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Consensus

Management of dyslipidemia in adults. A consensus statement from the French Society of Endocrinology (SFE), the French-speaking Diabetes Society (SFD), the New French-speaking Society of Atherosclerosis (NSFA) and the French Society of Cardiology (SFC)☆

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1. Introduction

Dyslipidemia, when it increases the level of lipoproteins rich in apolipoprotein B (apoB), induces increased risk of atherosclerotic cardiovascular disease (ASCVD). Lipid-lowering treatments that reduce the concentration of apoB-rich lipoproteins, and particularly LDL cholesterol (LDL-c), decrease cardiovascular morbidity and mortality [1]. The latest French guidelines on the management of dyslipidemia in adults date from 2016. Since then, numerous international guidelines have been published [2–5] and the management of dyslipidemia has become more complex with the emergence of new criteria for estimating cardiovascular risk, new LDL-c targets, and new treatments. It therefore seemed necessary to provide clinicians with updated recommendations on the subject, based on the latest scientific evidence.

2. Methodology

These guidelines were developed under the auspices of the French Society of Endocrinology (SFE), French-speaking Diabetes Society (SFD), New French-speaking Atherosclerosis Society (NSFA), and French Society of Cardiology (SFC). The working group consisted of 11 experts from different specialties: cardiology, endocrinology, diabetology, nutrition. For each topic, a bibliographic update was carried out, taking account of the main publications indexed in PubMed up to September 2025. The experts were asked to grade the recommendations according to the methodology used by the European Society of Cardiology [3] (Table 1).

The recommendations were reviewed by a group of nine experts (see Acknowledgments).

3. Initial assessment

3.1. Lipid abnormality profile: indications, conditions for performance

A standard serum lipid profile is necessary for the assessment of cardiovascular risk and is the first step in the diagnosis of dyslipidemia. Serum lipid profile also enables monitoring and adjustment of lipid-

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Table 1
Recommendation class and level of evidence (according to [6]).

Class (strength) of recommendations	Definition	Phrases used
Class I (high)	Evidence and/or consensus that a treatment or intervention is beneficial, effective, useful	Is recommended Is indicated/effective/beneficial Must be performed
Class II	Conflicting evidence and/or conflicting opinions regarding the usefulness/effectiveness of a treatment or intervention	
Class IIa (moderate)	Weight of evidence/opinion in favor of usefulness/effectiveness	Reasonable May be useful/effective/beneficial/achievable
Class IIb (low)	Utility/effectiveness less well established by evidence/opinion	May be considered/envisaged
Class III	Evidence or consensus that the treatment or intervention is not useful/effective and in some cases may be harmful	Not recommended Not indicated/useful/effective/beneficial
Level of evidence A	Data from several randomized clinical trials or meta-analyses	
Level of evidence B	Data from a single randomized clinical trial or several large non-randomized studies	
Level of evidence C	Expert opinion and/or small studies, retrospective studies, registries	

lowering treatment and assessment of therapeutic compliance, and helps patients adhere to the management of their cardiovascular risk. Based on current scientific data, standard serum lipid profiling is recommended for people:

- living with documented CVD (see below);
- with one of the following cardiovascular risk factors: high blood pressure (HBP), diabetes, obesity, chronic kidney disease (CKD), smoking;
- with family history of early cardiovascular disease (< 55 years in men, < 60 years in women);
- with dyslipidemia in first-degree relatives;
- living with HIV.

It may be performed:

- in apparently healthy individuals (in men aged 40 and over, in women aged 50 and over or from menopause onwards);
- before prescribing treatment likely to alter lipid parameters (immunosuppressants, retinoic acid, corticosteroids, etc.);
- in people with chronic inflammatory disease or autoimmune disease;
- in people with a disease or other condition associated with increased cardiovascular risk: obstructive sleep apnea syndrome (OSAS), active cancer, chronic obstructive pulmonary disease (COPD), men with erectile dysfunction, women with history of hypertensive pregnancy disorder.

As part of severe dyslipidemia screening due to family history, it is reasonable to perform standard lipid profile (SLP) in childhood or young adulthood.

Fasting is no longer systematically required for lipid analyses. Non-fasting tests have shown the same predictive power for non-HDL cholesterol (non-HDL-c) or apoB measurement as fasting tests [7,8]. However, fasting is recommended in case of hypertriglyceridemia (HTG) in order to obtain a more reliable LDL-c measurement.

The SPL includes direct measurement of total cholesterol, HDL cholesterol (HDL-c), and triglycerides (TG). LDL-c is generally calculated using the Friedewald formula. In case of HTG > 3.4 g/L or 3.8 mmol/L or very low values under intensive lipid-lowering treatment (e.g., PCSK9 inhibitors), direct measurement is recommended for greater reliability. Non-HDL-c level is obtained using the following formula: total cholesterol – HDL-c. It reflects the total cholesterol carried by apoB-rich lipoproteins, which are atherogenic. It is a robust alternative to LDL-c in case of HTG (diabetes, metabolic syndrome, renal failure, etc.) and non-HDL-c targets are 0.3 g/L (0.8 mmol/L) above LDL-c targets [9]. ApoB measurement is now standardized and can be performed by certain laboratories on an SLP prescription. It corresponds to the direct measurement of the number of circulating atherogenic particles. Target values based on cardiovascular risk are proposed in Section 6 below. It is also useful for etiological diagnosis of severe HTG and mixed hyperlipidemia, to differentiate between familial chylomicronemia syndrome (FCS), multifactorial chylomicronemia syndrome (MCS) in severe HTG and familial combined hyperlipidemia, and dysbetalipoproteinemia (see Section 7). The residual cholesterol concentration is obtained using the following formula: total cholesterol – HDL-c – LDL-c. Lipoprotein(a) (Lp(a)) is an independent causal risk factor for ASCVD. Its measurement is relevant for cardiovascular risk stratification. Individuals in whom it should be measured are detailed in Section 8.

3.2. *Ruling out secondary dyslipidemia*

Before concluding that dyslipidemia is primary, it is essential to rule out secondary causes (Table 2). This involves actively sreening for conditions or treatments that could induce hyperlipidemia. The initial non-systematic biological assessment, guided by the clinical and biological picture, may include: TSH, fasting venous blood glucose, creatinine (clearance calculation), proteinuria (urine dipstick), and liver function tests (AST, ALT, GGT, alkaline phosphatase, and total, free and conjugated bilirubin). Certain conditions are classically associated with lipid abnormalities. Hypothyroidism and cholestasis can cause hypercholesterolemia, often in a suggestive clinical context. Nephrotic syndrome is a major cause of severe mixed hyperlipidemia. Diabetes, metabolic syndrome, renal failure and chronic alcoholism are frequently responsible for HTG.

Many medications can also cause elevated LDL-C and/or TG levels, including: cyclosporine, retinoids, corticosteroids, ethinyl estradiol (oral), thiazides, beta-blockers, anabolic steroids, certain antiretrovirals, neuroleptics and several targeted therapies used in oncology (tyrosine kinase inhibitors [TKIs] and mTOR inhibitors).

3.3. *Cardiovascular risk assessment*

Cardiovascular risk assessment is essential in order to tailor the intensity of primary prevention, before any atherosclerotic events arise. The expected benefit of a treatment, its risk/benefit ratio and its efficiency (the number of patients to be treated to prevent 1 event) depend directly on the patient's absolute risk level [5].

Table 2
Main causes of secondary dyslipidemia.

	HCT	HTG	Diagnostic methods
TG » LDL-c			
Alcohol		+ +	Interview, CDT
Obesity		+	BMI
Diabetes	+	+ +	Fasting blood glucose, HbA1c
Sepsis		+	Complete blood count (CBC) – CRP
Cushing's syndrome		+	24-hour UFC, Dexamethasone suppression test, Cortisol at 0 h
Acromegaly		+	IGF-1
LDL-c » TG			
Hypothyroidism	+ + +	+	TSH
Cholestasis (CBP + +)	+ + +		Bilirubin, ALP, GGT
Hepatic cytolysis	+ +	+	AST, ALT
Anorexia nervosa	+		BMI
LDL-c ≈ TG			
Nephrotic syndrome	+ +	+ +	Proteinuria, albuminemia, edema
Chronic renal failure	+	+	Creatinine and GFR
Gammopathy, myeloma	+ +	+ +	PEP
Medications: oral estrogens, retinoids, corticosteroids, antiretrovirals, antipsychotics, immunosuppressants, mTOR inhibitors, ITKs	Variable	Variable	Interview

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CDT: carbohydrate deficient transferrin; CRP: C-reactive protein; GFR: glomerular filtration rate, GGT: gamma glutamyl transferase; HCT: hypercholesterolemia; HTG: hypertriglyceridemia; IGF-1: insulin growth factor 1; PBC: primary biliary cirrhosis; PEP: plasma protein electrophoresis, TSH: thyroid stimulating hormone; TKIs: tyrosine kinase inhibitors; UFC: urinary free cortisol.

Cardiovascular risk calculation models are mainly applicable to people who appear to be in good health. Table R1 summarizes indications for cardiovascular risk assessment using a risk model or score.

In apparently healthy individuals, without established CVD, it is recommended to use the SCORE 2 risk prediction algorithm between the ages of 40 and 69 years and the SCORE 2-OP algorithm between the ages of 70 and 89 to assess cardiovascular risk (https://heartscore.escardio.org/Calculate/quickcalculator.aspx?model=low). These two scores take account of age, gender, smoking, systolic blood pressure, and non-HDL-c. They were calculated based on the average cardiovascular risk for each country. For mainland France, it is appropriate to use the tables for areas with low cardiovascular risk. The scores establish the risk of fatal and non-fatal CVD over 10 years. The two scores should not be used in patients with CKD, diabetes, familial hypercholesterolemia (FH), or established ASCVD. Nor should they be used in individuals already receiving lipid-lowering therapy. Finally, they should not be used to "reassess" cardiovascular risk after an initial assessment leading to initiation of lipid-lowering therapy.

In people living with type-2 diabetes (T2D), cardiovascular risk can be assessed using the SCORE2-Diabetes risk algorithm [10]. This predictive model estimates the 10-year risk of CVD in people living with T2D. It incorporates the conventional risk factors from the SCORE 2 and SCORE 2-OP scales, plus diabetes-specific variables (age at diagnosis, glycated hemoglobin [HbA1c], and estimated glomerular filtration rate [eGFR]). It is reserved for asymptomatic individuals with no ASCVD and no target organ damage (retinopathy, nephropathy, neuropathy). However, it does not take albuminuria into account and only applies to people living with T2D aged 40 to 69 years. An algorithm developed by the SFD and SFC offers a more complex assessment of cardiovascular risk, taking account of more risk factors and vascular markers, and including people living with type-1 diabetes (T1D) [11] (Table 3).

3.4. Cardiovascular risk levels

In subjects with no documented ASCVD, CKD, diabetes or HF, the SCORE 2 and SCORE 2-OP algorithms can be used to estimate a level of cardiovascular risk (Table 3) [6]. In addition, 4 groups of subjects are identified separately (Table 3):

- people living with CKD, without diabetes or known ASCVD;
- people living with FH and considered to be at high or very high cardiovascular risk if treatment is delayed;
- people living with diabetes, who are considered to be at least at moderate cardiovascular risk;
- and people with documented ASCVD, all of whom are at very high risk.

ASCVD can be documented clinically, or unequivocally by imaging. Documented clinical ASCVD includes history of myocardial infarction (MI), acute or chronic coronary syndrome, coronary revascularization, ischemic stroke or transient ischemic attack (TIA), aortic aneurysm, and peripheral arterial disease (PAD). Subclinical ASCVD unequivocally documented on imaging includes > 50% stenosis on coronary angiography, coronary computed tomography angiography (CTA), or carotid or femoral ultrasound, and coronary calcium score (CAC) > 300 Agatston units (AU) [6]. Primary stenosis prevention corresponds to absence of documented clinical ASCVD, while secondary cardiovascular prevention corresponds to the presence of documented clinical ASCVD. Between these two situations, there is a continuum of atherosclerotic disease, where subclinical ASCVD incurs at very high cardiovascular risk.

The SCORE 2 and SCORE 2-OP algorithms are imperfect tools for estimating cardiovascular risk at the individual level, which they are liable to underestimate [13]. Thus, in individuals with moderate cardiovascular risk or with LDL-c at the limit of therapeutic targets, it is reasonable to identify clinical situations that may alter the level of cardiovascular risk. These situations are detailed in Table 4. However, it is not currently possible to quantify the extent to which the presence of one or more of these situations increases cardiovascular risk, and imaging may improve cardiovascular risk stratification.

Table 3
Cardiovascular risk level based on clinical situation (adapted from [1,6,12]).

Long-term CV risk level	**Person in apparent good health**	**Chronic kidney disease** (without ASCVD or diabetes)	**Diabetes**	**Heterozygous familial hypercholesterolemia**
Very high	SCORE 2 or SCORE 2-OP: ≥ 20%	eGFR < 30 mL/min/1.73m² eGFR 30-44 mL/min/1.73m² and ACR ≥ 30 mg/g eGFR 45-59 mL/min/1.73m² and ACR > 300 mg/g	With at least one of the following factors: - Atrial fibrillation or heart failure - LDL-c >1.9 g/L - ACR > 300 mg/g - eGFR <30 mL/min/1.73m² - Q wave abnormalities (ECG) - Left ventricular abnormality (Echo-Function/hypertrophy) - Peripheral arterial stenosis ≥ 50% CAC: ≥ 60 years: ≥ 300 AU < 60 years: ≥ 100 AU	With ASCVD or other CVD risk factors
High	SCORE2 or SCORE 2-OP: ≥ 10% and < 20%	eGFR 30-44 mL/min/1.73m² and ACR < 30 mg/g eGFR 45-59 mL/min/1.73m² and ACR 30-300 mg/g eGFR > 60 mL/min/1.73m² and ACR > 300 mg/g	Perform a CAC if at least 2 of the following factors are present: - Duration > 10 years for T2D, > 20 years for T1D - Family history of premature ASCVD - Persistently uncontrolled risk factors (HbA1c, LDL-c, non-HDL-c, blood pressure, smoking) - ACR: 30-300 mg/g or eGFR: 30-60 ml/min/1.73m² - Severe retinopathy, autonomic neuropathy, erectile dysfunction - Low physical activity CAC: ≥ 60 years: ≥ 100 AU ≤ 50 years: 11-100 IU	Isolated, with late introduction (>18 years in men, > 30 years in women) of cholesterol-lowering treatment
Moderate	SCORE 2 or SCORE 2-OP ≥ 2% and <10%	eGFR > 60 mL/min/1.73m² and ACR 30-300 mg/g eGFR 45-59 mL/min/1.73m² and ACR <30 mg/g	T2D < 10 years or T1D < 20 years, uncomplicated CAC: > 50 years: 10-100 IU 0-10 IU	FH without ASCVD, no other CV risk factors, treated early (< 18 years in men, < 30 years in women)
Low	< 40 years old with no other CVRF SCORE 2 or SCORE 2-OP < 2%			

ACR: albuminuria-creatinine ratio; ASCVD: atherosclerotic cardiovascular disease; CAC: coronary artery calcium score; CV: cardiovascular; eGFR: estimated glomerular filtration rate, FH: familial hypercholesterolemia, T1D: type 1 diabetes, T2D: type 2 diabetes.

3.5. Contribution of imaging to cardiovascular risk assessment

Non-invasive imaging of subclinical atherosclerotic disease is a pragmatic and effective means of improving cardiovascular risk stratification, particularly in primary prevention in asymptomatic subjects, especially in case of moderate cardiovascular risk [14,15].

3.5.1. CAC

CAC improves the cardiovascular risk stratification (upward or downward), particularly in individuals close to decision thresholds. Therefore, it is not recommended to perform this test in individuals with very high cardiovascular risk or in secondary prevention, in individuals under 40 years of age (who usually have atheroma that is not yet calcified), or in very elderly individuals and/or those whose general condition and life expectancy would make preventive treatment futile. It is also not recommended to perform a new CAC within 5 years of the first examination [16]. A high CAC increases the estimated risk, while zero or low CAC decreases it. CAC results should be interpreted both in absolute terms (scores > 300 AU reflect very high individual risk, equivalent to secondary prevention) [17] and in relative terms, com-

Table 4
CV risk modifiers (according to [6]).

CV risk modifiers to be taken into account in individuals with moderate CV risk or LDL-c at the threshold for therapeutic intervention
Family history of premature CV disease (before age 55 in men, before age 60 in women)
High-risk ethnicity (e.g., Southeast Asia)
Symptoms of stress and psychosocial stress factors
Social deprivation
Obesity
Physical inactivity
Chronic inflammatory or autoimmune disease (persistently elevated usCRP levels > 2 mg/L)
Major psychiatric disorders
History of premature menopause
Hypertensive disorder of pregnancy
HIV infection
Obstructive sleep apnea syndrome

hsCRP: high sensitivity C-reactive protein; CV: cardiovascular; HIV: human immunodeficiency virus.

paring them to the expected values in a population of the same age and gender. A score above the 75th percentile indicates greater cardiovascular risk compared to peers; conversely, a score of zero AU has a strong negative predictive value for cardiovascular ischemic events over a period of 5 (diabetes) to 10 years (general population). This test is particularly useful for reclassifying subjects with moderate cardiovascular risk, as well as in FH [18] and diabetes [19,20]. For the sake of harmonization, we set a single threshold of 300 AU to define very high cardiovascular risk in people living with diabetes based on the SFD/SFC algorithm (Table 3). It should be noted, however, that CAC does not assess non-calcified plaques or the severity of stenosis.

3.5.2. Coronary computed tomography angiography (CCTA)

Coronary computed tomography angiography (CCTA) can detect coronary stenosis and predict cardiac events. In the SCOT-HEART study, its use reduced heart attack and death in patients with stable chest pain [21]. Its prognostic value compared to CAC remains to be confirmed.

3.5.3. Carotid ultrasound

Carotid ultrasound allows measurement of intima-media thickness (IMT), which is no longer recommended for cardiovascular risk stratification due to a lack of standardization or demonstrated benefit [22,23]. However, the presence of carotid plaques could help stratify cardiovascular risk in patients at moderate risk, although predictive capacity is lower [24]. Femoral plaques, although strongly linked to the presence of coronary artery disease [25,26], have not been evaluated for improving cardiovascular risk stratification.

3.5.4. Arterial stiffness

Arterial stiffness, assessed by measuring pulse wave velocity, although correlated with cardiovascular risk, is poorly standardized, limiting use, and the predictive value is lower than or CAC.

3.5.5. The ankle-brachial index (ABI)

The ankle-brachial index (ABI) is of limited value in reclassification due to the low prevalence of abnormal values and false negatives related to medial calcification.

3.5.6. Cardiac echocardiography

Cardiac echocardiography, despite improvements in technique for detecting and quantifying cardiac calcification [27], is not recommended for predicting ischemic cardiovascular risk due to the lack of evidence of added value if cardiovascular examination is normal.

4. Therapeutic lifestyle modifications

4.1. General

Therapeutic lifestyle modifications (TLMs) involve dietary change, regular physical activity and combating sedentary lifestyle. They are the first step in therapeutic management, before prescribing drug treatment, in primary prevention in the absence of severe dyslipidemia, as soon as LDL-c exceeds 1.3 g/L (3.4 mmol/L) and/or TG exceeds 1.5 g/L (1.7 mmol/L) [28]. TLMs may make it possible to avoid drug treatment for moderate dyslipidemia or dyslipidemia that is highly responsive to TLMs, such as most cases of hypertriglyceridemia (20–50% reduction in TG, except in severe genetic forms) [29]. In other cases (secondary prevention, FH and severe dyslipidemia), TLMs are systematically combined to drug treatment, as inseparable and complementary.

Dietary advice must take into account patients' eating habits. It has two objectives: (i) to contribute to improving the lipid profile; (ii) to help reduce cardiovascular risk, regardless of lipid profile, partly by improving blood pressure, insulin resistance and qualitative changes in lipoproteins.

4.2. Dietary measures to improve lipid profile

4.2.1. In hypercholesterolemia

In hypercholesterolemia, the effect of dietary measures on lowering cholesterol varies from one individual to another and depends on initial LDL-c level. They can reduce total cholesterol and LDL-c levels by 10–15%, or even more in hyper-responders.

It is recommended to reduce excessive intake of saturated fatty acids (FAs) from animal sources (fatty red meat, processed meat, offal, cheese, butter, cream, full-fat dairy products) or vegetable sources (palm oil, copra) to less than 7% of total energy intake (TEI) [3]. Saturated FAs are the dietary factor with the greatest impact on LDL-c concentration. Each 1% increase in calories from saturated FAs is accompanied by an increase in LDL-c of 0.008 to 0.016 g/L (0.02 to 0.04 mmol/L) [29]. Unlike other saturated FAs (lauric, myristic, and palmitic acids), stearic acid (found in cocoa butter and dark chocolate) does not increase LDL-c concentration [30]. Trans-FAs from partial hydrogenation of fats (pastries, cakes, cookies) have the same effect on LDL-c as saturated FAs, with an additional effect on lowering HDL-c. Their intake should be limited as much as possible and to a maximum of 1% of TEI [3].

It is recommended to favor unsaturated FAs of animal origin (poultry, fatty fish such as salmon, sardines, cod) and vegetable sources of omega-9 monounsaturated FAs (olive oil) or rich in omega-3 (rapeseed, soybean, nuts) and margarines with omega-9, -6, and -3. Monounsaturated FAs have a favorable effect on LDL-c when substituted for saturated FAs. Intake of around 15% of TEI is recommended. Polyunsaturated FAs (PUFAs) lower LDL-c and, to a lesser extent, HDL-c when they replace saturated FAs. Excessive intake of n-6 FAs in the form of vegetable oils rich in n-6 FAs (sunflower, peanut) upsets the balance between n-3 and n-6 FA intake. It is desirable to increase the proportion of n-6 FAs in the diet at the expense of saturated FAs, but this should not exceed 10% of TEI.

For example, based on these recommendations, for a person with hypercholesterolemia who has an energy requirement of 2000 kcal/day, the intake of saturated FA should be < 110 g/week, which is equivalent to 7 servings of cheese, 3 fatty hamburgers, or 5 knobs of butter; trans-fat intake should be < 15 g/week (1 croissant or 2 cookies a week); and n-6 PUFAs intake should be < 155 g/week (maximum 3–4 tablespoons a day of sunflower/soybean oil, but to be replaced in part by olive/rapeseed/nut oil).

It is recommended to consume between 25 and 40 g of fiber per day, including 7 to 13 g soluble fiber (for example, 2 fruits + 2 vegetables + 1 serving of legumes + 1 serving of whole grains + a handful of oilseeds). Increasing your intake of sources of dietary fiber (whole grains and whole wheat bread, legumes, fruits and vegetables) and mainly

Table R1 Recommendations for initial assessment.

Recommendations	Class	Level of evidence
Standard serum lipid profile:		
should be performed in all individuals with ≥ 1 of the following cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidemia, obesity), family history of early cardiovascular disease, FH, HIV infection	I	B
may be performed in men over 40 and women over 50 years or post-menopausal women with no known cardiovascular risk factors	IIa	B
can be performed in individuals with chronic inflammatory disease or autoimmune disease	IIa	C
can be performed in individuals with a disease or condition associated with increased cardiovascular risk: active cancer, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome (OSAS), men with erectile dysfunction, women with history of hypertensive disorders of pregnancy	IIa	C
When screening for severe dyslipidemia due to family history, it is reasonable to perform a standard serum lipid profile in young adults or children	IIa	B
Assessment of cardiovascular risk can be considered every 5 years after an initial assessment where cardiovascular risk is low or moderate and in the absence of intercurrent cardiovascular events	IIb	C
In apparently healthy individuals aged 40 to 69 without ASCVD, diabetes, CKD or FH, initial 10-year cardiovascular risk assessment can be performed using SCORE 2	IIa	B
In apparently healthy individuals aged 70 to 89 without ASCVD, diabetes, CKD, or FH, the initial assessment of 10-year cardiovascular risk can be performed using SCORE 2-OP	IIa	B
Cardiovascular risk stratification in people living with diabetes, for primary cardiovascular prevention, aged 35 to 75, can be performed using the SFD/SFC algorithm	IIa	C
People with documented clinical or subclinical ASCVD should be considered at very high cardiovascular risk	I	A
People living with diabetes can be considered to have at least moderate cardiovascular risk, in the long-term	IIa	A
People living with CKD stage G3a/A2, G3b to G5, and A3 should be considered to have a high or very high cardiovascular risk[a]	I	A
LDL-c calculation is recommended as the primary target for assessing cardiovascular risk	I	A
Calculation of non-HDL-C is recommended to or assess cardiovascular risk in individuals with moderate HTG, diabetes, metabolic syndrome or obesity	I	A
ApoB measurement is recommended to assess cardiovascular risk in individuals with moderate HTG, diabetes, metabolic syndrome, or obesity	I	A
Measuring CAC score may be useful in improving the stratification of moderate cardiovascular risk in people over 40 years of age	IIa	A
Assessment of carotid plaque may be considered to improve cardiovascular risk stratification	IIb	B
The use of other vascular imaging techniques is not recommended	III	B

CAC: coronary artery calcium; FH: familial hypercholesterolemia; ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease.

[a] CDK prognosis according to stage is summarized in Supplementary Table 1.

soluble fiber (pectins, beta-glucans from oats and barley) is effective in lowering cholesterol levels. Consuming 10 g/day of soluble fiber is associated with 6–15% reduction in LDL-c.

The impact of dietary cholesterol on serum cholesterol levels is low and varies from one individual to another compared to that of different FAs. Egg yolk is the food richest in cholesterol not associated with FAs. The numerous studies conducted on the link between cholesterol consumption (mostly from eggs) and increased LDL-c or ASCVD are inconclusive [31]. Nevertheless, it is reasonable to limit egg consumption to 7 per week.

4.2.2. *In hypertriglyceridemia*

In hypertriglyceridemia, lifestyle modifications are an essential part of therapeutic management. When properly followed, they can reduce TG levels by up to 50%, even in case of susceptibility genotype.

In common forms of HTG, benefit on the lipid profile is observed for ≥ 5 weight loss. The weight loss goal, which may be higher, is based on calorie restriction (which should generally not exceed −500 kcal/day) combined with increased physical activity. It is also important to reduce or even stop consuming alcohol and foods or drinks that are sugary or contain fructose. Simple sugars should be limited to ≤ 10% TEI. Refined carbohydrates, which are low in fiber and have a high glycemic index, promote HTG; it is recommended to limit overall carbohydrate intake to 45–50% TEI, favoring minimally refined, fiber-rich carbohydrates. Enriching the diet with fiber should be encouraged, as should shifting consumption from saturated to polyunsaturated or omega-3 FAs. In hyperchylomicronemia, total fat intake should be restricted even further, to < 10–15% TEI (< 30 g per day) in FCS. Medium-chain triglycerides (provided in the diet in the form of oil), which pass directly into the portal circulation and do not contribute to formation of chylomicrons, can increase lipid and calorie intake without risk of increasing TG levels during FCS. Supplementation with fat-soluble vitamins and omega-3 FAs is necessary for these extremely restricted lipid intakes.

4.3. *Dietary measures in case of overweight and/or obesity*

In case of excess weight, even a modest 5–10% reduction in body weight improves lipid abnormalities and has a favorable effect on other cardiovascular risk factors often present in people with dyslipidemia. The beneficial effects of weight loss on metabolic markers have been demonstrated, but the benefit for cardiovascular morbidity and mortality is less clear [32].

4.4. *Dietary measures to reduce cardiovascular risk*

The Mediterranean diet has the highest level of evidence for cardiovascular prevention [33]. It is rich in polyphenols, vitamins and carotenoids with antioxidant effects: fruit and vegetables (5 fruits and vegetables per day), vegetable oils including extra-virgin olive oil, and nuts (30 g/day). It is characterized by low amounts of red meat, which is associated cardiovascular risk regardless of its saturated FA content. It includes eating fish twice a week, including oily fish once a week (salmon, sardines, mackerel, herring), and a high intake of fiber and vegetables, including legumes. Processed foods and sugary products are not recommended. The Mediterranean diet is recommended for cardiovascular prevention.

4.5. Dietary supplements

4.5.1. Phytosterols

Phytosterols are compounds naturally present in plant-based foods, particularly vegetable oils, nuts, seeds and cereal products, but in small quantities (a few hundred milligrams consumed each day). Meta-analyses showed a 5–8% reduction in LDL-c for a supranutritional intake of 2 g/day of phytosterols, with a dose-response effect that reaches a plateau at 3 g/day [34,35]. Phytosterol-enriched foods can further reduce LDL-c by 10%, at the cost of an increase in phytosterolemia. Mendelian randomization analyses provide evidence for a deleterious effect of phytosterols on the risk of coronary heart disease, both directly and via cholesterol [36]. To date, there are no randomized controlled trials demonstrating clinical benefit of phytosterol-enriched products in terms of cardiovascular events. Thus, foods enriched with phytosterols have a cholesterol-lowering effect, but increase phytosterolemia and have not been proven to reduce cardiovascular risk. They can lead to beta-carotene deficiencies. In its 2014 report, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) "considers that the data currently available do not allow phytosterol-enriched foods to be considered an appropriate means of preventing CVD at the population level" [37]. Phytosterols are not recommended for lowering cardiovascular risk.

4.5.2. Red yeast rice

Red yeast rice, a dietary supplement used to lower LDL-c, is produced by fermenting yeast grown on rice. During fermentation, several compounds are formed, including various monacolins, such as monacolin K, which is structurally identical to lovastatin and inhibits the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. In 2022, the European Commission required a limit of 3 mg/day of monacolin K (which corresponds to very low doses of statin) and a ban on its use in children, pregnant women, people over 70, and patients already taking cholesterol-lowering medication. In addition, some products on the market have been found to be contaminated with mycotoxins, which are toxic and potentially carcinogenic. Red yeast rice dietary supplements expose users to adverse events (particularly muscular) similar to those associated with other statins. These supplements are not an alternative to drugs used to treat high cholesterol and should not be used in combination with a statin or as a substitute for a statin, as they are less effective and their safety has not been established [38]. In the absence of dedicated studies, the use of red yeast rice is not recommended for lowering cardiovascular risk.

4.6. Physical activity

Regular appropriate physical activity (Supplementary Table 1) is beneficial for overall well-being and cardiovascular health. It is recommended for patients with dyslipidemia. The expected effect on improving the lipid profile is marginal for LDL-c, but more pronounced for TG reduction (up to 25%) and HDL-c elevation (around 10%) [39–41]. Improvement is independent of weight loss [39]. Among the types of physical exercise, a longer aerobic activity compared to other types correlates with a greater improvement in the lipid profile [39]. This is also true, but to a lesser extent, for higher intensity activity [39]. Anaerobic physical activity is also associated with improvement in lipid profile [42]. Overall, any sustained physical activity, even of low intensity and short duration, leads to a more favorable lipid profile than a sedentary lifestyle and has a beneficial effect on all cardiovascular risk factors [43]. Conversely, prolonged sedentary behavior is associated with increased cardiovascular risk, even when physical activity levels are equal. Thus, promoting physical activity and combating sedentary lifestyles are two complementary actions that should be recommended [43].

4.7. Alcohol consumption

Non-excessive alcohol consumption in individuals without any particular genetic predisposition leads to isolated moderate increase in HDL-c, which would explain only half of the controversial association between non-excessive alcohol consumption and a slight reduction in cardiovascular risk [44]. This J-shaped curve for cardiovascular risk was observed in several cohort studies regardless of the type of alcohol consumed: wine, beer or other alcoholic beverages [45]. However, recent epidemiological studies did not find a link between moderate alcohol consumption and lower cardiovascular risk. The risk of stroke, atrial fibrillation, and cancer increases with minimal alcohol consumption without a J-curve [46].

Chronic excessive consumption of alcohol (maximum 10 standard drinks per week, without exceeding 2 standard drinks per day) induces HTG of varying intensity depending on polygenic predisposition to HTG, with an unusual phenotype, since HTG is associated with normal or even high HDL-c. This phenotype should systematically lead to screening on interview and clinical examination for excessive comsumption and, in the event of denial, to quantification of markers of alcohol abuse (carbohydrate deficient transferrin [CDT] or phosphatidylethanol [PEth]).

Excessive alcohol consumption should be investigated during MCS, but in current practice it is a factor in only a minority of cases. Identification is critical because, in addition to increasing HTG, it is an established trigger for acute pancreatitis.

For pure hypercholesterolemia, the recommendations for moderation applicable to the general population apply. In cases of HTG, consumption should be drastically reduced or even completely stopped in case of dependence.

4.8. Smoking

Regular smoking has a negative impact on lipid parameters: 1–2% increase in LDL-c and 9–11% increase in TG, 6% decrease in HDL-c [47,48]. It promotes abdominal obesity and has a diabetogenic effect [49], which is dose-dependent [50]. It is a major cardiovascular risk factor, particularly through the metabolic abnormalities it induces [51]. Smoking cessation is therefore essential in cardiovascular prevention, and smoking cessation support should be systematically offered to patients who smoke and have dyslipidemia. Nicotine replacement therapies (patches, oral forms) are covered by French health insurance and can be prescribed not only by doctors but also by nurses, dentists, physical therapists and midwives. Varenicline and bupropion (rarely used) are also approved for use in smoking cessation and may also be used as a complement to behavioral therapy [52].

E-cigarettes, although controversial, may help adult smokers quit smoking, particularly when used in combination with patches. Their sale to minors is prohibited. There is insufficient data on their long-term effects.

5. Lipid-lowering drugs

5.1. Statins

5.1.1. Effectiveness

Statins reduce hepatic cholesterol synthesis by inhibiting hydroxymethylglutaryl-CoA reductase (HMG CoA). This reduction in intracellular cholesterol increases the number of LDL receptors (LDLR) on the surface of hepatocytes, which increases the uptake of LDL particles circulating in the blood. Statins therefore mainly reduce LDL-c and apoB concentrations. Low-intensity statins induce a 20–30% reduction in LDL-c concentration, moderate-intensity statins a 30–50% reduction, and high-intensity statins a 50–60% reduction (Table 5) [53]. The reduction is subject to significant interindividual variation [54,55]. Poor response can be explained by poor compliance or by

Table R2 Recommendations for "Therapeutic lifestyle changes" to improve lipid profile.

Recommendations	Class	Level of evidence
Lifestyle changes to lower LDL cholesterol		
Reduce intake of saturated fatty acids from animal or vegetable sources to less than 7% of total energy intake	I	A
Limit trans-fatty acid intake to less than 1% of total energy intake	I	A
Choose unsaturated fatty acids from animal and plant sources	I	A
Increase fiber intake to between 25 and 40 g per day, including 7–13 g of soluble fiber	I	A
Limit egg consumption to 7 per week	II	B
Increase physical activity and limit sedentary behavior	I	B
Lifestyle changes to lower triglycerides		
Weight loss (≥ 5% of body weight) is desirable and effective in common forms of HTG	I	A
Drastically reduce alcohol consumption (or even stop completely in case of dependence)	I	A
Limit overall carbohydrate intake to 45–50% of total energy intake, favoring unrefined, fiber-rich carbohydrates and limiting simple sugars (fructose, monosaccharides)	I	A
Increase physical activity and limit sedentary behavior	I	A
Enrich diet with fiber and polyunsaturated fatty acids (omega-3) and limit saturated fatty acids	I	B
Lifestyle changes to increase HDL-c		
Limit trans-fatty acid intake to < 1% total energy intake	I	A
Weight loss if overweight	I	A
Increase physical activity and limit sedentary behavior	I	A
Quit smoking	I	B

HTG: hypertriglyceridemia.

genetic predisposition [56,57]. The effect on HDL-c concentration is small, with an increase of 2–8% in a meta-analysis of 37 randomized trials evaluating simvastatin, atorvastatin and rosuvastatin [58]. A decrease in TG concentration of 10–20% is generally observed. The decrease is more pronounced for high-intensity statins [59].

Numerous meta-analyses demonstrated the benefits of statins for cardiovascular morbidity and mortality in primary and secondary prevention [1,60]. A 21% reduction in major cardiovascular events and a 10% reduction in all-cause mortality were reported for each 1 mmol/L (0.39 g/L) reduction in LDL-c concentration [1,60].

5.1.2. Tolerance

Muscle disorders, which are distinct from myopathy, are the most common adverse effect attributed to statins, with cramps, muscle pain and/or muscle weakness, associated with a plasma creatine phosphokinase (CK) concentration that is normal or less than 10-fold the normal level. Observational studies reported prevalence of muscle disorders without elevated CK of 10–15% [61,62]. However, in randomized, blinded clinical trials comparing statins versus placebo, frequency of muscle disorder was only slightly higher with statins [63–67]. No significant difference in the proportion of statin discontinuation due to adverse effects was reported. Furthermore, during the initial phase of the ASCOT-LLA double-blind placebo-controlled trial, there was no difference in the incidence of muscle disorder, whereas in the non-randomized open-label extension phase, muscle disorders were more frequent in subjects treated with statins [68]. This study highlighted the role of the nocebo effect in the occurrence of muscle disorders. More recently, two randomized "N-of-1" trials, consisting of a series of periods during which treatment (in this case, a statin), a placebo or, in some cases, no treatment was administered, with sequence randomized, demonstrated the nocebo effect of statins [69,70]. In both studies, the majority of intolerant patients (~60%) reported as much pain with statins as with placebo, casting doubt on the reality of statin-induced muscle intolerance. The fact that pain was half as severe when patients took no treatment compared to placebo further illustrates the nocebo effect.

Ultimately, there is no evidence of a causal link between muscle disorder (excluding myopathy) and statin use. Randomized clinical trials reported an incidence of statin-associated muscle disorder of 10 to 20 cases per year per 10,000 subjects treated [62].

However, the risk of myopathy, defined as muscle disorder associated with CK levels more than 10-fold higher than normal, associated with statin use has been proven. Annual incidence is estimated at 1 case per 10,000 patients treated. Rhabdomyolysis, its most severe form, is even rarer, with an estimated annual incidence of 2 to 3 cases per 100,000 patients treated [62,71]. The risk resolves quickly when treatment is stopped [72]. The risk of myopathy is dose-dependent [73]. It is also higher when statins metabolized by cytochrome P450 3A4 (CYP3A4) (simvastatin, atorvastatin) are combined with certain drugs (Table 6), in people of Asian origin, individuals over 80 years of age, women and in case of hypothyroidism and diabetes [62].

The use of statins has been shown to be dose-dependently associated with increased in the risk of T2D [74]. Annual incidence of new cases of diabetes is estimated at 5 to 10 cases per 10,000 patients treated [62]. Classic risk factors for T2D (age, overweight, insulin resistance, and prediabetes) are associated with an increased risk of diabetes linked to statin use [75]. However, the benefits associated with a lower absolute risk of cardiovascular events outweigh the risks associated with the onset of diabetes (ratio around 3:1) [62].

The increased risk of hemorrhagic stroke associated with statin use is controversial, with some meta-analyses finding moderate risk and others finding none [76,77].

No difference in the incidence of renal failure was observed in randomized placebo-controlled studies [62]. One meta-analysis showed a slowing of the decline in renal function associated with statin use, but no difference in the progression to chronic renal failure [78].

Moderate elevation in liver enzymes is reported in 0.5 to 2% of patients treated with statins. Cases of hepatocellular failure are very rare (approximately 1 case per 100,000 users) in post-marketing studies [62], with no certainty as to causality.

A meta-analysis of 35 studies found no link between statin use and risk of cancer [79]. And finally, no link was found between statin use and cognitive decline or onset of dementia [80,81].

5.1.3. Drug interactions

Several important interactions between antiretrovirals, and particularly protease inhibitors, and statins should be noted (Table 6). Simvastatin is contraindicated in case of use of protease inhibitors or cobicistat. Pravastatin, rosuvastatin, and fluvastatin are not metabolized by CYP3A4 and can therefore be safely prescribed with protease inhibitors. Integrase inhibitors, which are currently very predominantly prescribed, do not interact with statins. It is advisable to use the University of Liverpool website, which indicates the risk of drug interactions with all medications (https://www.hiv-druginteractions.org/). Overall, it is recommended to favor statins that do not interact with CYP3A4 (ro-

Table 5
Effects of lipid-lowering drugs on plasma concentrations of LDL-c, HDL-c, TG, and Lp(a).

		Effects on lipid parameters	
Statins	Low intensity Fluvastatin 20–40 mg Pravastatin 10–20 mg Simvastatin 10 mg	LDL-c: −20 to −30%	TG: −10 to −20% HDL-c: +2 to +8% Lp(a): no effect
	Moderate intensity Atorvastatin 10–20 mg Fluvastatin 80 mg Pravastatin 40 mg Simvastatin 20–40 mg Rosuvastatin 5 mg	LDL-c: −30 to −50%	
	High intensity Atorvastatin 40–80 mg Rosuvastatin 10–20 mg	LDL-c: ≥ −50%	
Ezetimibe		LDL-c: −10 to −22% HDL-c: +3% TG: −8%	
PCSK9 inhibitors (evolocumab, alirocumab)		LDL-c: −50 to −60% Lp(a): −20% HDL-c: +5 to +10% TG: −5 to 15%	
Bempedoic acid		LDL-c: −17 to −28% Lp(a): minimal HDL-c: minimal TG: minimal	
Lomitapide		LDL-c: −50% TG: −50% Lp(a): −20 to −30%	
ANGPTL3 inhibitor		LDL-c: −50% TG: −50% Lp(a): −15 to −20%	
Fibrates		TG: −20 to −50% HDL-c: +5 to +20% LDL-c: −5 to +20%	
Omega-3 polyunsaturated fatty acids		TG: −10 to −45% LDL-c and HDL-c: no effect	
ApoC3 inhibitors		TG: −60% LDL-c: −10% HDL-c: +30%	

Table 6
Main drugs that may interact with statins metabolized by cytochrome P450 3A4 (simvastatin, atorvastatin) and increase the risk of muscle disorders (adapted from [3]).

Calcium channel blockers	Verapamil, diltiazem, amlodipine
Anti-infective agents	Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, protease inhibitors
Others	Cyclosporine, danazol, amiodarone, ranolazine, gemfibrozil

suvastatin, pravastatin, fluvastatin). It is recommended to start with a low dose and increase gradually, monitoring for muscular side effects.

In transplant patients, close attention must be paid to possible side effects due to drug interactions, particularly with statins. Cyclosporine, which is metabolized by the CYP3A4 enzyme, can increase systemic exposure to all statins and the risk of myopathy. It should not be combined with rosuvastatin (biliary transporter). Tacrolimus, also metabolized by CYP3A4, presents less risk of interaction with statins. Other drugs that influence CYP3A4 activity should be avoided if possible and used with extreme caution in patients receiving both calcineurin inhibitors and statins.

5.2. *Ezetimibe*

Ezetimibe is an inhibitor of intestinal cholesterol absorption. It acts on the Niemann–Pick C1-like 1 protein (NPC1L1). Decreased in intestinal cholesterol absorption thus increasing the amount of cholesterol taken up by the liver, which leads to an increase in the amount of LDLR in the liver. Prescribed at a single dose of 10 mg/day, ezetimibe reduces LDL-c concentrations by 15–22%, with significant interindividual variations [82]. A 3% increase in plasma HDL-c concentration and an 8% decrease in plasma TG concentration were reported in a meta-analysis [83].

Ezetimibe is well tolerated. Randomized controlled trials did not show any greater elevation in transaminases when ezetimibe was used alone or in combination with a statin [82–84]. Cases of severe hepatic insufficiency whenit is used alone or in combination with statins are very rare [82]. The incidence of myalgia and elevated CK is low and

no higher in patients treated with ezetimibe alone compared to placebo or a statin, or in patients treated with ezetimibe in combination with a statin compared to a statin alone [83,85]. Ezetimibe should be used with caution in patients treated with cyclosporine.

Ezetimibe was effective in terms of cardiovascular protection, in combination with simvastatin 40 mg/day, in the IMPROVE-IT study, with a significant 7% reduction in major cardiovascular events [86].

5.3. PCSK9 inhibitors

PCSK9 inhibitors work by blocking the inhibitory action of proprotein convertase subtilisin/kexin type 9 (PCSK9) on LDLR, thereby increasing expression in hepatocytes and catabolism of LDL-c [87]. This therapeutic class includes several molecules with different mechanisms of action. Human monoclonal antibodies (alirocumab and evolocumab) act by binding circulating PCSK9, thereby preventing binding to the extracellular domain of LDLR. They require subcutaneous administration, with injections every 2 weeks or every month and result in a major reduction in LDL-c concentrations of 50–60% [88,89] (Table 5). Inclisiran is a small interfering RNA (siRNA) that acts by blocking hepatic expression of PCSK9 and thus secretion into the bloodstream. Hepatic vectorization is ensured by the addition of a GalNAc residue to the siRNA, which interacts with the asialoglycoprotein receptor (ASGPR) specifically expressed in the liver [90]. After the first administration, a second injection is required at 3 months, then frequency is reduced to every 6 months, with around 50% reduction in LDL-c. Leroadalcibep is a fusion protein that combines adnectin, a protein that binds PCSK9, and albumin to extend its half-life, allowing monthly subcutaneous injections. Binding to PCSK9 via adnectin inhibits binding to LDLR, resulting in a 60% reduction in LDL-c [91].

It is important to note that the effect of PCSK9 inhibitors, particularly on LDL-c, is potentiated by combination with a statin. It is therefore not recommended to stop statins when introducing a PCSK9 inhibitor, if they are well tolerated, as this could lead to a significant loss of their cholesterol-lowering effect.

In addition to lowering LDL-c, PCSK9 inhibitors are also associated with 20% reduction in Lp(a), possibly via a decrease in hepatic production [92]. PCSK9 inhibition has little effect on TG and HDL-c concentrations (Table 5).

PCSK9 inhibition with evolocumab or alirocumab was associated with a reduction in major cardiovascular events: −15% in both the FOURIER [88] and ODYSSEY OUTCOMES studies [89]. Cardiovascular morbidity and mortality studies are ongoing with inclisiran, which is not currently marketed in France.

Tolerance of PCSK9 inhibitors is satisfactory, with no muscle pain or myopathy, even in patients who are intolerant to statins. Only minor injection site reactions were reported, in 3% of cases. At up to 8 years', there was no increase in new cases of diabetes [93–95]. To date, no difference in safety profile has been observed between extracellular (monoclonal antibodies) and intracellular (inclisiran) PCSK9 inhibition strategies.

5.4. Bempedoic acid

Bempedoic acid is an oral lipid-lowering agent that acts by inhibiting ATP citrate lyase (*ACLY*), an enzyme upstream of HMG-CoA reductase in the hepatic cholesterol biosynthesis pathway. Its mechanism of action is therefore similar to that of statins: by reducing hepatic cholesterol production, it stimulates the LDLR expression on the surface of hepatocytes, thereby promoting LDL catabolism and lowering LDL-c. Unlike statins, it is a prodrug that is activated only in the liver and not in the muscles, which reduces the risk of myopathy [96].

The lipid-lowering efficacy of bempedoic acid has been demonstrated in several randomized trials, with 17 to 28% reduction in LDL-c, depending whether as monotherapy or in combination, but also in non-HDL-c and apoB [97], while the effect on HDL-c, TG, and Lp(a) is generally minimal. However, it should be noted that bempedoic acid has a beneficial effect on inflammation, with an approximately 20% reduction in CRP-us [97,98]. Mendelian randomization genetic analyses demonstrated a benefit of *ACLY* inhibition on the risk of atherosclerotic cardiovascular events, similar to that observed with HMG-CoA reductase inhibition [99]. These data were confirmed by the CLEAR Outcomes randomized cardiovascular morbidity and mortality trial conducted in patients at high cardiovascular risk who were intolerant to statins, in which bempedoic acid (180 mg/day) reduced major adverse cardiovascular events (MACEs) by 13% and myocardial infarction by 23%, with no effect on the risk of stroke or death after a median follow-up of 40.6 months [98].

The tolerance profile is generally good, with no significant muscle pain, even in patients intolerant to statins. However, there is increased risk of hyperuricemia or even gout attacks and a moderate increase in transaminases.

Bempedoic acid is thus a potential alternative for patients who are intolerant to statins, but it is not yet commercially available in France.

5.5. Lomitapide

Lomitapide works by blocking the production of chylomicrons by the intestine and of very-low-density lipoproteins (VLDL) by the liver, by inhibiting microsomal triglyceride transfer protein (MTP), which plays a key role in the assembly of lipoproteins containing ApoB [100]. Use of lomitapide (5 to 60 mg/day orally) is limited to homozygous familial hypercholesterolemia (hoFH), following validation of its use in the national CEDRA (Center of Expertise for Rare Dyslipidemias). It reduces cholesterol and TG concentrations by approximately 50%, with a 20–30% reduction in Lp(a) concentrations [101]. Interestingly, the lipid-lowering action of lomitapide is independent of LDLR action, explaining its efficacy in hoFH (even in cases of biallelic null *LDLR* variants). Use is limited by its tolerance profile, which shows digestive disorders (abdominal pain, diarrhea with steatorrhea), fat-soluble vitamin deficiency, and hepatic steatosis, which may be accompanied by liver function abnormalities, requiring close monitoring [102]. No data are available on efficacy in terms of cardiovascular prevention, given the small number of patients treated.

5.6. Evinacumab

Evinacumab is a human monoclonal antibody that inhibits angiopoietin-like 3 protein (ANGPTL3), blocking the action of ANGPTL3 and thereby promoting the action of lipoprotein lipase (LPL) and hydrolysis of TG-rich lipoproteins. Inhibition of ANGPTL3 also promotes LDL catabolism via a pathway independent of LDLR, which is still poorly understood. Evinacumab requires monthly infusions. It reduces LDL-c concentration by around 50%, including in hoFH patients with a biallelic null variant of *LDLR* [103]. There is an additional reduction in TG of 50% and in Lp(a) of 15 to 20%. In case of FCS, no decrease in TG is observed. The tolerance profile is excellent, with no hepatic steatosis in particular [104]. Immuno-allergic reactions have been reported, justifying the injection in a hospital setting. Indications are limited to hoFH patients after validation by the national CEDRA.

5.7. Fibrates

Fibrates are agonists of peroxisome proliferator-activated receptors alpha (PPARα), and are strongly expressed in the liver, heart, kidneys, and muscles. Their mechanism of action is complex. Activation of PPARα receptors regulates the expression of genes involved in multiple metabolic pathways, including lipid metabolism. This decreases hepatic production of VLDL and increases expression of LPL, which promotes intravascular lipolysis. Fibrates mainly act on plasma TG concentration, with decreases of 20–50%, depending on the molecule. They also cause a 5–20% increase in plasma HDL-c concentration. The effect on plasma

LDL-c concentration varies, with a 5–20% decrease in case of hypercholesterolemia but a significant increase in case of HTG. The effect on lipid parameters depends on the initial lipid profile. Thus, the most pronounced effects on TG and HDL-c are observed in subjects with low HTG and/or HDL-c concentration (< 0.4 g/L, < 1.03 mmol/L) [105,106].

Use of fibrates as monotherapy is associated with increased risk of myopathy, which is 5.5 times higher than with statins as monotherapy, even though the absolute risk is low [107]. Risk is higher in case of diabetes, renal failure or hypothyroidism and in elderly patients [107]. The risk of myopathy and rhabdomyolysis is higher with gemfibrozil than with fenofibrate [107]. Gemfibrozil should not be combined with a statin, as it significantly increases the risk of myopathy by increasing the plasma concentration of statins.

Fibrates were associated with a reversible decrease in estimated glomerular filtration rate (eGFR) of 2.7 mL/min/1.73 m^2 in a meta-analysis [108]. However, they were not associated with increased risk of renal failure [107,108]. They are contraindicated if GFR is < 30 mL/min/1.73 m^2 and dose should not exceed 67 mg/day (in their micronized form) if eGFR is between 30 and 60 mL/min/1.73 m^2. A meta-analysis reeported an increased risk of sporadic acute pancreatitis [109], which is probably lithiasic in origin [107].

It should be noted that only gemfibrozil provided cardiovascular protection when used as monotherapy ahead of statins in two randomized trials [110,111]. However, a meta-analysis of clinical trials analyzed in subgroups showed a 35% reduction in coronary events in subjects with high or very high cardiovascular risk and a TG concentration > 2 g/L (> 2.26 mmol/L) and low HDL-c concentration [112]; the latest randomized trials of cardiovascular morbidity and mortality, conducted with fenofibrate in combination with statins, failed to demonstrate any benefit [113], or more recently with pemafibrate in the PROMINENT study [114] in case of combined dyslipidemia in people living with T2D.

5.8. Polyunsaturated fatty acids of the omega-3 family

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) act by reducing hepatic production of VLDL [115]. At doses of 2 to 4 g/day, they cause a dose-dependent 10–45% reduction in plasma TG concentration. The most significant decreases are observed for the highest initial plasma TG concentrations (> 7.5 g/L) (> 8.5 mmol/L) [116–119]. Omega-3 FAs are no longer covered by French national health insurance.

The main adverse effects of omega-3 FAs are gastrointestinal (belching, nausea, diarrhea). The safety profile is generally satisfactory, with no increase in the risk of bleeding at the recommended doses [116–120].

Data on cardiovascular benefit are controversial. Large randomized trials of cardiovascular morbidity and mortality (the ASCEND [121] and VITAL [122] studies, testing a combination of 460 mg of EPA + 380 mg of DHA, or the STRENGTH study [123], testing a combination of EPA and DHA at 4 g/day) did not confirm benefit. Only the REDUCE-IT study with high-dose icosapent ethyl (IPE) (4 g/day) was associated with a significant 25% reduction in major cardiovascular events (cardiovascular death, non-fatal MI and stroke, unstable angina, and coronary revascularization) compared to placebo (paraffin oil) in people with HTG in secondary prevention or living with T2D on statins [120]. However, the mechanism of action remains unclear because the cardioprotective effect of IPE does not correlate with a decrease in TG concentration and is compounded by the anti-inflammatory effect of IPE with a significant 40% decrease in CRP-us. The REDUCE-IT study also observed an increased risk of bleeding and atrial fibrillation. To date, IPE is not available in France.

5.9. Apolipoprotein C3 (ApoC3) inhibitors

ApoC3 inhibitors act by blocking expression of ApoC3, which is an inhibitor of LPL activity. ApoC3 inhibition stimulates TG hydrolysis, partly via an LPL-independent pathway [124], and it also acts by promoting hepatic catabolism of TG-rich lipoproteins (TRLs) and their remnants. In line with these observations, Mendelian randomization analyses showed that individuals carrying "loss-of-function" variants in the *APOC3* gene had lower TG concentrations and lower risk of cardiovascular events than non-carriers [125,126].

The first molecules developed were antisense oligonucleotides that block the transcription and secretion of apoC3 by the liver. Volanesorsen was tested in FCS, with 77% concentration, including in patients with no LPL activity [127]. The use of volanesorsen is restricted to FCS patients with history of acute pancreatitis. It requires consultation with the national CEDRA, and close monitoring of platelets due to the risk of thrombocytopenia.

New molecules are currently in development. Olezarsen is a third-generation anti-apoC3 antisense oligonucleotide that has better hepatic targeting due to the addition of a GalNAc tail, and a better tolerance profile with no thrombocytopenia and fewer injection site reactions. There was also a significant 88% reduction in the risk of acute pancreatitis in the olezarsen arm vs. the placebo arm [128]. Anti-apoC3 siRNAs, such as plozasiran (1 subcutaneous injection every 3 months), produce similar results in terms of TG reduction and risk of acute pancreatitis in FCS [129].

6. Management of isolated hypercholesterolemia

6.1. Therapeutic indications

The indication for cholesterol-lowering treatment is established on the basis of assessment of cardiovascular risk, as detailed in Section 3 above.

With regard to low or moderate cardiovascular risk, despite the absence of randomized controlled trials defining specific LDL-c or non-HDL-c targets, our expert group agrees on the importance of targets for the management of cardiovascular risk by the physician and for patient adherence to prevention.

In light of the available scientific data, we preferred not to distinguish between the threshold for therapeutic intervention and the therapeutic target. Therapeutic targets, particularly for LDL-c, based on cardiovascular risk level, are summarized in Table 7. The LDL-c targets of < 0.55 g/L (1.4 mmol/L) and < 0.7 g/L (1.8 mmol/L) are defined on the basis of the average concentrations achieved in secondary prevention trials. French epidemiological studies showed that the average LDL-c concentration in apparently healthy French adults is around 1.3 g/L (3.4 mmol/L) [28,130]. We therefore set an arbitrary target (in the absence of relevant data) of LDL-c of 1.3 g/L (3.4 mmol/L) for low cardiovascular risk.

Statins are the first-line drug treatment [1]. For people with low or moderate cardiovascular risk, statin treatment may be initiated as part of a shared medical decision if LDL-c levels remain above the therapeutic target despite well-conducted lifestyle modifications. For people with high or very high cardiovascular risk, it is recommended to introduce statin therapy, along with lifestyle modifications, depending on the gap between current levels and targets.

Depending on the difference between the LDL-c value and the therapeutic target, a low-, medium- or high-intensity statin may be proposed (Table 5), at the lowest initial dose for primary cardiovascular prevention. A gradual increase in dose may be proposed to the patient during follow-up, depending on whether the LDL-c therapeutic target is achieved. This dose titration allows the threshold for onset of adverse muscular effects to be identified. If the difference with the therapeutic target remains significant (> 30%), combination with a second-line treatment may be proposed. The second-line treatment for isolated hypercholesterolemia is ezetimibe [86]. In case of formal contraindication to statins or proven intolerance, treatment with ezetimibe alone may be considered. Third-line treatment for hypercholesterolemia is based on PCSK9 inhibitors (alirocumab and evolocumab), indicated for primary prevention only in cases where LDL apheresis is indicated in FH

Table 7
Therapeutic targets based on CV risk level.

	LDL cholesterol	Non-HDL cholesterol	Apolipoprotein B
Low CV risk	< 1.30 g/L	< 1.60 g/L	< 1.40 g/L
Moderate CV risk	< 1.00 g/L	< 1.30 g/L	< 1.00 g/L
High CV risk	< 0.70 g/L	< 1.00 g/L	< 0.80 g/L
Very high CV risk	< 0.55 g/L	< 0.85 g/L	< 0.65 g/L

(LDL-c > 3 g/L [> 7.8 mmol/L] under maximum oral treatment) and for secondary prevention when hypercholesterolemia is insufficiently controlled (LDL-c > 0.7 g/L) (> 1.8 mmol/L) under statin and/or ezetimibe treatment, or in cases of intolerance or formal contraindication to statins and/or ezetimibe [88,89]. In patients with high or very high CV risk, when the therapeutic target is not achieved with the available therapeutic options, a reduction of at least 50% in LDL-c from baseline LDL-c must be achieved.

Bempedoic acid is a last-resort treatment option, which should soon be available for people with high CV risk or established ASCVD, particularly in case of statin intolerance [98].

Before starting statin treatment, it is necessary to perform: (1) liver function tests to rule out cytolysis; (2) CK tests to rule out muscle disease in subjects at risk of myopathy (chronic renal failure [eGFR < 60 mL/min/1.73 m^2], hypothyroidism, elderly subjects [> 80 years old], known muscle disorder, history of elevated CK, combination of statin + fenofibrate); and (3) fasting venous blood glucose tests to screen for diabetes or prediabetes in at-risk individuals (overweight or obese, family history of diabetes). The presence of progressive liver disease or CK levels 5-fold higher than normal are contraindications for statin therapy. Statins may be used with caution in case of liver failure. A follow-up serum lipid profile and transaminase testing is performed 4 to 12 weeks after any introduction or adjustment of lipid-lowering treatment, then annually once treatment has stabilized. Seventy-five percent of the effect of a statin is achieved 1 week after introduction, and the effect is also lost rapidly when the statin is discontinued [131]. Persistent transaminase elevation, > 3-fold higher than the normal level, should lead to a dose reduction or discontinuation. CK levels are measured case of muscle symptoms. If CK levels are > 10-fold higher than the normal level, statin treatment is stopped permanently. If CK levels are between 4 and 10 times the normal level, statin treatment is suspended until CK levels return to normal, and is then reintroduced at a lower dose.

6.2. *Familial hypercholesterolemia (FH)*

FH is an autosomal co-dominant genetic disorder characterized by high levels of circulating cholesterol from birth, incurring high or even very high cardiovascular risk in case of late treatment: 10-fold higher than in non-FH subjects [132]. FH exists in two forms: heterozygous, which is very common (prevalence 1/300), and homozygous (1/300,000), which is rare and much more severe.

Heterozygous FH (hetFH) should be suspected in case of LDL-c concentrations > 1.9 g/L (4.9 mmol/L) in adults and > 1.6 g/L (4.1 mmol/L) in children, in the absence of HTG [133], especially if there is history of hypercholesterolemia over several generations. The DUTCH clinical-biological score (Supplementary Table 2) can be used to predict FH, but is valid only in adults. Definitive diagnosis is based on genetic analysis, which is now easily performed in several French laboratories on samples taken in healthcare facilities. FH is caused by variants that are likely pathogenic or pathogenic on one of the "canonical" genes: *LDLR (~ 75% of mutations)*, *APOB (~7% of mutations)*, *PCSK9 (< 1% of mutations)*, *APOE (< 1% of mutations)* [134]. When a monogenic variant is identified, cascade screening in the family with standard serum lipid profile and/or genetic testing should be performed. Diagnosis should be made early, and statin treatment is recommended from the age of 8, to limit the impact of hypercholesterolemia on long-term cardiovascular risk [133]. Cardiovascular risk is high or even very high in these patients, especially if treatment is started late, and particularly in young people. Cardiovascular events are mainly coronary, and the average age at the first event in France is 47, with high risk of recurrence [135]. The recommended LDL-c targets are < 0.7 g/L (1.8 mmol/L) in the absence of additional cardiovascular risk factors, < 0.55 g/L (1.4 mmol/L) in the presence of additional cardiovascular risk factors (including elevated Lp(a) or late initiation of treatment [> 18 years in men, > 30 years in women]), and < 1.30 g/L (3.4 mmol/L) in children [3]. In adults who started effective treatment early (before 18 years in men, before 30 years in women), in the absence of additional cardiovascular risk factors and in the absence of evidence for atherosclerosis, the recommended LDL-c target is < 1 g/L (2.6 mmol/L).

The homozygous form (hoFH) should be considered in children or young adults with very high LDL-c concentrations (often ≥ 4 g/L [10.3 mmol/L]), extravascular cholesterol deposits, and family history of hypercholesterolemia in both parents [136]. Early diagnosis is essential, as these young homozygous FH patients are at significant risk of dying from cardiovascular disease before the age of 20 if left untreated. Atheromatous lesions are mainly located on the coronary ostia and aortic root; supravalvular aortic stenosis is common in young people. There is a rare diseases reference center (CEDRA) dedicated to the complex management of these patients, which must be multidisciplinary and carried out in specialized centers.

7. Management of isolated hypertriglyceridemia (HTG) and mixed hyperlipidemia

HTG is a common dyslipidemia linked to several predisposing genetic variants interacting with environmental factors such as excessive consumption of sugars (particularly fructose) or alcohol, sedentary lifestyle, and unfavorable comorbidities: abdominal obesity, T2D, especially in case of poor glycemic control, HTG-inducing medications, and smoking.

It is particularly atherogenic when associated with hypercholesterolemia (mixed dyslipidemia) and/or in case of an underlying metabolic syndrome and/or when particularly severe (MCS) [137].

When it involves hepatic overproduction of VLDL and/or is associated with metabolic syndrome, metabolic dysfunction-associated steatotic liver disease (MASLD) is frequently present and must be taken into account.

7.1. *Clinical and biological presentation*

7.1.1. *Moderate HTG*

Very common, it is often associated with metabolic syndrome and is exacerbated by uncontrolled diabetes. Patients with moderate forms do

Table R3 Recommendations for the management of isolated hypercholesterolemia.

Recommendations	Class	Level of evidence
For secondary cardiovascular prevention, an LDL-c target of < 0.55 g/L is recommended, regardless of age	I	A
In primary cardiovascular prevention, in people living with diabetes with very high cardiovascular risk[a], an LDL-c target of < 0.55 g/L is recommended	I	B
For primary cardiovascular prevention in people living with FH with very high cardiovascular risk[a], an LDL-c target of < 0.55 g/L is recommended	IIa	C
For primary cardiovascular prevention in apparently healthy individuals with very high cardiovascular risk[a] and aged < 75 years, an LDL-c target of < 0.55 g/L is reasonable	IIa	C
For primary cardiovascular prevention in people living with diabetes with high cardiovascular risk[a], an LDL-c target of < 0.70 g/L is recommended	I	B
For primary cardiovascular prevention in people living with FH with high cardiovascular risk[a], an LDL-c target of < 0.70 g/L is a reasonable. In adults who have started effective treatment early (before age 18 in men, before 30 in women), in the absence of additional cardiovascular risk factors and in the absence of evidence of atherosclerosis, an LDL-c target of < 1 g/L is reasonable	IIa	C
For primary cardiovascular prevention in apparently healthy individuals with high cardiovascular risk[a] and aged < 75 years, an LDL-c target of < 0.70 g/L is reasonable	IIa	C
For primary cardiovascular prevention in people living with diabetes and moderate cardiovascular risk[a], an LDL-c target of < 1 g/L is recommended	I	B
For primary cardiovascular prevention in apparently healthy individuals with moderate cardiovascular risk[a], an LDL-c target of < 1 g/L is reasonable	IIa	C
For primary cardiovascular prevention in apparently healthy individuals with low cardiovascular risk[a], a target LDL-c level of < 1.3 g/L is reasonable	IIa	C
It is recommended to use a statin in first-line to achieve the therapeutic LDL-c target	I	A
It is recommended to use ezetimibe in second-line if the LDL-c target is not achieved with the maximum tolerated dose of statin	I	B
For secondary cardiovascular prevention, it is recommended to use a PCSK9 inhibitor if LDL-c is > 0.7 g/L on statin and ezetimibe at the maximum tolerated dose	I	A
The use of phytosterols is not recommended for lowering cardiovascular risk	III	B
The use of red yeast rice is not recommended for lowering LDL cholesterol	III	B

[a] Cardiovascular risk level detailed in Table 3.

not have extravascular lipid deposits. Atherogenicity is exacerbated by metabolic syndrome [138].

The typical biological phenotype involves HTG fluctuating between 1.5 and 5 g/L (1.7 and 5.7 mmol/L). There is often a decrease in HDL-c in case of HTG. Paradoxically normal HDL-c levels should systematically lead to investigation for alcoholism, estrogen therapy, or corticosteroid therapy [139].

7.1.2. Severe and major HTG

Severe and major HTG is defined by TG levels between 5 and 8.8 g/L (5.7 and 10 mmol/L) for severe forms and > 8.8 g/L (> 10 mmol/L) for major forms [140]. The latter correspond to hyperchylomicronemia with two distinct entities: familial chylomicronemia syndrome (FCS) and multifactorial chylomicronemia syndrome (MCS).

FCS is a very rare autosomal recessive disease ($2/10^6$) linked to homozygous or double heterozygous or composite heterozygous genetic mutations of the genes involved in intravascular lipolysis of triglyceride-rich lipoproteins (TRLs), with predominantly deleterious LPL mutations. The major risk of severe or major HTG in FCS is acute pancreatitis, which can be recurrent and life-threatening. In FCS, plasma apoB concentration is not elevated and ischemic cardiovascular risk is little or not increased.

MCS is 50 times more common than FCS. It results from a polygenic genetic predisposition (heterozygous mutation and/or accumulation of common genetic variants) modulated by secondary HTG factors [141]. A clinical-biological score can be used to differentiate these patients from those suspected of having FCS, in whom genetic testing would be indicated [142] (Supplementary Table 3). In MCS, HTG with elevated apoB is indicative of atherogenic dyslipidemia [143,144]. MCS is also associated with increased risk of acute pancreatitis and with cardiovascular risk [145].

In addition, some patients with partial familial lipodystrophy may have moderate to severe HTG. This should be investigated through careful clinical examination [146].

7.1.3. Mixed hyperlipidemia

7.1.3.1. Familial combined hyperlipidemia (FCH). Familial combined hyperlipidemia (FCH) is common, affecting 1–2% of the general population. It results from hepatic overproduction of VLDL with a partial defect in intravascular lipolysis, which also interacts strongly with metabolic syndrome. Certain predisposing variants are common to both entities [147]. There is an accumulation of small VLDL and LDL particles, as seen by a marked increase in plasma apoB concentration [148]. This enables FCH to be differentiated from dysbetalipoproteinemia, which is characterized by relatively low apoB concentrations. Due to the polygenic origin of FCH, HTG and/or hypercholesterolemia are found in many relatives, most often after the age of 40, with high inter- and intra-individual variability [149]. In children and adolescents, lipid profiles appear normal, but LDL-c and TG concentrations are often above the 90th percentile. There are no tendinous xanthomas in FCH. However, corneal arcs and xanthelasmas may occur.

FCH has a delayed atherogenic character compared to FH because hypercholesterolemia occurs later in life. Nevertheless, the long-term ischemic cardiovascularV risk is equivalent due to its intertwining with metabolic syndrome [150].

The typical biological phenotype includes fluctuating moderate to severe HTG, ranging from 1.5 to 8.8 g/L (1.7 to 10 mmol/L), with rare transient decompensations into hyperchylomicronemia (TG > 10 mmol/L). Hypercholesterolemia is concomitant, with LDL-c generally ranging between 1.6 and 3.0 g/L (4.1 and 7.7 mmol/L) and elevated non-HDL-c. ApoB levels are consistently high. HTG > 1.5 mmol/L associated with apoB concentration > 1.2 g/L has been proposed as a diagnostic criterion [148].

7.1.3.2. Dysbetalipoproteinemia. Dysbetalipoproteinemia results from a defect in hepatic clearance of IDL. It is rare (1/5000): 50 to 100 times less common than FCH [151]. There are two main etiological forms. Carriers of the E2 variant of apoE (E2/E2) (recessive presentation) with coexisting comorbidities and polygenic HTG show an extremely fluc-

tuating phenotype. The minority monogenic form (25%) affects patients with a missense mutation in apoE that disrupts hepatic clearance of IDLs through negative dominance over the other apoE allele.

In both cases, there is accumulation of circulating IDLs, which do not normally accumulate in the blood. Dysbetalipoproteinemia sometimes decompensates into hyperchylomicronemia due to failure to clear chylomicron remnants.

The clinical phenotype is extremely variable and fluctuates depending on diet. It rarely develops before the age of 40 in men and the menopause in women. In a minority of cases, patients with chronic decompensation may develop tuberous xanthomas (elbows, front of the knees). The appearance of xanthomas, yellowish deposits that are sometimes slightly raised, on the palmar creases and wrist creases resolves quickly within a few weeks once the decompensation has been resolved. These xanthomas have been reported in cases of homozygous hypercholesterolemia and severe cholestasis [152].

Dysbetalipoproteinemia is an atherogenic dyslipidemia with onset of ischemic complications from the age of 50 onwards, or even earlier in cases of other cardiovascular risk factors. Proportionally, these patients have 4-fold higher prevalence of lower limb arteriopathy than in cases of hetFH [153].

In biological phenotype, TG concentration usually varies between 3 and 6 g/L (3.4 and 6.8 mmol/L) but may temporarily decompensate into multifactorial hyperchylomicronemia. Total cholesterol fluctuates between 3 and 6 g/L (7.8 and 15.5 mmol/L). Non-HDL-c is elevated. Calculating LDL-c is inaccurate and often impossible because HTG exceeds 3.4 g/L (3.8 mmol/L). HDL-c is lowered. ApoB levels are normal or slightly elevated relative to the severity of hypercholesterolemia. In HTG, this translates into a total cholesterol/apoB ratio > 2.6 (expressed in g/L) [154]. Given the very high sensitivity and specificity of this ratio, confirmatory genetic testing is optional.

7.2. Associated comorbidities

All primary HTG is aggravated by metabolic syndrome and T2D in proportion to the extent of the glycemic imbalance. Under the pressure of secondary factors, it can sometimes temporarily decompensate into hyperchylomicronemia.

Hepatic steatosis (MASLD) is frequently present in HTG (accentuated lipogenesis), with fibrotic forms being rarer (exacerbated by T2D or alcoholism). This justifies screening for liver fibrosis by calculating the fibrosis-4 (FIB-4) score and, depending on the result, performing liver elastometry.

7.3. Biological assessment in HTG

Positive diagnosis is based on a standard serum lipid profile and apoB measurement (for etiological diagnosis and assessment of atherogenicity). Diagnosis of comorbidities is based on transaminase measurement, platelet count (for FIB-4 calculation), fasting blood glucose, and even HbA1c.

Differential diagnosis is based on TSH and creatinine (GFR) levels, as well as a urine strip test to check for proteinuria. If alcoholism is suspected, a test for CDT or Peth may be carried out.

7.4. Treatments

7.4.1. Lifestyle changes

Lifestyle changes are a priority for HTG. These are detailed in Section 4.

7.4.2. Controlling secondary HTG factors

Controlling secondary HTG factors involves adjusting treatment with oral estrogen, clomiphene, tamoxifen, corticosteroids, protease inhibitors, retinoids, mTOR inhibitors, and certain antipsychotics (olanzapine, quetiapine). In case of T2D, glycemic control must be optimized. In case of insulin resistance with MASLD, treatment with GLP-1 receptor (GLP1-R) agonists should be considered in accordance with their marketing authorizations and nqtionql health insurance status for T2D and even, in future, obesity and MASLD [155,156]. GLP-1R agonists are not contraindicated in severe HTG with regard to the risk of acute pancreatitis.

Given their levels of evidence in cardiovascular prevention, statins are preferred in order to achieve the LDL-c target (defined according to the patient's cardiovascular risk level) and to reduce non-HDL-c and apoB (Table 7).

When the LDL-c (and non-HDL-c) target is achieved with statins, there is no consensus on the use of specific treatment for residual HTG (TG > 2 or 5 g/L) (> 2.3 or 5.6 mmol/L). There are two options:

- based on meta-analyses and clinical trials analyzed in subgroups, a fibrate (fenofibrate) may be considered in individuals with high or very high cardiovascular risk and TG concentration > 2 g/L (2.3 mmol/L) in combination with low HDL-c (< 0.40 g/L [1.03 mmol/L] in men, < 0.50 g/L [1.3 mmol/L] in women) [157,158]. Molecules in this therapeutic class have not shown any clear cardiovascular benefit outside this subgroup of patients (TG > 2 g/L (> 2.3 mmol/L) and low HDL-c). Fibrates are an option in the European EAS-ESC guidelines [3], US Endocrine Society guidelines [158] and the AHA guidelines, only in third-line [2]. The fibrate option is discussed in case of clear residual HTG (> 5 g/L) (> 5.6 mmol/L), particularly in MCS, speculating on a reduction in the risk of acute pancreatitis, which has not been demonstrated with fibrates [109];
- based on the REDUCE-IT clinical trial, which showed a 26% reduction in cardiovascular events despite a moderate decrease in TG concentration, IPE at 4 g/day is indicated in the European [3] and American guidelines, in addition to a statin, in patients with high or very high cardiovascular risk with HTG between 1.35 and 4.99 g/L (1.5–5.6 mmol/L). However, it is not yet available in France. Low- or high-dose EPA + DHA combinations did not show any convincing cardiovascular benefit in meta-analyses [159].

In case of FCS, the mainstay of treatment is a drastically low-fat diet: 10–15% of total energy intake, or 20–30 g of fat per day. An intake of medium-chain triglycerides, which are not readily incorporated into chylomicrons, may help increase daily calorie intake from lipids in certain circumstances, such as in children. Conventional treatments for HTG, such as fibrates or omega-3, generally have little or no effect.

Volanesorsen is only approved for patients with genetically confirmed FCS with insufficient response to diet and treatment aimed at reducing TG and who have a history of pancreatitis. The decision must be made with CEDRA. In case of diagnostic or therapeutic difficulties, CEDRA's opinion is desirable.

8. Special situations

8.1. People living with diabetes

Lipid abnormalities play an important role in the development of atherosclerosis and increase the risk of cardiovascular events in patients living with type 1 (T1D) or type 2 (T2D) diabetes [160–163]. In patients living with T1D or T2D, LDL-c is a major cardiovascular risk factor. In individuals with T2D, hyperlipidemia and low HDL-c are also observed, as well as qualitative and functional abnormalities in lipoproteins that are detrimental to cardiovascular health [162]. Individuals living with T1D also have qualitative and functional lipoprotein abnormalities that promote atheroma and increase the risk of cardiovascular events [163]. The level of cardiovascular risk in diabetes is specified in Table 3.

The cardiovascular benefit of reducing plasma LDL-c concentration in people living with diabetes has been clearly demonstrated by numerous prospective clinical studies. A meta-analysis confirmed a significant

Table R4 Recommendations for "isolated hypertriglyceridemia and mixed hyperlipidemia".

Recommendations	Class	Level of evidence
ApoB testing is recommended to characterize mixed hyperlipidemia and limit the need for genetic testing	I	C
In case of hyperchylomicronemia, the FCS score is recommended to distinguish between FCS and MCS and limit the need for genetic testing	I	C
The FIB-4 score is recommended to screen for MASLD in case of HTG	I	C
In genetically confirmed FCS with history of acute pancreatitis, anti-apoC-III should be initiated	I	A
In individuals with high or very high cardiovascular risk and moderate HTG (1.5–5 g/L), IPE (icosapent ethyl: 2 g twice daily) should be considered in addition to a statin	IIa	B
In individuals with high or very high cardiovascular risk who have achieved their LDL-c target but have HTG > 2 g/L and low HDL-c (< 0.4 g/L in men, < 0.5 g/L in women), treatment with fenofibrate may be considered in addition to a statin	IIb	C
In individuals with persistent HTG (> 5 g/L) despite lifestyle modifications, treatment with fibrates and/or IPE/omega-3 fatty acids may be considered	IIb	C

FCS: familial chylomicronemia syndrome; HTG: hypertriglyceridemia; MASLD: metabolic dysfunction-associated steatotic liver disease; MCS: multifactorial chylomycronemia syndrome.

21% reduction in the risk of any major cardiovascular event for a 1 mmol/L (0.39 g/L) reduction in LDL-c in individuals living with T1D or T2D [164].

However, in individuals living with diabetes who have achieved their LDL-c target, there is a residual cardiovascular risk linked to abnormalities in diabetic atherogenic dyslipidemia not controlled by statins [162,165]. In T2D, HTG and low HDL-c are implicated in this residual cardiovascular risk [165,166]. It is therefore advisable to also achieve a non-HDL-c target [11].

Pharmacological agents that reduce TG and increase HDL-c have not clearly demonstrated cardiovascular benefit. Based on meta-analyses and clinical trials analyzed in subgroups, a fibrate (fenofibrate) may be considered in patients with high or very high cardiovascular risk and TG levels > 2 g/L in combination with low HDL cholesterol (< 0.40 g/L [1.03 mmol/L] in men, < 0.50 g/L [1.3 mmol/L] in women) [157,158]. The PROMINENT study did not demonstrate the efficacy of pemafibrate in reducing cardiovascular risk in people living with T2D, but it should be noted that, while pemafibrate reduces plasma TG, it significantly increases LDL-c concentration (+14%) [114]. In T2D, GLP-1R agonists are useful, as they have a triglyceride-lowering effect, which is more pronounced postprandially [167], accelerate the catabolism of TG-rich lipoproteins, and show cardiovascular benefit [155,156,168,169].

8.2. Individuals living with CKD

CKD is defined as an abnormality in kidney structure or function lasting more than 3 months. It is classified according to its cause, GFR level, and albuminuria (Supplementary Table 4).

In adults, decreased GFR is associated with an increased risk of ASCVD regardless of other CVD risk factors [170]. Patients with CKD and established ASCVD have much higher mortality than patients with ASCVD and normal renal function [171]. The level of cardiovascular risk in CKD is specified in Table 3.

In advanced CKD, TG concentrations are high and HDL-c concentrations are low. There is also an increase in the proportion of small dense LDL particles. The kidney also plays a role in Lp(a) catabolism, with a tendency for Lp(a) concentrations to increase as renal function declines [172]. These lipoprotein abnormalities are reversible after kidney transplantation, although immunosuppressive treatments may induce secondary dyslipidemia at a later stage [3].

In the 4D study, which involved 1200 people with diabetes undergoing hemodialysis, atorvastatin had no significant effect on the risk of CVD [173]. Similarly, the randomized controlled AURORA study, which tested the cardiovascular efficacy of rosuvastatin (10 mg/day) versus placebo in 2776 patients on hemodialysis, showed no benefit with treatment [174]. On the other hand, in the SHARP study, which recruited 9270 patients with CKD (stages 3A-5) undergoing dialysis (n = 3023) or not (n = 6247), the combination of simvastatin (20 mg) and ezetimibe (10 mg) reduced the risk of major cardiovascular events by 17% compared with placebo [175]. However, the trial was not sufficiently powered to evaluate the effects on the primary endpoint separately in dialysis and non-dialysis patients.

Although the benefits of statin-based lipid-lowering therapy are clearly demonstrated in mild to moderate CKD, there remains controversy regarding more advanced cases, particularly in patients under dialysis. In a meta-analysis comparing the results of three trials conducted in CKD with results of other trials with statin a smaller relative reduction in atherosclerotic cardiovascular events was found in patients with CKD as estimated GFR decreased, with comparable LDL-c reduction (with no benefit in dialysis patients) [176]. This decrease in relative risk reduction as GFR decreases implies that, at least in non-dialysis patients, more intensive lipid-lowering treatments are needed to achieve the same benefit, whereas the mechanism of atheroma plaque stabilization via cholesterol-lowering treatment is no longer involved. There are no randomized trials with PCSK9 inhibitors specifically in the CKD population, particularly for stages 4 and 5. In a subgroup analysis of the randomized FOURIER trial with evolocumab, the magnitude of LDL-c reduction, relative clinical efficacy, and safety were comparable across all groups of CKD patients, including 4443 with CKD ≥ stage 3 (median eGFR: 51.1 mL/min) compared with placebo. The absolute reduction in the rate of cardiovascular events was greater with evolocumab than placebo when CKD was more advanced, due to higher cardiovascular risk [177]. However, in the ODYSSEY OUTCOMES study, alirocumab did not reduce the risk of cardiovascular events in patients with eGFR < 60 mL/min at baseline (n = 2122), even though the reduction in LDL-c was comparable to that observed in patients without CKD [178].

Recommendations for the management of dyslipidemia in patients with CKD are summarized in Table R5.

Immunosuppressive drugs can cause an increase in total cholesterol and TG concentrations, and in the proportion of small, dense LDL particles. These effects vary depending on the drug. Transplant patients are at high or very high cardiovascular risk. There is a lack of randomized trials to determine the clinical efficacy of statins in kidney transplant patients. Nevertheless, in transplant patients with high cardiovascular risk, it seems reasonable to extrapolate the benefit of treatment with statins, or even ezetimibe, in individuals with moderately low GFR. The issue of drug interactions with statins in this population is detailed in Section 5.

8.3. Individuals living with high blood pressure

Combined hypertension and dyslipidemia is common [179]. The two conditions additively or even synergistically increase the cardiovascular risk [180,181]. In primary prevention, blood pressure measurement should therefore be included in the cardiovascular risk assessment to de-

fine the LDL-c target. This can be done using a cardiovascular risk score such as SCORE 2 [180], paying close attention to the following situations that immediately place the patient at high or very high (CKD stage 4–5) risk: severe hypertension (> 180/110 mmHg), left ventricular hypertrophy on ECG or echocardiography, retinal and cerebral microvascular damage, moderate CKD (stage 3) [182].

Despite the conflicting results of the randomized ASCOT (positive) and ALLHAT-LLT (negative) studies, meta-analysis seems to indicate that the benefit of lipid-lowering therapy is maintained in hypertensive patients [183]. There are no specific recommendations on the management of dyslipidemia in hypertensive patients in secondary prevention, as these patients are automatically classified as having very high cardiovascular risk.

8.4. People living with chronic inflammatory disease

Recent studies showed that the prevalence and incidence of CVD are 30% to 50% higher in patients with inflammatory rheumatism than in the general population [184]. The risk of MI and stroke is particularly high in systemic lupus erythematosus (SLE). The data are less clear for chronic inflammatory bowel disease, but an increased risk of stroke has been reported.

Chronic inflammation contributes to endothelial dysfunction and macrophage accumulation, accelerating formation of atherosclerotic plaque. It can also lead to changes in lipid metabolism, causing dyslipidemia. In rheumatoid arthritis (RA), total cholesterol and LDL-c tend to decrease during active inflammatory phases. Despite these low levels, cardiovascular risk remains high, a phenomenon known as the "lipid paradox." In contrast, during remission, total cholesterol and LDL-c levels increase. In SLE, there is an increase in total cholesterol, TG, and oxidized LDL. HDL can become pro-inflammatory, contributing to atherosclerosis. The presence of anti-beta2GPI antibodies, which can complex with oxidized LDL particles, may also play a role in accelerating atheroma. Traditional cardiovascular risk factors, such as hypertension, smoking, and obesity, are also more common. All of these parameters increase cardiovascular risk.

Assessing cardiovascular risk in these patients is complex, as traditional tools do not take disease activity into account. European guidelines suggest multiplying the estimated cardiovascular risk by 1.5 for people living with RA. Prevention includes controlling traditional cardiovascular risk factors and optimizing treatment of the inflammatory disease [3,185].

Controlling the inflammatory activity of the disease is therefore crucial to reducing cardiovascular risk. Treatments such as methotrexate and anti-TNF-alpha agents can help modulate inflammation and improve the lipid profile. High-dose corticosteroids should be used with caution due to their association with increased cardiovascular risk. Janus kinase (JAK) inhibitors are a new class of treatment, but their impact on cardiovascular risk requires further study [186,187]. Statins are recommended for treating dyslipidemia in these patients, with efficacy similar to that in the general population.

8.5. People living with HIV

The risk of developing cardiovascular disease, particularly coronary artery disease, is almost double in individuals living with HIV compared to the general population. Dyslipidemia is a significant risk factor in HIV, with 40% prevalence [188].

HIV-induced dyslipidemia and lipodystrophy were common with the use of first-generation protease inhibitors, but with the advent of newer therapies, lipodystrophy has become less common and the incidence of dyslipidemia has decreased. The mechanisms associated with the onset of dyslipidemia and lipodystrophy are complex and still poorly understood.

The most common lipid abnormality in patients living with HIV is HTG. HDL-c levels drop rapidly after HIV infection, followed by a decrease in LDL-c. After starting antiretroviral therapy, LDL-c, total cholesterol and TG levels increase, while HDL-c levels remain low. As HIV infection progresses to AIDS, there is a significant increase in TG and TG-rich lipoproteins, including VLDL, which could increase the risk of ASCVD. There is also an increase in the concentration of small dense atherogenic LDL particles.

The first generations of antiproteases doubled the risk of MI and were associated with higher levels of LDL-c, VLDL and TG. Thymidine nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, didanosine, lamivudine, stavudine, zalcitabine) cause an increase in TG and a decrease in HDL-c, while non-thymidine NRTIs and non-nucleoside RTIs (NNRTIs) have less effect on lipid metabolism. Integrase inhibitors, the most recent family, have few metabolic effects. They are recommended in first-line for HIV infection.

In dyslipidemia induced by antiretroviral therapy, and particularly older-generation protease inhibitors, it is advisable to switch to a newer generation or even another molecular family, such as integrase inhibitors, while bearing in mind the risk of viral resistance and reduction in viral replication. Drug interactions with antiretroviral treatments are detailed in Section 4.

A standard serum lipid profile should be performed in all people living with HIV at the time of diagnosis and 1 to 3 months after initiation of antiretroviral therapy. Each time the antiretroviral therapy is changed, a new serum lipid profile should be performed 1 to 3 months after initiation. In individuals with one or more cardiovascular risk factors, this assessment should be performed every 6 to 12 months.

Lifestyle modifications should be implemented, as for the general population (see Section 4).

The REPRIEVE study [189], demonstrated for the first time a significant cardiovascular benefit of pitavastatin 4 mg (a moderate-intensity statin, not available in France) in people living with HIV at low or moderate risk for cardiovascular primary prevention. A 35% relative reduction in the incidence of the primary composite endpoint was observed in favor of pitavastatin. Statins have not been specifically evaluated in patients living with HIV for secondary prevention.

Ezetimibe was associated with reduced LDL-c concentration in a meta-analysis in people living with HIV [190]. PCSK9 inhibitors can be used in people living with HIV, for the same indications and French national health insurance cover as in the general population.

For secondary cardiovascular prevention, the recommendations are the same as for the general population, with a target LDL-c level of < 0.55 g/L (1.4 mmol/L) and a 50% reduction in LDL-c from baseline. If the patient does not achieve an LDL-c level below 0.7 g/L (1.8 mmol/L), treatment with ezetimibe followed by a PCSK9 inhibitor should be initiated.

In primary cardiovascular prevention, the SCORE 2 CV risk estimation model can be used to classify patients as high, moderate, or low risk. Recent guidelines from the European AIDS Society [191] recommend atorvastatin 10 mg or rosuvastatin 5 mg in patients at moderate cardiovascular risk, and discussion in patients at low risk.

8.6. Dyslipidemia in women

8.6.1. Management of dyslipidemia in women

Cardiovascular disease is the second leading cause of death in women. The effectiveness of statins in women, especially in primary prevention, has long been debated. Solid data from the Cholesterol Treatment Trialists' Collaboration, based on 27 randomized controlled trials involving 175,000 people, including 47,000 women, showed that statin treatment effectively reduces rates of major coronary events, strokes, coronary revascularization, and mortality in similar proportions in both sexes [192]. This benefit is observed in both primary and secondary prevention. In people whose absolute risk of cardiovascular events over 5 years is < 10%, the absolute number of major vascular events prevented per 1000 people treated over 5 years for each 1 mmol/L reduction in LDL-c is 12 in men and 9 in women. Other lipid-lowering

drugs (ezetimibe and PCSK9 inhibitors) [193–195] are equally effective in women as in men. However, a meta-analysis of real-world studies and a Mendelian randomization analysis showed that PCSK9 inhibition was slightly less effective in lowering LDL-c in women [196]. Muscle-related side effects of statins are twice as common in women and men [197]. Guidelines for primary cardiovascular prevention specific to women were issued by the American Heart Association in 2020 [198].

8.6.2. *Changes in lipid profile during pregnancy and risks associated with dyslipidemia during pregnancy*

Plasma concentrations of lipid parameters increase physiologically throughout pregnancy, particularly in the third trimester, with TG increasing by 50–100% and LDL-c by 30–50% [199].

The impact of the physiological increase in LDL-c and the discontinuation of lipid-lowering treatments during pregnancy on the cardiovascular risk of patients undergoing secondary cardiovascular prevention or with very high cardiovascular risk is still poorly documented, but could contribute to recurrence of cardiovascular events during pregnancy and to increased cardiovascular risk for women living with FH [200].

In women with moderate to severe HTG before pregnancy, particularly in severe genetic forms (MCS or FCS), increased TG levels during pregnancy increase the risk of acute gestational pancreatitis, which can be life-threatening for both mother and fetus [200,201].

8.6.3. *Use of lipid-lowering drugs during pregnancy and breastfeeding*

No lipid-lowering drugs are indicated during pregnancy except cholestyramine, which is not absorbed by the intestine. Nevertheless, digestive side effects generally limit its use during pregnancy [200].

Epidemiological data on statin exposure during pregnancy are reassuring regarding risk of teratogenicity [200,202]. Interventional studies with pravastatin (10 to 40 mg/day) from the second or third trimester to prevent preeclampsia did not report any adverse effects [203]. These data led the US food and drug administration (FDA) in 2021 to lift the contraindication for the use of statins during pregnancy and to allow their use on a case-by-case basis, and particularly pravastatin in women at high cardiovascular risk.

According to the CRAT (Reference Center on Teratogenic Agents, updated January 2025), in certain exceptional situations such as FH, after consulting a specialist, if refraining from treatment during pregnancy would result in loss of opportunity for the mother, a statin may be considered, with preference for pravastatin, which has been better evaluated in the second and third trimesters.

With regard to breastfeeding, the CRAT (updated January 2025) indicates that the amount of pravastatin and atorvastatin in breast milk is very low ($< 0.1\%$ of the maternal daily dose). There is little data on rosuvastatin and other lipid-lowering treatments. According to the CRAT, if a statin is necessary, pravastatin and atorvastatin can be considered during breastfeeding.

LDL apheresis is possible during pregnancy in cases of severe uncontrolled hypercholesterolemia in women with proven ASCVD.

Data are limited for ezetimibe or anti-PCSK9 monoclonal antibodies, although exposure data did not reveal any teratogenicity to date [200].

With regard to fibrates, possible teratogenicity was reported in animals. The AHA suggests reintroducing fibrates from the second trimester if TG remains > 5 g/L (> 5.6 mmol/L) despite lifestyle changes, or > 10 g/L (> 11.3 mmol/L) for the American College of Obstetricians and Gynecologists in women with history of acute pancreatitis. Plasmapheresis sessions may also be given during pregnancy, but only in case of particularly dangerous HTG or in the event of acute pancreatitis [200,201].

8.6.4. *Contraception and dyslipidemia*

The impact of estrogen-progestogen contraception on arterial cardiovascular risk depends on the dose of estrogen, type of progestogen and administration route [204]. Overall, combined contraceptives have an adverse effect on the risk of MI and stroke, which is even more pronounced in women with dyslipidemia and smoking habits. Progestin-only contraceptives used not to be associated with increased risk of MI [205]; however, a recent, contemporary study of the entire population of Denmark showed an association between all hormonal contraceptives (oral estrogen-progestin contraceptives, vaginal rings, oral progestins, or implants) and MI and stroke; only levonorgestrel intrauterine device contraception was not associated with an increased risk of arterial events [206]. Estrogen-progestogen contraception is formally contraindicated in women with personal history of ischemic heart disease, stroke, complicated heart valve disease, deep vein thrombosis, migraine with aura, uncontrolled hypertension (SBP ≥ 160 mmHg, DBP ≥ 100 mmHg), known thrombophilia or a hereditary risk factor for thrombosis (factor V Leiden mutation, prothrombin mutation, protein S or C deficiency, and antithrombin deficiency), or active smoking at age 35 or older [207,208]. Proven severe dyslipidemia is not a contraindication to contraception: prescription of estrogen-progestogen contraception must be subject to individualized assessment of the risk/benefit ratio, taking account of level of LDL-c (controlled or not, depending on the cardiovascular risk), other risk factors (smoking, hypertension, diabetes, overweight) and patient preferences. In women with well-controlled FH, treated early and without cardiovascular risk factors, estrogen-progestogen contraception is possible. In these situations, non-hormonal or progestogen-only contraception (implant, hormonal IUD, microprogestogen pill) is often preferable, and this should be discussed with the patient, taking her preferences into account. Estrogen-progestogen contraceptives can cause an increase in TG and, to a lesser extent, cholesterol. It is recommended that lipid levels be monitored when contraception is started and then annually. Choice of contraception in patients with polycystic ovary syndrome (PCOS) requires careful assessment of the metabolic profile, and preference is often given to progestogens alone or intrauterine devices, particularly in case of cardiovascular risk factors.

8.6.5. *Menopause and dyslipidemia*

Perimenopause and menopause can be accompanied by metabolic changes that increase cardiovascular risk: elevated total cholesterol, LDL-c, apoB, and TG, weight gain, visceral fat accumulation, elevated blood pressure and inflammatory markers [209]. Some of the changes in lipid profile and increased atherogenicity during the perimenopausal period are associated with fluctuations in hormone levels and occur independently of chronological age. Early menopause (before 40 years) is associated with a significant increase in cardiovascular risk, and particularly ischemic cardiovascular risk. Hormone replacement therapy (HRT) may have beneficial cardioprotective effects in women with low cardiovascular risk, under the age of 60, when started within the first 10 years after onset of menopause [210]. However, it should not be prescribed specifically for the purpose of reducing cardiovascular risk [211]. In women with moderate cardiovascular risk, HRT should be limited to cases of severe climacteric symptoms or osteoporosis, administered transdermally (patches or gel) based on natural estradiol combined with micronized progesterone, which appear to have a more favorable vascular risk profile, and for the shortest possible duration. Oral HRT increases TG by 5% to 15%, while transdermal HRT decreases TG concentrations by 5% to 30% [212]. HRT is contraindicated in women undergoing secondary cardiovascular prevention or with high cardiovascular risk [211].

8.7. *People over 75 years of age*

The age of 75 is usually used to define an elderly person. However, it is important to take account of their state of health, distinguishing between those who are "vigorous," "frail," and "dependent and/or in very poor health." The clinical frailty score can be used for this [213].

A large Danish cohort study with 91,131 subjects aged 20 to 100 years undergoing primary cardiovascular prevention at inclusion, showed that increased LDL-c concentration was associated with increased risk of CVD regardless of age. Elevated LDL-c was associated with a significant increase in the risk of MI and CVD in subjects aged 70 to 100 years, compared with those aged 20 to 69 years [214].

There are few randomized clinical trials evaluating the efficacy of lipid-lowering treatments specifically in subjects over 75 years of age. Data for subjects over 80 years of age are scarce. In primary cardiovascular prevention, data on the cardiovascular efficacy of lipid-lowering treatments in subjects over 75 years of age are contradictory. A meta-analysis looked at 24,674 subjects aged 65 and over (mean age, 73) from 8 randomized studies (statins vs. placebo). It showed a significant reduction in the risk of MI and stroke, but not in cardiovascular or all-cause mortality [215]. A meta-analysis of the JUPITER and HOPE 3 studies (rosuvastatin vs. placebo) showed a significant 26% reduction in cardiovascular events in subjects aged 70 and over, but all-cause and cardiovascular mortality were not assessed [216]. In addition, the number of subjects over the age of 80 was small. The randomized controlled EWTOPIA study compared ezetimibe to placebo specifically in subjects aged 75 years and older. More than 86% of subjects had 1 to 2 cardiovascular risk factors at baseline. The study showed a significant 34% reduction in major cardiovascular events [217]. A retrospective cohort study showed that statin therapy initiated in subjects without history of CVD was associated with a significant 24% reduction in cardiovascular events (angina, MI, coronary revascularization, stroke, cardiovascular mortality) in subjects with T2D aged 74 to 85 years, but not in those over 85 years of age or in non-diabetics [218].

However, in a meta-analysis of 28 randomized controlled trials involving 186,854 subjects, 14,483 (8%) of whom were over 75 years of age, statins were not associated with a significant reduction in major cardiovascular events (MI, stroke, coronary revascularization) in subjects aged 75 years and older [219]. In a recent meta-analysis of 29 randomized controlled trials involving 244,090 subjects, 8.8% of whom were aged 75 years or older, the use of lipid-lowering treatments (statins, ezetimibe, and PCSK9 inhibitors) was not associated with a reduction in major cardiovascular events in primary prevention in subjects aged 75 years and older [220]. Nevertheless, a French cohort study of 120,173 subjects showed that discontinuing statin therapy, previously prescribed for primary cardiovascular prevention, from the age of 75 was associated with a 33% increase in the risk of cardiovascular events compared to the group continuing treatment during an average follow-up of 2.4 years after discontinuation [221].

In secondary cardiovascular prevention, several studies reported a benefit of lipid-lowering treatments on cardiovascular morbidity and mortality in subjects over the age of 75. In the CTT meta-analysis, statins were associated with a 15% reduction in major cardiovascular events per 1 mmol/L reduction in LDL-c in subjects aged 75 years and older [219]. In a meta-analysis, cholesterol-lowering therapy (statins, ezetimibe, or PCSK9 inhibitors) was associated with a 23% reduction in the risk of major cardiovascular events per 1 mmol/L reduction in LDL-c in subjects aged 75 years and older [222].

With regard to therapeutic targets, there is sufficient data on secondary CV prevention to set an LDL-c threshold of < 0.55 g/L (1.4 mmol/L), like for younger subjects [222]. However, in primary cardiovascular prevention, there is insufficient evidence to recommend LDL-c targets based on cardiovascular risk after the age of 75. The LDL-c target should take account of life-expectancy and treatment benefit, frailty, comorbidities and patient choice. A meta-analysis on subjects aged 50 to 75 years showed that, in primary prevention, statins must be used for at least 2.5 years to prevent a major cardiovascular event, and thus that life-expectancy must be at least 2.5 years to introduce a statin in primary prevention [223]. Randomized trials are underway to determine the benefit of lipid-lowering treatment in primary prevention in subjects over 75 years of age with high cardiovascular risk.

8.8. Lipoprotein (a)

Lp(a) is recognized as an independent cardiovascular risk factor and causality in atherosclerotic CVD was demonstrated in Mendelian randomization studies [224,225]. It is a complex particle whose structure confers atherogenic, inflammatory and antifibrinolytic properties. It consists of an LDL lipoprotein particle associated with an additional glycoprotein, apolipoprotein(a) (apo(a)), which is structurally related to fibrinogen. Its physiological role remains poorly understood and its catabolism unclear.

When the concentration is high, Lp(a) is atherogenic, due to its "LDL-like" structure and ability to accumulate esterified cholesterol in the arterial wall. It is also thrombogenic due to apo(a)'s ability to reduce fibrinolysis. In addition, it transports oxidized phospholipids, which contribute to inflammation and oxidative stress in the vascular wall, promoting formation of atherosclerotic plaque and valvular calcifications. Elevated Lp(a) levels increase the risk of calcified aortic valve stenosis [226].

The concentration of Lp(a) is mainly genetically determined and remains relatively stable throughout an individual's life outside of inflammatory phases, as it is not significantly influenced by dietary habits or lifestyle. However, in women, the concentration increases by around 10% after menopause [227]. It is therefore recommended that testing be repeated after menopause. Renal failure increases Lp(a) concentration, while conversely, liver failure or hyperthyroidism decrease it. The test, which is not currently French national health insurance, should not be performed in case of inflammation or intercurrent disease, but is relevant for CVR stratification. It is therefore recommended that Lp(a) be measured at least once in a lifetime in certain risk groups [226]:

- early coronary artery disease (< 55 years in men, < 60 years in women);
- FH;
- family history of early cardiovascular disease (< 55 years in men, < 60 years in women);
- recurrent coronary artery disease despite optimal lipid-lowering therapy;
- T1D, T2D, or CKD.

Recently, a group of international experts proposed that Lp(a) levels be measured in the entire population, preferably early in life [228].

An Lp(a) threshold of ≥ 125 nmol/L (approximately ≥ 0.5 g/L) is generally considered high and suggests an increased risk of ASCVD in Caucasian patients [229]. It is also important to correct the LDL-c concentration in patients with high Lp(a), as some of the cholesterol contained in Lp(a) may falsely elevate the calculated LDL-c. The correction formula is: Corrected LDL-c (mg/dL) = LDL-c (mg/dL) – [Lp(a) (mg/dL) × 0.30].

Currently, there is no specific drug treatment targeting Lp(a) that is available and covered by French national health insurance for routine use. It is recommended to intensify lipid-lowering treatment in patients with Lp(a) > 250 nmol/L (1 g/L) and to perform imaging (CAC or carotid Doppler) [226]. Although they may cause a very modest increase in Lp(a), statins remain the first-line treatment due to their overall cardiovascular benefit. If LDL-c targets are not met, the addition of ezetimibe or PCSK9 inhibitors is recommended. PCSK9 inhibitors, although primarily targeting LDL-c, have also been shown to reduce Lp(a) by approximately 20–30% [230,231].

New injectable therapies specifically designed to reduce Lp(a) are currently under development, including antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). Molecules such as pelacarsen (ASO) specifically target apo(a) mRNA, leading to a significant reduction (up to 80%) in plasma Lp(a) concentrations [232]. Molecules (siRNA) such as olpasiran, zerlasiran and lepodisiran also act by inhibiting apo(a) production by the liver, with significant reductions in Lp(a) (up to 100%) and a potentially less frequent dosing regimen

Table R5 Recommendations for specific populations.

Recommendations	Class	Level
People living with diabetes		
Statins are recommended to achieve target LDL-c levels in people living with T2D and T1D (< 0.55 g/L if very high CV risk, < 0.70 g/L if high cardiovascular risk, < 1 g/L if moderate cardiovascular risk)	I	A
In individuals with diabetes and high or very high CV risk who have achieved their LDL-c target, with HTG > 2 g/L and low HDL-c (< 0.4 g/L in men, < 0.5 g/L in women), treatment with fenofibrate may be considered in addition to a statin	IIb	C
In individuals living with T2D who have diabetic dyslipidemia, the choice of a GLP-1R agonist should be considered	IIa	A
People living with CKD		
People living with CKD stage G3a/A2, G3b to G5 and A3 are at high or very high risk of cardiovascular events*	I	A
Statins or a combination of statins and ezetimibe is recommended in people with moderate to severe CKD who are not on dialysis	I	A
In individuals already being treated with lipid-lowering drugs at the start of dialysis, it is reasonable to continue the drugs, particularly in individuals with ASCVD	IIa	C
In dialysis patients without established ASCVD, it is not recommended to initiate statin therapy.	III	A
People living with hypertension		
Blood pressure measurement is recommended in case of dyslipidemia to assess the level of cardiovascular risk.	I	C
Severe hypertension (> 180/110 mmHg), cardiac, cerebral or retinal damage due to hypertension, or stage 3 CKD secondary to hypertension indicate high cardiovascular risk. Stage 4-5 CKD secondary to hypertension indicate very high cardiovascular risk	I	C
People living with HIV		
A standard serum lipid profile should be performed in all individuals living with HIV at the time of diagnosis of infection and 1 to 3 months after initiation of antiretroviral therapy Each time antiretroviral therapy is changed, a new lipid profile should be performed 3 to 6 months after initiation	I	B
For people living with HIV in cardiovascular secondary prevention, initiation of lipid-lowering therapy is recommended under the same conditions as in the general population	I	C
In people living with HIV undergoing primary cardiovascular prevention, the initiation of statin therapy is reasonable in case of moderate cardiovascular risk	IIa	B
In people living with HIV undergoing primary cardiovascular prevention, statin therapy may be considered in cases of low cardiovascular risk	IIb	B
Dyslipidemia in women		
Statins are recommended for primary cardiovascular prevention in women with high cardiovascular risk, with the same indications and objectives as for men	I	A
Statins are recommended for secondary cardiovascular prevention in women with the same indications and objectives as in men	I	A
Estrogen-progestogen contraception is contraindicated in women with personal history of ischemic heart disease, stroke, complicated heart valve disease, deep vein thrombosis, migraine with aura, uncontrolled hypertension, known thrombophilia, or a hereditary risk factor for thrombosis, or active smoking at age 35 or older	I	A
In women with dyslipidemia or cardiovascular risk factors, non-hormonal or progestogen-only contraception (implant, hormonal IUD, microprogestogen pill) is reasonable	IIa	B
Dietary measures and behavioral changes (physical activity and combating sedentary lifestyle) should be started early in perimenopause to limit cardiovascular risk	I	B
HRT should not be used for cardiovascular protection	III	A
HRT is contraindicated in women undergoing secondary cardiovascular prevention or at high cardiovascular risk	III	A
Transdermal forms of estrogen and micronized progesterone are preferred in women with moderate cardiovascular risk and in women with HTG	I	B
Statin therapy may be considered in women with early menopause (< 40 years of age), whether natural or surgically induced	IIb	C
Cardiovascular assessment may be beneficial before any pregnancy plans in women being treated for dyslipidemia or presenting atherogenic dyslipidemia	IIa	C
Genetic counseling should be provided before pregnancy for women with genetic forms of dyslipidemia	I	C
It is not recommended to monitor lipid levels during pregnancy in patients with no history of dyslipidemia prior to pregnancy or in patients with low/moderate cardiovascular risk prior to pregnancy	III	C
It is recommended that TG levels be monitored at the beginning of pregnancy and regularly throughout in women with history of severe or moderate HTG (particularly when occurring under estrogen-progestogen therapy) who are at risk of major decompensation (> 10 mmol/L) due to the risk of acute gestational pancreatitis, which can threaten prognosis for both fetus and mother	I	C
The therapeutic lifestyle changes recommended for dyslipidemia should be continued during pregnancy and breastfeeding	I	C
Lipid-lowering treatments will generally be discontinued when pregnancy is planned, or at the latest as soon as pregnancy is diagnosed, in patients who were receiving treatment prior to pregnancy	I	C
The opinion of a specialist from a Lipid and Atherosclerosis Clinicobiological Center (CCBL), a member of the CEDRA network, or a dyslipidemia multidisciplinary team should be sought, if possible during the pre-conception period, regarding management of lipid-lowering drugs during the pre-conception period and pregnancy; continuation or resumption during pregnancy and breastfeeding should be discussed on an individual in case of: – very high cardiovascular risk or secondary cardiovascular prevention before pregnancy; – homozygous or heterozygous FH; – history of major HTG or major gestational HTG (TG > 10 mmol/L), with or without history of acute pancreatitis	I	C
People over 75 years of age		
Lipid-lowering therapy in subjects over 75 years of age is recommended for secondary cardiovascular prevention under the same conditions as in under-75-year-olds, taking life expectancy into account	I	A
Lipid-lowering therapy may be considered for primary cardiovascular prevention in subjects aged > 75 years with high or very high cardiovascular risk, taking life expectancy into account	IIb	B
It is not recommended to discontinue ongoing statin therapy in individuals over 75 years of age for primary cardiovascular prevention, in the absence of factors that would challenge the risk/benefit ratio	III	B

Table R5 (*Continued*)

Recommendations	Class	Level
People with high Lp(a)		
Lp(a) concentration > 125 nmol/L (≈0.5 g/L) is considered high and leads to a dose-dependent increase in the risk of atherosclerotic disease in Caucasians	I	A
An Lp(a) test should be performed at least once in the following at-risk cases: – early coronary artery disease; – FH; – family history of early ASCVD; – recurrent coronary artery disease despite optimal lipid-lowering therapy; – T1D or T2D or CKD	IIa	C
Targeting LDL-c reduction may be considered in patients with Lp(a) > 250 nmol/L (1 g/L)	IIb	B

ASCVD: atherosclerotic cardiovascular disease; CCBL: Clinical and Biological Lipid and Atherosclerosis Centers; CEDRA: Center of Expertise for Rare Dyslipidemias; CKD: chronic kidney disease; FH: familial hypercholesterolemia; HRT: hormone replacement therapy; HTG: hypertriglyceridemia; T1D: type 1 diabetes; T2D: type 2 diabetes; TG: triglycerides.

[233]. Studies are underway with pelacarsen, olpasiran, and lepolisiran in patients undergoing secondary cardiovascular prevention and with elevated Lp(a) (≥ 175 mmol/L), to evaluate the impact of Lp(a) reduction on cardiovascular events [234].

8.9. Rare dyslipidemias

In addition to homozygous FH and dysbetalipoproteinemia, which are discussed in Sections 6 and 7, rare dyslipidemias are mainly hypolipidemias.

8.9.1. Hypoalphalipoproteinemia or HypoHDLemia [235,236]

The common forms are moderate, generally observed in associated HTG or metabolic syndrome, one of the criteria for which is HDL-c < 0.35 g/L (< 0.9 mmol/L). They are detailed in Section 7.

Rare, primary forms are more severe. They are co-dominantly inherited and may involve an absence of circulating HDL. They require expertise at a CEDRA specialized center.

Previous lipid profiles can be used to ensure that hypoHDLemia is not recent and therefore secondary (severe inflammatory syndrome, sepsis, liver failure, intestinal malabsorption, cancer-related malnutrition).

Primary forms are rare. Tangier disease is caused by mutations in the *ABCA1* gene, which prevents the cellular export of unesterified cholesterol to form nascent HDL from apolipoprotein A1 (apoA1). It leads to accumulation of sterols in the lymphoid organs, with hypertrophy of the tonsils and spleen. There is often sensory-motor peripheral neuropathy in all 4 limbs, which can become disabling. The eyelids present ectropion and there is occasional corneal opacity. In addition to undetectable HDL-c concentrations, there is a 50% reduction in LDL-c and moderate HTG. Increased cardiovascular risk is observed mainly when non-HDL-c is > 0.7 g/L (1.8 mmol/L). Ischemic cardiovascular complications, when HDL-c is undetectable, occur from the age of 50 and are much less severe than in hoFH.

Other rare causes include deleterious variants of ApoA1 or lecithin cholesterol acyl transferase (LCAT). In LCAT deficiency, corneal opacification is more pronounced if the deficiency affects only HDL, resulting in a condition known as "fish-eye disease". Forms of LCAT deficiency affecting HDL and LDL cause less marked corneal opacity, but induce severe glomerulopathy due to glomerular lipid deposits and corpuscular hemolytic anemia.

ApoA1 mutations are inconsistently pro-atherogenic, and LCAT mutations have less impact than those in Tangier disease.

Currently, there is no specific treatment outside of clinical research, and therapeutic strategy consists in treating complications symptomatically and attempting to reduce ischemic cardiovascular risk by preventively lowering LDL-c via statins.

8.9.2. Hypobetalipoproteinemia (HypoLDLemia) [237]

Hypobetalipoproteinemia is defined by LDL-c or apoB value below the 5th percentile for age and gender. Secondary forms (previously normal LDL-c) should be excluded: malnutrition, intestinal malabsorption, liver failure, hyperthyroidism, veganism.

Most often, this involves apoB synthesis deficiency, leading to hepatic steatosis with an increased risk of complications inherent in metabolic syndrome or T2D and variants predisposing to hepatic fibrosis.

The most common situation is dominant inheritance, with hypobetalipoproteinemia typically between 0.25 and 0.5 g/L found in 1 parent and 50% of children. Triglyceridemia is normal or slightly low, and HDL-c is preserved.

The heterozygous form, linked to truncations in the *APOB* gene, incurs a lower risk of ischemic cardiovascular complications [238] but a higher risk of hepatic fibrosis, increasing with age [239]. It is assessed in adults by calculating the FIB-4 score and measuring liver elastometry as appropriate.

Other heterozygous or homozygous forms correspond to genetic variants that increase clearance of apoB-containing lipoproteins (PCSK9, ANGPTL3). They do not cause liver disease, and confer cardiovascular protection.

Homozygous forms of APOB and MTP (abetalipoproteinemia) mutations lead to more severe forms of lipid malabsorption with progressive hepatic fibrosis and organ damage including retinitis pigmentosa, cardiomyopathy, and peripheral neuropathy. The clinical picture in Anderson disease (SAR1B deficiency) is mainly digestive and generally less severe. These rare genetic disorders require systematic evaluation at a reference center with periodic follow-up tailored to the individual case. They are often diagnosed in pediatrics [237].

9. Guidance for individuals with dyslipidemia

Physicians seeking advice on the management of severe and/or complex dyslipidemia may refer their patients to one of the Clinical and Biological Lipid and Atherosclerosis Centers (CCBL), a list of which, along with contact details, is available on the NSFA website (https://www.nsfa.asso.fr/ccbl/).

Physicians suspecting rare dyslipidemia (such as hoFH or familial chylomicronemia) should refer their patients to a rare dyslipidemia reference center in the CEDRA network of the FIRENDO rare

diseases network (https://www.firendo.fr/annuaire-des-membres-de-la-filiere/page).

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Appendix A. Supplementary data [240]

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ando.2025.102471.

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