

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (1)

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (2)

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Association of Percutaneous Cardiovascular Interventions (EAPCI).

Councils: Council for Cardiology Practice, Council on Hypertension, Council on Stroke.

Working Groups: Aorta and Peripheral Vascular Diseases, Atherosclerosis and Vascular Biology, Cardiovascular Pharmacotherapy, e-Cardiology, Thrombosis.

ESC Classes of recommendations

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

ESC Levels of evidence

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

New recommendations (1)

Cardiovascular imaging for assessment of ASCVD risk

Assessment of arterial (carotid and/or femoral) plaque burden on arterial ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.

Cardiovascular imaging for assessment of ASCVD risk

CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.

Lipid analyses for CVD risk estimation

Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.

New recommendations (2)

Drug treatments of patients with hypertriglyceridaemia

In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statins.

Treatment of patients with heterozygous FH

In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) should be considered.

Treatment of dyslipidaemias in older people

Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤ 75 .

Treatment of dyslipidaemias in older people

Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.

New recommendations (3)

Treatment of dyslipidaemias in DM

In patients with T2DM at very-high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) is recommended.

In patients with T2DM at high risk, an LDL-C reduction of $\geq 50\%$ from baseline and an LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) is recommended.

Statins are recommended in patients with T1DM who are at high or very-high risk.

Treatment of dyslipidaemias in DM

Intensification of statin therapy should be considered before the introduction of combination therapy.

If the goal is not reached, statin combination with ezetimibe should be considered.

Treatment of dyslipidaemias in DM

Statin therapy is not recommended in pre-menopausal patients with DM who are considering pregnancy or not using adequate contraception.

New recommendations (4)

Lipid-lowering therapy in patients with ACS

For patients who present with an ACS, and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.

Changes in recommendations (1)

2016	2019
Lipid analyses for CVD risk estimation	Lipid analyses for CVD risk estimation
ApoB should be considered as an alternative risk marker whenever available, especially in individuals with high TG.	ApoB analysis is recommended for risk assessment, particularly in people with high TG, DM, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG, DM, obesity, or very low LDL-C.

Changes in recommendations (2)

2016	2019
Pharmacological LDL-C lowering	Pharmacological LDL-C lowering
If the LDL goal is not reached, statin combination with a cholesterol absorption inhibitor should be considered.	If the goals are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.

Changes in recommendations (3)

2016	2019
Pharmacological LDL-C lowering	Pharmacological LDL-C lowering
In patients at very-high risk, with persistent high LDL-C despite treatment with maximal tolerated statin dose, in combination with ezetimibe or in patients with statin intolerance, a PCSK9 inhibitor may be considered.	For secondary prevention, patients at very-high risk not achieving their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended. 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 statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.

Changes in recommendations (4)

2016	2019
Drug treatments of hypertriglyceridaemia	Drug treatments of hypertriglyceridaemia
Statin treatment may be considered as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia.	Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [TG >2.3 mmol/L (200 mg/dL)].

Changes in recommendations (5)

2016	2019
Treatment of patients with heterozygous FH	Treatment of patients with heterozygous FH
Treatment should be considered to aim at reaching an LDL-C <2.6 mmol/L (<100 mg/dL) or in the presence of CVD <1.8 mmol/L (<70 mg/dL). If targets cannot be reached, maximal reduction of LDL-C should be considered using appropriate drug combinations.	For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.

Changes in recommendations (6)

2016	2019
Treatment of patients with heterozygous FH	Treatment of patients with heterozygous FH
Treatment with a PCSK9 antibody should be considered in FH patients with CVD or with other factors putting them at very-high risk for CHD, such as other CV risk factors, family history, high Lp(a), or statin intolerance.	Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.

Changes in recommendations (7)

2016

Treatment of dyslipidaemias in older adults

Since older people often have comorbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger people.

2019

Treatment of dyslipidaemias in older adults

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, and then titrated upwards to achieve LDL-C treatment goals.

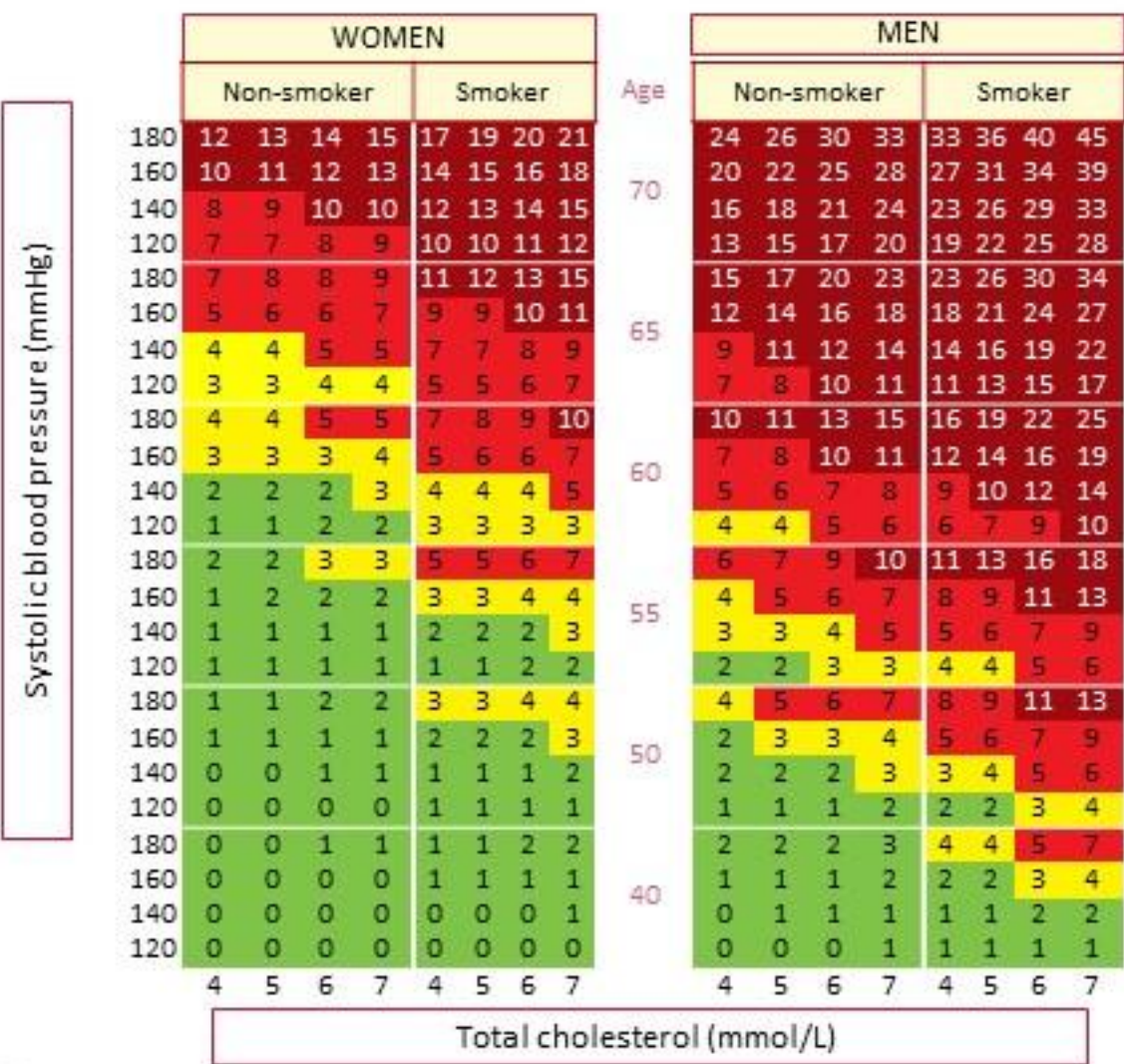
Changes in recommendations (8)

2016	2019
Lipid-lowering therapy in patients with ACS	Lipid-lowering therapy in patients with ACS
If the LDL-C target is not reached with the highest tolerated statin dose and/or ezetimibe, PCSK9 inhibitors may be considered on top of lipid-lowering therapy; or alone or in combination with ezetimibe in statin-intolerant patients or in whom a statin is contraindicated.	If the LDL-C goal is not achieved after 4 - 6 weeks despite maximal tolerated statin therapy and ezetimibe, addition of a PCSK9 inhibitor is recommended.

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe



SCORE chart for European populations at high cardiovascular disease risk

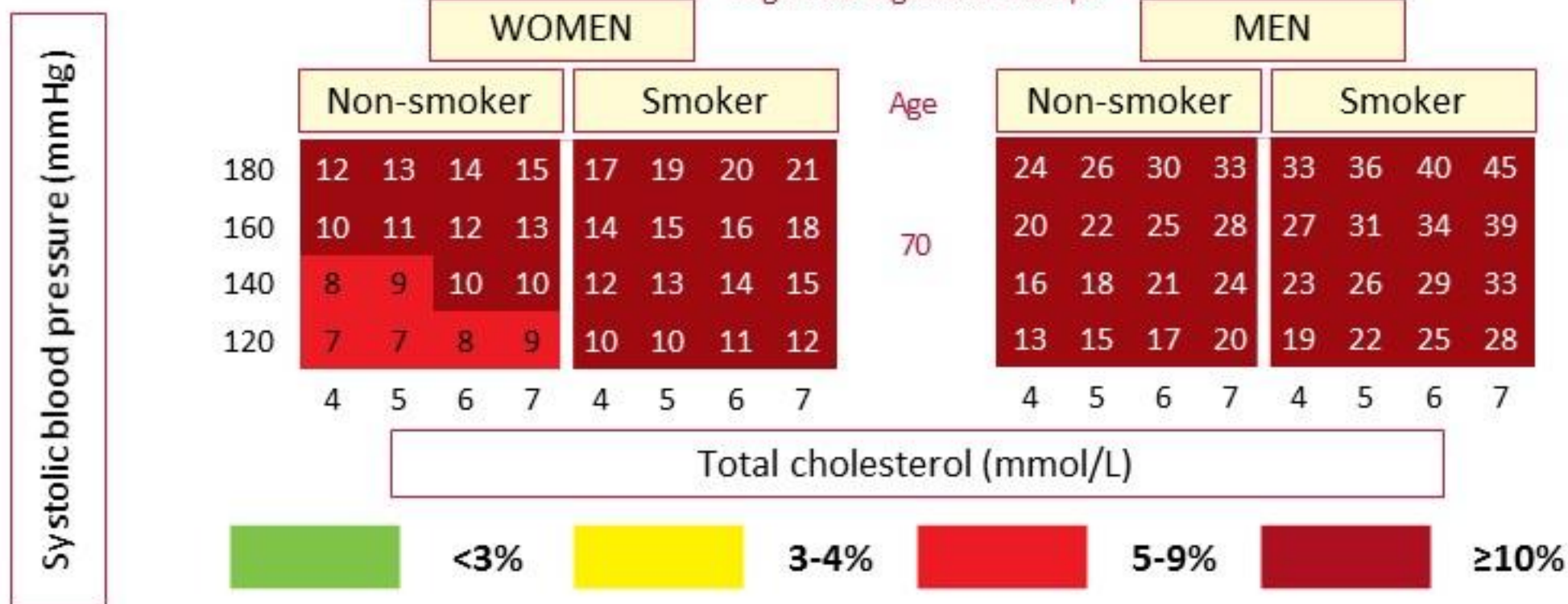


SCORE chart for European populations at high cardiovascular disease risk (1)

SCORE Cardiovascular Risk Chart

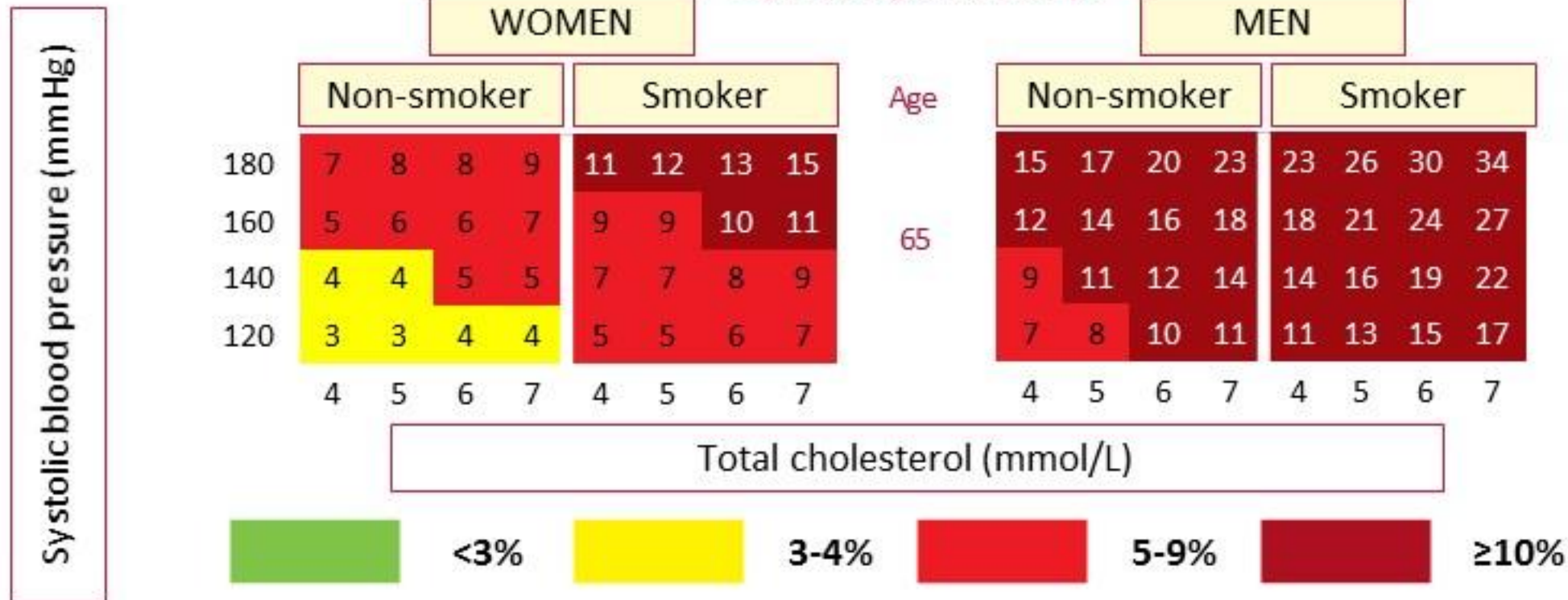
10-year risk of fatal CVD

High-risk regions of Europe



SCORE chart for European populations at high cardiovascular disease risk (2)

SCORE Cardiovascular Risk Chart
10-year risk of fatal CVD
High-risk regions of Europe

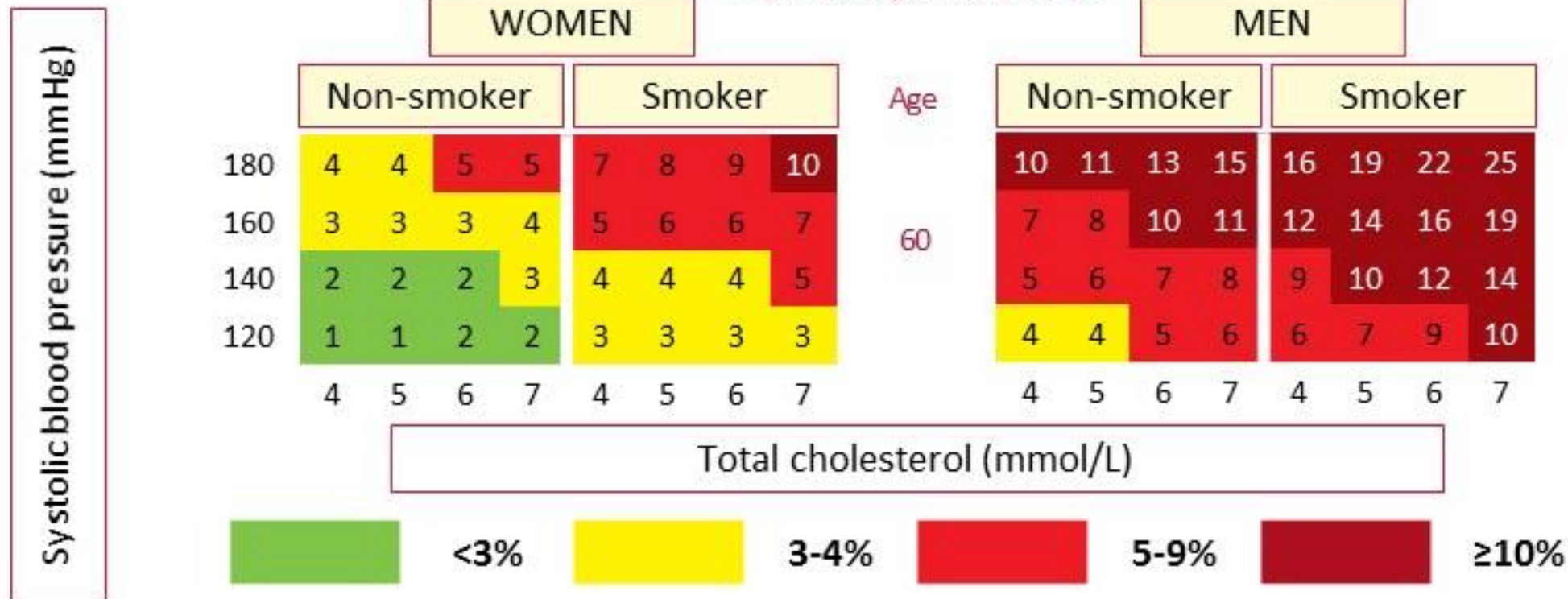


SCORE chart for European populations at high cardiovascular disease risk (3)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe

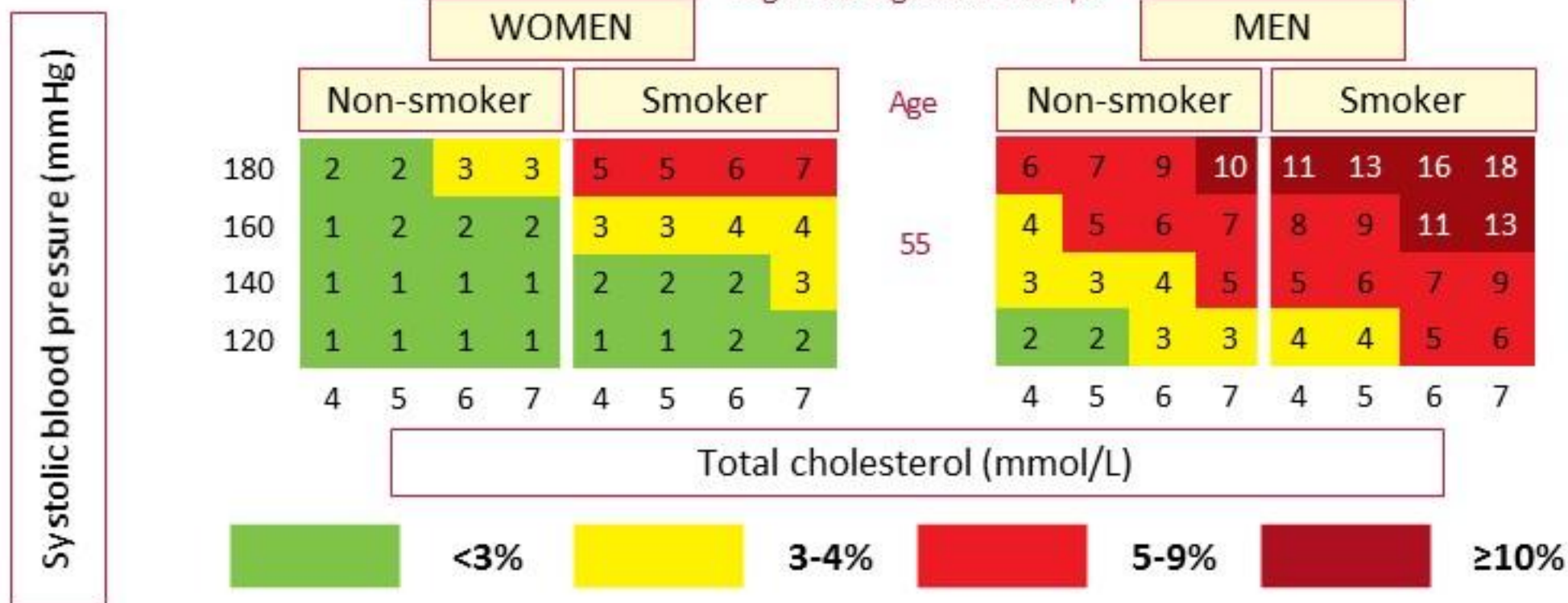


SCORE chart for European populations at high cardiovascular disease risk (4)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe

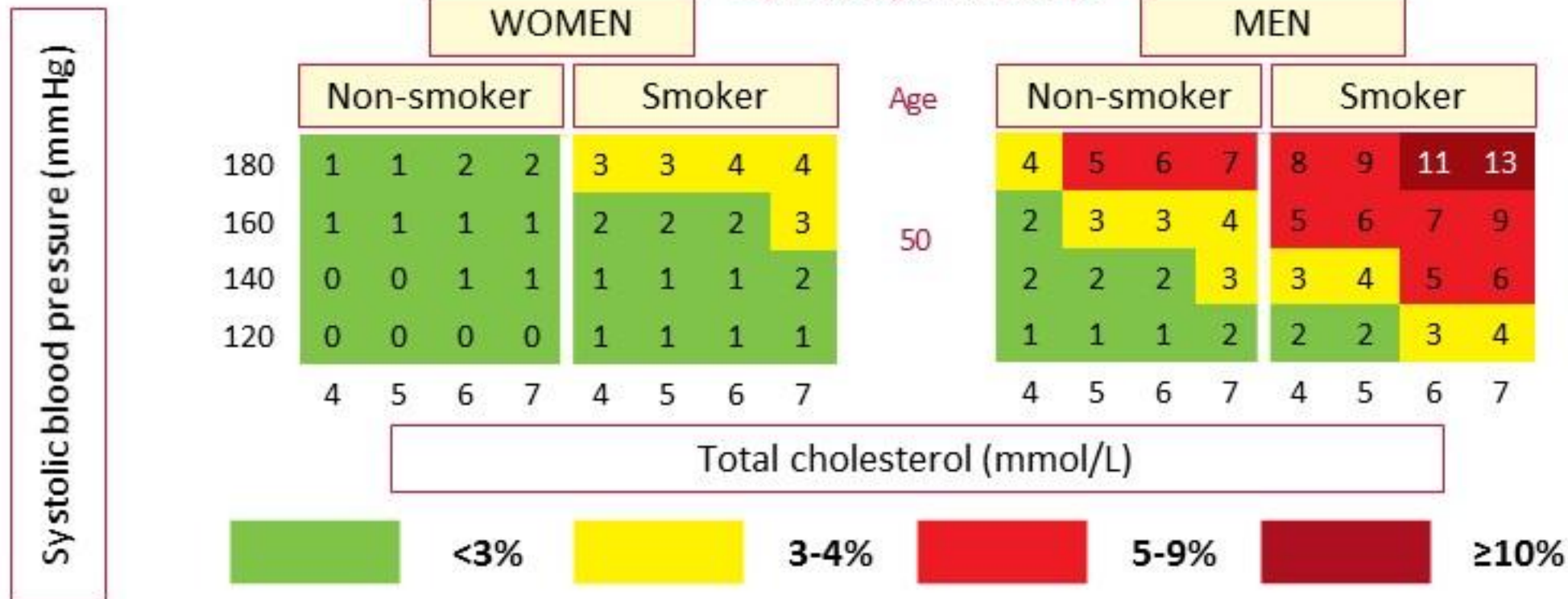


SCORE chart for European populations at high cardiovascular disease risk (5)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe

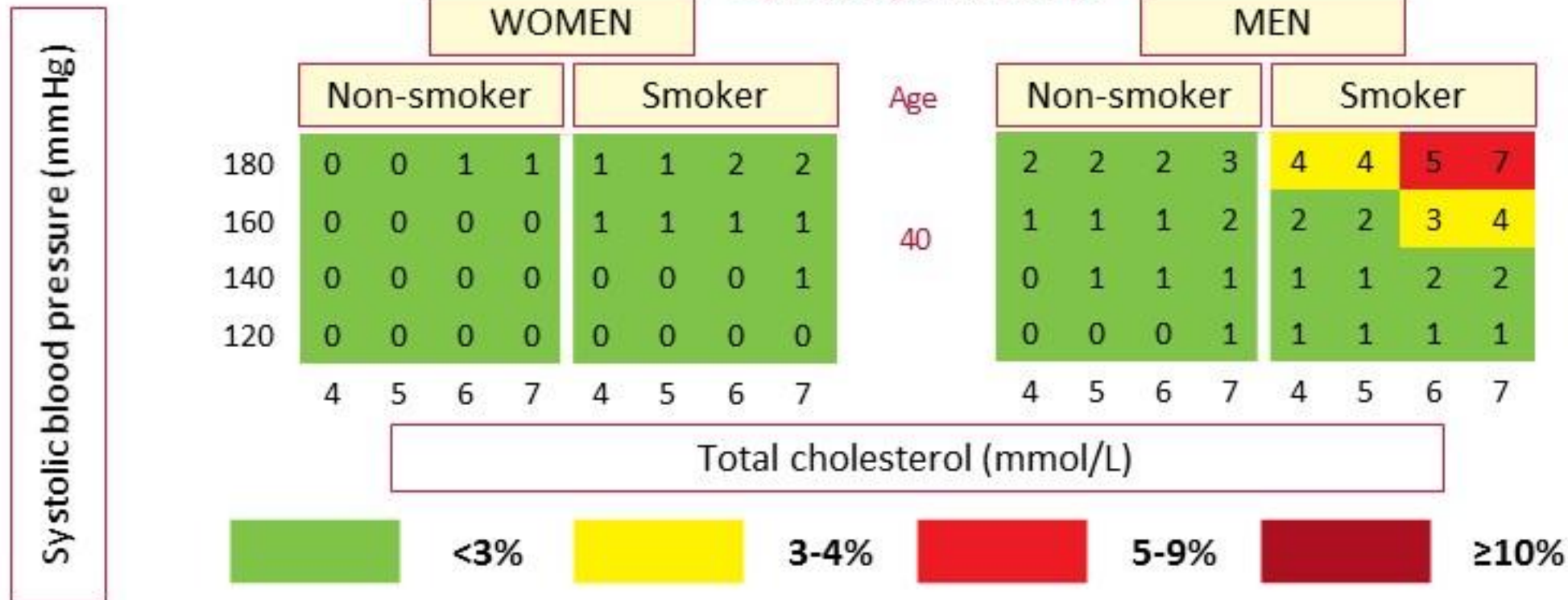


SCORE chart for European populations at high cardiovascular disease risk (6)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe

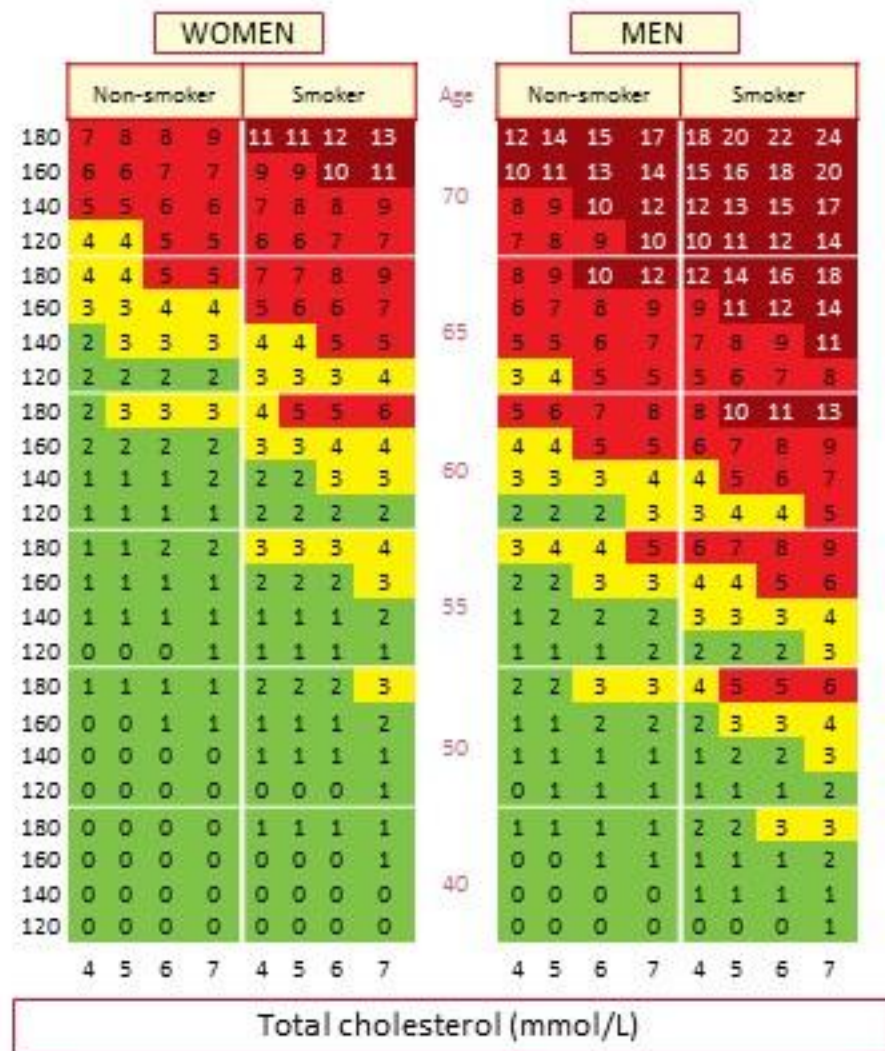


SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe

Systolic blood pressure (mmHg)



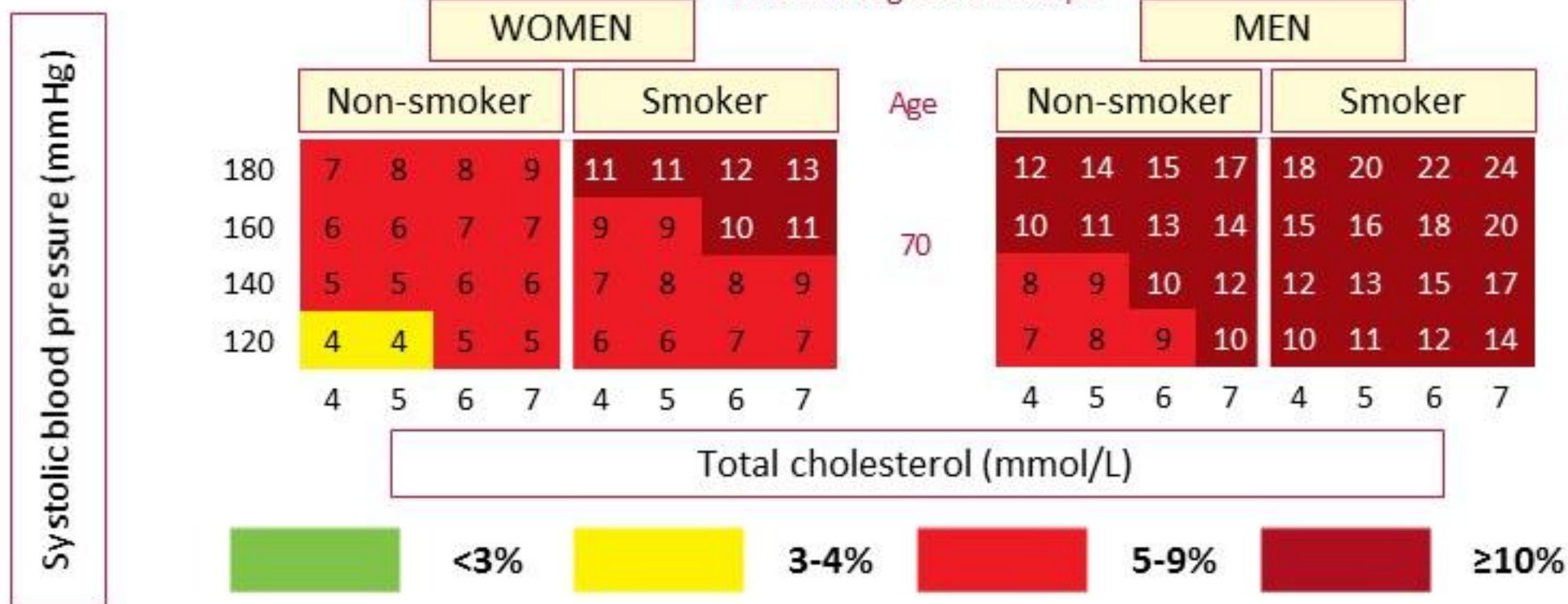
SCORE chart for European populations at low cardiovascular disease risk



©ESC

SCORE chart for European populations at low cardiovascular disease risk (1)

SCORE Cardiovascular Risk Chart
10-year risk of fatal CVD
Low-risk regions of Europe

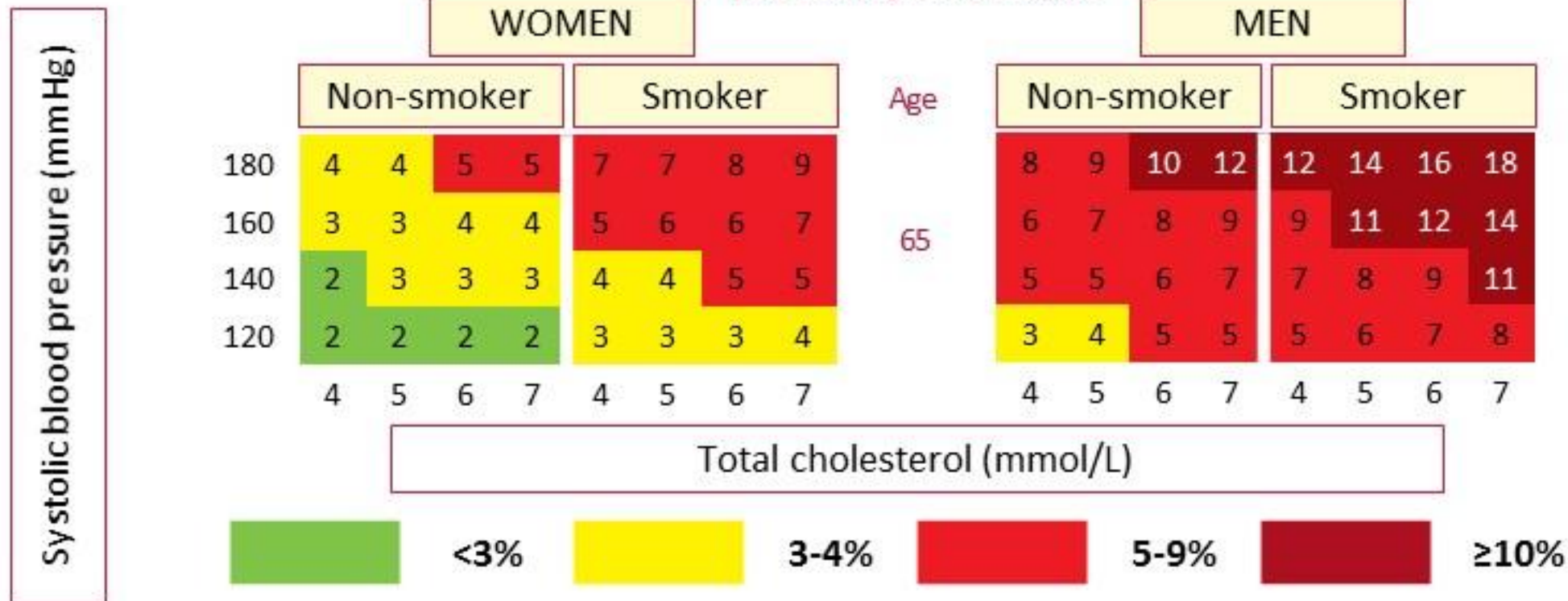


SCORE chart for European populations at low cardiovascular disease risk (2)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe

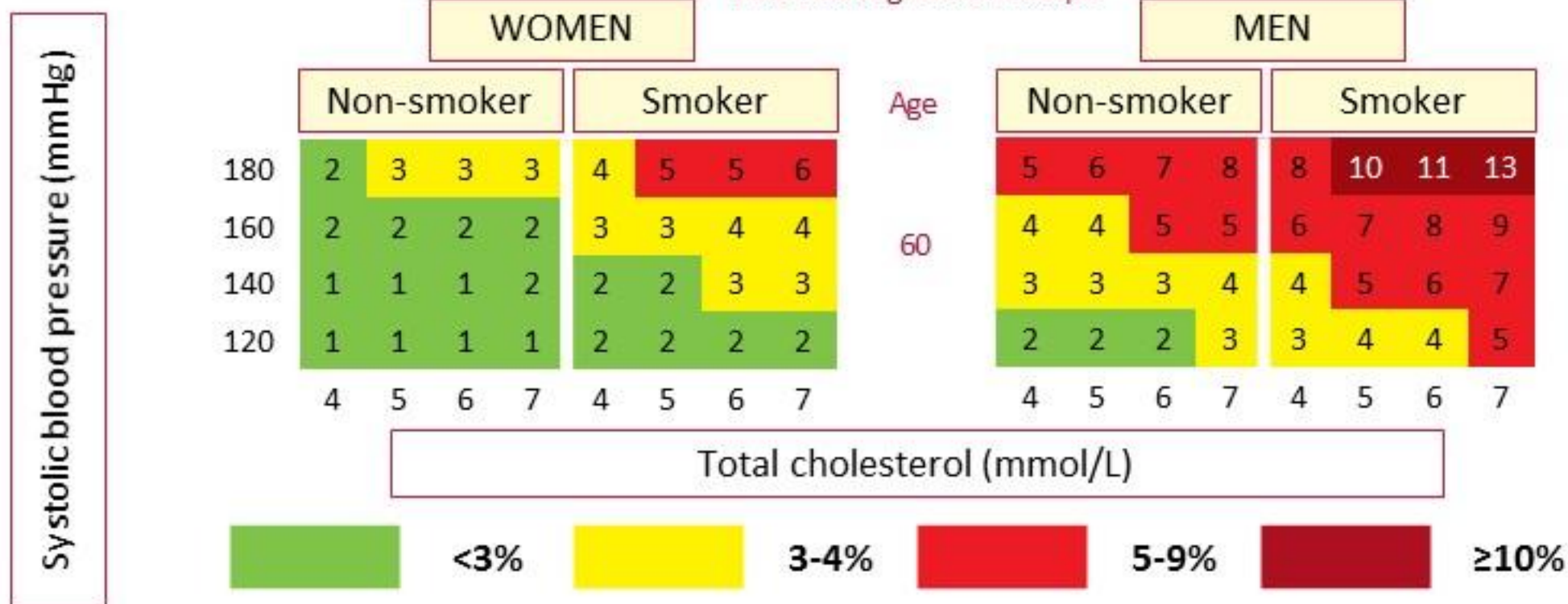


SCORE chart for European populations at low cardiovascular disease risk (3)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe



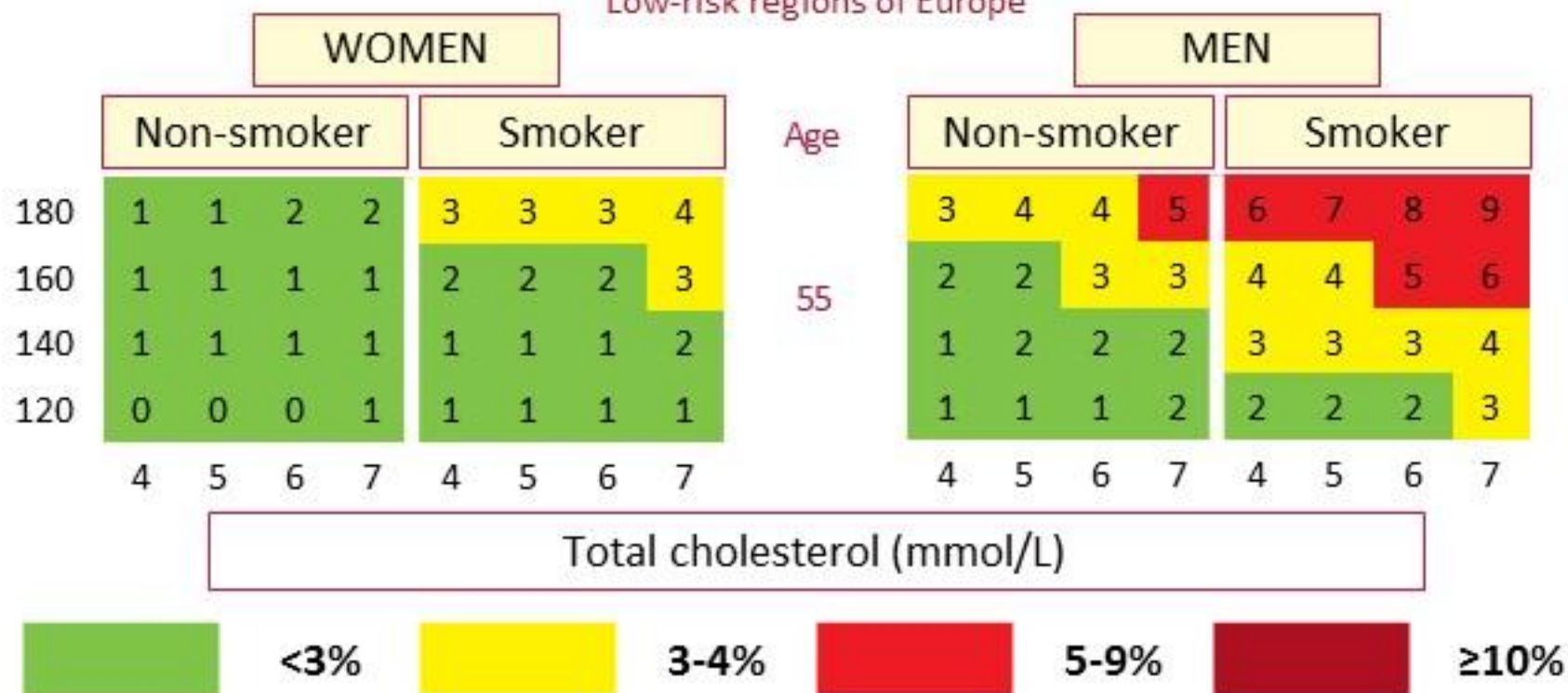
SCORE chart for European populations at low cardiovascular disease risk (4)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe

Systolic blood pressure (mmHg)

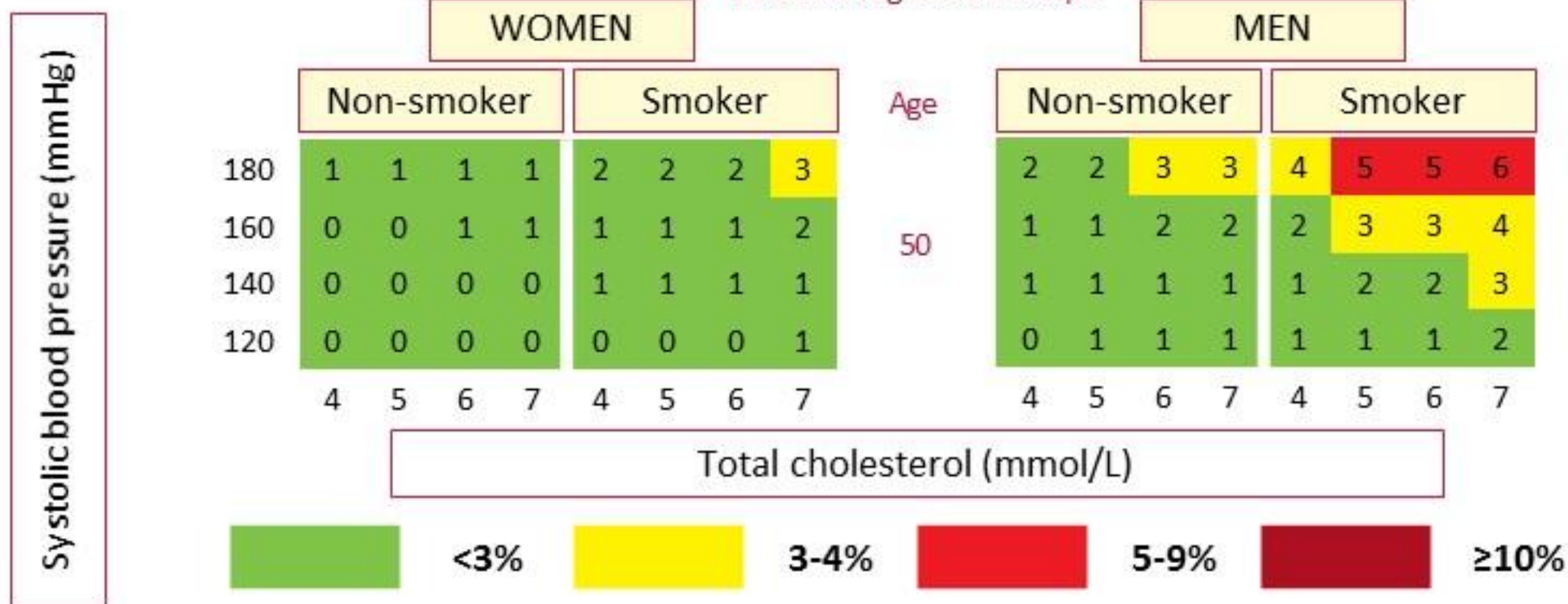


SCORE chart for European populations at low cardiovascular disease risk (5)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe



SCORE chart for European populations at low cardiovascular disease risk (6)

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe

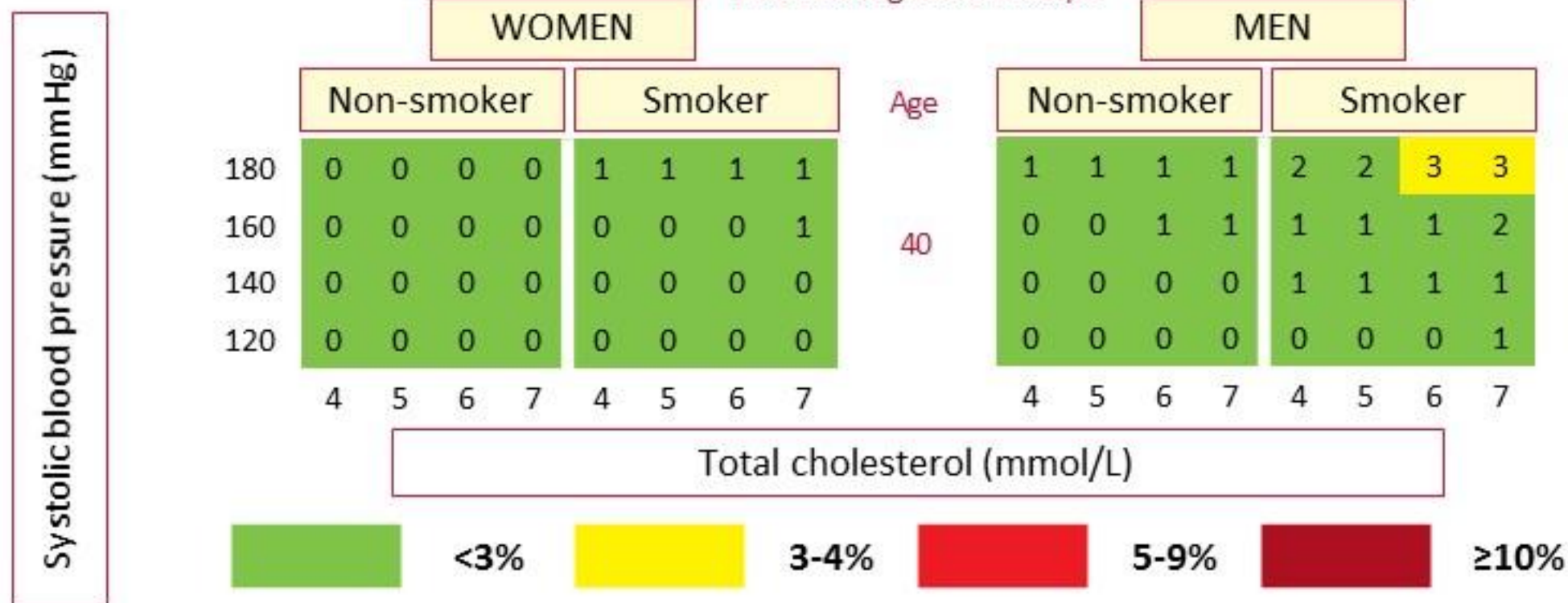
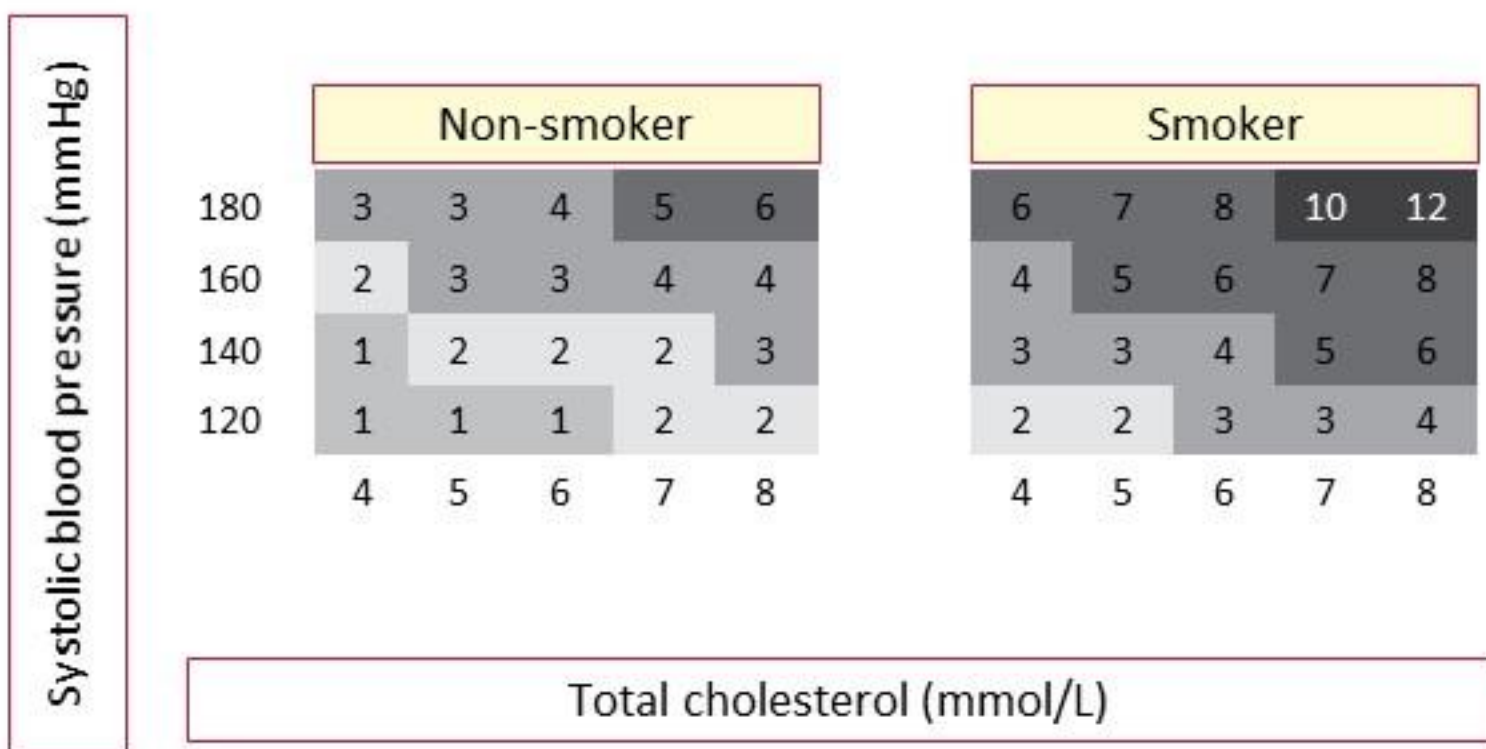


Chart for estimating the relative risk for 10-year cardiovascular mortality in young people



10-year risk of fatal CVD

Low-risk regions of Europe (age interactions included)

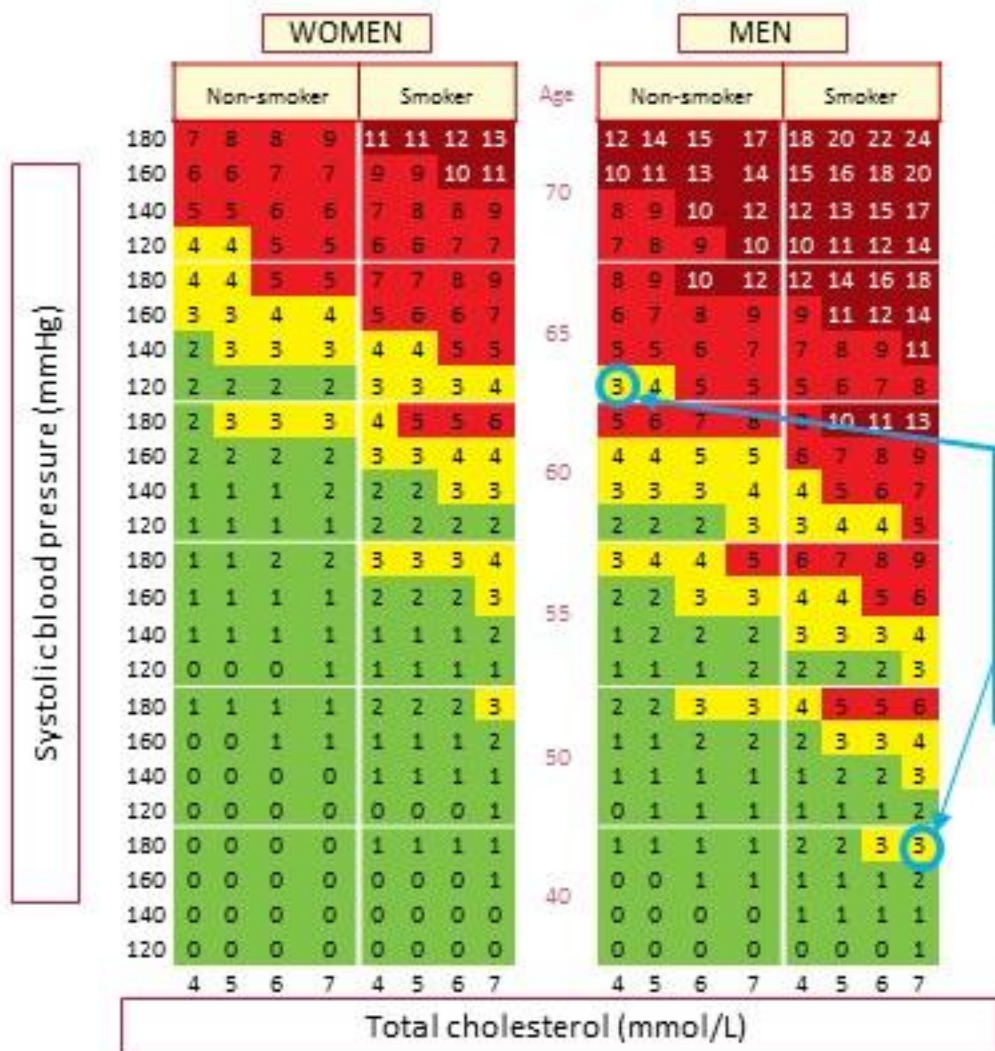


Illustration of the risk age concept

The risk of this 40-year old male smoker with risk factors is the same (3-4%) as that of a 65-year-old man with ideal risk factor levels— therefore his risk age is 65 years.



Illustration of the risk age concept (1)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)

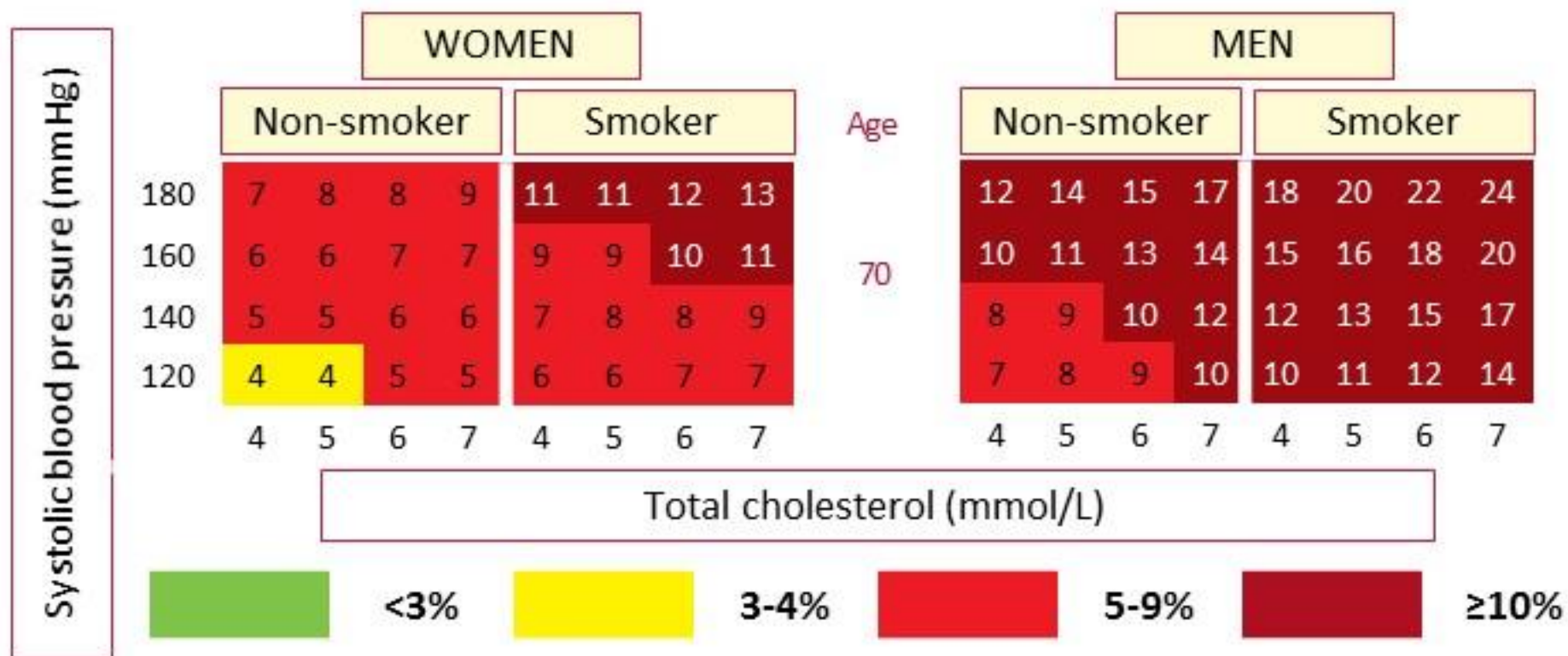


Illustration of the risk age concept (2)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)

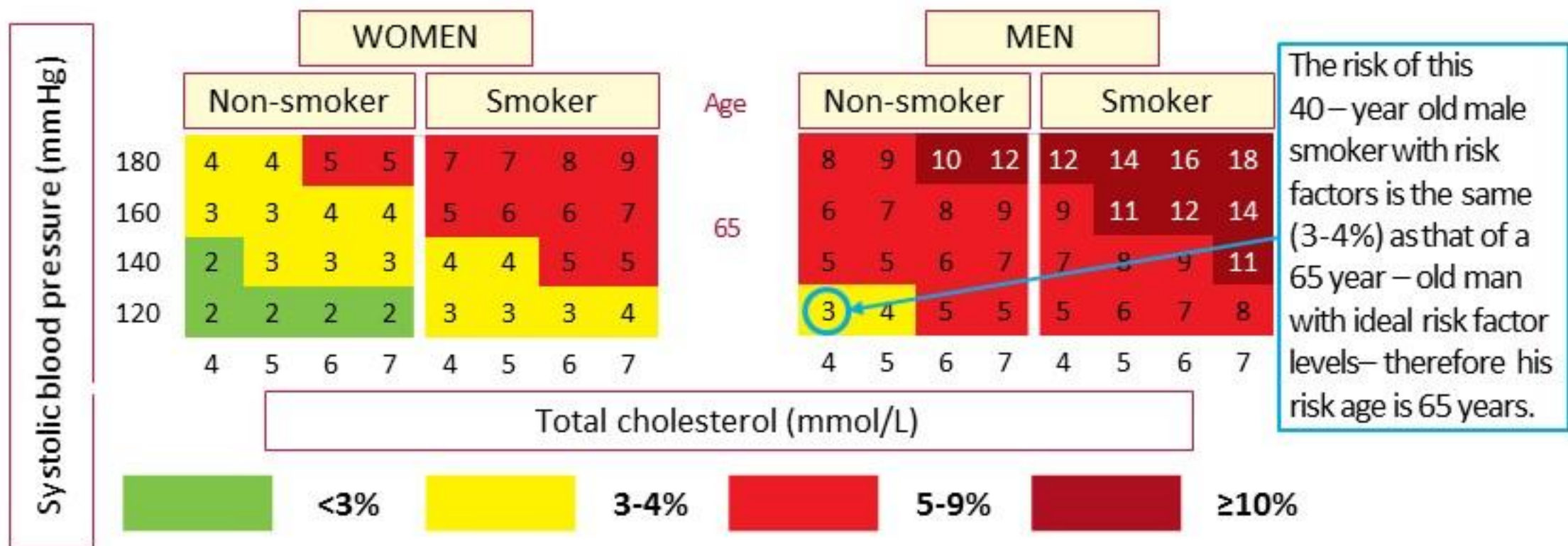


Illustration of the risk age concept (3)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)

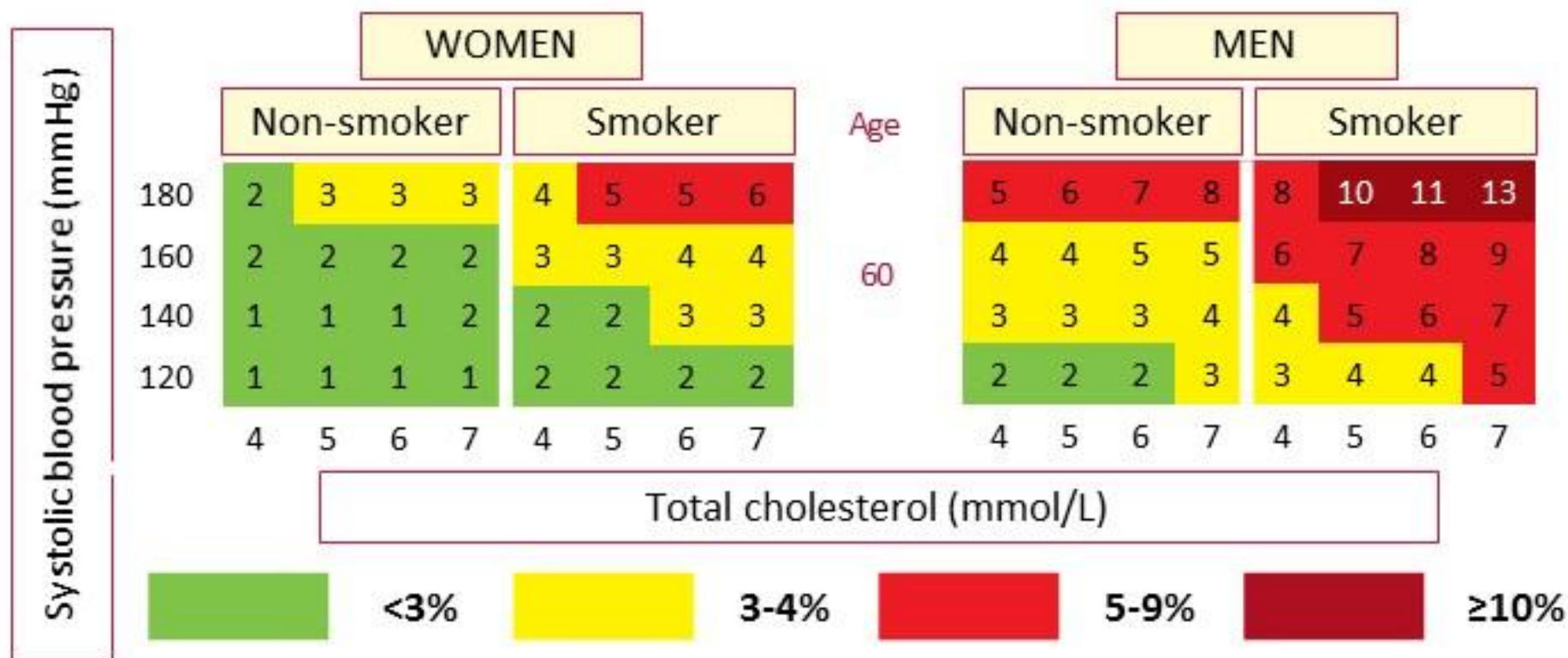


Illustration of the risk age concept (4)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)

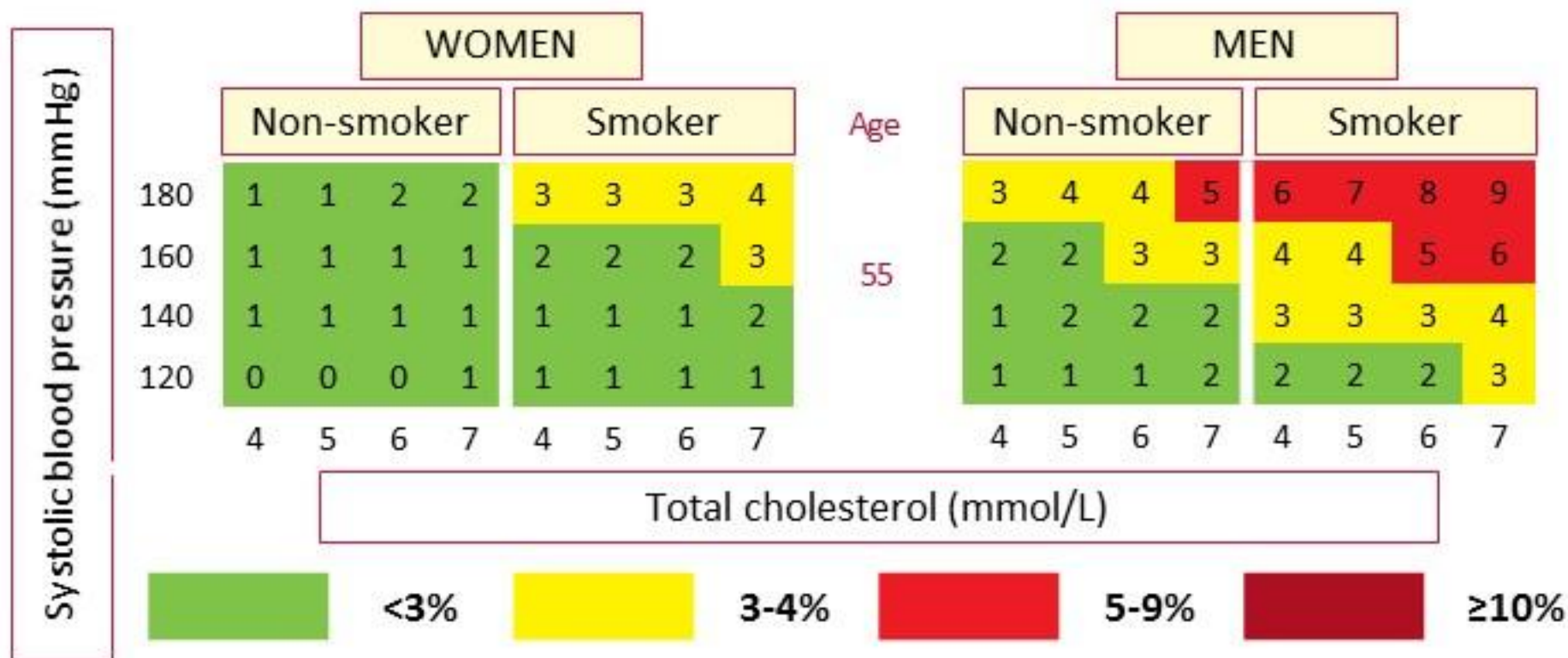


Illustration of the risk age concept (5)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)

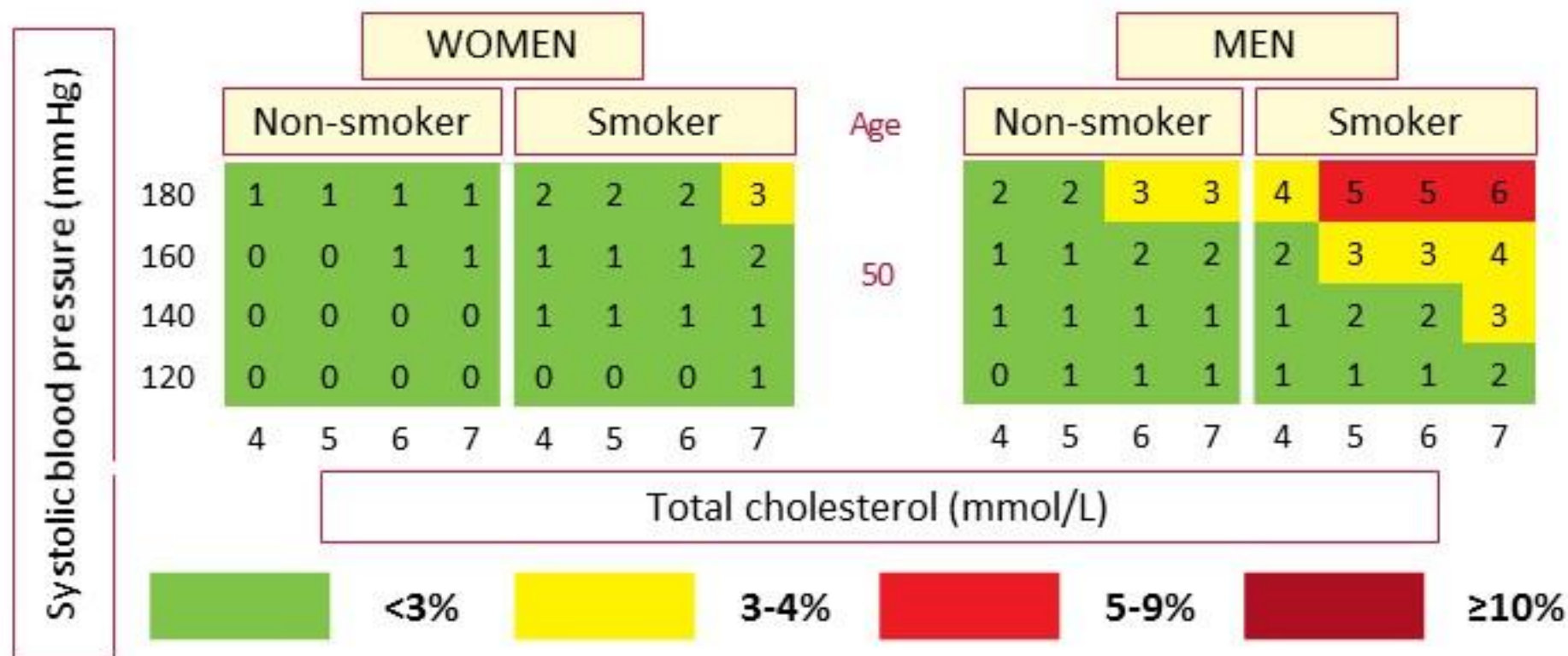
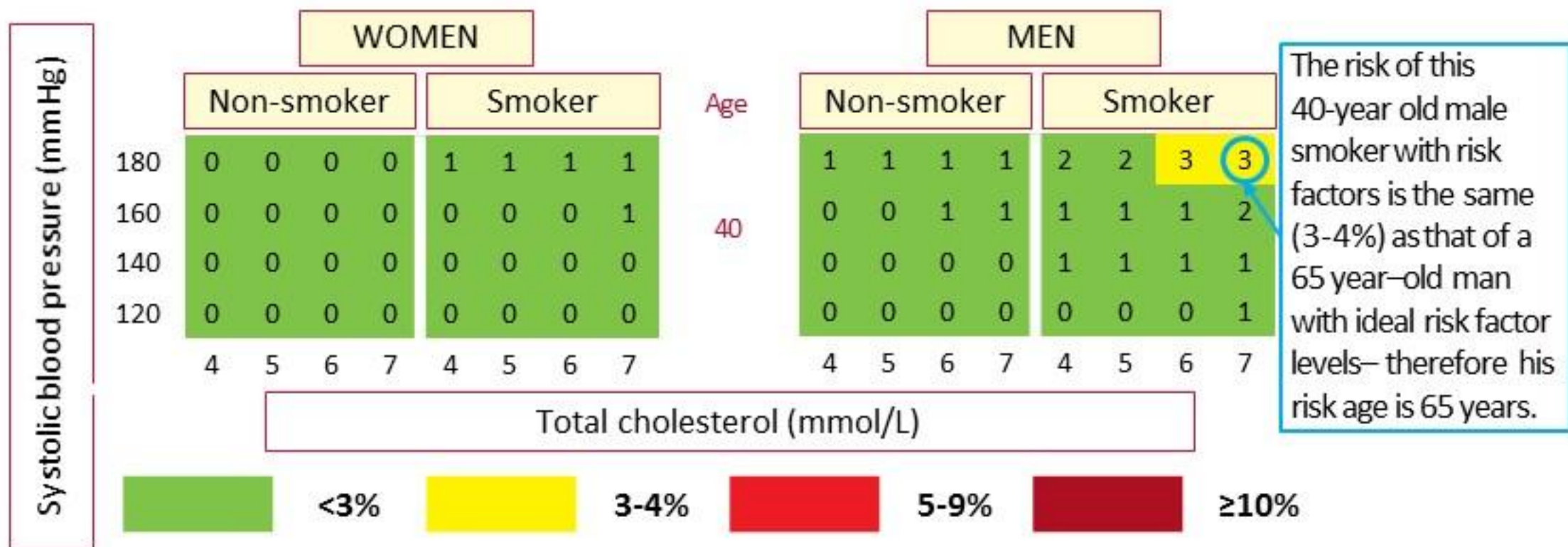
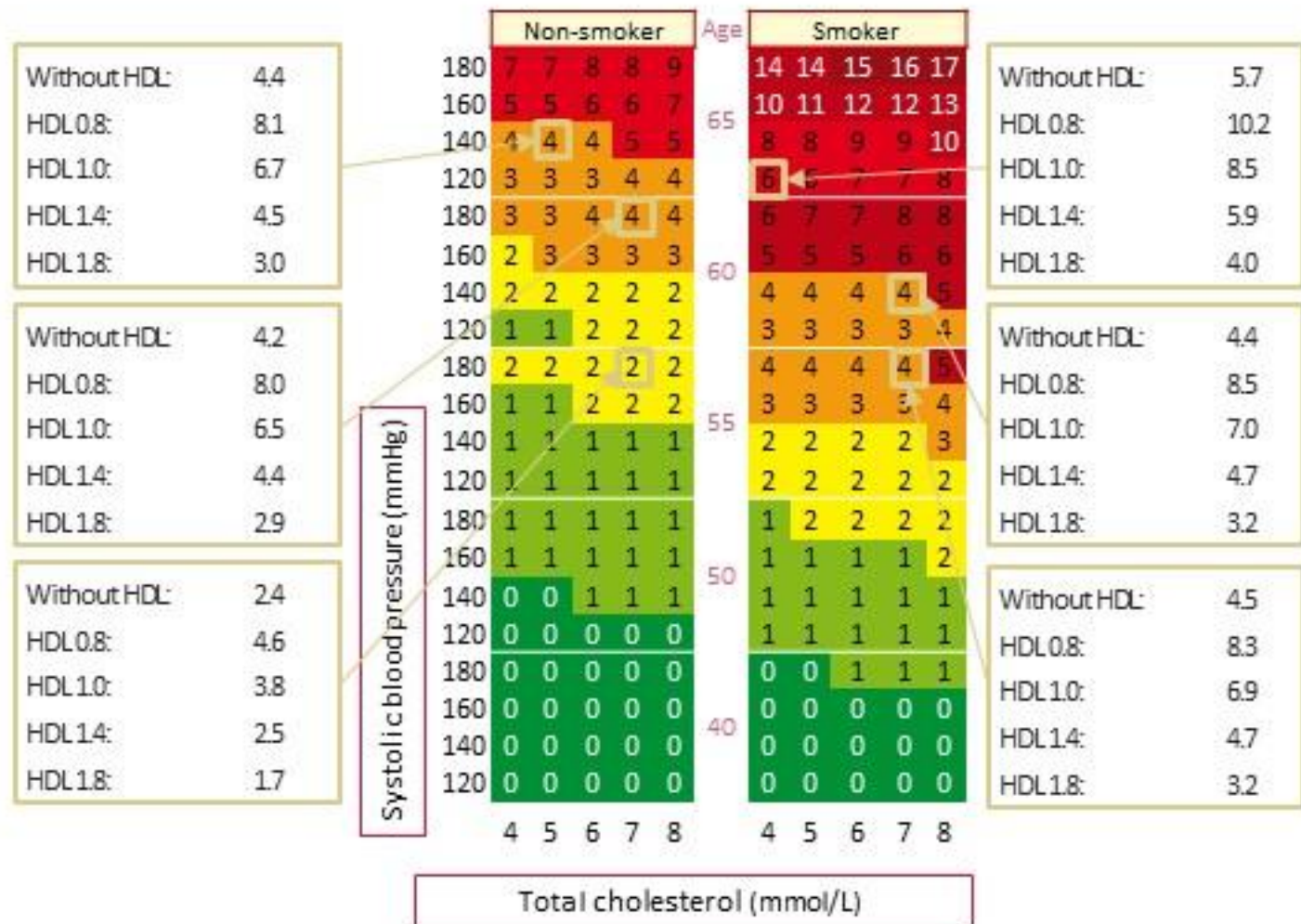


Illustration of the risk age concept (6)

10-year risk of fatal CVD
Low-risk regions of Europe (age interactions included)





Without HDL:	4.4
HDL 0.8:	8.1
HDL 1.0:	6.7
HDL 1.4:	4.5
HDL 1.8:	3.0

Without HDL:	4.2
HDL 0.8:	8.0
HDL 1.0:	6.5
HDL 1.4:	4.4
HDL 1.8:	2.9

Without HDL:	2.4
HDL 0.8:	4.6
HDL 1.0:	3.8
HDL 1.4:	2.5
HDL 1.8:	1.7

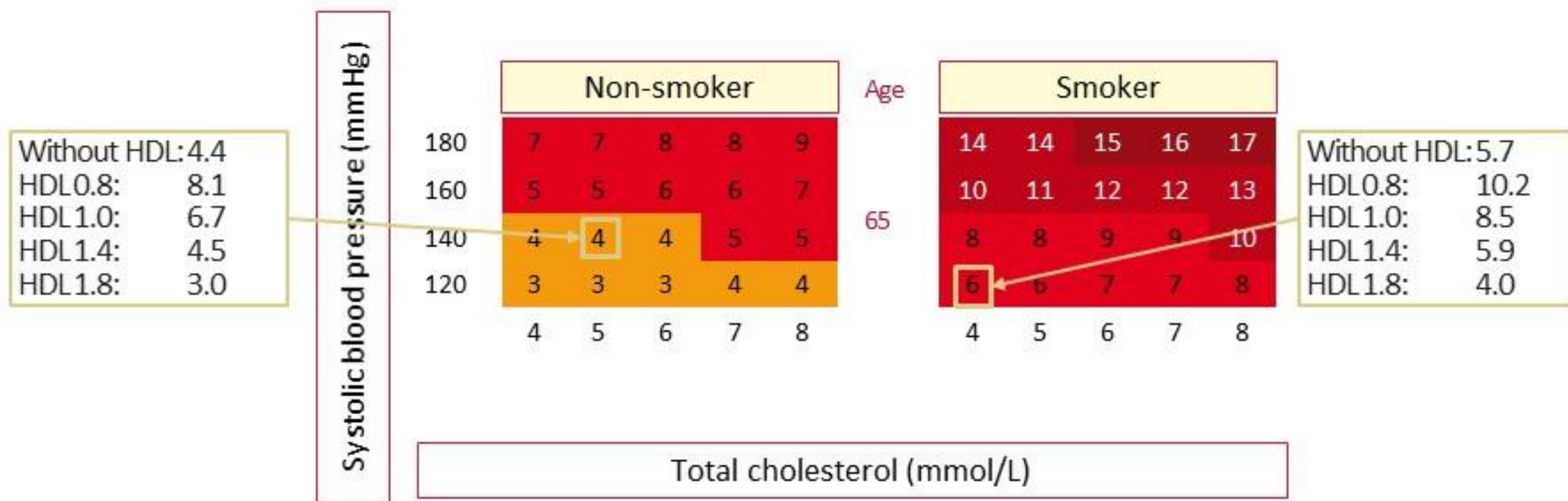
Without HDL:	5.7
HDL 0.8:	10.2
HDL 1.0:	8.5
HDL 1.4:	5.9
HDL 1.8:	4.0

Without HDL:	4.4
HDL 0.8:	8.5
HDL 1.0:	7.0
HDL 1.4:	4.7
HDL 1.8:	3.2

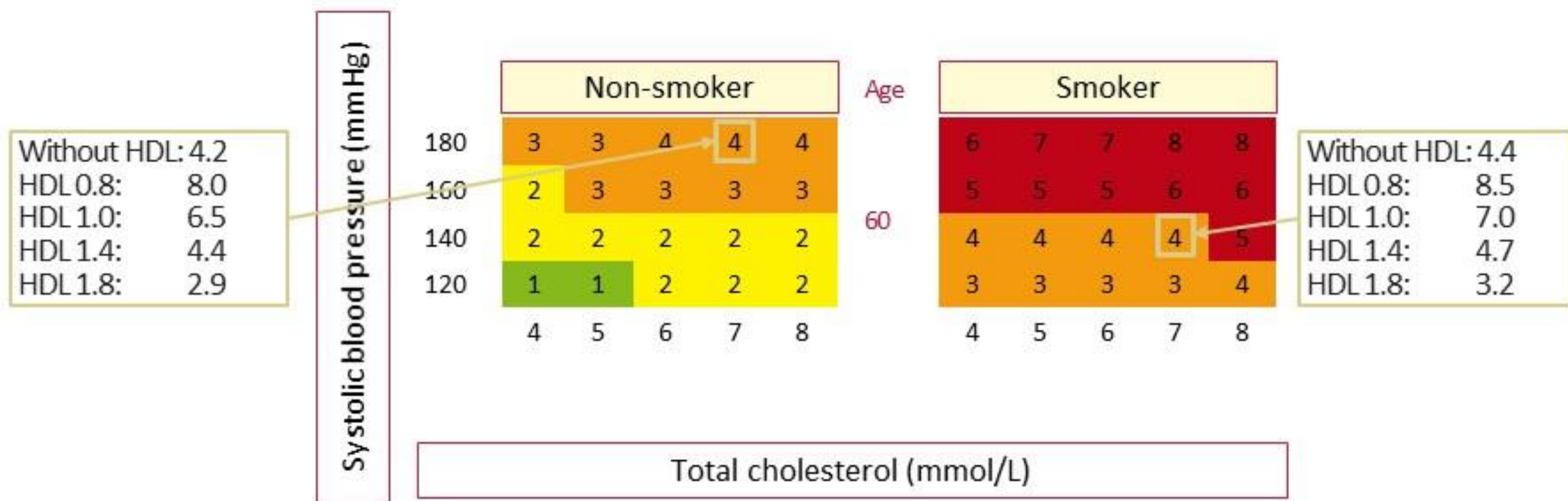
Without HDL:	4.5
HDL 0.8:	8.3
HDL 1.0:	6.9
HDL 1.4:	4.7
HDL 1.8:	3.2

Risk function with high-density lipoprotein cholesterol for women in populations at high cardiovascular disease risk

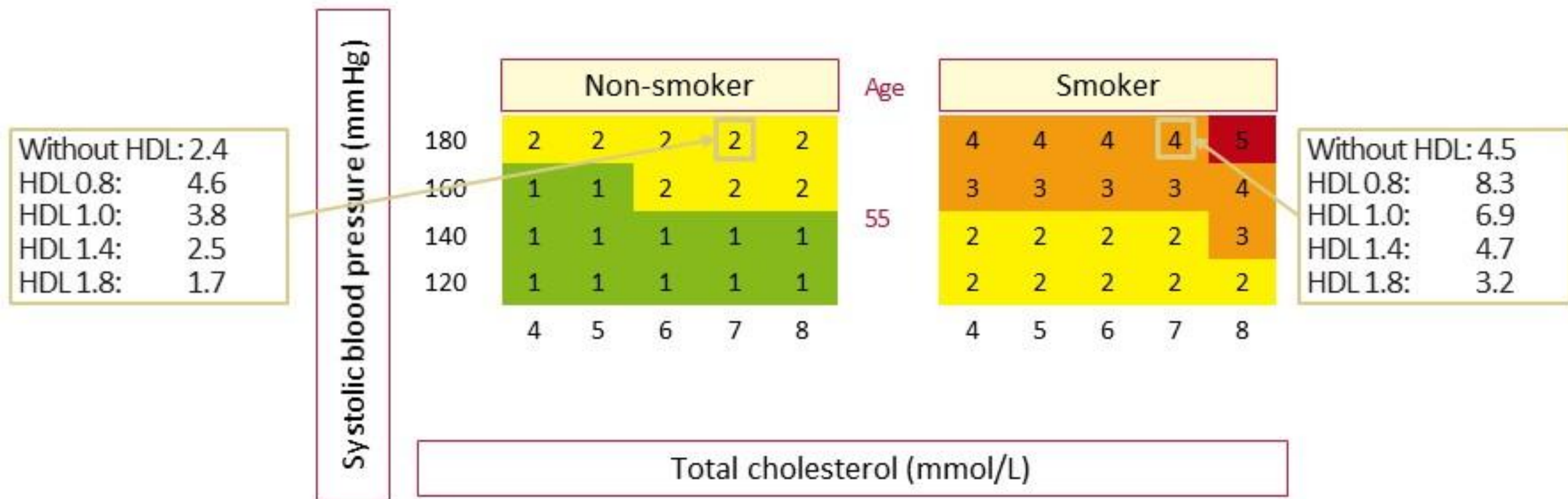
Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk (1)



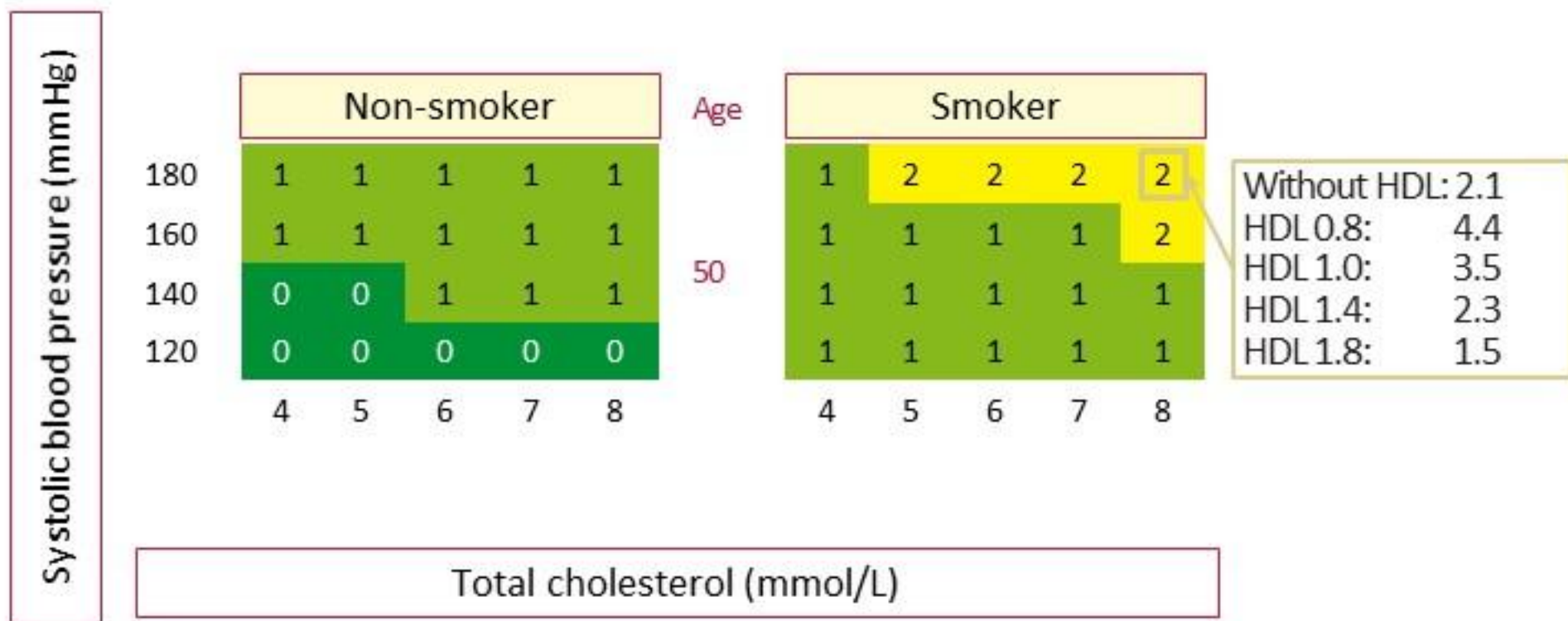
Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk (2)



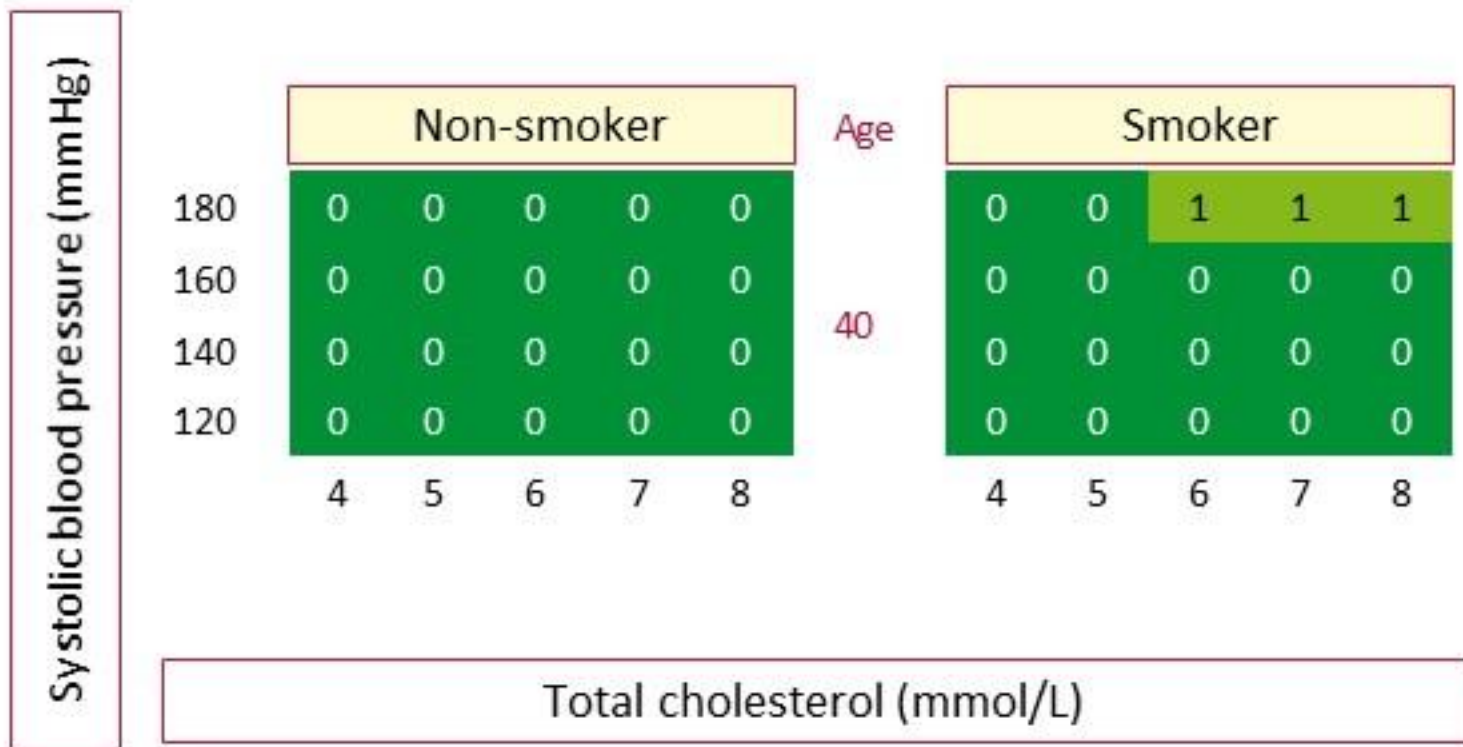
Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk (3)

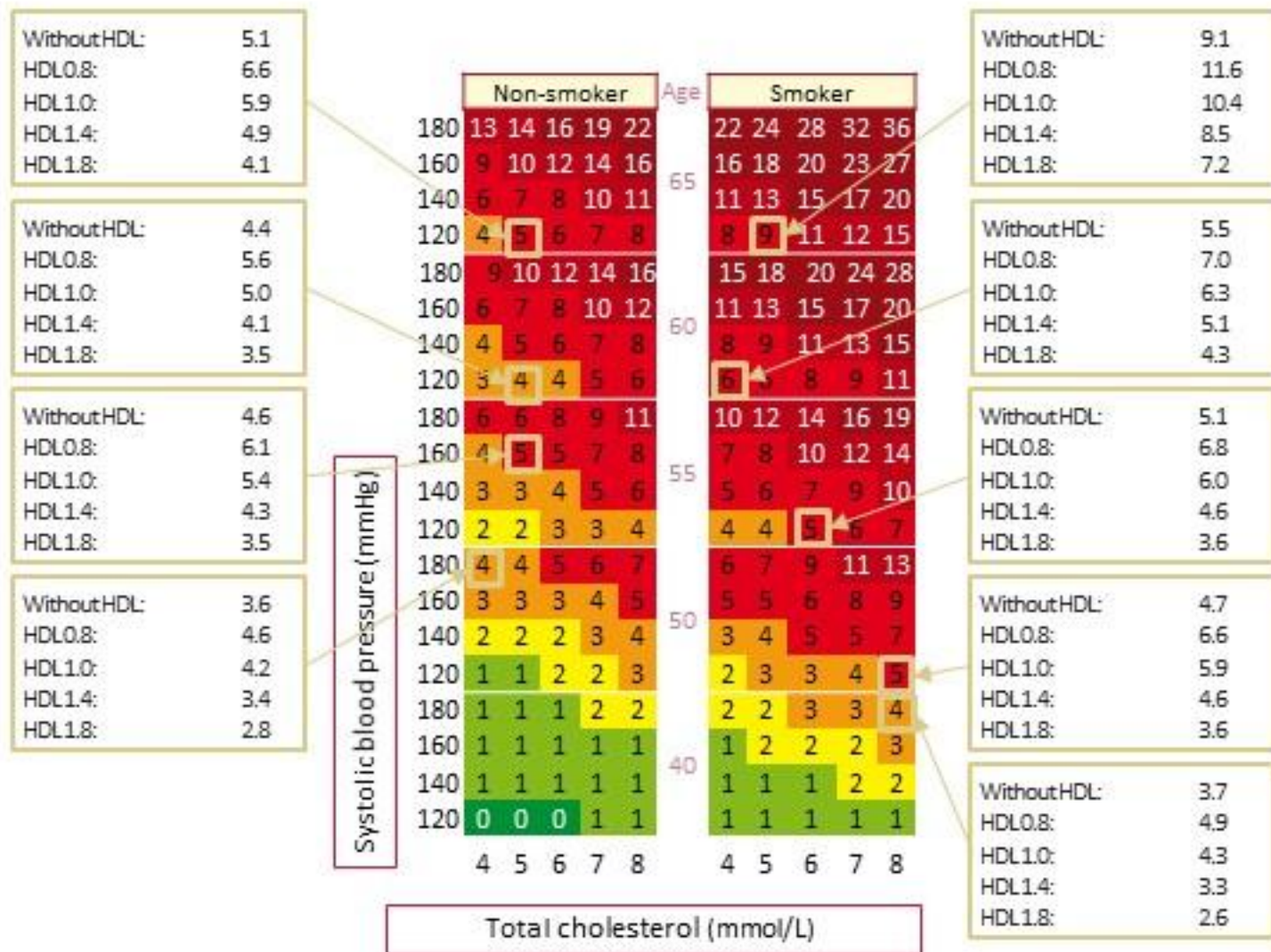


Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk (4)



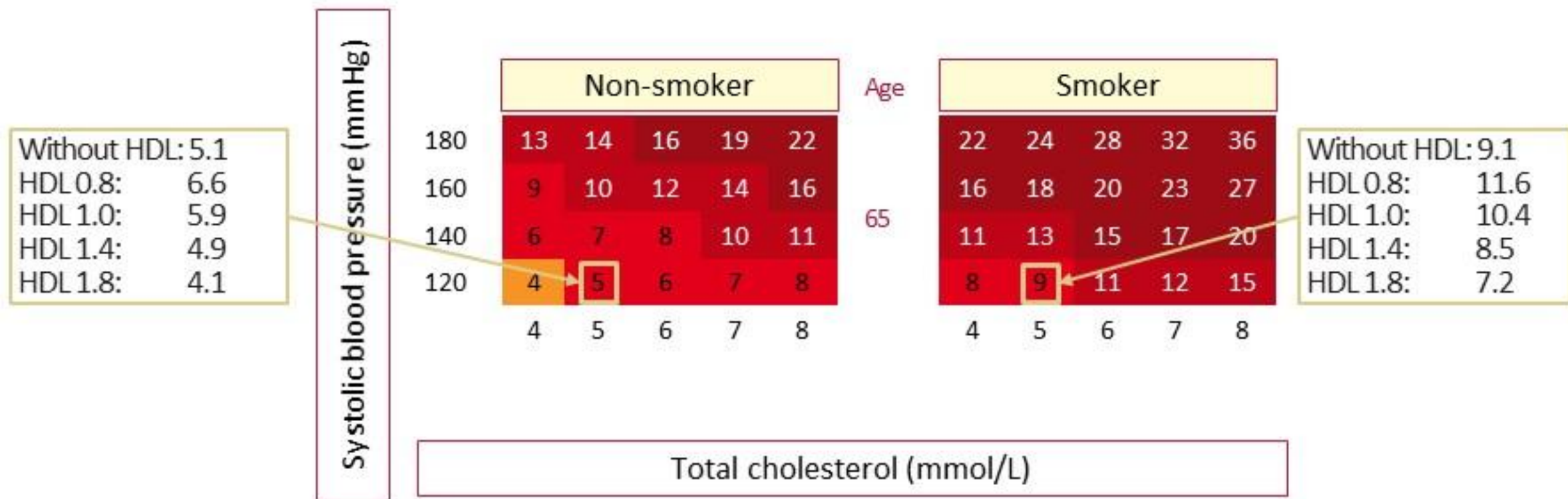
Risk function with high-density lipoprotein (HDL) cholesterol for women in populations at high cardiovascular disease risk (5)



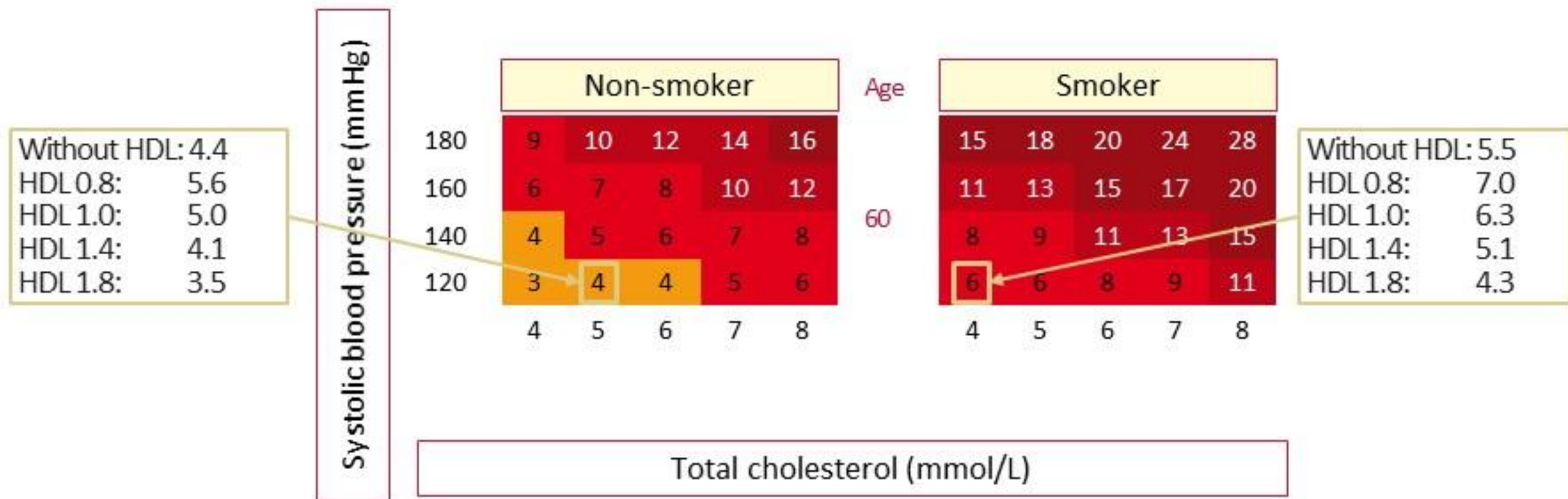


Risk function with high-density lipoprotein cholesterol for men in populations at high cardiovascular disease risk

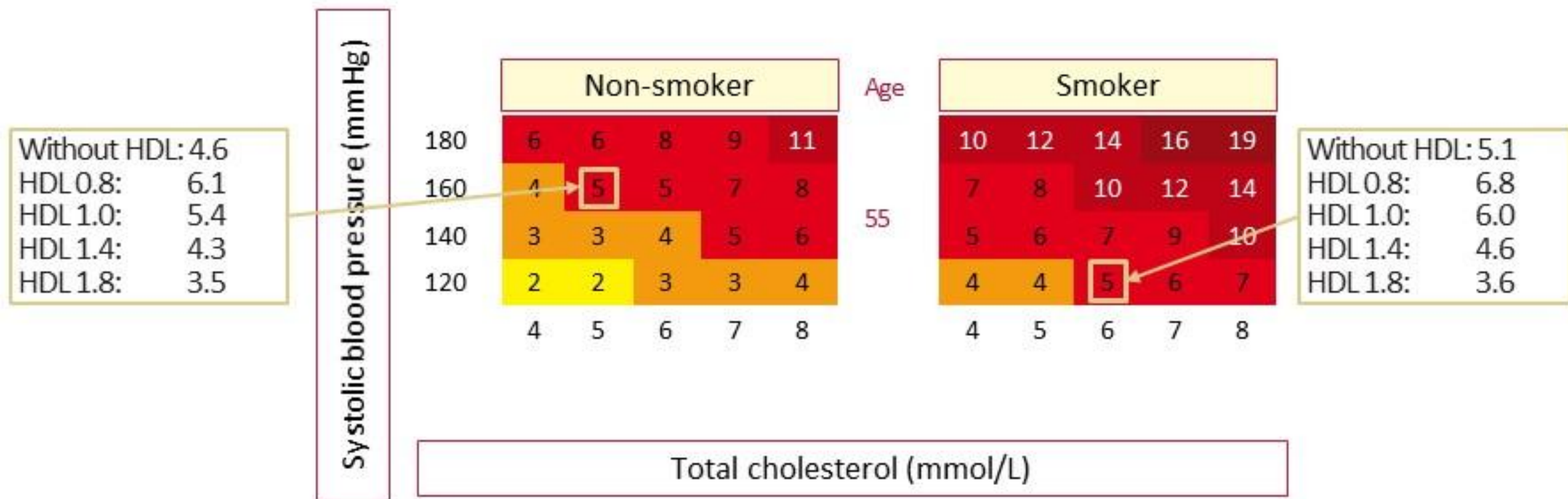
Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk (1)



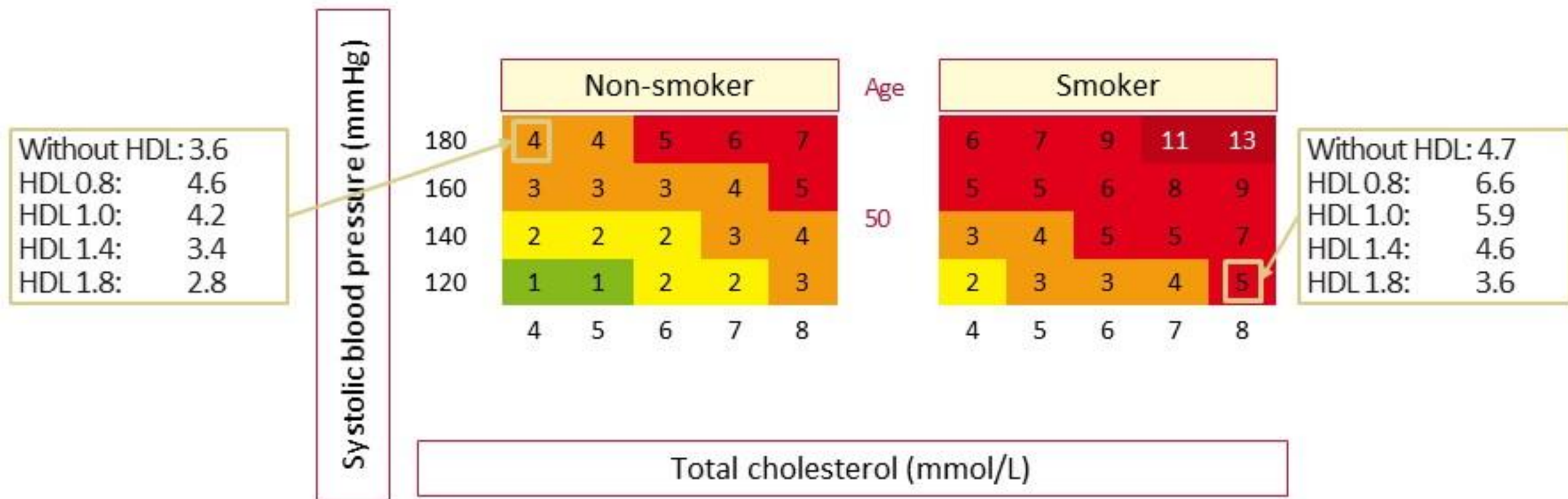
Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk (2)



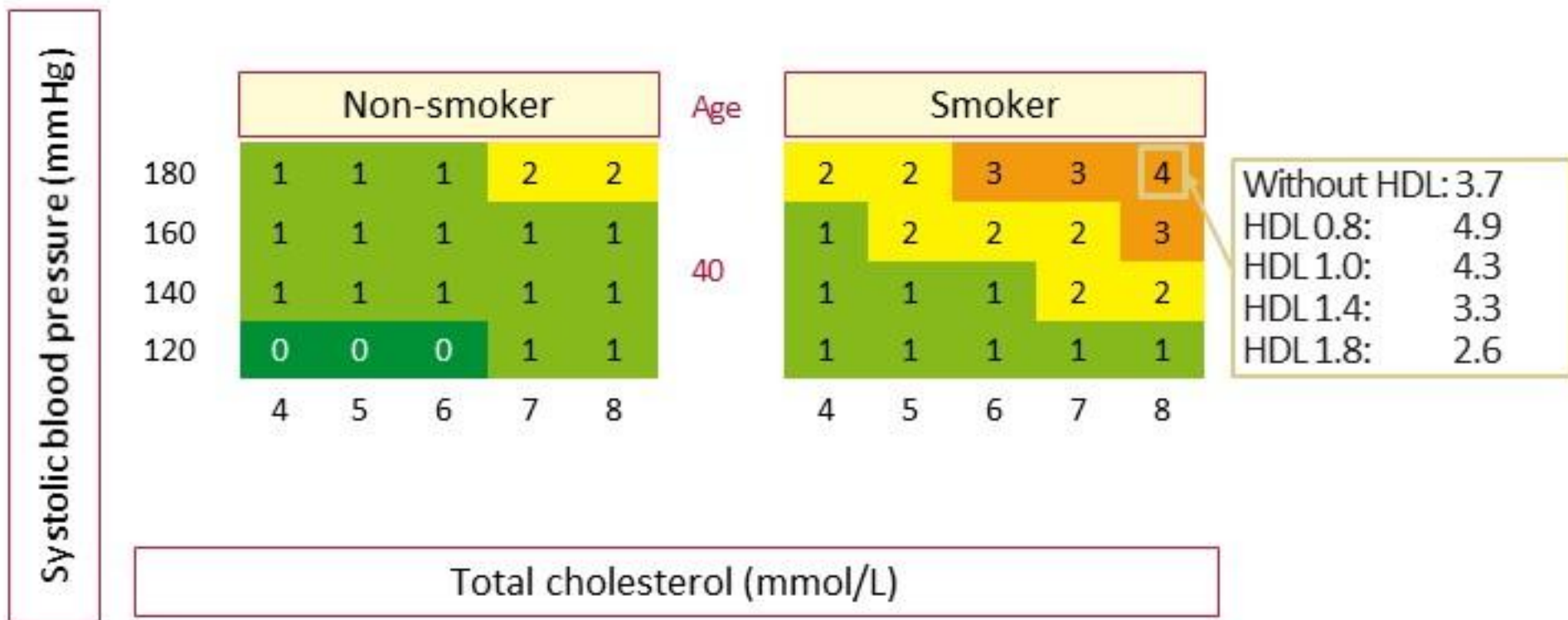
Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk (3)



Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk (4)



Risk function with high-density lipoprotein (HDL) cholesterol for men in populations at high cardiovascular disease risk (5)



Recommendations for cardiovascular disease risk estimation

Recommendations	Class	Level
Total risk estimation using a risk estimation system such as SCORE is recommended for asymptomatic adults >40 years of age without evidence of CVD, DM, CKD, familial hypercholesterolaemia, or LDL-C >4.9 mmol/L (>190 mg/dL).	I	C
It is recommended that high- and very-high-risk individuals are identified on the basis of documented CVD, DM, moderate-to-severe renal disease, very high levels of individual risk factors, FH, or a high SCORE risk. It is recommended that such patients are considered as a priority for advice and management of all risk factors.	I	C
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM or FH.	III	C

How to use the risk estimation charts

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

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

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

The charts may be used to give some indication of the effects of reducing risk factors, given that there is apparently a time lag before the risk reduces. In general, people who stop smoking halve their cumulative risk over a relatively short period of time.

Risk estimation charts for different countries

The **low-risk charts** should be considered for use in Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Netherlands, Norway, Malta, Portugal, Slovenia, Spain, Sweden, Switzerland and United Kingdom.

The **high-risk charts** should be considered for use in Albania, Algeria, Armenia, Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lebanon, Libya, Lithuania, Montenegro, Morocco, Poland, Romania, Serbia, Slovakia, Tunisia and Turkey.

Some countries have a **CVD mortality rate more than 350/100 000**, and the **high-risk chart may underestimate risk**. These are Azerbaijan, Belarus, Bulgaria, Egypt, Georgia, Kazakhstan, Kyrgyzstan, North Macedonia, Republic of Moldova, Russian Federation, Syria, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.

Qualifiers

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

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

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

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

Factors modifying SCORE risks (1)

Social deprivation – the origin of many of the causes of CVD.

Obesity and central obesity as measured by the body mass index and waist circumference, respectively.

Physical inactivity.

Psychosocial stress including vital exhaustion.

Family history of premature CVD (men: <55 years; women: <60 years).

Chronic immune-mediated inflammatory disorder.

Factors modifying SCORE risks (2)

Major psychiatric disorders.

Treatment for human immunodeficiency virus (HIV) infection.

Atrial fibrillation.

Left ventricular hypertrophy.

Chronic kidney disease.

Obstructive sleep apnoea syndrome.

Non-alcoholic fatty liver disease.

Risk estimation: key messages (1)

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

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

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

Risk estimation: key messages (2)

Certain individuals declare themselves to be at high or very-high CVD risk without needing risk scoring and require immediate attention to all risk factors. This is true for patients with documented CVD, diabetes, familial hypercholesterolaemia, chronic kidney disease, carotid or femoral plaques, coronary artery calcium (CAC) score >100, or extreme Lp(a) elevation.

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

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

The total risk approach allows flexibility – if optimal control cannot be achieved with one risk factor, trying harder with the other factors can still reduce risk.

Cardiovascular risk categories (1)

Very-high-risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging.

Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularisation (PCI, CABG and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis) or on carotid ultrasound.

DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

(>20 years). Severe CKD (eGFR <30 mL/min/1.73m²).

A calculated SCORE $\geq 10\%$ for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

Cardiovascular risk categories (2)

High-risk	<p>People with:</p> <ul style="list-style-type: none">Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP \geq180/110mmHg.Patients with FH without other major risk factors.Patients with DM without target organ damage*, with DM duration \geq10 years or another additional risk factors.Moderate CKD (eGFR 30–59 mL/min/1.73m²).A calculated SCORE \geq5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	<p>Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE \geq1% and <5% for 10-year risk of fatal CVD.</p>
Low-risk	<p>Calculated SCORE <1% for 10-year risk of fatal CVD.</p>

*Target organ damage is defined as microalbuminuria, retinopathy or neuropathy

Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease

Recommendations	Class	Level
Arterial (carotid and/or femoral) plaque burden on ultrasonography should be considered as a risk modifier in individuals at low or moderate risk.	IIa	B
CAC score assessment with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low or moderate risk.	IIb	B

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Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

Total CV risk (SCORE) %		Untreated LDL-C levels					
		<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥ 190 mg/dL)
Primary Prevention	<1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥1 to <5, or moderate risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A
	≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
Secondary Prevention	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
	Class ^a /Level ^b	IIa/B	IIa/A	I/A	I/A	I/A	I/A
	Very-high risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	I/A	I/A	I/A	I/A	I/A	

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Total CV risk (SCORE)%	Untreated LDL-C levels					
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Primary Prevention						
< 1 Low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A	IIa/A
≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A

Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels (1)

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Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels (2)

≥5 to <10, or high-risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/B	IIa/A	I/A	I/A	I/A	I/A
Secondary Prevention						
Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	I/A	I/A	I/A	I/A	I/A

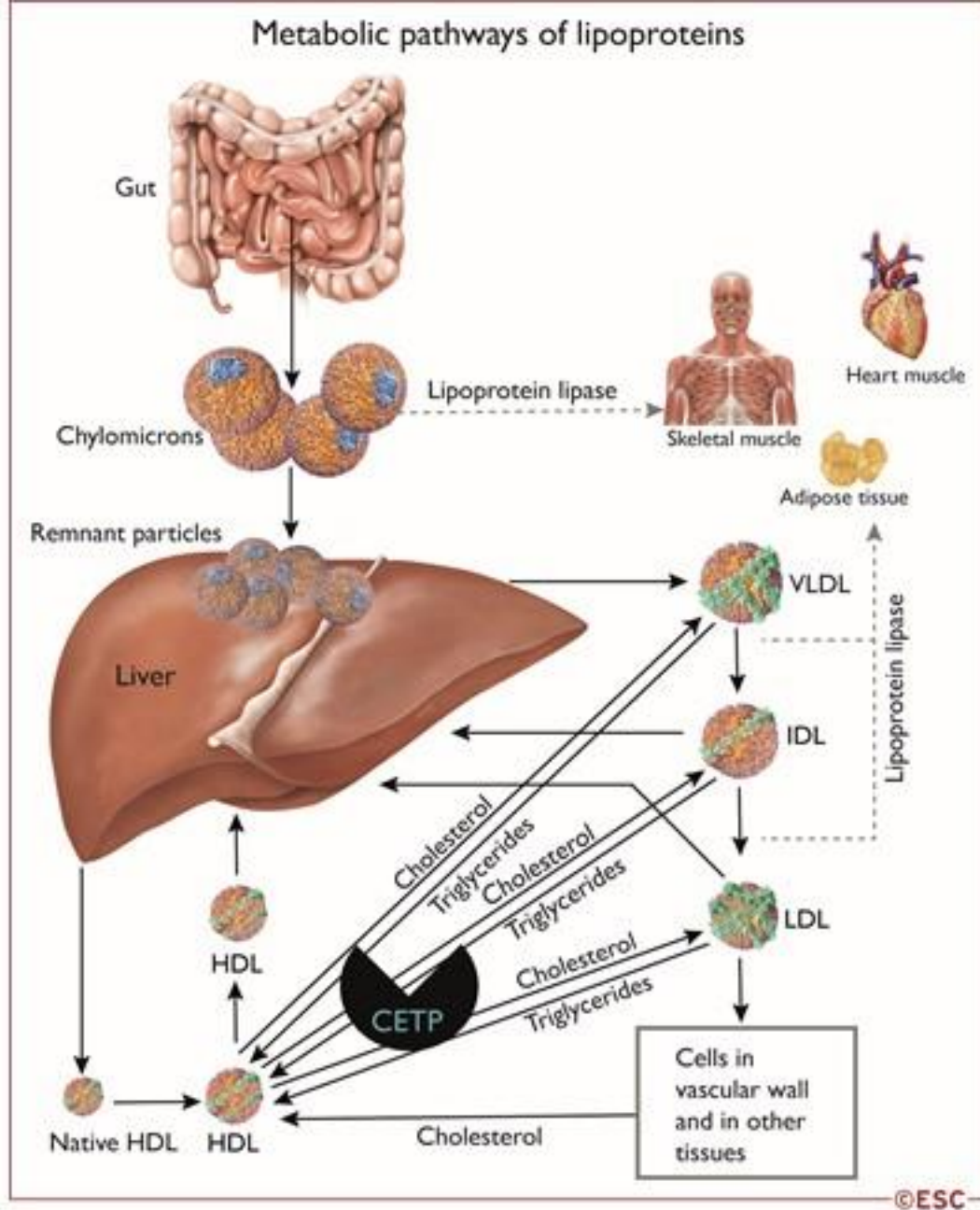
Intervention strategies as a function of total cardiovascular risk and untreated low-density lipoprotein cholesterol levels

Total CV risk (SCORE)%	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Primary Prevention						
<1 Low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	I/C	I/C	IIa/A	IIa/A
≥1 to <5, or moderate risk (see Table 1)	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	I/C	I/C	IIa/A	IIa/A	IIa/A	IIa/A

Total CV risk (SCORE)%	Untreated LDL-C levels					
	<1.4mmol/L (55 mg/dL)	1.4to <1.8mmol/L (55 to <70mg/dL)	1.8to <2.6mmol/L (70to <100mg/dL)	2.6to <3.0mmol/L (100to <16mg/dL)	3.0to <4.9mmol/L (116to <190mg/dL)	≥4.9mmol/L (≥190mg/dL)
≥5 to <10, or high-risk (see Table 1)	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	IIa/A	IIa/A	I/A	I/A	I/A
≥10, or at very-high-risk due to a risk condition (see Table 1)	Lifestyle advice	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention	Lifestyle Intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/B	IIa/A	I/A	I/A	I/A	I/A

Total CV risk (SCORE)%	Untreated LDL-C levels					
	<1.4 mmol/L (55 mg/dL)	1.4 to <1.8 mmol/L (55 to <70 mg/dL)	1.8 to <2.6 mmol/L (70 to <100 mg/dL)	2.6 to <3.0 mmol/L (100 to <116 mg/dL)	3.0 to <4.9 mmol/L (116 to <190 mg/dL)	≥4.9 mmol/L (≥190 mg/dL)
Secondary Prevention						
Very-high-risk	Lifestyle intervention, consider adding drug if uncontrolled	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention	Lifestyle intervention and concomitant drug intervention
Class ^a /Level ^b	IIa/A	I/A	I/A	I/A	I/A	I/A

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Lipoprotein transport and metabolism

Recommendations for lipid analyses for cardiovascular disease risk estimation (1)

Recommendations	Class	Level
TC is to be used for the estimation of total CV risk by means of the SCORE system.	I	C
HDL-C analysis is recommended to further refine risk estimation using the online SCORE system.	I	C
LDL-C analysis is recommended as the primary lipid analysis for screening, diagnosis and management.	I	C
TG analysis is recommended as a part of the routine lipid analysis.	I	C

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Recommendations for lipid analyses for cardiovascular disease risk estimation (2)

Recommendations	Class	Level
Non-HDL-C evaluation is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or very low LDL-C.	I	C
ApoB analysis is recommended for risk assessment, particularly in people with high TG, diabetes, obesity or metabolic syndrome, or very low LDL-C. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis and management, and may be preferred over non-HDL-C in people with high TG, diabetes, obesity or very low LDL-C.	I	C

Recommendations for lipid analyses for cardiovascular disease risk estimation (3)

Recommendations	Class	Level
Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia.	IIa	C
Lp(a) should be considered in selected patients with a family history of premature CVD, and for reclassification in people who are borderline between moderate and high-risk.	IIa	C

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Treatment targets and goals for cardiovascular disease prevention (1)

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on whole grain products, vegetables, fruit and fish.
Physical activity	3.5–7 hours moderately vigorous physical activity per week or 30–60 min most days.
Body weight	BMI 20–25 kg/m ² , waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg ^a

^a Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.

Treatment targets and goals for cardiovascular disease prevention (2)

LDL-C

Very-high-risk in primary or secondary prevention

A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline^b and an LDL-C goal of <1.4mmol/L (<55 mg/dL).

No current statin use: this is likely to require high-intensity LDL-lowering therapy.

Current LDL-lowering treatment: an increased treatment intensity is required.

High risk: A therapeutic regimen that achieves at least a 50% LDL-C reduction from baseline^b and an LDL-C goal of <1.8mmol/L (<70 mg/dL).

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^bThe term 'baseline' refers to the LDL-C level in a person not taking any lipid lowering medication, or to the extrapolated baseline value for those who are on current treatment.

Treatment targets and goals for cardiovascular disease prevention (3)

LDL-C	Moderate risk: A goal of <2.6 mmol/L (<100 mg/dL). Low risk: A goal of <3.0 mmol/L (<116 mg/dL)
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6 and 3.4 mmol/L (<85, 100 and 130 mg/dL) for very-high-, high- and moderate-risk people, respectively.
Apolipoprotein B	ApoB secondary goals are <65, 80 and 100 mg/dL for very-high-, high- and moderate-risk people, respectively.
Triglycerides	No goal but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Recommendations for treatment goals for low-density lipoprotein cholesterol (1)

Recommendations	Class	Level
In secondary prevention patients at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention, for individuals at very-high risk but without FH, an LDL-C reduction of at least 50% from baseline ^d and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	Ia	C

The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

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Recommendations for treatment goals for low-density lipoprotein cholesterol (2)

Recommendations	Class	Level
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.	IIb	B
In patients at high risk, an LDL-C reduction of at least 50% from baseline ^d and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.	I	A

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The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

Recommendations for treatment goals for low-density lipoprotein cholesterol (3)

Recommendations	Class	Level
In individuals at moderate risk ^c , an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	Ila	A
In individuals at low risk ^c an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.	Ilb	A

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^c For definitions see Table 1.

Impact of specific lifestyle changes on lipid levels (1)

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
Avoid dietary trans fat	++	A
Reduce dietary saturated fat	++	A
Increase dietary fibre	++	A
Use functional foods enriched with phytosterols	++	A

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Impact of specific lifestyle changes on lipid levels (2)

EAS



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of Cardiology

	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TC and LDL-C levels		
Use red yeast rice nutraceuticals	++	A
Reduce excessive body weight	++	A
Reduce dietary cholesterol	+	B
Increase habitual physical activity	+	B

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Impact of specific lifestyle changes on lipid levels (3)

EAS



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	Magnitude of the effect	Level of evidence
Lifestyle interventions to reduce TG-rich lipoprotein levels		
Reduce excessive body weight	+	A
Reduce alcohol intake	+++	A
Increase habitual physical activity	++	A
Reduce total amount of dietary carbohydrate	++	A
Use supplements of n-3 polyunsaturated fat	++	A
Reduce intake of mono- and disaccharides	++	B
Replace saturated fat with mono- or polyunsaturated fat	+	B

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Impact of specific lifestyle changes on lipid levels (4)

	Magnitude of the effect	Level of evidence
Lifestyle interventions to increase HDL-C levels		
Avoid dietary trans fat	++	A
Increase habitual physical activity	+++	A
Reduce excessive body weight	++	A
Reduce dietary carbohydrates and replace them with unsaturated fat	++	A
Modest consumption in those who take alcohol may be continued	++	B
Quit smoking	+	B

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Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile (1)

Food choices	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cereals	Whole grains	Refined bread, rice and pasta, biscuits, corn flakes	Pastries, muffins, pies, croissants
Vegetables	Raw and cooked vegetables	Potatoes	Vegetables prepared in butter or cream

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Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile (2)

Food choices	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Legumes	Lentils, beans, fava beans, peas, chickpeas, soybean		
Fruit	Fresh or frozen fruit	Dried fruit, jelly, jam, canned fruit, sorbets, popsicles, fruit juice	
Sweets and sweeteners	Non-caloric sweeteners	Sucrose, honey, chocolate, candies	Cakes, ice creams, fructose, soft drinks

Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile (3)

Food choices	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Meat and fish	Lean and oily fish, poultry without skin	Lean cuts of beef, lamb, pork or veal, seafood, shellfish	Sausages, salami, bacon, spare ribs, hot dogs, organ meats
Dairy food and eggs	Skim milk and yogurt	Low-fat milk, low-fat cheese and other milk products, eggs	Regular cheese, cream, whole milk and yogurt

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Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile (4)

Food choices	To be preferred	To be used with moderation	To be chosen occasionally in limited amounts
Cooking fat and dressings	Vinegar, mustard, fat-free dressings	Olive oil, non-tropical vegetable oils, soft margarines, salad dressing, mayonnaise, ketchup	Trans fats and hard margarines (better to avoid them), palm and coconut oils, butter, lard, bacon fat
Nuts/seeds		All, unsalted (except coconut)	Coconut
Cooking procedures	Grilling, boiling, steaming	Stir-frying, roasting	Frying

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Summary of lifestyle measures and healthy food choices for managing total cardiovascular risk (1)

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

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

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

Foods rich in trans fatty acids should be avoided totally; foods rich in saturated fatty acids (SFAs) (tropical oils, fatty or processed meat, sweets, cream, butter, regular cheese) should be replaced with the above foods and with monounsaturated fat (extra virgin olive oil) and polyunsaturated fat (non-tropical vegetable oils) in order to keep SFA intake <10% (<7% in the presence of high plasma cholesterol values).

Summary of lifestyle measures and healthy food choices for managing total cardiovascular risk (2)

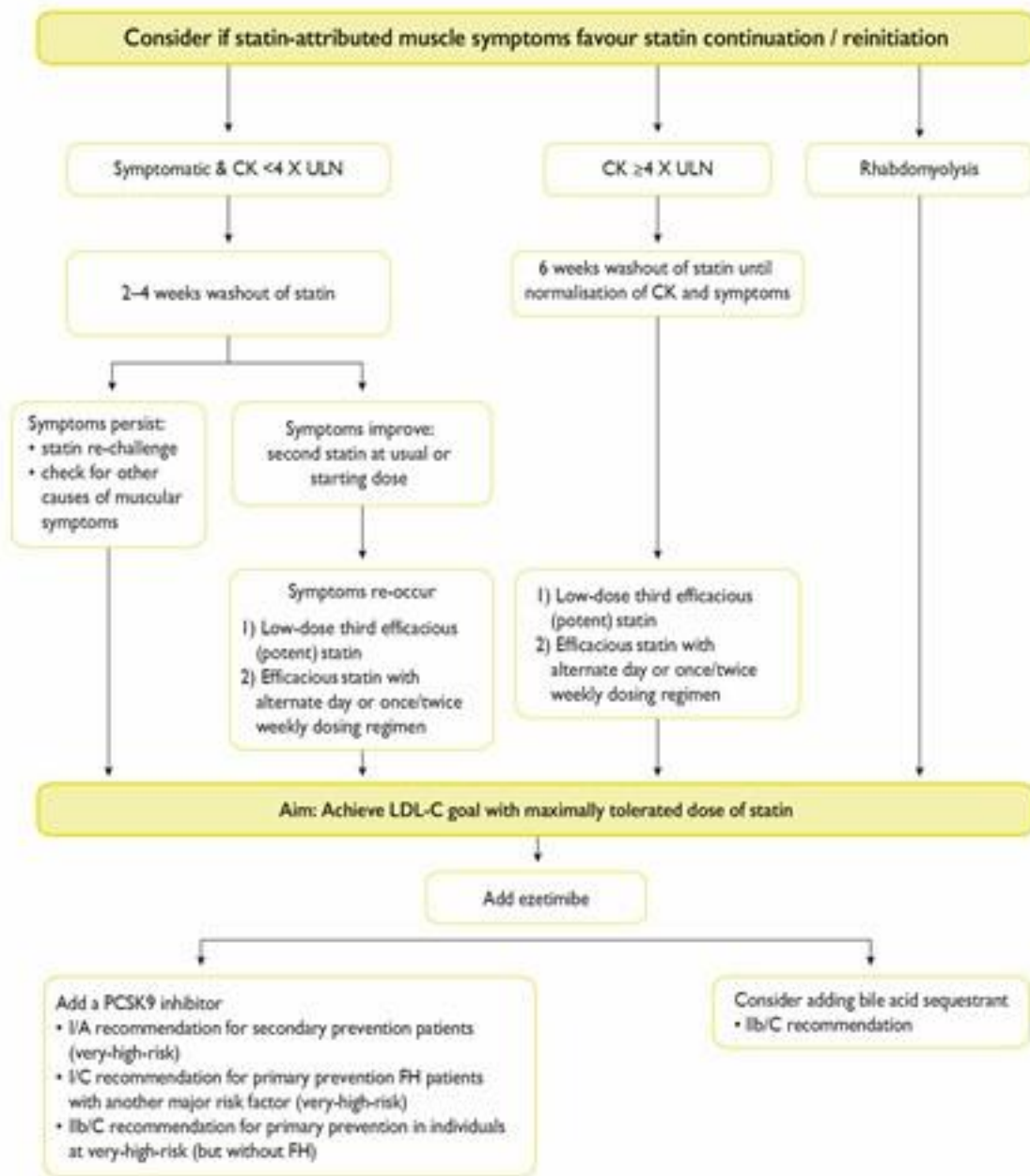
Salt intake should be reduced to <5 g/day by avoiding table salt and limiting salt in cooking, and by choosing fresh or frozen unsalted foods; many processed and convenience foods, including bread, are high in salt.

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

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

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

Use of and exposure to tobacco products should be avoided.



Algorithm for treatment of muscular symptoms during statin treatment

Consider if statin-attributed muscle symptoms
favour statin continuation / reinitiation

Symptomatic &
CK <4 X ULN

CK ≥4 X ULN

Rhabdomyolysis

2–4 weeks
washout of statin

6 weeks washout of statin
until normalisation of CK and
symptoms

Symptoms
persist:
• statin re-
challenge
• check for
other causes
of muscular
symptoms

Symptoms
improve:
second statin
at usual or
starting dose

Symptoms re-occur
1) Low-dose third
efficacious
(potent) statin
2) Efficacious statin
with alternate day
or once/twice
weekly dosing
regimen

1) Low-dose third
efficacious
(potent) statin
2) Efficacious statin
with alternate day
or once/twice
weekly dosing
regimen

Algorithm for treatment of muscular symptoms during statin treatment (1)

Aim: Achieve LDL-C goal with maximally tolerated dose of statin

Add ezetimibe

Add a PCSK9 inhibitor

- I/A recommendation for secondary prevention patients (very-high-risk)
- I/C recommendation for primary prevention FH patients with another major risk factor (very-high risk)
- IIb/C recommendation for primary prevention in individuals at very-high-risk (but without FH)

Consider adding bile acid sequestrant

- IIb/C recommendation

Algorithm for treatment of muscular symptoms during statin treatment (2)

Physical and chemical characteristics of human plasma lipoproteins

	Density (g/mL)	Diameter (nm)	TGs (%)	Cholesteryl esters (%)	PLs(%)	Cholesterol (%)	Apolipoproteins	
							Major	Others
Chylomicrons	<0.95	80-100	90-95	2-4	2-6	1	ApoB-48	ApoA-I, A-II, A-IV, A-V
VLDL	0.95-1.006	30-80	50-65	8-14	12-16	4-7	ApoB-100	ApoA-I, C-II, C-III, E, A-V
IDL	1.006-1.019	25- 30	25- 40	20- 35	16- 24	7- 11	ApoB-100	ApoC-II, C-III, E
LDL	1.019-1.063	20- 25	4- 6	34- 35	22- 26	6- 15	ApoB-100	
HDL	1.063-1.210	8-13	7	10-20	55	55	ApoA-I	ApoA-II, C-III, E, M
Lp(a)	1.006-1.125	25-30	4-8	35-46	17-24	6-9	Apo(a)	ApoB-100

Recommendations for pharmacological low-density lipoprotein cholesterol lowering (1)

Recommendations	Class	Level
It is recommended to prescribe a high-intensity statin up to the highest tolerated dose to reach the goals ^c set for the specific level of risk.	I	A
If the goals ^c are not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.	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 statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C

^c For definitions see Full Text.

Recommendations for pharmacological low-density lipoprotein cholesterol lowering (2)

Recommendations	Class	Level
For secondary prevention, patients at very-high risk not achieving their goal ^c on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal on a maximum tolerated dose of statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), ezetimibe should be considered.	Ila	C

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Recommendations for pharmacological low-density lipoprotein cholesterol lowering (3)

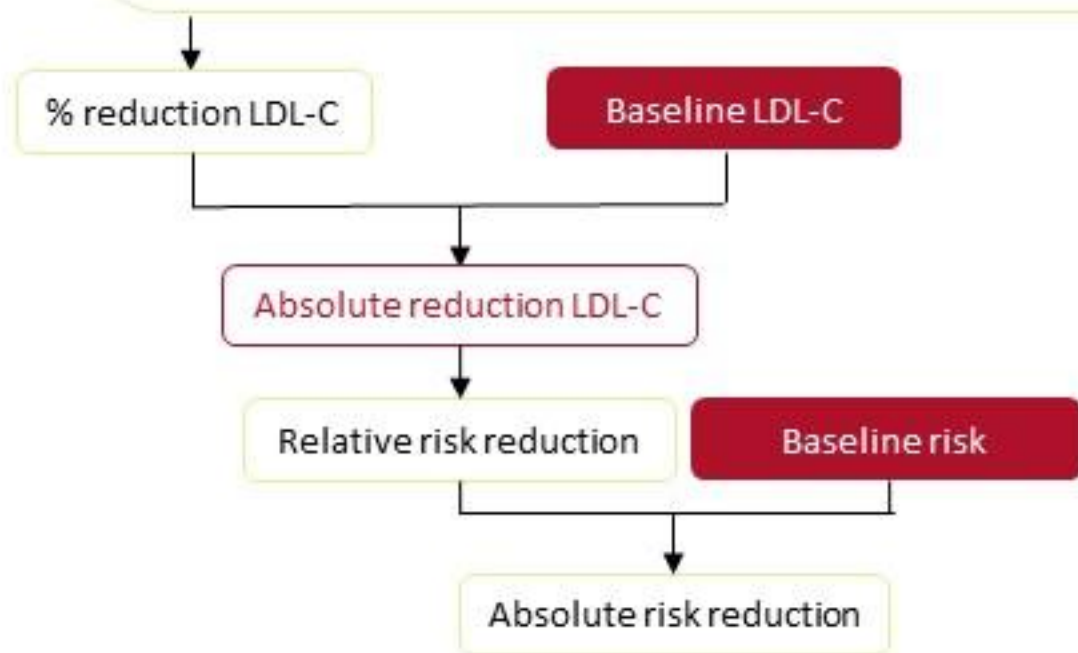
Recommendations	Class	Level
If a statin-based regimen is not tolerated at any dosage (even after re-challenge), a PCSK9 inhibitor added to ezetimibe may also be considered.	IIb	C
If the goal ^f is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

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^f For definitions see Full Text.

Intensity of lipid lowering treatment

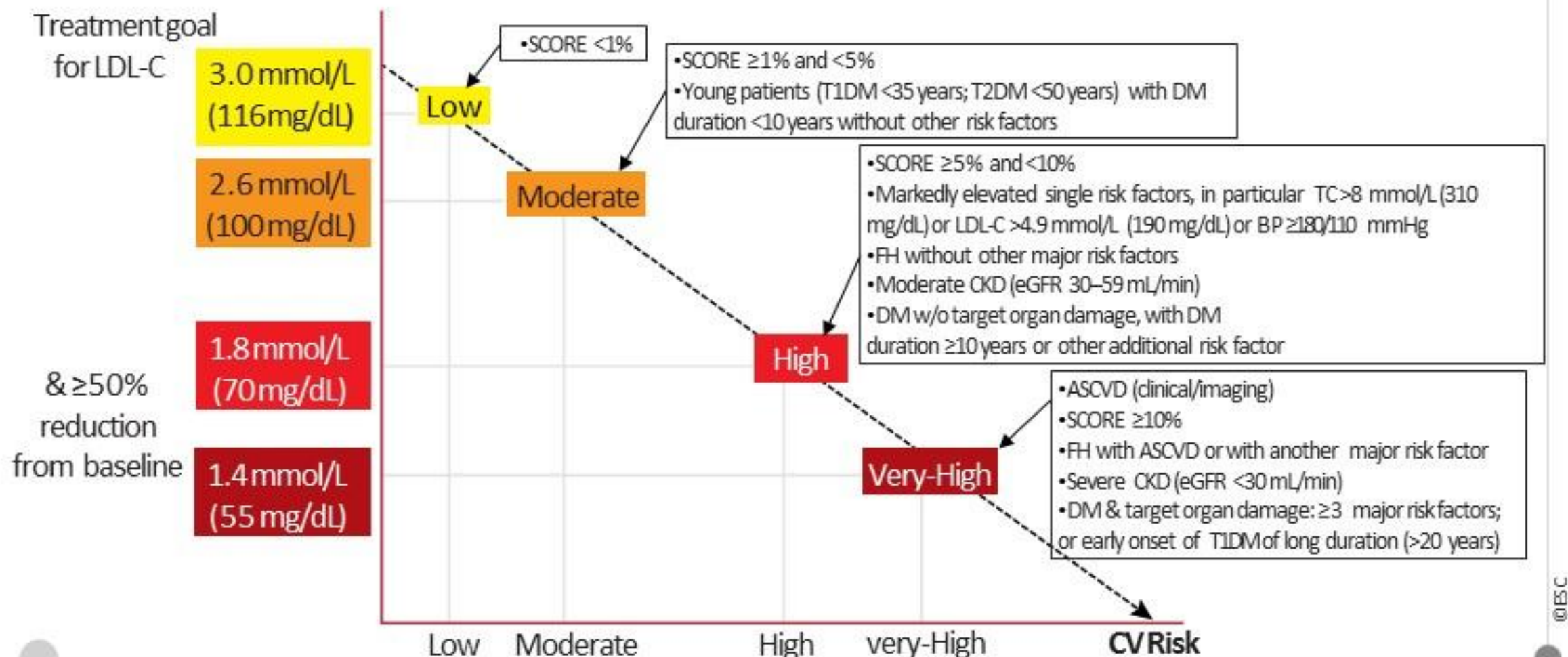
Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

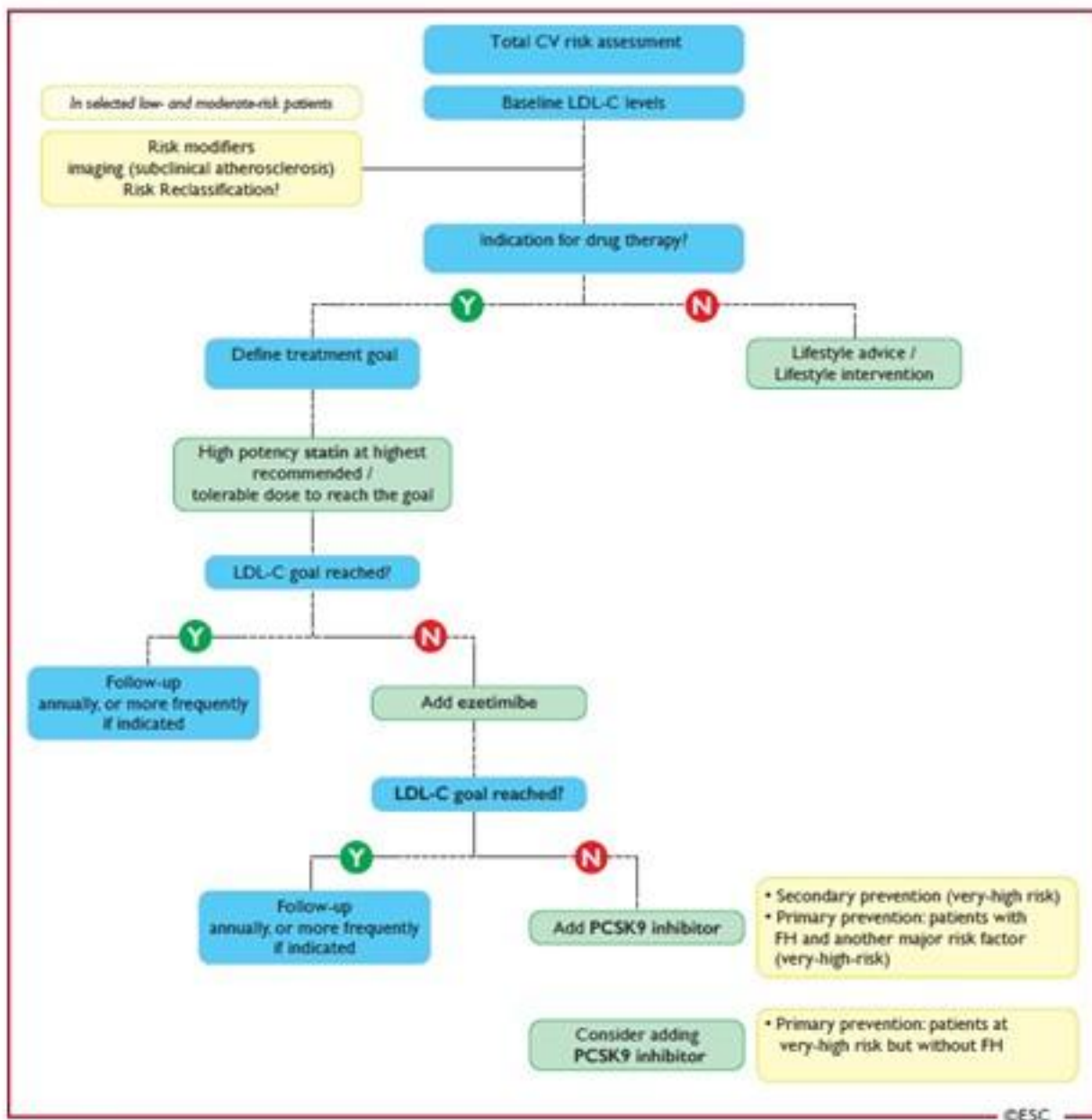


Expected clinical benefit of low-density lipoprotein cholesterol lowering therapies

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

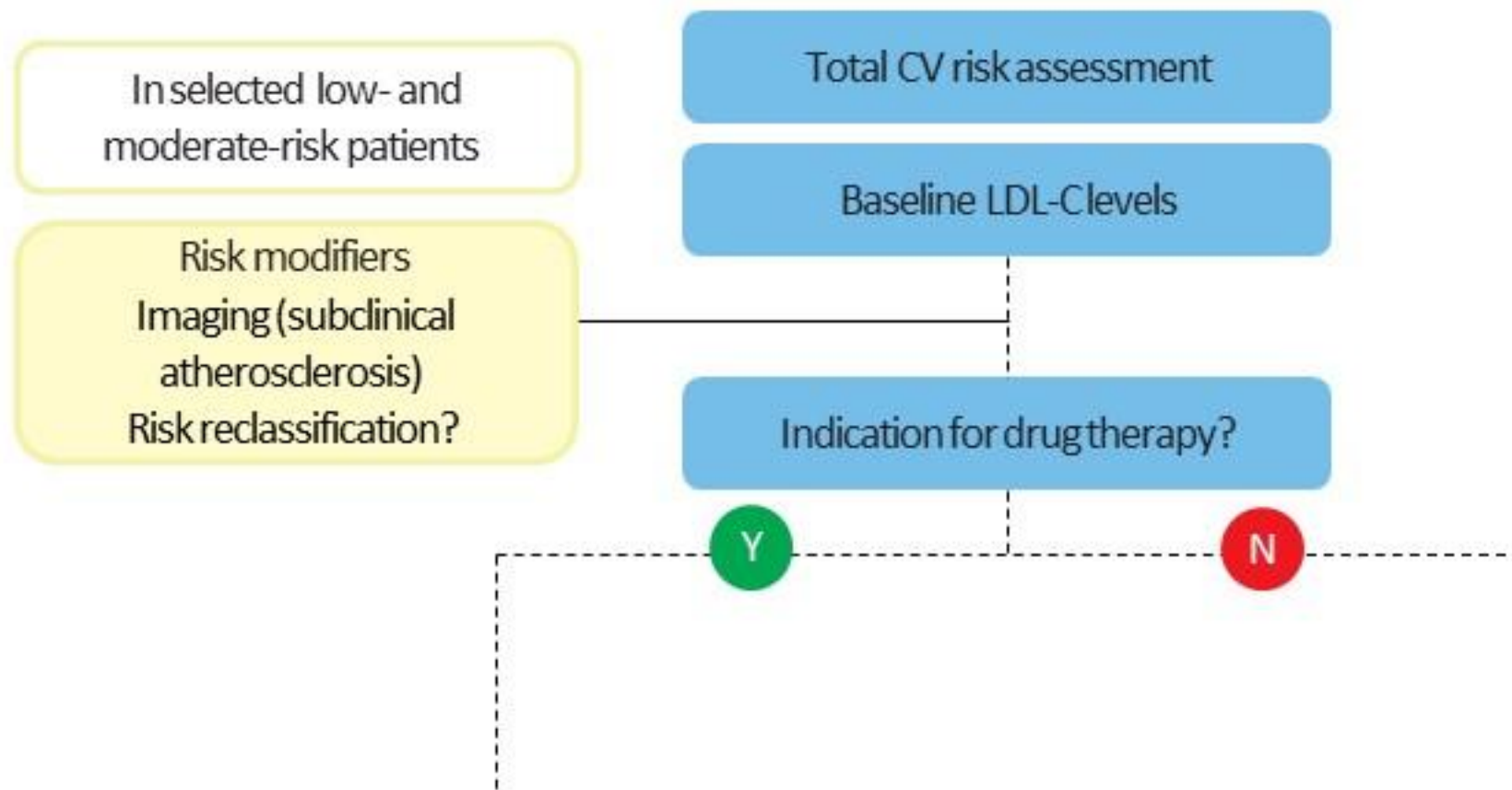
Central Illustration Upper panel Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



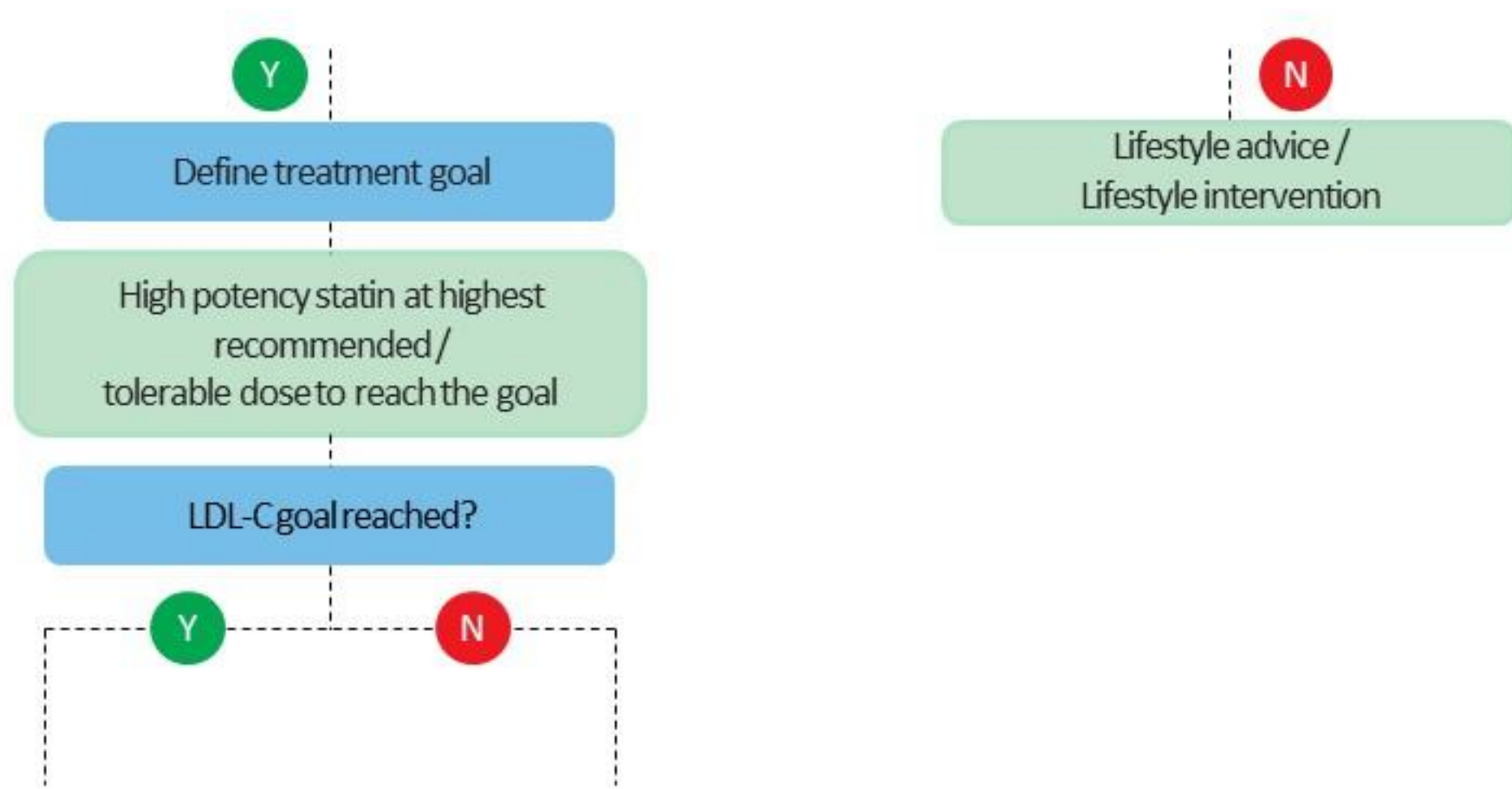


Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering

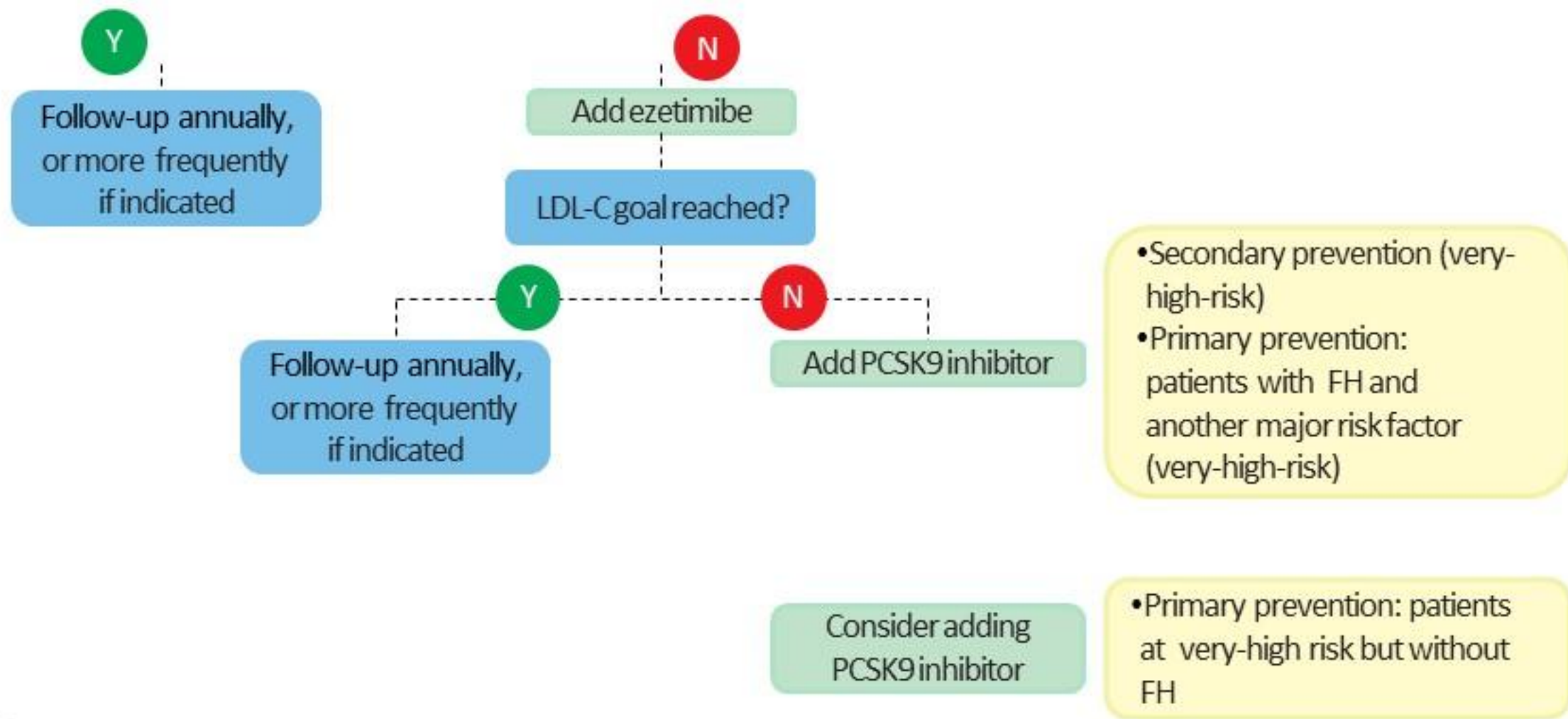
Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (1)



Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (2)



Central Illustration Lower panel: Treatment algorithm for pharmacological LDL-C lowering (3)



Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach

LDL-C, mmol/L (mg/dL)	Reduction obtainable with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high-intensity statin
	Plus ezetimibe		Plus ezetimibe		
4.5	3.2	2.5	2.3	1.6	0.9
(175)	(123)	(96)	(88)	(61)	(35)
4.3	3.0	2.4	2.2	1.5	0.9
(165)	(116)	(91)	(83)	(58)	(33)
4.0	2.8	2.2	2.0	1.4	0.8
(155)	(109)	(85)	(78)	(54)	(31)
3.7	2.6	2.0	1.9	1.3	0.7
(145)	(102)	(80)	(73)	(51)	(29)
3.5	2.5	1.9	1.8	1.2	0.7
(135)	(95)	(74)	(68)	(47)	(27)
3.2	2.2	1.8	1.6	1.1	0.6
(125)	(88)	(69)	(63)	(44)	(25)
3.0	2.1	1.7	1.5	1.1	0.6
(116)	(81)	(63)	(58)	(40)	(23)
2.7	1.9	1.5	1.4	0.9	0.5
(105)	(74)	(58)	(53)	(37)	(21)
2.5	1.8	1.4	1.3	0.9	0.5
(95)	(67)	(52)	(48)	(33)	(19)
2.2	1.5	1.2	1.1	0.8	0.4
(85)	(60)	(47)	(43)	(30)	(17)
1.9	1.3	1.0	1.0	0.7	0.4
(75)	(53)	(41)	(38)	(26)	(15)

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

Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (1)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high-intensity statin
		Plus ezetimibe		Plus ezetimibe	
4.5 (175)	3.2 (123)	2.5 (96)	2.3 (88)	1.6 (61)	0.9 (35)
4.3 (165)	3.0 (116)	2.4 (91)	2.2 (83)	1.5 (58)	0.9 (33)

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Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (2)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high- intensity statin
		Plus ezetimibe		Plus ezetimibe	
4.0 (155)	2.8 (109)	2.2 (85)	2.0 (78)	1.4 (54)	0.8 (31)
3.7 (145)	2.6 (102)	2.0 (80)	1.9 (73)	1.3 (51)	0.7 (29)

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Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (3)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high- intensity statin
		Plus ezetimibe		Plus ezetimibe	
3.5 (135)	2.5 (95)	1.9 (74)	1.8 (68)	1.2 (47)	0.7 (27)
3.2 (125)	2.2 (88)	1.8 (69)	1.6 (63)	1.1 (44)	0.6 (25)

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Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (4)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high- intensity statin
		Plus ezetimibe		Plus ezetimibe	
3.0 (116)	2.1 (81)	1.7 (63)	1.5 (58)	1.1 (40)	0.6 (23)
2.7 (105)	1.9 (74)	1.5 (58)	1.4 (53)	0.9 (37)	0.5 (21)

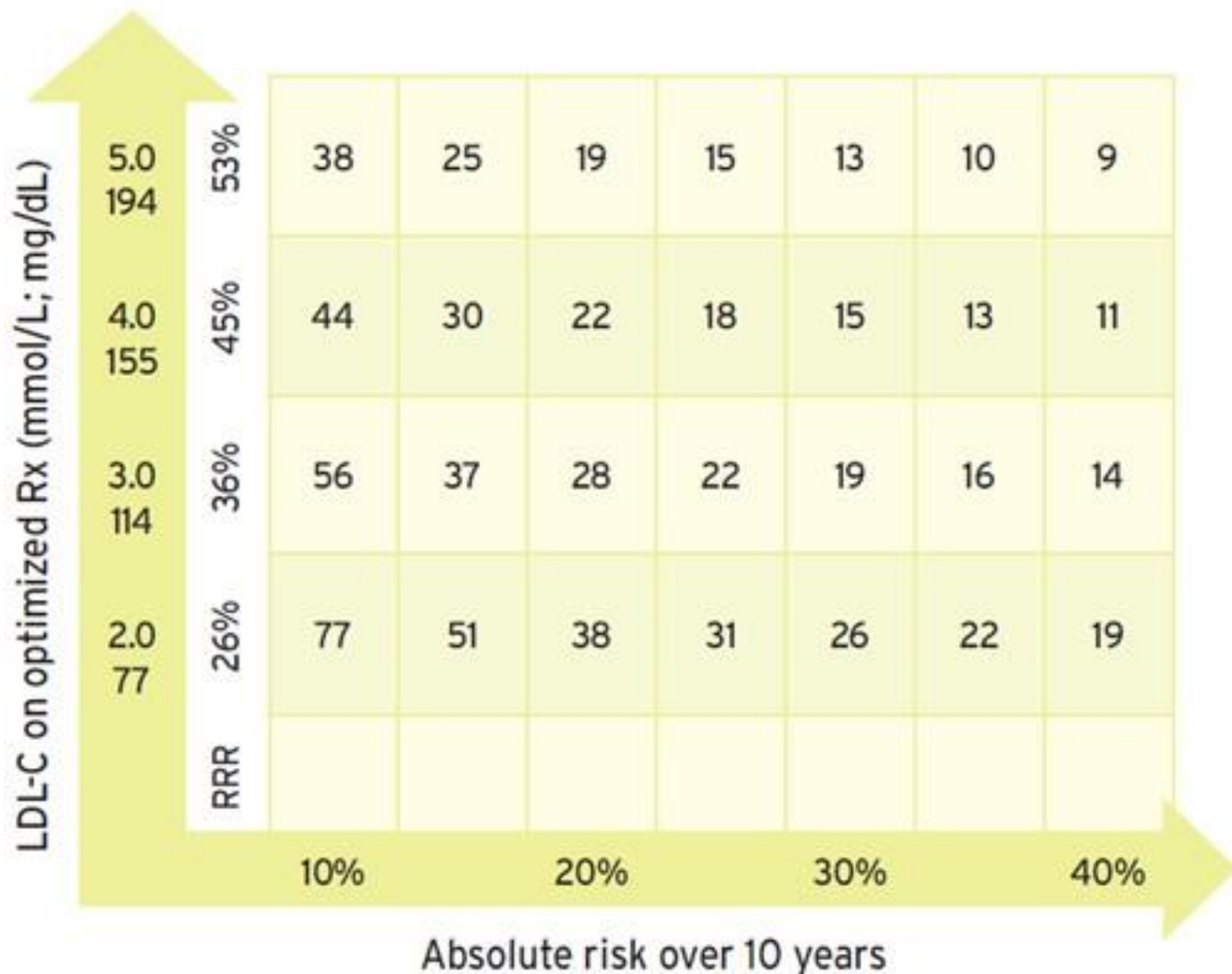
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Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (5)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high- intensity statin
		Plus ezetimibe		Plus ezetimibe	
2.5 (95)	1.8 (67)	1.4 (52)	1.3 (48)	0.9 (33)	0.5 (19)
2.2 (85)	1.5 (60)	1.2 (47)	1.1 (43)	0.8 (30)	0.4 (17)

Achievable reductions of low-density lipoprotein cholesterol as a function of the therapeutic approach (6)

Starting LDL-C, mmol/L (mg/dL)	Achievable LDL-C levels with different therapeutic strategies				
	Moderate-intensity statins		High-intensity statins		PCSK9 inhibitor plus high- intensity statin
		Plus ezetimibe		Plus ezetimibe	
19 (75)	1.3 (53)	1.0 (41)	1.0 (38)	0.7 (26)	0.4 (15)



NNT (>5 years) as function of estimated 10-year risk of ACVE, starting LDL-C (on optimized statin/ezetimibe therapy), and average relative risk reduction associated with LDL-C drop of 60%

Prioritising information when educating patients

Need to know and do








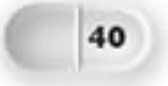

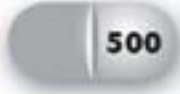


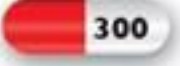




e.g. Important information about diagnosis,
key treatment and management of prescribed medications

Nice to know and do

Information that may be covered but can wait for
a second consultation

Not necessary now, do later

e.g. Provide information, using leaflets, booklets or
web-based resources, about additional services
that can be provided

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

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Images to improve recall for drug adherence

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Recommendations for drug treatments of patients with hypertriglyceridaemia (1)

Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (>200 mg/dL)).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	Ia	B

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Recommendations for drug treatments of patients with hypertriglyceridaemia (2)

Recommendations	Class	Level
In primary prevention patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	B
In high-risk patients who are at LDL-C goal with TG >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C

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Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (1)

Criteria	Points
1) Family history	
First-degree relative with known premature (men <55 years; women <60 years) coronary or vascular disease, or first-degree relative with known LDL-C above the 95th percentile	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, or children <18 years of age with LDL-C above the 95th percentile	2
2) Clinical history	
Patient with premature (men <55 years; women <60 years) coronary artery disease	2
Patient with premature (men <55 years; women <60 years) cerebral or peripheral vascular disease	1

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Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (2)

Criteria	Points
3) Physical examination ^a	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL-C levels (without treatment)	
LDL-C ≥ 8.5 mmol/L (≥ 325 mg/dL)	8
LDL-C 6.5–8.4 mmol/L (251–325 mg/dL)	5
LDL-C 5.0–6.4 mmol/L (191–250 mg/dL)	3
LDL-C 4.0–4.9 mmol/L (155–190 mg/dL)	1

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^a Exclusive of each other (i.e. maximum 6 points if both are present).
www.escardio.org/guidelines

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia (3)

Criteria	Points
5) DNA analysis	
Functional mutation in the <i>LDLR</i> , <i>ApoB</i> or <i>PCSK9</i> genes	8
Choose only one score per group, the highest applicable (diagnosis is based on the total number of points obtained)	
A 'definite' FH diagnosis requires >8 points	
A 'probable' FH diagnosis requires 6–8 points	
A 'possible' FH diagnosis requires 3–5 points	

Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (1)

Recommendations	Class	Level
It is recommended to consider the diagnosis of FH in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C (in adults >5 mmol/L [>190 mg/dL], in children >4 mmol/L [>150 mg/dL]), and in first-degree relatives of FH patients.	I	C
It is recommended that FH should be diagnosed using clinical criteria and confirm, when available, with DNA analysis.	I	C

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Recommendations for the detection and treatment of patients with heterozygous familial hypercholesterolaemia (2)

Recommendations	Class	Level
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended to treat FH patients with ASCVD or who have another major risk factor as very-high-risk, and those with no prior ASCVD or other risk factors as high-risk.	I	C
For FH patients with ASCVD who are at very-high risk, treatment to achieve at least a 50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C

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Recommendations for the detection & treatment of patients with heterozygous familial hypercholesterolaemia (3)

Recommendations	Class	Level
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if homozygous FH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with a statin from 8–10 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.	IIa	C

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Management of dyslipidaemia in women

Statin treatment is recommended for primary prevention of ASCVD in high-risk women.

Statins are recommended for secondary prevention in women with the same indications and goals as in men.

Lipid-lowering drugs should not be given when pregnancy is planned, during pregnancy or during the breastfeeding period. However, for severe FH patients, bile acid sequestrants (which are not absorbed) and/or LDL apheresis may be considered.

Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged ≤ 75 .	I	A
Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.	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, and then titrated upwards to achieve LDL-C treatment goals.	I	C

Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes mellitus

Dyslipidaemia represents a cluster of lipid and lipoprotein abnormalities, including elevation of both fasting and post-prandial TG, ApoB, and small dense LDL, and low HDL-C and ApoA1 levels.

Non-HDL-C or ApoB are good markers of TRLs and remnants, and are a secondary objective of therapy. Non-HDL-C <2.6 mmol/L (<100 mg/dL) and ApoB <80 mg/dL are desirable in those at high-risk, and non-HDL-C <2.2 mmol/L (<85 mg/dL) and ApoB <65 mg/dL in those at very high-risk. For those at very high-risk with recurrent ASCVD events, a goal of non-HDL-C <1.8 mmol/L (<70 mg/dL) and ApoB <55 mg/dL may be considered.

Atherogenic dyslipidaemia is one of the major risk factors for CVD in people with type 2 diabetes, and in people with abdominal obesity and insulin resistance or impaired glucose tolerance.

Recommendations for the treatment of dyslipidaemias in diabetes (1)

Recommendations	Class	Level
In patients with T2DM at very-high risk, an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
In patients with T2DM at high risk ^c an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high or very-high risk.	I	A

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Recommendations for the treatment of dyslipidaemias in diabetes (2)

Recommendations	Class	Level
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with ezetimibe should be considered.	IIa	B
Statin therapy is not recommended in pre-menopausal patients with diabetes who are considering pregnancy or not using adequate contraception.	III	C
Statin therapy may be considered in both T1DM and T2DM patients aged ≤ 30 years with evidence of end organ damage and/or LDL-C > 2.5 mmol/L as long as pregnancy is not being planned.	IIb	C

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Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes (1)

Recommendations	Class	Level
In all ACS patients without any contra-indication or definite history of intolerance, it is recommended to initiate or continue high dose statin as early as possible, regardless of initial LDL-C values.	I	A
Lipid levels should be re-evaluated 4–6 weeks after ACS to determine whether a reduction of at least 50% from baseline and goal levels of LDL-C <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin treatment doses adapted accordingly.	IIa	C
If the LDL-C goal is not achieved after 4–6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended.	I	B

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Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes (2)

Recommendations	Class	Level
If the LDL-C goal is not achieved after 4–6 weeks despite maximal tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
In patients with confirmed statin intolerance or in patients in whom a statin is contra-indicated, ezetimibe should be considered.	IIa	C
For patients who present with an ACS and whose LDL-C levels are not at goal despite already taking a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor early after the event (if possible, during hospitalization for the ACS event) should be considered.	IIa	C

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Recommendations for lipid-lowering therapy in very-high-risk patients undergoing percutaneous coronary intervention

Recommendations	Class	Level
Routine pre-treatment or loading (on the background of chronic therapy) with high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI.	IIa	B

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Recommendations for lipid-lowering therapy for prevention of atherosclerotic cardiovascular disease events in patients with prior ischaemic stroke

Recommendations	Class	Level
Patients with a history of ischaemic stroke or TIA are at very-high risk of ASCVD, particularly recurrent ischaemic stroke, so it is recommended that they receive intensive LDL-C-lowering therapy.	I	A

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Recommendations for the treatment of dyslipidaemias in chronic heart failure or valvular heart diseases

Recommendations	Class	Level
Initiation of lipid-lowering therapy is not recommended in patients with heart failure in the absence of other indications for their use.	III	A
Initiation of lipid-lowering treatment is not recommended in patients with aortic valvular stenosis without CAD to slow progression of aortic valve stenosis in the absence of other indications for their use.	III	A

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Recommendations for lipid management in patients with moderate to severe (KDOQI stages 3–5) chronic kidney disease

Recommendations	Class	Level
It is recommended that patients with Kidney Disease Outcomes Quality Initiative stage 3–5 CKD are considered to be at high or very-high risk of ASCVD.	I	A
The use of statins or statin/ezetimibe combination is recommended in patients with non-dialysis-dependent stage 3–5 CKD.	I	A
In patients already on statins, ezetimibe or a statin/ ezetimibe combination at the time of dialysis initiation, continuation of these drugs should be considered, particularly in patients with ASCVD.	IIa	C
In patients with dialysis-dependent CKD and free of ASCVD, commencing statin therapy is not recommended.	III	A

Recommendations for low-density lipoprotein lowering in solid organ transplant patients

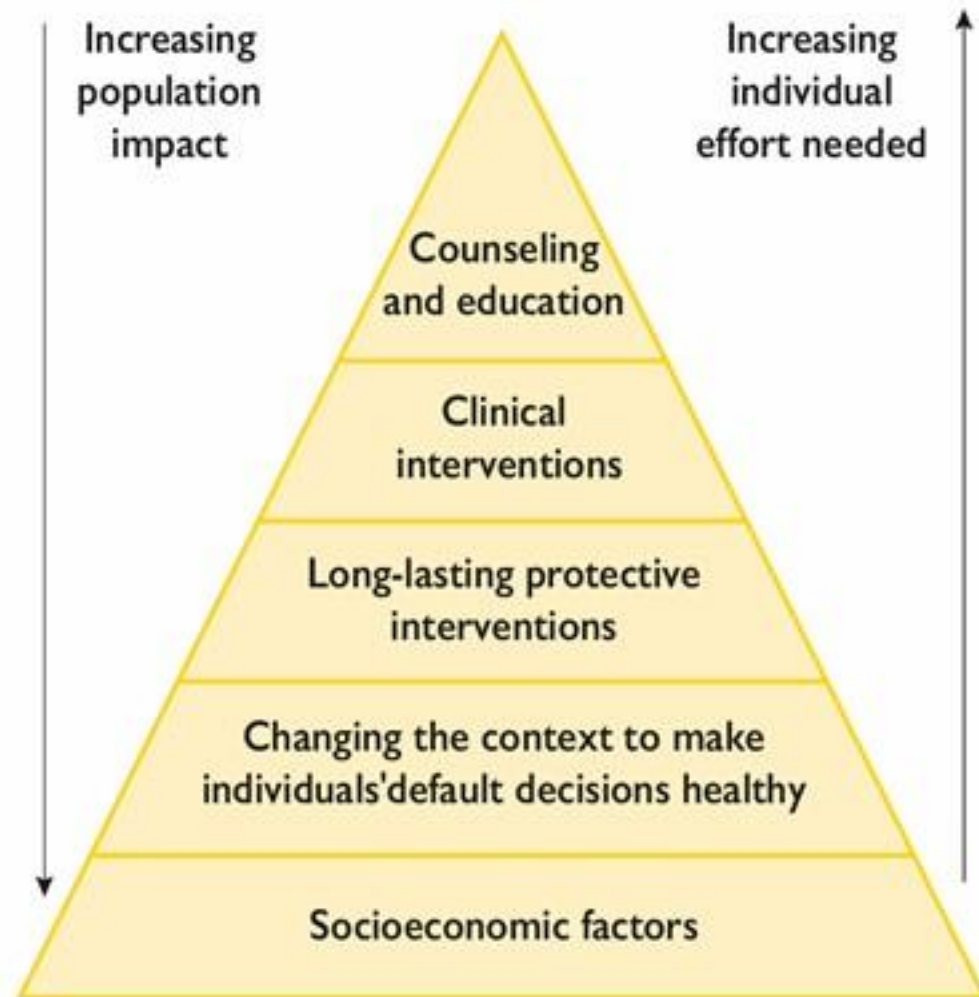
Recommendations	Class	Level
Statins should be considered as first-line agents in transplant patients. Initiation should be at low doses with careful up-titration and with caution regarding potential drug–drug interactions, particularly for patients on ciclosporin.	Ila	B
In patients who are intolerant of statins or those with significant dyslipidaemia despite maximally tolerated statin treatment, alternative or additional therapy with ezetimibe may be considered.	Ilb	C

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

Recommendations	Class	Level
In patients with PAD, lipid-lowering therapy, including a maximum tolerated dose of statin, plus ezetimibe or a combination with a PCSK9 inhibitor if needed, is recommended to reduce the risk of ASCVD events.	I	A

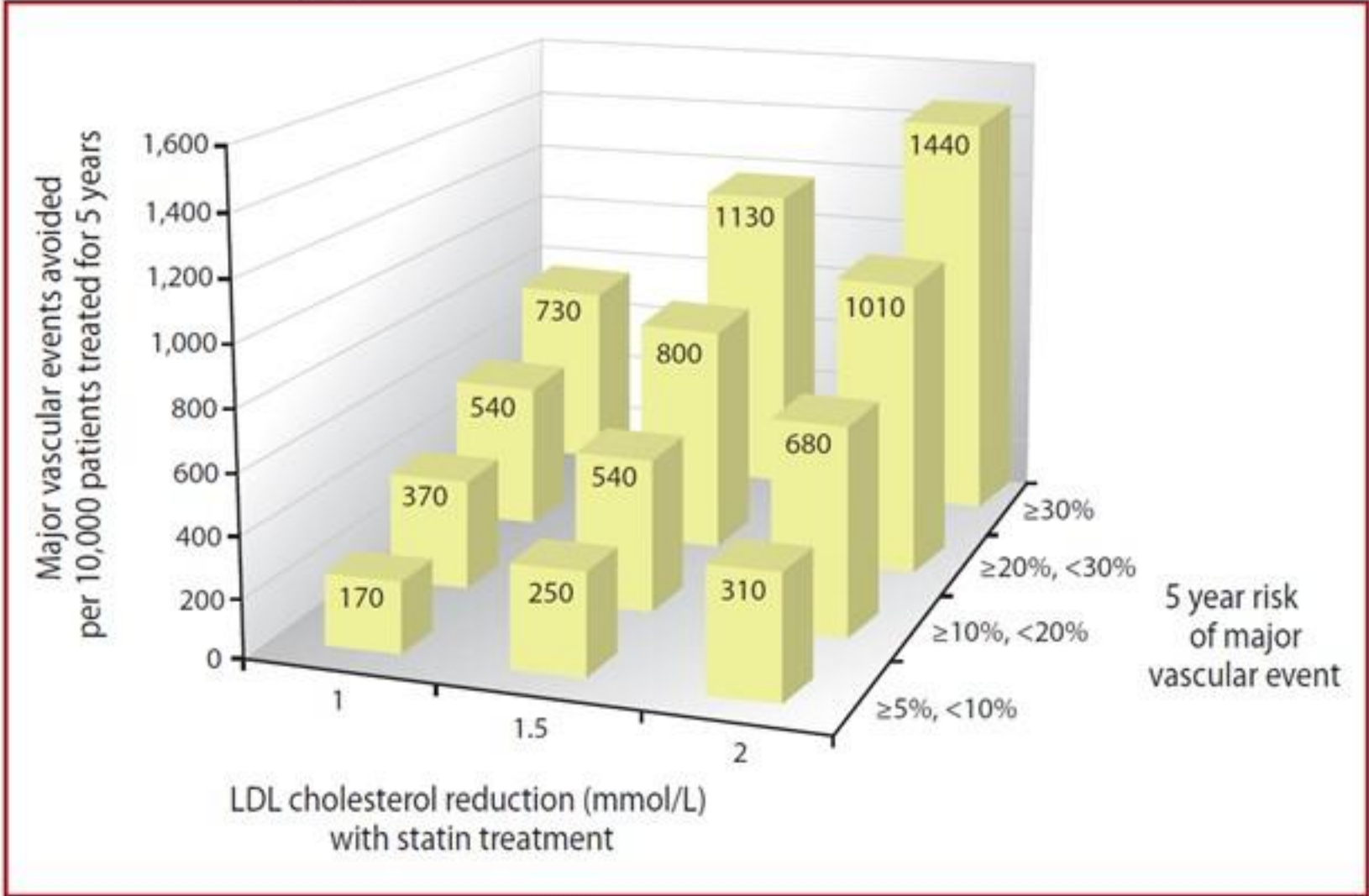
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Health impact pyramid

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Absolute reductions in major vascular events with statin therapy



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Recommendations for the management of dyslipidaemias in patients with severe mental illness

Recommendations	Class	Level
It is recommended that SMI is used as a modifier for estimating total ASCVD risk.	I	C
It is recommended that the same guidelines for the management of total ASCVD risk are used in patients with SMI as are used in patients without such disease.	I	C
It is recommended that in patients with SMI intensified attention is paid to adherence to lifestyle changes and to compliance with drug treatment.	I	C

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Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (1)

Testing lipids

How often should lipids be tested?

- Before starting lipid-lowering drug treatment, at least two measurements should be made, with an interval of 1–12 weeks, with the exception of conditions where concomitant drug treatment is suggested, such as acute coronary syndromes (ACS) and very-high-risk patients.

How often should a patient's lipids be tested after starting lipid-lowering treatment?

- 8 (\pm 4) weeks after starting treatment.
- 8 (\pm 4) weeks after adjustment of treatment until the goal is achieved.

How often should lipids be tested once a patient has achieved the target or optimal lipid level?

- Annually (unless there are adherence problems or other specific reasons for more frequent reviews).

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (2)



Monitoring liver and muscle enzymes

How often should liver enzymes (alanine aminotransferase [ALT]) be routinely measured in patients on lipid-lowering drugs?

- Before treatment.
- Once 8–12 weeks after starting a drug treatment or after dose increase.
- Routine control of ALT thereafter is not recommended during statin treatment, unless symptoms suggesting liver disease evolve. During treatment with fibrates, control of ALT is still recommended.

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Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (3)

Monitoring liver and muscle enzymes

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT <3x upper limit of normal (ULN):

- Continue therapy.
- Recheck liver enzymes in 4–6 weeks.

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (4)



Monitoring liver and muscle enzymes

What if liver enzymes become elevated in a person taking lipid-lowering drugs?

If ALT ≥ 3 x ULN:

- Stop lipid-lowering therapy or reduce dose and recheck liver enzymes within 4–6 weeks.
- Cautious reintroduction of therapy may be considered after ALT has returned to normal.
- If ALT remains elevated check for the other reasons.

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Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (5)

Monitoring liver and muscle enzymes

How often should creatine kinase (CK) be measured in patients taking lipid-lowering drugs?

Pre-treatment:

- Before starting therapy.
- If baseline CK is $>4x$ ULN, do not start drug therapy; recheck.

Monitoring:

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease, or athletes.

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (6)

Monitoring liver and muscle enzymes

What if CK becomes elevated in a person taking lipid-lowering drugs? Re-evaluate indication for statin treatment.

If $\geq 4 \times$ ULN:

- If CK $> 10 \times$ ULN: stop treatment, check renal function and monitor CK every 2 weeks.
- If CK $< 10 \times$ ULN: if no symptoms, continue lipid-lowering therapy while monitoring CK between 2 and 6 weeks.
- If CK $< 10 \times$ ULN: if symptoms present, stop statin and monitor normalization of CK, before re-challenge with a lower statin dose.
- Consider the possibility of transient CK elevation for other reasons such as exertion.
- Consider myopathy if CK remains elevated.
- Consider combination therapy or an alternative drug.

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (7)

Monitoring liver and muscle enzymes

What if CK becomes elevated in a person taking lipid-lowering drugs? Re-evaluate indication for statin treatment.

If $<4\times$ ULN:

- If no muscle symptoms, continue statin (patient should be alerted to report symptoms; check CK).
- If muscle symptoms, monitor symptoms and CK regularly.
- If symptoms persist, stop statin and re-evaluate symptoms after 6 weeks; re-evaluate indication for statin treatment.
- Consider re-challenge with the same or another statin..

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (8)



Monitoring liver and muscle enzymes

- Consider low-dose statin, alternate day or once/twice weekly dosing regimen or combination therapy.

In which patients should glycated haemoglobin (HbA1c) or blood glucose be checked?

- Regular checks of HbA1c or glucose should be considered in patients at high-risk of developing diabetes, and on high-dose statin treatment.
- Groups to be considered for glucose control are the elderly and patients with metabolic syndrome, obesity or other signs of insulin resistance.

Cost-effectiveness of cardiovascular disease prevention by lipid modification

Prevention of CVD by lifestyle changes, medication, or both is cost-effective in many scenarios, including population-based approaches and actions directed at individuals at increased CVD risk.

Cost-effectiveness depends on several factors, including baseline CVD risk and LDL levels, cost of treatment, and uptake of preventive strategies.

Interventions to prevent CVD are more cost-effective among individuals and populations at higher CVD risk.

Cost-effectiveness analyses are importantly informed by assumptions about long-term disease prognosis and treatment effects. Strengthening of the evidence to inform these assumptions is encouraged.

Cost-effectiveness of cardiovascular disease prevention by lipid modification: Gaps in the evidence

Cost-effectiveness requires evidence for effects of interventions on health and healthcare over a long time period; modelling techniques fill gaps. More data are needed from RCTs and observational studies.

Direct evidence of effects of lipid-modifying treatments on overall mortality, particularly among people at low-to-moderate CVD risk, older people, and for newer interventions, is lacking. Long-term post-trial follow-up in RCTs should be encouraged.

The cost-effectiveness of using lifetime CVD risk and more precise CVD risk scores to target interventions needs further investigation.

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Methods for enhancing adherence to lifestyle changes

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

Recommendations for the treatment of dyslipidaemias in chronic immune-mediated inflammatory diseases

Recommendations	Class	Level
CIID is a risk modifier and should be considered when estimating total ASCVD risk.	IIa	C
The use of lipid-lowering drugs only on the basis of the presence of CIID is not recommended.	III	C

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Recommendations for lipid-lowering drugs in human immunodeficiency virus patients

Recommendations	Class	Level
Lipid-lowering therapy (mostly statins) should be considered in HIV patients with dyslipidaemia to achieve the LDL-C goal as defined for high-risk patients. The choice of statin should be based on their respective potential drug-drug interactions.	Ia	C

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

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

Genetic disorders of lipoprotein metabolism (1)

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
HeFH	1 in 200-250	LDLR APO B PCSK9	↑ LDL-C
HoFH	1 in 160 000-320 000	LDLR APO B PCSK9	↑↑ LDL-C
FCH	1 in 100/200	USF1 + modifying genes	↑LDL-C ↑VLDL-C ↑ ApoB
Familial dysbetalipoproteinaemia	1 in 5000	APO E	↑↑ IDL and chylomicron remnants (βVLDL)

Genetic disorders of lipoprotein metabolism (2)

Disorder	Prevalence	Gene(s)	Effect on lipoproteins
Familial lipoprotein lipase deficiency (familial chylomicron syndrome)	2 in 10 ⁶	LPL APO C2 ApoAV, GPIHBP1 LMF1	↑↑chylomicrons and VLDL-C
Tangier disease (analphalipoproteinaemia)	1 in 10 ⁶	ABCA 1	↓↓HDL-C
Familial LCAT deficiency	1 in 10 ⁶	LCAT	↓HDL-C

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Committee for
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Guidelines for the Management
of Dyslipidaemias:
Lipid Modification to Reduce
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