon LJ, Fanzo J, Hawkes C, Zurayk R, Rivera JA, De Vries W, Majele Sibanda L, Afshin A, Chaudhary A, Herrero M, Agustina R, Branca F, Lartey A, Fan S, Crona B, Fox E, Bignet V, Troell M, Lindahl T, Singh S, Cornell SE, Srinath Reddy K, Narain S, Nishtar S, Murray CJL. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *Lancet* 2019;**393**:447–492.
412. World Health Organization. A healthy diet sustainably produced. https://apps.who.int/iris/bitstream/handle/10665/278948/WHO-NMH-NHD-18.12-eng.pdf?ua=1 (21 July 2020).

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413. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njolstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, de la Camara AG, Volzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Blazer DG, 2nd, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundstrom J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulou A, Kuhn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Despres JP, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjonneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J, Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–1523.
414. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, Bian Z, Bennett DA, Chen Y, Dong C, Hu R, Zhou G, Yu B, Jia W, Parish S, Clarke R, Davey Smith G, Collins R, Holmes MV, Li L, Peto R, Chen Z, China Kadoorie Biobank Collaborative Group. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. *Lancet* 2019;**393**:1831–1842.
415. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, Prieto-Merino D, Dehghan A, Trompet S, Wong A, Cavadino A, Drogan D, Padmanabhan S, Li S, Yesupriya A, Leusink M, Sundstrom J, Hubacek JA, Pikhart H, Swerdlow DI, Panayiotou AG, Borinskaya SA, Finan C, Shah S, Kuchenbaecker KB, Shah T, Engmann J, Folkersen L, Eriksson P, Ricceri F, Melander O, Sacerdote C, Gamble DM, Rayaprolu S, Ross OA, McLachlan S, Vikhireva O, Sluijs I, Scott RA, Adamkova V, Flicker L, Bockxmeer FM, Power C, Marques-Vidal P, Meade T, Marmot MG, Ferro JM, Paulos-Pinheiro S, Humphries SE, Talmud PJ, Mateo Leach I, Verweij N, Linneberg A, Skaaby T, Doevendans PA, Cramer MJ, van der Harst P, Klungel OH, Dowling NF, Dominiczak AF, Kumari M, Nicolaides AN, Weikert C, Boeing H, Ebrahim S, Gaunt TR, Price JF, Lannfelt L, Peasey A, Kubinova R, Pajak A, Malyutina S, Voevoda MI, Tamosiunas A, Maitland-van der Zee AH, Norman PE, Hankey GJ, Bergmann MM, Hofman A, Franco OH, Cooper J, Palmen J, Spiering W, de Jong PA, Kuh D, Hardy R, Uitterlinden AG, Ikram MA, Ford I, Hypponen E, Almeida OP, Wareham NJ, Khaw KT, Hamsten A, Husemoen LL, Tjonneland A, Tolstrup JS, Rimm E, Beulens JW, Verschuren WM, Onland-Moret NC, Hofker MH, Wannamethee SG, Whincup PH, Morris R, Vicente AM, Watkins H, Farrall M, Jukema JW, Meschia J, Cupples LA, Sharp SJ, Fornage M, Kooperberg C, LaCroix AZ, Dai JY, Lanktree MB, Siscovick DS, Jorgenson E, Spring B, Coresh J, Li YR, Buxbaum SG, Schreiner PJ, Ellison RC, Tsai MY, Patel SR, Redline S, Johnson AD, Hoogeveen RC, Hakonarson H, Rotter JI, Boerwinkle E, de Bakker PI, Kivimaki M, Asselbergs FW, Sattar N, Lawlor DA, Whittaker J, Davey Smith G, Mukamal K, Psaty BM, Wilson JG, Lange LA, Hamidovic A, Hingorani AD, Nordestgaard BG, Bobak M, Leon DA, Langenberg C, Palmer TM, Reiner AP, Keating BJ, Dudbridge F, Casas JP, InterAct Consortium. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. *BMJ* 2014;**349**:g4164.
416. Zeraatkar D, Johnston BC, Bartoszko J, Cheung K, Bala MM, Valli C, Rabassa M, Sit D, Milio K, Sadeghirad B, Agarwal A, Zea AM, Lee Y, Han MA, Vernooij RWM, Alonso-Coello P, Guyatt GH, El Dib R. Effect of Lower Versus Higher Red Meat Intake on Cardiometabolic and Cancer Outcomes: A Systematic Review of Randomized Trials. *Ann Intern Med* 2019;**171**:721–731.
417. Zhong VW, Van Horn L, Greenland P, Carnethon MR, Ning H, Wilkins JT, Lloyd-Jones DM, Allen NB. Associations of Processed Meat, Unprocessed Red Meat, Poultry, or Fish Intake With Incident Cardiovascular Disease and All-Cause Mortality. *JAMA Intern Med* 2020;**180**:503–512.
418. Zheng J, Huang T, Yu Y, Hu X, Yang B, Li D. Fish consumption and CHD mortality: an updated meta-analysis of seventeen cohort studies. *Public Health Nutr* 2012;**15**:725–737.
419. Mullee A, Romaguera D, Pearson-Stuttard J, Viallon V, Stepien M, Freisling H, Fagherazzi G, Mancini FR, Boutron-Ruault MC, Kuhn T, Kaaks R, Boeing H, Aleksandrova K, Tjonneland A, Halkjaer J, Overvad K, Weiderpass E, Skeie G, Parr CL, Quiros JR, Agudo A, Sanchez MJ, Amiano P, Cirera L, Ardanaz E, Khaw KT, Tong TYN, Schmidt JA, Trichopoulou A, Martimianaki G, Karakatsani A, Palli D, Agnoli C, Tumino R, Sacerdote C, Panico S, Bueno-de-Mesquita B, Verschuren WMM, Boer JMA, Vermeulen R, Ramne S, Sonestedt E, van Guelpen B, Holgersson PL, Tsilidis KK, Heath AK, Muller D, Riboli E, Gunter MJ, Murphy N. Association Between Soft Drink Consumption and Mortality in 10 European Countries. *JAMA Intern Med* 2019;**179**:1479–1490.
420. World Health Organization. Guideline: sugars intake for adults and children. https://www.who.int/publications/i/item/9789241549028 (21 July 2020).
421. Sundfor TM, Svendsen M, Heggen E, Dushanov S, Klemsdal TO, Tonstad S. BMI modifies the effect of dietary fat on atherogenic lipids: a randomized clinical trial. *Am J Clin Nutr* 2019;**110**:832–841.
422. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans fatty acids and cardiovascular disease. *N Engl J Med* 2006;**354**:1601–1613.
423. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG, Karanja N, Lin PH, DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001;**344**:3–10.
424. Mente A, O'Donnell M, Rangarajan S, Dagenais G, Lear S, McQueen M, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Li W, Lu Y, Yi S, Rensheng L, Iqbal R, Mony P, Yusuf R, Yusoff K, Szuba A, Oguz A, Rosengren A, Bahonar A, Yusufali A, Schutte AE, Chifamba J, Mann JF, Anand SS, Teo K, Yusuf S, PURE, EPIDREAM and ONTARGET/TRANSCEND Investigators. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet* 2016;**388**:465–475.
425. Cappuccio FP, Campbell NR. Population Dietary Salt Reduction and the Risk of Cardiovascular Disease: A Commentary on Recent Evidence. *J Clin Hypertens (Greenwich)* 2017;**19**:4–5.
426. He FJ, Ma Y, Campbell NRC, MacGregor GA, Cogswell ME, Cook NR. Formulas to Estimate Dietary Sodium Intake From Spot Urine Alter Sodium-Mortality Relationship. *Hypertension* 2019;**74**:572–580.
427. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ* 2013;**346**:f1378.
428. Manson JE, Cook NR, Lee IM, Christen W, Bassuk SS, Mora S, Gibson H, Gordon D, Copeland T, D'Agostino D, Friedenberg G, Ridge C, Bubes V, Giovannucci EL, Willett WC, Buring JE, VITAL Research Group. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *N Engl J Med* 2019;**380**:33–44.
429. Huang T, Afzal S, Yu C, Guo Y, Bian Z, Yang L, Millwood IY, Walters RG, Chen Y, Chen N, Gao R, Chen J, Clarke R, Chen Z, Ellervik C, Nordestgaard BG, Lv J, Li L, China Kadoorie Biobank Collaborative Group. Vitamin D and cause-specific vascular disease and mortality: a Mendelian randomisation study involving 99,012 Chinese and 106,911 European adults. *BMC Med* 2019;**17**:160.
430. Threapleton DE, Greenwood DC, Evans CE, Cleghorn CL, Nykjaer C, Woodhead C, Cade JE, Gale CP, Burley VJ. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2013;**347**:f6879.
431. Zhang Z, Xu G, Liu D, Zhu W, Fan X, Liu X. Dietary fiber consumption and risk of stroke. *Eur J Epidemiol* 2013;**28**:119–130.
432. Yao B, Fang H, Xu W, Yan Y, Xu H, Liu Y, Mo M, Zhang H, Zhao Y. Dietary fiber intake and risk of type 2 diabetes: a dose-response analysis of prospective studies. *Eur J Epidemiol* 2014;**29**:79–88.
433. Giacco R, Costabile G, Della Pepa G, Anniballi G, Griffo E, Mangione A, Cipriano P, Viscovo D, Clemente G, Landberg R, Pacini G, Rivellese AA, Riccardi G. A whole-grain cereal-based diet lowers postprandial plasma insulin and triglyceride levels in individuals with metabolic syndrome. *Nutr Metab Cardiovasc Dis* 2014;**24**:837–844.
434. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, Hu FB. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* 2014;**349**:g4490.
435. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet* 2006;**367**:320–326.
436. Dauchet L, Amouyel P, Hercberg S, Dallongeville J. Fruit and vegetable consumption and risk of coronary heart disease: a meta-analysis of cohort studies. *J Nutr* 2006;**136**:2588–2593.
437. Luo C, Zhang Y, Ding Y, Shan Z, Chen S, Yu M, Hu FB, Liu L. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;**100**:256–269.
438. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr* 2014;**100**:278–288.
439. World Cancer Research Fund, American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, 2018. https://www.wcrf.org/dietandcancer/recommendations/limit-red-processed-meat (21 July 2020).
440. Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, Khan H, Baena CP, Prabhakaran D, Hoshen MB, Feldman BS, Pan A, Johnson L, Crowe F, Hu FB, Franco OH. Vitamin D and risk of cause

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specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ* 2014;**348**:g1903.
441. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012;**308**:1024–1033.
442. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, AlAbdulghafoor FK, Summerbell CD, Worthington HV, Song F, Hooper L. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev* 2018;**7**:CD003177.
443. Aung T, Halsey J, Kromhout D, Gerstein HC, Marchioli R, Tavazzi L, Geleijnse JM, Rauch B, Ness A, Galan P, Chew EY, Bosch J, Collins R, Lewington S, Armitage J, Clarke R, Omega-3 Treatment Trialists' Collaboration. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77917 Individuals. *JAMA Cardiol* 2018;**3**:225–234.
444. Hu Y, Hu FB, Manson JE. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. *J Am Heart Assoc* 2019;**8**:e013543.
445. Nicholls SJ, Lincoff AM, Garcia M, Bash D, Ballantyne CM, Barter PJ, Davidson MH, Kastelein JJP, Koenig W, McGuire DK, Mozaffarian D, Ridker PM, Ray KK, Katona BG, Himmelmann A, Loss LE, Rensfeldt M, Lundstrom T, Agrawal R, Menon V, Wolski K, Nissen SE. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. *JAMA* 2020;**324**:2268–2280.
446. Tverdal A, Selmer R, Cohen JM, Thelle DS. Coffee consumption and mortality from cardiovascular diseases and total mortality: Does the brewing method matter? *Eur J Prev Cardiol* 2020;**27**:1986–1993.
447. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. *BMJ* 2017;**359**:j5024.
448. Ras RT, Geleijnse JM, Trautwein EA. LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. *Br J Nutr* 2014;**112**:214–219.
449. Peng D, Fong A, Pelt AV. Original Research: The Effects of Red Yeast Rice Supplementation on Cholesterol Levels in Adults. *Am J Nurs* 2017;**117**:46–54.
450. Zomer E, Gurusamy K, Leach R, Trimmer C, Lobstein T, Morris S, James WP, Finer N. Interventions that cause weight loss and the impact on cardiovascular risk factors: a systematic review and meta-analysis. *Obes Rev* 2016;**17**:1001–1011.
451. Wing RR, Espeland MA, Clark JM, Hazuda HP, Knowler WC, Pownall HJ, Unick J, Wadden T, Wagenknecht L, Action for Health in Diabetes (Look AHEAD) Study Group. Association of Weight Loss Maintenance and Weight Regain on 4-Year Changes in CVD Risk Factors: the Action for Health in Diabetes (Look AHEAD) Clinical Trial. *Diabetes Care* 2016;**39**:1345–1355.
452. Howell S, Kones R. "Calories in, calories out" and macronutrient intake: the hope, hype, and science of calories. *Am J Physiol Endocrinol Metab* 2017;**313**:E608–E612.
453. Ge L, Sadeghirad B, Ball GDC, da Costa BR, Hitchcock CL, Svendrovski A, Kiflen R, Quadri K, Kwon HY, Karamouzian M, Adams-Webber T, Ahmed W, Damanhoury S, Zeraatkar D, Nikolakopoulou A, Tsuyuki RT, Tian J, Yang K, Guyatt GH, Johnston BC. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. *BMJ* 2020;**369**:m696.
454. Tobias DK, Chen M, Manson JE, Ludwig DS, Willett W, Hu FB. Effect of low-fat diet interventions versus other diet interventions on long-term weight change in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2015;**3**:968–979.
455. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: A systematic review and meta-analysis. *Diabetes Obes Metab* 2017;**19**:1223–1232.
456. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, Sharma P, Fraser C, MacLennan G. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. *BMJ* 2017;**359**:j4849.
457. Mancini JG, Filion KB, Atallah R, Eisenberg MJ. Systematic Review of the Mediterranean Diet for Long-Term Weight Loss. *Am J Med* 2016;**129**:407–415 e404.
458. Sofi F, Dinu M, Pagliai G, Cesari F, Gori AM, Sereni A, Becatti M, Fiorillo C, Marcucci R, Casini A. Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet). *Circulation* 2018;**137**:1103–1113.
459. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian Diets and Weight Reduction: a Meta-Analysis of Randomized Controlled Trials. *J Gen Intern Med* 2016;**31**:109–116.
460. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* 2019;**393**:434–445.
461. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, Sikand G, Aspry KE, Soffer DE, Willard KE, Maki KC. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. *J Clin Lipidol* 2019;**13**:689–711 e681.
462. Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett WC, Solomon SD. Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health* 2018;**3**:e419–e428.
463. Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL. Effectiveness of Intermittent Fasting and Time-Restricted Feeding Compared to Continuous Energy Restriction for Weight Loss. *Nutrients* 2019;**11**:2442.
464. Kane JA, Mehmood T, Munir I, Kamran H, Kariyanna PT, Zhyvotovska A, Yusupov D, Suleman UJ, Gustafson DR, McFarlane SI. Cardiovascular Risk Reduction Associated with Pharmacological Weight Loss: A Meta-Analysis. *Int J Clin Res Trials* 2019;**4**:131.
465. Barber S, Thornicroft G. Reducing the Mortality Gap in People With Severe Mental Disorders: The Role of Lifestyle Psychosocial Interventions. *Front Psychiatry* 2018;**9**:463.
466. Richards SH, Anderson L, Jenkinson CE, Whalley B, Rees K, Davies P, Bennett P, Liu Z, West R, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease. *Cochrane Database Syst Rev* 2017;**4**:CD002902.
467. Gullikson M, Burell G, Vessby B, Lundin L, Toss H, Svardsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary Health Care project (SUPRIM). *Arch Intern Med* 2011;**171**:134–140.
468. Orth-Gomer K, Schneiderman N, Wang HX, Walldin C, Blom M, Jernberg T. Stress reduction prolongs life in women with coronary disease: the Stockholm Women's Intervention Trial for Coronary Heart Disease (SWITCHD). *Circ Cardiovasc Qual Outcomes* 2009;**2**:25–32.
469. Blumenthal JA, Sherwood A, Smith PJ, Watkins L, Mabe S, Kraus WE, Ingle K, Miller P, Hinderliter A. Enhancing Cardiac Rehabilitation With Stress Management Training: A Randomized, *Clinical Efficacy Trial. Circulation* 2016;**133**:1341–1350.
470. Pizzi C, Rutjes AW, Costa GM, Fontana F, Mezzetti A, Manzoli L. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *Am J Cardiol* 2011;**107**:972–979.
471. Kim JM, Stewart R, Lee YS, Lee HJ, Kim MC, Kim JW, Kang HJ, Bae KY, Kim SW, Shin IS, Hong YJ, Kim JH, Ahn Y, Jeong MH, Yoon JS. Effect of Escitalopram vs Placebo Treatment for Depression on Long-term Cardiac Outcomes in Patients With Acute Coronary Syndrome: A Randomized Clinical Trial. *JAMA* 2018;**320**:350–358.
472. He W, Zhou Y, Ma J, Wei B, Fu Y. Effect of antidepressants on death in patients with heart failure: a systematic review and meta-analysis. *Heart Fail Rev* 2020;**25**:919–926.
473. Angermann CE, Gelbrich G, Stork S, Gunold H, Edelmann F, Wachter R, Schunkert H, Graf T, Kindermann I, Haass M, Blankenberg S, Pankuweit S, Prettin C, Gottwik M, Bohm M, Faller H, Deckert J, Ertl G, MOOD-HF Study Investigators and Committee Members. Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial. *JAMA* 2016;**315**:2683–2693.
474. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014;**348**:g1151.
475. Prochaska JJ, Hall SE, Delucchi K, Hall SM. Efficacy of initiating tobacco dependence treatment in inpatient psychiatry: a randomized controlled trial. *Am J Public Health* 2014;**104**:1557–1565.
476. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, McMurdo M, Mead GE. Exercise for depression. *Cochrane Database Syst Rev* 2013:CD004366.
477. Opie RS, Itsiopoulos C, Parletta N, Sanchez-Villegas A, Akbaraly TN, Ruusunen A, Jacka FN. Dietary recommendations for the prevention of depression. *Nutr Neurosci* 2017;**20**:161–171.
478. Palmer VJ, Lewis M, Stylianopolous V, Furler J. Primary care prevention of the cardiovascular health crisis for people with severe mental illnesses: The elephant in the room. *Aust J Gen Pract* 2018;**47**:846–850.
479. Druss BG, von Esenwein SA, Compton MT, Rask KJ, Zhao L, Parker RM. A randomized trial of medical care management for community mental health settings: the Primary Care Access, Referral, and Evaluation (PCARE) study. *Am J Psychiatry* 2010;**167**:151–159.
480. Osborn D, Burton A, Walters K, Atkins L, Barnes T, Blackburn R, Craig T, Gilbert H, Gray B, Hardoon S, Heinkel S, Holt R, Hunter R, Johnston C, King

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M, Leibowitz J, Marston L, Michie S, Morris R, Morris S, Nazareth I, Omar R, Petersen I, Peveler R, Pinfold V, Stevenson F, Zomer E. *Primary care management of cardiovascular risk for people with severe mental illnesses: the Primrose research programme including cluster RCT*. Southampton (UK); 2019.
481. Seldenrijk A, Vogelzangs N, Batelaan NM, Wieman I, van Schaik DJ, Penninx BJ. Depression, anxiety and 6-year risk of cardiovascular disease. *J Psychosom Res* 2015;**78**:123–129.
482. Gilsanz P, Kubzansky LD, Tchetgen Tchetgen EJ, Wang Q, Kawachi I, Patton KK, Fitzpatrick AL, Kop WJ, Longstreth WT, Jr., Glymour MM. Changes in Depressive Symptoms and Subsequent Risk of Stroke in the Cardiovascular Health Study. *Stroke* 2017;**48**:43–48.
483. Smolderen KG, Buchanan DM, Gosch K, Whooley M, Chan PS, Vaccarino V, Parashar S, Shah AJ, Ho PM, Spertus JA. Depression Treatment and 1-Year Mortality After Acute Myocardial Infarction: Insights From the TRIUMPH Registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status). *Circulation* 2017;**135**:1681–1689.
484. Smolderen KG, Spertus JA, Gosch K, Dreyer RP, D'Onofrio G, Lichtman JH, Geda M, Beltrame J, Safdar B, Bueno H, Krumholz HM. Depression Treatment and Health Status Outcomes in Young Patients With Acute Myocardial Infarction: Insights From the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). *Circulation* 2017;**135**:1762–1764.
485. Tully PJ, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2015;**5**:e009128.
486. Honkola J, Hookana E, Malinen S, Kaikkonen KS, Junttila MJ, Isohanni M, Kortelainen ML, Huikuri HV. Psychotropic medications and the risk of sudden cardiac death during an acute coronary event. *Eur Heart J* 2012;**33**:745–751.
487. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA* 2003;**290**:86–97.
488. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, Lung Health Study Research Group. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;**142**:233–239.
489. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev* 2018;**5**:CD000146.
490. HughesJR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007:CD000031.
491. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2016:CD006103.
492. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2019;**4**:CD013308.
493. Woolf KJ, Zabad MN, Post JM, McNitt S, Williams GC, Bisognano JD. Effect of nicotine replacement therapy on cardiovascular outcomes after acute coronary syndromes. *Am J Cardiol* 2012;**110**:968–970.
494. Suissa K, Lariviere J, Eisenberg MJ, Eberg M, Gore GC, Grad R, Joseph L, Reynier PM, Filion KB. Efficacy and Safety of Smoking Cessation Interventions in Patients With Cardiovascular Disease: A Network Meta-Analysis of Randomized Controlled Trials. *Circ Cardiovasc Qual Outcomes* 2017;**10**:e002458.
495. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, Willett WC, Manson JE, Hu FB, Sun Q. Smoking Cessation, Weight Change, Type 2 Diabetes, and Mortality. *N Engl J Med* 2018;**379**:623–632.
496. Mons U, Muezzinler A, Gellert C, Schottker B, Abnet CC, Bobak M, de Groot L, Freedman ND, Jansen E, Kee F, Kromhout D, Kuulasmaa K, Laatikainen T, O'Doherty MG, Bueno-de-Mesquita B, Orfanos P, Peters A, van der Schouw YT, Wilsgaard T, Wolk A, Trichopoulou A, Boffetta P, Brenner H, CHANCES Consortium. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ* 2015;**350**:h1551.
497. Gellert C, Schottker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med* 2012;**172**:837–844.
498. Prugger C, Wellmann J, Heidrich J, De Bacquer D, De Backer G, Perier MC, Empana JP, Reiner Z, Fras Z, Jennings C, Kotseva K, Wood D, Keil U, EUROASPIRE Study Group. Readiness for smoking cessation in coronary heart disease patients across Europe: Results from the EUROASPIRE III survey. *Eur J Prev Cardiol* 2015;**22**:1212–1219.
499. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T. Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews. *Addiction* 2014;**109**:1414–1425.
500. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, Cassavar D, Dion D, Haught H, Mehta SR, Baril JF, Lambert C, Madan M, Abramson BL, Dehghani P, EVITA Investigators. Varenicline for Smoking Cessation in Hospitalized Patients With Acute Coronary Syndrome. *Circulation* 2016;**133**:21–30.
501. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet* 2016;**387**:2507–2520.
502. Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, Lawrence D, St Aubin L, Anthenelli RM. Cardiovascular Safety of Varenicline, Bupropion, and Nicotine Patch in Smokers: A Randomized Clinical Trial. *JAMA Intern Med* 2018;**178**:622–631.
503. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2020;**10**:CD010216.
504. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med* 2019;**380**:629–637.
505. Li J, Hajek P, Pesola F, Wu Q, Phillips-Waller A, Przulj D, Myers Smith K, Bisal N, Sasieni P, Dawkins L, Ross L, Goniewicz ML, McRobbie H, Parrott S. Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. *Addiction* 2020;**115**:507–517.
506. Kavousi M, Pisinger C, Barthelemy JC, Smedt D, Koskinas K, Marques-Vidal P, Panagiotakos D, Prescott EB, Tiberi M, Vassiliou VS, Lochen ML. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020:2047487320941993.
507. European Heart Network. Electronic cigarettes and cardiovascular disease – *an update from the European Heart Network* http://www.ehnheart.org/component/attachments/attachments.html?task=attachment&id=3093 (21 July 2020).
508. Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Bejot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, Guidoux C, Hobeanu C, Kim YJ, Lapergue B, Lavallee PC, Lee BC, Lee KB, Leys D, Mahagne MH, Meseguer E, Nighoghossian N, Pico F, Samson Y, Sibon I, Steg PG, Sung SM, Touboul PJ, Touze E, Varenne O, Vicaut E, Yelles N, Bruckert E, Treat Stroke to Target Investigators. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. *N Engl J Med* 2020;**382**:9.
509. Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Boren J, Catapano AL, Descamps OS, Fisher E, Kovanen PT, Kuivenhoven JA, Lesnik P, Masana L, Nordestgaard BG, Ray KK, Reiner Z, Taskinen MR, Tokgozoglu L, Tybjaerg-Hansen A, Watts GF, European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J* 2011;**32**:1345–1361.
510. Cartier LJ, Collins C, Lagace M, Douville P. Comparison of fasting and non-fasting lipid profiles in a large cohort of patients presenting at a community hospital. *Clin Biochem* 2018;**52**:61–66.
511. Sampson M, Ling C, Sun Q, Harb R, Ashmaig M, Warnick R, Sethi A, Fleming JK, Otvos JD, Meeusen JW, Delaney SR, Jaffe AS, Shamburek R, Amar M, Remaley AT. A New Equation for Calculation of Low-Density Lipoprotein Cholesterol in Patients With Normolipidemia and/or Hypertriglyceridemia. *JAMA Cardiol* 2020;**5**:540–548.
512. Penson P, Martin SS, Henney NC, Banach M. Comparison of LDL-C calculation by friedewald and martin/hopkins methods in 12,243 adults from the United States of America [abstract]. *Eur Heart J* 2020;**41**(Suppl 2):2932.
513. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, Simes RJ, Durrington P, Hitman GA, Welch KM, DeMicco DA, Zwinderman AH, Clearfield MB, Downs JR, Tonkin AM, Colhoun HM, Gotto AM, Jr., Ridker PM, Kastelein JJ. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA* 2012;**307**:1302–1309.
514. Welsh C, Celis-Morales CA, Brown R, Mackay DF, Lewsey J, Mark PB, Gray SR, Ferguson LD, Anderson JJ, Lyall DM, Cleland JG, Jhund PS, Gill JMR, Pell JP, Sattar N, Welsh P. Comparison of Conventional Lipoprotein Tests and Apolipoproteins in the Prediction of Cardiovascular Disease. *Circulation* 2019;**140**:542–552.
515. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM, IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *N Engl J Med* 2015;**372**:2387–2397.
516. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017;**376**:1713–1722.

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517. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM, ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018;**379**:2097–2107.
518. Ridker PM, Rose LM, Kastelein JJP, Santos RD, Wei C, Revkin J, Yunis C, Tardif JC, Shear CL, Studies of PCSK9 Inhibition and the Reduction of vascular Events (SPIRE) Investigators. Cardiovascular event reduction with PCSK9 inhibition among 1578 patients with familial hypercholesterolemia: Results from the SPIRE randomized trials of bococizumab. *J Clin Lipidol* 2018;**12**:958–965.
519. Mozaffarian D. Natural trans fat, dairy fat, partially hydrogenated oils, and cardiometabolic health: the Ludwigshafen Risk and Cardiovascular Health Study. *Eur Heart J* 2016;**37**:1079–1081.
520. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, de Craen AJ, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ* 2009;**338**:b2376.
521. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol* 2008;**52**:1769–1781.
522. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–1405.
523. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, Du Y, Pordy R, Gipe DA, ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015;**9**:758–769.
524. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceska R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA, GAUSS-3 Investigators. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. *JAMA* 2016;**315**:1580–1590.
525. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellstrom B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R, SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**:2181–2192.
526. Schreml J, Gouni-Berthold I. Role of Anti-PCSK9 Antibodies in the Treatment of Patients with Statin Intolerance. *Curr Med Chem* 2018;**25**:1538–1548.
527. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, Evans S, Law M, MacMahon S, Martin S, Neal B, Poulter N, Preiss D, Ridker P, Roberts I, Rodgers A, Sandercock P, Schulz K, Sever P, Simes J, Smeeth L, Wald N, Yusuf S, Peto R. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* 2016;**388**:2532–2561.
528. Myocardial Infarction Genetics Consortium Investigators, Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, Fontanillas P, Gupta N, Duga S, Goel A, Farrall M, Saleheen D, Ferrario P, Konig I, Asselta R, Merlini PA, Marziliano N, Notarangelo MF, Schick U, Auer P, Assimes TL, Reilly M, Wilensky R, Rader DJ, Hovingh GK, Meitinger T, Kessler T, Kastrati A, Laugwitz KL, Siscovick D, Rotter JI, Hazen SL, Tracy R, Cresci S, Spertus J, Jackson R, Schwartz SM, Natarajan P, Crosby J, Muzny D, Ballantyne C, Rich SS, O'Donnell CJ, Abecasis G, Sunaev S, Nickerson DA, Buring JE, Ridker PM, Chasman DI, Austin E, Kullo IJ, Weeke PE, Shaffer CM, Bastarache LA, Denny JC, Roden DM, Palmer C, Deloukas P, Lin DY, Tang ZZ, Erdmann J, Schunkert H, Danesh J, Marrugat J, Elosua R, Ardissino D, McPherson R, Watkins H, Reiner AP, Wilson JG, Altshuler D, Gibbs RA, Lander ES, Boerwinkle E, Gabriel S, Kathiresan S. Inactivating mutations in NPC1L1 and protection from coronary heart disease. *N Engl J Med* 2014;**371**:2072–2082.
529. Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, Xue A, Scott R, Wasserman SM, Stroes E. Clinical Profile of Statin Intolerance in the Phase 3 GAUSS-2 Study. *Cardiovasc Drugs Ther* 2016;**30**:297–304.
530. Ray KK, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, Bisch JA, Richardson T, Jaros M, Wijngaard PLJ, Kastelein JJP, ORION-10 and ORION-11 Investigators. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med* 2020;**382**:1507–1519.
531. Triglyceride Coronary Disease Genetics Consortium, Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J. Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies. *Lancet* 2010;**375**:1634–1639.
532. Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Z, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablik M, Wong ND, Banach M. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr Rev* 2017;**75**:731–767.
533. Vallejo-Vaz AJ, Fayyad R, Boekholdt SM, Hovingh GK, Kastelein JJ, Melamed S, Barter P, Waters DD, Ray KK. Triglyceride-Rich Lipoprotein Cholesterol and Risk of Cardiovascular Events Among Patients Receiving Statin Therapy in the TNT Trial. *Circulation* 2018;**138**:770–781.
534. Chapman MJ, Redfern JS, McGovern ME, Giral P. Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* 2010;**126**:314–345.
535. ACCORD Study Group, Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff DC, Jr., Cushman WC, Simons-Morton DG, Byington RP. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1563–1574.
536. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet* 2005;**366**:1849–1861.
537. Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70-100 years: a contemporary primary prevention cohort. *Lancet* 2020;**396**:1644–1652.
538. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019;**393**:407–415.
539. Gencer B, Marston NA, Im K, Cannon CP, Sever P, Keech A, Braunwald E, Giugliano RP, Sabatine MS. Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet* 2020;**396**:1637–1643.
540. Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;**371**:117–125.
541. Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, Freitag DF, Pennells L, Peters SA, Hart CL, Haheim LL, Gillum RF, Nordestgaard BG, Psaty BM, Yeap BB, Knuiman MW, Nietert PJ, Kauhanen J, Salonen JT, Kuller LH, Simons LA, van der Schouw YT, Barrett-Connor E, Selmer R, Crespo CJ, Rodriguez B, Verschuren WM, Salomaa V, Svardsudd K, van der Harst P, Bjorkelund C, Wilhelmsen L, Wallace RB, Brenner H, Amouyel P, Barr EL, Iso H, Onat A, Trevisan M, D'Agostino RB, Sr., Cooper C, Kavousi M, Welin L, Roussel R, Hu FB, Sato S, Davidson KW, Howard BV, Leening MJ, Leening M, Rosengren A, Dorr M, Deeg DJ, Kiechl S, Stehouwer CD, Nissinen A, Giampaoli S, Donfrancesco C, Kromhout D, Price JF, Peters A, Meade TW, Casiglia E, Lawlor DA, Gallacher J, Nagel D, Franco OH, Assmann G, Dagenais GR, Jukema JW, Sundstrom J, Woodward M, Brunner EJ, Khaw KT, Wareham NJ, Whitsel EA, Njolstad I, Hedblad B, Wassertheil-Smoller S, Engstrom G, Rosamond WD, Selvin E, Sattar N, Thompson SG, Danesh J. Association of Cardiometabolic Multimorbidity With Mortality. *JAMA* 2015;**314**:52–60.
542. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, Park JG, White JA, Bohula EA, Braunwald E, IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) Investigators. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With Versus Without Diabetes Mellitus: Results From IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018;**137**:1571–1582.
543. Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice

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Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int* 2014;**85**:1303–1309.
544. Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellstrom B, Jardine AG, Wanner C, Holdaas H, Fulcher J, Haynes R, Landray MJ, Keech A, Simes J, Collins R, Baigent C. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol* 2016;**4**:829–839.
545. Barylski M, Nikfar S, Mikhailidis DP, Toth PP, Salari P, Ray KK, Pencina MJ, Rizzo M, Rysz J, Abdollahi M, Nicholls SJ, Banach M, Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy–a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res* 2013;**72**:35–44.
546. Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, Ritz E, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;**353**:238–248.
547. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Gronhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Suleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wuthrich RP, Gottlow M, Johnsson E, Zannad F, AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;**360**:1395–1407.
548. Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, Snapinn S, Harris KE, Aurup P, Edelman JM, Wedel H, Lindholm LH, Dahlof B, LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004;**292**:2343–2349.
549. Sehestedt T, Jeppesen J, Hansen TW, Wachtell K, Ibsen H, Torp-Pedersen C, Hildebrandt P, Olsen MH. Risk prediction is improved by adding markers of subclinical organ damage to SCORE. *Eur Heart J* 2010;**31**:883–891.
550. Perrone-Filardi P, Coca A, Galderisi M, Paolillo S, Alpendurada F, de Simone G, Donal E, Kahan T, Mancia G, Redon J, Schmieder R, Williams B, Agabiti-Rosei E. Non-invasive cardiovascular imaging for evaluating subclinical target organ damage in hypertensive patients: A consensus paper from the European Association of Cardiovascular Imaging (EACVI), the European Society of Cardiology Council on Hypertension, and the European Society of Hypertension (ESH). *Eur Heart J Cardiovasc Imaging* 2017;**18**:945–960.
551. Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, Patel A, Cass A, Neal B, Poulter N, Mogensen CE, Cooper M, Marre M, Williams B, Hamet P, Mancia G, Woodward M, Macmahon S, Chalmers J, ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol* 2009;**20**:1813–1821.
552. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–967.
553. Sundstrom J, Arima H, Jackson R, Turnbull F, Rahimi K, Chalmers J, Woodward M, Neal B, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of blood pressure reduction in mild hypertension: a systematic review and meta-analysis. *Ann Intern Med* 2015;**162**:184–191.
554. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *J Hypertens* 2014;**32**:2285–2295.
555. SPRINT Research Group, Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med* 2015;**373**:2103–2116.
556. Patel A, ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;**370**:829–840.
557. Williamson JD, Supiano MA, Applegate WB, Berlowitz DR, Campbell RC, Chertow GM, Fine LJ, Haley WE, Hawfield AT, Ix JH, Kitzman DW, Kostis JB, Krousel-Wood MA, Launer LJ, Oparil S, Rodriguez CJ, Roumie CL, Shorr RI, Sink KM, Wadley VG, Whelton PK, Whittle J, Woolard NF, Wright JT, Jr., Pajewski NM, SPRINT Research Group. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *JAMA* 2016;**315**:2673–2682.
558. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels - updated overview and meta-analyses of randomized trials. *J Hypertens* 2016;**34**:613–622.
559. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC, Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;**362**:1575–1585.
560. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009;**122**:290–300.
561. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012;**59**:1124–1131.
562. Rea F, Corrao G, Merlino L, Mancia G. Early cardiovascular protection by initial two-drug fixed-dose combination treatment vs. monotherapy in hypertension. *Eur Heart J* 2018;**39**:3654–3661.
563. Salam A, Kanukula R, Atkins E, Wang X, Islam S, Kishore SP, Jaffe MG, Patel A, Rodgers A. Efficacy and safety of dual combination therapy of blood pressure-lowering drugs as initial treatment for hypertension: a systematic review and meta-analysis of randomized controlled trials. *J Hypertens* 2019;**37**:1768–1774.
564. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Gulsin GS, Beech A, Maresova V, Topham PS, Stanley A, Thurston H, Smith PR, Horne R, Widimsky J, Keavney B, Heagerty A, Samani NJ, Williams B, Tomaszewski M. Biochemical Screening for Nonadherence Is Associated With Blood Pressure Reduction and Improvement in Adherence. *Hypertension* 2017;**70**:1042–1048.
565. MacDonald TM, Williams B, Webb DJ, Morant S, Caulfield M, Cruickshank JK, Ford I, Sever P, Mackenzie IS, Padmanabhan S, McCann GP, Salsbury J, McInnes G, Brown MJ, British Hypertension Society Programme of Prevention And Treatment of Hypertension With Algorithm-based Therapy (PATHWAY). Combination Therapy Is Superior to Sequential Monotherapy for the Initial Treatment of Hypertension: A Double-Blind Randomized Controlled Trial. *J Am Heart Assoc* 2017;**6**:e006986.
566. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J, ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;**366**:895–906.
567. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, Hester A, Gupte J, Gatlin M, Velazquez EJ, ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;**359**:2417–2428.
568. Yusuf S, Lonn E, Pais P, Bosch J, Lopez-Jaramillo P, Zhu J, Xavier D, Avezum A, Leiter LA, Piegas LS, Parkhomenko A, Keltai M, Keltai K, Sliwa K, Chazova I, Peters RJ, Held C, Yusoff K, Lewis BS, Jansky P, Khunti K, Toff WD, Reid CM, Varigos J, Accini JL, McKelvie R, Pogue J, Jung H, Liu L, Diaz R, Dans A, Dagenais G, HOPE-3 Investigators. Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease. *N Engl J Med* 2016;**374**:2032–2043.
569. Matsuzaki M, Ogihara T, Umemoto S, Rakugi H, Matsuoka H, Shimada K, Abe K, Suzuki N, Eto T, Higaki J, Ito S, Kamiya A, Kikuchi K, Suzuki H, Tei C, Ohashi Y, Saruta T, Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial Group. Prevention of cardiovascular events with calcium channel blocker-based combination therapies in patients with hypertension: a randomized controlled trial. *J Hypertens* 2011;**29**:1649–1659.
570. Weir MR, Hsueh WA, Nesbitt SD, Littlejohn TJ, 3rd, Graff A, Shojaee A, Waverczak WF, Qian C, Jones CJ, Neutel JM. A titrate-to-goal study of switching patients uncontrolled on antihypertensive monotherapy to fixed-dose combinations of amlodipine and olmesartan medoxomil +/- hydrochlorothiazide. *J Clin Hypertens (Greenwich)* 2011;**13**:404–412.
571. Volpe M, Christian Rump L, Ammentorp B, Laeis P. Efficacy and safety of triple antihypertensive therapy with the olmesartan/amlodipine/hydrochlorothiazide combination. *Clin Drug Investig* 2012;**32**:649–664.
572. Williams B, MacDonald TM, Morant SV, Webb DJ, Sever P, McInnes GT, Ford I, Cruickshank JK, Caulfield MJ, Padmanabhan S, Mackenzie IS, Salsbury J, Brown MJ, British Hypertension Society programme of Prevention And Treatment of Hypertension With Algorithm based Therapy (PATHWAY) Study Group. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. *Lancet Diabetes Endocrinol* 2018;**6**:464–475.
573. Agarwal R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, Ma J, White WB, Williams B. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a

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phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2019;**394**:1540–1550.
574. Krieger EM, Drager LF, Giorgi DMA, Pereira AC, Barreto-Filho JAS, Nogueira AR, Mill JG, Lotufo PA, Amodeo C, Batista MC, Bodanese LC, Carvalho ACC, Castro I, Chaves H, Costa EAS, Feitosa GS, Franco RJS, Fuchs FD, Guimaraes AC, Jardim PC, Machado CA, Magalhaes ME, Mion D, Jr., Nascimento RM, Nobre F, Nobrega AC, Ribeiro ALP, Rodrigues-Sobrinho CR, Sanjuliani AF, Teixeira M, Krieger JE, ReHOT Investigators. Spironolactone Versus Clonidine as a Fourth-Drug Therapy for Resistant Hypertension: The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment). *Hypertension* 2018;**71**:681–690.
575. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.
576. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA, ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;**367**:2204–2213.
577. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P, Banerjee A, Barnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, Catala-Lopez F, Feigin VL, Fernandes JC, Fischer F, Gebru AA, Gona P, Gupta R, Hankey GJ, Jonas JB, Judd SE, Khang YH, Khosravi A, Kim YJ, Kimokoti RW, Kokubo Y, Kolte D, Lopez A, Lotufo PA, Malekzadeh R, Melaku YA, Mensah GA, Misganaw A, Mokdad AH, Moran AE, Nawaz H, Neal B, Ngalesoni FN, Ohkubo T, Pourmalek F, Rafay A, Rai RK, Rojas-Rueda D, Sampson UK, Santos IS, Sawhney M, Schutte AE, Sepanlou SG, Shifa GT, Shiue I, Tedla BA, Thrift AG, Tonelli M, Truelsen T, Tsilimparis N, Ukwaja KN, Uthman OA, Vasankari T, Venketasubramanian N, Vlassov VV, Vos T, Westerman R, Yan LL, Yano Y, Yonemoto N, Zaki ME, Murray CJ. Global Burden of Hypertension and Systolic Blood Pressure of at Least 110 to 115 mm Hg, 1990-2015. *JAMA* 2017;**317**:165–182.
578. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S, PURE (Prospective Urban Rural Epidemiology) Study investigators. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, *and low-income countries. JAMA* 2013;**310**:959–968.
579. Siu AL, US Preventive Services Task Force. Screening for high blood pressure in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2015;**163**:778–786.
580. Huang CJ, Chiang CE, Williams B, Kario K, Sung SH, Chen CH, Wang TD, Cheng HM. Effect Modification by Age on the Benefit or Harm of Antihypertensive Treatment for Elderly Hypertensives: A Systematic Review and Meta-analysis. *Am J Hypertens* 2019;**32**:163–174.
581. Verma AA, Khuu W, Tadrous M, Gomes T, Mamdani MM. Fixed-dose combination antihypertensive medications, adherence, and clinical outcomes: A population-based retrospective cohort study. *PLoS Med* 2018;**15**:e1002584.
582. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 4. Effects of various classes of antihypertensive drugs - overview and meta-analyses. *J Hypertens* 2015;**33**:195–211.
583. Sattar N, Preiss D. HbA1c in type 2 diabetes diagnostic criteria: addressing the right questions to move the field forwards. *Diabetologia* 2012;**55**:1564–1567.
584. The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2013;**34**:3035–3087.
585. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, Ross HM, McIlvenna Y, Welsh P, Kean S, Ford I, McConnachie A, Messow CM, Sattar N, Taylor R. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019;**7**:344–355.
586. Taheri S, Zaghloul H, Chagoury O, Elhadad S, Ahmed SH, El Khatib N, Amona RA, El Nahas K, Suleiman N, Alnaama A, Al-Hamaq A, Charlson M, Wells MT, Al-Abdulla S, Abou-Samra AB. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, *randomised controlled trial. Lancet Diabetes Endocrinol* 2020;**8**:477–489.
587. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;**352**:837–853.
588. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompoint S, de Galan BE, Joshi R, Travert F. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560–2572.
589. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;**352**:854–865.
590. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019;**393**:31–39.
591. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Kober L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol* 2019;**7**:776–785.
592. Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, D'Alessio DA, Davies MJ. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020;**63**:221–228.
593. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD, VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**:129–139.
594. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Sr., Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, Del Prato S, Harmony Outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;**392**:1519–1529.
595. Ferrannini G, Gerstein H, Colhoun HM, Dagenais GR, Diaz R, Dyal L, Lakshmanan M, Mellbin L, Probstfield J, Riddle MC, Shaw JE, Avezum A, Basile JN, Cushman WC, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Pais P, Pirags V, Pogosova N, Raubenheimer PJ, Sheu WH, Ryden L. Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin. *Eur Heart J* 2020:[Online ahead of print].
596. Crowley MJ, McGuire DK, Alexopoulos AS, Jensen TJ, Rasmussen S, Saevereid HA, Verma S, Buse JB. Effects of Liraglutide on Cardiovascular Outcomes in Type 2 Diabetes Patients With and Without Baseline Metformin Use: Post Hoc Analyses of the LEADER Trial. *Diabetes Care* 2020;**43**:e108–e110.
597. Neuen BL, Arnott C, Perkovic V, Figtree G, de Zeeuw D, Fulcher G, Jun M, Jardine MJ, Zoungas S, Pollock C, Mahaffey KW, Neal B, Heerspink HJL. Sodium-glucose co-transporter-2 inhibitors with and without metformin: A meta-analysis of cardiovascular, kidney and mortality outcomes. *Diabetes Obes Metab* 2021;**23**:382–390.
598. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW, CREDENCE Trial Investigators. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
599. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjostrom CD, Toto RD, Langkilde AM, Wheeler DC, DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020;**383**:1436–1446.
600. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjostrand M, Langkilde AM, DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019;**381**:1995–2008.
601. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Bohm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP,

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Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F, EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020;**383**:1413–1424.
602. Sattar N, McMurray JJ, Cheng AY. Cardiorenal risk reduction guidance in diabetes: can we reach consensus? *Lancet Diabetes Endocrinol* 2020;**8**:357–360.
603. Gong Q, Zhang P, Wang J, Ma J, An Y, Chen Y, Zhang B, Feng X, Li H, Chen X, Cheng YJ, Gregg EW, Hu Y, Bennett PH, Li G, Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019;**7**:452–461.
604. Celis-Morales CA, Petermann F, Hui L, Lyall DM, Iliodromiti S, McLaren J, Anderson J, Welsh P, Mackay DF, Pell JP, Sattar N, Gill JMR, Gray SR. Associations Between Diabetes and Both Cardiovascular Disease and All-Cause Mortality Are Modified by Grip Strength: Evidence From UK Biobank, a Prospective Population-Based Cohort Study. *Diabetes Care* 2017;**40**:1710–1718.
605. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S, Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *Lancet* 2009;**373**:1765–1772.
606. Control Group, Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, Evans GW, Gerstein HC, Holman RR, Moritz TE, Neal BC, Ninomiya T, Patel AA, Paul SK, Travert F, Woodward M. Intensive glucose control and macrovascular outcomes in type 2 diabetes. *Diabetologia* 2009;**52**:2288–2298.
607. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR, TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2015;**373**:232–242.
608. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I, SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;**369**:1317–1326.
609. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F, EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;**369**:1327–1335.
610. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, Alexander JH, Pencina M, Toto RD, Wanner C, Zinman B, Woerle HJ, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, McGuire DK, CARMELINA Investigators. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial. *JAMA* 2019;**321**:69–79.
611. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117–2128.
612. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;**377**:644–657.
613. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS, DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019;**380**:347–357.
614. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK, VERTIS CV Investigators. Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *N Engl J Med* 2020;**383**:1425–1435.
615. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Ryden L, Xavier D, Atisso CM, Dyal L, Hall S, Rao-Melacini P, Wong G, Avezum A, Basile J, Chung N, Conget I, Cushman WC, Franek E, Hancu N, Hanefeld M, Holt S, Jansky P, Keltai M, Lanas F, Leiter LA, Lopez-Jaramillo P, Cardona Munoz EG, Pirags V, Pogosova N, Raubenheimer PJ, Shaw JE, Sheu WH, Temelkova-Kurktschiev T, REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, *randomised placebo-controlled trial*. *Lancet* 2019;**394**:121–130.
616. Marx N, Davies MJ, Grant PJ, Mathieu C, Petrie JR, Cosentino F, Buse JB. Guideline recommendations and the positioning of newer drugs in type 2 diabetes care. *Lancet Diabetes Endocrinol* 2021;**9**:46–52.
617. Writing Group for the DCCT/EDIC Research Group, Orchard TJ, Nathan DM, Zinman B, Cleary P, Brillon D, Backlund JY, Lachin JM. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015;**313**:45–53.
618. Petrie JR, Chaturvedi N, Ford I, Brouwers M, Greenlaw N, Tillin T, Hramiak I, Hughes AD, Jenkins AJ, Klein BEK, Klein R, Ooi TC, Rossing P, Stehouwer CDA, Sattar N, Colhoun HM, REMOVAL Study Group. Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017;**5**:597–609.
619. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, Patrono C, Roncaglioni MC, Zanchetti A. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;**373**:1849–1860.
620. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;**348**:1329–1339.
621. Chiarito M, Sanz-Sanchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, Condorelli G, Ferrante G, Stefanini GG. Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020;**395**:1487–1495.
622. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
623. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN, ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2018;**53**:34–78.
624. ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018;**379**:1529–1539.
625. Seidu S, Kunutsor SK, Sesso HD, Gaziano JM, Buring JE, Roncaglioni MC, Khunti K. Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. *Cardiovasc Diabetol* 2019;**18**:70.
626. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM, ASPREE Investigator Group. Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *N Engl J Med* 2018;**379**:1509–1518.
627. Gaziano JM, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick PB, Howard G, Pearson TA, Rothwell PM, Ruilope LM, Tendera M, Tognoni G, ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**392**:1036–1046.
628. Abdelaziz HK, Saad M, Pothineni NVK, Megaly M, Potluri R, Saleh M, Kon DLC, Roberts DH, Bhatt DL, Aronow HD, Abbott JD, Mehta JL. Aspirin for Primary Prevention of Cardiovascular Events. *J Am Coll Cardiol* 2019;**73**:2915–2929.
629. Zheng SL, Roddick AJ. Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA* 2019;**321**:277–287.
630. Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur Heart J* 2019;**40**:607–617.
631. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA* 2006;**295**:306–313.
632. Halvorsen S, Andreotti F, ten Berg JM, Cattaneo M, Coccheri S, Marchioli R, Morais J, Verheugt FW, De Caterina R. Aspirin therapy in primary

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cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol* 2014;**64**:319–327.
633. Yusuf S, Joseph P, Dans A, Gao P, Teo K, Xavier D, Lopez-Jaramillo P, Yusoff K, Santoso A, Gamra H, Talukder S, Christou C, Girish P, Yeates K, Xavier F, Dagenais G, Rocha C, McCready T, Tyrwhitt J, Bosch J, Pais P, International Polycap Study 3 Investigators. Polypill with or without Aspirin in Persons without Cardiovascular Disease. *N Engl J Med* 2021;**384**:216–228.
634. Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, Holland L, Wilson K, Bhala N, Hawkey C, Hochberg M, Hunt R, Laine L, Lanas A, Patrono C, Baigent C. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *Lancet Gastroenterol Hepatol* 2018;**3**:231–241.
635. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GY, Verheugt FW, Huber K, Grove EL, Morais J, Husted S, Wassmann S, Rosano G, Atar D, Pathak A, Kjeldsen K, Storey RF, ESC Working Group on Cardiovascular Pharmacology and Drug Therapy and ESC Working Group on Thrombosis. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. *Eur Heart J* 2013;**34**:1708–1713, 1713a-1713b.
636. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N Engl J Med* 2017;**377**:1119–1131.
637. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ, CIRT Investigators. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *N Engl J Med* 2019;**380**:752–762.
638. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev* 2016:CD001800.
639. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev* 2019;**1**:CD003331.
640. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf MI, Hackbusch M, Voller H, Schmid JP, Davos CH. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: Update of the Cardiac Rehabilitation Outcome Study (CROS-II). *Eur J Prev Cardiol* 2020;**27**:1756–1774.
641. Santiago de Araujo Pio C, Marzolini S, Pakosh M, Grace SL. Effect of Cardiac Rehabilitation Dose on Mortality and Morbidity: A Systematic Review and Meta-regression Analysis. *Mayo Clin Proc* 2017;**92**:1644–1659.
642. van Halewijn G, Deckers J, Tay HY, van Domburg R, Kotseva K, Wood D. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. *Int J Cardiol* 2017;**232**:294–303.
643. Santiago de Araujo Pio C, Chaves GS, Davies P, Taylor RS, Grace SL. Interventions to promote patient utilisation of cardiac rehabilitation. *Cochrane Database Syst Rev* 2019;**2**:CD007131.
644. Jorstad HT, von Birgelen C, Alings AM, Liem A, van Dantzig JM, Jaarsma W, Lok DJ, Kragten HJ, de Vries K, de Milliano PA, Withagen AJ, Scholte Op Reimer WJ, Tijssen JG, Peters RJ. Effect of a nurse-coordinated prevention programme on cardiovascular risk after an acute coronary syndrome: main results of the RESPONSE randomised trial. *Heart* 2013;**99**:1421–1430.
645. Jennings C, Kotseva K, De Bacquer D, Hoes A, de Velasco J, Brusaferro S, Mead A, Jones J, Tonstad S, Wood D, EUROACTION PLUS Study Group. Effectiveness of a preventive cardiology programme for high CVD risk persistent smokers: the EUROACTION PLUS varenicline trial. *Eur Heart J* 2014;**35**:1411–1420.
646. Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faergeman O, EUROACTION Study Group. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. *Lancet* 2008;**371**:1999–2012.
647. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K, Cowie A, Zawada A, Taylor RS. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev* 2017;**6**:CD007130.
648. Jin K, Khonsari S, Gallagher R, Gallagher P, Clark AM, Freedman B, Briffa T, Bauman A, Redfern J, Neubeck L. Telehealth interventions for the secondary prevention of coronary heart disease: A systematic review and meta-analysis. *Eur J Cardiovasc Nurs* 2019;**18**:260–271.
649. Verschueren S, Eskes AM, Maaskant JM, Roest AM, Latour CHM, Op Reimer WS. The effect of exercise therapy on depressive and anxious symptoms in patients with ischemic heart disease: A systematic review. *J Psychosom Res* 2018;**105**:80–91.
650. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, Whellan D, O'Connor C, Keteyian SJ, Coats A, Davos CH, Dalal HM, Dracup K, Evangelista LS, Jolly K, Myers J, Nilsson BB, Passino C, Witham MD, Yeh GY, ExTraMATCH II Collaboration. Impact of Exercise Rehabilitation on Exercise Capacity and Quality-of-Life in Heart Failure: Individual Participant Meta-Analysis. *J Am Coll Cardiol* 2019;**73**:1430–1443.
651. Shields GE, Wells A, Doherty P, Heagerty A, Buck D, Davies LM. Cost-effectiveness of cardiac rehabilitation: a systematic review. *Heart* 2018;**104**:1403–1410.
652. Bjarnason-Wehrens B, McGee H, Zwisler AD, Piepoli MF, Benzer W, Schmid JP, Dendale P, Pogosova NG, Zdrenghea D, Niebauer J, Mendes M, Cardiac Rehabilitation Section European Association of Cardiovascular Prevention and Rehabilitation. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:410–418.
653. Benzer W, Rauch B, Schmid JP, Zwisler AD, Dendale P, Davos CH, Kouidi E, Simon A, Abreu A, Pogosova N, Gaita D, Miletic B, Bonner G, Ouarrak T, McGee H, EuroCaReD study group. Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. *Int J Cardiol* 2017;**228**:58–67.
654. Kabboul NN, Tomlinson G, Francis TA, Grace SL, Chaves G, Rac V, Daou-Kabboul T, Bielecki JM, Alter DA, Krahn M. Comparative Effectiveness of the Core Components of Cardiac Rehabilitation on Mortality and Morbidity: A Systematic Review and Network Meta-Analysis. *J Clin Med* 2018;**7**:514.
655. Anderson L, Brown JP, Clark AM, Dalal H, Rossau HK, Bridges C, Taylor RS. Patient education in the management of coronary heart disease. *Cochrane Database Syst Rev* 2017;**6**:CD008895.
656. Borjesson M, Dellborg M, Niebauer J, LaGerche A, Schmied C, Solberg EE, Halle M, Adami E, Biffi A, Carre F, Caselli S, Papadakis M, Pressler A, Rasmusen H, Serratosa L, Sharma S, van Buuren F, Pelliccia A. Recommendations for participation in leisure time or competitive sports in athletes-patients with coronary artery disease: a position statement from the Sports Cardiology Section of the European Association of Preventive Cardiology (EAPC). *Eur Heart J* 2019;**40**:13–18.
657. Abreu A, Frederix I, Dendale P, Janssen A, Doherty P, Piepoli MF, Voller H, Secondary Prevention and Rehabilitation Section of EAPC. Standardization and quality improvement of secondary prevention through cardiovascular rehabilitation programmes in Europe: The avenue towards EAPC accreditation programme: A position statement of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020:2047487320924912.
658. Hansen D, Rovelo Ruiz G, Doherty P, Iliou MC, Vromen T, Hinton S, Frederix I, Wilhelm M, Schmid JP, Abreu A, Ambrosetti M, Garcia-Porrero E, Coninx K, Dendale P, EAPC EXPERT working group. Do clinicians prescribe exercise similarly in patients with different cardiovascular diseases? Findings from the EAPC EXPERT working group survey. *Eur J Prev Cardiol* 2018;**25**:682–691.
659. Hansen D, Dendale P, Coninx K, Vanhees L, Piepoli MF, Niebauer J, Cornelissen V, Pedretti R, Geurts E, Ruiz GR, Corra U, Schmid JP, Greco E, Davos CH, Edelmann F, Abreu A, Rauch B, Ambrosetti M, Braga SS, Barna O, Beckers P, Bussotti M, Fagard R, Faggiano P, Garcia-Porrero E, Kouidi E, Lamotte M, Neunhauserer D, Reibis R, Spruit MA, Stettler C, Takken T, Tonoli C, Vigorito C, Voller H, Doherty P. The European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool: A digital training and decision support system for optimized exercise prescription in cardiovascular disease. Concept, definitions and construction methodology. *Eur J Prev Cardiol* 2017;**24**:1017–1031.
660. Abell B, Glasziou P, Hoffmann T. The Contribution of Individual Exercise Training Components to Clinical Outcomes in Randomised Controlled Trials of Cardiac Rehabilitation: A Systematic Review and Meta-regression. *Sports Med Open* 2017;**3**:19.
661. Kotseva K, De Backer G, De Bacquer D, Ryden L, Hoes A, Grobbee D, Maggioni A, Marques-Vidal P, Jennings C, Abreu A, Aguiar C, Badariene J, Bruthans J, Castro Conde A, Cifkova R, Crowley J, Davletov K, Deckers J, De Smedt D, De Sutter J, Dilic M, Dolzhenko M, Dzerve V, Erglis A, Fras Z, Gaita D, Gotcheva N, Heuschmann P, Hasan-Ali H, Jankowski P, Lalic N, Lehto S, Lovic D, Mancas S, Mellbin L, Milicic D, Mirrakhimov E, Oganov R, Pogosova N, Reiner Z, Stoerk S, Tokgozoglu L, Tsioufis C, Vulic D, Wood D, EUROASPIRE Investigators. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol* 2019;**26**:824–835.
662. Resurreccion DM, Moreno-Peral P, Gomez-Herranz M, Rubio-Valera M, Pastor L, Caldas de Almeida JM, Motrico E. Factors associated with non-participation in and dropout from cardiac rehabilitation programmes: a systematic review of prospective cohort studies. *Eur J Cardiovasc Nurs* 2019;**18**:38–47.

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663. Hamilton SJ, Mills B, Birch EM, Thompson SC. Smartphones in the secondary prevention of cardiovascular disease: a systematic review. *BMC Cardiovasc Disord* 2018;**18**:25.
664. Giannuzzi P, Temporelli PL, Marchioli R, Maggioni AP, Balestroni G, Ceci V, Chieffo C, Gattone M, Griffo R, Schweiger C, Tavazzi L, Urbinati S, Valagussa F, Vanuzzo D, GOSPEL Investigators. Global secondary prevention strategies to limit event recurrence after myocardial infarction: results of the GOSPEL study, a multicenter, randomized controlled trial from the Italian Cardiac Rehabilitation Network. *Arch Intern Med* 2008;**168**:2194–2204.
665. Rose G. Sick individuals and sick populations. *Int J Epidemiol* 1985;**14**:32–38.
666. Rose G. Strategy of prevention: lessons from cardiovascular disease. *Br Med J (Clin Res Ed)* 1981;**282**:1847–1851.
667. Sniderman AD, Thanassoulis G, Wilkins JT, Furberg CD, Pencina M. Sick Individuals and Sick Populations by Geoffrey Rose: Cardiovascular Prevention Updated. *J Am Heart Assoc* 2018;**7**:e010049.
668. Doyle YG, Furey A, Flowers J. Sick individuals and sick populations: 20 years later. *J Epidemiol Community Health* 2006;**60**:396–398.
669. Sorensen K, Pelikan JM, Rothlin F, Ganahl K, Slonska Z, Doyle G, Fullam J, Kondilis B, Agrafiotis D, Uiters E, Falcon M, Mensing M, Tchamov K, van den Broucke S, Brand H, HLS-EU Consortium. Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). *Eur J Public Health* 2015;**25**:1053–1058.
670. Magnani JW, Mujahid MS, Aronow HD, Cene CW, Dickson VV, Havranek E, Morgenstern LB, Paasche-Orlow MK, Pollak A, Willey JZ, American Heart Association Council on Epidemiology and Prevention, Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, Council on Peripheral Vascular Disease, Council on Quality of Care and Outcomes Research, Council S. Health Literacy and Cardiovascular Disease: Fundamental Relevance to Primary and Secondary Prevention: A Scientific Statement From the American Heart Association. *Circulation* 2018;**138**:e48–e74.
671. Jorgensen T, Capewell S, Prescott E, Allender S, Sans S, Zdrojewski T, De Bacquer D, de Sutter J, Franco OH, Logstrup S, Volpe M, Malyutina S, Marques-Vidal P, Reiner Z, Tell GS, Verschuren WM, Vanuzzo D, PEP section of EACPR. Population-level changes to promote cardiovascular health. *Eur J Prev Cardiol* 2013;**20**:409–421.
672. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR, Jr., Kraus WE, Kris-Etherton PM, Krummel DA, Popkin BM, Whitsel LP, Zakai NA, American Heart Association Council on Epidemiology and Prevention, Council on Nutrition, Physical Activity and Metabolism, Council on Clinical Cardiology, Council on Cardiovascular Disease in the Young, Council on the Kidney in Cardiovascular Disease, Council on Peripheral Vascular Disease, the American Heart Association Advocacy Coordinating Committee. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:1514–1563.
673. Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013;**382**:1039–1048.
674. Shah AS, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* 2015;**350**:h1295.
675. Al-Kindi SG, Brook RD, Biswal S, Rajagopalan S. Environmental determinants of cardiovascular disease: lessons learned from air pollution. *Nat Rev Cardiol* 2020;**17**:656–672.
676. Haines A, Ebi K. The Imperative for Climate Action to Protect Health. *N Engl J Med* 2019;**380**:263–273.
677. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:267–315.
678. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
679. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
680. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
681. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
682. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM, TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
683. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.
684. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flugel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Mollmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schuhlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tolg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A, ISAR-REACT 5 Trial Investigators. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2019;**381**:1524–1534.
685. Navarese EP, Khan SU, Kolodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, Trabattoni D, Ohman EM, Wallentin L, Roe MT, James S. Comparative Efficacy and Safety of Oral P2Y12 Inhibitors in Acute Coronary Syndrome: Network Meta-Analysis of 52 816 Patients From 12 Randomized Trials. *Circulation* 2020;**142**:150–160.
686. Hahn JY, Song YB, Oh JH, Cho DK, Lee JB, Doh JH, Kim SH, Jeong JO, Bae JH, Kim BO, Cho JH, Suh IW, Kim DI, Park HK, Park JS, Choi WG, Lee WS, Kim J, Choi KH, Park TK, Lee JM, Yang JH, Choi JH, Choi SH, Gwon HC, SMART-DATE investigators. 6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet* 2018;**391**:1274–1284.
687. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;**371**:2155–2166.
688. Bonaca MP, Braunwald E, Sabatine MS. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction. *N Engl J Med* 2015;**373**:1274–1275.
689. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, Held C, Andersson M, Himmelmann A, Ridderstrale W, Leonsson-Zachrisson M, Liu Y, Opolski G, Zateyshchikov D, Ge J, Nicolau JC, Corbalan R, Cornel JH, Widimsky P, Leiter LA, THEMIS Steering Committee and Investigators. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med* 2019;**381**:1309–1320.
690. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EW, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK, ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; doi: 10.1093/eurheartj/ehab368.
691. Phillips CO, Wright SM, Kern DE, Singa RM, Shepperd S, Rubin HR. Comprehensive discharge planning with postdischarge support for older patients with congestive heart failure: a meta-analysis. *JAMA* 2004;**291**:1358–1367.
692. Stewart S, Vandenbroek AJ, Pearson S, Horowitz JD. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. *Arch Intern Med* 1999;**159**:257–261.
693. McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004;**44**:810–819.

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694. Feltner C, Jones CD, Cene CW, Zheng ZJ, Sueta CA, Coker-Schwimmer EJ, Arvanitis M, Lohr KN, Middleton JC, Jonas DE. Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**:774–784.
695. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002;**8**:216–224.
696. Greene SJ, Vaduganathan M, Lupi L, Ambrosy AP, Mentz RJ, Konstam MA, Nodari S, Subacius HP, Fonarow GC, Bonow RO, Gheorghiade M, EVEREST Trial Investigators. Prognostic significance of serum total cholesterol and triglyceride levels in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial). *Am J Cardiol* 2013;**111**:574–581.
697. Sharma A, Lavie CJ, Borer JS, Vallakati A, Goel S, Lopez-Jimenez F, Arbab-Zadeh A, Mukherjee D, Lazar JM. Meta-analysis of the relation of body mass index to all-cause and cardiovascular mortality and hospitalization in patients with chronic heart failure. *Am J Cardiol* 2015;**115**:1428–1434.
698. Gupta PP, Fonarow GC, Horwich TB. Obesity and the obesity paradox in heart failure. *Can J Cardiol* 2015;**31**:195–202.
699. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, Levine B, Drazner M, Berry J. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail* 2015;**8**:33–40.
700. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL, HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1439–1450.
701. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014:CD003331.
702. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;**316**:1429–1435.
703. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA* 1995;**273**:1450–1456.
704. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999;**100**:2312–2318.
705. SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
706. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
707. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
708. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E, PIONEER-HF Investigators. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med* 2019;**380**:539–548.
709. DeVore AD, Braunwald E, Morrow DA, Duffy CI, Ambrosy AP, Chakraborty H, McCague K, Rocha R, Velazquez EJ, PIONEER-HF Investigators. Initiation of Angiotensin-Neprilysin Inhibition After Acute Decompensated Heart Failure: Secondary Analysis of the Open-label Extension of the PIONEER-HF Trial. *JAMA Cardiol* 2020;**5**:202–207.
710. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, Fonseca C, Goncalvesova E, Cavusoglu Y, Fernandez A, Chaaban S, Bohmer E, Pouleur AC, Mueller C, Tribouilloy C, Lonn E, ALB J, Gniot J, Mozheiko M, Lelonek M, Noe A, Schwende H, Bao W, Butylin D, Pascual-Figal D, TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. *Eur J Heart Fail* 2019;**21**:998–1007.
711. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vitovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Janosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;**283**:1295–1302.
712. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**:1651–1658.
713. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;**334**:1349–1355.
714. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**:2001–2007.
715. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;**106**:2194–2199.
716. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
717. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA, SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–225.
718. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
719. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B, EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
720. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Rizkala AR, Sabarwal SV, Shah AM, Shah SJ, Shi VC, van Veldhuisen DJ, Zannad F, Zile MR, Cikes M, Goncalvesova E, Katova T, Kosztin A, Lelonek M, Sweitzer N, Vardeny O, Claggett B, Jhund PS, Solomon SD. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. *Circulation* 2020;**141**:338–351.
721. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, Hillege H, Samani NJ, Zannad F, Dickstein K, Lang CC, Cleland JG, Ter Maaten JM, Metra M, Anker SD, van der Harst P, Ng LL, van der Meer P, van Veldhuisen DJ, Meyer S, Lam CSP, ASIAN-HF investigators, Voors AA. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. *Lancet* 2019;**394**:1254–1263.
722. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM, VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2020;**382**:1883–1893.
723. Faris RF, Flather M, Purcell H, Poole-Wilson PA, Coats AJ. Diuretics for heart failure. *Cochrane Database Syst Rev* 2012:CD003838.
724. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *Int J Cardiol* 2002;**82**:149–158.
725. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
726. Swedberg K, Komajda M, Bohm M, Borer J, Robertson M, Tavazzi L, Ford I, SHIFT Investigators. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol* 2012;**59**:1938–1945.
727. Cinà CS, Devereaux PJ, McFalls EO, ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med*. 2004; **351**: 2795-804. *Vasc Med* 2006;**11**:61-63.
728. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of

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vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;**314**:1547–1552.
729. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533.
730. Minchin M, Roland M, Richardson J, Rowark S, Guthrie B. Quality of Care in the United Kingdom after Removal of Financial Incentives. *N Engl J Med* 2018;**379**:948–957.
731. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Jr., Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN, African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;**351**:2049–2057.
732. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–2236.
733. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, Forsting M, Harnof S, Klijn CJ, Krieger D, Mendelow AD, Molina C, Montaner J, Overgaard K, Petersson J, Roine RO, Schmutzhard E, Schwerdtfeger K, Stapf C, Tatlisumak T, Thomas BM, Toni D, Unterberg A, Wagner M, European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014;**9**:840–855.
734. Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S. Distribution and Temporal Trends From 1993 to 2015 of Ischemic Stroke Subtypes: A Systematic Review and Meta-Analysis. *Stroke* 2018;**49**:814–819.
735. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, Nicoll JAR, Sudlow CLM, Cordonnier C, Wardlaw JM, Smith C, Al-Shahi Salman R. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. *Lancet Neurol* 2018;**17**:232–240.
736. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
737. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;**154**:1449–1457.
738. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
739. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
740. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
741. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Korv J, Lal A, Putaala J, Werring DJ. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J* 2019;**4**:198–223.
742. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
743. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**:71–86.
744. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;**367**:1665–1673.
745. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlof B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW, PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;**359**:1238–1251.
746. Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS, SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. *N Engl J Med* 2016;**375**:35–43.
747. SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;**367**:817–825.
748. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;**354**:1706–1717.
749. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ, MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;**364**:331–337.
750. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY, Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. *N Engl J Med* 2018;**379**:215–225.
751. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC, CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;**369**:11–19.
752. Liu M, Counsell C, Sandercock P. Anticoagulants for preventing recurrence following ischaemic stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2000:CD000248.
753. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP, Jr., Jackson CM, Pullicino P, Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444–1451.
754. Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y, Johnston SC, THALES Steering Committee and Investigators. Ticagrelor Added to Aspirin in Acute Nonsevere Ischemic Stroke or Transient Ischemic Attack of Atherosclerotic Origin. *Stroke* 2020;**51**:3504–3513.
755. Johnston SC, Amarenco P, Denison H, Evans SR, Himmelmann A, James S, Knutsson M, Ladenvall P, Molina CA, Wang Y, THALES Investigators. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. *N Engl J Med* 2020;**383**:207–217.
756. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmunzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K, RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. *N Engl J Med* 2019;**380**:1906–1917.
757. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ, NAVIGATE ESUS Investigators. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. *N Engl J Med* 2018;**378**:2191–2201.
758. PATS Collaborating Group. Post-stroke antihypertensive treatment study. A preliminary result. *Chin Med J (Engl)* 1995;**108**:710–717.
759. Wang WT, You LK, Chiang CE, Sung SH, Chuang SY, Cheng HM, Chen CH. Comparative Effectiveness of Blood Pressure-lowering Drugs in Patients who have Already Suffered From Stroke: Traditional and Bayesian Network Meta-analysis of Randomized Trials. *Medicine (Baltimore)* 2016;**95**:e3302.
760. Odden MC, McClure LA, Sawaya BP, White CL, Peralta CA, Field TS, Hart RG, Benavente OR, Pergola PE. Achieved Blood Pressure and Outcomes in the

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Secondary Prevention of Small Subcortical Strokes Trial. *Hypertension* 2016;**67**:63–69.
761. White CL, Szychowski JM, Pergola PE, Field TS, Talbert R, Lau H, Peri K, Benavente OR, Secondary Prevention of Small Subcortical Strokes Study Investigators. Can blood pressure be lowered safely in older adults with lacunar stroke? The Secondary Prevention of Small Subcortical Strokes study experience. *J Am Geriatr Soc* 2015;**63**:722–729.
762. Amarenco P, Bogousslavsky J, Callahan A, 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;**355**:549–559.
763. Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM, Rotterdam Scan Study. Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. *Stroke* 2003;**34**:1126–1129.
764. Bernick C, Kuller L, Dulberg C, Longstreth WT, Jr., Manolio T, Beauchamp N, Price T, Cardiovascular Health Study Collaborative Reseach Group. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. *Neurology* 2001;**57**:1222–1229.
765. Debette S, Beiser A, DeCarli C, Au R, Himali JJ, Kelly-Hayes M, Romero JR, Kase CS, Wolf PA, Seshadri S. Association of MRI markers of vascular brain injury with incident stroke, mild cognitive impairment, dementia, and mortality: the Framingham Offspring Study. *Stroke* 2010;**41**:600–606.
766. Katsanos AH, Filippatou A, Manios E, Deftereos S, Parissis J, Frogoudaki A, Vrettou AR, Ikonomidis I, Pikilidou M, Kargiotis O, Voumvourakis K, Alexandrov AW, Alexandrov AV, Tsivgoulis G. Blood Pressure Reduction and Secondary Stroke Prevention: A Systematic Review and Metaregression Analysis of Randomized Clinical Trials. *Hypertension* 2017;**69**:171–179.
767. Society for Vascular Surgery Lower Extremity Guidelines Writing Group, Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Mills JL, Moneta GL, Murad MH, Powell RJ, Reed AB, Schanzer A, Sidawy AN, Society for Vascular Surgery. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg* 2015;**61**:2S–41S.
768. Singh S, Armstrong EJ, Sherif W, Alvandi B, Westin GG, Singh GD, Amsterdam EA, Laird JR. Association of elevated fasting glucose with lower patency and increased major adverse limb events among patients with diabetes undergoing infrapopliteal balloon angioplasty. *Vasc Med* 2014;**19**:307–314.
769. Momsen AH, Jensen MB, Norager CB, Madsen MR, Vestersgaard-Andersen T, Lindholt JS. Drug therapy for improving walking distance in intermittent claudication: a systematic review and meta-analysis of robust randomised controlled studies. *Eur J Vasc Endovasc Surg* 2009;**38**:463–474.
770. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC, Jr., Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, Banerjee S, Creager MA, Bhatt DL, REACH Registry Investigators. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J* 2014;**35**:2864–2872.
771. Murphy SA, Cannon CP, Blazing MA, Giugliano RP, White JA, Lokhnygina Y, Reist C, Im K, Bohula EA, Isaza D, Lopez-Sendon J, Dellborg M, Kher U, Tershakovec AM, Braunwald E. Reduction in Total Cardiovascular Events With Ezetimibe/Simvastatin Post-Acute Coronary Syndrome: The IMPROVE-IT Trial. *J Am Coll Cardiol* 2016;**67**:353–361.
772. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS. Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation* 2018;**137**:338–350.
773. Schmit K, Dolor RJ, Jones WS, Vemulapalli S, Hasselblad V, Subherwal S, Heidenfelder B, Patel MR. Comparative effectiveness review of antiplatelet agents in peripheral artery disease. *J Am Heart Assoc* 2014;**3**:e001330.
774. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Aboyans V, Alings M, Kakkar AK, Keltai K, Maggioni AP, Lewis BS, Stork S, Zhu J, Lopez-Jaramillo P, O'Donnell M, Commerford PJ, Vinereanu D, Pogosova N, Ryden L, Fox KAA, Bhatt DL, Misselwitz F, Varigos JD, Vanassche T, Avezum AA, Chen E, Branch K, Leong DP, Bangdiwala SI, Hart RG, Yusuf S, COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:219–229.
775. The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS), Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO). *Eur Heart J* 2018;**39**:763–816.
776. Bavry AA, Anderson RD, Gong Y, Denardo SJ, Cooper-Dehoff RM, Handberg EM, Pepine CJ. Outcomes Among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the INternational VErapamil-SR/Trandolapril STudy. *Hypertension* 2010;**55**:48–53.
777. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
778. Shahin Y, Barnes R, Barakat H, Chetter IC. Meta-analysis of angiotensin converting enzyme inhibitors effect on walking ability and ankle brachial pressure index in patients with intermittent claudication. *Atherosclerosis* 2013;**231**:283–290.
779. Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev* 2013:CD005508.
780. Aronow WS, Ahn C. Effect of beta blockers on incidence of new coronary events in older persons with prior myocardial infarction and symptomatic peripheral arterial disease. *Am J Cardiol* 2001;**87**:1284–1286.
781. Bullen C. Impact of tobacco smoking and smoking cessation on cardiovascular risk and disease. *Expert Rev Cardiovasc Ther* 2008;**6**:883–895.
782. Mazari FA, Khan JA, Samuel N, Smith G, Carradice D, McCollum PC, Chetter IC. Long-term outcomes of a randomized clinical trial of supervised exercise, percutaneous transluminal angioplasty or combined treatment for patients with intermittent claudication due to femoropopliteal disease. *Br J Surg* 2017;**104**:76–83.
783. Fakhry F, Spronk S, van der Laan L, Wever JJ, Teijink JA, Hoffmann WH, Smits TM, van Brussel JP, Stultiens GN, Derom A, den Hoed PT, Ho GH, van Dijk LC, Verhofstad N, Orsini M, van Petersen A, Woltman K, Hulst I, van Sambeek MR, Rizopoulos D, Rouwet EV, Hunink MG. Endovascular Revascularization and Supervised Exercise for Peripheral Artery Disease and Intermittent Claudication: A Randomized Clinical Trial. *JAMA* 2015;**314**:1936–1944.
784. Jansen SCP, Hoorweg BBN, Hoeks SE, van den Houten MML, Scheltinga MRM, Teijink JAW, Rouwet EV. A systematic review and meta-analysis of the effects of supervised exercise therapy on modifiable cardiovascular risk factors in intermittent claudication. *J Vasc Surg* 2019;**69**:1293–1308 e1292.
785. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
786. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013;**31**:1281–1357.
787. Ostergren J, Sleight P, Dagenais G, Danisa K, Bosch J, Qilong Y, Yusuf S, HOPE study investigators. Impact of ramipril in patients with evidence of clinical or subclinical peripheral arterial disease. *Eur Heart J* 2004;**25**:17–24.
788. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, Newby LK, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, Marwick TH, Conference Participants. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2019;**74**:1823–1838.
789. Charytan DM, Sabatine MS, Pedersen TR, Im K, Park JG, Pineda AL, Wasserman SM, Deedwania P, Olsson AG, Sever PS, Keech AC, Giugliano RP, FOURIER Steering Committee and Investigators. Efficacy and Safety of Evolocumab in Chronic Kidney Disease in the FOURIER Trial. *J Am Coll Cardiol* 2019;**73**:2961–2970.
790. Herrington WG, Preiss D, Haynes R, von Eynatten M, Staplin N, Hauske SJ, George JT, Green JB, Landray MJ, Baigent C, Wanner C. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018;**11**:749–761.
791. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved Outcomes by Integrated Care of Anticoagulated Patients with Atrial Fibrillation Using the Simple ABC (Atrial Fibrillation Better Care) Pathway. *Am J Med* 2018;**131**:1359–1366 e1356.
792. Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Sung JH, Pak HN, Lee MH, Joung B, Lip GYH. Improved Population-Based Clinical Outcomes of Patients with Atrial Fibrillation by Compliance with the Simple ABC (Atrial

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Fibrillation Better Care) Pathway for Integrated Care Management: A Nationwide Cohort Study. *Thromb Haemost* 2019;**19**:1695–1703.
793. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated Care Management of Patients With Atrial Fibrillation and Risk of Cardiovascular Events: The ABC (Atrial fibrillation Better Care) Pathway in the ATHERO-AF Study Cohort. *Mayo Clin Proc* 2019;**94**:1261–1267.
794. Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GY. ABC (Atrial fibrillation Better Care) Pathway and Healthcare Costs in Atrial Fibrillation: The ATHERO-AF Study. *Am J Med* 2019;**132**:856–861.
795. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–2060.
796. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–2231.
797. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–2169.
798. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med* 2020;**382**:20–28.
799. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol* 2015;**66**:985–996.
800. Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, Oto A, Potpara TS, Steffel J, Marin F, de Oliveira Figueiredo MJ, de Simone G, Tzou WS, Chiang CE, Williams B, Reviewers, Dan GA, Gorenek B, Fauchier L, Savelieva I, Hatala R, van Gelder I, Brguljan-Hitij J, Erdine S, Lovic D, Kim YH, Salinas-Arce J, Field M. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), *Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). Europace* 2017;**19**:891–911.
801. Dzeshka MS, Shantsila A, Shantsila E, Lip GYH. Atrial Fibrillation and Hypertension. *Hypertension* 2017;**70**:854–861.
802. Huxley RR, Misialek JR, Agarwal SK, Loehr LR, Soliman EZ, Chen LY, Alonso A. Physical activity, obesity, weight change, and risk of atrial fibrillation: the Atherosclerosis Risk in Communities study. *Circ Arrhythm Electrophysiol* 2014;**7**:620–625.
803. Conen D, Albert CM. Alcohol consumption and risk of atrial fibrillation: how much is too much? *J Am Coll Cardiol* 2014;**64**:290–292.
804. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol* 2014;**64**:281–289.
805. Lavie CJ, Thomas RJ, Squires RW, Allison TG, Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clin Proc* 2009;**84**:373–383.
806. Mont L. Arrhythmias and sport practice. *Heart* 2010;**96**:398–405.
807. Menezes AR, Lavie CJ, De Schutter A, Milani RV, O'Keefe J, DiNicolantonio JJ, Morin DP, Abi-Samra FM. Lifestyle modification in the prevention and treatment of atrial fibrillation. *Prog Cardiovasc Dis* 2015;**58**:117–125.
808. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ* 1998;**316**:1784–1785.
809. Baldesberger S, Bauersfeld U, Candinas R, Seifert B, Zuber M, Ritter M, Jenni R, Oechslin E, Luthi P, Scharf C, Marti B, Attenhofer Jost CH. Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists. *Eur Heart J* 2008;**29**:71–78.
810. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace* 2008;**10**:618–623.
811. Nielsen JR, Wachtell K, Abdulla J. The Relationship Between Physical Activity and Risk of Atrial Fibrillation-A Systematic Review and Meta-Analysis. *J Atr Fibrillation* 2013;**5**:789.
812. Khan H, Kella D, Rauramaa R, Savonen K, Lloyd MS, Laukkanen JA. Cardiorespiratory fitness and atrial fibrillation: A population-based follow-up study. *Heart Rhythm* 2015;**12**:1424–1430.
813. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, Kalman JM, Sanders P. Associations of Obstructive Sleep Apnea With Atrial Fibrillation and Continuous Positive Airway Pressure Treatment: A Review. *JAMA Cardiol* 2018;**3**:532–540.
814. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, Hylek EM, Mahaffey KW, Freeman JV, Chang P, Holmes DN, Peterson ED, Piccini JP, Gersh BJ, ORBIT-AF Investigators. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation-Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015;**169**:647–654 e642.
815. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, Soliman EZ, Al-Mallah MH. Meta-Analysis of Continuous Positive Airway Pressure as a Therapy of Atrial Fibrillation in Obstructive Sleep Apnea. *Am J Cardiol* 2015;**116**:1767–1773.
816. Shukla A, Aizer A, Holmes D, Fowler S, Park DS, Bernstein S, Bernstein N, Chinitz L. Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence: A Meta-Analysis. *JACC Clin Electrophysiol* 2015;**1**:41–51.
817. Fatemi O, Yuriditsky E, Tsioufis C, Tsachris D, Morgan T, Basile J, Bigger T, Cushman W, Goff D, Soliman EZ, Thomas A, Papademetriou V. Impact of intensive glycemic control on the incidence of atrial fibrillation and associated cardiovascular outcomes in patients with type 2 diabetes mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). *Am J Cardiol* 2014;**114**:1217–1222.
818. Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, Baranowski B, Hussein A, Saliba W, Wazni O. Association Between Pre-Ablation Glycemic Control and Outcomes Among Patients With Diabetes Undergoing Atrial Fibrillation Ablation. *JACC Clin Electrophysiol* 2019;**5**:897–903.
819. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
820. Forman DE, Maurer MS, Boyd C, Brindis R, Salive ME, Horne FM, Bell SP, Fulmer T, Reuben DB, Zieman S, Rich MW. Multimorbidity in Older Adults With Cardiovascular Disease. *J Am Coll Cardiol* 2018;**71**:2149–2161.
821. Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M, Rahimi K. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. *PLoS Med* 2018;**15**:e1002513.
822. Buddeke J, Bots ML, van Dis I, Liem A, Visseren FLJ, Vaartjes I. Trends in comorbidity in patients hospitalised for cardiovascular disease. *Int J Cardiol* 2017;**248**:382–388.
823. Dunlay SM, Chamberlain AM. Multimorbidity in Older Patients with Cardiovascular Disease. *Curr Cardiovasc Risk Rep* 2016;**10**:3.
824. Jani BD, Nicholl BI, McQueenie R, Connelly DT, Hanlon P, Gallacher KI, Lee D, Mair FS. Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. *Europace* 2018;**20**:f329–f336.
825. Tisminetzky M, Goldberg R, Gurwitz JH. Magnitude and Impact of Multimorbidity on Clinical Outcomes in Older Adults with Cardiovascular Disease: A Literature Review. *Clin Geriatr Med* 2016;**32**:227–246.
826. Bell SP, Saraf AA. Epidemiology of Multimorbidity in Older Adults with Cardiovascular Disease. *Clin Geriatr Med* 2016;**32**:215–226.
827. Hall M, Dondo TB, Yan AT, Mamas MA, Timmis AD, Deanfield JE, Jernberg T, Hemingway H, Fox KAA, Gale CP. Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: Latent class analysis of a nationwide population-based cohort. *PLoS Med* 2018;**15**:e1002501.
828. Kim DH, Rich MW. Patient-Centred Care of Older Adults With Cardiovascular Disease and Multiple Chronic Conditions. *Can J Cardiol* 2016;**32**:1097–1107.
829. Rahimi K, Lam CSP, Steinhubl S. Cardiovascular disease and multimorbidity: A call for interdisciplinary research and personalized cardiovascular care. *PLoS Med* 2018;**15**:e1002545.
830. World Health Organization. *Global Action Plan for the Prevention and Control of NCDs 2013-2020*. https://www.who.int/publications/i/item/9789241506236 (22 June 2021).
831. Song Z, Ji Y, Safran DG, Chernew ME. Health Care Spending, Utilization, and Quality 8 Years into Global Payment. *N Engl J Med* 2019;**381**:252–263.
832. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes* 2020:[Online ahead of print].
833. Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet JP, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M,

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Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H, ESC Scientific Document Group, Halvorsen S, Jernberg T, Jortveit J, Blondal M, Ibanez B, Hassager C. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. *Eur Heart J Acute Cardiovasc Care* 2021;**10**:224–233.

834. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N, Reviewers, Boveda S, Deneke T, Defaye P, Conte G, Lenarczyk R, Providencia R, Guerra JM, Takahashi Y, Pisani C, Nava S, Sarkozy A, Glotzer TV, Martins Oliveira M. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* 2021;**23**:494–495.
835. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. *Eur Heart J* 2019;**40**:2745–2749.
836. Casey DE, Jr., Thomas RJ, Bhalla V, Commodore-Mensah Y, Heidenreich PA, Kolte D, Muntner P, Smith SC, Jr., Spertus JA, Windle JR, Wozniak GD, Ziaeian B. 2019 AHA/ACC Clinical Performance and Quality Measures for Adults With High Blood Pressure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol* 2019;**74**:2661–2706.
837. Drozda JP, Jr., Ferguson TB, Jr., Jneid H, Krumholz HM, Nallamothu BK, Olin JW, Ting HH. 2015 ACC/AHA Focused Update of Secondary Prevention Lipid Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol* 2016;**67**:558–587.

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