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ESC/EAS Guidelines

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

The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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1 Supplementary tables and figures

Supplementary Table 1 Total cardiovascular disease risk assessment systems

System	Risk	Variables	Reference
Framingham models	10-year risk of CHD events	Gender, age, TC, HDL-C, SBP, smoking status, diabetes, hypertensive treatment	[1]
Systematic Coronary Risk Estimation (SCORE)	10-year risk of CVD mortality	Gender, age, TC or TC/HDL-C ratio, SBP, smoking status	[2]
ASSIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network)	10-year risk of first CVD event	Gender, age, TC, HDL-C, SBP, smoking (number of cigarettes), diabetes, area-based index of deprivation, family history	[3]
QRISK2	10-year risk of first CVD event	Gender, age, TC to HDL-C ratio, SBP, smoking status, diabetes, area-based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity, rheumatoid arthritis, CKD stages 4–5, AF	[4]
Prospective Cardiovascular Munster Study (PROCAM)	Two separate scores calculate 10-year risk of major coronary events and cerebral ischaemic events	Age, gender, LDL-C, HDL-C, diabetes, smoking, SBP	[5]
Reynolds Risk Score	10-year risk of incident myocardial infarction, stroke, coronary revascularization, or CV death	Gender, age, SBP, smoking, high-sensitivity C-reactive protein, TC, HDL-C, family history of premature MI (parent aged <60 years), HbA1c if diabetic	[6,7]
CUORE	10-year risk of first CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment	[8]
Pooled Cohort equations	10-year risk of CVD event	Age, gender, TC, HDL-C, diabetes, smoking, SBP, hypertensive treatment, race	[9]
Globorisk	10-year risk of CVD mortality	Age, gender, smoking, SBP, diabetes, TC	[10]

AF = atrial fibrillation; BMI = body mass index; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction, SBP = systolic blood pressure; TC = total cholesterol.

Supplementary Table 2 **Low-density lipoprotein cholesterol achievable as a function of the starting value and the desired per cent reduction**

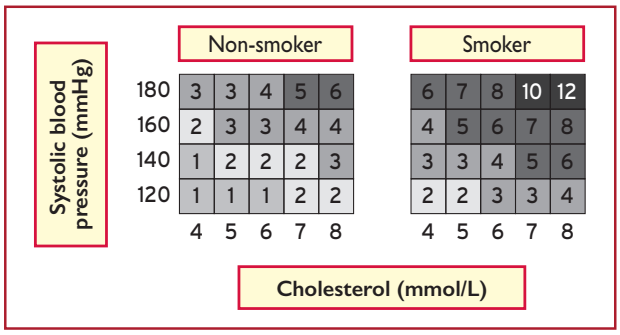
Starting LDL-C, mmol/L (mg/dL)	LDL-C goals, mmol/L (mg/dL) 50%
6.2 (240)	<3.1 (120)
5.9 (230)	<3.0 (116)
5.7 (220)	<2.8 (110)
5.4 (210)	<2.7 (105)
5.2 (200)	<2.6 (100)
4.9 (190)	<2.5 (95)
4.7 (180)	<2.3 (90)
4.4 (170)	<2.2 (85)
4.1 (160)	<2.1 (80)
3.9 (150)	<1.9 (75)
3.6 (140)	<1.8 (70)
3.4 (130)	<1.7 (65)
3.1 (120)	<1.6 (60)
2.8 (110)	<1.4 (55)
2.6 (100)	<1.3 (50)
2.3 (90)	<1.2 (45)
2.1 (80)	<1.0 (40)
1.8 (70)	<0.9 (35)

LDL-C = low-density lipoprotein cholesterol.

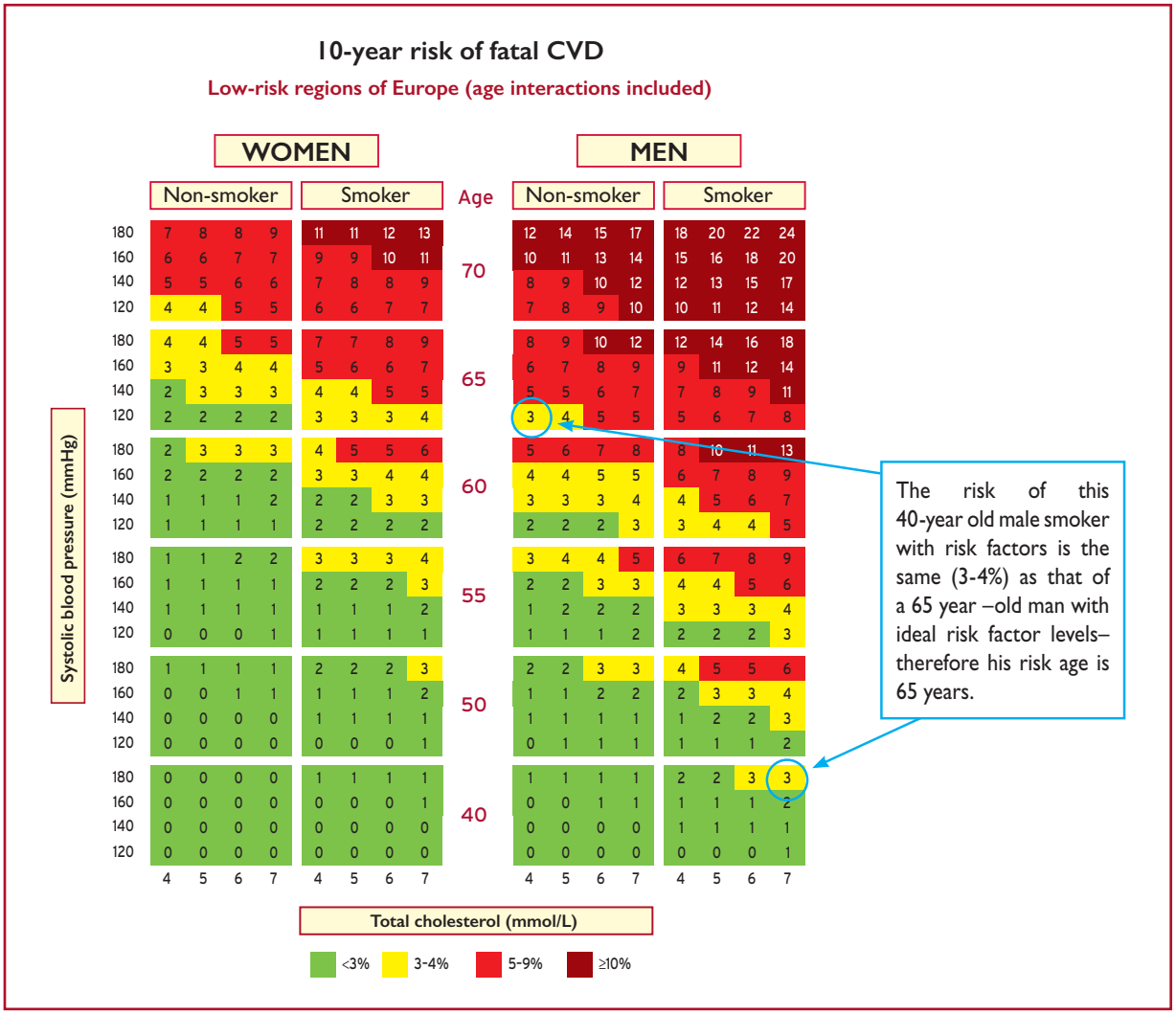
Supplementary Table 3 **Reduction of low-density lipoprotein cholesterol as a function of the therapeutic approach**

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)

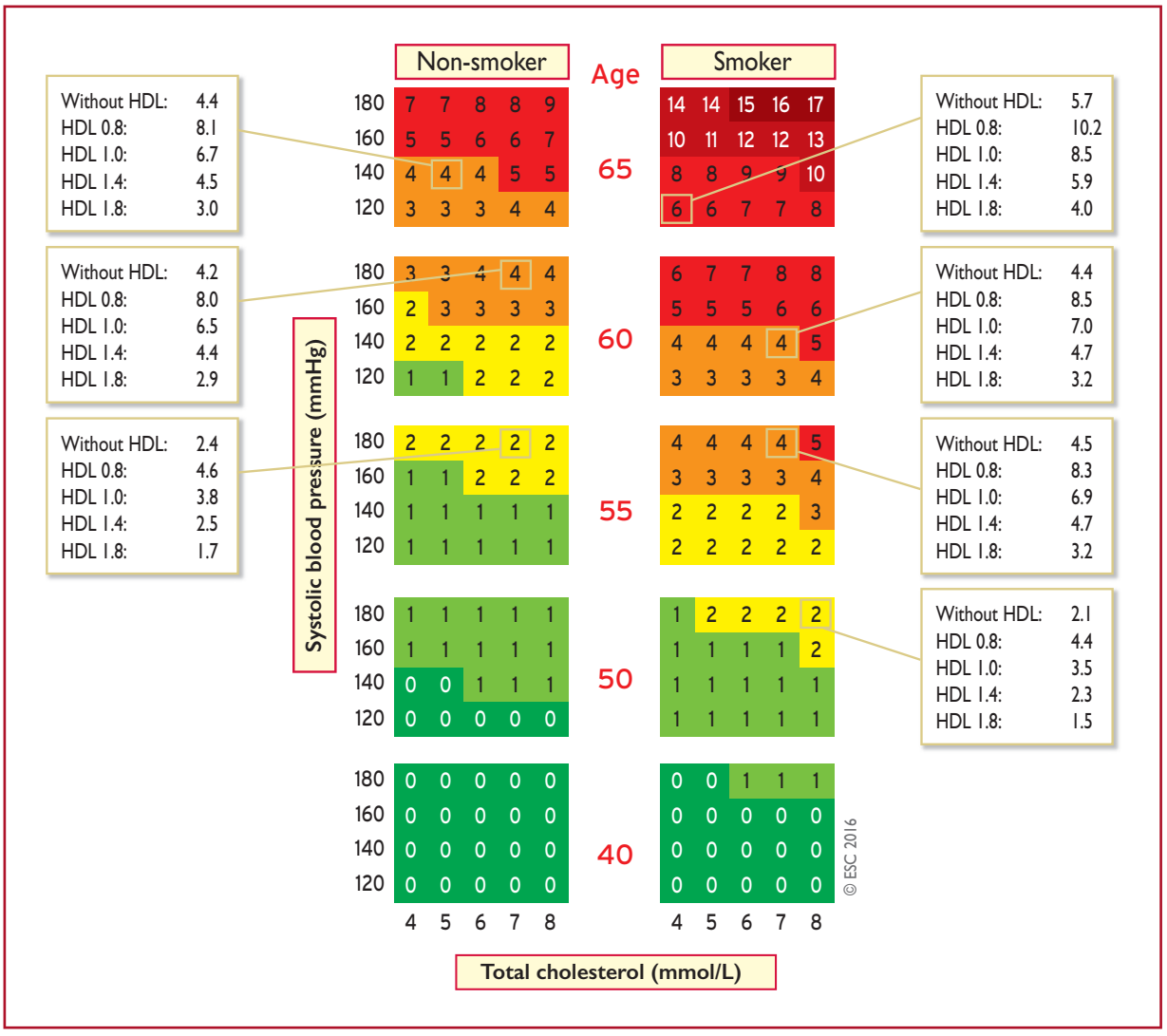
LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.



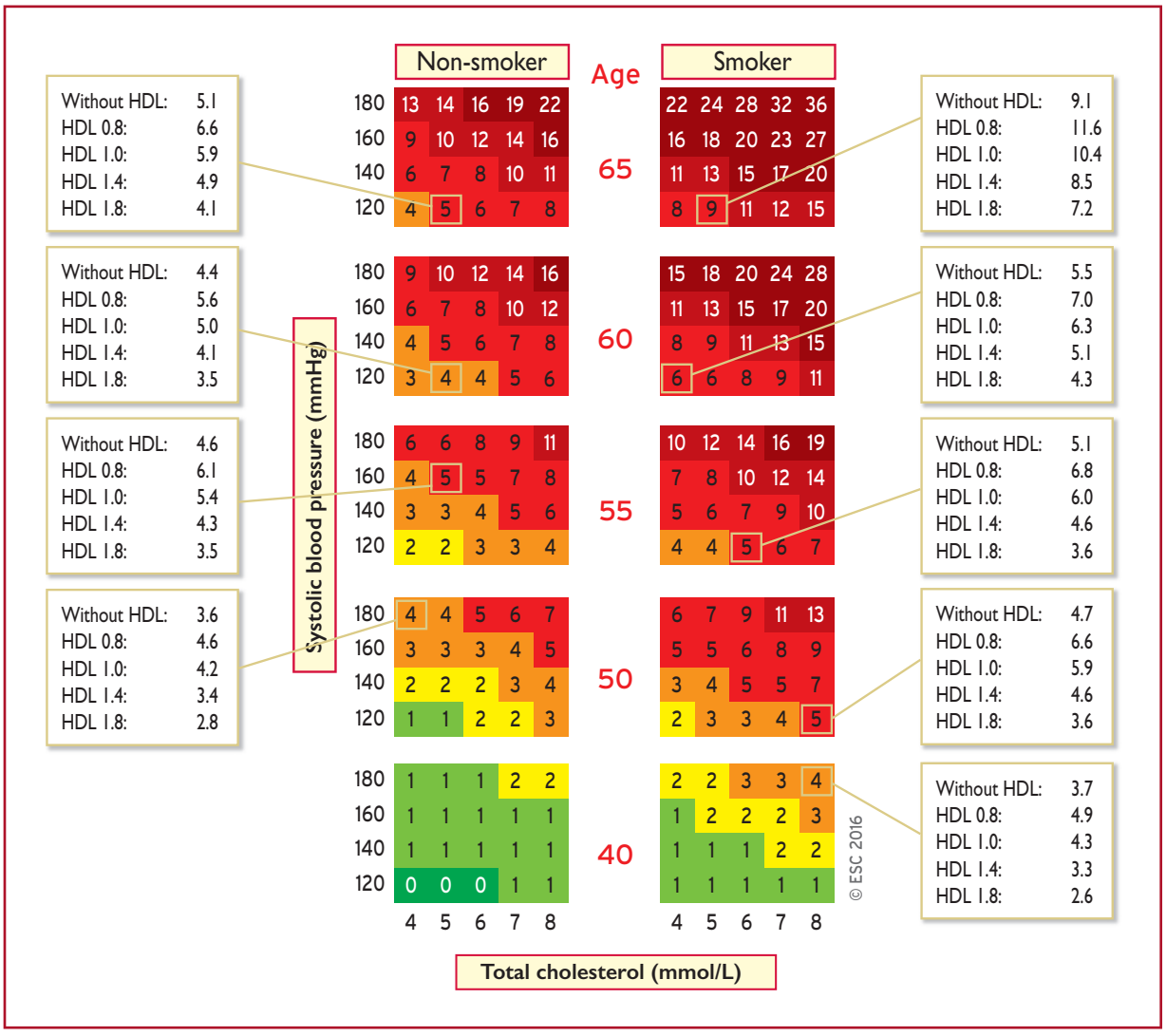
Supplementary Figure 1 Chart for estimating the relative risk for 10 year cardiovascular mortality in young people. This chart shows, for young people, the relative risk of 10 year cardiovascular mortality as compared with the risk in a non-smoker with systolic blood pressure 120 mm Hg and cholesterol of 4 mmol/L (bottom left corner). Cholesterol: 1 mmol/L = 38.67mg/dL.



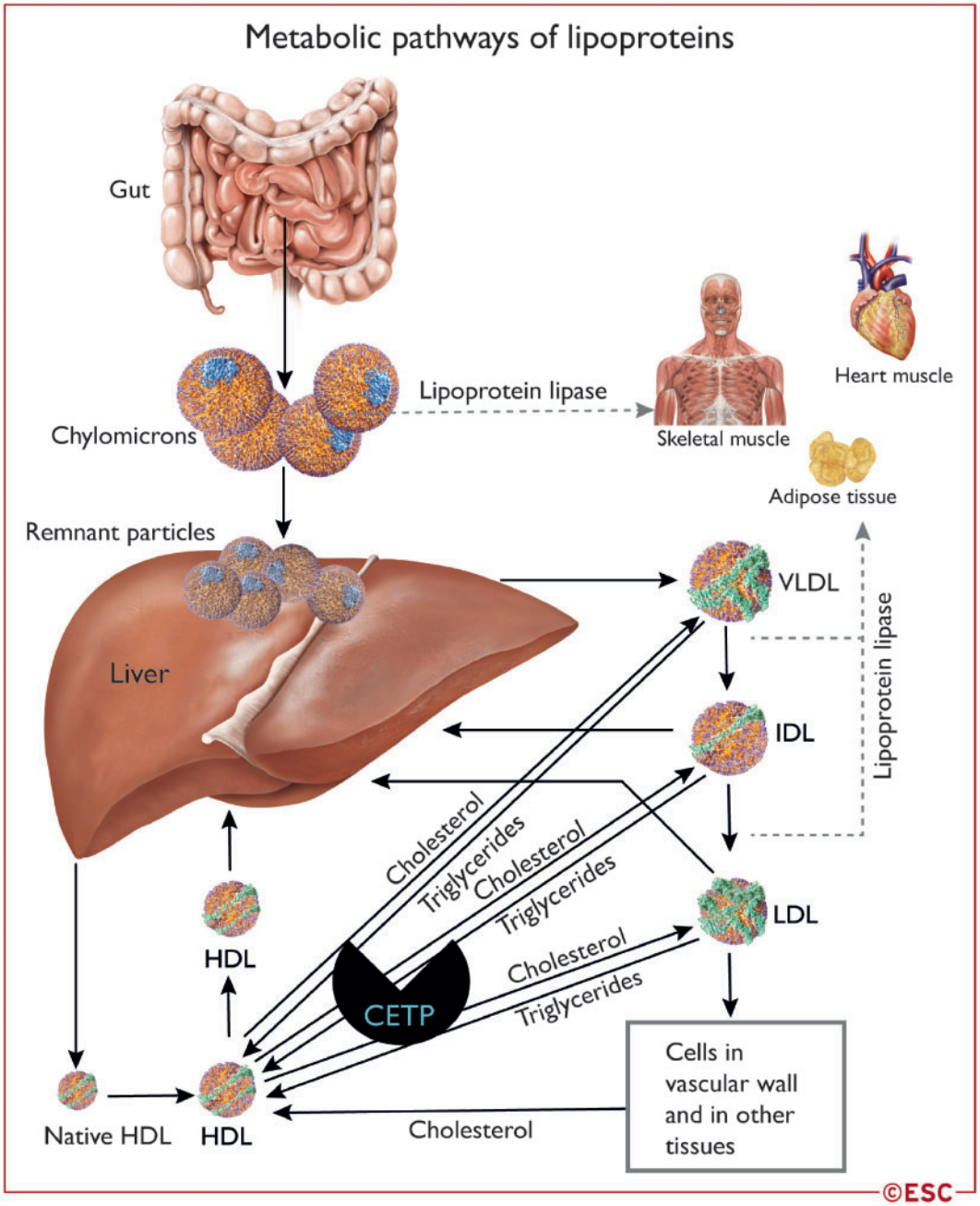
Supplementary Figure 2 Illustration of the risk age concept. CVD = cardiovascular disease.



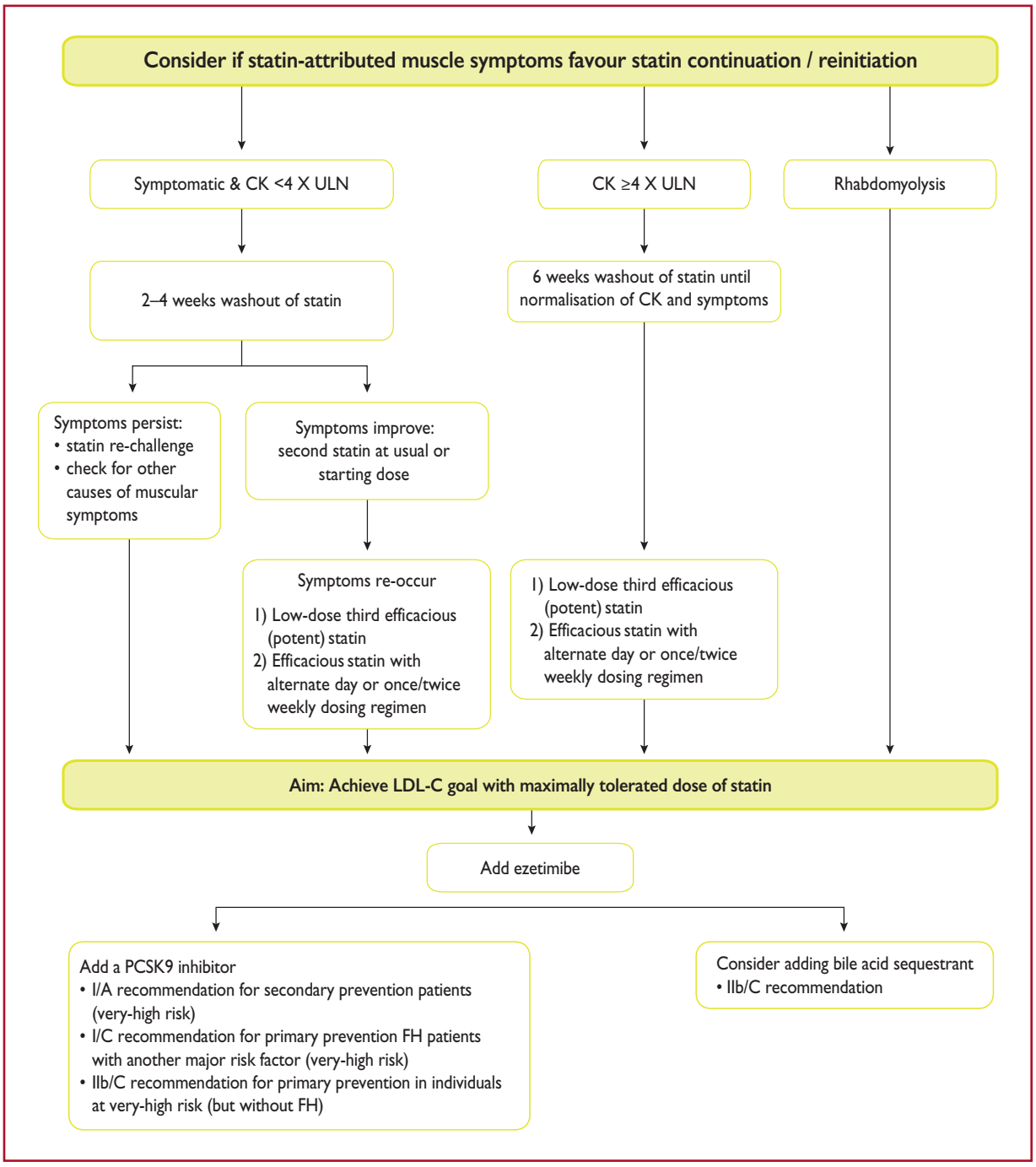
Supplementary Figure 3 Risk function with high-density lipoprotein cholesterol for women in populations at high cardiovascular disease risk. HDL = high-density lipoprotein.



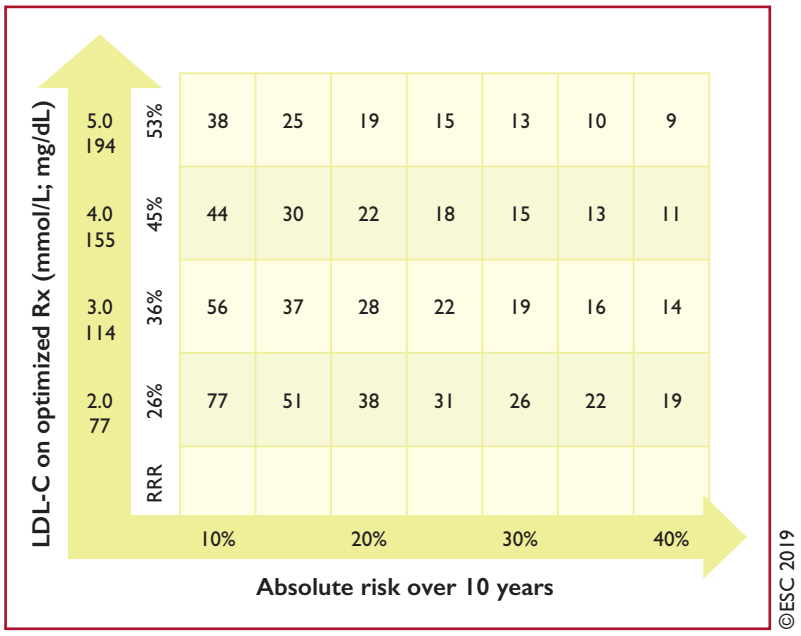
Supplementary Figure 4 Risk function with high-density lipoprotein cholesterol for men in populations at high cardiovascular disease risk. HDL = high-density lipoprotein.



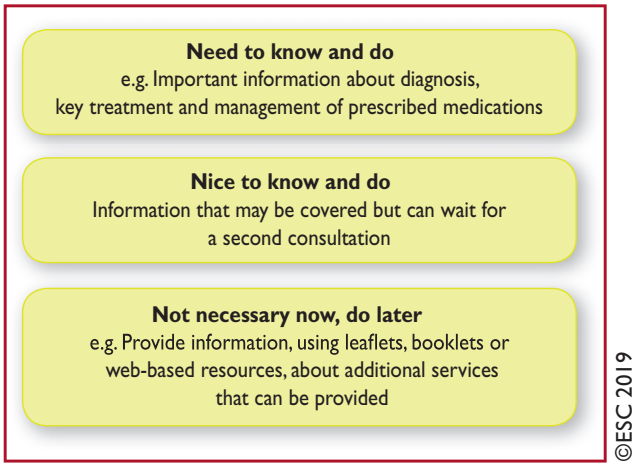
Supplementary Figure 5 Lipoprotein transport and metabolism. Most cholesterol is synthesized in the liver, where it is packaged together with triglycerides into lipoproteins containing one molecule of apolipoprotein B or utilized for bile acid synthesis. The apolipoprotein B-containing lipoproteins are secreted into the plasma as triglyceride-rich very low-density lipoproteins, and are hydrolysed to liberate triglycerides for energy storage and consumption to become smaller, denser, triglyceride-rich lipoprotein remnants. These remnant particles can be taken up by the liver, but most are progressively hydrolysed to become low-density lipoproteins. Most of the low-density lipoprotein particles are taken up by the liver hepatocytes for further metabolism and secretion in the bile. Some low-density lipoprotein is also taken up by peripheral cells as a source of cholesterol. Apolipoprotein A1-containing high-density lipoprotein particles transport excess cholesterol from the peripheral cells back to the liver in a process referred to as reverse cholesterol transport. The high-density lipoprotein particles can either transport cholesterol directly back to the liver, or interact with cholesterol ester transfer protein to exchange cholesterol for triglycerides with triglyceride-rich apolipoprotein B-containing lipoproteins. The transferred cholesterol can then be taken back to the liver, carried either by triglyceride-rich lipoproteins or by low-density lipoprotein particles. Triglycerides are a major source of energy for biological processes and are stored predominantly in adipose tissue. Triglycerides are transported from the liver to muscle cells for energy consumption, and to adipose cells for energy storage by triglyceride-rich very low-density lipoprotein particles and their remnants. Dietary fat in the form of triglycerides is digested in the gut and then converted back into triglycerides in enterocytes, where it is combined with cholesterol and a truncated form of apolipoprotein B to produce triglyceride-rich chylomicrons. These particles are much larger and contain much more triglycerides than very low-density lipoprotein particles. Under most conditions, very low-density lipoprotein particles and their remnants represent <10%, and chylomicrons <1%, of the total concentration of circulating apolipoprotein B-containing lipoproteins, even in the immediate post-prandial state. Apo = apolipoprotein; CETP = cholesterol ester transfer protein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; TRL = triglyceride-rich lipoprotein; VLDL = very low-density lipoprotein.



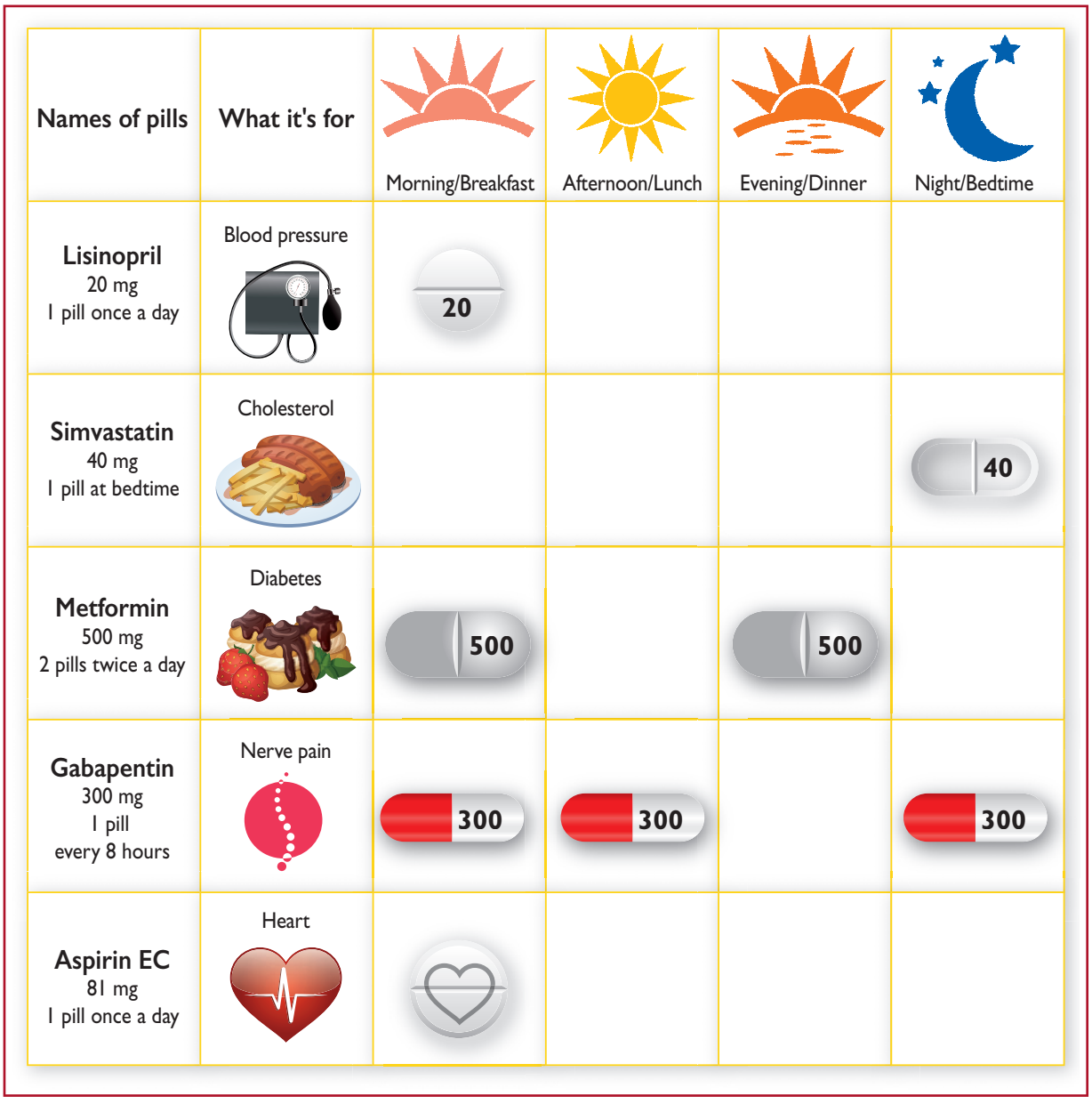
Supplementary Figure 6 Algorithm for the treatment of muscular symptoms during statin treatment. CK = creatine kinase; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; ULN = upper limit of normal.



Supplementary Figure 7 Number needed to treat (over 5 years) as a function of the estimated 10-year risk of a future atherosclerotic cardiovascular disease event, the starting low-density lipoprotein cholesterol level (on optimized statin/ezetimibe therapy), and the average relative risk reduction associated with a drug-induced low-density lipoprotein cholesterol drop of 60% (with anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies). Predicted relative risk reduction in the first column is associated with a proprotein convertase subtilisin/kexin type 9 inhibitor-induced 60% decrease in low-density lipoprotein cholesterol, based on a 22% risk reduction per 1.0 mmol/L (38.7 mg/dL) drop in low-density lipoprotein cholesterol. Modified from Annemans *et al.*[11] LDL-C = low-density lipoprotein cholesterol; RRR; relative risk reduction. Rx = treatment.



Supplementary Figure 8 Prioritizing information when educating patients.



Supplementary Figure 9 Images to improve recall. EC = enteric-coated.

2 Other features of a healthy diet contributing to cardiovascular disease prevention

The results of the PREDIMED (Prevención con Dieta Mediterránea) trial, in addition to a large body of evidence from large longitudinal studies, are clearly in support of a diet inspired by the traditional Mediterranean diet as an effective approach to lifestyle prevention of cardiovascular diseases (CVDs).[12,13] This type of diet is characterized by the regular consumption of extra-virgin olive oil, fruits, nuts, vegetables, and cereals; moderate intake of fish and poultry; and low intake of dairy products, red meat, processed meats, and sweets.[14] Dietary choices inspired by this model should be recommended for both primary and secondary prevention of CVD.

Furthermore, the consumption of large amounts of fruits and vegetables of different types provides a sufficient amount, and variety, of minerals, vitamins, and antioxidants, particularly polyphenols. New evidence is accumulating on the possible beneficial effects of these compounds—which are also present in olive oil, red wine, coffee, tea, and cocoa—on subclinical inflammation and endothelial function, as well as their beneficial influence on plasma TGs at fasting and particularly in the post-prandial period.

In relation to salt intake, the overall recommendation is to reduce sodium intake to ~2.0 g/day (equivalent of ~5.0 g salt/day), although recent data from the PURE study support a higher threshold.[15] This can be achieved not only by reducing the amount of salt used for food seasoning, but especially by reducing the consumption of foods preserved by the addition of salt; this recommendation should be more stringent in people with hypertension or metabolic syndrome.[16–18] This recommendation is prompted by the evidence of a causal association between sodium intake and blood pressure (BP), and by data showing that salt restriction has relevant BP-lowering effects.

Supplementary Box 1 lists lifestyle measures and healthy food choices for the management of total cardiovascular (CV) risk. All individuals should be advised on lifestyles associated with a lower CVD risk. High-risk people, in particular those with dyslipidaemia, should receive specialist dietary advice, if feasible.

3 Chronic immune-mediated inflammatory diseases

Patients with chronic immune-mediated inflammatory diseases (CIID) are at increased risk of developing atherosclerotic cardiovascular disease (ASCVD); this has been demonstrated for inflammatory bowel diseases,[19] rheumatoid arthritis (RA),[20] systemic lupus erythematosus,[21] systemic sclerosis,[22] and ankylosing spondylitis.[20]

In a large cohort study of 991 546 patients, free of ASCVD at baseline, systemic connective tissue diseases and RA were associated with an increased risk of incident ASCVD [hazard ratio (HR) 1.31, 95% confidence interval (CI) 1.15–1.49, and HR 1.31, 95% CI 1.15–1.49, respectively] followed by inflammatory bowel diseases (HR 1.12, 95% CI 1.01–1.25), independent of age, sex, CV risk factors, and drug use.[23]

Some treatments for controlling CIID, such as glucocorticoids, have a deleterious effect on ASCVD risk.[24] Some of the disease-modifying antirheumatic drugs may, in contrast, have a cardioprotective effect through the inhibition of systemic inflammation.[25–27]

The increased ASCVD risk in patients with CIID is not fully explained by a higher prevalence of the traditional CVD risk factors or by the use of drugs.[23] The immune system is believed to be involved in the pathogenesis of atherosclerosis.[28] A complex interaction between ASCVD risk factors and CIID-specific traits may lead to premature atherosclerosis and increased ASCVD risk.[29] When estimating risk of ASCVD in patients with CIID, it has been suggested that a factor of 1.5 should be applied in addition to known risk factors.[30]

The presence of CIID by itself is not an indication to prescribe lipid-lowering drugs to all patients with CIID. Furthermore, no specific low-density lipoprotein cholesterol (LDL-C) goal beyond that indicated by individual total ASCVD risk has been set for such patients (see recommendations below).

Supplementary Box 1 Summary of lifestyle measures and healthy food choices for the management of total cardiovascular risk

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 totally avoided; foods rich in SFAs (tropical oils, fatty or processed meat, sweets, cream, butter, and 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).
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, MetS, or DM.
Physical activity should be encouraged, aiming at regular physical exercise for ≥30 min/day every day.
Use of and exposure to tobacco products should be avoided.

DM = diabetes mellitus; MetS = metabolic syndrome; SFA = saturated fatty acids.

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

Recommendations	Class[a]	Level[b]
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

ASCVD = atherosclerotic cardiovascular disease; CIID = chronic immune-mediated inflammatory diseases.
[a]Class of recommendation.
[b]Level of evidence.

4 Human immunodeficiency virus patients

Human immunodeficiency disease (HIV)-infected patients typically have low TC, and LDL-C and high-density lipoprotein cholesterol (HDL-C) levels, as well as increased TG levels.[31,32] Antiretroviral treatment (ART) or highly active ART (when drugs are used in combination) causes marked increases in TC, LDL-C, TGs, and a predominance of small dense LDL particles, while HDL-C remains low. HIV-infected patients have a higher risk for CVD when compared with HIV-uninfected individuals [relative risk (RR) 1.61, 95% CI 1.43–1.83], while ART (and especially older protease inhibitors) further increases this risk up to two-fold (RR 2.00, 95% CI 1.70–2.37).[31,33,34] Nevertheless, the increase in absolute ASCVD risk with ART is moderate and should be considered in the context of the benefits of HIV treatment.

Statins are effective in reducing LDL cholesterol in patients with HIV infection, but drug interactions with ART need to be considered. Statins metabolized in the liver via cytochrome P450 (CYP) 3A4 or CYP2C9 are susceptible to drug interactions with protease inhibitors and the non-nucleoside reverse transcriptase inhibitor efavirenz. Pravastatin is not significantly metabolized via the CYP isoenzyme system and is therefore a preferred statin in HIV-infected individuals. A recent trial compared pravastatin with pitavastatin, and showed that pitavastatin led to a greater reduction in markers of immune activation and arterial inflammation.[35] Preferred statins include pravastatin, fluvastatin, pitavastatin, and rosuvastatin, although caution should be exercised. Combination of simvastatin or lovastatin with any protease inhibitor or efavirenz is not recommended.

The recommendations for lipid-lowering drugs in HIV patients are shown in below.

Recommendations for lipid-lowering drugs in human immunodeficiency virus patients

Recommendations	Class[a]	Level[b]
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.	IIa	C

HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation.
[b]Level of evidence.

5 Severe mental illness

Patients with severe mental illness (SMI)—such as schizophrenia, bipolar disorder, or major depressive disorder—have a life expectancy that is reduced by 10–17 years compared with the general population[36–38]; this is mainly due to premature mortality from non-communicable diseases among which ASCVD is a main contributor.

In 2017, results were published from a large-scale meta-analysis of 3 211 768 patients and 113 383 368 controls, demonstrating that patients with SMI had a 53% higher risk for having ASCVD, a 78% higher risk for developing ASCVD, and a 85% higher risk of dying from ASCVD compared with the regionally matched general population[39] The authors also identified some factors that increased the risk for ASCVD, including antipsychotic drugs and an elevated body mass index (BMI).

Some antipsychotics, antidepressants, anxiolytics, and mood stabilizers are associated with weight gain and cardiometabolic disturbances, including dyslipidaemia and dysglycaemia; these effects vary with different antipsychotic drugs. Unhealthy lifestyle factors such as sedentary behaviour, an unbalanced diet, and smoking of tobacco are more prevalent in these patients, and explain part of the increased ASCVD risk.[40–43]

Statins are equally effective in lowering LDL-C in psychiatric patients[44–46]; however, preventive actions taken both in regard to lifestyle and to the use of cardioprotective drugs in only a limited number of these patients. The odds of the use of statins was

approximately halved in patients with schizophrenia compared with controls.[47]

The recommendations for the management of dyslipidaemias in patients with SMI are listed in the below.

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

Recommendations	Class[a]	Level[b]
It is recommended that SMIs are used as modifiers 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

ASCVD = atherosclerotic cardiovascular disease, SMI = severe mental illness.
[a]Class of recommendation.
[b]Level of evidence.

6 Adhering to medications

Despite a wealth of evidence on the efficacy and effectiveness of statins in both primary and secondary prevention, adherence remains a consistent barrier, with rates of <50% demonstrated in several studies. Adherence declines over the duration of treatment[48–52]; however, this is truer in patients treated for primary compared with secondary prevention of CVD, with reported rates of ≤77% discontinuing their statins within 2 years. Adherence is better in patients recruited to clinical trials compared with those treated in the real world.[53,54] Not surprisingly, this non-adherence has an impact on healthcare costs, morbidity, hospital readmissions, and mortality.[55–59] Poor adherence rates are not only limited to statins but are also true of other lipid-lowering drugs and all medications used to prevent CVD, as demonstrated in a systematic review and meta-analysis.[60]

The reasons for non-adherence are complex and include misconceptions about tolerability on the part of both patients and professionals alike. These barriers prevent patients from gaining the maximum benefit from their treatment.

Various empirical models of health behaviour and behaviour change theory have been shown to predict adherence, including the Theory of Planned Behaviour[61] and the Health Belief Model.[62] Studies that have investigated adherence to medications in long-term conditions have identified factors such as high susceptibility, severity of the condition, strong intentions, and high self-efficacy as being associated with good adherence, while poor lifestyle habits and low perceived behavioural control are associated with poor adherence.[63] However, these theoretical models are limited in that they do not take into account important social, economic, health system, and therapy-related factors.[64] Most recently, the COM-B (Capability, Opportunity, and Motivation) theoretical model[65] developed by Michie et al.,[66] which takes a broader look at factors influencing adherence, has proposed a framework for assessing and addressing adherence, taking into account the interactions between capability (defined as both the psychological and physical capacity of an individual to engage in a behaviour), opportunities (defined as factors outside the control of an individual), and their motivation to do so.

Predictors of non-adherence with statins have been identified[48,67–69] and include their use in individuals for primary prevention as compared with their use in patients with disease, or with multiple risk factors, lower income, those who are elderly, complex polypharmacy, cost, and forgetfulness due to a lack of symptoms and psychological comorbidities. In addition, reasons for reluctance to collect a first prescription of statin medication were investigated in a cross-sectional telephone survey conducted in California from recruits to a randomized controlled trial (RCT).[70] The most commonly reported reasons included general concerns about the medication, wanting to try lifestyle measures first, and fear of adverse effects; however, a significant proportion reported financial hardship, or a lack of understanding of why they needed to take the medication and what the medication was for (indicating a need to address the patient–professional relationship and poor health literacy). Health literacy is defined as 'the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions' (http://nnlm.gov/outreach/consumer/hlthlit.html).

Poor health literacy is of particular concern in regard to medication adherence.[70] Elderly patients, and those with low socioeconomic status and chronic health conditions may be especially vulnerable. These patients may get confused, especially when their regimens are complex and include many drugs (polypharmacy) that need to be taken on more than one occasion per day. Important steps to empower patients to get more benefit from health interventions include the following[71]:

(1) Use good interpersonal skills (good eye contact and a warm manner) and an empathetic, non-judgmental attitude.
(2) Provide clear and simple instructions on a drug regimen backed up with written instructions, which can also be seen by a spouse or caregiver.
(3) Speak slowly in plain language and avoid medical jargon when giving instructions.
(4) Limit the number of instructions to no more than three key points (principle of 'need to know') (Supplementary *Figure 8*).
(5) Use 'teachback' to confirm understanding; e.g. 'I want to make sure that I explained things clearly. Let's review what we discussed. What are the three strategies that will help keep your cholesterol down?'
(6) Use supplemental materials—e.g. images, videos, and audio sources—to improve recall (Supplementary *Figure 9*).
(7) Encourage questions and discussion; enlist the family or others important to the individual.
(8) Motivational interviewing skills may be helpful in communicating with patients who are ambivalent, or who seem against starting or continuing with medications[72,73]:
    a. Counsel patients using the OARS method (**O**pen-ended questions, **A**ffirmation, **R**eflective listening, **S**ummarizing, see *Box 10* in the main document).

b. Use the 'elicit–provide–elicit' model to tailor the information you give (elicit what the patient wants to know, provide that information, and elicit from the patient how they can use this new knowledge to their benefit).
c. Acknowledge and reflect your patient's resistance.
d. Support your patient's autonomy to make their own decisions about their health and treatment.
e. Explore your patient's ambivalence to adhere to their treatment.
f. Develop a plan of action together and share decision-making.

(9) Build self-efficacy and confidence, drawing on social learning theory.[74]

Being able to identify patients with low health literacy is important. Indicators may include seeking help when an illness is already advanced, inarticulacy in explaining concerns, making excuses like 'I forgot my glasses' to cover for the shame associated with illiteracy, being passive or aggressive, and missing appointments.

Interventions to improve adherence were reviewed in a Cochrane review in 2010,[75] which looked at interventions to improve adherence to all forms of lipid-lowering therapy, including reminders, simplification of drug regimens, and provision of information and education. Most effective was reminders, such as setting alarms, connecting the taking of medication to other tasks to trigger memory, and phone reminders from nurses. Reminder systems have the potential to be developed with the help of innovations in technology, like the use of text messaging, the internet, and applications for mobile phones or tablets to assist in self-monitoring and management. Adherence research is weak in this area, mainly because it has not kept abreast of the rapid developments in technology[76]; however, these methods may come into their own in the future with a stronger knowledge base. Using information technologies to increase adherence is becoming increasingly important, especially since the current methods are not increasing adherence sufficiently. Electronic health records and e-prescription are increasingly being used. This can be used to flag high-risk patients, be a reminder for the patient and physician, and evaluate patient adherence and performance of the physician.[77]

Mobile technologies can be used to send reminders about or track medication, monitor activity and parameters like BP, and provide education for the patient.[78] The TEXTME trial showed that by using lifestyle-focused text messaging, it was possible to reduce BP, LDL-C, smoking, and BMI.[79] However, most trials assessing the effect of mobile technology on adherence are small and of short duration, and RCTs are lacking.

Prescription of a statin should include a shared decision-making approach[80] that engages the patient in a discussion before initiating treatment, especially when it is being considered for primary prevention of CVD. This discussion should be based on risk estimation and adequate communication of this risk to patients. Involving the patient in such a way is likely to be empowering and motivate adherence. This discussion is not exclusively about the prescription of a statin to manage lipids; a comprehensive approach includes addressing all lifestyle and other biomedical factors that contribute to CV risk.

Once treatment has been prescribed, communication should focus on conveying achievements in reaching goals, assessment of adherence and possible reasons for non-adherence, such as adverse effects. In relation to lipid-lowering medications, and statins in particular, misconceptions and misleading media reports are in abundance. Many patients report adverse effects of statins to their general practitioners and this may be because of an increased likelihood of anticipating them. However, a recent large review of RCTs[81] found that in 83 880 patients receiving blinded placebo-controlled statin therapy, few reported adverse effects were actually due to the drug being taken. This study calculated the PSN, defined as the proportion of symptoms not attributable to its pharmacological action, in order to provide general practitioners with a clear metric to use in advising their patients on whether reported symptoms are genuinely likely to be pharmacologically caused by the statin or not.

Recently, promising results for improving adherence have been demonstrated in the use of a fixed-dose combination drug or 'polypill' in both primary and secondary prevention. The Use of a Multidrug Pill In Reducing cardiovascular Events (UMPIRE) RCT[82] compared a fixed-dose combination containing aspirin, a statin, and two BP-lowering agents with usual care, in both primary and secondary prevention, in 2004 randomized patients in India and Europe. At 15 months, statistically significant differences between intervention and usual care were seen in self-reported adherence, and changes in systolic BP and LDL-C. The Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) study[83] had a cross-sectional first phase, which identified factors contributing to non-adherence after MI in 2118 patients from five countries in South America and Europe. In the second phase, 695 patients from the first phase were randomized to receive either a polypill—containing aspirin, statin, and ramipril in varying doses—or were given the three drugs separately. Adherence was measured with the self-reported Morisky–Green questionnaire and pill counts, and was statistically significantly superior in the intervention group compared with usual care at 9 months. In phase 1, factors associated with non-adherence were younger age, depression, complex regimen, poorer health insurance coverage, and low social support.

Given the demonstration of benefits for adherence with simplified dosing reported in a Cochrane overview of interventions to improve safe and effective medicine use by consumers,[84] it makes sense that a pill containing multiple medications in one tablet will enhance adherence. This overview also found that the use of self-management or self-monitoring programmes, as well as a regular pharmacy review of prescribed medications with a view to taking out unnecessary medications, was helpful.

Many of the studies included in the Cochrane review of interventions to improve medication adherence[76] drew on the support of allied professionals such as nurses and pharmacists to deliver complex interventions, which may include telephone follow-up, interim appointments, and monitoring of repeat prescriptions. The reviewed interventions may be difficult to replicate in everyday clinical care due to the cost and the availability of personnel. Team-based care, where nurse practitioners focus on chronic disease management, patient education, and transitions of care, and pharmacists assist with adherence to therapy and help patients with complex therapies, will increase adherence.[85] Drawing on the support of non-professional people within the social context of the patient—such as spouses, other family members, caregivers, or other key figures, as well as lay groups in the community—may prove to be a cost-effective way to improve adherence.

Supplementary Box 2 lists a number of tips for use when prescribing multiple medications to patients in order to help them adhere.

Supplementary Box 2 Tips to aid adherence to multiple drug therapies

'Agree on' rather than 'dictate' a drug regimen with your patient, and tailor it to his/her personal lifestyle and needs.
Back up verbal instructions with clear written instructions.
Simplify the dosing regimen and consider a fixed-dose combination pill where available.
Perform a regular review of medicines to minimize polypharmacy (or ask the pharmacist to assist).
Encourage self-monitoring, and use cues and technologies to act as reminders.
Provide information on common side effects and discuss management strategies.
Involve the partner, other family members, or the caregiver in the patient's treatment.

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