Ischemic Heart Diseases

Epidemiology, Risk Factors, prevention

Atherosclerotic cardiovascular 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 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

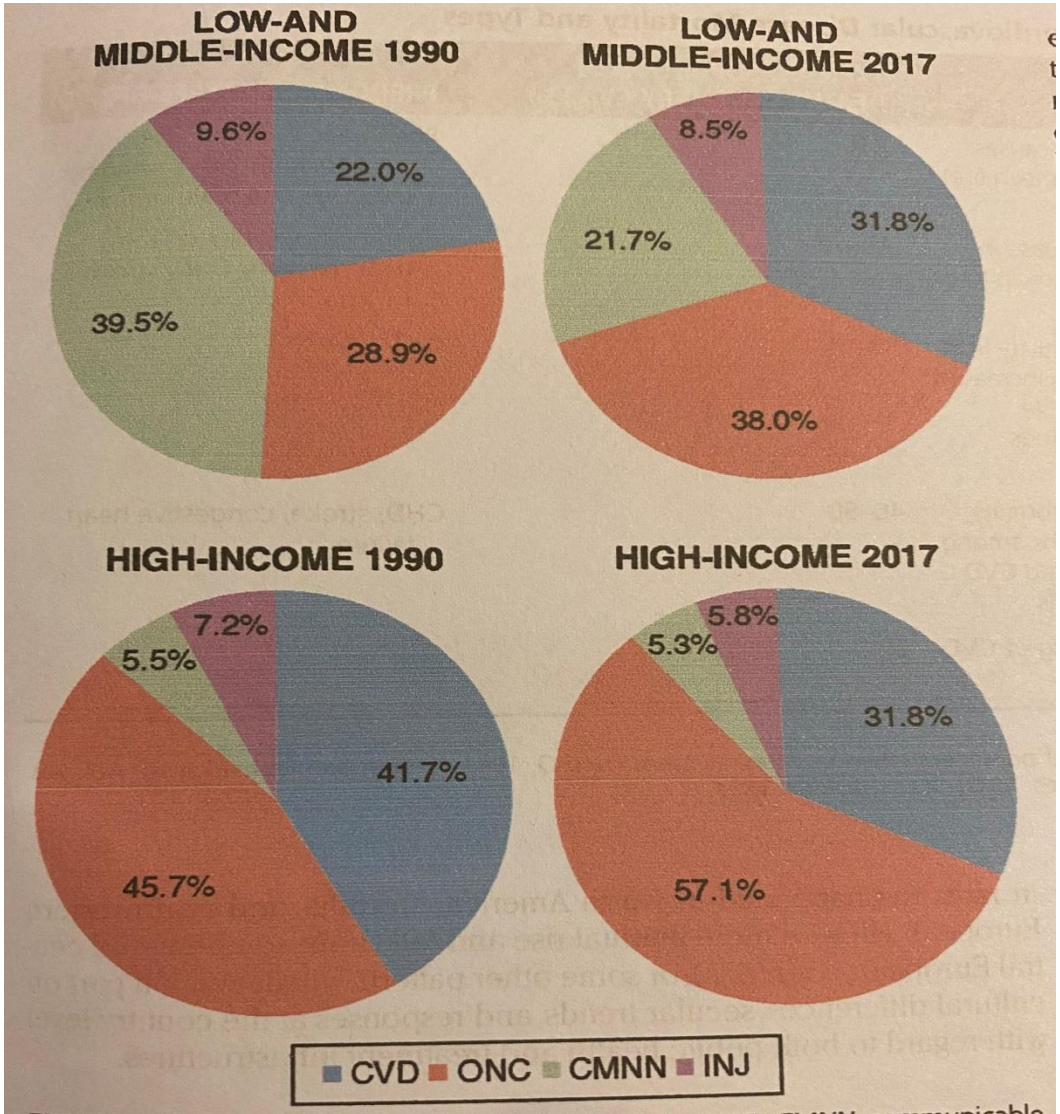


FIGURE 2.1 Changing pattern of mortality, 1990 to 2017. *CMNN*, communicable, maternal, neonatal, and nutritional diseases; *CVD*, cardiovascular disease; *INJ*, injury; *ONC*, other noncommunicable diseases. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017.)

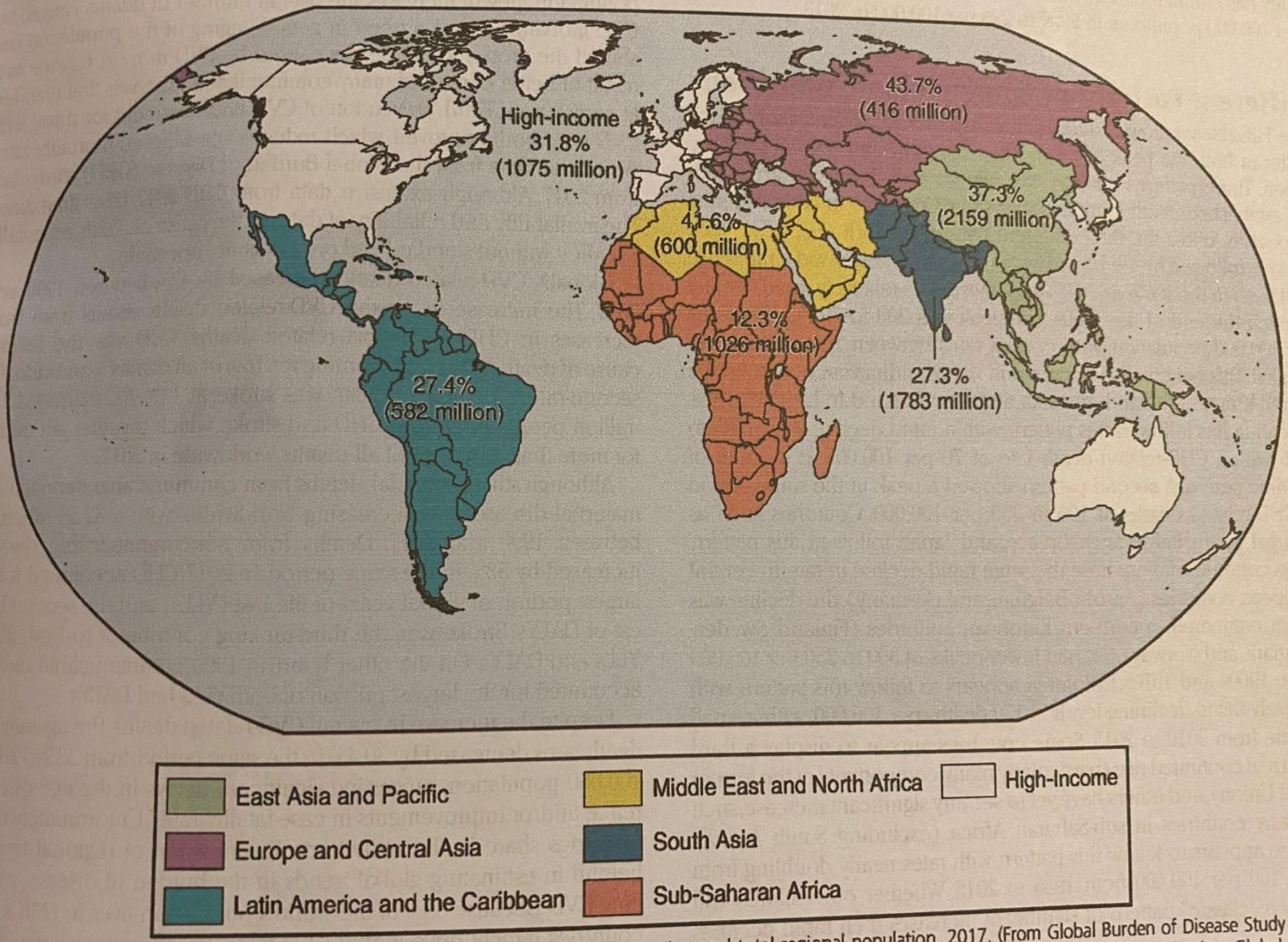


FIGURE 2.2 Cardiovascular disease deaths as a percentage of all deaths in each region and total regional population, 2017. (From Global Burden of Disease Study 2017. *...e-sex Specific All-cause and Cause-specific Mortality, 1990–2017*. Seattle: Institute for Health Metrics and Evaluation; 2017; and World Health Organization. Global Health ...servatory Data Repository. Demographic and socioeconomic statistics: population data by country. http://apps.who.int/gho/data/view.main.POP2040?lang=en.)

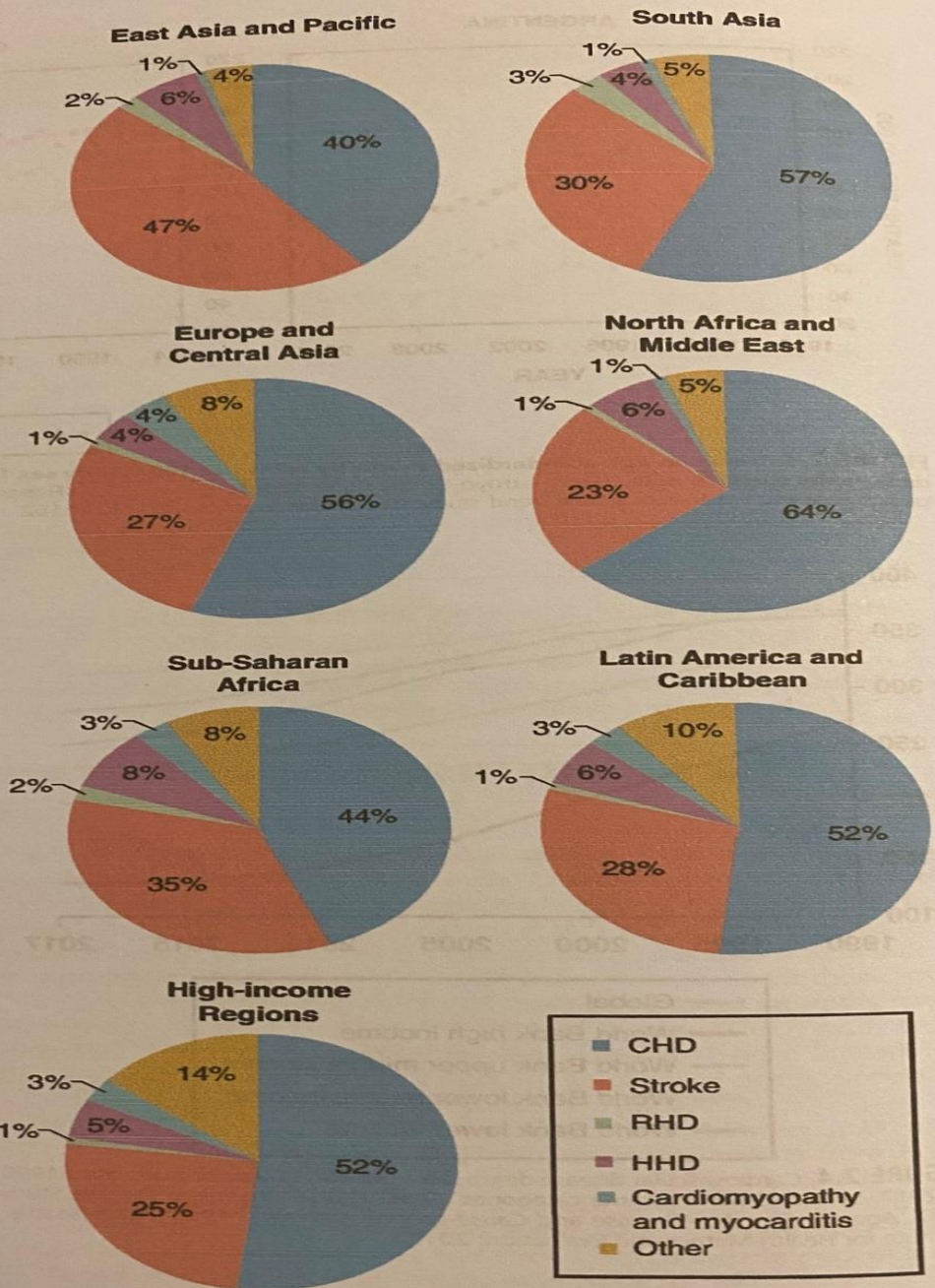


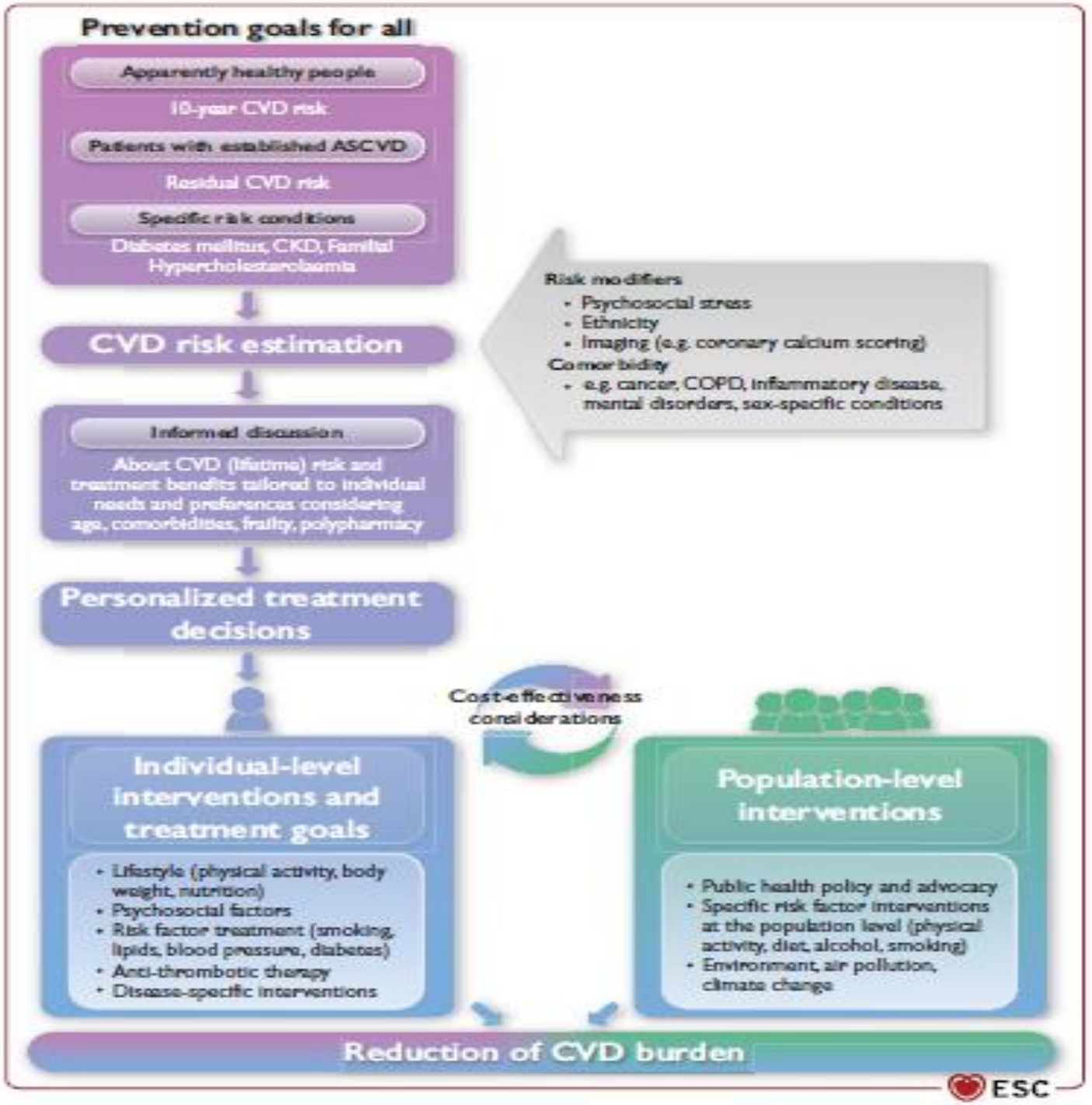
FIGURE 2.7 Cardiovascular disease death by specific cause and region. *CHD,* Coronary heart disease; *HHD,* hypertensive heart disease; *RHD,* rheumatic heart disease. (From Global Burden of Disease Study 2017. *Age-sex Specific All-cause and Cause-specific Mortality, 1990–2017.* Seattle: Institute for Health Metrics and Evaluation; 2017.)

Target population for assessing cardiovascular disease risk

CVD risk assessment or screening can be done opportunistically or systematically.

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.


Prevention goals for all
Apparently healthy people
10-year CVD risk
Patients with established ASCVD
Residual CVD risk
Specific risk conditions
Diabetes mellitus, CKD, Familial Hypercholesterolaemia
CVD risk estimation
Risk modifiers
Psychosocial stress
Ethnicity
Imaging (e.g. coronary calcium scoring)
Comorbidity
e.g. cancer, COPD, inflammatory disease, mental disorders, sex-specific conditions
Informed discussion
About CVD (lifetime) risk and treatment benefits tailored to individual needs and preferences considering age, comorbidities, frailty, polypharmacy
Personalized treatment decisions
Cost-effectiveness considerations
Individual-level interventions and treatment goals
Lifestyle (physical activity, body weight, nutrition)
Psychosocial factors
Risk factor treatment (smoking, lipids, blood pressure, diabetes)
Anti-thrombotic therapy
Disease-specific interventions
Population-level interventions
Public health policy and advocacy
Specific risk factor interventions at the population level (physical activity, diet, alcohol, smoking)
Environment, air pollution, climate change
Reduction of CVD burden
ESC

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

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.

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.

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 riskmodifiers and clinical conditions (comorbids).

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.

-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. 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.

Blood pressure

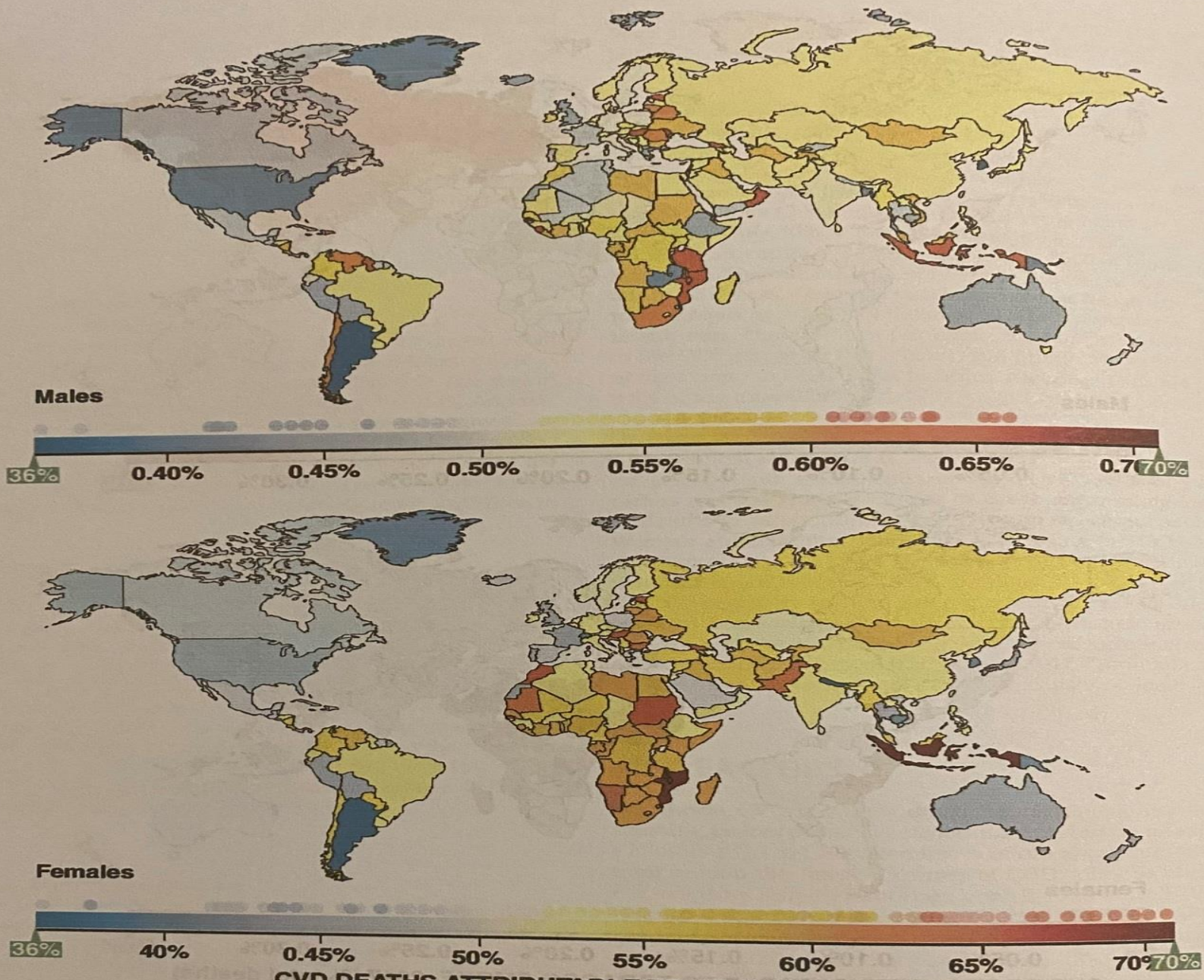
Longitudinal studies, genetic epidemiological studies, and RCTs have shown that raised BP is a major cause of both ASCVD and nonatherosclerotic CVD [particularly heart failure (HF)], accounting for **9.4** million deaths and **7%** of global disability adjusted life-years.

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.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.

Evidence suggests that lifetime BP **evolution differs** in women compared to men, potentially resulting in an increased CVD risk at lower BP thresholds.



GURE 2.9 Cardiovascular disease mortality attributable to high systolic blood pressure in 2017, percentage of total deaths, males versus females. (From Institute for Health etrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

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.

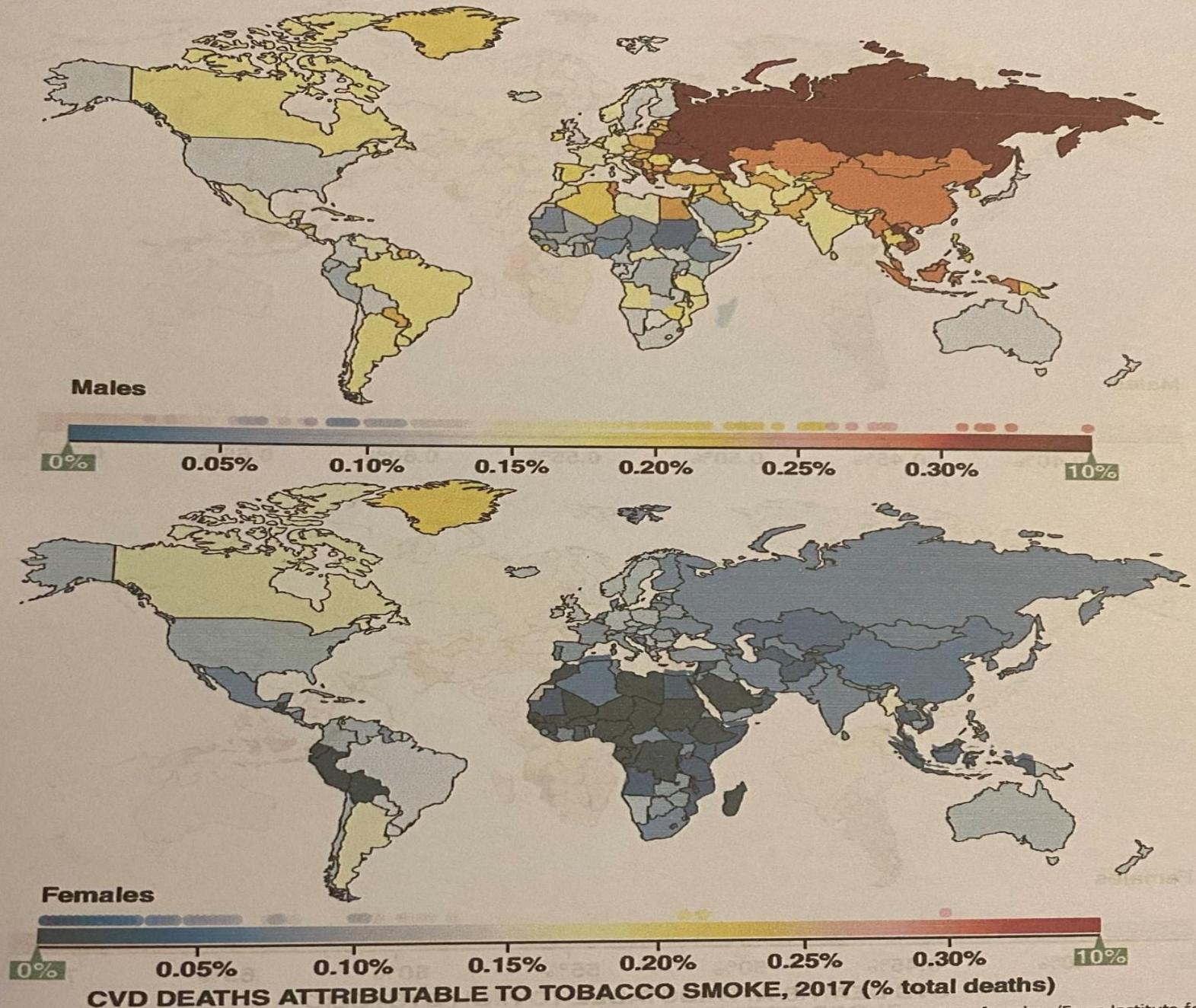
The CVD risk in smokers <50 years of age is **five-fold** higher than in non-smokers.

Prolonged smoking is more hazardous for women than for men.

Worldwide, after high SBP, smoking is the leading risk factor for disability adjusted life-years.

Second-hand smoke is associated with an increase in CVD risk.

Some smokeless tobacco is also associated with increased risk of CVD



GURE 2.8 Cardiovascular disease mortality attributable to tobacco smoke in 2017, percentage of total deaths, males versus females. (From Institute for Health M aluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

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.

Women with type 2 DM appear to have a particularly higher risk for stroke.

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

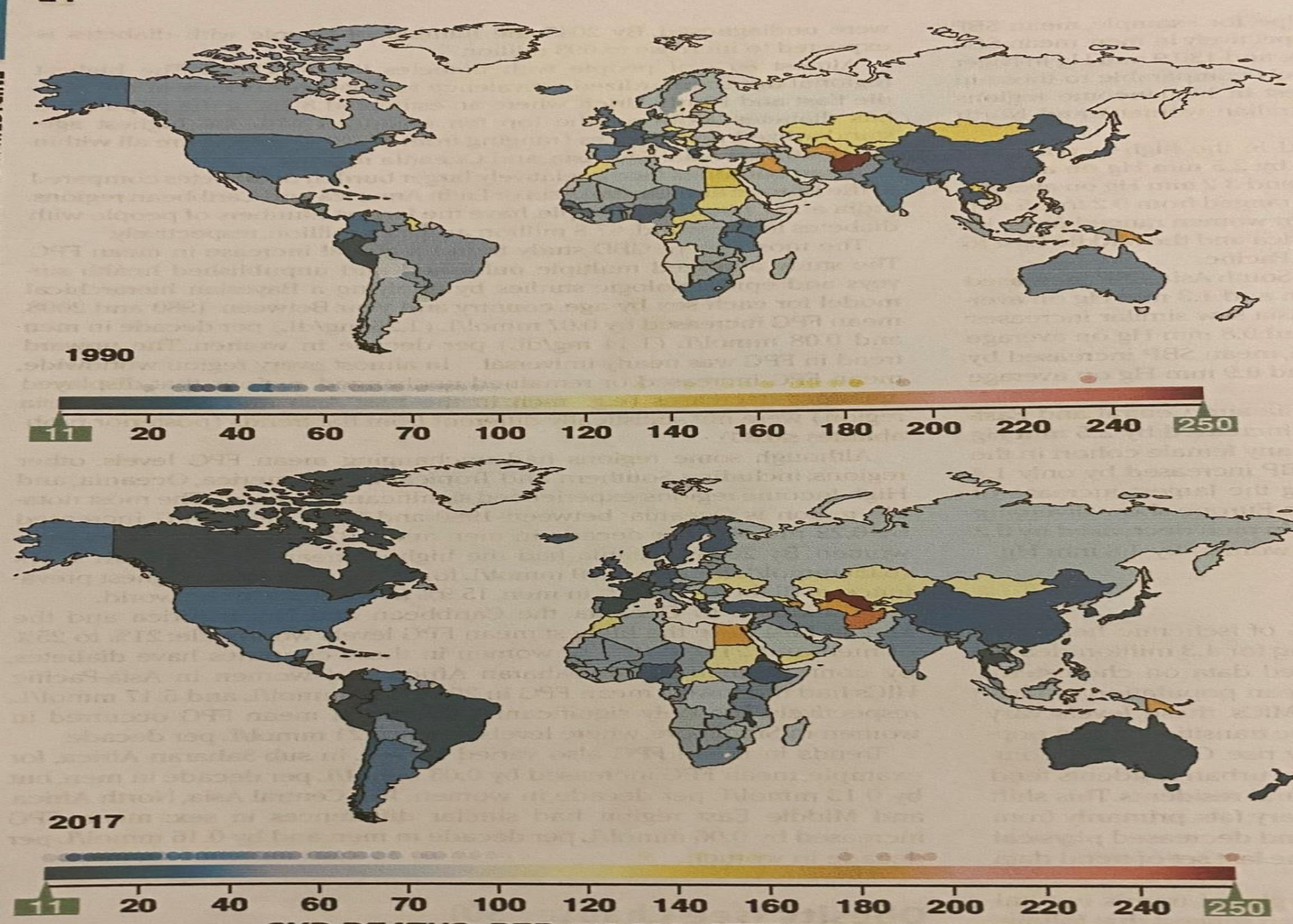


FIGURE 2.10 Cardiovascular disease mortality attributable to high fasting plasma glucose, deaths per 100,000, 1990 versus 2017. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

Adiposity

Mendelian randomization analyses suggest a linear relation between BMI and mortality in non-smokers and a J-shaped relation in ever-smokers.

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.

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**

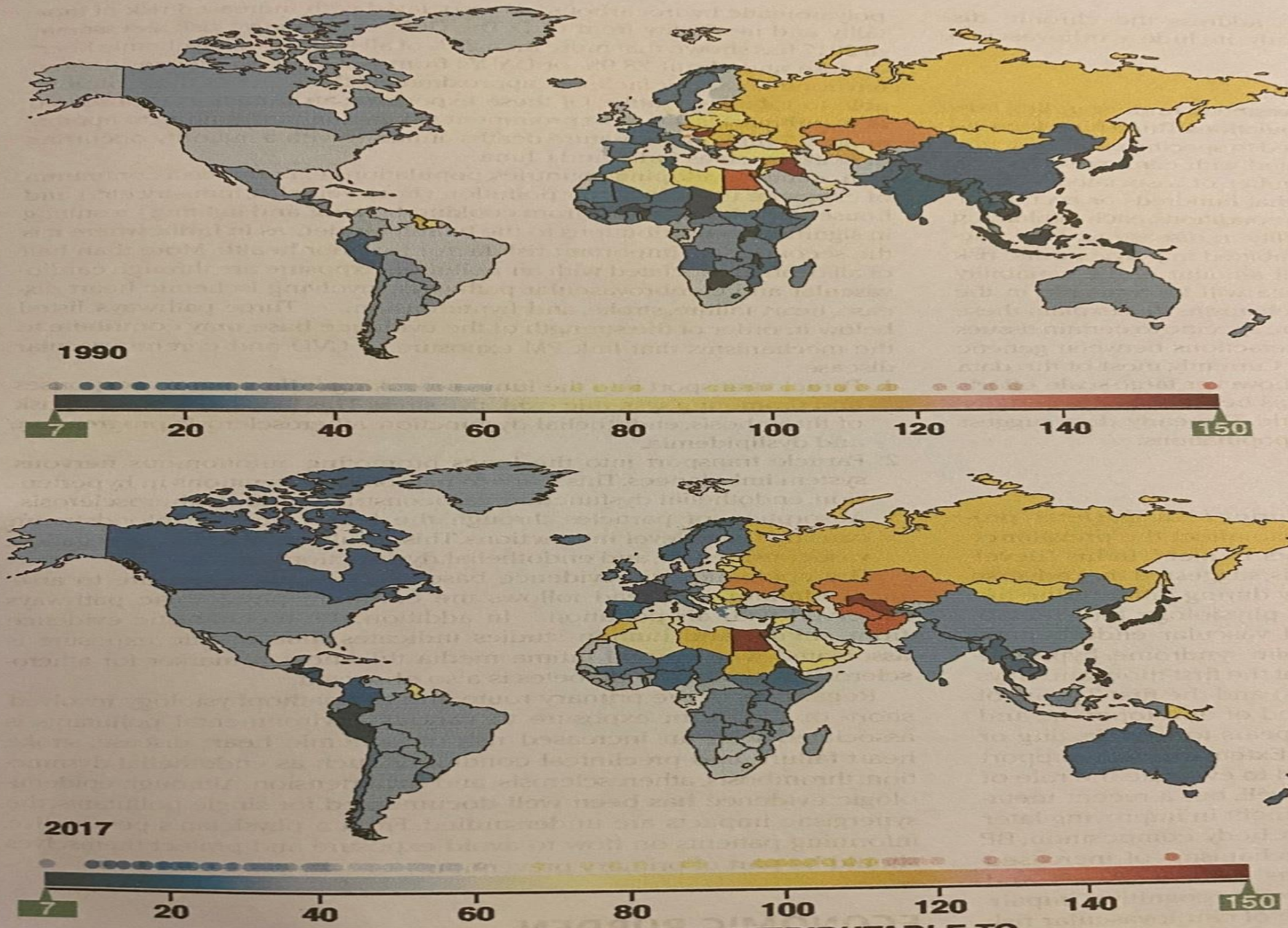


FIGURE 2.11 Cardiovascular disease mortality attributable to high body-mass index, deaths per 100,000, 1990 versus 2017. (From Institute for Health Metrics and Evaluation (IHME). *GBD Compare*. Seattle: IHME, University of Washington; 2017. http://vizhub.healthdata.org/gbd-compare.)

Sex and gender and their impact on health

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.

The influence of gender on an **individual's experience** and **access to healthcare** is paramount.

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, including in the field of CVD **and** ASCVD prevention.

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 disparitiesin the management of and outcomes after acute coronary syndromes (ACS).

Furthermore, CVD health after **menopause** transition, **pregnancy disorders,** and **gynaecologic condition**s have recently been reviewed

Cardiovascular disease risk classification

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.

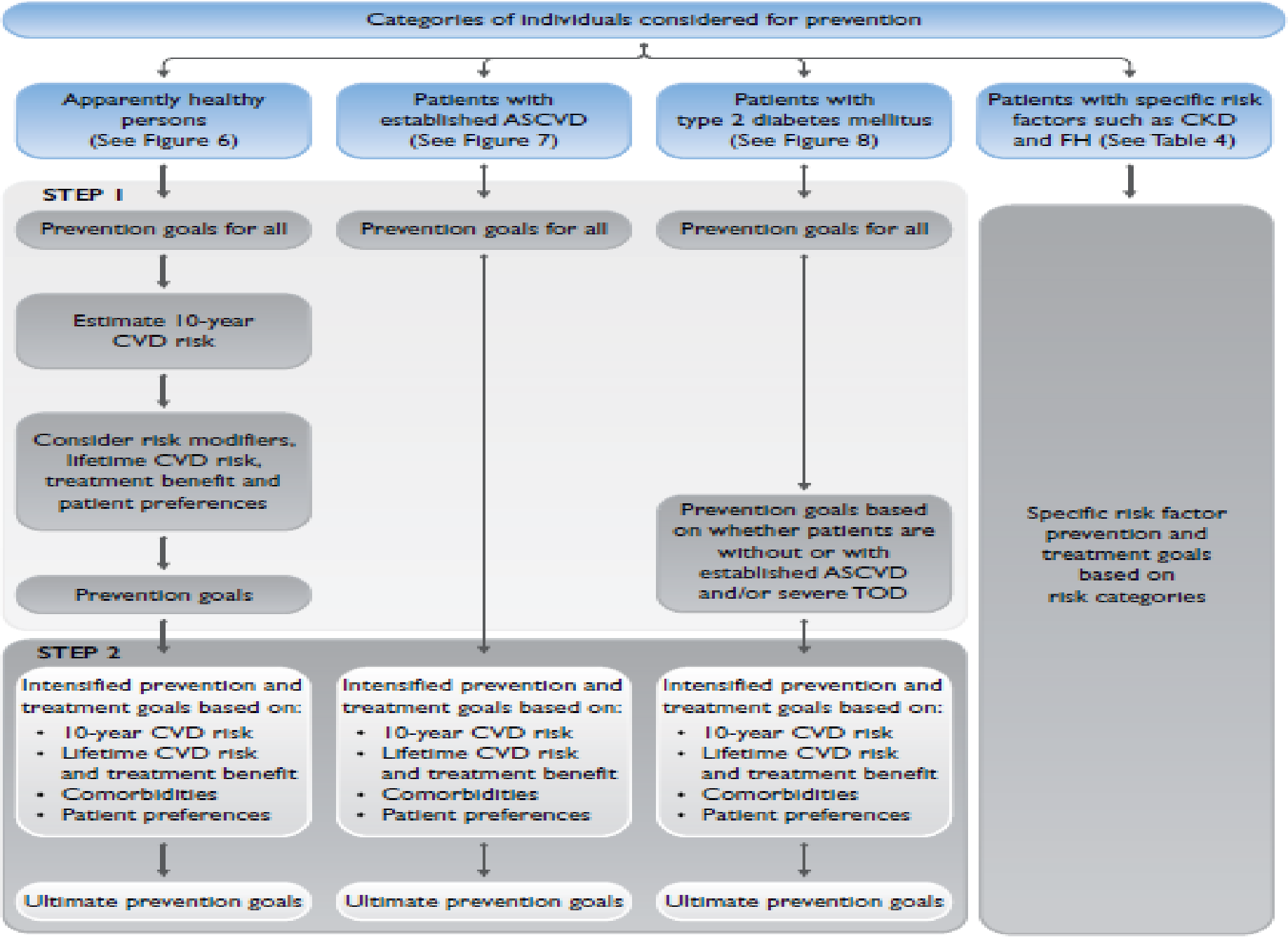
Conversely, men over 65 years and women over 75 years of age are almost always at **high** 10-year CVD risk.

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.**

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).


Categories of individuals considered for prevention
Apparently healthy persons (See Figure 6)
Patients with established ASCVD (See Figure 7)
Patients with type 2 diabetes mellitus (See Figure 8)
Patients with specific risk factors such as CKD and FH (See Table 4)
STEP 1
Prevention goals for all
Prevention goals for all
Prevention goals for all
Estimate 10-year CVD risk
Consider risk modifiers, lifetime CVD risk, treatment benefit and patient preferences
Prevention goals
Prevention goals based on whether patients are without or with established ASCVD and/or severe TOD
Specific risk factor prevention and treatment goals based on risk categories
STEP 2
Intensified prevention and treatment goals based on:
• 10-year CVD risk
• Lifetime CVD risk and treatment benefit
• Comorbidities
• Patient preferences
Intensified prevention and treatment goals based on:
• 10-year CVD risk
• Lifetime CVD risk and treatment benefit
• Comorbidities
• Patient preferences
Intensified prevention and treatment goals based on:
• 10-year CVD risk
• Lifetime CVD risk and treatment benefit
• Comorbidities
• Patient preferences
Ultimate prevention goals
Ultimate prevention goals
Ultimate prevention goals

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.

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.

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.

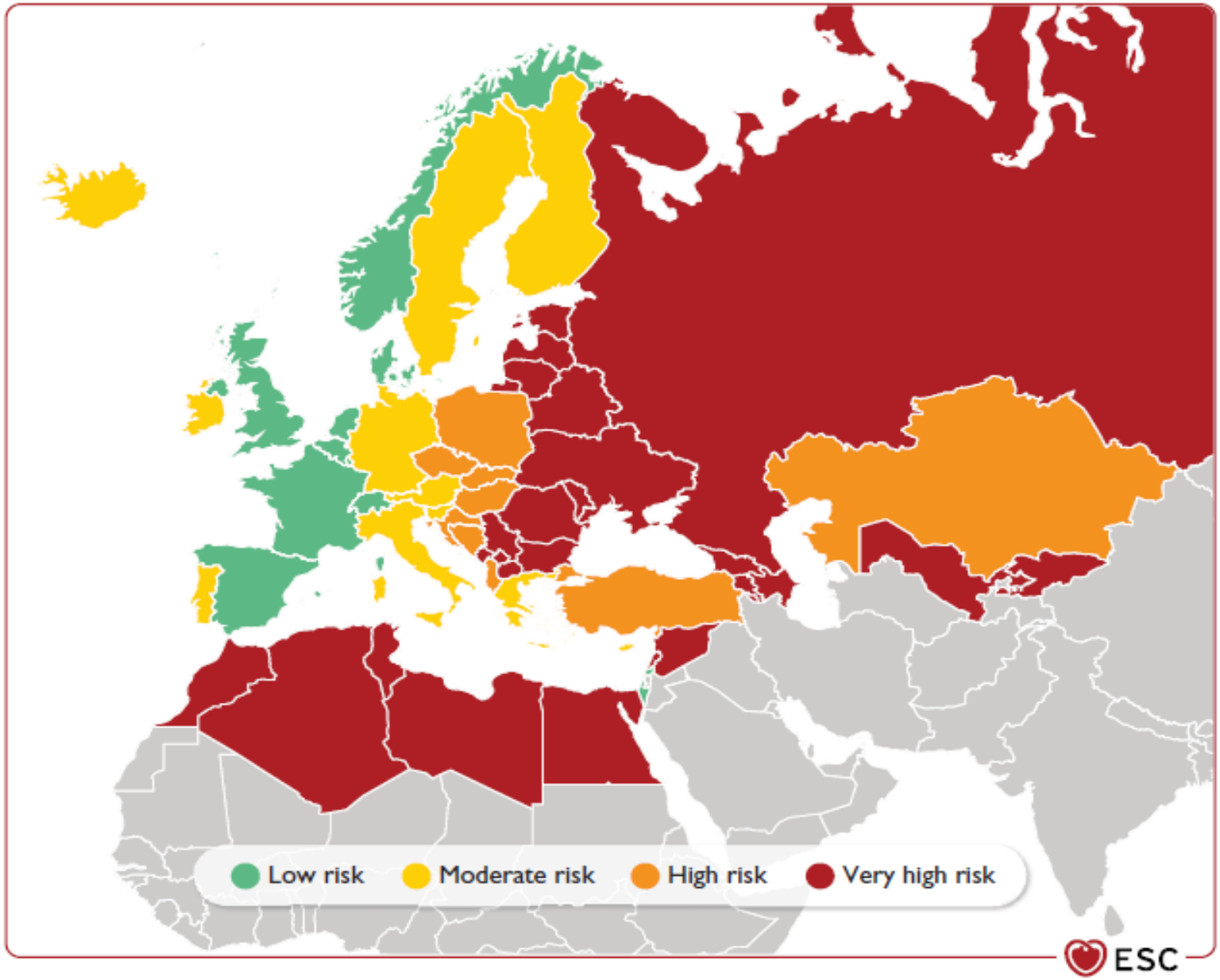


Figure 4 Risk regions based on World Health Organization cardiovascular mortality rates.[68,72,73]

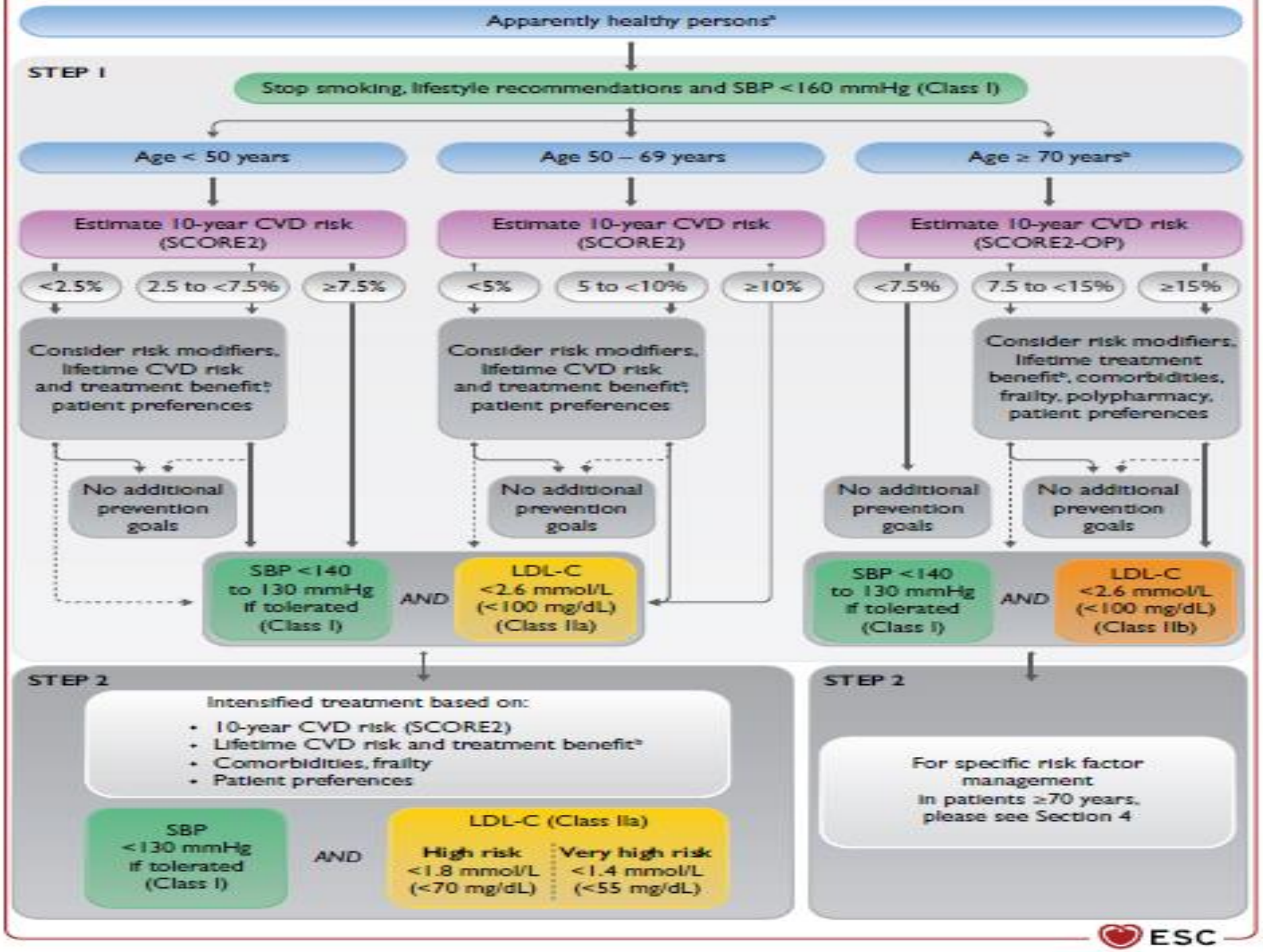
Table 5 Cardiovascular disease risk categories based on SCORE2 and SCORE2-OP in apparently healthy people according to age

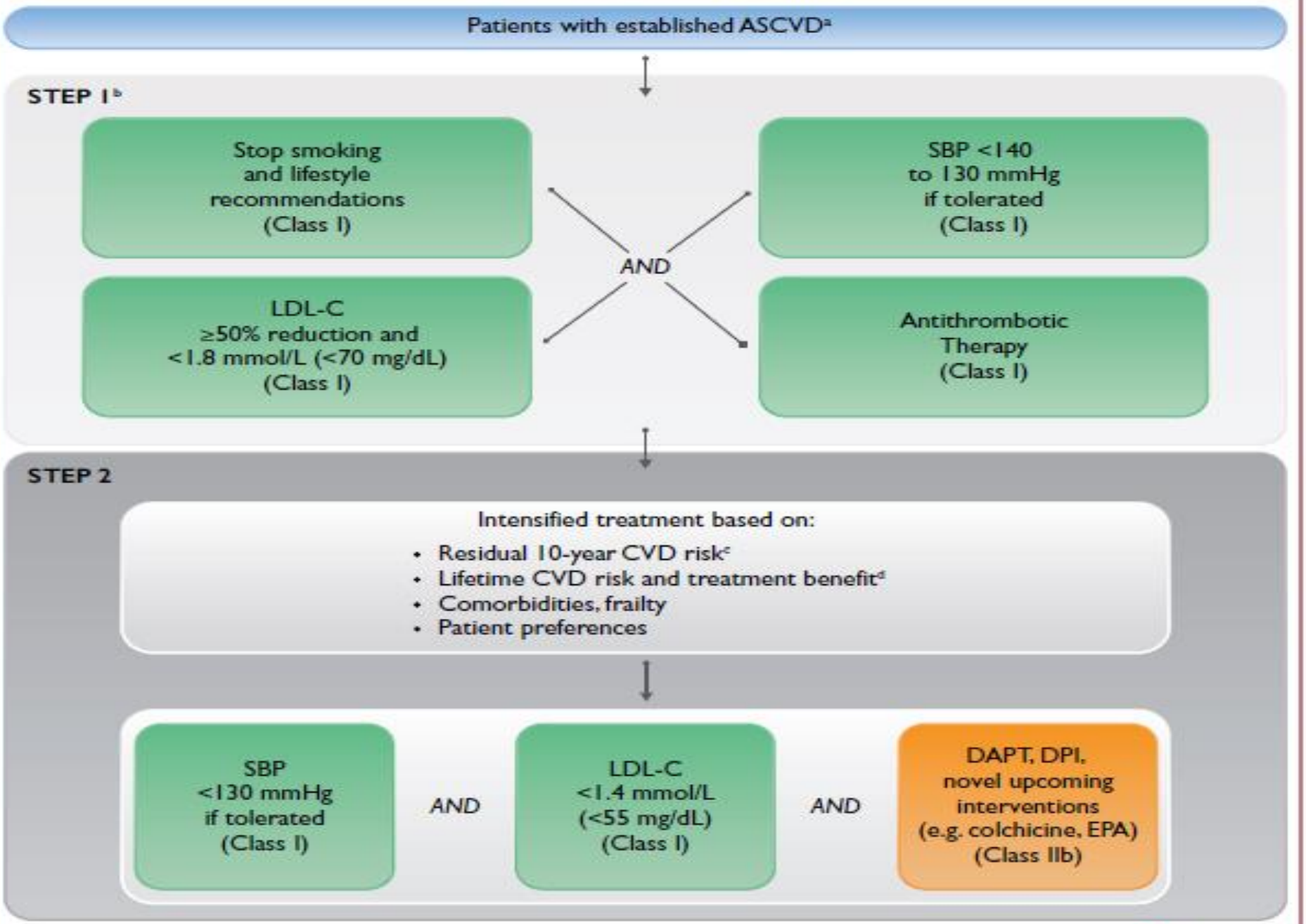
	<50 years	50–69 years	≥70 years[a]
Low-to-moderate CVD risk: risk factor treatment generally not recommended	<2.5%	<5%	<7.5%
High CVD risk: risk factor treatment should be considered	2.5 to <7.5%	5 to <10%	7.5 to <15%
Very high CVD risk: risk factor treatment generally recommended[a]	≥7.5%	≥10%	≥15%

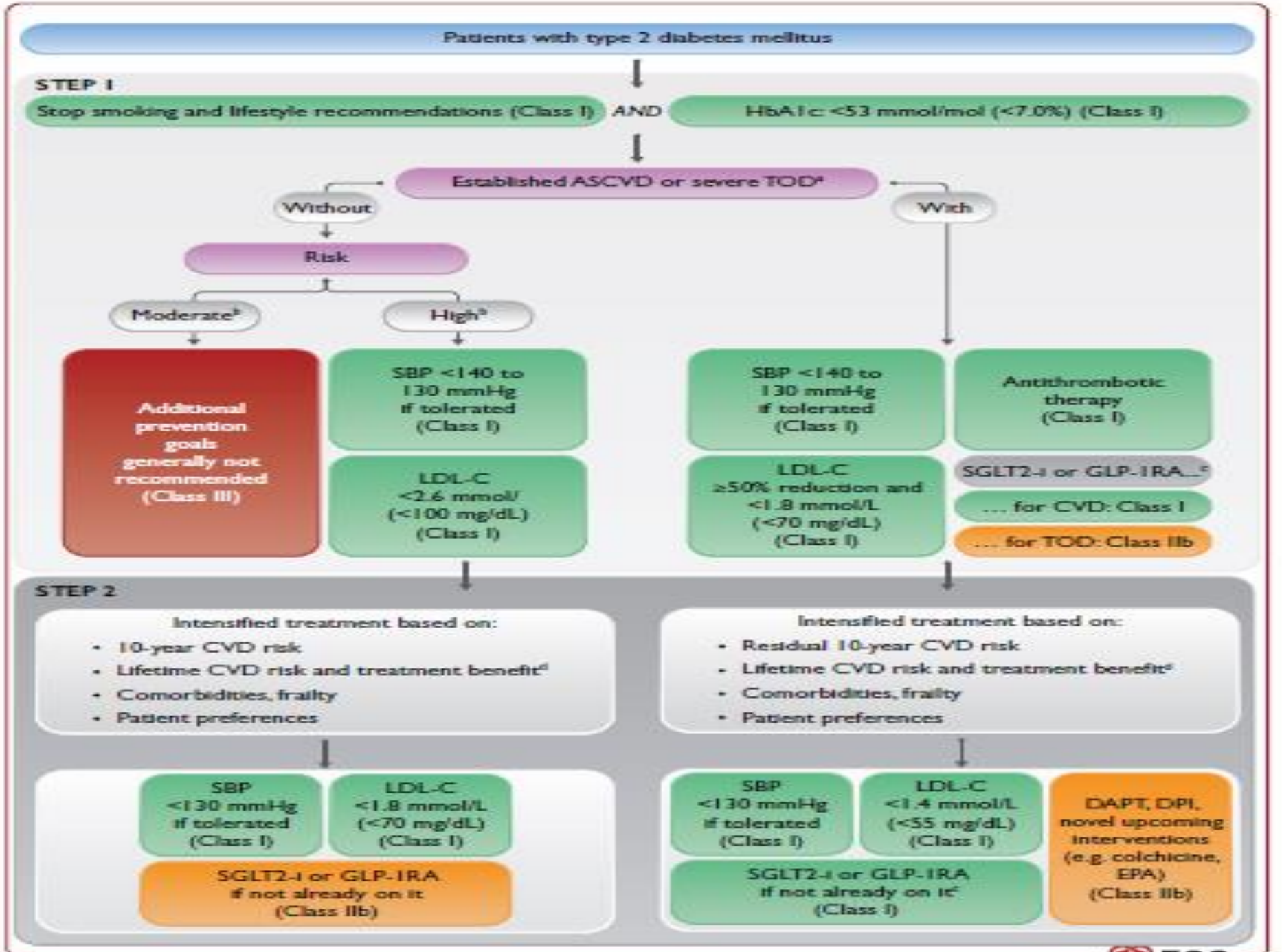
CVD = cardiovascular disease.

[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.


Apparently healthy persons[a]
STEP 1
Stop smoking, lifestyle recommendations and SBP <160 mmHg (Class I)
Age < 50 years
Age 50 – 69 years
Age ≥ 70 years[a]
Estimate 10-year CVD risk (SCORE2)
Estimate 10-year CVD risk (SCORE2)
Estimate 10-year CVD risk (SCORE2-OP)
<2.5%
2.5 to <7.5%
≥7.5%
<5%
5 to <10%
≥10%
<7.5%
7.5 to <15%
≥15%
Consider risk modifiers, lifetime CVD risk and treatment benefit[b]; patient preferences
Consider risk modifiers, lifetime CVD risk and treatment benefit[b]; patient preferences
Consider risk modifiers, lifetime treatment benefit[b], comorbidities, frailty, polypharmacy, patient preferences
No additional prevention goals
No additional prevention goals
No additional prevention goals
No additional prevention goals
SBP <140 to 130 mmHg if tolerated (Class I)
AND
LDL-C <2.6 mmol/L (<100 mg/dL) (Class IIa)
SBP <140 to 130 mmHg if tolerated (Class I)
AND
LDL-C <2.6 mmol/L (<100 mg/dL) (Class IIb)
STEP 2
Intensified treatment based on:
• 10-year CVD risk (SCORE2)
• Lifetime CVD risk and treatment benefit[b]
• Comorbidities, frailty
• Patient preferences
SBP <130 mmHg if tolerated (Class I)
AND
LDL-C (Class IIa)
High risk <1.8 mmol/L (<70 mg/dL)
Very high risk <1.4 mmol/L (<55 mg/dL)
STEP 2
For specific risk factor management in patients ≥70 years, please see Section 4


Patients with established ASCVD[a]
STEP 1[b]
Stop smoking and lifestyle recommendations (Class I)
SBP <140 to 130 mmHg if tolerated (Class I)
AND
LDL-C ≥50% reduction and <1.8 mmol/L (<70 mg/dL) (Class I)
Antithrombotic Therapy (Class I)
STEP 2
Intensified treatment based on:
• Residual 10-year CVD risk[c]
• Lifetime CVD risk and treatment benefit[d]
• Comorbidities, frailty
• Patient preferences
SBP <130 mmHg if tolerated (Class I)
AND
LDL-C <1.4 mmol/L (<55 mg/dL) (Class I)
AND
DAPT, DPI, novel upcoming interventions (e.g. colchicine, EPA) (Class IIb)


Patients with type 2 diabetes mellitus
STEP 1
Stop smoking and lifestyle recommendations (Class I)
AND
HbA1c <53 mmol/mol (<7.0%) (Class I)
Established ASCVD or severe TOD[a]
Without
With
Risk
Moderate[b]
High[b]
Additional prevention goals generally not recommended (Class III)
SBP <140 to 130 mmHg if tolerated (Class I)
LDL-C <2.6 mmol/ (<100 mg/dL) (Class I)
SBP <140 to 130 mmHg if tolerated (Class I)
LDL-C ≥50% reduction and <1.8 mmol/L (<70 mg/dL) (Class I)
Antithrombotic therapy (Class I)
SGLT2-i or GLP-1RA...[c]
... for CVD: Class I
... for TOD: Class IIb
STEP 2
Intensified treatment based on:
• 10-year CVD risk
• Lifetime CVD risk and treatment benefit[d]
• Comorbidities, frailty
• Patient preferences
SBP <130 mmHg if tolerated (Class I)
LDL-C <1.8 mmol/L (<70 mg/dL) (Class I)
SGLT2-i or GLP-1RA if not already on it (Class IIb)
Intensified treatment based on:
• Residual 10-year CVD risk
• Lifetime CVD risk and treatment benefit[d]
• Comorbidities, frailty
• Patient preferences
SBP <130 mmHg if tolerated (Class I)
LDL-C <1.4 mmol/L (<55 mg/dL) (Class I)
SGLT2-i or GLP-1RA if not already on it[c] (Class I)
DAPT, DPI, novel upcoming interventions (e.g. colchicine, EPA) (Class IIb)
ESC

Potential risk modifiers

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 has **direct** biological effects, but is also highly correlated with socioeconomic and behavioural risk factors (e.g. smoking, poor adherence).

Owing to the importance of stress symptoms among ASCVD patients, several guidelines and scientific statements recommend screening of ASCVD patients for psychological stress.

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

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?

2-Ethnicity

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.

- 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.

3-Imaging

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.

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.

3.2 Contrast computed tomography coronary angiography

CCTA allows identification of coronary stenoses and predicts cardiac events.

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.

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 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.

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.

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

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.

However, measurement difficulties and substantial publication bias argue against widespread use.

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.

An individual patient data metaanalysis concluded that the **reclassification potential of ABI was limited**, perhaps with the exception of women at **intermediate risk**.

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.

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).

Similarly, although the presence of **comorbidities** can exacerbate frailty within an individual, frailty is not the same as multimorbidity

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, with frailty itself rather than classical CVD risk factors predicting both all-cause and CVD mortality in the very old.

Importantly, the ability of frailty measures to improve CVD risk prediction has not been formally assessed.

Hence, **we do not recommendm** 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.

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.

5. Family history

Family history of premature CVD is a simple indicator of CVD risk, reflecting the genetic and environment interplay.

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.

However, family history only **marginally** improves the prediction of CVD risk beyond conventional ASCVD risk factors.

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.

6. Genetics

The aetiology of ASCVD has a genetic component, but this information **is not** currently used in preventive approaches.

Advances on polygenic risk scores for risk stratification could increase the use of genetics in prevention.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.

Polygenic risk scoring has shown some potential to improve ASCVD risk prediction for primary prevention, but the incremental prediction accuracy is relatively modest and needs further evaluation in both men and women.

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

7. Socioeconomic determinants

Low socioeconomic status and work stress are independently associated with ASCVD development and prognosis in both sexes.

The strongest association has been found between low income and CVD mortality, with a RR of 1.76 [95% confidence interval (CI) 1.452.14].

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.

8. Environmental exposure

Environmental exposures with CVD risk modifying potential include air and soil and water 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 2.510 mm in diameter, to fine (<2.5 mm; PM2.5), and ultrafine (<0.1 mm)] 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.

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.

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.

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 lg/m$_3$in exposure to PM; the long-term effects are associated mainly with PM.

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 is associated with improvements in inflammation, thrombosis, and oxidative stress, and a decrease in death from ischaemic heart disease.

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.

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. Creactive protein reflecting inflammation) or indicate early cardiac damage (e.g. **natriuretic peptides or high-sensitivity cardiac troponin).**

In the 2016 Guidelines,we recommended against the routine use of biomarkers because most do not improve risk prediction, and publication bias seriously distorts the evidence.

New studies confirm that C-reactive protein has limited additional value.

There is renewed interest in lipoprotein(a), but it too provides limited additional value in terms of reclassification potential.

Cardiac biomarkers are promising,but further work is needed.

10. Body composition

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.

Mendelian randomization analyses suggest a linear relation between BMI and mortality in never-smokers and a J-shaped relation in ever-smokers.

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.

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.

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.

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.

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

Risk factors and interventions at the individual level

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.

Optimizing cardiovascular risk management

1-Goals of clinician-patient communication

Clinicians should provide a personalized presentation of guidelines to improve understanding, encourage lifestyle changes, and support adherence to drug therapy.

Applying this in daily practice faces different barriers.

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.

2-How to improve motivation?

Communication strategies such as motivational interviewing are useful.

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.

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.

Healthcare professionals must consider capability, opportunity (physical, social, or environmental) and motivation for behavioural change.

Multidisciplinary behavioural approaches that combine the knowledge and skills of different caregivers are recommended

3-Optimizing drug adherence

Medication adherence ranges from 50% for primary ASCVD prevention to 66% for secondary prevention.

Physicians should consider non-adherence in every patient and inquire non-judgmentally about it.

Contributors to nonadherence 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.

Importantly, only substantial risk reduction motivates patients for preventive drug treatment, which obviates the need for appropriate risk communication.

Depression is another important factor, and adequate treatment thereof improves adherence.

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

4-Treatment goals

In the subsequent sections, different domains of individual treatment are discussed.

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 For details on treatment goals, how to achieve them, strengths of recommendations and levels of supporting evidence, please go to the relevant subsections.

Optimizing lifestyle

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.

1-Physical activity prescription

PA should be individually assessed and prescribed in terms of frequency, intensity, time (duration), type, and progression.

Recommendations regarding pre-participation screening can be found in previous ESC Guidelines.

Interventions shown to increase PA level or reduce sedentary behaviour include behaviour theorybased interventions, such as goal-setting, re-evaluation of goals, selfmonitoring,and feedback.

Using a wearable activity tracker may help increase PA.

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

2-Aerobic physical activity

Examples of aerobic PA include walking, jogging, cycling, etc.

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.

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.

PA accumulated in bouts of even **<10 min** is associated with favourable outcomes, including mortality

PA can be expressed in **absolute** or **relative** terms.

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.

An absolute measure does not consider individual factors such as body weight, sex, and fitness level

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.

Classification for both absolute and relative intensity and examples are presented in Table 7.

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

%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]

3-Resistance exercise

Resistance exercise in addition to aerobic PA is associated with lower risks of total CV events and all-cause mortality.

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.

In addition, older adults are recommended to perform multicomponent PA that combines aerobic, muscle-strengthening, and balance exercises to prevent falls

4-Sedentary behaviour

Sedentary time is associated with greater risk for several major chronic diseases and mortality.

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

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
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

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

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

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

1-Fatty acids

Risk of CHD is reduced when dietary **saturated** fats are replaced appropriately.

This is also the case when replacing meat and dairy foods.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.

Reducing saturated fatty acid intake to less than **10%** of energy may have additional benefits.

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%).

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.

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.

The **DASH** (Dietary Approaches to Stop Hypertension) trial showed a doseresponse relation between sodium reduction and BP reduction.

in a meta-analysis, salt reduction of 2.5 g/day resulted in a 20% reduction of ASCVD events (RR 0.80).

A U- or J-shaped relation between a low salt intake and ASCVD is debated.

Underlying illness and malnutrition may explain **both low food and salt intakes** as well as increased ASCVD.

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.

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

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

3-Fibre

Each 7 g/day higher intake of total fibre is associated with a 9% lower risk of CAD (RR 0.91).

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).

A high fibre intake may reduce postprandial glucose responses after carbohydrate-rich meals and also lower triglyceride levels.

3-Specific foods and food groups

3.1. Fruits, vegetables, and pulses.

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

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.

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

4-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.

Both pulses and nuts contain fibre and other bioactive components

5-Meat.

From both a health and an environmental point of view, a lower consumption of meat, especially processed meat, is recommended.

A restriction of red meat may have little or no effect on major cardiometabolic outcomes.

However, substituting red meat with high-quality plant foods (i.e. nuts, soy, and legumes) does improve LDL-C concentrations.

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.

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

6-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, and eating fish two to four times a week is associated with a 6% lower risk of stroke.

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

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 EthylIntervention Trial).

In the analysis excluding REDUCE-IT, fish oil reduced total ASCVD (RR 0.97) and CHD death (RR 0.92).

Including REDUCE-IT (a study done in participants with high triglycerides, comparing very high icosapent ethyl doses vs.mineral oil placebo) strengthened the results.

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.

7-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.

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.

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.

These data challenge the concept that moderate alcohol consumption is universally associated with lower CVD risk.

8-Soft drinks and sugar

Regular consumption of sugarsweetened 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.

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

9-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.

Non-filtered coffee includes boiled, Greek, and Turkish coffee and some espresso coffees.

Moderate coffee consumption (34 cups per day) is probably not harmful, perhaps even moderately beneficial

9-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.

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.

10-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.

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 extravirgin **olive** oil.

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

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

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

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

ASCVD = atherosderotic 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.

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

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

1-Smoking cessation

Stopping smoking is potentially the most effective of all preventive measures, with substantial reductions in (repeat) myocardial infarctions or death.

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.

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

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.

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.

Persistent or reuptake of smoking is common in patients with CHD, in particular in those with **severe depression and environmental exposures.**

Mood-management therapies may improve outcomes in patients with current or past depression

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

UK = United Kingdom.

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).

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.NRT shows no adverse effects in patients with ASCVD,but evidence of efficacy in this group is inconclusive.

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.

The antidepressant, bupropion, aids longterm smoking cessation with similar efficacy to NRT.Varenicline 1 mg b.i.d. (twice a day) increases quitting rates more than two-fold compared with placebo.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 hospitalfollowing ACS is efficacious and safe.The main side-effect of varenicline is nausea, but this usually subsides.

A causal link between varenicline and neuropsychiatric adverse events is unlikely.Varenicline, bupropion, and NRT do not increase serious CV adverse event risks during or after treatment.

Cytisine is effective for smoking cessation, but evidence to date is limited

2-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.The longterm effects of e-cigarettes on CV and pulmonary health, however, require more research.

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.

Despite being lower in toxicants than regular cigarettes, ‘heat-not-burn’ cigarettes do contain tobacco and should be discouraged.

Lipids

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.

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.

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.

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).

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

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.

This low goal was established based on data from recent Mendelian randomization studies, meta-analyses from the Cholesterol Treatment Trialists' Collaboration, RCTs such as IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), and—more recently—proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor clinical outcome studies.

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.

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 even 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

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

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

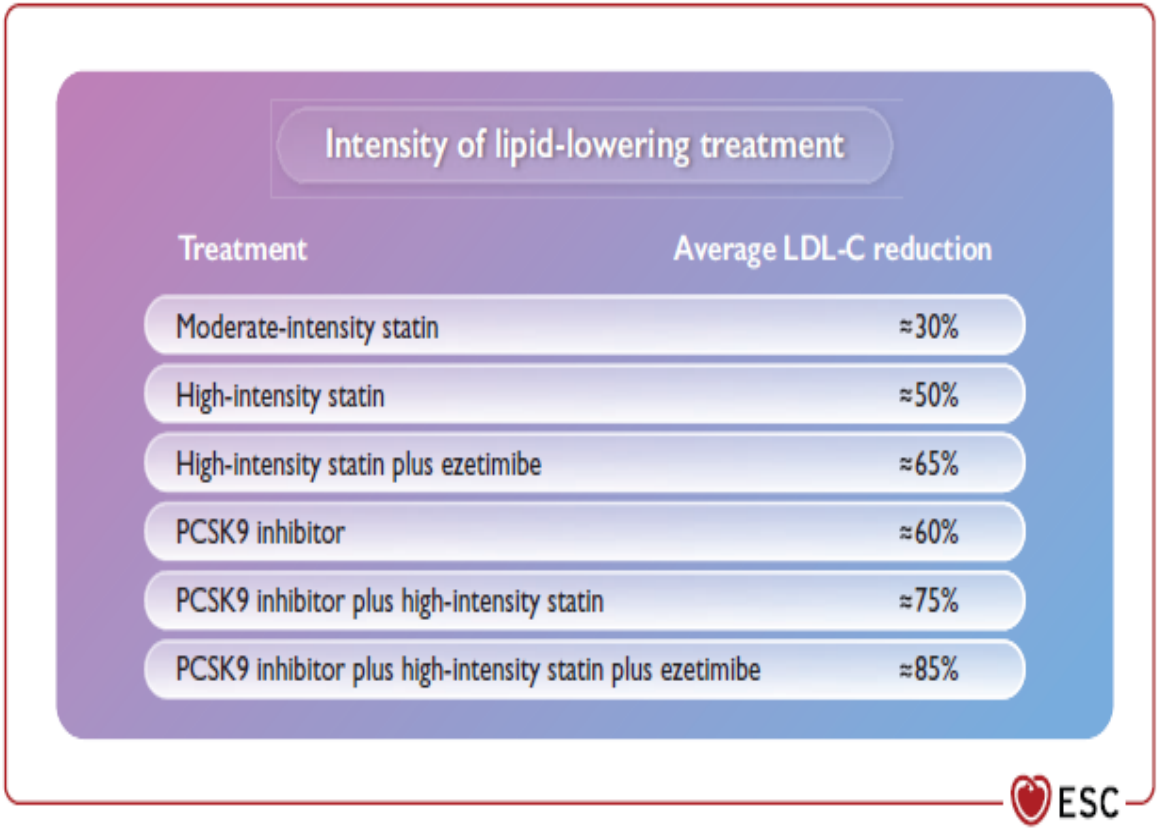


Figure 13 Expected low-density lipoprotein cholesterol reductions for combination therapies. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9. Adapted from Mach *et al.*[3]

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

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

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]

4.6.4. 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

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.

[a]Class of recommendation.

[b]Level of evidence.

Adapted from [3]

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

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

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
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

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]

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	

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.

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

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

[a]Class of recommendation.

[b]Level of evidence.

Adapted from [3]

Blood pressure

Hypertension is one of the most important preventable causes of premature morbidity and mortality.

It affects more than 150 million people across Europe, over 1 billion globally, with a prevalence of 30- 45% in adults, increasing with age to more than 60% in people aged >60 years, and accounting for 10 million deaths globally per annum.

Despite extensive evidence for the effectiveness of BPlowering treatments at reducing CVD risk and death, the detection, treatment, and control of BP in Europe and globally remains suboptimal.

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.

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.

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.

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.

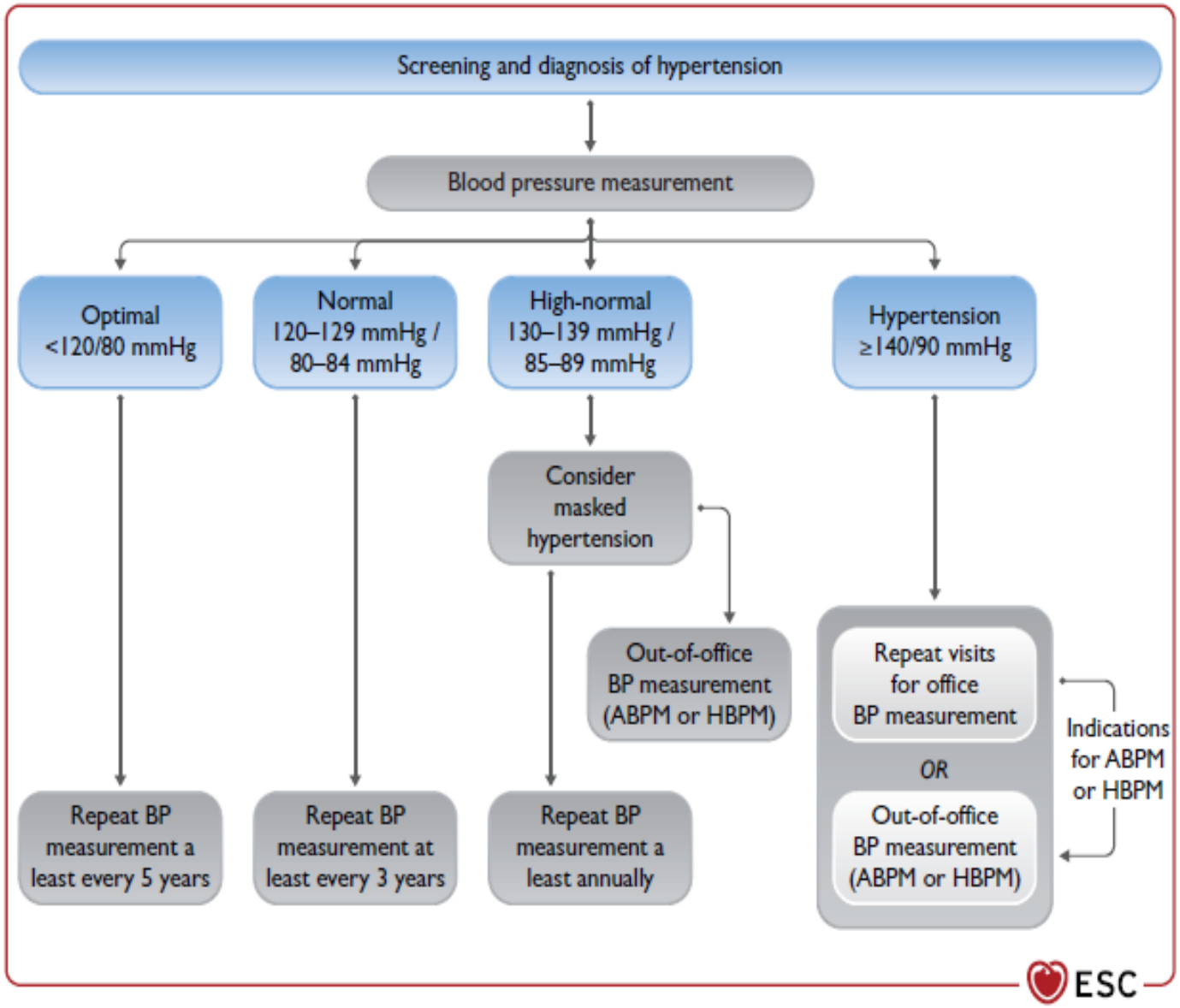


Figure 14 Screening and diagnosis of hypertension. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.

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.

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]

Treatment of hypertension

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

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.

1-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.

In many such cases, the absolute lifetime benefit per 10-mmHg reduction in SBP is at least moderate to high [(lifetime benefit calibrated in low-to-moderate CVD risk countries].

Also, the presence of HMOD(Hypertension mediated organ damage) 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.

3-Blood pressure treatment targets

When drug treatment is used, the aim is to control BP to target within 3 months.

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.

The recommended ultimate SBP treatment target range for younger patients (18-69 years) is 120-130 mmHg and lower than if tolerated.

The ultimate target SBP for patients aged >70 years is <140 mmHg and down to 130 mmHg if tolerated.

This change in the BP target range for older people compared with the 20-16 ESC prevention guidelines is supported by evidence that these treatment targets are safely achieved in many older patients and are associated with significant reductions in the risk of major stroke, HF, and CV death.

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 130-139mmHg.

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 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.

Compared to previous ESC/ESH Hypertension Guidelines, we changed the cut-off for identifying who is ’older’ from 65 to 70 years for reasons of consistency with other parts of the current guidelines.

Although a single age cut-off is provided, it is important to stress that biological age influences this threshold in clinical practice.

For example, a very fit 75-year-old person may qualify for a treatment policy normally reserved for those <70 and, vice versa, a very frail 65-year-old person should sometimes be considered ‘older’.BP targets for patient subgroups with various comorbidities are shown in Table 18.

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 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 125mmHg and home SBP <130 mmHg

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.

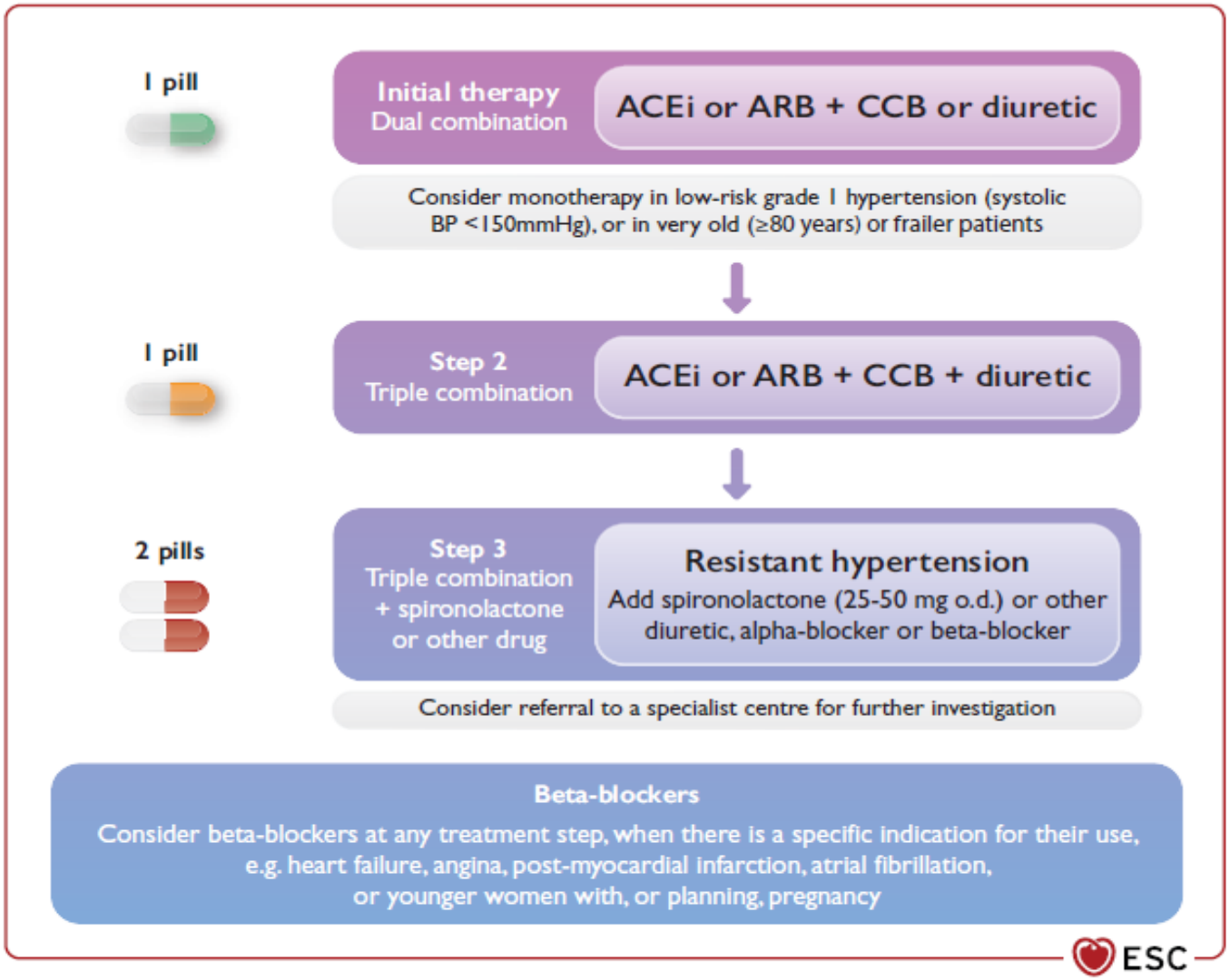


Figure 16 Core drug treatment strategy for hypertension. This algorithm is appropriate for most patients with hypertension-mediated organ damage, diabetes mellitus, cerebrovascular disease, and peripheral artery disease. ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin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

1-Drug treatment of hypertension

The most important driver of benefit is the magnitude of BP lowering.

Single-drug therapy will rarely achieve optimal BP control.

Initial therapy with a combination of two drugs should be considered usual care for hypertension.

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, and will reduce BP faster and reduce heterogeneity in response.

Moreover, initial combination therapy does not increase risk of adverse effects.

Initiating therapy with two drugs will also help overcome treatment inertia where patients remain on one drug long termdespite inadequate BP control.

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.

Single-pill combination therapy (if available) is the preferred strategy.

This strategy will control BP in most patients

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.

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.

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.

Betablockers 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).

Combinations of an ACE inhibitor and an ARB are not recommended because of no added benefit on outcomes and increased risk of harm.

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

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.

Potassium-binding drugs reduce the risk of hyperkalaemia.

When spironolactone is not tolerated, amiloride, alphablockers, beta-blockers, or centrally acting drugs, such as clonidine, have evidence supporting their use.

Renal denervation and device-based therapy may be considered for specific cases.

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

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

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
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

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

[a]Class of recommendation.

[b]Level of evidence.

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

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

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

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.

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.

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.

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 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 2.510 mm, fine particles <2.5 mm ($PM_{2.5}$), and ultrafine particles <0.1 mm in diameter) and gaseous pollutants such as ozone, nitrogen dioxide, volatile organic compounds, carbon monoxide, and sulphur dioxide, produced primarily by fossil fuel combustion.

Up to one-third of Europeans living in urban areas are exposed to levels exceeding EU air-quality standards.

The EU Commission released a policy package to be implemented by 2030,

with measures to reduce harmful emissions from traffic, energy plants, and agriculture

Indoor air pollution and exposure to noise must also be highlighted. Household air pollution, such as that produced from burning biomass, accounts for over 3 million deaths worldwide.

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

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.

The extent to which environmental exposures in **soil and water** contribute to CVD has also been established.

Interventions to reduce this pollution are required, including factory regulations and drinking water controls.

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

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.

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