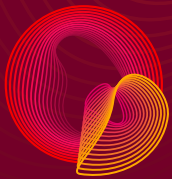

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The Clinician's Handbook: Dyslipidaemia and Atherosclerosis Prevention, Diagnosis and Treatment 2019 - Update 2023

A case-oriented approach to understanding the role of lipids and lipoproteins in atherosclerosis and cardiovascular disease, and recommendations for diagnosis and treatment

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ABBREVIATIONS AND ACRONYMS

ABI	Ankle brachial index
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ALT	Alanine aminotransferase
Apo(a)	Apolipoprotein(a)
ApoB	Apolipoprotein B
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
ASCVD	Atherosclerotic cardiovascular disease
AU	Agatston Unit
b.i.d.	Twice a day (bis in die)
BMI	Body mass index
BP	Blood pressure
CAC	Coronary artery calcium
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CKD	Chronic kidney disease
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DLCN	Dutch Lipid Clinic Network
DM	Diabetes mellitus
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
FCH	Familial combined hyperlipidaemia
FCS	Familial chylomicronaemia syndrome
FH	Familial hypercholesterolaemia
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol
HCTZ	Hydrochlorothiazide
HFpEF	Heart failure with preserved ejection fraction
IMT	Intima-media thickness
LAD	Left anterior descending
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	Lipoprotein(a)
LV	Left ventricular
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NT-proBNP	N-terminal pro B-type natriuretic peptide
o.d.	Once a day (omni die)
PAD	Peripheral arterial disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
REDUCE-IT	Reduction of Cardiovascular Events with EPA- Intervention Trial
SAMS	Statin-associated muscle symptoms
SCORE	Systematic Coronary Risk Estimation
SGLT2	Sodium glucose cotransporter 2
TC	Total cholesterol
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TGs	Triglycerides
TIA	Transient ischaemic attack
TRL	Triglyceride-rich lipoprotein
TSH	Thyroid stimulating hormone

THE CLINICIAN'S HANDBOOK

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Introduction

In recent years knowledge about lipids and lipoproteins as causative risk factors for atherosclerotic cardiovascular disease (ASCVD) has increased dramatically, largely due to new genetic tools that have aided our understanding of these connections. Not only were old lipid lowering drugs shown to reduce risk for ASCVD, but also new drugs, based on new concepts. Therefore new guidelines from the EAS and ESC were needed. The 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias (1) provide a thorough background to the guidelines, new treatments, and treatment goals.

Since the publication of the guidelines new lipid lowering drugs have been approved by European Medicines Agency (EMA) and in US by Food and Drug Administration (FDA), In this updated version of the Handbook, the role of these drugs is discussed in relation to the presented cases.

Additional EAS recommendations regarding Lp(a) assessment (2), the atherogenicity of hypertriglyceridemia (3) were published between 2020 and 2022. Furthermore, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice have been published (4).

The aim of this handbook is to use a case-oriented approach to discuss the guidelines. The selected cases represent common clinical situations where the guidelines should be adopted. They provide guidance for daily work with patients and could also be a basis for further discussion. The cases are based on actual cases and clinical experience.

As an introduction, a brief review of the guidelines is given, including some key tables that will be referred to in the case discussions. These tables are referred to by table number; in the cases tables are referred to as boxes, numbered separately for each case.

Lipid analyses

What lipids to analyse is thoroughly discussed in the guidelines. For a routine lipid analysis total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) are recommended. There is also emphasis on triglyceride-rich lipoproteins (TRL) and their remnants, which can be analysed as apolipoprotein B (ApoB) or as non-HDL-C. ApoB and non-HDL-C

Table 1 • Recommendations for lipid analyses for cardiovascular disease risk estimation.

Recommendations	Class[a]	Level[b]
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
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
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

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.
[a]Class of recommendation; [b]Level of evidence.

are recommended as secondary targets for treatment in patients with elevated TG, diabetes or the metabolic syndrome (***Table 1***).

Lp(a) measurement is getting more consideration due to a large new body of scientific and clinical evidence that has been recapitulated in our consensus (2). A tool to improve risk stratification is provided at http://www.lpaclinicalguidance.com/ and Lp(a) is a potential target when the results of CVOTs using anti apo(a) drugs is available.

Assessment of cardiovascular risk

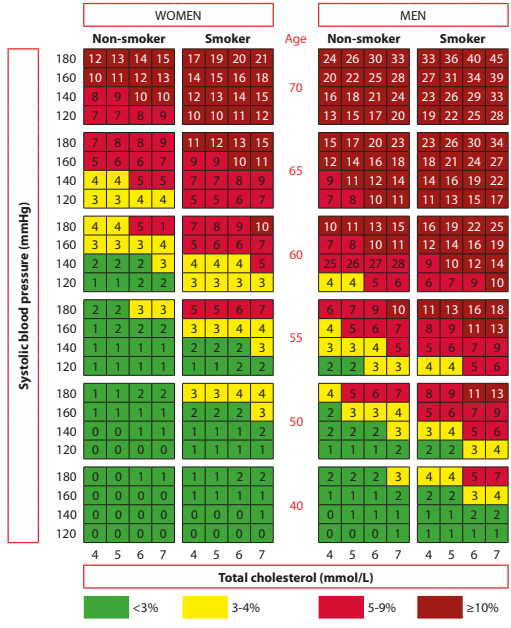
Estimation of cardiovascular risk is the most important first step in evaluation and decisions regarding treatment. In the guidelines cardiovascular (CV) risk means the likelihood of a person developing an atherosclerotic CV event over a defined period of time. Total cardiovascular disease (CVD) risk accounts for

Table 2 • SCORE chart for European Populations at high cardiovascular disease risk.

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

High-risk regions of Europe



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.

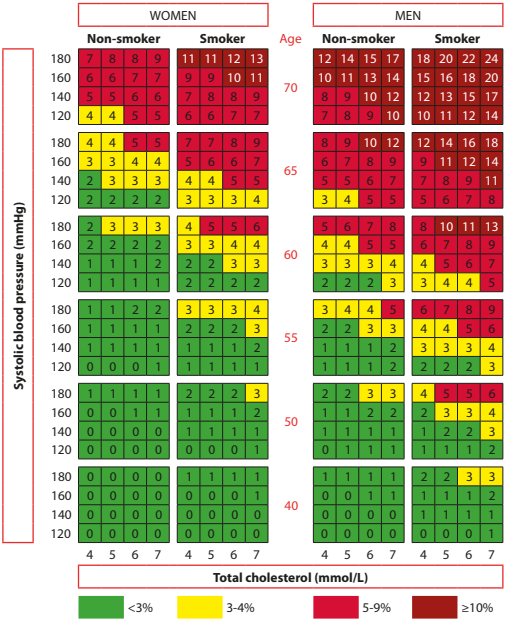
the combined effect of a number of risk factors on this risk estimate. The basis for risk estimation in the guidelines is the SCORE diagrams, which estimate the 10-year cumulative risk of a first fatal atherosclerotic CV event, based on age, gender, smoking, systolic blood pressure and TC. ***Tables 2*** and ***3*** show the charts for high- and low-risk regions in Europe.

Table 3 • SCORE chart for European Populations at low cardiovascular disease risk.

SCORE Cardiovascular Risk Chart

10-year risk of fatal CVD

Low-risk regions of Europe



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.

SCORE has several limitations:

- SCORE may give a false impression of low risk in young people.
- SCORE does not take into account a number of other risk factors that will modify the total risk (***Table 4***).
- SCORE does not include the elderly (>70 years of age).

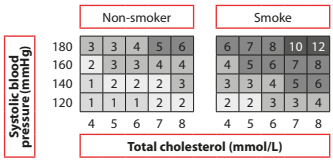
These and other aspects of risk estimation will be discussed in the cases.

Table 4 • Factors modifying Systematic Coronary Risk Estimation (SCORE) risk.

Social deprivation – the origin of many of the causes of CVD.
Obesity and central obesity, as measured by 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.
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.

CVD = cardiovascular disease.

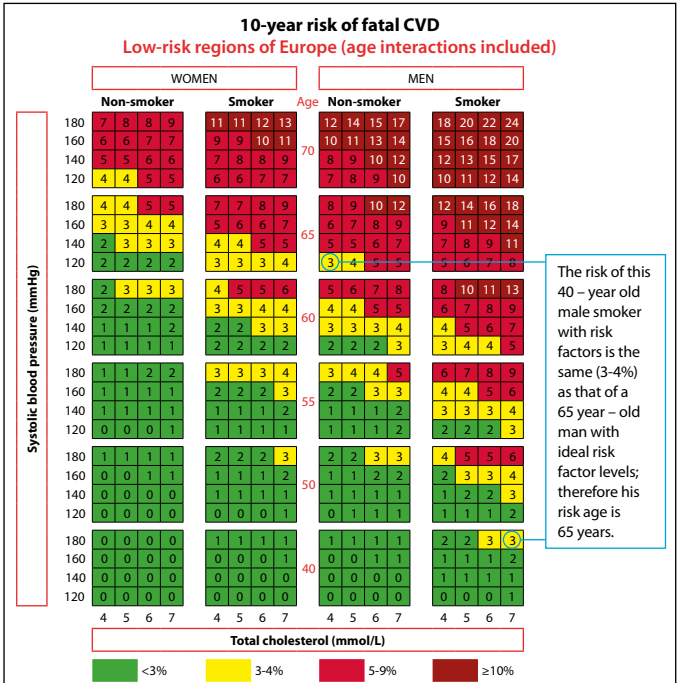
Table 5 • Chart for estimating the relative risk for 10-year cardiovascular mortality in young people.



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 mmHg and cholesterol of 4 mmol/L (bottom left corner). Cholesterol: 1 mmol/L = 38.67 mg/dL.

To better understand the risk concept other approaches to risk have been applied. One is to present risk as relative risk, i.e., a person's risk in relation to a case with optimal risk factor control (***Table 5***). Another approach presents risk as risk age, comparing a person's risk with the age of a person with the same risk, but with optimal risk factor control (***Table 6***).

Table 6 • Illustration of the risk age concept.



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.

Cardiovascular risk categories

To define optimal treatment the cases are categorized into four different levels of risk, according to SCORE, other risk factors and medical history. Definition of the risk categories is given in ***Table 7***. The very-high-risk subjects, i.e. those with the highest risk, benefit most from intense treatment with the best cost-benefit.

Less intense but still very efficacious lipid lowering is recommended for high-risk patients. Treatment may be considered in moderate-risk patients with a high level of low-density lipoprotein cholesterol (LDL-C) or other complicating factors.

Treatment goals

Treatment strategies and goals are summarized in ***Tables 8-10***. Compared with previous guidelines LDL-C goals are lowered to <1.4 mmol/L (<55 mg/dL) for very-high-risk patients and <1.8 mmol/L (<70 mg/dL) for high-risk patients, together with a reduction of LDL-C by at least 50% from baseline. The specific goals are given in ***Table 9***.

Furthermore, goals for ApoB and non-HDL-C are given as secondary targets. ApoB or non-HDL-C should be especially considered in patients with diabetes or the metabolic syndrome. Treatment goals for ApoB and non-HDL-C are defined in Cases 3 and 4.

Table 7 • Cardiovascular risk categories.

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 revascularization (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). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

Table 8 • 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 7)	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	I/C	I/C	IIa/A	IIa/A
	≥5 to <10, or high- risk (see table 7)	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]	I/C	I/C	I/C	I/C	IIa/A	IIa/A
	≥10, or at very-high- risk due to a risk condition (see table 7)	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]	I/C	I/C	I/C	I/C	IIa/A	IIa/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]	I/C	I/C	I/C	I/C	IIa/A	IIa/A

CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic Coronary Risk Estimation.
[a]Class of recommendation; [b]Level of evidence.

Table 9 • Recommendations for treatment goals for low-density lipoprotein cholesterol.

Recommendations	Class[a]	Level[b]
In secondary prevention patients at very-high-risk[c], 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	A
In primary prevention, for individuals at very-high-risk but without FH[c], 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[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
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,[c] 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
In individuals at moderate-risk[c], an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	IIa	A
In individuals at low-risk[c], an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.	IIb	A

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 7; [d]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.

Treatment

While the guidelines focus on dyslipidaemias, general risk factor treatment is also important, see ***Tables 10*** and ***11***.

Table 10 • Treatment targets and goals for cardiovascular disease prevention.

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]
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 a goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-C-lowering therapy. Current LDL-C-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 a goal of <1.8 mmol/L (<70 mg/dL). **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).

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated; [b]The 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.

In the treatment of dyslipidaemia a healthy lifestyle, especially diet, is the basis for success. Dietary guidelines are given in ***Table 11***. In many patients pharmacological treatment is needed to reach goals. Statins are always the first drugs of choice, but recent studies also emphasize the role of additional nonstatin drugs to reach goal. Both cholesterol absorption inhibitors and PCSK9 inhibitors are recommended, primarily as add- on treatments to a statin. Details on pharmacological treatment are given in ***Tables 9***, ***10***, ***12***, ***13***, ***14***.

Table 11 • Food choices to lower low-density lipoprotein cholesterol and improve the overall lipoprotein profile.

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
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
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
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

Table 12 • Recommendations for pharmacotherapy to lower low-density lipoprotein cholesterol.

Recommendations	Class[a]	Level[b]
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, combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention patients at very-high-risk not at goal[c] on a maximum tolerated dose of statin and ezetimibe, 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, 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.	II[a]	C
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[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 10.

Table 13 • 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.

Table 14 • Recommendations for lipid-lowering therapy in very-high-risk patients with acute coronary syndromes.

Recommendations	Class[a]	Level[b]
In all ACS patients without any contraindication 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 LDL-C goal <1.4 mmol/L (<55 mg/dL) have been achieved. Safety issues need to be assessed at this time and statin 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
If the LDL-C goal is not achieved after 4–6 weeks despite maximally tolerated statin therapy and ezetimibe, adding a PCSK9 inhibitor is recommended.	I	B
In patients with confirmed statin intolerance or 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

ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation; [b]Level of evidence.

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COMMENTS TO THE HANDBOOK IN ITS UPDATED VERSION 2023

RECENTLY APPROVED DRUGS

Since the publication of the guidelines new lipid lowering drugs have been approved by European Medicines Agency (EMA) and in the US by the Food and Drug Administration (FDA): inclisiran (Leqvio®), bempedoic acid (Nilemdo®), bempedoic acid in combination with ezetimibe (Nustendi®), icosapent ethyl (Vazkepa®) and volanesorsen (Waylivra®), and these are available for prescription in several countries.

Inclisiran

Inclisiran is a small interfering RNA blocking the synthesis of PCSK9. This is different from the antibody-based drugs that block PCSK9 function by binding circulating PCSK9 extracellularly. Inclisiran reduces LDL-C by about 50%, which is somewhat less than the antibody-based PCSK9 inhibitors (evolocumab and alirocumab). The drug is well tolerated and the most common side effect is injection site reaction. Recommended dosing of inclisiran is 284 mg as subcutaneous injection, initial dose followed by the same dose at three months and after that every six months. Thus, the dosing pattern might be more convenient compared with the antibody-based PCSK-9 inhibitors, possibly resulting in better compliance.

According to EMA inclisiran is indicated:

in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia), as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Clinical controlled end-point studies are lacking for inclisiran, but studies are ongoing.

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Bempedoic acid

Bempedoic acid is a prodrug, which is metabolized in the liver to its active form. Bempedoic acid inhibits the enzyme adenosine triphosphate (ATP)-citrate lyase, which lies two steps upstream from β-hydroxy β-methylglutaryl-CoA reductase in the cholesterol biosynthesis pathway. The recommended dose of bempedoic acid is 180 mg once daily.

In studies on patients with hypercholesterolaemia, bempedoic acid has been found to reduce LDL-C by about 17% in patients taking statin, and 24% in patients not on statin.

Bempedoic acid is also available in combination with ezetimibe. On top of statin the combination has been found to reduce LDL-C by about 35-40%.

According to EMA bempedoic acid is indicated:

in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.

Bempedoic acid has been found to increase plasma uric acid and the frequency of gout. Interestingly plasma levels of C-reactive protein is reduced and there is no clinically relevant effect on blood glucose or on glycated haemoglobin. A small increase in the occurrence of Achilles tendon rupture has also been observed.

Bempedoic acid should be avoided in patients with increased risk for Achilles tendon rupture.

Due to drug interactions bempedoic acid should not be given in combination with high dose simvastatin (>20 mg). Among statin-intolerant patients with a base line LDL-C at 139 mg/dL, treatment with bempedoic acid 180 mg/d (40.6 months median follow-up) decreased LDL-C plasma concentration by 21% versus placebo and reduced by 13.3% the risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) in the CLEAR Outcomes trial. (Nissen et al.).

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Icosapent ethyl

Icosapent ethyl (Vazkepa®) is a highly purified ethyl ester of icosapentaenoic acid, a Long Chain omega-3 fatty acid. At the dose of 4 g/day the drug has been shown to reduce cardiovascular disease in patients with established cardiovascular disease or diabetes with one additional risk factor (REDUCE-IT). The exact mechanism how icosapent ethyl reduces cardiovascular risk is not known. The drug reduces TG up to 20%. However, in REDUCE-IT the risk reduction was not correlated to TG reduction.

According to EMA icosapent ethyl is indicated:

to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and established cardiovascular disease, or diabetes and at least one other cardiovascular risk factor.

Icosapent ethyl is well tolerated. In RECUCE-IT, a small but significant increase in bleeding and atrial fibrillation was observed. Atrial fibrillation was more frequent in patients with a history of atrial fibrillation or flutter.

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Volanesorsen

Volanesorsen (Waylivra®) is an antisense oligonucleotide that binds to ApoC-III mRNA to prevent its translation and to decrease plasma ApoC-III. ApoC-III is an apolipoprotein which increases VLDL production and inhibits LPL activity and the hepatic clearance of triglyceride rich lipoproteins. The drug has been shown to decrease plasma triglyceride concentration in Familial Chylomiconemia syndrome and in Multifactorial Chylomicronemia syndrome.

According to EMEA Volanesorsen is indicated:

as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

The recommended starting dose is 285 mg injected subcutaneously once weekly for 3 months and subsequently every 2 weeks. Treatment should be initiated by and remain under the supervision of a physician experienced in the treatment of patients with FCS. Due to the occurrence of thrombopenia a tight monitoring of platelet count must be implemented and treatment must be adjusted according to the platelet count.

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RECENT RELATED PUBLICATIONS (2021-2022)

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

ESC published in 2021 global guidelines on cardiovascular disease prevention. In these guidelines the overall prevention is considered, such as hypertension, smoking, stress, diabetes, obesity etc.. Regarding dyslipidaemia the approach is somewhat different compared to the 2019 dyslipidaemia guidelines, with a stepwise introduction of treatment. However, the ultimate LDL-C goals are the same in both guidelines. Furthermore, all recommendations about treatments are almost identical.

In the 2021 guidelines a new risk-estimation tool is introduced (SCORE2). SCORE2 is based on non-HDL and estimates the risk for total cardiovascular events. SCORE is based on plasma cholesterol and estimates risk for cardiovascular death only. No obvious direct calibration between the two

systems is available, but a similar classification in very high, high and moderate risk groups are proposed in both guidelines. A new risk estimation system for older people (>70 years) is introduced, SCORE-OP. The previous SCORE algorithm is not adapted for people >70.

This Handbook is referring to the Dyslipidaemia and Atherosclerosis Prevention guidelines 2019, therefore we will use SCORE risk estimations in the case-discussions.

It should also be emphasized that in most cases the classification to high or very high risk is not based on SCORE but on the presence of clinical or subclinical disease or other preexisting conditions, as indicated below.

Very-high-risk subjects, independent of SCORE

- Documented ASCVD, either clinical or unequivocal on imaging.
  Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization.
- DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (>20 years).
- Severe CKD (eGFR <30 mL/min/1.73 m^2).
- FH with ASCVD or with another major risk factor.

High-risk subjects independent of SCORE

- 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 ≥180/110 mmHg.
- Patients with FH without other major risk factors.
- Patients with DM without target organ damage, with DM duration ≥10 years or another additional risk factors.
- Moderate CKD (eGFR 30–59 mL/min/1.73 m^2).

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Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement

This EAS consensus statement updates evidence for the role of Lp(a) in atherosclerotic cardiovascular disease (ASCVD) and aortic valve stenosis, provides clinical guidance for testing and treating elevated Lp(a) levels. It considers its inclusion in global risk estimation. Epidemiologic and genetic studies strongly support a causal and continuous association between Lp(a) concentration and cardiovascular outcomes in different ethnicities; elevated Lp(a) is a risk factor even at very low levels of low-density lipoprotein cholesterol.

High Lp(a) is associated with calcification of the aortic valve. It was not considered as a risk factor for venous thrombotic events and impaired fibrinolysis. Very low Lp(a) levels may associate with increased risk of diabetes mellitus meriting further study. Lp(a) has pro-inflammatory and pro-atherosclerotic properties, which may partly relate to its carried oxidized phospholipids.

Testing Lp(a) concentration at least once in adults and cascade testing in familial hypercholesterolaemia, or with family or personal history of (very) high Lp(a) or premature ASCVD is highly recommended. Without specific Lp(a)-lowering therapies, early intensive risk factor management is recommended, targeted according to global cardiovascular risk and Lp(a) level. Lipoprotein apheresis is an option for very high Lp(a) with progressive cardiovascular disease despite optimal management of risk factors. In conclusion, this statement reinforces evidence for Lp(a) as a causal risk factor for cardiovascular outcomes. Trials of specific Lp(a)-lowering treatments are ongoing and will be critical to confirm clinical benefit for cardiovascular disease and aortic valve stenosis.

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Triglyceride-rich lipoproteins and their remnants: metabolic insights, role in atherosclerotic cardiovascular disease, and emerging therapeutic strategies—a consensus statement from the European Atherosclerosis Society

The EAS consensus statement on triglyceride-rich lipoproteins and their remnants aims to define what is known about their structure, function, metabolism, and atherogenicity and to identify targeted therapeutic approaches to address residual risk associated with elevated TG levels.

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CASE 1. Very-high-risk patient in secondary prevention

Background data

The patient is a 60-year old, self-employed businessman, married with three adult children. He has for many years smoked 10 cigarettes a day. He comes to your clinic for a health check-up at his wife's insistence.

What do we need to know to estimate his risk?

Medical history

The patient had a subendocardial myocardial infarction (MI) 5 years ago. He was referred back to his GP but was lost to all follow-up. He is not currently taking medication, and has no family history of early CVD. There is no current history of chest pain.

Risk factors

Smoker, body mass index (BMI) 29 kg/m^2, waist circumference 105 cm, low physical activity.

Physical status: Moderate abdominal obesity. No xanthomas. Heart auscultation normal. Blood pressure (BP) 145/90 mmHg. Peripheral circulation normal.

Laboratory tests

On ECG there were no signs of his previous MI.

TC	5.2 mmol/L	(200 mg/dL)
TG	2.2 mmol/L	(193 mg/dL)
HDL-C	1.0 mmol/L	(38 mg/dL)
LDL-C	3.2 mmol/L	(123 mg/dL)

Blood glucose 6.9 mmol/L (124 mg/dL); Lp(a) 200 mg/dL.

What risk category is the patient?

The patient has a history of ASCVD which immediately makes him a very-high-risk patient (***Table 7***).

Without the previous MI the patient would be at high-risk with 6% risk for CVD death in 10 years based on SCORE (***Table 2***). Furthermore, the presence of abdominal obesity, high TG and low HDL-C and a high Lp(a) adds to his risk (***Table 4***). Thus SCORE is underestimating his risk.

Treatment

*Recommendation in **Table 8** is: Lifestyle intervention and concomitant drug intervention.*

In addition to pharmacological treatment a number of lifestyle factors should be intensely targeted. These include: stop smoking, increase physical activity, lose weight and aim for a more healthy diet (***Table 10***). The LDL-C goal is below 1.4 mmol/L (<55 mg/dL) (***Tables 9***, ***10***) and at least 50% reduction from the starting LDL-C. To achieve this goal treatment with a high intensity statin is recommended (***Table 12***). His moderately elevated blood pressure should be treated.

Actions taken

Quit-smoking programme, dietary advice and information about physical activity preferably, if available, in group sessions. Treatment started: atorvastatin 80 mg once daily (o.d.), angiotensin converting enzyme (ACE) inhibitor (enalapril 5 mg o.d.) and acetylsalicylic acid (75 mg per day).

Follow-up after 6 weeks

The patient has stopped smoking but has not lost weight. BP is 135/85 mmHg.

TC	3.6 mmol/L	(139 mg/dL)
TG	2.0 mmol/L	(177 mg/dL)
HDL-C	1.0 mmol/L	(38 mg/dL)
LDL-C	1.6 mmol/L	(61 mg/dL)

The patient has achieved a 50% reduction of LDL-C but is still not at target, i.e., below 1.4 mmol/L (<55 mg/dL). According to the guidelines (***Table 12***) ezetimibe 10 mg o.d. should be added.

Follow-up after a further 6 weeks

The patient is still a non-smoker. He tolerates his medication well and has lost 1 kg.

TC	3.4 mmol/L	(131 mg/dL)
TG	1.9 mmol/L	(168 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	1.4 mmol/L	(55 mg/dL)

As this patient had high TG initially we should also consider ApoB; this patient has reached the goal of <65 mg/dL.

Subsequent follow-up

Once the patient has achieved his targets follow-up regarding risk factors may be limited to once a year. However, adherence may be improved with closer follow-up and more discussion with the patient about his risk factors.

Comment 2023

The patient has reached his goal on current drugs. Further reduction of LDL C is not recommended and the patient is not fulfilling the criteria for treatment with icosapent ethyl. His very high Lp(a) plasma concentration should be kept in mind regarding the result of ongoing CVOT trials.
It raises the question of a familial screening.

CASE 2. Very-high-risk patient with a recurrent event (within 2 years)

Background data

The patient is a 66-year old man who has retired from work as a salesman. He is married with three adult children. He is a non-smoker, but has a history of hypertension that has been treated for 5 years with an ACE inhibitor. He has a family history of CVD; his father had an MI aged 67 and a brother died suddenly aged 63. His BMI is 24 kg/m^2.

The patient is now hospitalized with chest pain.
He is diagnosed with a subendocardial MI. Coronary angiography shows a high grade stenosis in a branch, which is treated with dilatation and stenting.

What do we need to know to estimate his risk?

His lipid profile from a sample taken the first day in hospital is:

TC	6.0 mmol/L	(231 mg/dL)
TG	1.8 mmol/L	(157 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	4.0 mmol/L	(155 mg/dL)

What risk category is the patient?

When the patient leaves hospital on the third day, what lipid lowering would you give him?
After this first MI the patient is at very-high-risk for future CV events (***Box 2.1***).

According to ***Table 9*** his LDL-C goal should be below 1.4 mmol/L (<55 mg/dL) and a 50% reduction from his starting level. To achieve this he is prescribed atorvastatin 80 mg o.d. In addition, he is prescribed an ACE inhibitor and antithrombotic drugs.

Box 2.1 • Cardiovascular risk categories.

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 revascularization (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). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated GFR; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

Follow-up after 6 weeks

At this follow-up visit the patient is in a generally good state, reports no chest pain and exercises with walks daily. Plasma lipid testing shows the following:

TC	4.0 mmol/L	(154 mg/dL)
TG	1.5 mmol/L	(130 mg/dL)
HDL-C	1.3 mmol/L	(50 mg/dL)
LDL-C	2.1 mmol/L	(80 mg/dL)

Is the LDL-C reduction at goal? No, as it is not below 1.4 mmol/L (<55 mg/dL), and he does not have 50% reduction from starting LDL-C (***Box 2.2***). What to do? Encourage the patient to take the prescribed medication, and go over, and give advice on his diet. Will this make him reach the goal? Probably not! Add ezetimibe 10 mg o.d. (***Table 14***).

Box 2.2 • Recommendations for treatment goals for low-density lipoprotein cholesterol.

Recommendations	Class[a]	Level[b]
In secondary prevention patients at very-high-risk[c], 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	A
In primary prevention, for individuals at very-high-risk but without FH[c], 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[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
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,[c] 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
In individuals at moderate-risk[c], an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	IIa	A
In individuals at low-risk[c], an LDL-C goal of <3.0 mmol/L (<116 mg/dL) may be considered.	IIb	A

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 7; [d]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.

Follow-up after a further 2 months

The patient is still in good shape, and reports no chest pains. Lipid testing at this visit is as follows:

TC	3.5 mmol/L	(135 mg/dL)
TG	1.5 mmol/L	(130 mg/dL)
HDL-C	1.3 mmol/L	(50 mg/dL)
LDL-C	1.5 mmol/L	(58 mg/dL)

Are we happy with this? The patient has achieved more than 50% reduction of LDL-C and is almost at LDL-C goal (***Box 2.2***). Adding another drug (PCSK9

Box 2.3 • Recommendations for pharmacological low-density lipoprotein cholesterol lowering.

Recommendations	Class[a]	Level[b]
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, combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention patients at very-high-risk not achieving their goal[c] on a maximum tolerated dose of statin and ezetimibe, 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, 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.	IIa	C
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[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 10.

inhibitor) in this situation may be considered (***Box 2.3***). A good judgement is to continue the same medication, as he has responded well and is almost at goal. Encourage improved lifestyle and diet.

Ten months later the patient comes to the hospital with chest pains

He now develops a new non-ST elevation acute coronary syndrome (ACS). Coronary angiography shows a thrombus in the left anterior descending (LAD) artery. The vessel is dilated and stented. There are also non-significant lesions at several other locations in all three coronary vessels. The patient recovers and is discharged to home. On discharge, his lipid status is as follows:

TC	3.5 mmol/L	(135 mg/dL)
TG	1.6 mmol/L	(141 mg/dL)
HDL-C	1.3 mmol/L	(50 mg/dL)
LDL-C	1.5 mmol/L	(58 mg/dL)

He is almost at LDL-C target for very-high-risk patients. Good? No, looking at ***Table 9*** he now belongs to a very-very-high-risk group with a recurrent event within 2 years, for whom a LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered (***Box 2.2***). So, do you think this patient should be treated for further LDL-C reduction? With widespread atherosclerosis in his coronaries and two recent MI, available data in this very-very-high-risk group suggest a substantial benefit from reducing LDL-C even below 1.0 mmol/L (40 mg/dL). Thus a PCSK9 inhibitor can be considered on top of current treatment.
He starts a PCSK9 inhibitor with injection every 2 weeks.

Follow-up after a further 4 weeks

The patient is responding well to his treatment and his LDL-C is 0.8 mmol/L (31 mg/dL). He does not report any side-effects and manages the injections very well. Prolonged dual antiplatelet therapy should also be considered.

Comment 2023

The patient is now on treatment goal and tolerates current drugs well. If the number of subcutaneous injection and the overall observance was a matter, inclisiran could be an alternative. However, in this case there was no problem with adherence to current treatment.

CASE 3. Diabetes patient at high-risk for ASCVD (Physically active man with Type 2 diabetes)

Background data

The patient is a 60-year old man with Type 2 diabetes (T2DM) diagnosed at age 56 years. He is married with two adult children. He has a family history of DM. He has never smoked and is physically active, playing tennis once a week and doing Nordic walking twice a week. He comes to his annual check-up at your clinic.

What do we need to know to estimate his risk?

Medical history

The patient has no current history of chest pain, palpitation or symptoms of cardiac disease. When questioned he reports feeling occasionally some shortness of breath after climbing up three floors of stairs to his office, but does not need to stop. There is no family history of early CVD. He also reports occasional cramps in his calves when doing Nordic walking, but the pain disappears when stopping.

Current medication

He is taking metformin 1.0 g twice-daily (b.i.d.), and sitagliptin 50 mg b.i.d. for glucose control. Enalapril comp o.d. (enalapril 20 mg + hydrochlorothiazide (HCTZ) 12.5 mg) was started 2 years ago to treat hypertension.

Risk factors

Non-smoker**,** T2DM duration less than 10 years, physically active.

Physical status

Moderate abdominal obesity with BMI 29.5 kg/m^2, waist circumference 98 cm, BP 135/90 mmHg, heart and lung auscultation normal.

Peripheral pulse palpitation: arteria (a.) poplitea ++/++, a. posterial tibial +/+, a. dorsalis pedis +/.

Laboratory tests

HbA1c is 7.8% (50 mmol/mol), and fasting blood glucose is 7.6 mmol/L (134 mg/dL). Self-monitoring of blood glucose at home gives values between 6.8 - 8.1 mmol/L (122 -148 mg/dL). Lipid testing results are as follows:

TC	4.4 mmol/L	(169 mg/dL)
TG	2.5 mmol/L	(220 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	2.5 mmol/L	(96 mg/dL)

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are within the normal range, serum-creatinine is 78 µmol/L, and eGFR = 75 mL/min/1.73 m^2 (normal). There is no microalbuminuria, and the 10-g monofilament test is normal.

What risk category is the patient?

As the patient has T2DM for less than 10 years without any clear organ damage and one additional risk factor (hypertension) he is at high-risk (see ***Table 7***).

Treatment

According to ***Box 3.1*** the patient has two risk factors that are not at goal: LDL-C and HbA1c. Non-HDL-C is also recommended as an additional risk index in diabetes patients (recommendations for lipid analyses in risk estimation are given in ***Table 1***).

LDL-C goals in this patient are 50% reduction in LDL-C and below 1.8 mmol/L (<70 mg/dL) (***Box 3.1***). In addition non-HDL-C is recommended as a secondary target with a goal below 2.6 mmol/L (<100 mg/dL) for diabetes patients at high-risk (***Box 3.2***).

As 50% reduction in LDL-C is required, a high intensity statin is needed.

Actions taken

As his medical history indicates potential for heart failure and peripheral artery disease (PAD) further evaluations are needed. The patient is referred for cardiology consultation.

Chest X-ray shows no clear dilation of the heart and the resting 12 - lead ECG shows no clear signals for left ventricular (LV) hypertrophy. Echocardiography shows a normal ejection fraction but suggests signals for mild heart failure

with preserved ejection fraction (HFpEF). NT-proBNP (N-terminal pro B-type natriuretic peptide) is mildly elevated. Treadmill exercise testing reveals mildly reduced exercise capacity as the peak workload was 70% with no signs of ischaemia.

Box 3.1 • Treatment targets and goals for cardiovascular disease prevention.

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]
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 a goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-C-lowering therapy. Current LDL-C-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 a goal of <1.8 mmol/L (<70 mg/dL). **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).

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated; [b]The 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.

Box 3.2 • 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 TRL 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.

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; TRLs = triglyceride-rich lipoproteins.

To evaluate potential PAD, the ankle brachial index (ABI) was measured; this was 0.85 representing a borderline value (normal >0.90). A 6-minute walking test was normal and post-exercise ABI remained undiagnostic. Duplex ultrasound revealed only minor abnormalities.

Treatment

Rosuvastatin 20 mg o.d. was initiated. As HbA1c was not at goal (<7.0% or 53 mmol/mol) (***Box 3.1***), improvement of glycaemic control is necessary. Recommendations require the evaluation of CVD status in choosing the next glucose-lowering agent which should have proven CV benefit. There are two options: a sodium-glucose cotransporter 2 (SGLT2) inhibitor or a glucagon-like peptide-1 (GLP-1) receptor agonist (while stopping the gliptin). As there is a signal for mild HFpEF, a SGLT2 inhibitor is initiated given evidence of reduction in heart failure.

The patient is also counselled about the positive effects of physical exercise and LDL-C lowering to prevent PAD.

Follow-up at 6 weeks

Physical status

The patient feels well and tolerates both new medications. He has continued his physical activities and is improving his diet, decreasing saturated fat and increasing intake of vegetables and fruits. There are no complaints of chest pain or dyspnoea even when exercising.

He has lost 2 kg, BP is 130/90 mmHg, and 12-lead resting ECG and heart and lung auscultations were normal.

Laboratory tests

HbA1c is 6.8% (51 mmol/mol) and fasting glucose is 6.5 mmol/L (117 mg/dL). Self-monitoring blood glucose levels are normal, with no hypoglycaemic symptoms. Liver enzymes and creatine kinase (CK) are normal. Lipid testing was as follows:

TC	3.9 mmol/L	(150 mg/dL)
TG	2.1 mmol/L	(185 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	1.6 mmol/L	(61 mg/dL)
Non-HDL-C	2.3 mmol/L	(88 mg/dL)

LDL-C goal [<1.8 mmol/L (<70 mg/dL)] and non-HDL-C goal [<2.6 mmol/L (<100 mg/dL)] have been achieved with current therapy.

The addition of a SGTL2 inhibitor on top of metformin + sitagliptin has reduced HbA1c below goal (<7% or 53 mmol/mol).

Subsequent follow-up

Follow-up of glucose and lipid control is recommended every 6 months. Repeat cardiac echography, NT-proBNP and ABI measurement are recommended annually in addition to careful follow-up of symptoms / signals of PAD or heart failure.

Comment 2023

Icosapent ethyl is now an available option. However on the top of rosuvastatin + ezetimibe combination + Liraglutide when both LDL and TG goals in high risk subjects are achieved and no side effects are reported there is no obvious need. Additionally the risk of atrial fibrillation already high in T2D may be increased by the high dose of EPA.

CASE 4. Diabetes patient at very-high-risk (A problematic diabetes patient)

Background data

The patient is a 66-year old man with T2DM (age at diagnosis 60 years), who retired a year ago. His wife had died due to cancer 2 years ago. He is an occasional smoker, but reports smoking more since the death of his wife. He comes for a routine diabetes check-up at the General Practitioner clinic.

What do we need to know to estimate his risk?

Medical history

His mother also had T2DM and died aged 72 years due to an acute MI. He has been on hypertension medication for 2 years (lisinopril 20 mg/HCTZ 12.5 mg daily). He also started simvastatin 20 mg o.d. at the same time as his LDL-C was 3.3 mmol/L (127 mg/dL).

He missed his earlier check-up 6 months ago. He sleeps badly and feels depressed. He is physically inactive. There is no history of chest pain or dyspnoea.

Diabetes medication

Metformin 1.0 g b.i.d. and saxagliptin 5 mg o.d. No self-monitoring of blood glucose.

Risk factors

The patient would be at very-high-risk according to ***Box 4.1*** as he has diabetes and three major risk factors (smoking, hypertension and dyslipidaemia) even without prior CVD diagnosis.

Physical status

His weight is 91 kg, height 179 cm, BMI 30 kg/m^2, and waist circumference 100 cm, indicative of abdominal obesity. BP is 155/95 mmHg on medication. Heart and lung auscultation, and peripheral arterial pulses are normal, with no clinical signs of neuropathy.

Box 4.1 • Cardiovascular risk categories.

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 revascularization (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). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

Laboratory tests

HbA1c is 8.0% (61 mmol/mol) and fasting blood glucose 9.2 mmol/L (166 mg/dL). Lipid testing is as follows:

TC	5.2 mmol/L	(200 mg/dL)
TG	2.5 mmol/L	(222 mg/dL)
HDL-C	1.0 mmol/L	(40 mg/dL)
LDL-C	2.7 mmol/L	(104 mg/dL)

Estimated GFR is 72 mL/min/1.73 m^2 with no microalbuminuria, and liver enzymes and other blood tests are normal. Resting 12-lead ECG is normal.

What risk category is the patient?

The patient would be at very-high-risk according to ***Box 4.1*** as he has diabetes and three major risk factors (smoking, hypertension and dyslipidaemia) even without any organ damage or prior CVD diagnosis. SCORE tables are not useful as he has diabetes. As the patient has multiple problems he was referred to the out-patient diabetes clinic.

Action taken

He was intensively counselled about his very high CVD risk to motivate him to stop smoking, make lifestyle changes including improved diet and physical activity and adhere to medical therapy. He had several meetings with a multidisciplinary team. A depressive score test (PHQ9) was performed.

Treatment

Recommendations for diabetes patients at very-high-risk are reduction of LDL-C by 50% and LDL-C goal below 1.4 mmol/L (<55 mg/dL) (***Box 4.2***).
As this requires high intensity lipid lowering therapy simvastatin was stopped and rosuvastatin 20 mg o.d. was initiated (***Box 4.3***).

Glycaemic control was not acceptable as the HbA1c goal of <7.0% (53 mmol/mol) was not reached. The process of choosing glucose-lowering therapy on the top of metformin + dipeptidyl peptidase 4 inhibitor might be highlighted by an evaluation of CVD status.

Box 4.2 • Recommendations for the treatment of dyslipidaemia in diabetes mellitus.

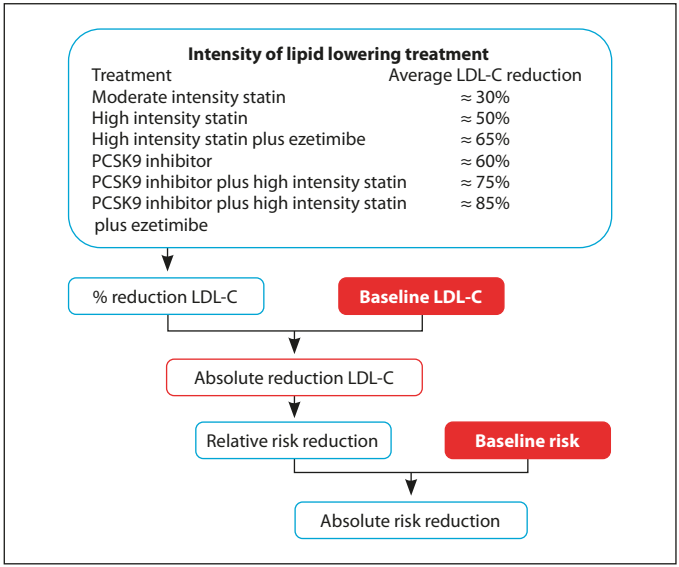
Recommendations	Class[a]	Level[b]
In patients with T2DM at very-high-risk[c], an LDL-C reduction of at least 50% from baseline and LDL-C goal of <1.4 mmol/L (55 mg/dL) is recommended.	I	A
In patients with T2DM at high-risk[c] can LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.8 mmol/L (< 70 mg/dL) is recommended.	I	A
Statins are recommended in patients with T1DM who are at high- or very-high-risk[c].	I	A
Intensification of statin therapy should be considered before the introduction of combination therapy.	IIa	C
If the goal is not reached, statin combination with a cholesterol absorption inhibitor 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 under the age of 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

LDL-C = low-density lipoprotein cholesterol; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Class of recommendation; [b]Level of evidence; [c]See *Table 10*.

Echocardiography was OK. As the patient had no signal suggestive of heart failure but had risk factors for accelerated atherosclerosis, a GLP-1 receptor agonist with proven CV benefit was initiated based on recent recommendations from the ADA and EASD. Stepwise increases of liraglutide were made to achieve injection of 1.8 mg daily following withdrawal of sitagliptin.

Hypertension therapy was not modified. Citalopram (10 mg) was initiated due to mild to moderate depression indicated by PHQ9 testing.

Box 4.3 • Expected clinical benefits of low-density lipoprotein cholesterol-lowering therapies.



Follow-up after 6 weeks

Physical status

The patient had stopped smoking and had lost 2 kg (body weight 89 kg), and his waist circumference was 96 cm. BP was 140/90 mmHg on lisinopril 20 mg/HCTZ 12.5 mg daily.

He had started walking about 30-45 minutes 2-3 times per week and joined a fitness club recommended by his friends. He reported mild nausea during the first 4 weeks on liraglutide therapy but the symptoms subsided gradually. His sleep pattern had changed positively. He was feeling well and was socially more active interacting with his children and grandchildren.

Laboratory tests

HbA1c was 7.3% (55 mmol/mol). Self-monitored fasting blood glucose levels were between 5.6 -7.2 mmol/L (100-130 mg/dL) during the last 2 weeks and postprandial values were less than 9.0 mmol/L (162 mg/dL). He reported no symptoms of hypoglycaemia. Lipid testing at this visit was:

TC	3.7 mmol/L	(141 mg/dL)
TG	2.0 mmol/L	(176 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	1.7 mmol/L	(66 mg/dL)
Non-HDL-C	2.6 mmol/L	(99 mg/dL)

ALT, AST, and creatine kinase (CK) were all normal.

Actions taken

Although the response to treatment changes was good targets for LDL-C <1.4 mmol/L (<55 mg/dL) and non-HDL-C <2.2 mmol/L (<85 mg/dL) were not achieved (***Boxes 4.3*** and ***4.4***). Add-on ezetimibe 10 mg o.d. was initiated instead of increasing the dose of rosuvastatin to 40 mg (***Box 4.3***). Counselling on his high-risk and the importance of controlling risk factors was emphasized.

Box 4.4 • Summary of dyslipidaemia in metabolic syndrome and type 2 diabetes mellitus.

Recommendations
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 TRL 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 patients high-risk. For patients 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.

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; TRLs = triglyceride-rich lipoproteins.

Follow-up after 3 months

Physical status

The patient has lost another 2 kg in weight (87 kg). Waist was 94 cm and BP 137/85 mmHg. He has continued to be physically active and a non-smoker, and reports feeling well. He has continued his medication as prescribed and had no problems with liraglutide.

Laboratory tests

HbA1c is 7.0 mmol/L (53 mmol/mol). Home blood glucose values are appropriate with none below 5.0 mmol/L (90 mg/dL) (fasting) or above 9.0 mmol/L (166 mg/dL) (postprandial) and no symptoms of hypoglycaemia.

Lipid values on rosuvastatin 20 mg + ezetimibe are as follows:

TC	3.2 mmol/L	(123 mg/dL)
TG	1.7 mmol/L	(150 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	1.3 mmol/L	(50 mg/dL)
Non-HDL-C	2.0 mmol/L	(77mg/dL)

Subsequent follow-up

Control of glycaemia, weight, lipids, and blood pressure have been very good and the targets were achieved (***Table 10***). Maintenance was emphasized. Follow-up was to be continued at 6-monthly intervals in the diabetes outpatient clinic but if he had any problems he was to contact the diabetes nurse at the clinic.

Comment 2023

Icosapent ethyl is now an available option. However on the top of rosuvastatin + ezetimibe combination + Liraglutide when LDL is at goal and TG are at an acceptable level in a high risk subject and no side effects are reported there is no obvious need. Additionally the risk of atrial fibrillation already high in T2D may be increased by the high dose of EPA.

CASE 5. Low-risk patient, primary prevention

Background data

The patient is a 50-year old female teacher, who is in good health. She is married with two adult children. Around the age of menopause, her gynaecologist undertook a check-up and referred her for advice due to the discovery of high total cholesterol (7.2 mmol/L or 280 mg/dL).

What do we need to know to estimate her risk?

Medical history

She has no significant medical history, no family history of CVD and is not taking any medication.

Risk factors

Non-smoker, BMI 23 kg/m^2, moderate physical activity.

Physical status

Physical examination including heart auscultation and peripheral circulation was normal. She reported recent tiredness and occasional moderate hair loss. BP was 125/80 mmHg.

Laboratory tests

TC	7.2 mmol/L	(280 mg/dL)
TG	1.4 mmol/L	(122 mg/dL)
HDL-C	1.8 mmol/L	(70 mg/dL)
LDL-C	4.8 mmol/L	(186 mg/dL)
Blood glucose	5.3 mmol/L	(96 mg/dL)

What should be the first step?

Sub-clinical hypothyroidism is common for females around the menopause. With the discovery of high cholesterol associated with some signals for hypothyroidism (asthenia, hair loss) we should check thyroid function.
Thyroid-stimulating hormone (TSH) was normal.

What risk category is the patient?

Using the SCORE table, the 10-year risk of fatal CVD is 0% in both high-risk and low-risk regions of Europe.
The patient is classified in the low-risk category.

Treatment

*Recommendation in **Table 8**: Lifestyle intervention, consider adding drug if uncontrolled.*
LDL-C lowering represents the primary target for lifestyle intervention. The recommended diet focuses on reduced consumption of saturated and trans fat, and increased dietary fibre and foods enriched with phytosterols (***Table 11***).

Actions taken

Advice about diet and regular physical activity.

Follow-up after 12 weeks

Physical status
No change in body weight, BP is 120/80 mmHg

Diet evaluation
Effective reduction of saturated fats.

Laboratory tests

TC	6.8 mmol/L	(263 mg/dL)
TG	1.3 mmol/L	(114 mg/dL)
HDL-C	1.8 mmol/L	(70 mg/dL)
LDL-C	4.4 mmol/L	(170 mg/dL)

According to the guidelines, an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered and pharmacological therapy is an option when the LDL-C goal is not achieved with lifestyle intervention. For this patient LDL-C remains far from the goal; however, the need for statin therapy was poorly received, including nutraceutical intervention. In this situation, a coronary artery calcium (CAC) score assessment with computed tomography should be considered.

The CAC score for this patient was 0 and the decision was to maintain lifestyle intervention alone.

Subsequent follow-up

Follow-up was advisable once a year to evaluate the lipid profile and lifestyle intervention. Family history for high LDL-C should be checked.

Comment 2023

The recommendations for this case remain unchanged. There is no indication to consider any of the new drugs. CAC score should be reiterated 5 years later.

CASE 6. Moderate-risk patient, primary prevention

Background data

The patient is a 55-year old man, working in a bank. A health check-up is required by his employer for a new insurance contract.

What do we need to know to estimate his risk?

Medical history

Family history of T2DM (father, grandmother). His father had an MI aged 62 years. He has no history of chest pain and is not on any medication.

Risk factors

Former smoker (stopped smoking aged 45 years), BMI 31 kg/m^2, waist circumference 108 cm (weight gain since stopping smoking), no physical activity.

Physical status

Abdominal obesity. No xanthomas. Normal physical examination. BP is 140/90 mmHg.

Laboratory tests

TC	6.0 mmol/L	(232 mg/dL)
TG	2.4 mmol/L	(210 mg/dL)
HDL-C	1.1 mmol/L	(43 mg/dL)
LDL-C	3.8 mmol/L	(147 mg/dL)

Blood glucose is 6.8 mmol/L (123 mg/dL), HbA1c 6.4%, eGFR 70 mL/min/1.73 m^2, and ALT 2 x upper limit of normal range.

What risk category is the patient?

Using SCORE (***Tables 2*** and ***3***), the 10-year risk of fatal CVD is 4% if the patient is resident in a high-risk region of Europe, or 2% if resident in a low-risk region. For both scenarios, the patient is classified as moderate-risk.
However, the patient has several factors (central obesity, physical inactivity) which modify this estimation of risk.

Treatment

*Recommendation in **Table 8**: Lifestyle intervention, consider adding drug if uncontrolled.*
Intense action on several lifestyle factors should be started, focusing on diet and exercise (reduction of caloric intake and regular moderate intensity exercise for ≥30 min/day).
The LDL-C goal for a patient at moderate-risk is <2.6 mmol/L (<100 mg/dL).

Actions taken

Dietary advice and advice for regular physical activity.

Follow-up after 8 weeks

Physical status
The patient has lost 3 kg but physical activity remains too low. Motivation for further weight loss is uncertain. There is no change in blood pressure.

Laboratory tests

TC	5.6 mmol/L	(217 mg/dL)
TG	2.0 mmol/L	(175 mg/dL)
HDL-C	1.1 mmol/L	(43 mg/dL)
LDL-C	3.6 mmol/L	(139 mg/dL)

Blood glucose is 6.7 mmol/L (120 mg/dL), HbA1c 6.3%, and ALT is 1.5 x upper limit of normal range.

There has been moderate improvement in the lipid profile, but persistence of moderately increased blood glucose and HbA1c (high risk of developing diabetes).

Actions taken

Beyond dietary advice, a moderate intensity statin is started with the expected ~ 30% reduction in LDL-C adequate to reach the LDL-C goal for moderate-risk patients. In parallel, an evaluation of sub-clinical atherosclerosis is proposed (CAC score) as a risk modifier in the risk assessment.

Follow-up after 8 weeks on atorvastatin 10 mg

Physical status

The patient tolerated atorvastatin 10 mg well and lost 1 kg.

Laboratory tests

TC	4.5 mmol/L	(174 mg/dL)
TG	1.8 mmol/L	(157 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	2.5 mmol/L	(97 mg/dL)

ALT was 1.7 x upper limit of normal range.

Result of CAC score

12 Agatston units.

This low CAC score, close to the 50th percentile, justified maintaining the patient in the moderate risk category.

Actions taken

Improvement of diet if feasible and continuation of the same treatment.

Further follow-up

Check lipid profile and blood glucose/HbA1c.
Advise patient to have a cardiological assessment (stress test).

Comment 2023

The recommendations for this case remain unchanged. There is no indication to consider any of the new drugs.

CASE 7. To make the best with a statin-intolerant patient

Background data

The patient is a 65-year old woman who just has sustained a subendocardial MI. On discharge from hospital she was prescribed an ACE inhibitor, antithrombotic treatment and a beta-blocker. For her lipids she was prescribed atorvastatin 80 mg o.d. In addition, lifestyle advice was given to reduce weight (BMI 28 kg/m^2). On admission to hospital her lipid tests were:

TC	5.0 mmol/L	(192 mg/dL)
TG	1.9 mmol/L	(165 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	3.0 mmol/L	(115 mg/dL)

What risk category is the patient?

The patient has sustained an MI and is therefore at very-high-risk for future CV events (***Table 7***). The LDL-C goal should be below 1.4 mmol/L (<55 mg/dL). Therefore, treatment is started with a high intensity statin.

Problems with the statin!

The patient is seen a month after the MI and has the following lipid test results:

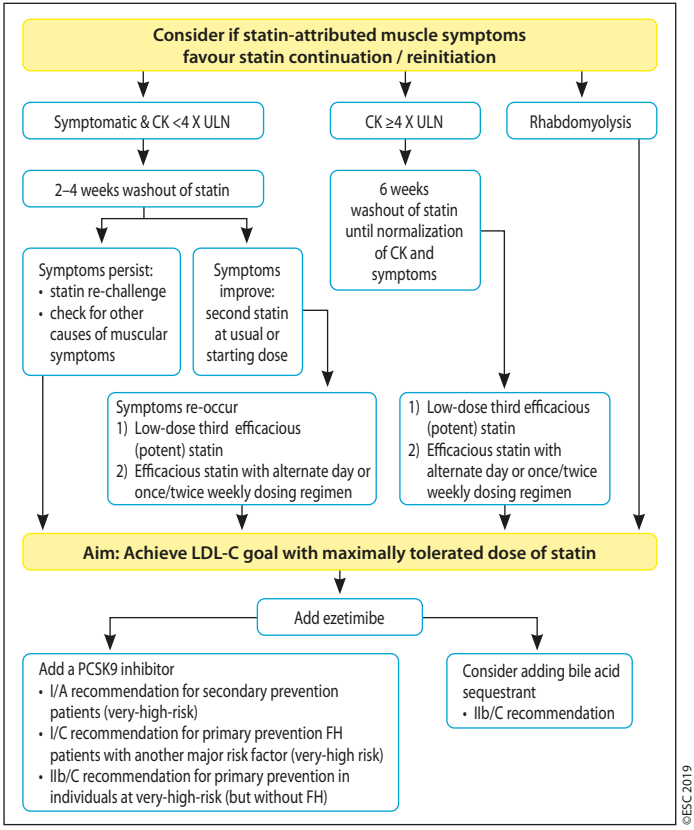
TC	5.0 mmol/L	(192 mg/dL)
TG	2.0 mmol/L	(174 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	3.0 mmol/L	(115 mg/dL)

Plasma lipids and BMI are still the same. What is the problem? The patient reports not taking atorvastatin as it gives her headache and general muscular fatigue.

What to do? She is at very-high-risk and her statin treatment can be life-saving. In the 2019 ESC/EAS guidelines the symptoms are discussed as SAMS (Statin Associated Muscle Symptoms). With muscle symptoms CK should be checked; this is done and the result is normal. It is important to emphasize to the patient the need for statin treatment and to discuss other possibilities for her symptoms.

An algorithm for the treatment of SAMS is given in the guidelines (***Box 7.1***). Interaction with the patient is most important. The statin is stopped for 4 weeks. The symptoms are reduced but do not resolve. CK is still normal.

Box 7.1 • Algorithm for the treatment of muscular symptoms during statin treatment.



Considering her very-high-risk for recurrent CVD events the patient agrees to try another statin: rosuvastatin 20 mg o.d.

Follow-up visit after 6 weeks

The patient reports that her symptoms worsened so she stopped taking rosuvastatin after 2 weeks. Her lipids were back to the high baseline levels. After a long discussion the patient agrees to take rosuvastatin 10 mg twice a week.

Follow-up visit after a further 6 weeks

The patient still has mild muscle symptoms, but considering her high risk for CVD can accept these symptoms. Current lipid levels are:

TC	4.3 mmol/L	(165 mg/dL)
TG	1.6 mmol/L	(139 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	2.4 mmol/L	(92 mg/dL)

LDL-C is still far from the goal of <1.4 mmol/L (<55 mg/dL). However, as the patient does not wish to increase the dose of statin it is decided to add ezetimibe 10 mg o.d.

Follow-up visit after a further 6 weeks

After 6 weeks the patient has no muscle symptoms, and has been taking rosuvastatin and ezetimibe as prescribed. Her lipid status is:

TC	3.8 mmol/L	(146 mg/dL)
TG	1.8 mmol/L	(159 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	1.8 mmol/L	(70 mg/dL)

The target of <1.4 mmol/L (<55 mg/dL) is not reached. The patient may consider increasing the dose of rosuvastatin to 10 mg three times a week.
New prescription: Rosuvastatin 10 mg three times per week, with ezetimibe 10 mg o.d.

Follow-up visit after 6 weeks

After 6 weeks the patient is essentially free from muscle symptoms and her lipids have improved:

TC	3.4 mmol/L	(131 mg/dL)
TG	1.6 mmol/L	(139 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	1.5 mmol/L	(58 mg/dL)

As the patient is now close to LDL-C goal it is decided to continue the same pharmacological treatment, but improve adherence with lifestyle measure. The patient is still overweight and diet is not optimal. There are still changes to be made!

Comment 2023

The patient almost reached the treatment goal with cautious up-titration of rosuvastatin in combination with ezetimibe. Bempedoic acid could have been an alternative to reach LDL-C target, especially so if the muscle symptoms had continued at a not-tolerated level even at low dose of statin.

CASE 8. Very-high-risk patient with familial hypercholesterolemia (FH)

How to diagnose and treat an FH patient who has had an MI.

Background data

The patient is a 52-year-old male with a history of hypercholesterolaemia. He is married with three children. He has never smoked, and exercises 2–3 times per week. He has hypercholesterolaemia since 30 years; he had an MI aged 38 years, and has been on statin therapy since then. His father died of an MI aged 48 years, having had "high cholesterol".

His mother has normal cholesterol levels with no history of ASCVD.

Height 1.78 m, weight 71.5 kg, BMI 24.1 kg/m^2, BP 120/75 mmHg. Cardiac and peripheral vascular examinations are normal. No xanthomas are visible.

Current medication

Atorvastatin 40 mg o.d.

Laboratory data

Fasting lipid profile:

TC	5.9 mmol/L	(228 mg/dL)
TG	1.1 mmol/L	(97 mg/dL)
HDL-C	1.0 mmol/L	(39 mg/dL)
LDL-C	4.4 mmol/L	(170 mg/dL)

All other laboratory tests were within normal limits.

Box 8.1 • Cardiovascular risk categories.

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 revascularization (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). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated GFR; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

What risk category is this patient?

Referring to ***Box 8.1*** the patient is at very-high-risk as he has had an MI. He is also far from LDL-C goal, which is below 1.4 mmol/L (<55 mg/dL) while the 50% reduction from baseline levels should have been achieved given the dose of atorvastatin (***Box 8.2*** and ***Table 9***).

With the presence of MI at a young age in the family and the very high LDL-C you should consider FH (***Box 8.3***).

Box 8.2 • Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019.

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100 mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	<2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

Box 8.3 • Recommendations for the detection of patients with heterozygous familial hypercholesterolaemia.

Recommendations	Class[a]	Level[b]
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 confirmed, when available, with DNA analysis.	I	C

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.
[a]Class of recommendation; [b]Level of evidence.

Action taken

The plasma lipid profile was repeated at follow-up. Echocardiogram revealed mild aortic valve sclerosis. Achilles tendon thickening was evident on doppler analysis.

Box 8.4 • Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia.

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
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
5) DNA analysis	
Functional mutation in the *LDLR, APOB or PCSK9 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	

CFH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Exclusive of each other (i.e. maximum 6 points if both are present).

Genetic testing is not available. Do we need to estimate whether the patient has FH? Although this is formally not required as the patient is already very-high-risk, it is useful to prompt cascade screening. The FH diagnosis was evaluated using the Dutch Lipid Clinic Network (DLCN) Score (***Box 8.4***).

Evaluation using the DLCN Score for FH

Patient had premature MI	2 points
Achilles tendon thickening on doppler analysis	6 points
Parent with premature coronary heart disease (CHD)	1 point
LDL-C 4.4 mmol/L (170 mg/dL)	8 points

(assuming a 50% reduction of LDL-C by current atorvastatin 40 mg treatment)
Total score 17 points: definitely FH.

Using the DLCN Score it is concluded that the patient has FH.

Consider cascade screening of FH in this patient

Cascade screening should be considered initially in first-degree relatives (parent, sibling or child).

Result of cascade screening
Patient's wife has normal cholesterol and LDL-C.
Patient's father died of CHD and had high cholesterol. Patient's mother has normal LDL-C.
Patient's children: two have normal LDL-C levels but the third, a girl aged 8 years has an untreated LDL-C of 4.65 mmol/L (180 mg/dL). This child was considered to have FH and was referred to a specialized paediatric clinic.

Next steps

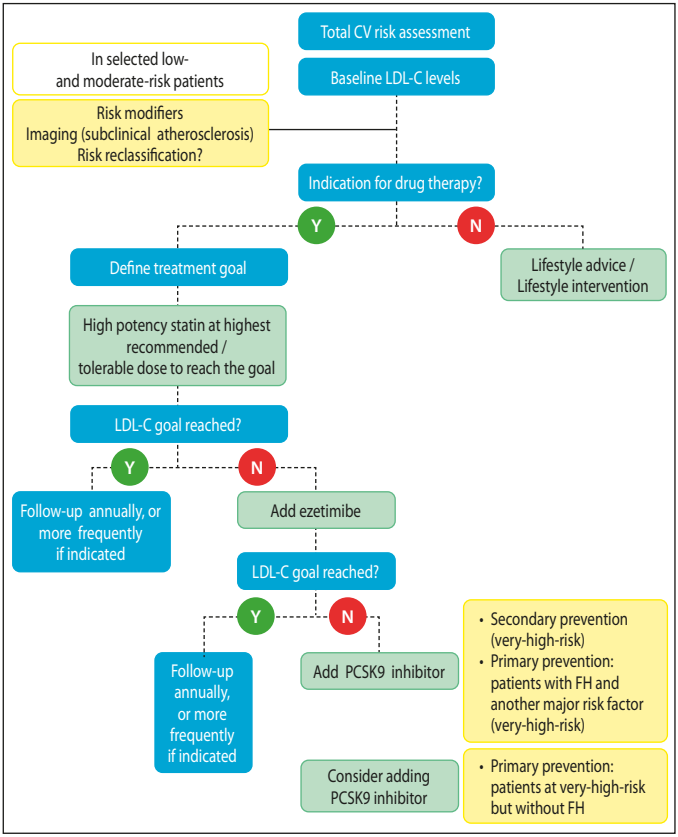
Given the patient's current LDL-C level of 4.39 mmol/L (170 mg/dL), what would be the appropriate next step?

- Stay on current therapy (atorvastatin 40 mg o.d.)?
- Prescribe rosuvastatin 40 mg o.d.?
- Add ezetimibe?
- Add a PCSK9 inhibitor?

The treatment algorithm for pharmacological LDL-C lowering is shown in ***Box 8.5***.

According to this algorithm the patient was switched to *rosuvastatin 40 mg o.d. plus ezetimibe* 10 mg o.d.

Box 8.5 • Treatment algorithm for pharmacological LDL-C lowering.



Follow-up after 6 weeks

The treatment was well tolerated, but LDL-C is still far from goal, 3.2 mmol/L (123 mg/dL).
Following the algorithm the patient started a PCSK9 inhibitor injected twice a month.

Follow-up after a further 4 weeks

The treatment was well tolerated and the patient managed the injections without problems. LDL-C is now 1.5 mmol/L (58 mg/dL).
The patient has achieved 50% reduction of LDL-C and is very close to the goal of <1.4 mmol/L (<55 mg/dL).
No further action for lipid lowering, with future follow-up every 6 months.

Comment 2023

Given the availability of a fixed dose combination of ezetimibe plus bempedoic acid, one could consider the fixed dose association after the statin: This would provide a further reduction of approx. 20% of LDL cholesterol, on the top of what was achieved with ezetimibe and statin, obtaining an LDL-C of about 2.6 mmol/L (100 mg/dL). This would not change the indication for a PCSK9 inhibitor. The choice of using a monoclonal antibody or inclisiran should be discussed with the patient, aiming at maximizing his adherence and persistence to therapy. The reimbursement of such treatment in primary prevention may differ according the regulations of each county.

CASE 9. Mild hypertriglyceridaemia in a high-risk patient

Background data

The patient is a 49-year old female. She has Type 2 diabetes mellitus (T2DM) diagnosed 7 years ago and is treated with metformin and sitagliptin. Her fasting glucose levels are between 6.7-7.8 mmol/L (120-140 mg/dL) and her average HbA1c is 7.2% (55 mmol/mol).
She has a history of high blood pressure and on treatment with perindopril + indapamide her blood pressure is maintained around 130/80 mmHg.

A carotid sonography showed an intima-media thickness (IMT) above the 75 percentile for her age and gender and a non-obstructive (<30% obstruction) plaque in the left common carotid artery.

She is a non-smoker sedentary with no menopausal symptoms. The patient is overweight, with a BMI of 29 kg/m^2.

Laboratory tests

TC	4.8 mmol/L	(187 mg/dL)
TG	3.1 mmol/L	(270 mg/dL)
HDL-C	1.1 mmol/L	(44 mg/dL)
LDL-C	2.3 mmol/L	(89 mg/dL)

Fasting plasma glucose (FPG) is 6.5 mmol/L (118 mg/dL), and HbA1c is 6.9% (52 mmol/mol).

What is the cardiovascular risk of this patient?

According to the 2019 ESC/EAS guidelines, patients with diabetes have a predefined moderate- to very-high-risk, and should not be evaluated with the SCORE tables.

The prespecified risk of diabetes patients varies according to the following aspects: diabetes type, age, years from diagnosis, target-organ damage (i.e., albuminuria, retinopathy, neuropathy), and additional risk factors (hypertension, central obesity, smoking, dyslipidaemia). Therefore, a comprehensive study to assess the presence of these conditions should be performed.

Application to this patient

The factors to be taken into account in this case were: age, 49 years; 7 years of diabetes evolution; no target-organ damage; hypertension; atherogenic dyslipidaemia (high TG, low HDL-C). The patient was overweight but not obese.

The carotid study could contribute to a better risk stratification. The presence of carotid plaques (<50% stenosis) would increase the risk status. In this case, a high IMT and a non-clinically significant plaque was detected, not fulfilling the characteristics to change the risk level.

According to the 2019 ESC/EAS guidelines this patient should be considered at high-risk (two additional risk factors) ***Box 9.1***.

What are the lipid targets in this case?

The main lipid target is LDL-C, which according the 2019 ESC/EAS guidelines should be below 1.8 mmol/L (<70 mg/dL) for individuals at high-risk. In addition, a 50% reduction from baseline LDL-C levels should be obtained.

Box 9.1 • Cardiovascular risk categories.

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 revascularization (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).
	Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors.
	Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors.
	Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors.
	Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated GFR; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

Moreover, in diabetes patients, some secondary targets may be considered (***Box 9.2***).

Box 9.2 • Treatment targets and goals for cardiovascular disease prevention.

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]
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 <1.4 mmol/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 <1.8 mmol/L (<70 mg/dL). **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).

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated; [b]The 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.

In this patient a non-HDL-C below 2.6 mmol/L (<100 mg/dL) and ApoB below 80 mg/dL may be considered as secondary targets. Additionally, lowering the TG level below 1.7 mmol/L (<150 mg/dL) would reduce the overall risk of this patient.

What treatment should be started?

In all patients with T2DM at high-risk, lifestyle therapeutic change must be implemented. In this patient this should be an increase in physical activity and adoption of a Mediterranean diet, with calorie restriction to reduce body weight.

According to the 2019 ESC/EAS guidelines treatment should start with statin able to reduce LDL-C by at least 50%: *Atorvastatin 40 mg o.d. was prescribed.*

Follow-up after 2 months

After 2 months the patient's metabolic parameters were as follows:

Lipid tests

TC	3.8 mmol/L	(147 mg/dL)
TG	3.2 mmol/L	(275 mg/dL)
HDL-C	0.8 mmol/L	(31 mg/dL)
LDL-C	1.4 mmol/L	(55 mg/dL)

BMI 29 kg/m^2; FPG 7.1 mmol/L (127 mg/dL); HbA1c 7.1% (54 mmol/mol); Non-HDL-C 3.0 mmol/L (116 mg/dL); ApoB 100 mg/dL.

A 50% reduction of LDL-C was not obtained. However, the patient had a LDL-C of 1.4 mmol/L (55 mg/dL), 0.4 mmol/L (15 mg/dL) below the the goal and therefore intensification of therapy was not considered at this time. ApoB is a secondary target for this patient and the goal is below 80 mg/dL
Diabetes therapy was changed to a SGLT2 inhibitor plus metformin, because there is proven evidence of benefit on CV risk.
TG-lowering therapy was considered.

Why treat high TG in this patient?

ApoB- and TG-containing lipoproteins have a role in atherogenesis. Increasing TG levels predisposes to proatherogenic qualitative and quantitative changes in atherogenic particles beyond LDL-C; therefore, therapy to reduce TG may be considered.

Randomized controlled trials to assess the effect of fibrates, niacin and cholesterol ester transfer protein (CETP) inhibitors against a background of statin therapy have been neutral or negative. However, a pre-specified subgroup analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed that fenofibrate produced a significant 31% relative risk reduction in diabetes patients with both high TG and low HDL-C, whereas the FIELD and the PROMINENT (pemafibrate) trials were negative.

The Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) showed a beneficial impact of icosapent ethyl 4-g daily in secondary prevention patients or patients with diabetes on pharmacological therapy with controlled LDL-C levels and TG levels between 135 mg/dL and 499 mg/dL.

Box 9.3 • Recommendations for drug treatment of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >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 levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.
[a]Class of recommendation; [b]Level of evidence.

Highly significant relative risk reductions of 25% in the primary endpoint and 26% in the secondary endpoints were observed. Moreover, all individual components of these endpoints were reduced including CV mortality with an almost statistically significant reduction in all-cause mortality.

According to these data the 2019 ESC/EAS guidelines recommend TG-lowering therapy in ***Box 9.3***. As icosapent ethyl was not available in Europe at this time, fenofibrate was started in this patient.

Follow-up after a further 2 months

After 2 months her metabolic parameters were:

TC	3.3 mmol/L	(128 mg/dL)
TG	1.8 mmol/L	(155 mg/dL)
HDL-C	1.2 mmol/L	(45 mg/dL)
LDL-C	1.3 mmol/L	(52 mg/dL)

ApoB 83 mg/dL. Fasting plasma glucose 6.7 mmol/L (121 mg/dL); HbA1c 6.7% (59 mmol/mol); BMI 28.7 kg/m^2.

LDL-C is below goal but close to 50% reduction from starting level and ApoB is at goal. This therapy regimen was maintained, and long-term follow-up visits were scheduled.

Comment 2023

The study Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) has shown a lack of efficacy in lowering cardiovascular events in this population, jeopardizing the role of pemafibrate.

Icosapent ethyl is now available as Vazkepa® and could become the choice for CV prevention via TG reduction if TG would have remained > 1.7 mmol/L.

Reference

Das Pradhan A, Glynn RJ, Fruchart JC, MacFadyen JG, Zaharris ES, Everett BM, Campbell SE, Oshima R, Amarenco P, Blom DJ, Brinton EA, Eckel RH, Elam MB, Felicio JS, Ginsberg HN, Goudev A, Ishibashi S, Joseph J, Kodama T, Koenig W, Leiter LA, Lorenzatti AJ, Mankovsky B, Marx N, Nordestgaard BG, Páll D, Ray KK, Santos RD, Soran H, Susekov A, Tendera M, Yokote K, Paynter NP, Buring JE, Libby P, Ridker PM; PROMINENT Investigators. *N Engl J Med.* 2022; 387: 1923-1934.

CASE 10. A case with severe hypertriglyceridaemia

Background data

The patient is a 52-year old working woman. She was referred for advice regarding a chronic uncontrolled hypertriglyceridaemia.

Past history

Substituted hypothyroidism (thyroiditis of Hashimoto)
Paroxysmal tachycardia
Bilateral rhizarthrosis

Current treatment

L-Thyroxin 112.5 µg/day
Flecainide acetate LP 100 mg/day
Atorvastatin 10 mg o.d.

Family history

Son aged 30 years with mild mixed dyslipidaemia.
Father with mixed dyslipidaemia and a history of type 2 diabetes.
Mother and sister do not have dyslipidaemia.
There is no history of ischaemic CV disease in the family.

Personal history

The patient's hypertriglyceridaemia was discovered when she was 22 years old. Her plasma TG concentration has fluctuated around 9 mmol/L for the last 20 years, with a peak of 21 mmol/L in 2012 without any obvious secondary factors.
She has never experienced acute pancreatitis.
She has a history of muscle pain on fenofibrate 200 mg/day.
Her maximal BMI was 34 kg/m^2 by the end of her pregnancy.
She has no history of T2DM, glucose intolerance or hypertension.
She has never smoked, does not drink alcohol, and has no history of illicit drug use.
She has a relatively healthy diet and practices aquagym once a week, and trekking on weekends.

Physical examination

The patient's BMI is 28.3 kg/m^2, and waist circumference is 95 cm.

She has no xanthomas, and no other extra-vascular lipid accumulation.
Her BP is 130/80 mmHg.
Her physical examination is normal.

Laboratory tests

Blood lipid profile (fasting) before atorvastatin treatment.

TC	8.5 mmol/L	(329 mg/dL)
TG	5.7 mmol/L	(505 mg/dL)
HDL-C	0.9 mmol/L	(35 mg/dL)
LDL-C	5.2 mmol/L	(201 mg/dL)
ApoB		190 mg/dL

Blood lipid profile (fasting) under atorvastatin treatment.

TC	6.0 mmol/L	(232 mg/dL)
TG	6.8 mmol/L	(602 mg/dL)
HDL-C	0.9 mmol/L	(35 mg/dL)
LDL-C	3.8 mmol/L	(147 mg/dL)
ApoB		143 mg/dL
Lp(a)		80 mg/dL

Blood glucose 5.1 mmol/L (93 mg/dL); uric acid 352 µmol/L.

First line diagnosis

Possible diagnoses to consider are familial combined hyperlipidaemia (FCH) with additional genetic factors leading to substantial chronic hypertriglyceridaemia or transient decompensation leading to multifactorial hyperchylomicronaemia syndrome.

The patient was at moderate to high-risk (dyslipidaemia + perimenopausal).

Her family history and high plasma ApoB concentration excludes a diagnosis of dysbetalipoproteinaemia; high ApoB suggests an increased number of small-size proatherogenic LDL-C. Data discussed in the guidelines strongly suggest that the causal effect of TG-rich lipoproteins and their remnants on the risk of ASCVD is determined by the circulating concentration of ApoB-containing particles rather than the TG content itself.

The patient's clinical history and her mixed lipid phenotype, including possible Non-Alcoholic SteatoHepatitis (NASH), support a diagnosis of familial combined hyperlipidaemia.

As this patient has a history of severe hypertriglyceridaemia, fasting blood samples are preferred for reliable and reproducible assessment of the lipid profile. A non-fasting lipid profile can be used to follow patients with type IIa hypercholesterolaemia. In patients with metabolic syndrome, diabetes, or hypertriglyceridaemia, calculated LDL-C should be interpreted with caution.

Actions taken

Assessment of subclinical atherosclerosis: ultrasound shows small atheromatous plaques on both carotid bifurcations, and minor atheroma on both external iliac arteries.
Coronary artery calcium score = 0.
Liver assessment for NASH: if available, request assessment of liver fat by fibroscan or magnetic resonance imaging (MRI).
Homogenous hyperechogenicity, normal portal circulation.
Liver Fibroscan CAP 310 dB/m S3 Steatosis Elasticity 8 KPa: -F2.

Considering coronary artery calcium score in this case classifies the patient as moderate-risk (Box 10.1)

A lipid lowering treatment is mandatory to protect the coronary arteries and to avoid worsening of atherosclerosis in the peripheral and carotid arteries. Furthermore, lipids are not at target for moderate-risk patients (LDL-C <2.6 mmol/L (<100 mg/dL), ApoB <100 mg/dL).

Box 10.1 • Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease.

Recommendations	Class[a]	Level[b]
Assessment of 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 should be considered as a risk modifier in the CV risk assessment of asymptomatic individuals at low- or moderate-risk.	IIb	B

CAC = coronary artery calcium; CT = computed tomography; CV = cardiovascular.
[a]Class of recommendation; [b]Level of evidence.

Genetic testing

Since the patient was seen at a university clinic a genetic assessment could be performed of genes involved in plasma TG regulation using next generation sequencing.

Findings were: E3E3, Apo AV p.D346H het variant class 3, LPL variant p.D36N het class 4, (apo C2, apo C3 GPIHBP1, LMF1, CREB3L3 neg.

The apo AV variant identified, involving a change in a highly conserved amino acid, has not been previously reported and is not found in large data-bases. The variant is considered to be deleterious based on in silico analysis using sift and mutation tester software. The LPL D36N het variant is frequent and associated with mild hypertriglyceridaemia in the general population. The patient has no composite heterozygous mutation leading to familial chylomicronaemia syndrome (FCS); she has a history of multifactorial chylomicronaemia syndrome with a het mutation of apo AV. The diagnosis is: Multifactorial Chylomicronaemia Syndrome occurring on a clinical background of polygenic combined hyperlipidemia.

Treatment

The patient received counselling to stop smoking, with the major challenge to maintain or possibly reduce her body weight by increasing physical activity. She was given advice on a hypocaloric balanced diet with 30% lipid, 45% carbohydrates and 25% protein, and to avoid any lipid or alcohol load.

Treatment recommendations are given in ***Box 10.2***. The REDUCE-IT trial demonstrated that in statin-treated patients with high CV risk and fasting TG levels between 1.52-1.63 mmol/L (135-499 mg/dL), high-dose (2 g b.i.d) icosapent ethyl, a highly purified and stable EPA significantly reduced the risk of ischaemic events, including CV death, by 25% over a median follow-up of 4.9 years. Therefore, the patient was asked to take (EPA + docosahexaenoic acid, DHA) 2 g/day (4 x 500 mg) to lower her plasma TG due to her previous fibrate intolerance (***Box 10.2***).

Atorvastatin was carefully uptitrated to 20 mg o.d. due to her history of fenofibrate intolerance and frequent cross-intolerance in order to reach the goal of LDL-C <2.6 mmol/L (<100 mg/dL).

Box 10.2 • Recommendations for drug treatment of patients with hypertriglyceridaemia.

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate should probably not be considered any more in combination with statins, EPA 2-4 g/d could be used as alternative in patients with a high risk of ASCVD.	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.	IIb	C

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acids; TG = triglyceride.
[a]Class of recommendation; [b]Level of evidence.

Her recent lipid profile (on atorvastatin 20 mg/day + EPA-DHA) was as follows:

TG	2.8 mmol/L	(248 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	2.9 mmol/L	(112 mg/dL)

Comments 2023

Waylivra® is not indicated in MCS.

Although not directly tested in the REDUCE-IT trial, which did not include specifically patients with severe hypertriglyceridemia, it might be preferable to use high dose of purified EPA (isocapent ethyl, Vazkepa®). Since Vazkepa® was not yet available in many European countries, pure EPA as nutritional supplement (1 g/cap) 2 g/day was proposed.

Combination treatment with a statin + fibrate is not recommended in this patient since she is in primary prevention and not at high-risk (CAC = 0), she had a history of fibrate intolerance and as the PROMINENT trial (pemafibrate treatment versus placebo) did not show a MACE reduction. Despite her

mixed lipid phenotype the priority is to target cholesterol.

Her coronary calcium score should be checked in 5 years when she is 57.

CASE 11. Very high Lp(a) level in primary prevention

Background data

The patient is a 42-year old man, seeking advice because his father and grandfather had an MI at an early age (48 and 52 years, respectively). A lipid test reveals a very high Lp(a) level (182 mg/dL). He does not smoke and has no other risk factor beyond this lipid abnormality.

What do we need to know to estimate his risk?

Medical history

No current medication. No current history of chest pain.

Risk factors

Family history of premature ASCVD and *very high Lp(a) levels*. He does not smoke, BMI is 24 kg/m^2 and undertakes moderate physical activity.

Physical status

No xanthomas. Heart auscultation is normal. BP is 132/82 mmHg. Peripheral circulation and ECG are normal.

Laboratory tests

Family history of MI at a young age should prompt Lp(a) measurement with lipid testing. The results are as follows:

TC	6.1 mmol/L	(238 mg/dL)
TG	1.4 mmol/L	(123 mg/dL)
HDL-C	1.5 mmol/L	(58 mg/dL)
LDL-C calc	3.4 mmol/L	(132 mg/dL)

Blood glucose is 5.4 mmol/L (97 mg/dL); creatinine clearance is normal. Lp(a) is confirmed as very high, 184 mg/dL.

Calculated LDL-C is the combination of "true" LDL-C and Lp(a)-C. It is thought that approximately one third of the Lp(a) level is cholesterol in Lp(a). In this case the patient has 1.6 mmol/L (61 mg/dL) of cholesterol in the Lp(a) particles.

LDL-C + Lp(a)-C = TC – HDL-C – (TG/2.2) for mmol/L
LDL-C + Lp(a)-C = TC – HDL-C – (TG/5) for mg/dL

What risk category is the patient?

The patient has a family history of premature ASCVD and a very high level of Lp(a) which is equivalent to the risk of FH according to the 2019 ESC/EAS guidelines (***Box 11.1***). Since Lp(a) levels have a strong genetic determinant, patients usually have a long life-time exposure.

The patient is therefore considered at high-risk. Using SCORE to evaluate risk would be misleading in this patient. Indeed the calculated SCORE shows that the patient is at low-risk (SCORE Chart in low-risk country see ***Table 3***).

Since the patient has no symptoms no imaging was performed. However, if imaging was performed and showed significant atherosclerosis the patient would be at very-high-risk. Stress ECG testing was normal.

Treatment

*Recommendation in **Table 8**: Lifestyle intervention and concomitant drug intervention.*
In addition to pharmacological treatment, a number of lifestyle factors should be intensely targeted, in particular increasing physical activity and dietary advice aiming for a more healthy diet (***Table 10***). These lifestyle changes will not have significant impact on Lp(a) levels but are associated with reduction in LDL-C and a lower risk of ASCVD.

The LDL-C goal is below 1.8 mmol/L (<70 mg/dL) and at least 50% reduction from starting levels (***Table 9***). To achieve this goal treatment with a high intensity statin is recommended (***Table 12***). However, the Lp(a) level does not decrease with statin treatment and the average decrease of Lp(a)-C plus LDL-C might be less than expected. (Average LDL-C decrease with 80 mg atorvastatin is 55%).

Box 11.1 • Recommendations for lipid analyses for cardiovascular disease risk estimation.

Recommendations	Class[a]	Level[b]
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
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
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

Apo = apolipoprotein; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); SCORE = Systematic Coronary Risk Estimation; TC = total cholesterol; TG = triglyceride.
[a]Class of recommendation; [b]Level of evidence.

Actions taken

Advice about diet and physical activity.
Atorvastatin 80 mg o.d.

Follow-up after 6 weeks

Laboratory tests

TC	4.0 mmol/L	(154 mg/dL)
TG	1.2 mmol/L	(106 mg/dL)
HDL-C	1.3 mmol/L	(51 mg/dL)
LDL-C	2.1 mmol/L	(82 mg/dL)

The patient has not achieved 50% reduction of calculated LDL-C and is not at goal if calculated LDL-C is considered.
If "true" LDL-C is calculated by subtracting Lp(a)-C, this corresponds to a very low "true" LDL-C (0.5 mmol/L or 21 mg/dL) and Lp(a)-C of 61 mg/dL.
HDL-C is slightly decreased, a result which can be observed with high dose atorvastatin.

Physical status

He is still a non-smoker. Tolerates his medication well.

Further follow-up

There might be a discussion on whether the patient has reached goal. Subsequent treatment with a combination of atorvastatin at the same dose and ezetimibe did not show any significant improvement in the lipid/lipoprotein profile. The patient continued on atorvastatin 80 mg with follow-up of risk factors once a year. The patient was highly motivated to continue the treatment and was reassured that a possible cause was found.

There is no available treatment for very high Lp(a) levels. Therefore LDL-C levels need to be as low as possible.

Comment 2023

Anti PCSK9 antibodies might be considered since they are associated with an up to 20% reduction of Lp(a). Reimbursement pattern depends on each country. New treatments specific for high Lp(a) are being developed but not yet available. Individuals with very high Lp(a) levels might be considered for aspirin therapy if they have other indications (e.g. very high ASCVD risk and low bleeding risk) and evidence for severe infraclinic atherosclerosis.

CASE 12. Isolated high Lp(a) in primary prevention

Background data

The patient is a 54-year old man referred by his GP with suspected FH. Lipid testing reveals LDL-C at 3.7 mmol/L (142 mg/dL) and a high Lp(a) level (74 mg/dL). The patient had a previous test at the age of 28 years (requested by a bank for a loan) which was normal.

What do we need to know to estimate his risk?

Medical history

No current medication. No current history of chest pain.

Risk factors

Both parents had slightly elevated cholesterol levels (aged 84 and 82 years without ASCVD) but the patient did not know their LDL-C. He does not smoke, BMI is 22 kg/m^2 and is moderately active.

Physical status

No xanthomas. Heart auscultation is normal. BP is 144/86 mmHg. Peripheral circulation and ECG are normal.

Laboratory tests

The results are as follows:

TC	5.8 mmol/L	(225 mg/dL)
TG	1.7 mmol/L	(150 mg/dL)
HDL-C	1.5 mmol/L	(58 mg/dL)
LDL-C	3.5 mmol/L	(135 mg/dL)
Lp(a)		76 mg/dL

Blood glucose is 5.2 mmol/L (94 mg/dL). Creatinine clearance is normal. Calculated LDL-C is the combination of "true" LDL-C and Lp(a)-C.

It is considered that approximately one third of Lp(a) level is Lp(a)-cholesterol; in this case the patient has 24 mg/dL of cholesterol in the Lp(a) particles.

LDL-C + Lp(a)-C = TC – HDL-C – (TG/2.2) for mmol/L
LDL-C + Lp(a)-C = TC – HDL-C – (TG/5) for mg/dL

The patient has no secondary causes of hyperlipidaemia although this will be checked as previous lipid values were normal.

What risk category is the patient?

The patient does not have FH as the calculated DLCN score is below 3 (For DLCN Score see ***Case 8***). Furthermore, given that the transmission does not appear to be autosomal dominant and lipid values were normal at age 28 provides a strong argument against the diagnosis of FH (usually characterized by high levels of LDL-C throughout life).

Considering the SCORE chart, and the fact that the patient has high Lp(a), the patient is classified as moderate-risk.

Treatment

*Recommendation in **Table 8**: Lifestyle intervention and concomitant drug intervention.*

Lifestyle recommendations: Increase physical activity and dietary advice aiming for a more healthy diet with special emphasis on reducing salt intake. These lifestyle changes will not have significant impact on Lp(a) levels but are associated with reduction in LDL-C and a lower risk of ASCVD.

The LDL-C goal is below 2.6 mmol/L (<100 mg/dL) (***Table 9***).
To achieve this goal treatment with a statin is recommended (***Table 12***). However, the Lp(a) level does not decrease with statin treatment and the average decrease of Lp(a)-C plus LDL-C might be less than expected.

Actions taken

Dietary advice including reduction in salt intake and advice about physical activity.
The patient was prescribed rosuvastatin 10 mg o.d.

Follow-up after 6 weeks

Laboratory tests

TC	4.0 mmol/L	(152 mg/dL)
TG	1.1 mmol/L	(97 mg/dL)
HDL-C	1.5 mmol/L	(58 mg/dL)
LDL-C	1.9 mmol/L	(74 mg/dL)

The patient has reached LDL-C goal.
Calculated LDL-C is 1.9 mmol/L (74 mg/dL) which corresponds to a "true" LDL-C of 1.3 mmol/L (50 mg/dL) and Lp(a)-C of 24 mg/dL

Physical status
Still a non-smoker. The patient tolerates his medication well. BP measured at home with reduced salt intake is normal.

Subsequent follow-up

The patient continued on rosuvastatin 10 mg o.d. with follow-up of risk factors once a year. The patient was highly motivated to continue the treatment and compliance was good. He was asked to inform his brother and sister to have a lipid check.

Comment 2023

Anti PCSK9 antibodies might be considered since they are associated with an up to 20% reduction of Lp(a). Reimbursement pattern depends on each country. New treatments specific for high Lp(a) are being developed but are not yet available.

CASE 13. Moderate-risk patient with high Calcium Score How to use the Calcium Score

Background data

The patient is a 50-year old lawyer from Poland with a stressful lifestyle, frequently eating fast-food. He is married with two children. He lives in a high-risk country according to the SCORE Cardiovascular Risk Chart. He is a current smoker and has, for many years, smoked 10 cigarettes a day. He was admitted for a cardiovascular check-up.

He has had a history of hypertension for 3 years, and is currently well controlled on an angiotensin receptor blocker (ARB)-diuretic combination therapy. There is no history of diabetes mellitus. His brother had a coronary stent implantation at age 53.

What do we need to know to estimate his risk?

Medical history

The patient has a history of hypertension which has been under control for 3 years, and no history of diabetes mellitus. He is a current smoker, smoking 10 cigarettes a day. He has a first-degree relative with premature coronary disease. There is no current history of chest pain.

Risk factors:

Current smoker, BMI 31 kg/m^2, waist circumference 114 cm, low physical activity.

Physical status

Abdominal obesity. No xanthomas. Heart auscultation and peripheral circulation were normal.

On physical examination, his BP was 120/70 mmHg. Tendon xanthomata and arcus cornealis were not detected.

Laboratory tests

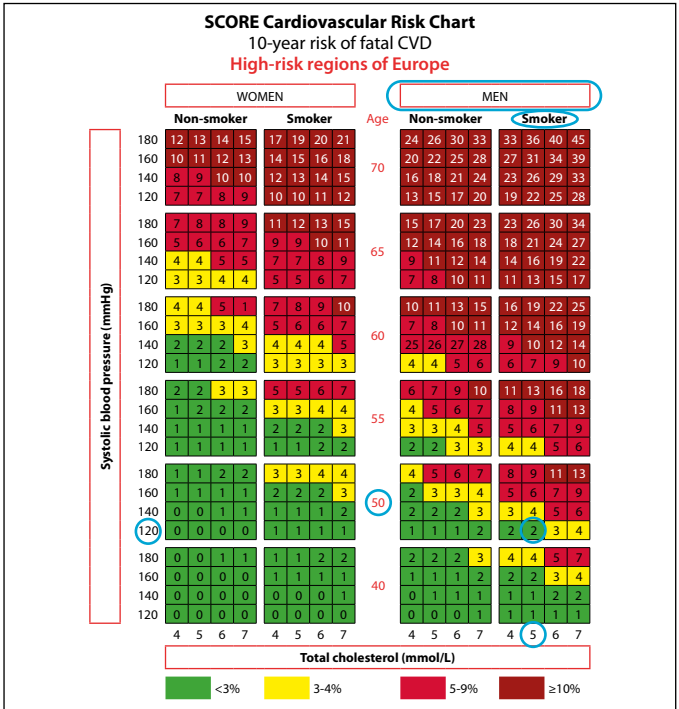
ECG is normal sinus rhythm. Fasting blood glucose level was 5.5 mmol/L (99 mg/dL). Haemoglobin, ALT, AST, and creatinine are within the normal range. His lipid profile is shown below:

TC	5.4 mmol/L	(209 mg/dL)
TG	1.2 mmol/L	(107 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	3.5 mmol/L	(135 mg/dL)

What risk category is the patient?

Based on his age (50 years), male gender, smoking status, systolic BP of 120 mmHg, and TC of 5.4 mmol/L (209 mg/dL), his SCORE risk is 2%, i.e. moderate-risk (***Box 13.1***).

Box 13.1 • Using SCORE chart to estimate risk.



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.

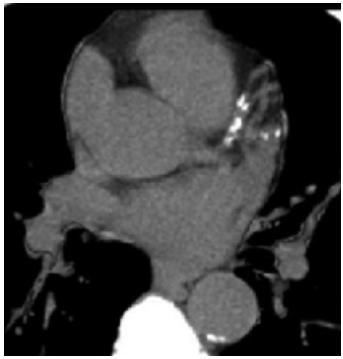
Box 13.2 • Factors modifying Systematic Coronary Risk Estimation.

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.
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.

CVD = cardiovascular disease.

Although SCORE risk is moderate, his family history and stressful lifestyle may be risk modifiers (***Box 13.2***). Therefore coronary artery calcium scoring (CAC score) was requested.
Coronary CT angiography with calcium scoring was performed and the CAC score was 250 AU; there was no significant stenosis (***Box 13.3***).
Because the CAC Score is above 100 AU, we may consider more aggressive risk reduction in this patient. The calcium score shows that the patient has a considerable calcified plaque burden.

Box 13.3 • CAC score= 250.



Treatment

*Recommendation in **Table 8**: Lifestyle intervention and concomitant drug intervention.*

In addition to pharmacological treatment a number of lifestyle factors should be intensely targeted. These include: stop smoking, increase physical activity, lose weight and dietary advice aiming for a more healthy diet.

The LDL-C goal is <2.6 mmol/L (<100 mg/dL) for this patient (***Box 13.4***). To achieve this goal, treatment with a moderate intensity statin is recommended.

Box 13.4 • Recommendations for treatment goals for low-density lipoprotein cholesterol.

Recommendations	Class[a]	Level[b]
In secondary prevention patients at very-high-risk[c], 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	A
In primary prevention, for individuals at very-high-risk but without FH[c], 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[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
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,[c] 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
In individuals at moderate-risk[c], an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.	IIa	A
In individuals at low-risk[c], an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.	IIb	A

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol.

[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 7; [d]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.

Actions taken

Quit-smoking programme, and advice about diet and physical activity are given to the patient. Atorvastatin 20 mg o.d. is prescribed.

Follow-up after 6 weeks

Physical status

The patient has stopped smoking. His eating habits have changed and his diet is better. He has lost a small amount of weight (2 kg) as he is unable to do proper exercise. BP is 115/75 mmHg.

Laboratory tests

TG	1.2 mmol/L	(106 mg/dL)
HDL-C	1.2 mmol/L	(46 mg/dL)
LDL-C	2.5 mmol/L	(97 mg/dL)

The patient has reached the LDL-C of <2.6 mmol/L (<100 mg/dL); however, because of the high plaque burden this patient may benefit from further LDL-C lowering.

Subsequent follow-up

Once the patient is at goal follow-up of risk factors may be limited to once a year. However adherence may be improved with closer follow-up and further discussion regarding risk factors (***Box 13.5***).

Box 13.5 • Summary of recommendations for monitoring lipids in patients, before and on lipid-lowering therapy.

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 prompt drug treatment is suggested, such as ACS and very-high-risk patients.
How often should a patient's lipids be tested after starting lipid-lowering treatment?
After starting treatment: 8 (± 4) weeks.
After adjustment of treatment: 8 (± 4) weeks 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).

Comment 2023

His LDL-C goal will be below 2.6 mmol/L(100 mg/dL) thus unchanged from what was suggested in the 2019 ESC/EAS guidelines. Guidelines also acknowledges that coronary artery calcium scoring can reclassify CVD risk upwards and downwards in addition to conventional risk factors, and may thus be considered for decision thresholds. Higher-than-expected CAC increases the person's calculated risk. Stress is also considered a mild risk modifier. Therefore this patient may benefit from further LDL C lowering by increasing the statin dose if tolerance was fine, by combining ezetimibe in case of partial statin intolerance.

CASE 14. Familial hypercholesterolaemia: A high-risk patient with Calcium Score = 0

Background data

This patient is a 27-year old male PhD student. He is not married and has one younger brother. During a routine check-up, his LDL-C level was found to be above 5.2 mmol/L (200 mg/dL) so he was referred to the clinic.
He is a non-smoker and his medical history is unremarkable. His father had an MI at the age of 51.

What do we need to know to estimate his risk?

Medical history
The patient has no history of diabetes mellitus, hypertension, and is a non-smoker. He has a family history of a first-degree relative with premature coronary disease as his father had an MI at the age of 51. No current medication. No current history of chest pain.

Risk factors
Non-smoker, BMI 24 kg/m^2, waist circumference 83 cm, low physical activity.

Physical status
On physical examination, his BP was 120/70 mmHg, and tendon xanthomata and arcus cornealis were not detected. There was no abdominal obesity. Heart auscultation and peripheral circulation were normal.

Laboratory tests

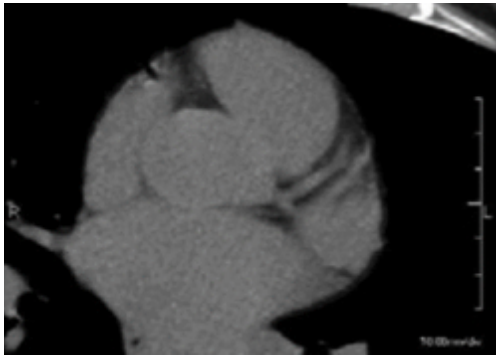
ECG is normal sinus rhythm. Fasting blood glucose level was 5.5 mmol/L (99 mg/dL). Haemoglobin, ALT, AST, and creatinine levels are within the normal range.

His lipid profile is shown below:

TC	8.8 mmol/L	(340 mg/dL)
TG	1.1 mmol/L	(97 mg/dL)
HDL-C	1.1 mmol/L	(42 mg/dL)
LDL-C	6.6 mmol/L	(255 mg/dL)

His calcium score is 0 (***Box 14.1***).

Box 14.1 • CAC score = 0.



What risk category is the patient?

Because this patient had an LDL-C above 4.9 mmol/L (>190 mg/dL) with a family history of premature MI, the possibility of FH was tested with the DLCN score (***Box 14.2***). According to the DLCN Score his total score was 6, indicating probable FH:

First-degree relative with premature coronary and/or vascular disease → **1 point**

LDL-C: 6.5 - 8.4 mmol/L (250-329 mg/dL) → **5 points.**

Box 14.2 • Dutch Lipid Clinic Network (DLCN) diagnostic criteria for familial hypercholesterolaemia.

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
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
5) DNA analysis	
Functional mutation in the *LDLR, APOB or PCSK9 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	

CAD = coronary artery disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Exclusive of each other (i.e. maximum 6 points if both are present).

After discussion with the patient, DNA analysis for functional mutations of the *LDLR, APOB* and *PCSK9* genes was performed. A heterozygous false sense mutation on the *LDLR* gene [10. Exon c.1432G>A p. (Gly478Arg)] was detected.

Once he was diagnosed with FH, his family was invited for genetic screening.

The patient has FH which automatically makes him a high-risk patient. According to the 2019 ESC/EAS guidelines, patients with markedly elevated single risk factors, in particular LDL-C >4.9 mmol/L (>190 mg/dL) are auto-

Box 14.3 • Cardiovascular risk categories.

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 revascularization (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). Severe CKD (eGFR <30 mL/min/1.73 m^2). A calculated SCORE ≥10% for 10-year risk of fatal CVD. FH with ASCVD or with another major risk factor.
High-risk	People with: 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 ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage*, with DM duration ≥10 years or another additional risk factors. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.
Moderate-risk	Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1% and <5% for 10-year risk of fatal CVD.
Low-risk	Calculated SCORE <1% for 10-year risk of fatal CVD.

ASCVD = atherosclerotic cardiovascular disease; ACS = acute coronary syndrome; BP = blood pressure; CABG = coronary artery bypass graft surgery; CKD = chronic kidney disease; CT = computed tomography; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated GFR; FH = familial hypercholesterolaemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol; TIA = transient ischaemic attack.
* Target organ damage is defined as microalbuminuria, retinopathy or neuropathy.

matically high-risk (***Box 14.3***). Although the calcium score is zero, this patient is at high-risk, relatively young and most likely has noncalcified plaques.

Coronary Calcium score is validated in male subjects older than 40 years and women older than 45 years.

Treatment

*Recommendation in **Table 8**: Lifestyle intervention and concomitant drug intervention.*

All patients should get a healthy lifestyle recommendation. For this patient, increased physical activity and dietary advice aiming for a more healthy diet were recommended (***Table 10***).

The LDL-C goal is below <1.8 mmol/L (<70 mg/dL) and at least 50% reduction. To achieve this goal, in addition to lifestyle intervention treatment with a high intensity statin is recommended.

Actions taken

Dietary advice and advice about physical activity is given to the patient.

In addition, atorvastatin 80 mg o.d. is prescribed. The patient is scheduled for a follow-up in 6 weeks to make sure he is adherent to recommendations, to check if he is at goal and to check for side effects (***Box 14.4***).

Box 14.4 • Summary of recommendations for monitoring lipids in patients, before and on lipid-lowering therapy.

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 prompt drug treatment is suggested, such as ACS and very high-risk patients.
How often should a patient's lipids be tested after starting lipid-lowering treatment?
After starting treatment: 8 (± 4) weeks.
After adjustment of treatment: 8 (± 4) weeks 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).

Follow-up after 6 weeks

Physical status

No weight reduction. BP is 115/70 mmHg.

Laboratory tests

TG	1.0 mmol/L	(89 mg/dL)
HDL-C	1.0 mmol/L	(39 mg/dL)
LDL-C	3.5 mmol/L	(135 mg/dL)

Box 14.5 • Recommendations for pharmacological low-density lipoprotein cholesterol lowering.

Recommendations	Class[a]	Level[b]
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
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.	IIa	C
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[c] is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation; [b]Level of evidence; [c]For definitions see Table 10.

The patient has not achieved 50% reduction of LDL-C and also is not at goal for LDL-C (i.e., <1.8 mmol/L or <70 mg/dL). He takes his medication regularly and tolerates it well. According to the 2019 ESC/EAS guidelines, ezetimibe 10 mg o.d. should be added. He should be asked to return for a follow-up (***Box 14.5***).

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If the patient is not at goal with the combination of high intensity statin and ezetimibe, a PCSK9 monoclonal antibody may be added to the treatment, since there is now more evidence for long term efficacy and safety of these agents. Inclisiran may be considered as an alternative option. Although CV outcome trials are pending, there is recently data published on its use in primary prevention. Furthermore, it may improve adherence in such a young patient with twice yearly injections. If high intensity statin is not tolerated, bempedoic acid combination with a lower dose statin and ezetimibe also is an option in this patient to get to goal. The aim here is to decrease the LDL cholesterol by keeping the patient at goal to prevent CV events.

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