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2016 European Guidelines on cardiovascular disease prevention in clinical practice – Web Addenda

The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)

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

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Web Contents

3b. How to intervene at the individual level: disease-specific intervention—atrial fibrillation, coronary artery disease, chronic heart failure, cerebrovascular disease, peripheral artery disease

3b.1 Atrial fibrillation

Key message

- Hypertension in atrial fibrillation (AF) patients doubles the risk of CV complications and must be treated in all grades.

Recommendations for atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
It is recommended to assess stroke risk by CHA_2DS_2-VASc score or $CHADS_2$ score, bleeding risk by HAS-BLED score and consider antithrombotic therapy.	I	A	1,2
In patients ≥65 years or with diabetes screening by pulse palpation, followed by ECG if irregular pulse, to detect atrial fibrillation is recommended.	I	B	1,2

ECG = electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

3b.1.1 Prevention of cardiovascular complications in atrial fibrillation

AF is the most common arrhythmia, with an estimated lifetime risk of 25%. AF is associated with increased risk of death, stroke, heart failure (HF), thromboembolism, cognitive dysfunction, hospitalization and reduced quality of life.[3] AF is associated with about a two-fold increased risk of AMI. Twenty per cent of strokes are caused by AF and the stroke risk is ~60% higher in women than in men. AF can be readily detected. It is recommended that in patients ≥65 years of age or with diabetes, opportunistic screening by pulse palpation for at least 30 sec should be performed, followed by an electrocardiogram (ECG) in those with an irregular pulse.[1,2]

Management of AF patients is aimed at preventing severe cardiovascular disease (CVD) complications associated with AF and relies on antithrombotic therapy with vitamin K antagonist therapy or non-vitamin K

antagonist oral anticoagulants. Recommendations for antithrombotic therapy should be based on risk factors for stroke and thromboembolism in addition to risk of bleeding. Stroke risk assessment with the CHA_2DS_2-VASc score or $CHADS_2$ score include the most common stroke risk factors. A bleeding risk assessment with the HAS-BLED is recommended for all AF patients. Residual high risk of death in anticoagulated AF patients remains a CVD prevention issue. Regarding rate and rhythm control in AF patients, we refer to the Guidelines for the Management of Atrial Fibrillation.[1,2]

3b.1.2 Prevention of cardiovascular disease risk factors in atrial fibrillation patients

Many classic CVD risk factors are also risk factors for AF, particularly age, smoking, sedentary habits, obesity, hypertension and diabetes.[4] Hypertension and AF often coexist and lead to doubling of all CVD complications and mortality in AF patients. Other clinical conditions associated with AF occurrence are hyperthyroidism, obstructive sleep apnoea, chronic kidney disease, inflammation, uric acid, major surgery, alcohol and coffee consumption and high-endurance physical activity.[3] Blood pressure (BP) measurement in AF patients should be performed with a standard auscultatory BP monitor, because automated BP monitors are inaccurate in measuring BP in AF patients. Antihypertensive treatment may contribute to reduce the risk in these high-risk patients, in addition to antithrombotic therapy. The main goal is BP reduction per se, and there are insufficient data to recommend specific drugs.[5] However, angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) should be considered the first choice in AF patients,[1] followed by β-blockers and mineralocorticoid antagonists. Obesity and diabetes in AF patients increase CVD risk by creating a prothrombotic state. Diabetes is included in the score for stroke risk assessment, while obesity is not. It is not known which obesity intervention is most cost effective in AF patients. Lifestyle risk interventions in AF patients have largely targeted physical activity, which should probably be encouraged, but studies have not shown the effect of physical activity on CVD in AF patients.[6] The presence of ischaemic heart disease and smoking increases the CVD risk despite antithrombotic therapy. Smoking cessation is therefore crucial. Less evidence is available on the effects of statins on major CVD outcomes in AF patients. These patients should be treated according to the SCORE recommendations and not merely because they have AF.

3b.1.3 Lone atrial fibrillation

In AF subjects <65 years of age, without heart disease or hypertension (lone AF) and without risk factors requiring antithrombotic therapy, AF is not associated with increased risk of stroke or death and antithrombotic therapy is not recommended. Lone AF is a diagnosis of exclusion. The risk of stroke in young patients with lone AF increases with advancing age or development of hypertension, underlining the importance of regular reassessment of risk factors over time.[1,2]

3b.2 Coronary artery disease

Key message

- Prevention is crucial for short- and long-term outcomes in coronary artery disease (CAD), and it should be started as soon as possible, with a multidimensional approach that combines feasibility and efficacy. An appropriate discharge plan should be considered.

Acute manifestations of CAD, associated complications and successive management and surveillance should be administered

Recommendations for coronary artery disease

	Recommendations	Class[a]	Level[b]	Ref[c]
Patient assessment	Clinical history taking, including the conventional risk factors for the development of CAD (such as for example glycaemic state) with revision of the clinical course (uncomplicated or complicated) of ACS is recommended.	I	A	7-9
	Physical examination is recommended.	I	C	9
	The ECG is predictive of early risk: It is recommended to obtain a 12-lead ECG and to have it interpreted by an experienced physician. It is recommended to obtain an additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.	I	B	9-11
	Additional ECG leads (V3R,V4R,V7–V9) are recommended if on-going ischaemia is suspected when standard leads are inconclusive.	I	C	
	A resting transthoracic echocardiogram is recommended in all patients for: a) exclusion of alternative causes of angina; b) regional wall motion abnormalities suggestive of CAD; c) measurement of LVEF for d) evaluation of diastolic function.	I	B	9-11
	Chest X-ray should be considered in patients with suspected HF.	IIa	C	
	Arrhythmic burden assessment (ventricular arrhythmias, AF and other supraventricular tachy-arrhythmias, and bradycardia, AV block, and intra-ventricular conduction defects) is recommended.	I	A	7–9, 12, 13
	Ambulatory monitoring should be considered in patients in whom arrhythmias are suspected.	IIa	C	
	Exercise stress testing should be considered to evaluate the efficacy of medical treatment or after revascularization, or to assist prescription of exercise after control of symptoms.	IIa	B	9, 14
	Exercise capacity and ischaemic threshold assessment should be considered by exercise maximal stress test (ergospirometry if available) to plan the exercise training programme.	IIa	B	9, 14
	An imaging stress test is recommended in patients with resting ECG abnormalities which prevent accurate interpretation of ECG changes during stress.	I	B	13
	An imaging stress test should be considered to assess the functional severity of intermediate lesions on coronary arteriography.	IIa	B	13

continued

Recommendations for coronary artery disease (continued)

Physical activity counselling	In the presence of exercise capacity >5 METs without symptoms, return to routine physical activity is recommended; otherwise, the patient should resume physical activity at 50% of maximal exercise capacity and gradually increase. Physical activity should be a combination of activities like walking, climbing stairs, cycling and supervised medically prescribed aerobic exercise training.	I	B	9, 15, 16
Exercise training	In low risk patients, at least 2 hours/week aerobic exercise at 55–70% of the maximum work load (METs) or heart rate at the onset of symptoms (≥1500 kcal/week) are recommended. In moderate to high-risk patients, an individualised programme is recommended, that starts with <50% maximum workload (METs), resistance exercise at least 1 hour/week, 10–15 repetitions per set to moderate fatigue. *(refer also to section 3a.3).*	I	B	9, 17–19
Diet/nutritional counselling	Caloric intake is recommended to be balanced by energy expenditure (physical activity) to achieve and maintain healthy BMI. Diet poor in cholesterol and saturated fat is recommended. *(refer also to section 3a.5).*	I	C	9, 15, 20
Weight control management	Normal-weight CAD patients should be advised to avoid weight gain. On each patient visit, it is recommended to consistently encourage weight control through an appropriate balance of physical activity, caloric intake, and formal behavioural programmes when indicated to achieve and maintain a healthy BMI. If waist circumference is ≥80 cm in women or ≥94 cm in men, it is recommended to initiate lifestyle changes and consider treatment strategies as indicated *(refer also to section 3a.6).*	I	B	9, 15, 20–23
Lipid management	According to lipid profile, statin therapy is recommended. *(refer also to section 3a.7).*	I	B	9,20,21
	Annual control of lipids, glucose metabolism and creatinine are recommended.	I	C	
BP monitoring	A structured approach is recommended. *(refer to section 3a.9).*	I	B	9,20,24
Smoking cessation	A structured approach is recommended. *(refer to section 3a.4).*	I	B	9, 20
Psychosocial management	Psychosocial risk factor screening should be considered. *(refer to section 2.4.2).*	IIa	B	9, 16,20
	Multimodal behavioural interventions is recommended. *(refer to section 3a.1 and 3a.2).*	I	A	9, 16,20

ACS = acute coronary syndrome; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; MET = metabolic equivalent; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

according to guidelines.[7,8,10–14,25] Beyond that, survivors need structured support to restore their quality of life and to maintain or improve functional capacity.[20] A comprehensive professional lifestyle intervention based on behavioural models of change, with different strategies from the more basic, family-based to the more structured and complex modalities, according to CV risk assessment and concomitant diseases is recommended.[9,10,20] Risk factor management in terms of effective risk factor control, physical activity advice, psychosocial support and appropriate prescription of and adherence to cardioprotective drugs are integral to helping patients regain as full a life as possible.[15–17,21–24, 26,27] In short, CAD patients are at high risk and preventive measures are key.

The prescription and adherence to behavioural recommendations in the immediate post-event care of CAD patients should have as high a priority as other preventive medications and invasive strategies, and justify an investment in establishing programmes that systematically enhance early lifestyle modification and prevention. In a large cohort of CAD patients from several countries enrolled in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) 5 randomized clinical trial,[26] adherence to behavioural advice (diet, physical activity and smoking cessation) after an acute manifestation of CAD was associated with a substantially lower risk of recurrence. Benefits were seen early (<6 months), and each behaviour modification was additive. Hence, clinical assessment, risk factor control and behavioural policies should start as soon as possible in the acute setting. Unfortunately, large proportions of patients still do not achieve the lifestyle, risk factor and therapeutic targets[28] and attendance at preventive programmes is still low.[29] To properly connect the acute and post-acute phase and to favour continuity of care and prevention, discharge planning is fundamental, as it selects and arranges the best next care setting and health care services, promotes patient and family preventive and education issues and organizes follow-up. A dedicated discharge letter can contribute to implementation:[30] beyond primary and secondary diagnosis, procedures and clinical progress descriptions, preventive concepts and recommendations oriented towards general and individual risk factor control, lifestyle intervention, medicine reconciliation and follow-up arrangements should be clearly announced.

Gap in evidence

- Although in CAD patients, prevention strategies have been demonstrated in observational studies, the best comprehensive tactic, setting and timing are still to be defined.

3b.3 Chronic heart failure

Key message

- CVD prevention in HF patients should start as soon as possible, and requires a multifaceted integrated tactic.

Recommendations for chronic heart failure

	Recommendations	Class [a]	Level [b]	Ref [c]
	The control of fluid status throughout the assessment of symptoms and signs is recommended.	I	B	11, 31
Patient assessment	Identification of precipitating CV and non-CV factors is recommended.	I	B	11, 31, 32
	Transthoracic echocardiography is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles.	I	A	11,31, 33
	12-lead ECG is recommended in all patients with HF in order to determine heart rhythm, heart rate, QRS morphology and duration, and to detect other relevant abnormalities. This information is needed to plan and monitor treatment.	I	C	
	The following diagnostic tests are recommended for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF: blood testing (natriuretic peptides, complete blood count –haemoglobin/hematocrit, WBC and platelet counts– potassium, sodium creatinine with estimated GFR-, C-reactive protein, uric acid, liver function tests fasting glucose, HbA1c, fasting lipid profile, TSH, ferritin, TSAT, iron/TIBC).	I	B	11,31,33
	Additional laboratory tests should be considered in patients admitted due to acute HF based on clinical indications.	IIa	C	
	Chest X-ray is recommended in patients with HF to detect/exclude alternative pulmonary or other diseases, which may contribute to dyspnoea. It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.	I	C	
	Exercise testing (ergospirometry if available) should be considered in patients with HF to prescribe adequate exercise training programme and to discriminate the origin of unexplained dyspnoea.	IIa	C	34
	Exercise testing (ergospirometry if available) may be considered in patients with HF to detect reversible myocardial ischaemia.	IIb	C	33
	Exercise testing (ergospirometry if available) is recommended in patients with HF as a part of the evaluation of patients for heart transplantation and/or mechanical circulatory support.	I	C	-
	Other imaging and non-imaging diagnostic tests should be considered in selected clinical situations.	IIa	B	11, 31, 32
Physical activity counselling is recommended.		I	B	11, 31, 32
Exercise training	Aerobic exercise training is recommended.	I	A	35,36
	High intensity interval training may be considered in selected patients.	IIb	B	37
	Respiratory training should be considered.	IIa	B	17, 38
	Resistance training may be considered.	IIb	C	17, 38
Weight control, cachexia and obesity management is recommended. *(refer also to section 3a.6).*		I	C	11, 31, 32
Diet/nutritional counselling should be considered. *(refer also to section 3a.5).*		IIa	C	11, 31, 32
Psychosocial management	Psychosocial screening should be considered. *(refer to section 2.4.2).*	IIa	C	11,31,32
	Psychosocial management is recommended. *(refer to section 3a.1 and 3a.2).*	I	A	11,31,32
Self-care management should be considered.		IIa	B	11, 32
Home care monitoring should be considered.		IIa	B	11, 32

CV = cardiovascular; GFR = glomerular filtration rate; HbA1c = glycated haemoglobin; HF = heart failure; TIBC = total iron-binding capacity; TSAT = transferrin saturation; TSH = thyroid-stimulating hormone; WBC = white blood cells.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

HF is a common, disabling and deadly disease that leads to frequent hospital admissions due to CV events.[39] HF patients are at high risk and they deserve special attention throughout a multifaceted and multidisciplinary intervention, starting as soon as possible during[26] and after[31] hospital admission in order to develop a lifelong structured prevention course. In-hospital, clinical management and risk assessment are decisive,[11,32] and selection of a test in daily practice should consider availability, local expertise and advantages/disadvantages, and in the case of several questions, which test can best answer them. CV prevention extends also to physical activity counselling, psychological support and patient/caregiver management education.[31] The clinical stage may impact recommendations for

preventive measures, as advanced HF might be associated with low BP and lipid profile, concomitant CV and non-CV diseases [such as AF, ventricular arrhythmia, non-revascularizable CAD, previous stroke/transient ischaemic attack (TIA), diabetes, anaemia, iron deficiency, chronic obstructive pulmonary disease, renal failure, liver dysfunction, sleep apnoea, cognitive impairment, depression, etc.] and future strategies (device therapy, heart transplantation and mechanical circulatory support) that require specialized interventions.[11]

Although congestion management is critical to improving symptoms and readmission risk, management extends beyond diuresis alone, and prevention of adverse CV events requires reducing cardiac injury, inhibiting maladaptive systemic responses and controlling relevant co-morbidities. Lifesaving HF therapies should be prescribed as recommended.[11] While the patient's condition and clinical progress are informative, monitoring systems that rely less on patient input are attractive.[40] Since most readmissions for HF exacerbations are attributable, at least in part, to poor self-care, non-adherence to medications and dietary advice and failure to act upon escalating symptoms, effective self-care is essential for CV prevention.[41]

Before leaving the hospital, several issues should be considered and discussed with the patient and caregivers. A discharge plan should be organized to build an appropriate management strategy aimed at preventing CV readmissions: congestion should be absent and a stable oral diuretic regimen established for at least 48 h.[11] Long-term disease-modifying therapy should be optimized as much as possible and appropriate education provided to the patient and family/caregivers. Pre- and post-discharge management should follow the standards of care and goals of treatment suggested by the ESC guidelines.[11]

Exercise training (ET) should be prescribed in outpatients as a fundamental preventive action in stable HF.[35,36] Since HF patients experience exercise intolerance due to several maladaptive changes, even when on optimal HF medical therapy,[42,43] exercise training can help reduce symptoms and impacts outcome. The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial showed a 7% reduction in all-cause mortality and all-cause hospitalization, even after adjustment for prespecified predictors of mortality.[36] However, adherence is crucial[44] and exercise intensity should be a balance between efficacy and safety.[45] ET protocols vary in most trials (see also section 3a.3), even though moderate to vigorous intensity exercise (50–60% peak $\dot{V}O_2$) is frequently employed, leading to an average 17% improvement in peak oxygen consumption.[46] In selected stable patients, high-intensity interval training may yield even greater improvements in peak $\dot{V}O_2$.[37] Before commencing any ET programme, clinical stability and functional evaluations are warranted,[17,38] and a comprehensive flowchart has been proposed.[38]

Prevention recommendations and intervention modalities in HF with preserved left ventricular ejection fraction HF are similar to that of HF with reduced ejection fraction; in particular, ET therapy has been shown to be effective and should be recommended.[47–49]

Gap in evidence

- Biomarkers may guide therapy in HF hospitalized patients, but further evidence is needed.

3b.4 Cerebrovascular disease

Key message

- CV risk management in patients with previous TIA or ischaemic stroke is generally comparable to that in patients with other ischaemic complications of atherosclerosis. However, treatments may differ between stroke types (ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage or cerebral venous sinus thrombosis) and causes.

Recommendation for cerebrovascular disease

Recommendation	Class[a]	Level[b]	Ref[c]
In patients with TIA or stroke, it is recommended to investigate the cause of the event and institute a cardiovascular disease prevention programme tailored to type and cause of stroke (specific guidelines are available).	I	A	2, 50–53

TIA = transient ischaemic attack.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

CV risk management in patients with previous TIA or ischaemic stroke is generally comparable to that in patients with other ischaemic complications of atherosclerosis. However, treatment may differ between stroke types (ischaemic stroke, intracerebral haemorrhage, subarachnoid haemorrhage or cerebral venous sinus thrombosis) and causes (e.g. cardio-embolism, large artery atherosclerosis or small vessel disease are the most important of many potential causes of ischaemic stroke). Details can be found in recent practice guidelines.[2,50–53] This paragraph will discuss some aspects specific to patients with TIA or stroke.

In patients with TIA or stroke included in the randomised Heart Protection Study or Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, either 40 mg of simvastatin or 80 mg of atorvastatin reduced the long-term risk of major CV events, but only atorvastatin reduced the risk of recurrent stroke.[54,55] Most of the included patients had had an ischaemic brain event, and the number of patients with prior intracerebral or subarachnoid haemorrhage included in statin trials was too small to recommend either starting a statin or withdrawing any statin the patient was using at the time of the haemorrhage.[51] This also applies to patients with TIA or ischaemic stroke of cardioembolic origin. Despite earlier suggestions to the contrary, there is no evidence that the use of statins is associated with an increased risk of intracerebral haemorrhage.[56] There are insufficient data on the effects

of other statins or other cholesterol-lowering treatments in patients with TIA or stroke, and there are also no relevant data supporting the benefit of aiming for a specific LDL-C target in this population.[50]

Starting BP reduction in the first 48 h after stroke onset generally does not improve outcome,[57,58] except possibly in patients who had a spontaneous intracerebral haemorrhage within the previous 6 h and who have a systolic blood pressure (SBP) of ≥150 mmHg or above. In these patients, intensive BP lowering (with a target systolic level <140 mmHg reached within 1 h) likely has a modest benefit.[59]

In patients with stroke or TIA that occurred >1 week earlier, the use of BP-lowering drugs reduces the risk of CAD or (recurrent) stroke.[60] The optimal drug regimen in this population is uncertain, because just a few strategies have been tested in sufficiently large trials. The evidence of benefit is greatest for diuretics alone or diuretics in combination with an ACE-I.[50,61] In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS), the relative reduction in the risk of recurrent stroke with the combination of indapamide and perindopril was independent of the baseline BP[62] and the risk reduction was larger with larger reductions in SBP.[63] However, data are limited and the evidence is not conclusive. For this reason, it appears reasonable to base the choice of a specific drug and BP target on individual patient characteristics, as described elsewhere in this guideline.

In patients with TIA or ischaemic stroke of presumed atherosclerotic origin, the combination of aspirin 30–300 mg daily and dipyridamole 200 mg twice daily is associated with a larger reduction in the risk of a major CV event than aspirin alone.[64] Clopidogrel 75 mg daily is as effective as the combination of aspirin and dipyridamole, but is associated with fewer side effects.[65] Patients with TIA or ischaemic stroke of presumed cardioembolic origin or stenosis of the carotid or vertebral artery should be treated according to the relevant guidelines.[2,50]

There is a marked lack of evidence on CVD prevention in patients with unruptured intracranial aneurysms and on secondary prevention after intracerebral haemorrhage during treatment with oral anticoagulation or subarachnoid haemorrhage, and randomized trials for these conditions are warranted.

Gaps in evidence

- For patients with cryptogenic stroke, it is uncertain whether non-vitamin K antagonist oral anticoagulants reduce the risk of future CV events more than antiplatelet drugs.
- The optimal secondary prevention strategy after subarachnoid haemorrhage is uncertain.

3b.5 Peripheral artery disease

Key message

- Peripheral artery disease (PAD) is asymptomatic in a large cohort of patients.
- Preventive treatment is identical to coronary and carotid prevention treatment, but specific studies for the PAD population and specific treatment targets are lacking.

Recommendations for peripheral artery disease

Recommendations	Class[a]	Level[b]	Ref[c]
In all PAD patients BP values controlled to values below 140/90 mmHg are recommended.	I	A	66-68
Antiplatelet therapy is recommended.	I	A	69
Statin therapy is recommended.	I	A	70
ACE-I therapy is recommended in patients with symptomatic PAD in patients with hypertension.	I	A	66
Exercise training is recommended in all patients with PAD.	I	A	71
It is recommended that all patients with PAD who smoke should be advised to stop smoking.	I	B	72
ACE-I therapy should be considered in patients with symptomatic PAD without hypertension.	IIa	A	66
ß-blockers should be considered.	IIa	B	73

ACE-I = angiotensin-converting enzyme inhibitors; BP = blood pressure; PAD = peripheral artery disease.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

The primary non-invasive test for the diagnosis of lower extremity PAD is the ankle–brachial index (ABI). In healthy persons, the ABI is >1.0. Usually an ABI <0.90 is used to define PAD. The actual sensitivity and specificity have been estimated at 79% and 96%, respectively.[74] For diagnosis in primary care, an ABI <0.8 or the mean of three ABIs <0.90 had a positive predictive value of ≥95%; an ABI >1.10 or the mean of three ABIs >1.00 had a negative predictive value of ≥99%.[75]

The German Epidemiologic Trial on Ankle Brachial Index Study Group included 6880 patients ≥65 years of age and demonstrated that 21% of the cohort had either asymptomatic or symptomatic PAD.[76]

The level of ABI also correlates with PAD severity, with a high risk of amputation when the ABI is <0.50. An ABI change >0.15 is generally required to consider worsening of limb perfusion over time or improvement of limb perfusion after revascularization.

Smoking is an important risk factor for PAD. In the general population, smoking increased the risk of PAD between two- and six-fold.[72]

Statins reduce the risk of mortality, CV events and stroke in patients with PAD with and without CAD.[70] The Antithrombotic Trialists' Collaboration meta-analysis[69] combined data from 42 randomized studies of 9706 patients with intermittent claudication and/or peripheral arterial bypass or angioplasty. The incidence of

vascular death, non-fatal MI and non-fatal stroke at follow-up was significantly decreased, by 23%, by antiplatelet drugs with respect to placebo. The efficacy of clopidogrel compared with aspirin was studied in the randomized Clopidogrel versus Aspirin in Patients at Risk for Ischaemic Events (CAPRIE) trial, including a subgroup of 6452 patients with PAD.[77] At 1.9 years follow-up, the annual combined incidence of vascular death, non-fatal MI and non-fatal stroke in the PAD group was 3.7% and 4.9% in the clopidogrel and aspirin groups, respectively, with a significant 23.8% decrease with clopidogrel, and no major differences in terms of safety.

Treatment with ACE-Is has shown a beneficial effect beyond a BP decrease in high-risk groups. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril significantly reduced cardiovascular events by 25% in patients with symptomatic PAD without known low ejection fraction or HF.[66] The ONTARGET trial showed the equivalence of telmisartan to ramipril in these patients.[67]

Importantly, β-blockers are not contraindicated in patients with PAD. A meta-analysis of 11 randomized controlled studies found that β-blockers did not adversely affect walking capacity or symptoms of intermittent claudication in patients with mild to moderate PAD.[73]

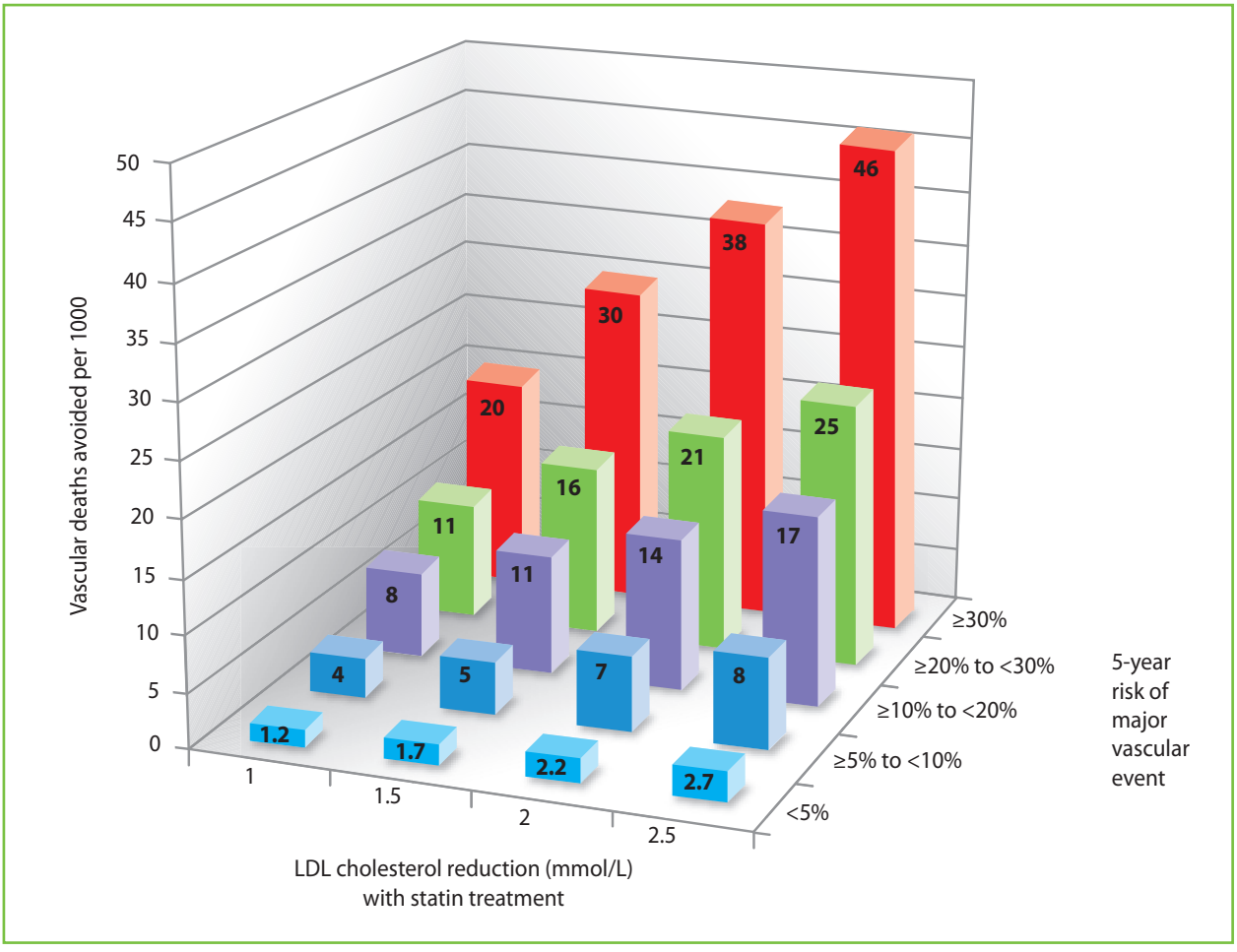
Symptoms can be treated conservatively or invasively. In patients with PAD, training therapy is effective in improving symptoms and increasing exercise capacity. In meta-analyses,[71] compared with usual care or placebo, exercise significantly improved maximal walking time, with an overall improvement in walking ability. The types of exercise varied from strength training to pole striding and upper or lower limb exercises, generally in supervised sessions, at least twice a week. Cilostazol, naftidrofuryl and pentoxyfilline improve pain-free distance. For other options, please refer to the ESC Guidelines on the diagnosis and treatment of peripheral arterial disease.[70]

Gap in evidence

- There are few studies specific for the PAD population. Most of the data comes from CAD patients with concomitant PAD. More specific data on the PAD population are needed.

4. Web Figures

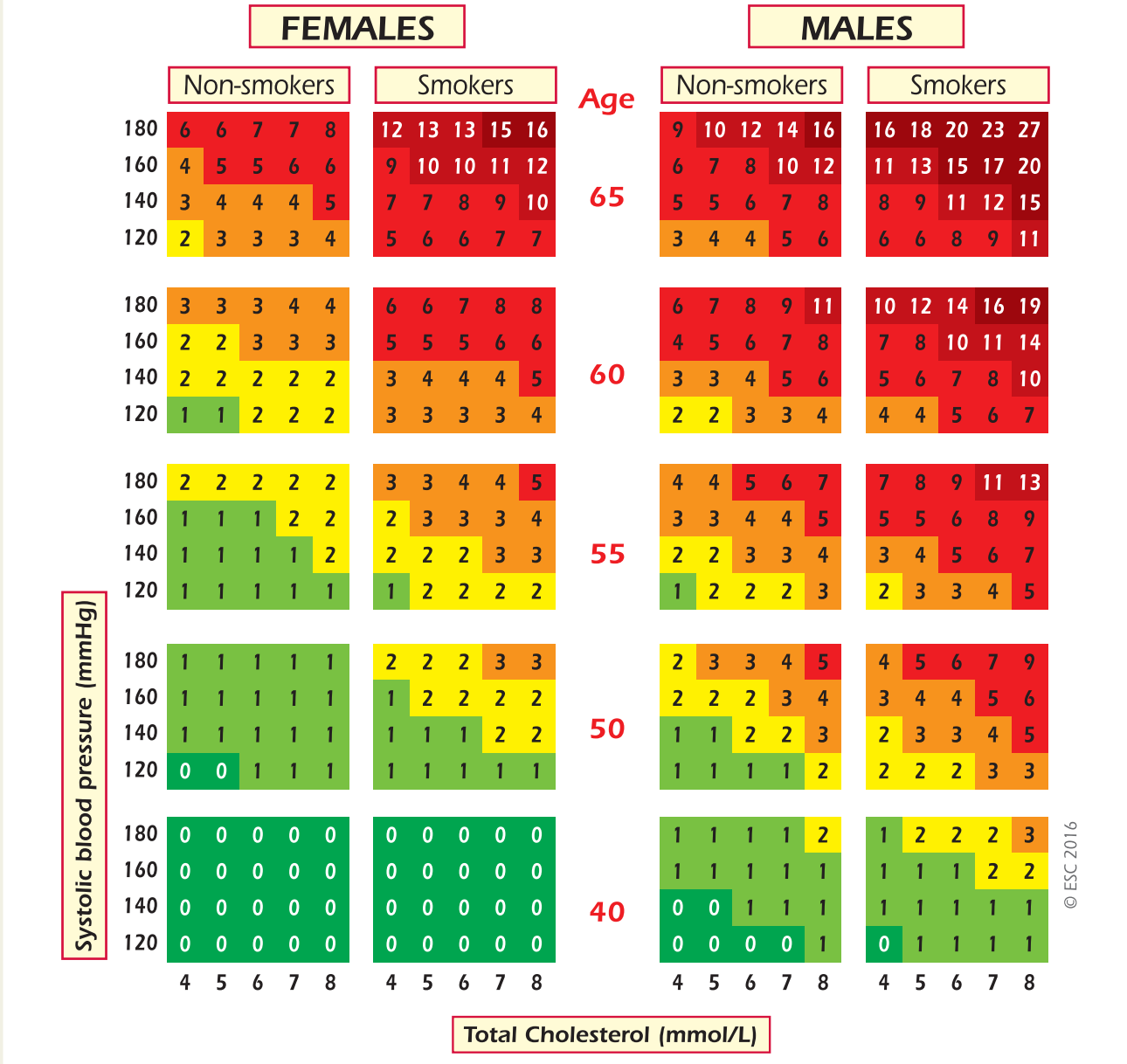
(A) Predicted vascular deaths avoided over 5 years from reductions in low-density lipoprotein cholesterol (LDL-C) with statin treatment at different levels of cardiovascular disease risk; the higher the baseline risk, the higher the number of deaths



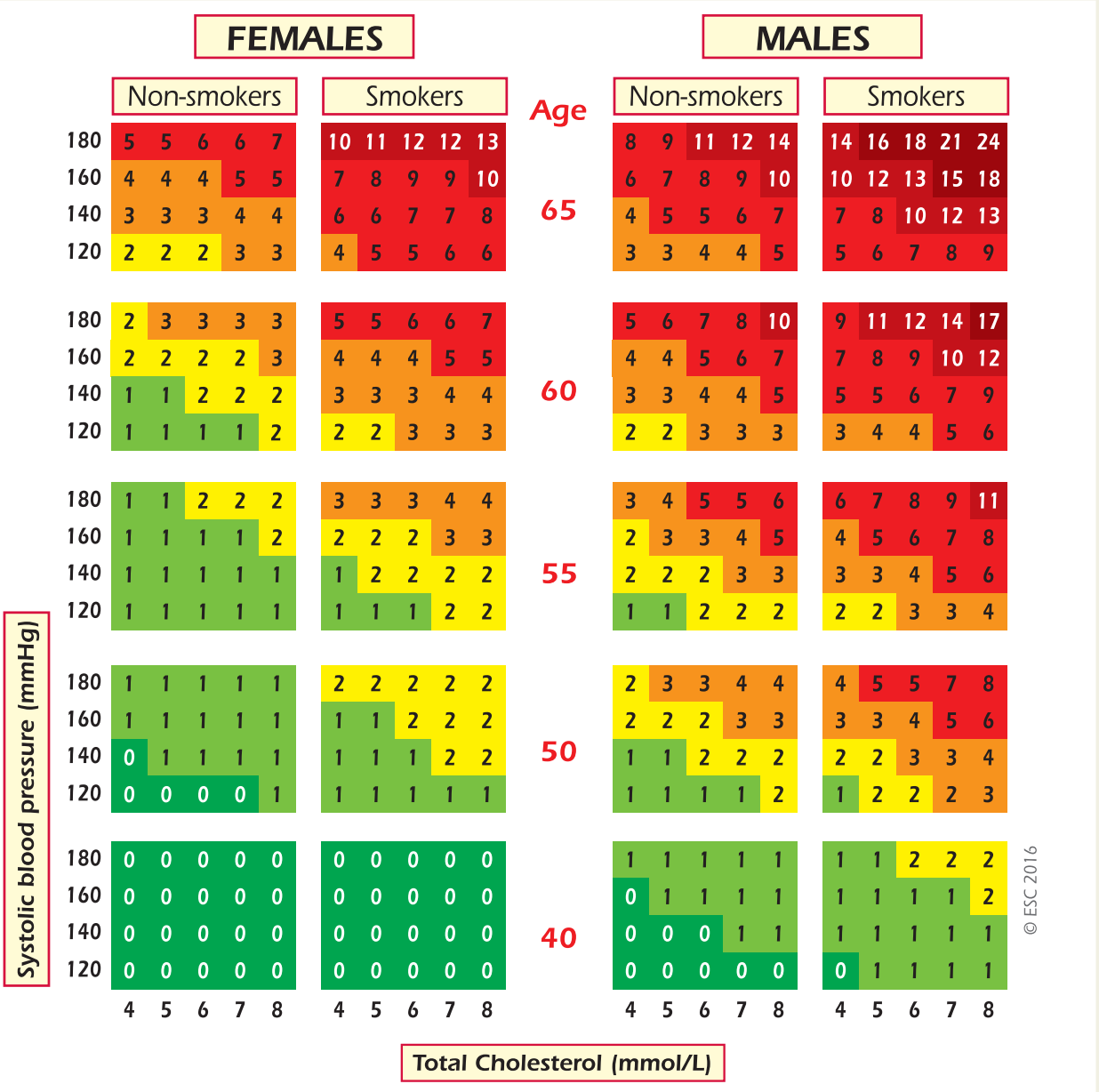
Web Figure A Predicted vascular deaths avoided over 5 years from reductions in low-density lipoprotein (LDL-C) with statin treatment at different levels of cardiovascular disease risks [Jackson R, Kerr A, Wells S. Vascular risk calculators essential but flawed clinical tools? Circulation 2013;127:1929–1931].

avoided by appropriate interventions [Jackson R, Kerr A, Wells S. Vascular risk calculators essential but flawed clinical tools? *Circulation* 2013;**127**:1929–1931].

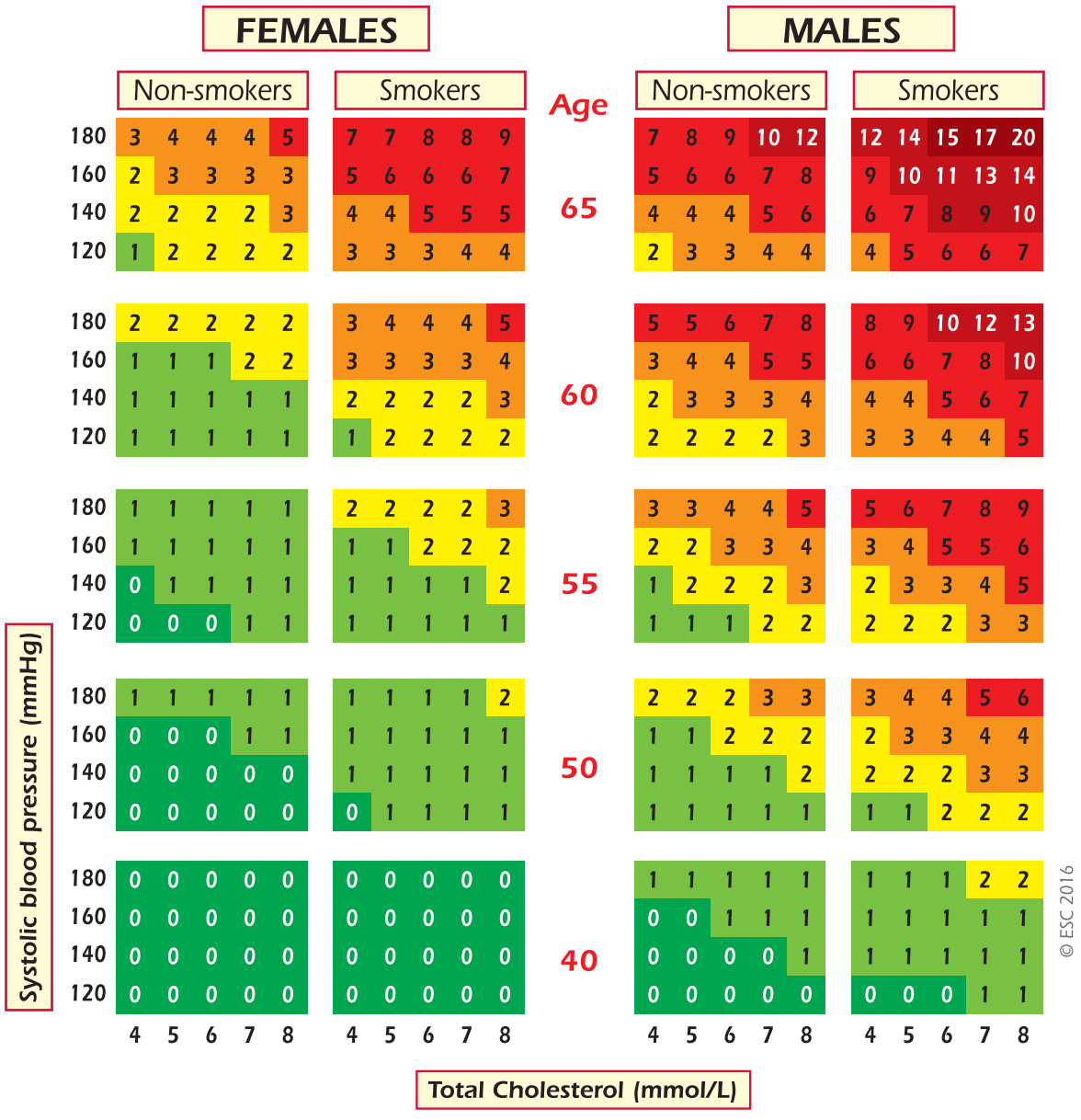
(B) SCORE chart for use in low-risk regions: HDL 0.8 mmol/L.
(C) SCORE chart for use in low-risk regions: HDL 1.0 mmol/L.
(D) SCORE chart for use in low-risk regions: HDL 1.4 mmol/L.
(E) SCORE chart for use in low-risk regions: HDL 1.8 mmol/L.
(F) SCORE chart for use in high-risk regions: HDL 0.8 mmol/L.
(G) SCORE chart for use in high-risk regions: HDL 1.0 mmol/L.
(H) SCORE chart for use in high-risk regions: HDL 1.4 mmol/L.
(I) SCORE chart for use in high-risk regions: HDL 1.8 mmol/L.
(J) Lifetime risk calculator based on the Joint British Societies recommendations on the prevention of cardiovascular disease (JBS3) web-based tool.
(K) Modified World Health Organization (WHO) smoking cessation algorithm.



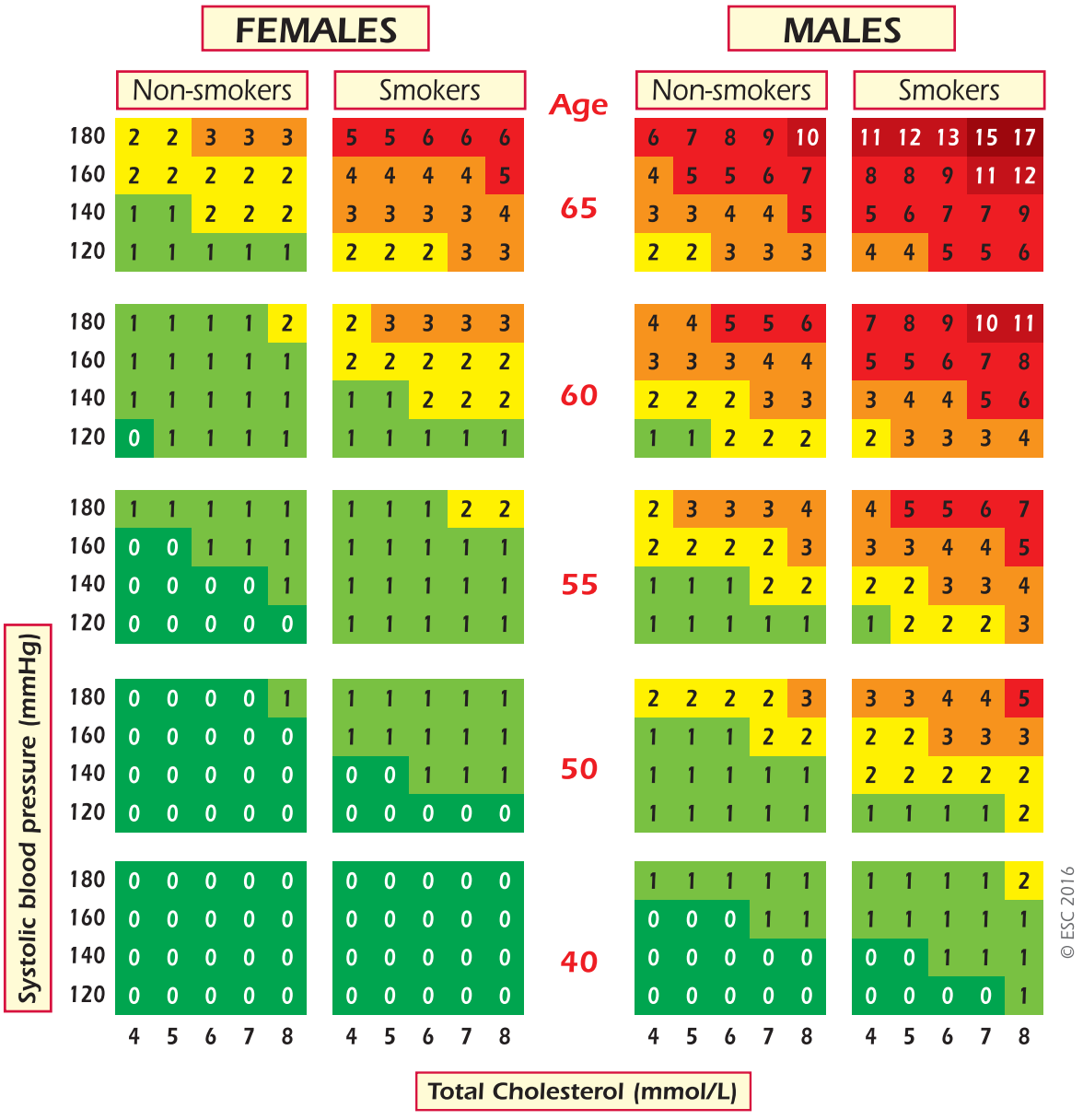
Web Figure B SCORE chart for use in low-risk regions – HDL 0.8 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



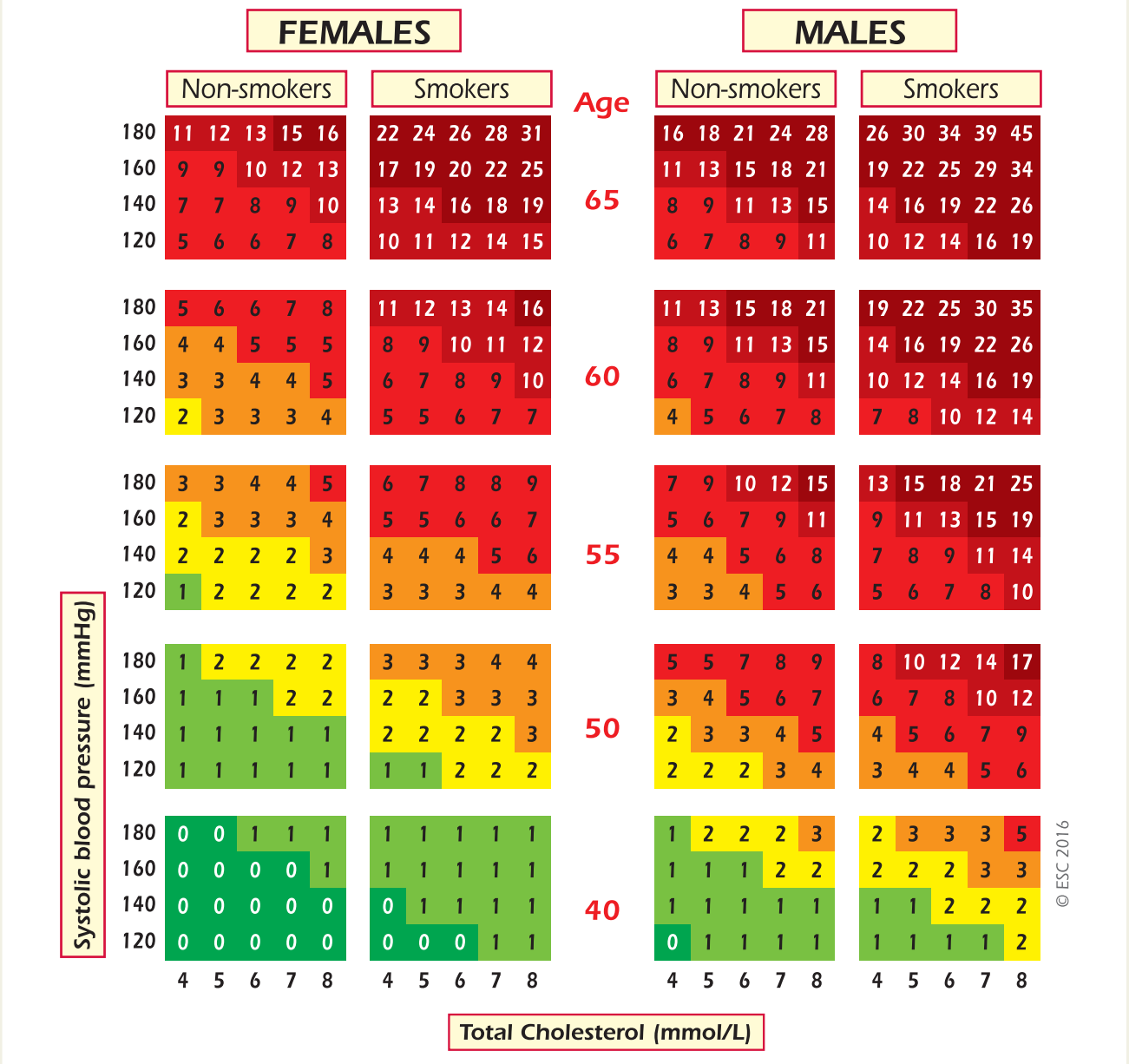
Web Figure C SCORE chart for use in low-risk regions – HDL 1.0 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



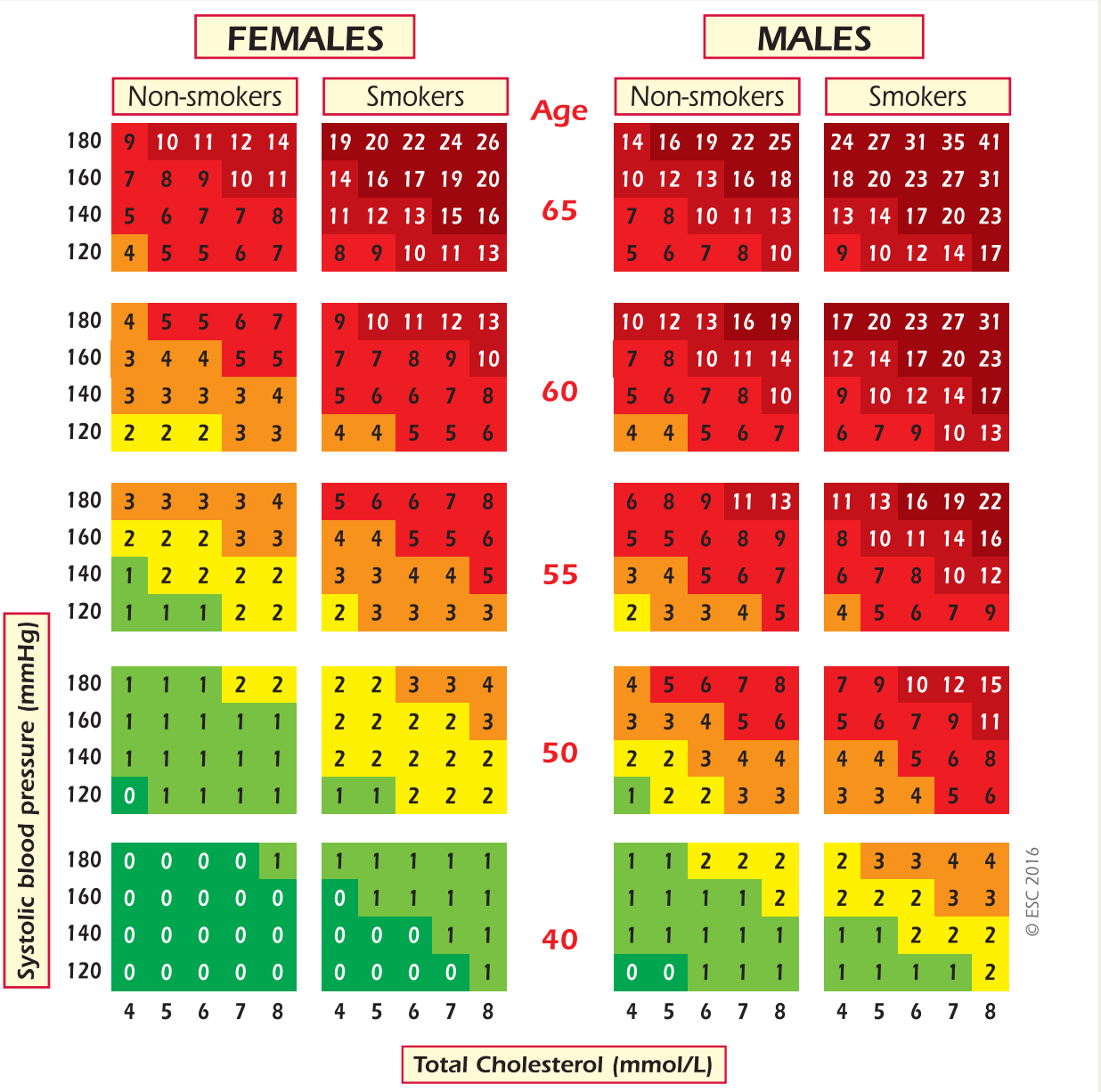
Web Figure D SCORE chart for use in low-risk regions – HDL 1.4 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



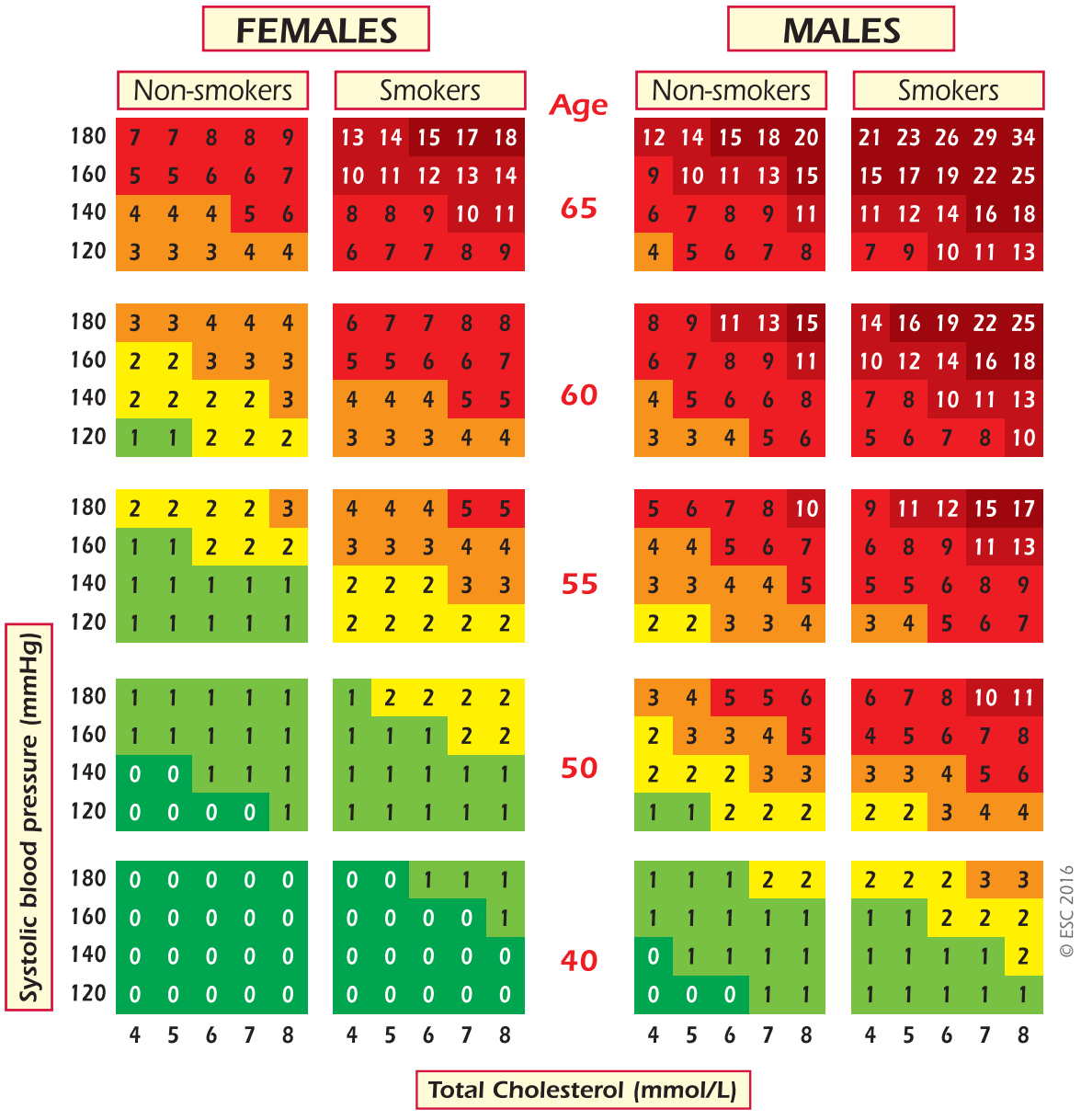
Web Figure E SCORE chart for use in low-risk regions – HDL 1.8 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



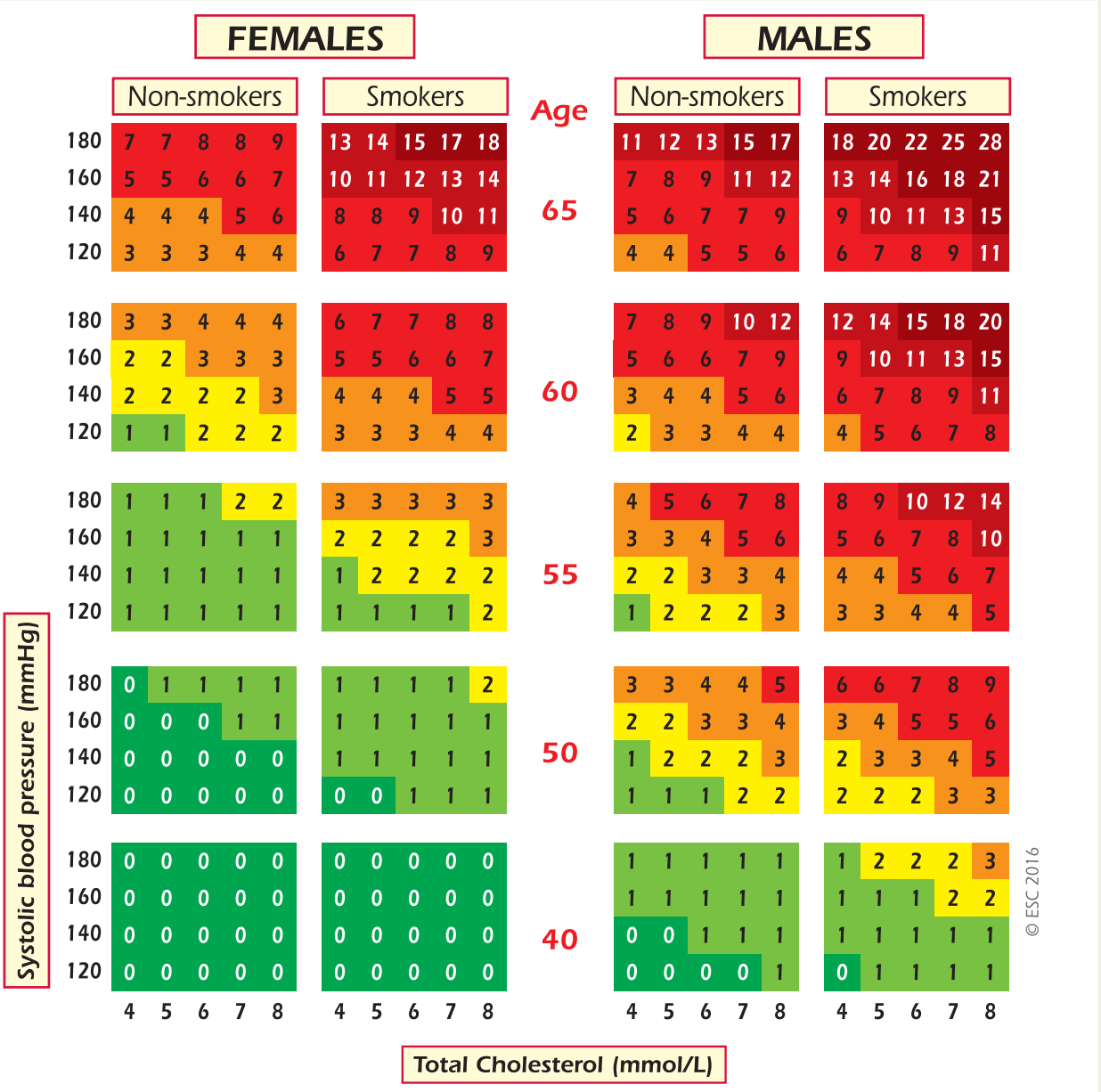
Web Figure F SCORE chart for use in high-risk regions – HDL 0.8 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



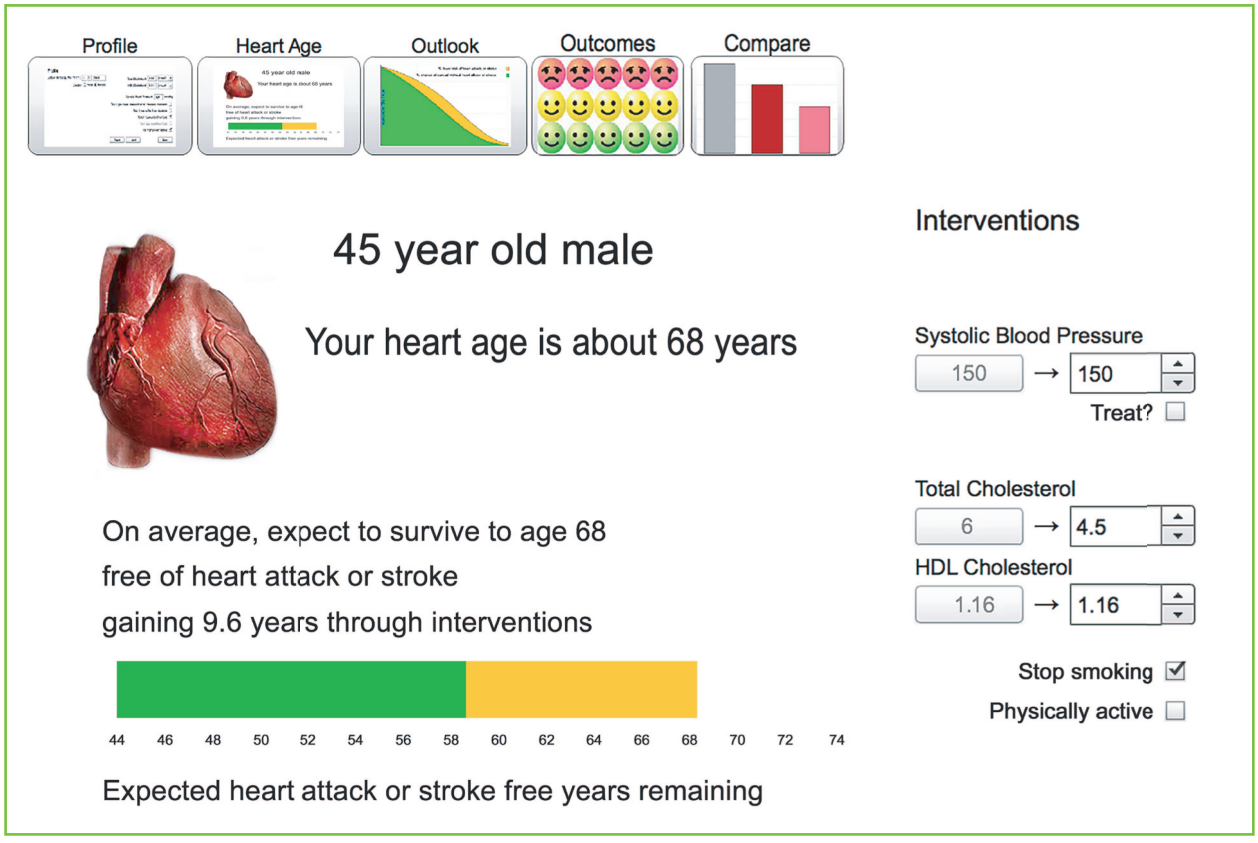
Web Figure G SCORE chart for use in high-risk regions – HDL 1.0 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



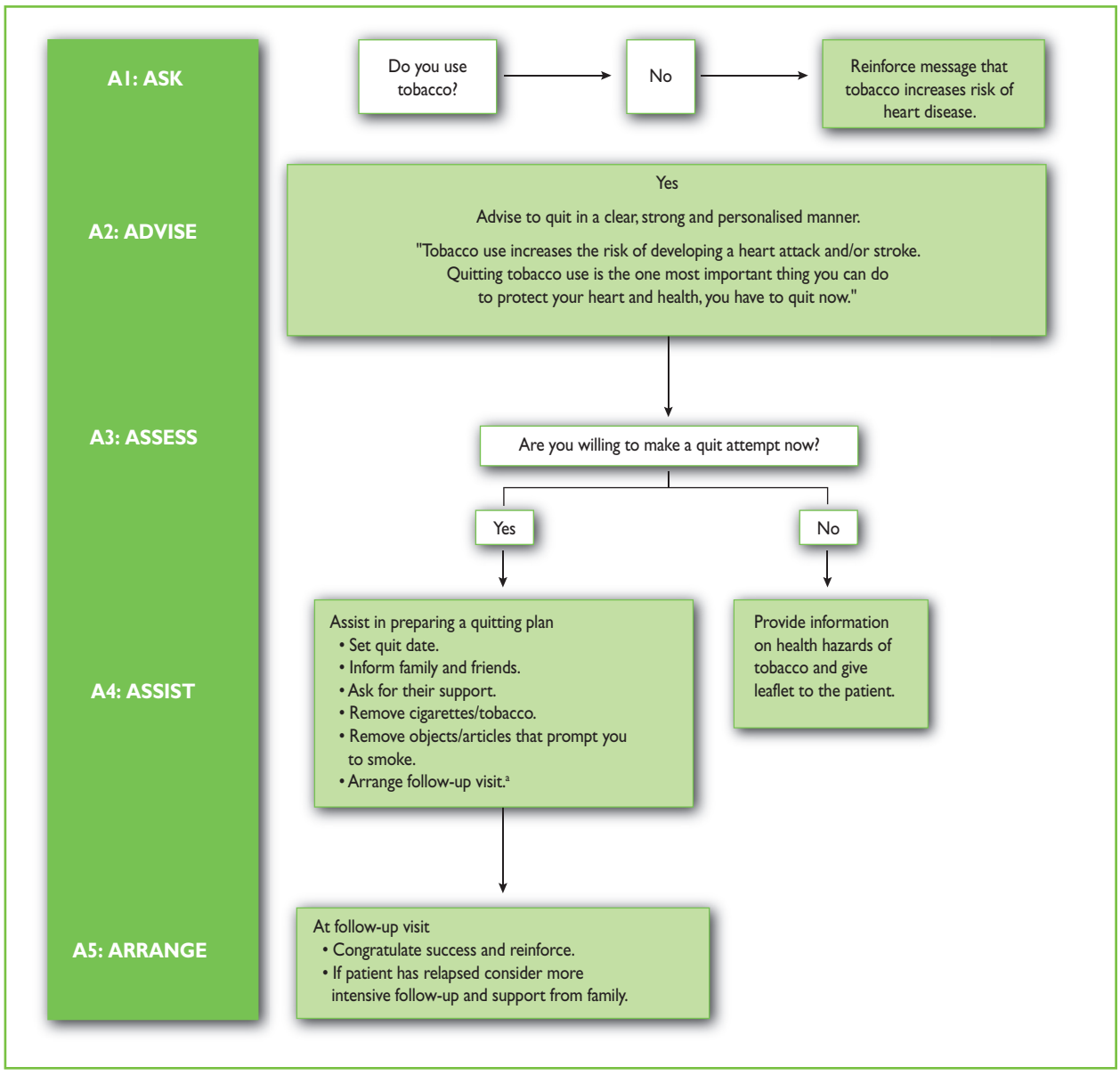
Web Figure H SCORE chart for use in high-risk regions – HDL 1.4 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



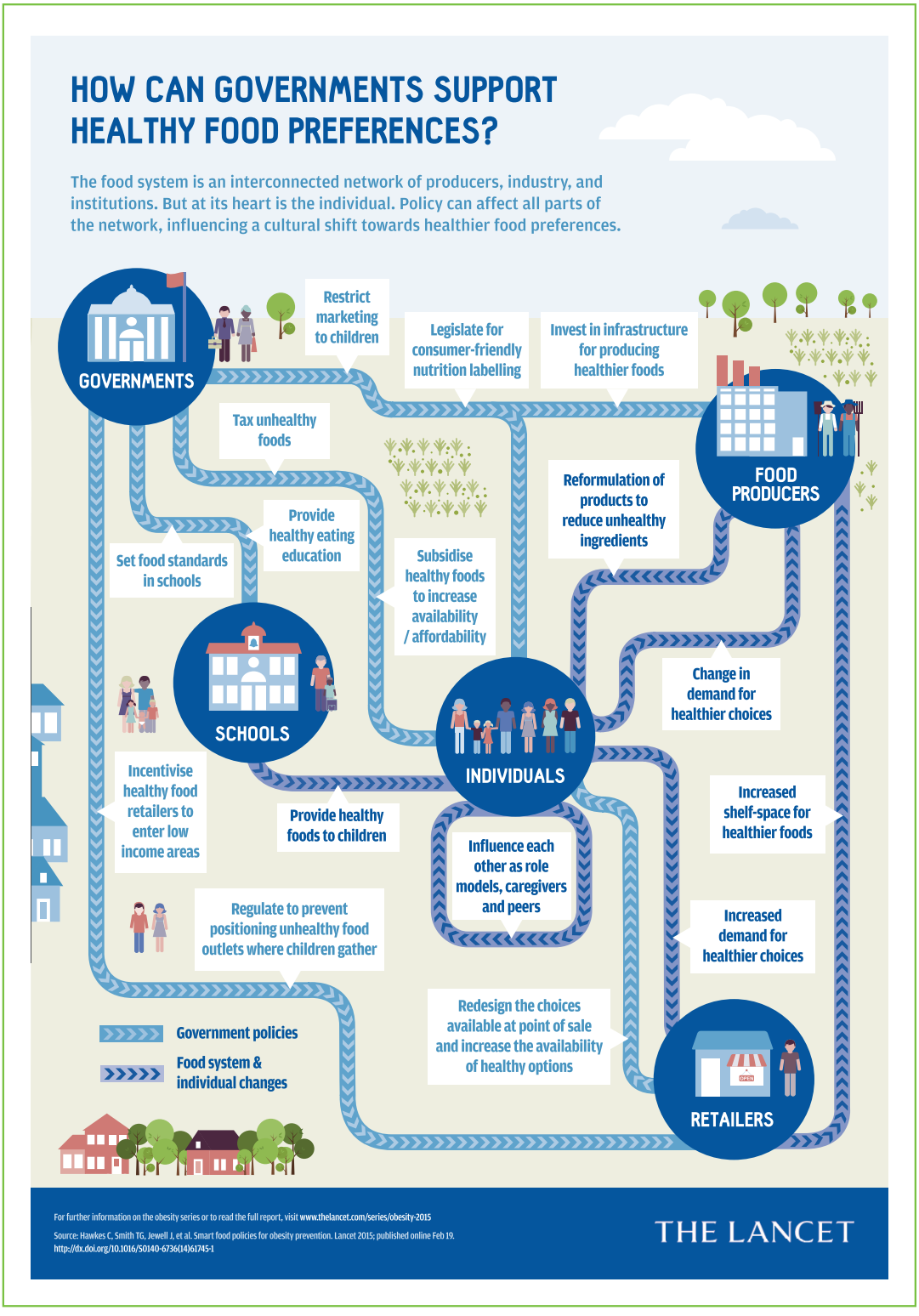
Web Figure I SCORE chart for use in high-risk regions – HDL 1.8 mmol/L. HDL = high-density lipoprotein; SCORE = Systematic Coronary Risk Estimation.



Web Figure J Lifetime risk calculator based on the JBS3 web-based tool.



Web Figure K Modified World Health Organization (WHO) smoking cessation algorithm. [a]Ideally second follow-up visit is recommended within the same month and every month thereafter for 4 months and evaluation after one year. If not feasible, reinforce counselling whenever the patient is seen for blood pressure monitoring. Taken with permission from WHO CVD risk management package.



Web Figure L How can governments support healthy food preferences? (Taken with permission from The Lancet)

(L) How can governments support healthy food preferences?

5. Web Tables

(A) Different risk factor combinations for more accurate estimation of risk ages

(B) Self-assessment questionnaires PAR-Q & YOU

(C) World Health Organization classification of body weight according to body mass index in adults

(D) Measures of general obesity and abdominal adiposity

Web Table A Table for different risk factor combinations for more accurate estimation of risk ages.

Systolic blood pressure (mmHg)	WOMEN Non-Smokers					WOMEN Smokers					Age	MEN Non-Smokers					MEN Smokers				
	180	78	80	>80	>80	>80	180	>80	>80	>80	>80	>80		180	>80	>80	>80	>80	>80	180	>80	>80	>80	>80	>80
	160	73	75	76	78	80	160	>80	>80	>80	>80	>80	65	160	76	79	>80	>80	>80	160	>80	>80	>80	>80	>80
	140	69	70	72	74	76	140	76	78	80	>80	>80		140	70	73	75	78	>80	140	>80	>80	>80	>80	>80
	120	65	66	68	69	71	120	72	73	75	77	79		120	65	67	70	72	75	120	75	77	>80	>80	>80
	180	72	73	75	76	78	180	79	>80	>80	>80	>80		180	76	78	>80	>80	>80	180	>80	>80	>80	>80	>80
	160	68	69	70	72	74	160	75	76	78	80	>80	60	160	70	72	75	78	80	160	80	>80	>80	>80	>80
	140	64	65	66	68	70	140	70	72	73	75	77		140	65	67	69	72	75	140	74	77	80	>80	>80
	120	60	61	63	64	66	120	66	68	69	71	73		120	60	62	64	67	69	120	69	71	74	77	80
	180	66	67	68	70	71	180	72	74	75	77	79		180	69	71	74	76	79	180	79	>80	>80	>80	>80
	160	62	63	64	66	67	160	68	69	71	73	74	55	160	64	66	68	71	74	160	73	76	79	>80	>80
	140	58	59	61	62	64	140	64	65	67	69	70		140	59	61	63	66	68	140	68	70	73	76	79
	120	55	56	57	59	60	120	61	62	63	64	66		120	55	57	59	61	64	120	63	65	68	70	73
	180	59	60	62	63	64	180	65	66	68	69	71		180	62	64	67	69	72	180	71	74	77	80	>80
	160	56	57	58	59	61	160	62	63	64	66	67	50	160	58	60	62	64	67	160	66	68	71	74	77
	140	53	54	55	56	58	140	58	59	61	62	64		140	54	56	58	60	62	140	61	64	66	68	71
	120	50	51	52	53	55	120	55	56	57	59	60		120	50	52	54	56	58	120	57	59	61	64	66
	180	53	54	55	56	57	180	58	59	60	62	63		180	56	58	60	62	64	180	64	66	68	71	74
	160	50	51	52	53	54	160	55	56	57	59	60	45	160	52	54	55	57	60	160	59	61	63	66	68
	140	48	48	49	50	52	140	52	53	54	55	57		140	48	50	52	54	56	140	55	57	59	61	64
	120	45	46	47	48	49	120	49	50	51	52	54		120	45	47	48	50	53	120	51	53	55	57	59
	180	47	48	49	50	51	180	51	52	53	54	55		180	49	51	52	54	56	180	56	58	60	62	65
	160	45	46	46	47	48	160	49	49	50	51	53	40	160	46	47	49	51	53	160	52	54	56	58	60
	140	43	43	44	45	46	140	46	47	48	49	50		140	43	44	46	47	49	140	48	50	52	54	56
	120	40	41	42	43	44	120	44	45	45	46	48		120	40	41	43	44	46	120	45	47	49	51	52
		4	5	6	7	8		4	5	6	7	8			4	5	6	7	8		4	5	6	7	8
		Total cholesterol (mmol/L)													Total cholesterol (mmol/L)										

Web Table B **Self-assessment questionnaires PAR-Q & YOU**

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

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Web Table C **World Health Organization classification of body weight according to body mass index in adults**

Adults (>18 years of age)	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese	≥30
Class 1	30–34.9
Class 2	35–39.9
Class 3	≥40

BMI = body mass index.

Web Table D **Measures of general obesity and abdominal adiposity**

A. Measures of general obesity • Body mass index
B. Measures of abdominal adiposity • Waist circumference • Waist : hip ratio • Waist : height ratio
C. Direct measures of fat mass • Bioelectrical impedance analysis • Skinfold thicknesses
D. Measures of general obesity and abdominal adiposity • Dual-energy X-ray absorptiometry • Ultrasound • Computed tomography • Magnetic resonance imaging

Web Table E **Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with statin (CYP3A4 inhibitors/ substrates or other mechanisms)**

CYP3A4 Inhibitors/substrates	Others
Cyclosporine, tacrolimus, sirolimus	Digoxin
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Fibrates (gemfibrozil)
Azole antifungals (fluconazole, itraconazole, ketoconazole, posaconazole)	Niacin
Calcium antagonists (mibefradil, diltiazem, verapamil)	
Nefazodone	
HIV protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir)	
Hepatitis C drugs (boceprevir, telaprevir)	
Danazol	
Amiodarone	
Grapefruit juice	
Sildenafil	
Warfarin	

Web Table F **Reasons for medication non-adherence according to the World Health Organization**

Category of non-adherence	Example
Health system	Poor quality of provider–patient relationship; poor knowledge on medication and/or low acceptance of guidelines; poor communication (e.g. limited, complex or confusing advice); lack of access to healthcare; lack of continuity of care.
Condition	Asymptomatic chronic disease (lack of physical cues); co-morbid mental health disorders (e.g. depression).
Patient	Physical impairments (e.g. vision problems or impaired dexterity); cognitive impairment; psychological/behavioural factors (e.g. lack of motivation, low self–efficacy, impulsivity); younger age.
Therapy	Complexity of regimen; side-effects.
Socio-economic	Low literacy; high medication costs; poor social support.

(E) Selected drugs that may increase the risk of myopathy and rhabdomyolysis when used concomitantly with statin (CYP3A4 inhibitors/substrates or other mechanisms)
(F) Reasons for medication non-adherence according to the World Health Organization

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