Hellenic Atherosclerosis Society

• GUIDELINES •

Hellenic Atherosclerosis Society Guidelines for the Diagnosis and Treatment of Dyslipidemias - 2023

Katsiki N*, Filippatos TD*, Vlachopoulos C, Panagiotakos D, Milionis H, Tselepis A, Garoufi A, Rallidis L, Richter D, Nomikos T, Kolovou G, Kypreos K, Chrysohoou C, Tziomalos K, Skoumas I, Koutagiar I, Attilakos A, Papagianni M, Boutari C, Kotsis V, Pitsavos C, Elisaf M, Tsioufis K, Liberopoulos E

*Equal contribution

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Abbreviations

ABCA1: ATP-binding cassette transporter
ACS: acute coronary syndrome
ALT: alanine aminotransferase
ANGPTL3: angiopoietin-like protein 3
Apo: apolipoprotein
ART: antiretroviral therapy
ASCVD: atherosclerotic cardiovascular disease
ASO: antisense oligonucleotides
BAS: bile acid sequestrants
BMI: body mass index
CETP: cholesteryl ester transfer protein
CHD: coronary heart disease
cIMT: carotid intima-media thickness
CK: creatine kinase
CKD: chronic kidney disease
CTT: Cholesterol Treatment Trialists
DHA: docosahexaenoic acid
EASO: European Association for the Study of Obesity
eGFR: estimated glomerular filtration rate
EMA: European Medicines Agency
EPA: eicosapentaenoic acid
ESC: European Society of Cardiology
EAS: European Atherosclerosis Society
FCHL: familial combined hyperlipidemia
FCS: familial chylomicronemia syndrome
FDA: US Food and Drug Administration
FH: familial hypercholesterolemia
GI: glycemic index
HbA1c: glycated hemoglobin
HDL-C: high-density lipoprotein cholesterol
HF: heart failure
HeFH: heterozygous familial hypercholesterolemia
HFmrEF: heart failure with mildly reduced ejection fraction
HFpEF: heart failure with preserved ejection fraction
HFrEF: heart failure with reduced ejection fraction
HL: hepatic lipase
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A reductase
HoFH: homozygous familial hypercholesterolemia
hsCRP: high-sensitivity C-reactive protein
IBD: inflammatory bowel disease
IDL: intermediate-density lipoprotein
LAL: lysosomal acid lipase
LAL-D: lysosomal acid lipase deficiency
LDL-C: low-density lipoprotein cholesterol
LDLR: low-density lipoprotein receptor
LPL: lipoprotein lipase
Lp(a): lipoprotein(a)
LVEF: left ventricular ejection fraction
MACE: major adverse cardiovascular events
MCS: multifactorial chylomicronemia syndrome
MEDPED: make early diagnosis to prevent early deaths
MTP: microsomal transfer protein
MUFA: monounsaturated fatty acids
NAFLD: non alcoholic fatty liver disease
NASH: non alcoholic steatohepatitis
NHLBI: National Heart, Lung, and Blood Institute
NNRTIs: non nucleoside reverse transcriptase inhibitors
NOD: new onset diabetes
NPCL1: Nieman Pick C1 like 1 protein
NRTIs: nucleoside reverse transcriptase inhibitors
NtRTIs: nucleotide reverse transcriptase inhibitors
OxPL: oxidized phospholipids
PAD: peripheral arterial disease
PAI-1: plasminogen activator inhibitor type 1
PCSK9: proprotein convertase subtilisin/kexin type 9
PFO: patent foramen oval
PIs: protease inhibitors
PPAR-α: peroxisome proliferator activated receptor a
PSS: plant sterols and stanols
PUFA: polyunsaturated fatty acids
RA: rheumatoid arthritis
RCT: randomized controlled trial
SAMS: statin-associated muscle symptoms
SCORE: Systematic Coronary Risk Estimation
sdLDL: small dense low-density lipoprotein
SFA: saturated fatty acids
siRNA: small interfering RNA
SLE: systematic lupus erythematosus
SRB1: scavenger receptor B class 1
T1D: type 1 diabetes
T2D: type 2 diabetes
TC: total cholesterol
TFA: trans fatty acids
TG: triglycerides
TIA: transient ischemic attack
ULN: upper limit of normal
VLDL: very low-density lipoprotein
WC: waist circumference

Trials mentioned in the text

4D: Die Deutsche Diabetes Dialyse

ACCORD: Action to Control Cardiovascular Risk in Diabetes

AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes

APPROACH: A Study of Volanesorsen (Formerly IONIS-APOCIIIRx) in Patients With Familial Chylomicronemia Syndrome

ATTEMPT: Assessing the treatment effect in metabolic syndrome without perceptible diabetes

AURORA: A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events

CLEAR: Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen

D:A:D: Data-collection on Adverse Effects of Anti-HIV Drugs

EPIC-HIV: Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection

EVO-HF: EVOlocumab in Stable Heart Failure With Reduced Ejection Fraction of Ischemic Etiology

FIELD: Fenofibrate Intervention and Event Lowering in Diabetes

FOURIER: Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk

GAUSS-3: Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects-3

GREACE: Greek Atorvastatin and Coronary Heart Disease Evaluation

HPS2-THRIVE: Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events

IDEAL: Incremental Decrease in End Points Through Aggressive Lipid Lowering

IMPROVE-IT: Improved Reduction of Outcomes: Vytorin Efficacy International Trial

Lp(a)HORIZON: Assessing the Impact of Lipoprotein (a) Lowering With Pelacarsen (TQJ230) on Major Cardiovascular Events in Patients With CVD

OCEAN(a)-DOSE: Olpasiran trials of Cardiovascular Events And lipoproteiN(a) reduction-DOSE

ODYSSEY OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab

ORION-9: Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolemia (HeFH)

ORION-10: Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol

ORION-11: Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol

PROMINENT: Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes

PROSPER: Pravastatin in elderly individuals at risk of vascular disease

REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial

REPRIEVE: Randomized Trial to Prevent Vascular Events in HIV

SCALE Diabetes: Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes

SHARP: Study of Heart and Renal Protection

SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels

STOMP: Statins on Skeletal Muscle Function and Performance

STRENGTH: Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia

TST: Treat Stroke to Target

VICTORION-2P: Study of Inclisiran to Prevent Cardiovascular (CV) Events in Participants With Established Cardiovascular Disease

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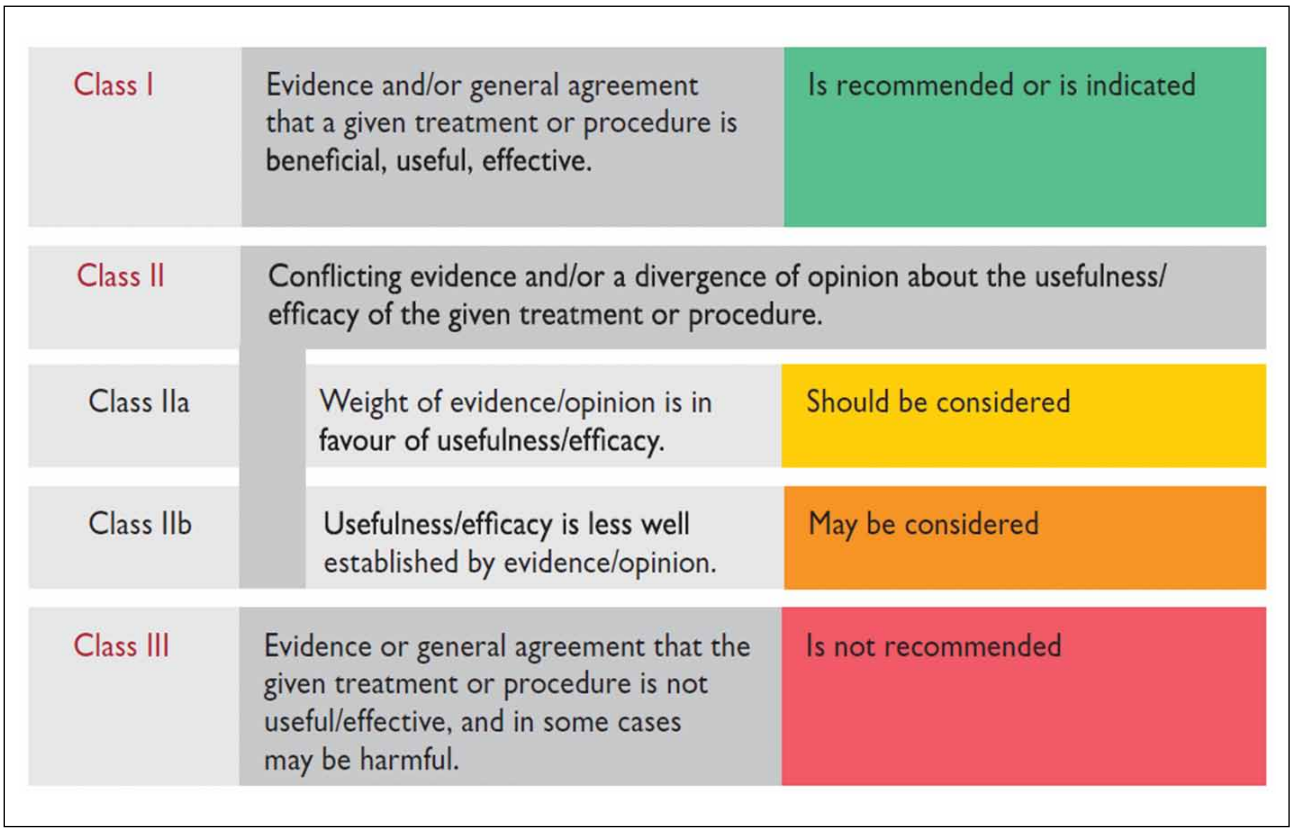

FIGURE 1. Classes of recommendations.

1 Total Atherosclerotic Cardiovascular Disease (ASCVD) Risk

According to the most recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidemias, the assessment of total ASCVD risk is strongly recommended[1]. It is now well understood and appreciated that atherosclerosis is the outcome of risk factors that usually co-exist and interact with each other, making risk estimation a difficult task.

The prediction of ASCVD events has received increased attention during the past years[2]. Allocating individuals that are vulnerable for developing an ASCVD event is a main target of most prevention programs, since it allows better management and facilitation of preventive efforts. One of the most well-known ASCVD risk models is the *Framingham Heart Study Sheets*. Since the early 1990s, many physicians and public health policy makers have used this risk model in clinical practice, strategic planning and research[3]. The *Framingham Heart Study* risk sheet provides estimates of developing angina pectoris, myocardial infarction, or coronary heart disease (CHD) death, over the course of 10 years, for persons without known heart disease. However, the challenge of correctly classifying individuals at high-risk is also a cornerstone in risk prediction modeling, since the up-to-date ASCVD risk models have been criticized for serious misclassification problems, especially when they applied to different populations than the ones they have been created[2]. For example, when the *Framingham Heart Study Sheets* were applied to other populations, especially non-Caucasian, a number of misclassifications occurred[4–7].

In 2003, the ESC Working Group on Epidemiology and Prevention proposed a risk prediction chart based on data from 12 European cohort studies, that included 205,000 persons and 2.7 million years of follow up, where 5,652 CHD fatal events were observed, i.e., the Systematic Coronary Risk Estimation (SCORE) project[8]. The classification of European countries as "*high*" and "*low*" risk was innovative for risk prediction. However, the inclusion of only 12 European cohorts raised several concerns about the applicability of the charts to estimate risk in other European countries.

In 2007, a calibration of the ESC SCORE for the Greek population, i.e., the HellenicSCORE, was introduced[9]. The HellenicSCORE is a statistical model that predicts the 10-year risk for fatal ASCVD events based on the sex, age, smoking habits, total cholesterol (TC) and systolic blood pressure levels of the Greek population and using the risk point-estimates suggested by the ESC SCORE model. Based on the Greek risk factor prevalence that was obtained from the baseline evaluation of the ATTICA study in 2001-2002[10], as well as the annual death rates from the World Health Organization mortality database for 2002[11], in accordance to the rules of the International Classification of Diseases, a recalibration method was proposed by the authors[9]. Specifically, information from the above mentioned national mortality statistics and ASCVD risk factor distributions were combined with ESC SCORE estimates of the relative risk factor effect in order to produce individual 10-year estimations of fatal ASCVD risk, given the age, gender, smoking status and levels of systolic blood pressure and TC. The recalibration method used was the one recommended by D'Agostino et al.[12], and performed separately for men and women. However, this calibration shared a serious methodological drawback, since no actual ASCVD events were used due to the lack of relevant follow-up studies in Greek population at that time. Moreover, the calibration methodology presumed that the statistics for ASCVD mortality and prevalence of risk factors are unchanged over time. Thus, it was a matter of emerging importance to validate the HellenicSCORE and the applied methodology considering potential changes through time.

Based on the 10-year follow-up of the ATTICA Study that was performed during 2011-2012[13], an updated ASCVD risk model, and a validation of the HellenicSCORE, always under the concept of the ESC SCORE charts, was developed[14]. According to the new data, the HellenicSCORE was an accurate tool for identifying individuals at high risk for fatal ASCVD outcome within the decade, but also for identifying individuals at high risk even for a non-fatal ASCVD. The accuracy of the estimation was robust for both genders and various sub-groups of the population. This proposed tool and the applied methodology can be valuable in ASCVD prevention at community setting, and may be adopted by other populations[14].

Recently, the HellenicScore II, a recalibration of the HellenicSCORE, was published based on newly derived risk factors data from the Hellenic National Nutrition and Health

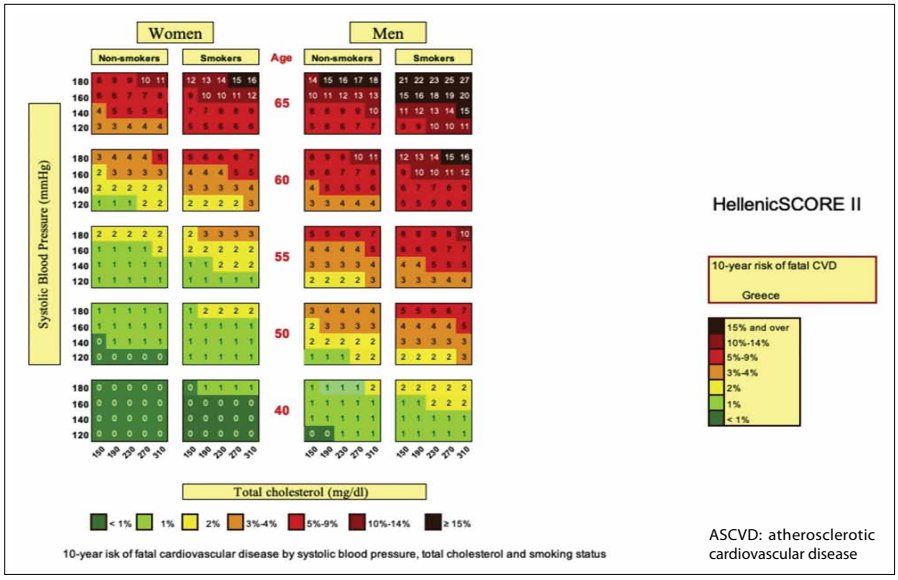

FIGURE 2. HellenicSCORE II – 10-year risk of fatal ASCVD in Greece. *(Adapted from Panagiotakos et al[15])*

Survey (HNNHS)[15] (**Figure 2**). HellenicScore II can now be calculated online at https://www.hellenicheartscore.gr/.

A limitation of HellenicScore II scoring system is that it considers only 3 CVD-related parameters. Other parameters may increase CVD risk (**Table 1**)[1,16]. These parameters should be taken into account for the estimation of total CVD risk and should be used as risk modifiers. It should be mentioned that data on Greek population aged lower than 40 or higher than 70 years are lacking.

Risk prediction scores have become useful tools in daily general practice, as well as for the development of future public health strategies to address the burden of ASCVD. Their use has also been suggested for all individuals in primary ASCVD prevention independently of their medical history, to better identify those at high risk. It is strongly believed that the knowledge of individual's ASCVD risk could motivate him/her to manage risk factors and thus, reduce the burden of the disease. Accuracy is a cornerstone of any risk prediction score; ethnic, genetic, social, cultural and risk factors, could lead to substantial variability in the prediction of ASCVD events.

Estimation of the risk of future ASCVD events through easily applicable scores is an attractive and dynamic field in public health research, as well as in primary prevention and medical practice since it has the potential to stimulate more effective preventive strategies. Thus, its use may accurately estimate the risk for a future ASCVD event of an individual, and be the reason that initiates individual's behavior changes, readiness to act on a new healthier lifestyle, through the various stages of change in human behavior. Clinicians, healthcare practitioners and public health policy makers may use this tool for better preventing the epidemic of ASCVD in the future.

TABLE 1. Parameters that increase ASCVD risk and should be considered as risk modifiers in individuals at low or moderate risk.

Social deprivation
Obesity, especially central obesity
Physical inactivity
Family history of premature ASCVD (men: <55 years; women: <60 years)
Major psychiatric disorders
Atrial fibrillation
Left ventricular hypertrophy
Obstructive sleep apnoea syndrome
Non-alcoholic fatty liver disease
History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia
High-risk race/ethnicities (e.g., South Asian ancestry)
Lipid-related markers • Persistently elevated, primary hypertriglyceridemia (≥175 mg/dL) • non–HDL-C >190 mg/dL • Elevated Lp(a) ≥50 mg/dL or ≥125 nmol/L • Elevated apoB ≥130 mg/dL (if measured)
Other biomarkers/imaging (if measured or done): • Elevated high-sensitivity C-reactive protein (≥2.0 mg/L) • ABI <0.9 • Arterial (carotid and/or femoral) plaque burden on ultrasonography • CAC score assessment with CT

ASCVD: atherosclerotic cardiovascular disease; non-HDL-C: non high-density lipoprotein cholesterol; Lp(a): lipoprotein a; apoB: apolipoprotein B; ABI: ankle brachial index; CAC: coronary artery calcium; CT: computed tomography

2 Laboratory Evaluation of Dyslipidemias

Dyslipidemias are associated with an increased risk of ASCVD. Therefore, lipid measurement is important for the estimation of the ASCVD risk and the appropriate treatment of dyslipidemias. Screening for dyslipidemia should be performed in:

- individuals with clinical manifestations of ASCVD
- clinical conditions associated with dyslipidemia and increased ASCVD risk such as diabetes, chronic kidney disease and autoimmune chronic inflammatory disorders
- subjects with clinical manifestations of genetic dyslipidemias such as familial hypercholesterolemia (FH)
- adults ≥18 years
- the offspring of patients with severe dyslipidemia
- family members of patients with premature ASCVD.

2.1 Lipid parameters

Laboratory evaluation of dyslipidemias involves the quantification of plasma lipids and is some cases, the apolipoprotein (apo) content of lipoprotein particles. In the daily clinical practice, plasma lipoprotein concentration is primarily estimated by determining the TC content, which in humans mainly reflects 3 major lipoprotein classes, i.e., very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Smaller amounts of cholesterol are contained in intermediate-density lipoprotein (IDL) and lipoprotein (a) [Lp(a)]. In addition to TC, lipid profile in clinical practice should include HDL-cholesterol (HDL-C) and triglycerides (TG)[1]. Serum LDL-cholesterol (LDL-C) levels are usually calculated using the Friedewald formula:

LDL-C = TC - HDL-C - (TG/5), in mg/dL,
or LDL-C = TC - HDL-C - (TG/2.2), in mmol/L[17]

The estimation of LDL-C levels by the Friedewald equation assumes that VLDL has a constant cholesterol/TG ratio (1:5 in mg or 1:2.2 in mmol). This formula has several limitations, the most important of which concerns patients with high TG levels (>400 mg/dL or >4.5 mmol/L). In this patient population, the Friedewald equation cannot be used. Another limitation of the Friedewald formula is that calculated LDL-C underestimates LDL-C at TG concentrations ≥177 mg/dL (2 mmol/L). Additionally, at very low LDL-C levels (i.e., <25 mg/dL; <0.64 mmol/L), calculated LDL-C may be misleading, especially in the presence of high TG levels. Amongst other indirect methods of LDL-C calculation the Sampson/NIH and the Martin-Hopkins equations are more accurate than Friedewald equation for the determination of LDL-C at TG levels >354 mg/dL and/or LDL-C<70 mg/dL[18,19].

To overcome the limitations of the Friedewald formula, direct enzymatic methods for measuring LDL-C are commercially available and can be performed with automatic analyzers. Calculated LDL-C and direct LDL-C are strongly correlated in the general population. However, direct LDL-C measurements also have limitations, including systematic bias, inaccuracy in patients with high TG levels and the need for fasting samples[19]. As an alternative to calculated LDL-C, the non-HDL-C can be estimated as TC minus HDL-C. Non-HDL-C is a measure of the cholesterol carried by all atherogenic apoB-containing lipoproteins, including the TG-rich lipoproteins and their remnants[20–23].

2.2 Lipid analyses for ASCVD risk estimation

The determination of TC levels is the most important lipid parameter to be measured for the estimation of the ASCVD risk using the HellenicSCORE II[15] (**Figure *2***). However, in some cases, TC may be misleading, such as in women, who often have high HDL-C levels, and in patients with diabetes or high TG, who often have low HDL-C levels. Thus, risk estimation can be significantly improved by including LDL-C and HDL-C levels.

Calculated or directly measured serum LDL-C levels are very important for the estimation of the ASCVD risk since LDL-C represents the primary therapeutic target in lipid-lowering treatment[1]. LDL-C measurement may also reveal the presence of markedly increased LDL-C levels, such as in FH patients, that suggest a lifetime cumulative exposure to high ASCVD risk.

Serum TG levels should be assessed to identify people at high ASCVD risk due to the presence of an increased concentration of atherogenic TG-rich lipoproteins and their remnants[1]. Serum TG levels are also important to identify individuals in whom the measured LDL-C may

underestimate LDL-C concentration and therefore ASCVD risk. This may be especially relevant in patients with low LDL-C levels, obesity, diabetes or metabolic syndrome[1]. Indeed, in patients with elevated TG concentrations, in obese individuals, in patients with diabetes or in cases with very low LDL-C levels, calculated LDL-C levels may underestimate the total concentration of cholesterol carried by LDL particles as well as total concentration of apoB-containing lipoproteins, thus underestimating ASCVD risk. In these patients, the measurement of apoB and non-HDL-C levels is recommended as a routine lipid analysis for screening, diagnosis and management of dyslipidemia[1]. ApoB provides an accurate estimate of the total concentration of atherogenic lipoprotein particles [LDL, VLDL, TG-rich remnant particles, and Lp(a)][24,25]. ApoB determination seems preferable to the calculation of non-HDL-C[1,20,21]. Standardized, automated, accurate and inexpensive methods for the direct quantitation of apoB levels are available.

The development of analytical methods for Lp(a) measurement remains a challenge due to the complex molecular structure of this lipoprotein and the variation in the size of apo(a)[1]. Furthermore, various assays report Lp(a) levels as either mass (mg/dL) or molar concentration (nmol/L). Therefore, there is still a need to establish a reliable and reproducible method for the quantification of Lp(a) mass or particle number. According to the latest ESC/EAS guidelines, Lp(a) can help to reclassify individuals borderline between moderate and high-risk as well as those with a family history of premature ASCVD[1]. Lp(a) measurement should be performed, at least once in the lifetime of each adult; in the presence of very high inherited Lp(a) levels (i.e., >180 mg/dL; >430 nmol/L), there is a lifelong risk of ASCVD equivalent to that related with heterozygous FH (HeFH)[1]. For further details on Lp(a), please see the *Lp(a)* section.

Recommendations for measuring lipids and lipoproteins to estimate ASCVD risk are summarized in **Table 2**.

2.3 Additional lipid and lipoprotein parameters

Lipoproteins consist of a heterogeneous population of particles. Evidence suggests that various subclasses of LDL and HDL may contribute differently to the estimation of the ASCVD risk. However, the causal association of these subclasses with ASCVD risk remains unclear. Among all lipoprotein subclasses, small-dense LDL (sdLDL) particles are strongly related to the pathogenesis of atherosclerosis, but they are not currently recommended for risk estimation[26].

ApoA1 is the major protein of HDL and provides a satisfactory estimate of HDL particles concentration. However, there is a high heterogeneity among HDL particles in apoA1 content; each HDL particle may carry from one to five apoA1 molecules. ApoA1 determination is not recommended in daily clinical practice. Ratios of atherogenic lipoproteins to HDL-C or apoA1 (TC:HDL-C, non-HDL-C:HDL-C, apoB:apoA1) have been evaluated for risk estimation in several clinical studies, but existing data is not enough to recommend routine use in ASCVD risk estimation[17,27].

ApoCIII is a key regulator of TG metabolism; high apoCIII plasma levels are associated with high plasma VLDL and TG levels. ApoCIII has been identified as a potentially important new ASCVD risk factor. Loss of apoCIII function mutations is associated with low TG levels and reduced

TABLE 2. Lipid analyses for ASCVD risk estimation.

Recommendations	Class of recommendation
TC is recommended for the estimation of fatal ASCVD risk by HellenicSCORE II	I
LDL-C is recommended as the primary lipid target for screening, diagnosis, and management of dyslipidemias	I
HDL-C is recommended to further refine risk estimation	I
TG measurement is recommended to be included in the routine lipid analysis	I
Non-HDL-C is recommended for risk assessment, especially in subjects with high TG levels, diabetes, obesity, or very low LDL-C levels	I
ApoB is recommended for risk assessment, in subjects with high TG levels, diabetes, obesity, metabolic syndrome, or very low LDL-C levels	I
ApoB can be used as a secondary target for screening, diagnosis and treatment of dyslipidemias and may be preferred over non-HDL-C	IIb
Lp(a) can be used to reclassify individual borderline between moderate and high-risk	IIa
Lp(a) measurement should be performed at least once in the lifetime of each adult	

ApoB: apolipoprotein B; ASCVD: atherosclerotic cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SCORE: Systematic Coronary Risk Estimation; TC: total cholesterol; TG: triglyceride; Lp(a): lipoprotein(a)

ASCVD risk. Therefore, apoCIII has been identified as a new potential therapeutic target. Currently, apoCIII measurement is not recommended on a routine basis[17,28,29].

2.4 Fasting versus non-fasting samples for lipid profile determination

For lipid analyses, blood samples are traditionally drawn in the fasting state. Recent studies have demonstrated that the difference in lipid parameters between fasting and non-fasting samples is small. However, food affects TG concentrations; higher plasma TG levels (by an average of 27 mg/dL; 0.3 mmol/L) were observed in non-fasting samples compared with fasting ones among 1093 adults, depending on the composition and the time frame of the last meal[30]. Some guidelines recommend non-fasting sampling[31–33]. Performance of a postprandial hypertriglyceridemia test has been suggested by an expert panel when fasting TG and non-fasting TG levels are 89-175 mg/dL (1-2 mmol/L) and 115-200 mg/dL (1.3-2.3 mmol/L), respectively, as an additional evaluation of cardiometabolic risk[34]. A certain oral fat tolerance test has been proposed consisting of 75 g fat, 25 g carbohydrate and 10 g proteins; an abnormal TG response, measured at 4 h after meal consumption, is defined as >220 mg/dL (2.5 mmol/L)[34]. Postprandial hypertriglyceridemia testing may be useful, especially in patients with metabolic syndrome, diabetes, chronic kidney disease (CKD) and non-alcoholic fatty liver disease[35].

According to the latest ESC/EAS guidelines for the management of dyslipidemias, for general risk screening, non-fasting samples seem to have the same prognostic value as fasting ones, especially regarding LDL-C[1,36]. If non-fasting sampling is performed in patients with metabolic syndrome, diabetes or hypertriglyceridemia, calculated LDL-C levels should be interpreted with caution[1]. Of note, fasting for apoB and non-HDL-C measurements is not required, since, even in the postprandial state, apoB48-containing chylomicrons typically represent <1% of the total concentration of circulating apoB-containing lipoproteins.

2.5 Genotyping

Several genes have been associated with ASCVD risk, however, presently, the use of genotyping for risk estimation in the general population is not recommended, since known risk loci account for only a small proportion of this risk[37]. FH diagnosis is primarily based on clinical presentation and laboratory tests. The diagnosis can be verified by detecting causative mutations. However, in most cases, the frequency of detectable mutations in patients with a clinically definite or probable HeFH is between 60-80%, suggesting that a large proportion of FH patients have either a polygenic cause of the disease or that other genes, yet unknown, are involved. Genetic testing and cascade screening is recommended in family members when the causative mutation is known, thus facilitating the efficient identification of new cases[1].

ApoE is present in 3 isoforms (apoE2, apoE3 and apoE4). For the diagnosis of familial dysbetalipoproteinemia (apoE2 homozygosity), plasma levels of cholesterol, TG and apoB should be determined. If suspicion is high, apoE genotyping can be performed[38].

2.6 Monitoring of lipids and other biochemical parameters in patients on lipid-lowering therapy

In patients who should receive hypolipidemic therapy, at least 2 measurements of lipid profile (TC, LDL-C, HDL-C and TG) should be performed, before starting therapy, with an interval of 1-12 weeks (**Table 3**). This recommendation does not refer to conditions in which prompt drug treatment is suggested, such as in acute coronary syndrome (ACS) and very high-risk patients. According to the standard practice for assessing the response to hypolipidemic therapy, lipid monitoring is performed at 8±4 weeks following initiation of therapy[1]. Once a patient has achieved the target lipid level, lipid monitoring should be performed annually, unless there are adherence problems or other reasons which require more frequent measurements[1].

To identify drug toxicity in patients on lipid-lowering therapy, safety biochemical tests are advised. These primarily include the measurement of alanine aminotranferase (ALT) and creatine kinase (CK)[1]. ALT determination is recommended before starting statin treatment, 8-12 weeks after statin initiation or after dose increase, as well as in cases with clinical indication of liver disease[1]. If ALT is <3 times the upper limit of normal (ULN), hypolipidemic therapy should be continued and ALT should be rechecked in 4-6 weeks. If ALT is ≥3xULN, statin therapy should be stopped or the dose be reduced, and ALT should be rechecked within 4-6 weeks[1]. Drug therapy may be cautiously reintroduced if ALT levels have returned to normal, but if ALT remains elevated, other reasons, unrelated to statin therapy, should be investigated.

Routine monitoring of CK during statin treatment is not recommended[1]. CK should be assessed in patients at high-risk for myopathy (e.g., very elderly with co-morbidities, patients with a history of muscle symptoms or those receiving interacting drugs). CK should be measured in all patients who present with muscle symptoms (pain and weakness); lipid-lowering therapy should be stopped if CK rises to >10xULN[1]. It should be emphasized that there is no

TABLE 3. Recommendations for monitoring lipids and other biochemical parameters during lipid-lowering therapy.

Recommendations	Class of recommendation
Lipid monitoring	
Before lipid-lowering therapy initiation, lipid levels (TC, LDL-C, HDL-C and TG) are recommended to be measured at least twice, with an interval of 1-12 weeks, except when immediate drug treatment is required, such as in ACS and very high-risk patients	I
For assessment of the response to hypolipidemic therapy, lipid monitoring is recommended to be performed at 8±4 weeks following treatment initiation or change in statin dose	I
Once target lipid level is achieved, lipid monitoring is recommended to be performed annually, unless there are adherence issues or other reasons requiring more frequent measurements	I
Determination of biochemical parameters to identify possible hypolipidemic drug side effects	
ALT measurement is recommended before and 8-12 weeks after the initiation of lipid-lowering treatment, 8-12 weeks after dose increase and in cases with clinical indications of liver disease	I
If ALT is increased but <3xULN, hypolipidemic therapy is recommended to be continued and ALT activity should be rechecked in 4-6 weeks	I
If ALT is ≥3xULN, lipid-lowering drugs should be discontinued, or their dose should be reduced; ALT measurement should be performed within 4-6 weeks. If ALT activity is normalized, drug therapy may be cautiously reintroduced If ALT remains elevated, other causes unrelated to hypolipidemic drug therapy should be considered and further investigated	IIa
Routine monitoring of CK is not recommended	III
CK is recommended to be measured before initiating lipid-lowering therapy (if >4xULN, treatment should not be started and CK levels should be re-evaluated), as well as in patients who develop myalgia	I
There is no predictive value of routine repeat CK testing for rhabdomyolysis	I
In patients at high-risk of developing diabetes (elderly, obese, with metabolic syndrome, or other signs of insulin resistance) and on high-dose statin therapy, measurements of HbA1c and fasting glucose should be performed annually during lipid-lowering therapy	IIa

ACS: acute coronary syndrome; ALT: alanine aminotransferase; CK: creatine kinase; HDL-C: high-density lipoprotein cholesterol; HbA1c: glycated hemoglobin; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; ULN: upper limit of normal

predictive value of repeat CK testing for rhabdomyolysis in patients on hypolipidemic drugs[39,40]. According to the latest ESC/EAS guidelines[1], CK levels should be assessed before starting lipid-lowering drugs; if CK is >4xULN, drug therapy should not be initiated and CK levels should be rechecked. For further recommendations in cases of statin-associated muscle symptoms (SAMS), with or without CK elevation, please see the *Statin intolerance* section.

Finally, in patients at high-risk of developing diabetes (such as the elderly, postmenopausal women and those with obesity and/or metabolic syndrome, a family history of diabetes or a history of gestational diabetes) that receive high-dose statin therapy, glycated hemoglobin (HbA1c) and fasting glucose should be regularly checked[41,42].

3 Lifestyle Recommendations for the Reduction of ASCVD Risk

3.1 Introduction

The adoption of healthy lifestyle patterns remains the cornerstone for the prevention and treatment of ASCVD in both primary and secondary prevention settings[43,44]. A healthy lifestyle includes the maintenance of a healthy body weight/composition, prudent dietary patterns, avoidance of smoking and regular physical activity. The lipid profile can be beneficially affected by healthy practices, mediating by this way the health promoting properties of therapeutic lifestyle changes.

3.2 Body weight

Dyslipidemia is a characteristic feature of obesity[45] and contributes to the increased ASCVD risk of obese people[46,47]. Body mass index (BMI) and waist circumference (WC) are commonly used in clinical practice. A person with a BMI between 25.0-29.9 Kg/m^2 is characterized as overweight, and with a BMI ≥30.0 Kg/m^2 as obese. BMI 30.0-34.9 Kg/m^2 indicates grade I obesity, 35.0-39.9 Kg/m^2 grade II obesity and ≥40 Kg/m^2 grade III (severe) obesity. WC is a crude estimate of abdominal adiposity. A WC >88 cm for women and >102 cm for men of European ancestry is indicative of abdominal adiposity[48–50].

Overweight/obesity is characterized by elevated levels of TG, VLDL, apoB, non-HDL-C and small dense LDL particles in parallel with low levels of HDL-C. Enrichment of HDL lipoproteins with TG, due to the activity of cholesteryl ester transfer protein (CETP), in combination with their lipolysis by hepatic lipase (HL), results to dysfunctional small HDL particles with a reduced affinity for apoA1 and impaired ability of reversed cholesterol transport. Such abnormalities in the quality of LDL and HDL particles contribute to the increased ASCVD risk in obese patients[51–53]. Insulin resistance is the main driving force, leading to lipid dysmetabolism in obesity[46,54].

A weight loss of >5% is a prerequisite for meaningful beneficial effects on lipid levels[55,56] (**Table 4**). The magnitude of this effect is variable and depends on baseline body status, extent of weight loss, lifestyle intervention applied and genetic background. In general, for every Kg decrease of body weight, TC, LDL-C and TG are decreased by 2.0, 0.8 and 1.3 mg/dL, respectively. HDL-C levels are reduced by 0.3 mg/dL during active weight loss, but they increase by 0.4 mg/dL from baseline values if the weight reduction is stabilized[56,57]. Low-carbohydrate diets favor improvements in HDL-C and TG in overweight/obese subjects, while low-fat diets favor reductions of LDL-C[56,58,59]. It should be emphasized that a weight loss of 5-10% requires an intensive intervention combining energy restriction, increased physical activity and behavioral modification under the guidance of specialized health professionals (doctors,

TABLE 4. Recommendations for body weight reduction in patients with dyslipidemia.

Recommendation	Class of recommendation
Weight status is recommended to be assessed to all individuals with an increased ASCVD risk, who are dyslipidemic or have excess body weight. Vice versa, overweight and obese individuals are prone to dyslipidemia and their lipid profile should be regularly determined	I
Body weight reduction by at least 5% is recommended for the improvement of dyslipidemia in overweight and obese individuals. This can be achieved by a caloric deficit of 300-500 Kcal/day combining caloric intake decrease and energy expenditure increase incorporated into intensive lifestyle interventions	I
Pharmacological treatment for obesity may be considered for obese or overweight individuals with weight-related comorbidities always in conjunction with lifestyle interventions.	IIb
Metabolic surgery, along with other weight-related comorbidities, may improve dyslipidemia in severely obese, dyslipidemic patients who meet specific criteria	IIb

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index

clinical nutritionists, psychologists and certified trainers)[55]. However, most patients regain weight in the long term.

If lifestyle interventions fail to induce or maintain weight loss then pharmacological treatment of obesity could be considered in combination with healthy lifestyle changes[60]. According to the European Association for the Study of Obesity (EASO) guidelines, pharmacotherapy is indicated as an adjust to lifestyle modifications in persons with a BMI ≥30 Kg/m^2 or a BMI ≥27 Kg/m^2 in the presence of comorbidities[61]. Currently approved antiobesity drugs in Europe include orlistat, liraglutide 3.0 mg, semaglutide 2.4 mg and naltrexone/bupropion combination, whereas in the US phentermine/topiramate combination is also indicated[61]. Among these medications[62], orlistat, a selective and reversible inhibitor of gastric pancreatic lipase[63,64], is able to reduce TC and LDL-C by 11-14 mg/dL and 8.5-11.5 mg/dL, respectively (placebo-subtracted reduction), at a dose of 120 mg, 3 times per day, irrespective of weight loss[65–69]. Studies with phentermine/topiramate, and naltrexone/bupropion show a significant modest reduction of TG and elevation of HDL-C[70]. Of note, liraglutide 3.0 mg was reported to significantly lower TC, VLDL and TG, and raise HDL-C in overweight/obese patients with type 2 diabetes (T2D) during the 56-week SCALE Diabetes randomized, double-blind, placebo-controlled trial[71].

If both lifestyle interventions and pharmacological treatment fail to achieve a normal BMI, bariatric surgery could be applied for obese patients fulfilling certain criteria[72]. Of note, according to EASO guidelines, metabolic surgery is recommended in patients with a BMI ≥40 Kg/m^2 or a BMI 35.0-39.9 Kg/m^2 plus comorbidities or a BMI 30.0-34.9 Kg/m^2 plus T2D[61]. Among all bariatric surgical techniques, the Roux-en-Y-gastric bypass (RYGB) and the biliopancreatic diversion (BPD) are more efficient to improve lipids, including reduction in LDL-C, TG and increase in HDL-C, with these beneficial effects being proportional to the magnitude of weight reduction[70,73,74].

3.3 Diet

The macro- and micro-nutrient content of daily diet and the adoption of dietary patterns along with the consumption of certain functional foods and dietary supplements may have a modest but significant effect on lipid profile. Healthy dietary habits can play a significant role in the primary prevention of dyslipidemia and lipid-related diseases, whereas at the same time it can act in conjunction with drug therapy for the improvement of lipid profile as well as for the secondary prevention of ASCVD (**Table 5**).

i) Macronutrient content of the diet

The reduction of dietary fat, irrespective of its quality, can lower TC and LDL-C, while it has no effect on TG, TC/HDL-C and LDL-C/HDL-C ratio[75]. Compared with low-fat diets, low carbohydrate diets have been reported to induce a greater weight loss and TG reduction, as well as greater increases in HDL-C and LDL-C (weighted mean differences: weight 2.2 kg, TG 23 mg/dL, HDL-C 5 mg/dL, LDL-C 6 mg/dL)[76]. Recent meta-analyses have shown that atherogenic dyslipidemia can be slightly improved in people with T2D, following a low carbohydrate diet (<40% of energy intake) compared with a low-fat diet (<30% of energy intake), while no differences were observed between high carbohydrate diets and diets containing low or moderate carbohydrates (<45% of energy intake)[77]. There is also evidence that high protein diets can lower TG levels in patients with T2D compared with low protein ones[78].

ii) Quality of dietary fat

The composition of dietary fat in saturated, monounsaturated and polyunsaturated fatty acids (SFA, MUFA, PUFA, respectively) is a crucial determinant of the impact of diet on lipid profile.

The amount of SFA in the diet (major sources: meat, dairy products, tropical oils) has the strongest impact on LDL-C levels (0.8-1.6 mg/dL of LDL-C increase for every 1% additional energy coming from SFA)[79]. The isocaloric replacement of carbohydrates with frequently consumed SFA (lauric, myristic, palmitic), excluding stearic acid, is associated with increases in TC, LDL-C and HDL-C[79,80]. Dietary changes leading to lower SFA intakes (<10% of total energy) can modestly affect cholesterol-containing lipoprotein levels. However, the impact of these changes depends on whether the SFA are replaced by MUFA, PUFA or carbohydrates. Replacement of energy from SFA with PUFA can lower TC, LDL-C, HDL-C and TC/HDL-C ratio and has the strongest hypocholestolemic effect compared with replacement of SFA with MUFA and carbohydrates[81,82]. A recent systemic review and meta-regression analysis found that the replacement of 1% energy from SFA with PUFA, MUFA or carbohydrates, decreased LDL-C by 2.1, 1.6 and 1.3 mg/dL, respectively[83]. Of note, the ability of PUFA to reduce circulating cholesterol is due to a reduced synthesis rate and increased clearance rate of LDL-C[84]. This effect could provide a 10% decrease in CHD risk for each 5% energy substitution[85], irrespective of the other beneficial actions of PUFA. Furthermore, MUFA and carbohydrates show a similar 6-7% hypocholesterolemic effect when they replace SFA[86]. However, carbohydrates can enhance atherogenic dyslipidemia (i.e., lower HDL-C and raise TG and sdLDL) more than MUFA, especially in people with insulin resistance and T2D[87,88].

TABLE 5. Dietary recommendations for patients with dyslipidemia.

Recommendation	Class of recommendation
Individualized nutritional counseling should be provided by a registered nutritionist to all patients with dyslipidemia for sustainable dietary changes[147,148]. The nutritionist should collaborate with the clinicians to achieve the maximal benefit.	IIa
Dietary fat is recommended to be consumed mainly via vegetable oils, fish and nuts. A total fat intake higher than 35% of total energy intake should be avoided, especially for people with mild to moderate hypercholesterolemia.	I
Patients with FH should restrict total fat to 20-35% of total energy intake, keeping in mind that very low-fat diets have the risk of inadequate intake of lipid soluble vitamins	IIa
SFA, MUFA and PUFA are recommended not to exceed 7, 20 and 10% of energy intake, respectively	I
The intake of omega-6 PUFA is recommended to range from 5 to 10% of energy intake, while that of omega-3 PUFA between 0.6-2.0%. A minimum intake of 500 mg/day EPA+DHA, preferably from fish, is recommended	I
Most carbohydrates are recommended to derive from unprocessed, non-refined food sources providing high amounts of dietary fibers with a hypocholesterolemic action and preventing increase of TG and decrease of HDL-C	I
Sugars, including those found in foods, should not exceed 10% of energy intake from food sources. A lower intake is needed for patients with atherogenic dyslipidemia (such as those with metabolic syndrome and T2D)	IIa
The consumption of trans fatty acids is recommended not to exceed 1% of energy intake	I
Hypercholesterolemic patients should limit dietary cholesterol consumption to no more than 300 mg/day	IIa
Legumes, vegetables, fruits and wholegrain cereals intake is recommended for the daily consumption of >25 g/day of dietary fibers. The inclusion of 3 g/day of oat and barley soluble fibers can lower LDL-C	I
The addition of 2 g/day of plant sterols/stanols in the diet of hypercholesterolemic patients (including patients with FH), in the form of supplements or functional foods, can significantly enhance LDL-C lowering combined with pharmaceutical treatment	IIb
The general population should consume 2-3 servings (150 g of cooked fish) preferably from fatty fish (e.g., sardines, anchovies, salmon) to achieve a daily consumption of 500 mg EPA-DHA. Higher doses of long-chain omega-3 fatty acids (2-4 g) from supplements, fish oils or enriched foods are required for a clinically significant improvement of hypertriglyceridemia	IIa
The daily consumption of 40-60 g/day of nuts (preferably walnuts, almonds, hazelnuts and flaxseed) can exert a meaningful reduction of LDL-C, especially in hypercholesterolemic patients	IIb
Social drinkers can moderately consume alcoholic beverages providing 20 g alcohol/day for men and 10 g alcohol/day for women. Wine is the recommended alcoholic beverage due to its cardioprotective properties. People with elevated TG must abstain from alcohol consumption	I

SFA: saturated fatty acids; MUFA: monounsaturated fatty acids; PUFA: polyunsaturated fatty acids; FH: familial hypercholesterolemia; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; T2D: type 2 diabetes; LDL-C: low-density lipoprotein cholesterol

iii) Trans fatty acids

Dietary trans fatty acids (TFA) are derived from dairy products, ruminant animal meat and foods of industrial origin under thermal and hydrogenation processes. Their intake ranges from 0.2 to 6.5% of total energy intake with most of them coming from processed foods. The consumption of TFA is associated with increased mortality and incidence of myocardial infarction and stroke[89,90]. In this context, a 2% increase of energy from TFA is related to a 23% increase of absolute vascular risk[91]. This is mainly due to their ability to raise LDL-C levels similarly to SFA but, unlike SFA, TFA also decrease HDL-C and LDL-C/HDL-C ratio[79,92]. Compared with TFA of industrial origin, ruminant TFA do not seem to adversely influence cholesterol levels at current dietary intakes[93], however this observation should be further established in future studies.

iv) Dietary cholesterol

Initial observations from epidemiological studies had shown an association of the amount of dietary cholesterol with its circulating levels. This led to guidelines recommending restriction of dietary cholesterol to less

than 200-300 mg/day[94,95]. However, there is evidence from recent data indicating that dietary cholesterol has a neutral effect on cholesterol levels or CHD risk[96,97]. The response of individuals to dietary cholesterol can vary substantially according to their genotype, body weight, insulin resistance status and background diet. There are 2 phenotypes, the hypo-responders (75-80% of the general population) and the hyper-responders (15-20%)[98]. A 3-fold higher response in LDL-C plasma levels is observed in the second phenotype compared with the first phenotype for 100 mg/day cholesterol intake modification[99]. In addition, SFA can act synergistically with dietary cholesterol to raise LDL-C levels[100]. Therefore, recommendations on dietary cholesterol should be individualized taking into consideration the dietary habits and genetic background of each person.

v) Quantity and quality of carbohydrates

The increased dietary intake of carbohydrates, especially when they are derived from refined foods, promotes atherogenic dyslipidemia (by decreasing HDL-C and increasing TG and small dense LDL)[58,59,79]. This harmful effect can be reversed when high carbohydrate diets involve increased consumption of dietary fibers and low glycemic index (GI) foods[101,102]. On the other hand, simple sugars (i.e., sucrose and fructose) are a significant source of daily carbohydrates, found in high quantities in sugar-sweetened beverages and corn syrup. The increased intake of simple sugars, especially fructose (>10% of energy intake), raise TG levels and make LDL particles more atherogenic[103,104].

The GI of a diet reflects the quality of carbohydrates. Low GI diets are characterized by higher consumption of dietary fibers and complex carbohydrates. The comparison of high with low GI diets revealed no differences in TG and HDL-C levels, whereas their effect on TC and LDL-C are conflicting[105,106]. This discrepancy could be, at least partly, explained by the fact that, despite its low GI, fructose induces atherogenic dyslipidemia. Therefore, the accurate determination of sucrose and fructose content of diet is necessary[107].

vi) Dietary fibers

The increased intake of dietary fibers, especially soluble fiber, can have a significant hypocholesterolemic effect. Foods rich in dietary fibers include vegetables, fruits, legumes, and whole grain cereals. The hypocholesterolemic effect of dietary fibers depends on the fiber composition, quantity and frequency of consumption[108]. A mean reduction in LDL-C levels by 1 mg/dL is expected for each g of water-soluble fibers added in daily diet[109]. LDL-C lowering is maximized at doses 25-30 g, achieving reductions of 10-15%[110,111]. Furthermore, beta-glycans found in barley and oats can lower LDL-C by 6% at daily doses of at least 3 g[112].

vii) Food groups with lipid modulating properties

The consumption of several food groups, at certain amounts daily, can favorably modulate lipid profile. Hypolipidemic properties are attributed to their unique composition, consisting of nutrients and phytochemicals which act in synergy.

Nuts and seeds have proven cardioprotective properties[113]. They are characterized by the presence of high amounts of MUFA and/or PUFA, dietary fibers, antioxidant phytochemicals, vitamins and trace minerals. The increased intake of nuts and/or seed at a daily dosage of 30-50 g has been associated with lower TC, LDL-C and LDL-C/HDL-C, without significantly affecting TG or HDL-C[114,115]. A strong body of evidence supports that walnut consumption, at daily dosages of 40-85 g, can reduce TC, LDL-C, apoB and TG levels (from 5 to 10 mg/dL) without affecting body weight or blood pressure[116]. A few studies indicate a mild hypocholesterolemic effect of almonds (50-100 g/day)[117], hazelnuts (30-70 g/day)[118] and flaxseed[119].

Whole grains (i.e., barley, brown/wild rice, buckwheat, cracked wheat, millet, oatmeal) exert a modest hypocholesterolemic effect (i.e., LDL-C reduction by 3-5 mg/dL) due to the presence of complex carbohydrates, soluble fibers and beta-glucans[120]. This effect is more evident in oat and barley via beta-glucans[121].

Recent meta-analyses report a mild hypocholesterolemic impact of green tea (LDL-C reduction by 7-9 mg/dL)[122], black tea (LDL-C reduction by 5 mg/dL)[123] and cocoa (LDL-C reduction by 6 mg/dL)[124].

A mild consumption of alcoholic beverages (30 g of alcohol/day) may have a small raising effect on HDL-C (by 4 mg/dL) and apoA1 levels[125]. Excess alcohol intake can have a major negative impact on TG levels, both in normolipidemic and hypertriglyceridemic individuals, due to its ability to increase hepatic VLDL-TG rate of synthesis and secretion[126].

viii) Dietary supplements - Functional foods - Nutraceuticals

Even though a wide range of commercially available supplements, functional foods and nutraceuticals claim to have lipid modulating activities, current evidence mainly support the TG-lowering activity of omega-3 PUFA and the hypocholesterolemic properties of plant sterols/stanols (PSS) and red yeast rice.

The increased consumption of long-chain omega-3 PUFA [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)], derived mainly from fatty fish, leads to a dose-

dependent reduction in TG levels at pharmacological doses of 2-4 g/day[127,128]. The hypotriglyceridemic effect of omega-3 PUFA is observed irrespective of the source, which could be fish, fish oils, supplements or EPA/DHA-enriched food sources[127–129]. Although omega-3 PUFA do not affect LDL-C and HDL-C levels[128], recent clinical studies have demonstrated an improvement in LDL atherogenicity (defined by the presence of less sdLDL particles) following omega-3 PUFA supplementation[130]. Of note, despite the well-documented hypotriglyceridemic effect, clinical trials and meta-analyses have failed to show that increased consumption of omega-3 PUFA decreases ASCVD risk[131–133], with the exception of icosapent ethyl. This highly purified EPA ethyl ester was reported to significantly decrease the composite of cardiovascular (CV) death, nonfatal myocardial infarction, nonfatal stroke, unstable angina or coronary revascularization, in 8179 statin-treated patients with elevated TG levels after a median of 4.9 years in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT)[134].

ix) Plant sterols and stanols

PSS are structural analogues of mammalian cholesterol found in most plant foods. The daily consumption of PSS ranges from 100 to 400 mg, however only pharmacological doses of 2-3 g/day can have a significant 7-10% LDL-C lowering effect, without affecting TG or HDL-C levels[135]. The effectiveness of PSS supplementation has been shown in short-term studies, while their long-term efficacy is uncertain[136]. A daily intake of 2-3 g PSS can only be achieved by the intake of PSS supplements, or the consumption of foods enriched with PSS. PSS can also act in conjunction with cholesterol lowering therapies, having a synergistic effect on LDL-C lowering[137]. Pleiotropic mechanisms can explain the hypocholesterolemic effect of PSS, but the main one is the displacement of cholesterol from enteric micelles, resulting in partial inhibition of cholesterol absorption[138,139]. PSS supplementation is generally safe, however there are some concerns about the potential of PSS to lower lipid soluble vitamins (i.e., A, D, E, K), especially E and carotenoids[140], and the atherogenic potential of oxidized phytosterols[141], especially in people with phytosterolemia or high absorbers of PSS.

Red yeast rice is the product of white rice fermentation with the fungus Monascus purpureus, which contains the monacolin K, i.e., a statin-like molecule inhibiting liver synthesis of cholesterol. The hypocholesterolemic efficacy of red yeast rice is different for each preparation due to the high variability of monacolin K content[142]. A significant lowering of cholesterol (by 20%) can be achieved by the intake of red yeast rice preparations with 2-10 mg/day of monacolin K[143]. However, concerns are raised for the safety of the long-term consumption of red yeast rice since it contains potential toxic phytochemicals[142]. Recently, based on reports of adverse effects linked to the use of products containing red yeast rice, European Committee restricted the individual portion of the product for daily consumption to no more than 3 mg of monacolins from red yeast rice[144]. The role of several nutraceuticals on lipids has been discussed by an international expert panel[145,146].

3.4 Physical activity and exercise

Body movements leading to energy expenditure have, through pleiotropic mechanisms, beneficial effects on human metabolism, including lipid metabolism. Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. It includes occupational, sports, conditioning, household, or other activities. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness. It includes aerobic exercise, resistance training or combined aerobic and resistance training[149]. Most randomized clinical trials investigating the effect of physical activity or exercise on ASCVD health are small, short-term and with a high risk of bias, which make the drawing of safe conclusions difficult. However, recent meta-analyses on this field give a clearer picture.

Increased physical activity can lower ASCVD risk by beneficially modifying several risk factors including dyslipidemia[150], whereas sedentary lifestyle has the opposite effect by raising TG and lowering HDL-C[151]. Lifestyle interventions, incorporating physical activity, in obese people can improve TC, LDL-C and TG (without affecting HDL-C), among other cardiometabolic risk factors[152]. Lifestyle interventions, combing diet and physical activity, are more effective in improving lipid profile than physical activity alone[153]. For example, implementation of moderate-to-vigorous-intensity physical activity programs, even in the workplace, was reported to decrease LDL-C in working-age women[154].

Regular supervised exercise training can exert a modest benefit on TG and HDL-C in healthy individuals[155] and patients with T2D[156], on intrahepatic TG in patients with non-alcoholic fatty liver disease (NAFLD)[157], and LDL-C in patients with type 1 diabetes (T1D)[158]. A few studies also indicate an exercise-induced improvement in lipoprotein subclass profile[159].

Aerobic exercise training (jogging, swimming, running, cycling) can improve lipid profile but the results are

inconsistent in terms of which lipid classes are improved by this intervention[160]. The most frequent observed change is a mild HDL-C elevation of approximately 5%, and a reduction of TG, especially in obese and/or patients with diabetes[161–163]. The effect of intensity or duration of the aerobic programs on lipid levels is controversial[164–166]. It seems that high-intensity interval training exerts similar lipid benefits as lower-intensity continuous training[167,168]. Meta-analyses found that, among different aerobic modalities, walking[169], endurance running[170] and cycling[171] are effective in improving lipid profile.

A meta-analysis demonstrated that resistance exercise can also lower TC, LDL-C and TG, and raise HDL-C in adults[172]. The quality of evidence is low so far to draw safe conclusions on whether the two modalities differ in their effect on lipid profile, or whether their combination is better that the two modalities separately[173,174]. Of note, the more enjoyable participation in recreational team sports, mainly soccer, was able to decrease TC and LDL-C levels[175,176].

The recommendations for physical activity and exercise in patients with dyslipidemia are presented in **Table 6**.

TABLE 6. Recommendations for physical activity and exercise in patients with dyslipidemia.

Recommendation	Class of recommendation
Regular physical activity can favorably alter lipids and lipoproteins. Patients with dyslipidemia must be encouraged to achieve at least 30 min/day of physical activity	I
A hypocholesterolemic effect can be attained by 40 min/day of moderate to intense aerobic training for >3 days/week	I
Moderate-intensity aerobic exercise 150 min/week, separated in sessions of 30 min, can favorably modify cardiometabolic health, including lipid profile	I
Muscle-strengthening resistance training should be considered at least twice per week at a moderate intensity.	IIa
Patients who are reluctant to follow structured exercise programs should be encouraged to participate in supervised recreational team sports activities	IIa

4 Clinical Pharmacology of Lipid-Lowering Drugs

4.1 Introduction

The correction of abnormal levels of blood lipids contributes significantly to the prevention of ASCVD. Therapeutic changes in diet and lifestyle are essential elements of overall ASCVD prevention, but once these changes fail, pharmacotherapy for the treatment of dyslipidemias becomes imperative.

4.2 Pathophysiology of Dyslipidemias

Lipoproteins are involved in 3 major metabolic pathways in the circulation: 1) the chylomicron pathway, responsible for the transport and distribution of food lipids; 2) the VLDL and LDL pathway, which is responsible for the transport and distribution of lipids synthesized in the liver; and 3) the HDL pathway, responsible for the transport and redistribution of cholesterol and other lipids among tissues, including the liver. Although these 3 pathways are distinct, they are all functionally interrelated. Many different proteins, such as apolipoproteins, enzymes, lipid transport proteins, lipoprotein receptors and lipid transporters, are involved in maintaining lipoprotein homeostasis in the circulation via these pathways[177].

TG-rich lipoproteins include chylomicrons, VLDL and their remnants. Chylomicrons are produced in the intestine. The dietary lipids absorbed by intestinal epithelial cells are transferred to apoB48 via microsomal transfer protein (MTP) to form chylomicrons, which are then secreted into systemic circulation through the lymphatic system. In the blood circulation, chylomicron TGs are hydrolyzed by lipoprotein lipase (LPL). This step converts chylomicrons into chylomicron remnants, which acquire apoE. ApoE mediates rapid clearance of chylomicron remnants by members of the LDL receptor (LDLR) superfamily. VLDL lipoprotein particles are synthesized in the liver[177]. Hepatic cholesterol and TG are transferred to apoB100 via hepatic MTP to form nascent VLDL particles that are secreted directly into the circulation. As in chylomicrons, VLDL-TG are hydrolyzed via LPL and are converted to IDL and then to LDL, which are also removed from members of the LDLR superfamily.

The amount of cholesterol present in peripheral tissues far exceeds the amount that these tissues can catabolize. Thus, there are mechanisms mediated by HDL to remove excess cholesterol and redistribute it to the sites that it is most needed. The biosynthesis of HDL occurs exclusively in circulation[178] via a complex route[179–181]. In the early stages of HDL synthesis, apoA1 interacts with the ATP-binding cassette transporter (ABCA1) gaining phospholipids and cholesterol. Through a series of poorly understood intermediate steps, the minimally lipidated apoA1 is gradually converted into HDL-like particles, which are then transformed into spherical particles by the action of lecithin:cholesterol acetyltransferase (LCAT). ApoA1, in both discoidal and spherical HDL particles, interacts functionally with the scavenger receptor B class 1 (SRB1), through which it delivers cholesterol to the liver and other tissues[179,182–184]. SRB1 is also known as the HDL receptor. Additional steps in HDL metabolism include the transfer of cholesterol esters to VLDL/LDL via CETP, the hydrolysis of phospholipids and residual TG by various lipases [such as LPL, HL and endothelial lipase (EL)] and transport of phospholipids from VLDL/LDL to HDL through the phospholipid transfer protein (PLTP)[177].

The pathological disturbances of lipoprotein metabolism include the increase in LDL-C, non-HDL cholesterol (non-HDL-C) and serum TG, which are all known to trigger ASCVD. Cholesterol deposition in the arterial wall is essential for the formation of the atherosclerotic plaque. Thus, increased cholesterol transport in the arteries through lipoproteins containing apoB (i.e., VLDL, lipoprotein remnants and LDL) may be considered as the main mechanism of atherosclerosis development. The reverse process, in which HDL removes excess cholesterol from the arterial wall and shuttles it to the liver, is protective against atherogenesis; other atheroprotective actions of HDL include antioxidant and anti-inflammatory properties[185,186].

Hypertriglyceridemia is associated with NAFLD, which in its more severe form, can lead to steatohepatitis and cirrhosis. Severe hypertriglyceridemia may lead to acute pancreatitis.

4.3 Categories of lipid-lowering drugs - Sites of action - Clinical pharmacology

Although the sites of actions (pharmacological targets) of lipid-lowering drugs differ, the central mechanism for

most of these agents focuses on the direct or indirect reduction of the intracellular amount of cholesterol in the hepatocytes. This effect then triggers the expression of LDLRs and increase their number on hepatocyte cell membrane, resulting in enhanced uptake of cholesterol-rich LDL particles from the bloodstream. Exceptions to this mechanism include newer lipid-lowering drugs targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) protein as well as drugs for the treatment of hypertriglyceridemia and homozygous FH (HoFH).

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), the rate-limiting enzyme in cholesterol biogenesis pathway in hepatocytes. Thus, statins reduce intracellular cholesterol synthesis as well as cholesterol stores, promoting the expression of LDLR on the surface of hepatocytes and the uptake of LDL from the circulation. Currently, there are 7 different statins available: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin and pitavastatin. Lovastatin and simvastatin are prodrugs (lactones), which are activated by hydrolysis and conversion to corresponding hydroxylic acid. Statins are well absorbed after oral administration and are metabolized by the liver. Except from pravastatin, statins are metabolized via CYP (mainly via 3A4), and this metabolic process is an important source of drug-drug interactions with drugs that affect hepatic metabolic enzymes, as is the permeability glycoprotein (P-gp). Drug interactions should always be considered when prescribing statin therapy. **Table 7** presents the possible interactions of statins with other drugs based on the recommendations of the American Heart Association[187]. **Table 8** presents the interactions of statins with Paxlovid™, an antiviral agent widely used in patients at high risk of a severe form of COVID-19[188].

Statins are well-tolerated, and their most common side effect is a transient and usually clinically insignificant increase in serum transaminases in about 1% of patients. In addition, a relatively rare adverse event of statins is an asymptomatic increase of CK, and even more rare the possibility of myositis and rhabdomyolysis. It should be emphasized, however, that well-localized muscular pain, as well as joint pain are not statin related. Muscular side effects are exacerbated when statins are combined with gemfibrozil. Patients on statin treatment (either monotherapy or in combination with other lipid-lowering drugs) should be informed about the possibility of statin-induced myositis, and thus the need to contact their doctor if they experience any musculoskeletal symptoms, generalized muscular discomfort, pain, tenderness or weakness.

Statins differ also in their potency, with atorvastatin and rosuvastatin being the most potent statins. It should be noted that, despite the effectiveness of statins in lowering LDL-C levels and ASCVD risk, residual ASCVD risk still remains, up to 70%, as reported by a previous meta-analysis[189].

Bile acid sequestrants (BAS) are either non-absorbable ion-exchange resins with positive charge (i.e., cholestyramine and colestipol) which bind the anions of bile salts in the intestinal tract by electrostatic forces, or non-absorbable polymers (non-anion exchange resins) such as colesevelam, which binds bile acids and form an insoluble complex. All resins act by disrupting the enterohepatic cycle and increasing the excretion of bile acids through the feces. The intestinal amount of bile acids is only 3-5 g, but as enterohepatic recycling takes place 5-10 times a day, an average of 20-30 g of bile acid is transported between the intestine and the liver every 24 hours. As the resins bind and drastically reduce the bile acid stores, an increased amount of hepatic cholesterol is converted to bile acids, resulting in a decrease in intracellular hepatic cholesterol concentration and an upregulation of LDLR expression. Consequently, the reduction of intrahepatic cholesterol triggered by resins is mainly responsible for their LDL-C lowering effect (up to 20-25%). However, there is a compensatory increase in hepatic TG production (via increased production and secretion of TG-rich lipoproteins), and thus these drugs are contraindicated in cases of severe hypertriglyceridemia[190].

BAS are generally insoluble and are administered as a suspension with water or orange juice. Their administration is associated with constipation, flatulence, anorexia, abdominal fullness, and occasional diarrhea, observed in up to 50% of the patients. These side effects are dose-dependent and may discourage the use of resins. The cationic resins cholestyramine and colestipol can also bind anionic drugs (such as warfarin, digoxin, thiazide diuretics, phenobarbitone and thyroid hormones), and therefore these drugs should be taken 1 hour before or 4 hours after resin ingestion to prevent reduced absorption. Resins also bind fat-soluble vitamins (A, D, E, K) in the intestine, predisposing to disorders such as prolongation of prothrombin time by lowering vitamin K levels. Colesevelam is more selective for intestinal bile acids compared with cholestyramine and colestipol, and is less likely to affect the absorption of other concomitantly used medications (but this possibility is not excluded)[191].

Ezetimibe inhibits the action of Nieman Pick C1 like 1 protein (NPCL1) in the intestinal tract. NPCL1 is the only cholesterol transporter in the intestine, which mediates the intake of dietary cholesterol. Approximately 30-70% of serum cholesterol is attributed to dietary cholesterol absorbed by the intestine. The net effect of reduced absorption of dietary cholesterol is the reduction of intracellular cholesterol concentration in the hepatocytes, which

TABLE 7. Summary of known interactions between statins and other drugs.

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Amiodarone	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of lovastatin	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of simvastatin	Combination may be considered
Amlodipine	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.8-fold increase in AUC of simvastatin	Combination may be considered
Conivaptan	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3-fold increase in AUC of lovastatin	Combination is potentially harmful
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3-fold increase in AUC of simvastatin	Combination is potentially harmful
Colchicine	Atorvastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination maybe considered
	Fluvastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Lovastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Pitavastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Pravastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination maybe considered
	Rosuvastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination is reasonable
	Simvastatin	Increased statin or colchicine exposure/ increased risk for muscle-related toxicity	Variable	Combination may be considered
Cyclosporine/ tacrolimus/ everolimus/ sirolimus*	Atorvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 6- to15-fold increase in AUC of atorvastatin	Combination may be considered
	Fluvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Moderate 2- to 4-fold increase in AUC of fluvastatin	Combination may be considered
	Lovastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5- to 20-fold increase in AUC of lovastatin	Combination is potentially harmful
	Pitavastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5-fold increase in AUC of pitavastatin	Combination is potentially harmful
	Pravastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 5- to10-fold increase in AUC of pravastatin	Combination may be considered
	Rosuvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 7-fold increase in AUC of rosuvastatin	Combination may be considered
	Simvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	Severe 6- to 8-fold increase in AUC of simvastatin	Combination is potentially harmful

TABLE 7. Summary of known interactions between statins and other drugs *(continued)*.

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Digoxin	Atorvastatin	Increased levels of digoxin	Minor 1.2-fold increase in AUC	Combination is reasonable
Diltiazem	Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 51% increase in AUC of atorvastatin	Combination is reasonable
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3.6-fold increase in AUC of lovastatin	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 4.6-fold increase in AUC of simvastatin	Combination may be considered
Dronedarone	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased statin exposure/increased risk for muscle-related toxicity	Unknown Expected to be similar to simvastatin 3.9-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased statin exposure/increased risk for muscle-related toxicity	Moderate 3.9-fold increase in AUC of simvastatin	Combination may be considered
Fenofibrate/ fenofibric acid	Atorvastatin	Potential increase in muscle-related toxicity	Insignificant 1.0-fold increase in AUC of atorvastatin	Combination is reasonable
	Fluvastatin	Potential increase in muscle-related toxicity	Specific data not available but magnitude likely to be minor	Combination is reasonable
	Lovastatin	Potential increase in muscle-related toxicity	Specific data not available but magnitude likely to be minor	Combination is reasonable
	Pitavastatin	Potential increase in muscle-related toxicity	Insignificant 1.2-fold increase in AUC of pitavastatin	Combination is reasonable
	Rosuvastatin	Potential increase in muscle-related toxicity	Insignificant 1.1-fold increase in AUC of rosuvastatin	Combination is reasonable
	Simvastatin	Potential increase in muscle-related toxicity	Insignificant 1.1-fold increase in AUC of simvastatin If taken at same time,1.05-fold increase	Combination is reasonable
Gemfibrozil	Atorvastatin†	Decreased metabolism of atorvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.4-fold increase in AUC of atorvastatin	Combination may be considered
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC of lovastatin	Combination should be avoided
	Pitavastatin†	Decreased metabolism of pitavastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.5-fold increase in AUC of pitavastatin	Combination may be considered
	Pravastatin	Decreased metabolism of pravastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2-fold increase in AUC of pravastatin	Combination should be avoided
	Rosuvastatin†	Decreased metabolism of rosuvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Minor 1.6- to 1.9-fold increase in AUC of rosuvastatin	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC of simvastatin	Avoid combination

TABLE 7. Summary of known interactions between statins and other drugs *(continued)*.

Interacting Agent	Statin	Effect	Magnitude	Recommendation
Ranolazine	Lovastatin	Increased statin exposure/increased risk for muscle-related toxicity	Specific data not available but likely similar to simvastatin, which is 1.9-fold increase in AUC	Combination may be considered
	Simvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.9-fold increase in AUC of simvastatin	Combination may be considered
Ticagrelor	Atorvastatin	Increased statin exposure/increased risk for muscle-related toxicity	Minor 1.4-fold increase in AUC	Combination is reasonable
	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Unknown but expected to be similar to simvastatin Moderate 2- to 3-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2- to 3-fold increase in AUC	Combination may be considered
Verapamil	Lovastatin	Decreased metabolism of lovastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 3.6-fold increase in AUC	Combination may be considered
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	Moderate 2.5-fold increase in AUC	Combination may be considered
Warfarin	Fluvastatin	Increased INR/potential for increased bleeding	Variable	Combination therapy is useful
	Lovastatin	Increased INR/potential for increased bleeding	Variable	Combination is useful
	Rosuvastatin	Increased INR/potential for increased bleeding	Variable	Combination is useful
	Simvastatin	Increased INR/potential for increased bleeding	Up to 30% change in INR	Combination is useful

Magnitude of drug-drug interactions based on AUC increase:
minor, >1.25 to <2
moderate, ≥2 to 4.9
and severe ≥5

AUC = area under the curve, INR = international normalized ratio

*Changes in magnitude of statin AUC are reported with cyclosporine. Limited data exist with tacrolimus, everolimus, and sirolimus.

†Use in combination is recommended only when other options have failed

in turn triggers an induction in LDLR expression. Ezetimibe is a prodrug which, after hepatic metabolism, is converted into an effective inhibitor of NPCL1, the glucuronide of ezetimibe (with a half-life of $t_{1/2}$ = 22 hours) that is excreted in the bile. It is effective as monotherapy and at a dose of 10 mg it causes a mean reduction of ≈17% in LDL-C. Ezetimibe is usually administered in combination with a statin, resulting in a further mean reduction of 14-23% in LDL-C concentration[192,193]. Its tolerability is similar to that of placebo, so ezetimibe has largely displaced bile acid binding resins in everyday clinical practice[190].

PCSK9 inhibitors increase the recycling of LDLRs to the cell membrane of the hepatocyte by reducing their degradation, since PCSK9 is the protein that marks the LDL receptor for catabolism. It follows that PCSK9 inhibition significantly increases the number of functional LDLRs on hepatocyte cell membrane, promoting a dramatic reduction of LDL-C in the circulation.

Currently, there are two human monoclonal antibodies in clinical use (i.e., alirocumab and evolocumab) targeting the PCSK9 protein. The Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial (ClinicalTrials.gov identifier, NCT01764633) showed that inhibition of PCSK9 by evolocumab resulted in a massive LDL-C decrease in patients treated with a combination of a statin and evolocumab[194].

TABLE 8. Interactions of statins with PaxlovidTM. *(Adapted from Vuorio et al[188])*

Lovastatin	Highly dependent on CYP3A metabolism	Contraindicated
Simvastatin	Highly dependent on CYP3A metabolism	Contraindicated
Rosuvastatin	Less dependent on CYP3A metabolism	Use the lowest possible dose
Atorvastatin	Less dependent on CYP3A metabolism	Use the lowest possible dose
Pravastatin	Not dependent on CYP3A metabolism	Recommended
Fluvastatin	Not dependent on CYP3A metabolism	Recommended

Briefly, mean LDL-C levels were maintained for 48 weeks at 30 mg/dL in the evolocumab-treated patients, leading to a significant 15% reduction of the primary end-point (a composite of CVD death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) compared with placebo[194]. Similarly, the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial (ODYSSEY Outcomes) (Clinicaltrials.gov identifier NCT01663402) showed that the composite primary end-point event (death from CHD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was significantly reduced by 15% in the alirocumab versus placebo group after a median follow-up of 2.8 years[195].

Even after this aggressive LDL-C lowering by statin-PCSK9 inhibitor combination, there is still a substantial residual ASCVD risk. Interestingly, accumulating evidence suggests that this residual risk exists even at very low levels of circulating LDL-C[196] and can be better quantified by non-HDL-C than by LDL-C[197]. No interactions of alirocumab and evolocumab with other drugs have been reported and their action does not appear to be influenced by hepatic metabolism. Alirocumab is administered at a dose of 75-150 mg every two weeks or 300 mg monthly, and evolocumab at a dose of 140 mg every two weeks or 420 mg monthly, as a therapeutic option for the treatment of primary hypercholesterolemia or mixed dyslipidemia, only if LDL-C remains at undesirably high levels despite the maximum dose of other hypolipidemic drugs (i.e., statins and ezetimibe).

In addition to the two monoclonal antibodies (i.e., alirocumab and evolocumab), a long-acting small interfering RNA (siRNA) PCSK9 inhibitor (inclisiran)[198] has already been approved [by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)] and chemical inhibitors[199] are under pharmaceutical development. Additionally, base editing to ablate expression of PCSK9 and thereby lower blood levels of LDL-C has been established in non-human primates and mouse models and the first human trial has been announced to start on 2023[200].

Inclisiran is a siRNA that acts by inhibiting the hepatic synthesis of PCSK9; its double-stranded molecule has a triantennary N-acetylgalactosamine (GalNAc) modification that ensures rapid uptake by the liver through the asialoglycoprotein receptors which are exclusively expressed on hepatocytes[201]. Inclisiran is then bound to the RNA-induced silencing complex in the cytoplasm, where it binds to the mRNA precursor of PCSK9, thus suppressing the expression of the *PCSK9* gene[201]. Importantly, via this mechanism of action, inclisiran acts specifically in the liver (where circulating PCSK9 is predominantly produced), thus maximizing its efficacy (by achieving sustained reductions of LDL-C in the long-term), and minimizing its systemic exposure and the risk of off-target inhibition[202]. Indeed, inclisiran was shown to provide durable and robust decreases of PCSK9 and LDL-C, when administered subcutaneously once every 6 months, after the initial and 3-month doses[203].

In detail, there are 3 phase III randomized controlled trials (RCTs) that established the efficacy, safety and tolerability profile of inclisiran[202]. The Trial to Evaluate the Effect of Inclisiran Treatment on Low Density Lipoprotein Cholesterol (LDL-C) in Subjects With Heterozygous Familial Hypercholesterolemia (HeFH) (ORION-9) trial included 482 HeFH patients (median age 56 years; 47% men; mean baseline LDL-C 153 mg/dL) that were randomized to receive subcutaneous injections of 300 mg inclisiran sodium or placebo on days 1, 90, 270, and 450[204]. Overall, 90.4% (436/482) of patients was on statins (73.8% on high-intensity statin) and 52.9% (255/482) on ezetimibe. At day 510, LDL-C was significantly reduced by 39.7% (95%CI -43.7 to -35.7) in the inclisiran group, whereas it increased by 8.2% (95%CI 4.3 to 12.2) in the placebo group (between-group difference -47.9%, 95%CI -53.5 to -42.3; p<0.001). Furthermore, the time-averaged percent change in LDL-C between day 90 and 540 was -38.1% (95%CI -41.1 to -35.1) in the inclisiran group and +6.2% (95%CI 3.3 to 9.2) in the placebo group (between-group difference -44.3%, 95%CI -48.5 to -40.1; p<0.001)[204]. Inclisiran was well-tolerated and adverse events did not differ between the 2 groups.

The Inclisiran for Participants With Atherosclerotic Cardiovascular Disease and Elevated Low-density Lipoprotein Cholesterol (ORION-10) trial included 1561 US patients with ASCVD (mean age 66 years; 69.4% men; mean baseline LDL-C 105 mg/dL) randomly assigned (in a 1:1 ratio) to receive either inclisiran sodium (300 mg) or placebo[205].

89.2% of patients were treated with a statin (68% received high-intensity statins), whereas only 9.9% were on ezetimibe. Each patient received 4 injections: on day 1, 90, 270 and 450; the end-of-trial visit was on day 540. At day 510, LDL-C increased by 1.0% in the placebo group, whereas it decreased by 51.3% in the inclisiran group (between-group difference -52.3%, 95%CI —-5.7 to -48.8; p<0.001)[205]. The time-adjusted change in LDL-C between day 90 and 540, as compared with baseline, was 2.5% with placebo and -51.3% with inclisiran (between-group difference -53.8%, 95%CI -56.2 to -51.3; p<0.001). Apart from mild injection-site adverse events, which were more common in the inclisiran group (1.7 vs 0.9%), no other differences were reported in side-effects between the 2 groups[205].

The Inclisiran for Subjects With ASCVD or ASCVD-Risk Equivalents and Elevated Low-density Lipoprotein Cholesterol (ORION-11) trial involved 1617 patients (from Europe and South Africa) with ASCVD (n=1414) or an ASCVD risk equivalent (n=203), defined as T2D (n=132), FH (n=30) or a 10-year Framingham Risk Score ≥20% (n=41)[205]. The mean age of the study population was 64.8 years, 71.7% were men and mean baseline LDL-C was 105 mg/dL. Overall, 94.7% of the patients were taking statins (78.6% of high intensity) and only 7.1% ezetimibe. The study design was the same as in ORION-10. On day 510, LDL-C increased by 4.0% in the placebo group and lowered by 45.8% in the inclisiran group (between-group difference -49.9%, 95%CI -53.1 to -46.6; p<0.001). The time-adjusted LDL-C change was 3.4% with placebo and -45.8% with inclisiran (between-group difference -49.2%, 95%CI -51.6 to -46.8; p<0.001). Mild reaction in the injection site was observed in 23 (2.8%) patients treated with inclisiran and in 3 (0.4%) patients on placebo. The rates of other adverse events did not differ between the 2 study groups[205].

Apart from lowering LDL-C, inclisiran can beneficially affect other lipid parameters. Indeed, in a meta-analysis of the above-mentioned 3 RCTs (involving a total 3660 patients with hypercholesterolemia), inclisiran was found to significantly decrease LDL-C by 51% (95%CI 48 to 53%; p<0.001) compared with placebo, which was related to a 24% lower rate of major adverse CV events (risk ratios 0.76; 95%CI 0.61 to 0.92)[206]. Inclisiran also significantly reduced TC (by 37%), apoB (by 41%), and non-HDL-C (by 45%) (all p<0.001). Of note, except for mild injection site reaction occurring more frequently in the inclisiran group, there were no other differences in adverse events, abnormalities in liver tests or CK levels between the 2 groups[206]. Currently, inclisiran is approved as an adjunct treatment to diet and maximally tolerated statin therapy (or other lipid-lowering drugs, if statins are not tolerated) for adults with HeFH or ASCVD who require additional LDL-C decrease[207,208]. The drug is administered at a dose of 300 mg inclisiran sodium as an initial subcutaneous injection, with a second dose given at 3 months, and then as a continued treatment every 6 months. A recent patient-level, pooled analysis of ORION-9, -10 and -11 suggested potential benefits for major adverse cardiovascular events (MACE) reduction, since inclisiran significantly reduced composite MACE [OR (95% CI): 0.74 (0.58–0.94)], but not fatal and non-fatal MIs [OR (95% CI): 0.80 (0.50–1.27)] or fatal and non-fatal stroke [OR (95% CI): 0.86 (0.41–1.81)]. [209]. The results of the ongoing phase III trial VICTORION-2P (ClinicalTrials.gov Identifier: NCT05030428), which evaluates the effect of inclisiran on major adverse CVD events in patients with ASCVD, will shed more light into the clinical usefulness of this new cholesterol-reducing drug.

Bempedoic acid is an oral non-statin LDL-C-lowering drug which inhibits cholesterol biosynthesis by acting in the same pathway as statins but at an earlier step[210]. In particular, bempedoic acid inhibits the activity of ATP citrate lyase, an enzyme located upstream 3-hydroxy-3-methyl-glutaryl-CoA reductase (which is the target of statins), leading to upregulation of LDLR, and thus reduction of LDL-C levels in the circulation[211]. Bempedoic acid is administered at a dose of 180 mg daily as a prodrug and is converted to active drug exclusively in the liver (but not muscles), thus minimizing the risk of muscle-related side-effects, such as myalgia and myopathy. Of note, based on available data, the drug does not have a diabetogenic effect[211]. Apart from lipid-lowering, bempedoic acid also exerts an anti-inflammatory effect by lowering high-sensitivity C-reactive protein (hsCRP)[210].

The efficacy of bempedoic acid has been evaluated both when given as monotherapy and when combined with other lipid-lowering drugs, and particularly statins and ezetimibe. Phase III trials with bempedoic acid are a part of the ongoing Cholesterol Lowering via Bempedoic acid, an ACL-inhibiting Regimen (CLEAR) trial series. Among them, the CLEAR Wisdom trial, randomized 779 patients at high-risk CV on maximally tolerated statin treatment (mean age 64.3 years; 36.3% women; mean baseline LDL-C 120 mg/dL) to bempedoic acid (180 mg) or placebo for 52 weeks[212]. Bempedoic acid decreased LDL-C levels significantly greater than placebo at week 12 [-15.1 vs +2.4%, respectively; difference, -17.4%, 95%CI -21.0 to -13.9%; p<0.001). Significant reductions were also observed in TC, non-HDL-C, apoB and hsCRP in bempedoic-treated patients compared with placebo[212]. The CLEAR Harmony trial included 2230 patients (1488 on bempedoic acid and 742 on placebo) with ASCVD (97.6%), HeFH (3.5%) or both (mean age 66.1 years; 73% men; mean baseline LDL-C 103 mg/dL)[213]. Patients were on maximally tolerated

statin therapy (49.9% high-intensity, 43.5% moderate-intensity), whereas 7.7% were taking ezetimibe and 3.6% a fibrate in addition to statins. At week 12, bempedoic acid reduced LDL-C by 16.5% (difference vs placebo in change from baseline, -18.1%, 95%CI -20.0 to -16.1; p<0.001)[213]. Efficacy findings were consistent, independently of the intensity of background statin therapy. Furthermore, the bempedoic acid plus ezetimibe fixed-dose combination was shown to reduce LDL-C significantly more than placebo (-38%; p<0.001), ezetimibe alone (-23.2%; p<0.001) or bempedoic acid monotherapy (-17.2%; p<0.001) in a 12-week phase III trial involving 301 high-risk patients (62.5% had ASCVD and/or HeFH) on maximally tolerated statin (mean age 64.3 years; 50.5% women; mean baseline LDL-C approximately 150 mg/dL)[214].

The CLEAR Outcomes trial is still ongoing and assesses the effect of bempedoic acid on major CV events in statin-intolerant patients with ASCVD or at high CV risk (ClinicalTrials.gov Identifier: NCT02993406).

Bempedoic acid has been approved by the FDA and the EMA in 2020 as an adjunct to diet and maximally tolerated statin therapy for the treatment of patients with established ASCVD or HeFH requiring further LDL-C lowering[215,216]. Bempedoic acid can be used alone as well as in combination with a statin or other lipid-lowering drugs in statin-intolerant patients[216]. A fixed-dose combination of bempedoic acid with ezetimibe is already available in some countries. Reported adverse effects of bempedoic acid include hyperuricemia, gout and tendon Achille rupture[217].

Fibrates (fibric acid derivatives) are activators of the nuclear receptor "peroxisome proliferator-activated receptor alpha" (PPAR-α) in the hepatocytes. Although the exact mechanism of action of fibrates is complex and not fully understood, they mainly reduce the secretion of hepatic VLDL and increase LPL activity, promoting the effective reduction of serum TG[218]. This class of drugs includes bezafibrate, ciprofibrate, fenofibrate and gemfibrozil. Fibrates increase the oxidation of fatty acids in both the liver and muscles. In the liver, these drugs reduce the secretion of TG-rich lipoproteins, while in the muscles they increase both LPL activity and the intake of fatty acids from the circulation.

Fibrates are well absorbed by the gastrointestinal tract, bound to plasma proteins, and are mainly excreted by the kidneys, either unchanged or in the form of metabolites. On average, fibrates reduce serum TG by 20-30% and serum TC by 10-15%. These drugs are contraindicated in cases of severely impaired hepatic or renal function. Rarely, fibric acid derivatives may cause myositis, mainly in patients with impaired renal function, or when administered in combination with a statin[218,219]. Fibrates enhance the effect of oral anticoagulants and are also likely to reversibly increase serum creatinine.

In terms of CV risk reduction, the evidence mainly supports a beneficial role for fibrates only in certain patient populations, especially in those with atherogenic dyslipidemia (e.g., metabolic syndrome, insulin resistance, T2D)[220]. For example, and with regard to fenofibrate, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study involved 9795 T2D patients (not on a statin at baseline) that were followed up for 5 years[221]. Fenofibrate led to a non-significant reduction of the primary endpoint (CHD death or non-fatal MI) compared with placebo (HR 0.89, 95%CI 0.75-1.05; p=0.16), including a significant 24% reduction in non-fatal MI (HR 0.76, 95%CI 0.62-0.94; p=0.010) and a non-significant increase in CHD mortality (HR 1.19, 95%CI .90-1.57; p=0.22)[221]. It has been suggested that fenofibrate effects may have been masked by almost double the use of lipid-lowering drugs (other than fenofibrate, e.g., statins) in the placebo group (36 vs. 19%)[220]. Of note, significant decreases were observed in coronary revascularisation (HR 0.79, 95%CI 0.68-0.93; p=0.003), albuminuria progression (p=0.002) and retinopathy needing laser treatment (5.2 vs 3.6%, p=0.0003) in fenofibrate group compared with placebo[221] . In the Action to Control Cardiovascular Risk in Diabetes (ACCORD)-Lipid trial (n=5518 T2D patients; mean follow-up 4.7 years), fenofibrate (as add-on to simvastatin) significantly lowered the risk of the primary outcome (non-fatal MI, non-fatal stroke or CVD death) by 28.6% compared with simvastatin and placebo, but only in the subgroup of patients with low HDL-C (≤34 mg/dL) and high TG (≥204 mg/dL)[222].

Pemafibrate is a novel, selective, PPAR-α agonist with a superior balance of efficacy and safety, due to its increased binding affinity to PPARα, thus achieving improved potency and safety profile via exerting specific effects on target genes, but not on off-target genes[223]. Among other advantages, pemafibrate is metabolized in the liver and excreted into the bile, whereas other available fibrates are predominantly excreted from the kidneys[224]. Furthermore, pemafibrate can improve liver tests and is less likely to deteriorate kidney function [i.e., decrease estimated glomerular filtration rate (eGFR) or increase serum creatinine], whereas available fibrates may worsen both hepatic and renal parameters[224].

With regard to clinical data, a pooled analysis of 6 RCTs (n=1253, with and without statin therapy) showed that pemafibrate 0.4 mg daily significantly decreased TG by approximately 50% in both groups compared with placebo at 12 weeks[225]. Similar results were found in another meta-analysis of 7 RCTs (n=1623) with significant improvements in TG, HDL-C, non-HDL-C levels, and the homeostasis model assessment of insulin resistance in the pemafibrate group

compared with placebo[226]. The benefits in lipid profile (i.e., reduction in TG and non-HDL-C, and increases in HDL-C) induced by pemafibrate were sustained over 52 weeks, as shown in the PROVIDE study[227]. The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) study was conducted in T2D patients with atherogenic dyslipidemia (i.e., TG≥200 mg/dL and HDL-C ≤40 mg/dL)[228]. However, this trial was stopped early as the results of a planned interim analysis showed that pemafibrate did not significantly reduce the incidence of CV events compared with placebo despite a significant decrease in TG, VLDL cholesterol, remnant cholesterol, and apo C-III levels[228].

Nicotinic acid and its derivatives reduce fatty acid production in tissues as well as hepatic secretion of VLDL and HDL clearance. They also enhance the activity of LPL. However, its use in everyday clinical practice has almost been abandoned due to the lack of niacin efficacy in preventing primary outcome events in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial (ClinicalTrials.gov number, NCT00120289)[229] and the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)[230]. The latter study showed that extended-release niacin with laropiprant (Tredaptive) was associated with an increased incidence of T2D and diabetes-related adverse events, as well as increased rates of serious adverse events related to the gastrointestinal and musculoskeletal system, skin, infections and bleeding[230]. Based on these findings, Tredaptive was withdrawn from the market in 2013[231]. It should be noted however that the evidence from the AIM-HIGH and the HPS2-THRIVE trials remain highly controversial due to design limitations[232,233]. Taking into consideration the data from the latest well-designed clinical trials in hypertriglyceridemic patients at risk for CVD (i.e. PROMINENT trial) and the inverse correlation between HDL-C levels and plasma TG levels, the clinical benefit for HDL-C raising therapies should be re-evaluated in hypertriglyceridemic subjects at increased CVD risk. As an example, niacin which, in addition to raising HDL-C by 30%, decreases TG by 30%, LDL-C by 14%, and Lp(a) by 32% is one such candidate[233].

Omega-3 fatty acids, EPA and DHA, are administered in the form of either TG, carboxyl esters or ethyl esters. They reduce both TG levels and VLDL-apoB-100 levels but have no clinical benefit for the treatment of hypercholesterolemia. It should be noted that omega-3 ethyl esters are likely to promote the conversion of VLDL to LDL, thus increasing the levels of LDL-C[234]. Omega-3 fatty acids were approved in several EU countries since 2000 for use after a heart attack at a dose of 1 g/day in combination with other drugs. At the time of their approval, the available data showed a benefit in reducing CHD events. However, in 2019 the EMA confirmed that omega-3 fatty acids containing a combination of EPA and DHA ethyl esters at a daily dose of 1 g are not effective in preventing recurrence of CHD events in patients who had previously suffered a myocardial infarction[235]. Therefore, these agents were no longer to be used for ASCVD prevention after a myocardial infarction, even though they are still being used for the treatment of hypertriglyceridemia at 2-4 g/day dose.

The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) (ClinicalTrials.gov number, NCT01492361), a multicenter, randomized double-blind study in hypertriglyceridemic patients, showed that daily administration of eicosapentaenoic acid ethyl ester (2 g twice a day) significantly reduced (by 25%) the incidence of ischemic episodes, stroke and CVD death compared with placebo after a median follow-up of 4.9 years[134]. However, patients treated with the drug experienced more frequent atrial fibrillation and minor bleeding episodes[236]. Both the FDA and the EMA have approved the use of EPA as an adjunctive therapy to reduce the risk of ASCVD events among statin-treated patients with hypertriglyceridemia (defined as TG ≥150 mg/dL) who have either established ASCVD or T2D plus ≥1 additional CV risk factors[237,238].

The Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) evaluated the effects of 4 g/day omega-3 fatty acids (EPA and DHA) or a matching corn oil comparator in 13,078 patients (mean age 62.5 years; 65% men; 56% with ASCVD; 70% with T2D; median TG 240 mg/dL; median LDL-C 75 mg/dL)[133]. This study was terminated early due to interim analysis showing a low probability for benefit with omega-3 fatty acids since the primary outcome (of CV death, MI, stroke, coronary revascularization or hospitalization for unstable angina) occurred in 12.0% of the omega-3 fatty acids group compared with 12.2% in the placebo group (p=0.84)[133]. Furthermore, patients on omega-3 fatty acids had a higher rate of gastrointestinal adverse events, investigator-reported new-onset atrial fibrillation and study drug discontinuation. A possible explanation for the different outcomes of these 2 clinical trials (i.e., REDUCE-IT and STRENGTH) could relate to the different omega-3 fatty acid formulations and comparators used (i.e., mineral vs corn oil)[133].

Since omega-3 fatty acids are incorporated into cell membranes, they can affect the functionality of biological membranes and the activity of transmembrane receptors (e.g., ability of ion channels to respond to stimuli). They

also have anti-inflammatory activity through competitive inhibition of cyclooxygenase and lipoxygenase activity, thereby reducing the conversion of arachidonic acid to proinflammatory eicosanoids, while also promoting the production of lipid mediators that activate the anti-inflammatory activity of resolvins[239]. Of note, statin-triggered production of specialized pro-resolving mediators has been proposed as a novel mechanism of statin-induced anti-inflammatory properties[240].

Lomitapide is approved for the treatment of HoFH in both the US and Europe. It inhibits the action of MTP, which catalyzes the transport of TG, cholesterol and phosphatidylcholine esters between biological membranes[241] and is essential for the synthesis and secretion of VLDL in the liver[242]. Lomitapide does not require the expression of a functional LDLR to reduce LDL-C levels. It was approved in 2013 following a phase 3 clinical trial (ClinicalTrials.govIdentifier: NCT00943306) in 29 adults showing a sustained reduction of up to 50% in LDL-C after 26 weeks[243]. Lomitapide is orally administered, absorbed easily, and undergoes extensive first-pass metabolism in the liver. It has a half-life of approximately 29 hours, consistent with the time required to achieve stable blood levels (i.e., 6 days), and its pharmacokinetics exhibit a dose-dependent relationship at doses between 10 and 50 mg following multiple dosing. The pharmacological effect of LDL-C lowering is stabilized after 14 days of continuous administration. Lomitapide use should be accompanied by a low-fat diet (fat <20% of total calories) to avoid fat malabsorption and diarrhea. Treatment with lomitapide increases serum transaminases and predisposes to severe hepatic steatosis and steatorrhea. Since lomitapide significantly inhibits the activity of P450 3A4 (CYP3A4), it may lead to significant drug-drug interactions that should be taken into consideration while prescribing lomitapide.

Volanesorsen is a chimeric antisense therapeutic oligonucleotide, targeting the mRNA of apoCIII, that has been approved by the EMA for the treatment of familial hyperchylomicronemia syndrome[244]. Approval was based on the results of the APPROACH trial (ClinicalTrials.gov Identifier: NCT02211209) in 66 participants with serum TG ≥750 mg/dL who were given once weekly volanesorsen 300 mg subcutaneously for 52 weeks[245]. Volanesorsen was found to reduce serum TG by up to 70%, but its long-term effects were not evaluated and remain yet unknown. The drug reduced pancreatitis in patients with a history of recurrent pancreatitis (≥2 events in the last 5 years). The main side effects were irritation at the site of injection and reduction in platelet numbers. No interactions with other drugs were observed[245].

Evinacumab is a monoclonal antibody against the angiopoietin-like protein 3 (ANGPTL3) that has been shown to halve LDL-C levels in patients with HoFH via an LDL-R independent mechanism[246]. In a phase III RCT involving 65 statin-treated patients with HoFH, evinacumab (administered intravenously every 4 weeks) significantly decreased LDL-C by 47.1% after 24 weeks, whereas it increased by 1.9% in the placebo group (between group difference: -49.0%, 95%CI -65.0 to -33.1%; p<0.001)[247]. Evinacumab has been approved for the treatment of HoFH by both FDA and EMA[248,249].

5 Lp(a) and ASCVD Risk

Lipoprotein (a) [Lp(a)] consists of an LDL particle to which a plasminogen-like glycoprotein, apo(a), is linked by a single disulfide bond. Apo(a) is encoded by the *LPA* gene and is highly polymorphic[250]. The basis for apo(a) size heterogeneity relates to a copy number variation in one of its protein domains, kringle IV type 2 (KIV-2), which exists in 5 to 50 identically repeated copies[250].

Plasma Lp(a) levels vary widely among individuals and are primarily genetically determined by variations in the *LPA* gene. Due to the structural homology of apo(a) to plasminogen, Lp(a) adversely influences fibrinolysis and exhibits pro-coagulant effects[251]. Furthermore, Lp(a) is proatherogenic due to its LDL moiety and promotes atherosclerosis at high plasma levels. Like LDL, Lp(a) enters the subendothelial space of the artery wall where it can be retained. A key role in the proatherogenic activities of Lp(a) may also be attributed to its content of oxidized phospholipids (OxPL) which are preferentially associated with this lipoprotein and exert a variety of pro-inflammatory effects[252]. In this regard, clinical studies support the hypothesis that the risk of ASCVD related to Lp(a) is, at least partially, driven by its OxPL content[252]. OxPL may also significantly contribute to the increased risk of aortic stenosis associated with Lp(a)[252,253].

Data from epidemiological databases, mendelian randomization studies and genome-wide association studies support the role of Lp(a) as a causal risk factor for ASCVD, linking Lp(a) levels to CV events[254]. Epidemiological studies suggest a log-linear relationship between circulating Lp(a) levels and the risk of ASCVD that is independent of other lipid measures and conventional risk factors. Furthermore, Mendelian randomization studies demonstrate that lifelong exposure to higher Lp(a) levels is causally associated with an increased ASCVD risk[255]. In this context, the causal association of Lp(a) with ASCVD risk was shown to be proportional to the absolute increase in plasma Lp(a) levels, and individuals with extremely high Lp(a) levels (i.e., >180 mg/dL; 64.2 mmol/L) may have an increased lifetime risk of ASCVD similar to HeFH patients[256]. According to genome-wide association studies, *LPA* variants are strongly related to increased Lp(a) levels and higher ASCVD risk[257]. Therefore, Lp(a) is an important ASCVD risk and a potential target for ASCVD prevention[255].

5.1 Use of Lp(a) in ASCVD risk stratification

Plasma Lp(a) levels are stable over time since they are genetically determined. Measurement of Lp(a) levels should be performed at least once in each individual's lifetime, to identify the presence of inherited very high levels of Lp(a) , and therefore a very high risk of ASCVD[1,254]. Lp(a) assessment can also help to identify individuals at ASCVD risk higher than that estimated by other lipid or lipoprotein measurements or reflected by the Hellenic-SCORE II[15] (**Figure 2**). Indeed, Lp(a) should be considered for reclassifying individuals at borderline between moderate and high 10-year ASCVD risk[1]. Furthermore, Lp(a) should be measured in patients with a family history of premature ASCVD (**Table 9**).

There are several methods for the determination of Lp(a) mass, but they are influenced by the variation in apo(a) isoform size[258]. Therefore, it is preferable to measure Lp(a) molar concentration (in nmol/L)[259].

5.2 Treating high Lp(a) levels

To date, there are no drugs available to drastically reduce plasma Lp(a) levels[254]. However, there are some lipid-lowering drugs that can lower Lp(a), in a nonspecific way, since they also decrease other lipid parameters, especially LDL-C[260]. In this context, nicotinic acid (niacin)

TABLE 9. Lp(a) determination for ASCVD risk stratification.

Recommendation	Class
Lp(a) levels are recommended to be measured at least once in each person's lifetime	I
Lp(a) assessment should be considered for the reclassification of patients having a borderline estimated 10-year ASCVD risk	IIa
Lp(a) levels are recommended to be measured in patients with a family history of premature ASCVD	I

ASCVD: atherosclerotic cardiovascular disease; Lp(a): lipoprotein(a)

decreases Lp(a) by 20-30%, however previous randomized trials did not provide evidence that this lowering effect reduces the ASCVD risk. CETP inhibitors and mipomersen exert similar effects on Lp(a) levels (i.e., reductions by 20-30%). In contrast, statins may affect plasma Lp(a) levels in various ways; some studies reported no effect, whereas others demonstrated an increase in Lp(a) levels (by 10-20%) after statin treatment[260]. Apheresis induces acute reduction of Lp(a) by >60% in parallel with LDL-C decrease[261].

PCSK9 inhibition by the monoclonal antibodies alirocumab and evolocumab, was reported to reduce plasma Lp(a) concentration by 20-30%[262]. A recent post hoc analysis of the ODYSSEY OUTCOMES trial with alirocumab, found that Lp(a) lowering contributed independently to ASCVD event reduction[263]. Inclisiran, a siRNA for the *PCSK9* gene in hepatocytes, can also reduce Lp(a) levels (by up to 25%)[264].

Although it is expected that lowering Lp(a) levels may translate into clinical benefit, it is unclear how much Lp(a) must be reduced to achieve significant ASCVD risk reduction. A previous Mendelian randomization study suggested that large absolute changes in Lp(a) levels are required for a significant reduction in the ASCVD risk[256]. Specifically, it was suggested that a decrease in Lp(a) concentration of >100 mg/dL is required to achieve a benefit equivalent to 39 mg/dL of LDL-C lowering[256]. Others proposed that reductions of >50% of baseline Lp(a) levels may be needed for potential ASCVD benefits to occur[260].

A large reduction in Lp(a) levels has been achieved with the use of the specific antisense oligonucleotide (ASO) pelacarsen [formerly known as IONIS-APO(a)-L_{Rx} or AKCEA-APO(a)-L_{Rx}] directed towards apo(a)[265]. In particular, in phase 1 and 2 trials, this antisense therapy selectively and dose-dependently lowered Lp(a) concentrations by approximately 90%[265]. In accordance to these results, the AKCEA-APO(a)-L_{Rx} Trial showed dose-dependent Lp(a) reductions with this specific ASO, reaching a maximum of 80%, in patients being under lipid-lowering therapy with statins, ezetimibe and PCSK9 inhibitors[266]. The pivotal phase 3 CV outcomes study of pelacarsen, Lp(a)HORIZON (NCT04023552), has reached 50% enrollment and is expected to firmly establish whether lowering Lp(a) will result into an ASCVD risk reduction[267].

TABLE 10. Effect of lipid-lowering therapeutic agents on Lp(a) levels.

Drug	Effect on Lp(a) levels
Statins	No significant effect or even increase up to 20%
Apheresis	Acute reduction by >60%
Nicotinic acid (niacin)	Reduction by 20-30%
PCSK9 inhibitors	Reduction by 20-30%
Inclisiran	Reduction by ~25%
CETP inhibitors	Reduction by 20-30%
Specific ASO towards apo(a)	Reduction by 80-90%
siRNA against apo(a)	Reduction by 80-98%

ASO: antisense oligonucleotide; CETP: cholesteryl ester transfer protein; Lp(a): lipoprotein(a); PCSK9: proprotein convertase subtilisin/kexin type 9, siRNA: small interfering RNA

Olpasiran is a N-acetylgalactosamine-conjugated siRNA designed to directly inhibit LPA mRNA translation in hepatocytes. In a phase 1 dose-escalation trial (ClinicalTrials.gov: NCT03626662), olpasiran at doses of 9 mg or higher reduced Lp(a) levels by 71–97%[268]. In the double-blind placebo-controlled phase 2 OCEAN(a)-DOSE clinical study, olpasiran was given at doses up to 225 mg subcutaneously every 12 weeks in 281 adult patients with Lp(a) concentration>150 nmol/L and evidence of ASCVD resulting to a significant reduction in Lp(a) of ≤90%[269,270]. Olpasiran effects on CV events will be examined in a phase III trial. Another siRNA, SLN360, dose-dependently reduced Lp(a) concentration up to 98% in a phase I trial including 32 participants with elevated Lp(a) levels and no known CVD[271].

Currently, the only option for patients at risk with high Lp(a) levels is an intensified treatment of the modifiable risk factors, and primarily LDL-C. In difficult cases, LDL apheresis is the treatment of choice[272].

Table 10 summarizes the effects of lipid-lowering drugs on Lp(a) levels.

6 Familial Combined Hyperlipidemia (FCHL)

FCHL constitutes the most prevalent familial hyperlipidemia, with an incidence of 1-2% of the general population and 20-35% of patients with a history of myocardial infarction[273]. This entity was described for the first time simultaneously by Goldstein et al., Hazzard et al., and Kwiterovich et al[274]. The usual phenotype of FCHL consists of mixed hyperlipidemia, hypercholesterolemia or hypertriglyceridemia in combination with high levels of apoB100[274]. This phenotype variability might also be observed in the same individual at different time periods. FCHL is associated with other metabolic-related disorders such as abdominal obesity, insulin resistance, T2D, arterial hypertension, NAFLD and metabolic syndrome[275]. The disease is characterized by phenotypic fluctuations in the same family (up to 50% of the offspring), high levels of apoB100 and the presence of premature CHD. The combination of serum apoB100 >120 mg/dL and TG >133 mg/dL (1.5 mmol/L) as well as family history of premature CHD are sufficient for the diagnosis of FCHL[276].

FCHL is an oligogenic entity with variable penetrance[277,278]. The fluctuating lipid profile of FCHL is the result of interaction between genetic variants, modifying LDL-C and TG levels, and environmental factors. Loci on chromosomes 1q 21-23, 11p 14.1-q12.1, 16q22-24.1 have been associated with onset of the disease[279]. One of the genes in region 1q 21-23 is the upstream transcription factor 1 gene (USF1) that regulates the expression of several enzymes and lipoproteins involved in lipid and glucose metabolism, through the activation of nearly 40 genes[280–283]. Furthermore, the *ANGPTL3* gene and several single-nucleotide polymorphisms (SNPs) have been associated with FCHL[284].

The main disorder of FCHL is a disbalance between de-novo lipogenesis and b-oxidation of free fatty acids, in favor of the former, resulting in hepatic fat accumulation and VLDL overproduction. Apart from the increased production of VLDL particles, major pathophysiological mechanisms of FCHL are decreased clearance of VLDL particles[273], as well as increased production and impaired clearance of apo B[285]. Also, oxidative stress[286] and vascular inflammation[287] are increased in individuals with FCHL. Previous studies have shown elevated plasminogen activator inhibitor type 1 (PAI-1) levels in FCHL, being associated with IR and metabolic syndrome features, as well as increased carotid intima thickness and decreased adiponectin levels, all of which are surrogate markers of ASCVD risk[287,288]. FCHL shares metabolic and biochemical disorders with metabolic syndrome, IR, T2D and NAFLD, thus being related to increased ASCVD risk (especially CHD)[274,289–291]. In this context, it is estimated that 10-14% of patients with early CHD have FCHL[274,292].

Similar to the general population, hypolipidemic treatment initiation and goals in patients with FCHL are based on the HellenicSCORE II tables (**Figure 2**)[1,15]. Emphasis should be placed on the family history of CHD and the coexistence of high LDL-C and TG levels, which further increase the risk of CHD, to decide on treatment intensity. Statins constitute the treatment of choice. The addition of ezetimibe, PCSK9 inhibitors, fibrates and omega-3 fatty acids follows the same principles as in the general population.

7 Familial Chylomicronemia Syndrome (FCS)

FCS is a rare hereditary, autosomal recessive disorder of the metabolism of TG-rich lipoproteins with an incidence of 1/1,000,000 worldwide, usually occurring during childhood[293]. Disease-related mutations have been reported in 6 genes [i.e., *LPL, apoCII, apoA5, LMF1, GPIHBP1, and G3PDH1 (GPD1)*] which, in their homozygous form or in combined heterozygosity, lead to impaired clearance of chylomicrons and therefore to severely increased plasma TG levels. These mutations are responsible for 2/3 of FCS cases[294].

Another more common clinical entity, characterized by high TG levels, that is indistinguishable from FCS, is the multifactorial chylomicronemia syndrome (MCS). It is characterized by the combination of heterozygous loss of function mutations in responsive genes with co-morbidities that result in increased plasma TG concentrations (such as uncontrolled T2D, obesity, hypothyroidism, pregnancy) and environmental factors (alcohol abuse, malnutrition and drugs including glucocorticoids, ethinylestradiol, and neuroleptics). After an overnight stay of serum within test tube, there is a characteristic milky floating layer above the other plasma components that remain turbid[293].

According to the Fredrickson classification, most FCS patients have type V, rather than type I, phenotype[295]. Clinical manifestations involve abdominal pain of varied intensity and recurrent episodes of acute pancreatitis that may lead to chronic pancreatitis, pancreatic insufficiency and type 3c diabetes[296]. The risk of incident acute pancreatitis rises by 4% for every 100 mg/dL (1.1 mmol/L) increase in TG levels[297]. Other clinical features include transient eruptive xanthomas of the trunk and extremities, retinal lipemia (i.e., a milky appearance of the retinal vessels), hepatosplenomegaly, as well as neurological symptoms (e.g., irritability, memory disorders, dementia and depression)[298].

The distinction between FCS and MCS is difficult since they have the same clinical and biological phenotype. Diagnosis is guided by the consideration of several parameters. For example, FCS, unlike MCS, is a monogenic disorder with constant serum TG levels >885 mg/dL (10 mmol/L) and reduced LPL activity following heparin stimulation, although, this test is rarely performed in clinical practice. In MCS, plasma TG levels vary and can be lowered after diet and fibrate therapy, which is not the case with FCS. FCS occurs in younger patients, without secondary factors, except for pregnancy and contraceptive oral oestrogen use, while individuals with MCS are typically overweight with Metabolic syndrome. Furthermore, acute pancreatitis is more common in FCS than in MCS patients, where a low-fat diet usually reduces serum TG levels[299]. A diagnostic score based on 8 biological/clinical parameters has been proposed to help distinguish FCS and MCS, as a reliable phenotypic tool until next-generation sequencing is widely available[298] (**Table 11**).

The main therapeutic goal is the reduction of acute pancreatitis risk by TG-lowering <500 mg/dL. A strict hy-

TABLE 11. FCS: A practical diagnostic scoring system (parameters in non-acute setting).

1.	Fasting TG >885 mg/dL (10 mmol/L) for 3 consecutive measurements (+5) Fasting TG >1770 mg/dL (20 mmol/L) at least once (+1)
2.	Previous fasting TG <177 mg/dL (2 mmol/L) (-5)
3.	Absence of secondary factors (except pregnancy and ethinylestradiol use) (+2)
4.	History of pancreatitis (+1)
5.	Unexplained recurrent abdominal pain (+1)
6.	No history of familial combined hyperlipidemia (+1)
7.	No response (defined by TG decrease <20%) to hypolipidemic treatment (+1)
8.	Onset of symptoms at: < 40 years (+1) < 20 years (+2) < 10 years (+3)

FCS score:
≥10: FCS very likely
≤ 9: FCS unlikely
≤ 8: FCS very unlikely

Secondary factors include alcohol, diabetes, metabolic syndrome, hypothyroidism, corticosteroid therapy and drugs.

If diagnosis made during pregnancy, a second assessment is necessary to confirm the diagnosis at post-partum.

FCS: familial chylomicronemia syndrome; TG: triglycerides

polipidemic diet is often the cornerstone of management, but it is not always sufficient to prevent recurrences of acute pancreatitis. Most TG-lowering drugs, such as fibrates and fish oils, are not effective in FCS. New therapeutic approaches such as apoCIII ASOs[300,301] and ANGPTL3 ASOs or monoclonal antibodies, are under investigation[302–304]. Volanesorsen, an ASO inhibitor of apoCIII, has been licensed for treatment of FCS by the EMA[305].

8 Familial Dysbetalipoproteinemia

Familial dysbetalipoproteinemia or type III hyperlipoproteinemia or hyperlipoproteinemia of remnants is characterized by the marked accumulation of cholesterol-enriched remnant lipoproteins particles of hepatic and intestinal origin. It is an extremely atherogenic dyslipoproteinemia[306] and quite rare, with a prevalence of 0.4% in men and 0.2% in women (mainly after menopause not using hormone therapy), as reported by The Lipid Research Clinics survey[307]. It is an autosomal recessive disease with varied penetration.

This metabolic disorder is related to the course and clearance of chylomicrons and VLDL particles (TG-rich apoB lipoproteins) from the liver[308]. The accumulation and enrichment in cholesterol of these particles, as they acquire excess cholesterol ester during their prolonged stay in the circulation, leads to increased cholesterol/TG and cholesterol/apoB ratios as well as pathological electrophoretic properties of remnants. The number of LDL particles is not raised and total plasma apoB levels are within normal range, due to the impaired conversion of VLDL to LDL[309]. This is the only dyslipidemia in which ASCVD risk is not directly related to apoB concentration.

A large proportion of patients are homozygous for apoE2 isoform. ApoE2, unlike E3 and E4 isoforms, has low binding affinity for hepatic receptors influencing the degradation of chylomicrons and VLDL particles. ApoE2 homozygosity alone is not sufficient for the development of familial dysbetalipoproteinemia. The presence of a co-morbidity with increased TG-rich lipoprotein production is required, such as FCHL, T2D, obesity, drugs or hypothyroidism.

Lipidemic profile is characterized by an increase in serum TC and TG levels of about 620-885 mg/dL (7-10 mmol/L). In severe cases, patients present with xanthomas on palms and wrists as well as tuberous xanthomas over the elbows and knees. The disease is related with an increased risk for early CHD and accelerated atherosclerosis of the femoral and tibial arteries[310].

The diagnosis of familial dysbetalipoproteinemia is traditionally based on plasma ultracentrifugation and electrophoresis, revealing a broad β-VLDL bundle. Ultracentrifugation derived ratios VLDL/TG ≥0.30 and VC/VT ≥0.35 (VC: cholesterol of the chylomicrons and VLDL; VT: TGs of the chylomicrons and VLDL) for serum TG levels ranging from 150 to 1000 mg/dL (1.7 to 11.3 mmol/L) are diagnostic[311,312]. The ratios of TC/apoB >6.2 together with TG/apoB <10 can also be used for diagnosis[309].

Familial dysbetalipoproteinemia should be treated promptly after the diagnosis. Typical therapy consists of a statin and the addition of a fibrate if plasma TG levels remain elevated. Management of the underlying exacerbating cause is mandatory.

9 Lysosomal Acid Lipase Deficiency (LAL-D)

LAL-D is a rare autosomal recessive lysosomal storage disease. Mutations of the LIPA gene markedly impair the activity of LAL. LAL catalyzes the intracellular hydrolysis of cholesteryl esters and TG of LDL particles into free cholesterol and free fatty acids[313,314]. LAL deficiency leads to a progressive concentration of cholesterol esters and TG in the liver, spleen, joints, macrophages, vessel wall, and other organs[315,316].

LAL-D is rare (1:175,000) and manifests with 2 phenotypes according to the degree of LAL deficiency depending on the type of mutation. The most severe phenotype with complete LAL deficiency (Wolman disease) presents early in infancy with growth failure, vomiting, diarrhea, hepatomegaly, malabsorption, and hepatic insufficiency, leading to death in the first 12 months[317]. The less severe phenotype is characterized by residual activity of LAL (CESD: cholesteryl ester storage disease), occurs in children and adults and is characterized by high levels of LDL-C and decreased HDL-C, transaminase elevation and hepatomegaly[317]. The lipid profile is similar with this of familial dyslipidemias, such as HeFH and FCHL which are distinguished based on a detailed family history. The diagnosis of LAL-D can be established by identification of deficient LAL activity or mutations in the LIPA gene.

LAL-D reduces life expectancy. In 2015 long-term enzyme replacement therapy with recombinant human enzyme LAL sebelipase alfa was approved for the management of LAL-D, administered intravenously every 2 weeks[318]. Treatment with sebelipase alfa improves dyslipidemia, lipid concentration in lysosomes, and hepatic abnormalities[319]. The effect remains stable during long-term use[320]. Treatment increases survival and improves symptomatology in both infants and adults[321].

10 Homozygous Familial Hypercholesterolemia

HeFH is now considered to affect one in 200-250 births, which make this disease the most common monogenic disorder[322–326]. HoFH occurs in one of 160,000-300,000 births[327]. HoFH patients may have the same mutation in both alleles of the same gene, different mutations in each allele of the same gene (compound heterozygotes) or mutations in two different genes affecting LDLR function (double heterozygotes) (**Figure 3**).

Frequently, the phenotypes of HeFH and HoFH overlap. This happens because the phenotype of FH is influenced by many factors such as heterogeneity of monogenic causes, heterogeneous and polygenic variant classes, gene-gene and gene-environment interactions, epigenetic effects, and others. Additionally, plasma LDL-C concentrations are affected not only by large-effect monogenic variants but also by small-effect gene variants[328,329]. For example, the severity of hypercholesterolemia phenotype in double heterozygotes (one *LDLR* and one *apoB* mutations, **Figure 3**) is between HeFH and HoFH[330]. The most severe phenotype in some carriers of the same HeFH mutation can be due to an additional influence of *apoE* gene polymorphisms[331,332]. The influence of environmental parameters may occur within the affected members of the same family with various plasma LDL-C levels among examined patients and more distant relatives.

HoFH clinical manifestation is characterized by ex-

TABLE 12. Simon Broome Register criteria for FH diagnosis.

FH DIAGNOSIS	CLINICAL CRITERIA
Definite	LDL-C in adults >190 mg/dL (4.9 mmol/L) LDL-C in children >155 mg/dL (4.0 mmol/L) plus DNA-based* evidence or tendon xanthomas in the patient or in a first- or second-degree relative
Possible	Family history of myocardial infarction at an age of <50 years in a second-degree relative or at an age of <60 years in a first-degree relative or Family history of LDL-C in adult first- or second-degree relative >190 mg/dL (4.9 mmol/L) or >155 mg/dL (4.0 mmol/L) in a child or sibling aged <16 years

*DNA-based evidence of an *LDLR*, *apoB* and *PCSK9* mutations

FH: Familial Hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; *LDLR*: low-density lipoprotein receptor gene; *apoB*: apolipoprotein B gene; *PCSK9*: proprotein convertase subtilisin/kexin type 9 gene

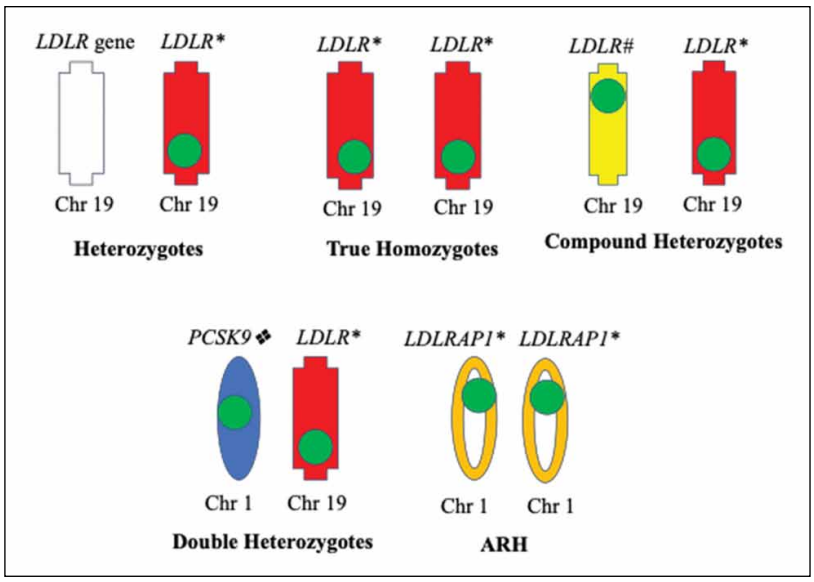

FIGURE 3. Combination of genetic mutation showing homozygous familial hypercholesterolemia phenotype.

*, #, ❖ = pathogenic mutations, Chr = chromosome, ARH = Autosomal recessive hypercholesterolemia. Same mutation in the same gene = True homozygote; Different mutations in the same gene = Compound heterozygotes; Combination of mutations in different genes = Double heterozygotes.

TABLE 13. The MEDPED criteria for FH diagnosis.

Age (years)	1-degree relative TC in mg/dL	2-degree relative TC in mg/dL	3-degree relative TC in mg/dL	General Population TC in in mg/dL
<20	220	230	240	270
20-29	240	250	260	290
30-39	270	280	290	340
≥40	290	300	310	360

MEDPED: US Make Early Diagnosis to Prevent Early Deaths; FH: Familial Hypercholesterolemia; TC = total cholesterol

tensive xanthomas, marked premature and progressive ASCVD and TC >500 mg/dL (12.9 mmol/L). Most patients develop CHD and aortic stenosis before the age of 20 and die before the age of 30 years. Thus, elevated plasma LDL-C concentration, tendon xanthomas or corneal arcus, and personal or family history of premature CHD have been applied to develop guidelines for identification of patients with FH. The most widely used are United Kingdom Simon Broome Register criteria (**Table 12**) and the Dutch Lipid Clinic Network criteria[333] (**Table 18**).

The less widely used are the US Make Early Diagnosis to Prevent Early Death (MEDPED) criteria[334] (**Table 13**) and the definition of severe FH by International Atherosclerosis Society[335] (**Table 14**).

Additionally, there are criteria for the diagnosis of HoFH from the American Heart Association[336] (**Table 16**) and the EAS[337] (**Table 15**).

TABLE 14. International Atherosclerosis Society criteria for the diagnosis of FH.

CLINICAL CRITERIA
1. Untreated LDL-C >390 mg/dL
2. Untreated LDL-C >310 mg/dL and one high-risk feature
3. Untreated LDL-C >190 mg/dL and two high-risk features*

*High-risk features are: age >40 years without treatment; cigarette smoking; male gender; lipoprotein(a) >75 nmol/L (30 mg/dL); HDL-C <40 mg/dL; hypertension; diabetes; family history of early cardiovascular disease in first-degree relatives (of age <55 years in men and of <60 years in women); chronic kidney disease (i.e., estimated glomerular filtration rate of <60 mL/min/1.73 m^2; and a body mass index of >30 kg/m^2.

FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol

TABLE 15. European Atherosclerosis Society criteria for the diagnosis of HoFH.

- Genetic confirmation of 2 mutant alleles at the LDLR, apoB, PCSK9, or LDLRAP1 gene locus.
- OR
- Untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥310 mg/dL (8 mmol/L)* together with either cutaneous or tendon xanthomas before the age of 10 or untreated elevated LDL-C levels consistent with HeFH in both parents.

* These LDL-C levels are only indicative; lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH.

HoFH: Homozygous Familial Hypercholesterolemia; LDLR: low-density lipoprotein receptor gene; apoB: apolipoprotein B gene; PCSK9: proprotein convertase subtilisin/kexin type 9 gene; LDL-C: low-density lipoprotein cholesterol

10.1 Homozygous familial hypercholesterolemia treatment

Early identification and prompt referral to a lipid clinic is vital. Management of HoFH should involve a combination of healthy lifestyle, statin + ezetimibe treatment started as early as possible, and lipoprotein apheresis (preferably by the age of 5 and not later than 8 years). Nowadays, several drug therapeutic options are available for patients

TABLE 16. American Heart Association criteria for the diagnosis of HeFH and HoFH.

ICD-10 Category HeFH (E78.01)	LDL-C ≥160 mg/dL (4.1 mmol/L) for children LDL-C ≥190 mg/dL (4.9 mmol/L) for adults and with one first-degree relative similarly affected or with premature atherosclerotic cardiovascular disease or with positive genetic testing for an LDL-C-raising gene defect (LDLR, apoB or PCSK9)
ICD-10 Category, HoFH (E78.01)	LDL-C ≥390 mg/dL (10 mmol/L) and one or both parents with clinically diagnosed FH, positive genetic testing for an LDL-C rise gene defect (LDLR, apoB or PCSK9), or autosomal-recessive FH If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >390 mg/dL (10 mmol/L) with aortic valve disease or xanthomas at <20 years of age, HoFH is highly likely
ICD-10 Category, Family History of FH (83.42)	The presence of a first-degree relative with confirmed FH

FH: Familial Hypercholesterolemia; HoFH: Homozygous Familial Hypercholesterolemia; HeFH: Heterozygous Familial Hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; *LDLR*: low-density lipoprotein receptor gene; *apoB*: apolipoprotein B gene; *PCSK9*: proprotein convertase subtilisin/kexin type 9 gene

TABLE 17. Recommendations for the management of dyslipidemia in patients with HoFH.

Recommendations	Class of recommendation
At diagnosis, CV risk must be assessed, and treatment must be started as soon as possible	I
Some patients will require lipoprotein apheresis preferably by the age of 5 and not later than 8 years	I
In primary prevention, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL (<1.4 mmol/L) should be considered for individuals with HoFH at very high risk	IIa
In primary prevention, HoFH patiets should achieve an LDL-C <70 mg/dL and ≥50% decrease from baseline	IIa
In secondary prevention, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <55 mg/dL (1.4 mmol/L) is recommended	I

HoFH: Homozygous Familial Hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol

with HoFH. Patients may need 3 or more drugs to reach LDL-C goals[338–340]. In secondary prevention, LDL-C should be reduced by ≥50% from baseline and <55 mg/dL (<1.4 mmol/L)[1]. HoFH patients at very high risk have the same LDL-C targets. In primary prevention, HoFH patients should achieve an LDL-C <70 mg/dL and ≥50% decrease from baseline (**Table 17**).

According to several guidelines, statins are the first-line drug therapy for patients with FH[1,322,326,335–337,341,342]. A high dose of high potency statin (atorvastatin or rosuvastatin) is recommended. Ezetimibe should always be added. The addition of PCSK9 inhibitors or inclisiran, a long-acting siRNA inhibitor of PCSK9 synthesis, may lead to further reduction of LDL-C levels. However, patients with HoFH may have a variable LDL-C response, which is dependent on residual LDLR activity; no response may be observed in patients with receptor null or negative mutations[343]. Evinacumab, an ANGPTL3 inhibitor, is also effective for LDL-C reduction in patients with HoFH and has been approved by both the FDA and the EMA for HoFH treatment[247–249]. Lomitapide should be considered as additional treatment for further LDL-C lowering[337].

Liver is the most important organ for the clearance of LDL particles. Thus, liver transplantation should correct the molecular defect and decrease plasma LDL-C levels[334–337]. Until now, liver transplantation is the only definitive therapy available for patients with HoFH and is considered after the presentation of ASCVD. Liver transplantation performed before the onset of ASCVD is not recommended, due to several adverse events (e.g., operative complications, post-transplantation surgical complications and mortality, infections, transplant rejection, de novo autoimmunity, primary sclerosing cholangitis, vascular and biliary complications, chronic hepatitis and side effects and life-long immunosuppressive therapy)[337]. Another disadvantage of liver transplant is the lack of donors. Orthotopic liver transplantation may be recommended in younger HoFH patients when lipoprotein apheresis is not available, or cannot be tolerated, and plasma LDL-C is not satisfactory controlled with intensive pharmacotherapy[334].

In women with HoFH, contraception and pregnancy should be discussed. Women wanting to become pregnant should be counselled and undergo detailed CV risk evaluation[337]. Hormonal contraception is generally contraindicated in HoFH, and thus other contraceptive methods are preferred. Surgery may be considered to remove large cutaneous or tuberous xanthomas for either functional or cosmetic reasons.

11 Heterozygous Familial Hypercholesterolemia

HeFH is a common autosomal dominant genetic disease, affecting approximately 1 in 200-300 adults[344]. HeFH is caused by mutations in one of the genes critical for LDL receptor-mediated catabolism of LDL, involving the *LDLR, apoB and PCSK9*[345]. The main characteristic of patients with HeFH is the increased incidence of early onset ASCVD. CHD presents during the 4th to 5th decade of life in HeFH men and during the 5th to 6th decade of life in HeFH women. Without treatment, approximately 85% percent of male patients at the age of 60 years will have suffered a myocardial infarction[346]. Peripheral arterial disease (PAD) is also 6 times more prevalent in patients with HeFH compared with normolipidemic controls, whereas, notably, cerebrovascular disease does not appear to be more frequent in HeFH[347]. The diagnosis of HeFH is made based on family and clinical history, physical examination, LDL-C levels, and genetic testing. The Dutch Lipid Clinic Network criteria are frequently used to establish the diagnosis of HeFH (**Table 18**)[348]. First-degree relatives should be evaluated for the presence of HeFH (family screening) since they have a 50% probability to suffer from the disease.

In patients with HeFH and established ASCVD, T2D or stage 4-5 CKD, LDL-C target is <55 mg/dL[1]. In patients with HeFH but without these comorbidities, LDL-C target is <70 mg/dL[1]. All HeFH patients should be counseled to implement lifestyle changes that decrease LDL-C levels, including exercise, low-fat diet, and weight loss. Other concomitant CV risk factors should be treated aggressively (hypertension, diabetes, smoking).

Statins are the mainstay of treatment of HeFH and the

TABLE 18. Dutch Lipid Clinic Network diagnostic criteria for FH.

Criteria	Points
1) Family history	
First-degree relative with known premature (men: < 55 years, women: < 60 years) coronary or vascular disease, or	1
First-degree relative with known LDL-C levels above the 95th percentile	2
First-degree relative with tendinous xanthomata and/or arcus cornealis, or	
children < 18 years of age with LDL-C above the 95th percentile	
2) Clinical history	
Patients with premature (men: <55 years, women: <60 years) coronary artery disease	2
Patients with premature (men: <55 years, women: <60 years) cerebral or peripheral arterial disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before the age of 45 years	4
4) LDL-C levels	
LDL-C >325 mg/dL	8
LDL-C 251-325 mg/dL	5
LDL-C 191-250 mg/dL	3
LDL-C 155-190 mg/dL	1
5) DNA analysis	
Functional mutation in the *LDLR*, *apoB* or *PCSK9* gene	8

Choose only one score per group, the highest applicable.

Diagnosis (based on the total number of points obtained):
"Definite" FH diagnosis: > 8 points
"Probable" FH diagnosis: 6-8 points
"Possible" FH diagnosis: 3-5 points

FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; LDLR: low-density lipoprotein receptor; PCSK9: proprotein convertase subtilisin/kexin type 9

TABLE 19. Recommendations for the management of dyslipidemia in patients with HeFH.

Recommendation	Class of recommendation
The Dutch Lipid Clinic Network criteria must be used to establish the diagnosis of HeFH	I
First-degree relatives of patients with HeFH must be evaluated for the presence of FH	I
In patients with HeFH and established ASCVD, LDL-C target is <55 mg/dL and a ≥50% reduction from baseline LDL-C levels must be considered	I
In patients with HeFH and T2D or stage 4-5 CKD, LDL-C target is <55 mg/dL and a ≥50% reduction from baseline LDL-C levels should be considered	IIa
In patients with HeFH but without these comorbidities, LDL-C target is <70 mg/dL	IIa
The most potent statins at the maximal tolerated dose mut be used to achieve the LDL-C target (atorvastatin 40-80 mg or rosuvastatin 20-40 mg)	I
In patients with HeFH who do not reach LDL-C targets despite treatment with the highest recommended or tolerable dose of a potent statin, adding ezetimibe must be considered	I
In patients with HeFH who do not achieve LDL-C targets despite statin/ezetimibe combination treatment, adding a PSCK9 inhibitor must be considered	I
In patients with HeFH who do not achieve LDL-C targets despite statin/ezetimibe combination treatment, adding a bile acid sequestrant or bembedoic acid may be considered	IIb

HeFH: familial hypercholesterolemia; ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; T2D: type 2 diabetes; CKD: chronic kidney disease; PCSK9: proprotein convertase subtilisin/kexin type 9

most potent statins at the maximal tolerated dose should be used (atorvastatin 40-80 mg or rosuvastatin 20-40 mg). In a cohort study of 2,146 patients with FH without established CHD followed-up for 8.5 years, statin treatment reduced the risk for CHD by 76%[349]. Importantly, the risk of myocardial infarction in statin-treated patients was similar to that in age-matched controls from the general population[349]. Of note, these benefits were achieved despite moderate-intensity statin treatment; indeed, 68% of the patients were treated with simvastatin (mean dose 33 mg) and only 12% were treated with atorvastatin (mean dose 50 mg)[349]. Accordingly, mean achieved LDL-C levels were 156 mg/dL, i.e., considerably higher than currently recommended targets. In a more recent retrospective study in 2,447 patients with HeFH, moderate- to high-intensity statin therapy lowered the risk for CHD and mortality by 44%[350].

However, even the most potent statins at the highest recommended doses (i.e., atorvastatin 80 mg and rosuvastatin 40 mg) cannot reduce LDL-C levels by more than 55%[351]. In patients who do not reach LDL-C targets despite treatment with the highest recommended or tolerable dose of a potent statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg), adding ezetimibe should be considered and is expected to reduce LDL-C levels by approximately 24%. In patients with HeFH who do not achieve LDL-C goals despite statin/ezetimibe combination treatment, adding a PCSK9 inhibitor should be considered. In these patients, the addition of a PCSK9 inhibitor can lower LDL-C levels by 50-60%, resulting in achievement of LDL-C targets in 41-68% of patients[352,353]. BAS may also be considered in patients with HeFH who do not attain LDL-C goals despite statin/ezetimibe combination treatment. However, BAS are frequently poorly tolerated and induce rather small reductions in LDL-C concentrations (by 10-16%)[190].

Table 19 summarizes the recommendations for LDL-C targets and treatment strategies in HeFH patients.

12 Dyslipidemia in Acute Coronary Syndromes

Current literature claims that the reduction in LDL-C levels induced by pharmaceutical agents, results in a proven clinical benefit against the development of atherosclerosis and its complications. Therefore, in patients with ACS, administration of hypolipidemic drug treatment is necessary to prevent the recurrence of ASCVD complications. Indeed, LDL-C reduction has been shown to improve ASCVD morbidity and mortality in patients with CHD. Double-blind randomized clinical trials with statins, both in primary and secondary prevention settings, have demonstrated a clear clinical benefit of reducing LDL-C[354]. In this context, in ACS patients, administration of high-intensity statins protects against death and major ASCVD events[355,356] (**Table 20**).

The Cholesterol Treatment Trialists (CTT) meta-analysis, with data from a total of 170,000 patients enrolled in 26 randomized statin trials, found that a decrease in LDL-C by 39 mg/dL (1 mmol/L) led to a significant reduction in major vascular events (by 22%) and all-cause mortality (by 10%, mainly due to CHD or other cardiac causes), regardless of baseline lipid parameters[357].

The ESC and ESC/EAS guidelines for the treatment of patients with ACS are clearly in favor of the immediate and large reduction in LDL-C levels in these patients[1,358]. The recommendation is to achieve LDL-C levels <55 mg/dL (1.4 mmol/L) and a decrease of LDL-C by ≥50% from baseline values[1,358]. This is suggested to be achieved primarily by the administration of high doses of more potent statins, as there is ample evidence of the beneficial effect of statins in preventing the recurrence of ASCVD events[355,356] (**Table 20**).

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), ACS patients treated with simvastatin 40 mg and ezetimibe 10 mg combination therapy achieved lower LDL-C levels compared with those on simvastatin and placebo (53.7 vs 69.5 mg/dL; 1.4 vs 1.8 mmol/L)[359]. The co-administration of simvastatin with ezetimibe for a median of 6 years was accompanied by a

TABLE 20. Recommendations for lipid treatment in patients with ACS.

Recommendations	Class of recommendation
LDL-C is recommended to be measured within 48 h after an ACS	I
A high-dose statin therapy is recommended to be initiated or continued as early as possible in all ACS patients (without any contraindication or definite history of intolerance), irrespective of baseline LDL-C levels	I
Lipid levels should be rechecked 4-6 weeks after the ACS	IIa
In a statin naïve patient with LDL-C >110 mg/dL, high-intensity statin plus ezetimibe should be administered	IIa
In statin-treated patients, statin therapy must be immediately uptitrated to atorvastatin 40-80 mg or rosuvastatin 20-40 mg at hospital admission. LDL-C must then be measured within 48 h and if ≥70 mg/dL, ezetimibe should be administered during hospitalization	I IIa
If the LDL-C target is not achieved after 4-6 weeks with the maximally tolerated statin dose, adding ezetimibe is recommended	I
If the LDL-C target is not achieved after 4-6 weeks with the maximally tolerated statin dose plus ezetimibe, adding a PCSK9 inhibitor is recommended	I
In patients presenting with ACS whose LDL levels are off target despite receiving a maximally tolerated dose of statin and ezetimibe, the addition of a PCSK9 inhibitor should be considered early after the event (even during hospitalization for the ACS)	IIa

ACS: acute coronary syndrome; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

6% reduction in the relative risk of developing the primary endpoint, i.e., CV death, ACS, coronary revascularization (≥30 days after randomization) or stroke[359]. The safety analysis did not show any increase in the incidence of the most frequent statin-related adverse events with the addition of ezetimibe, and confirmed the neutral effect of ezetimibe on glucose metabolism[359]. Based on these positive results of the IMPROVE-IT trial, if the LDL-C goal cannot be achieved after 4-6 weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended in patients with ACS[1,358,360].

In the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial, 18,924 patients who had an acute ACS 1 to 12 months prior to the study initiation and with LDL-C >70 mg/dL (1.8 mmol/L) were randomized to receive either alirocumab or placebo for a median follow-up of 2.8 years[195]. Patients on alirocumab had a significantly lower incidence of the composite primary endpoint (death from CHD, unstable angina requiring hospitalization, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke) compared with placebo (HR 0.85; 95% CI 0.78 to 0.93; p<0.001)[195]. The main benefit was due to reductions in ACS and ischemic stroke incidence. Furthermore, total mortality rate was lower in the alirocumab group than in the placebo (3.5 vs 4.1; HR 0.85; 95%CI 0.73 to 0.98)[195]. In terms of safety, the incidence of side effects was similar in the 2 groups, except for local injection-site reactions which were more frequent in the alirocumab group (3.8 vs 2.1% in the placebo). Based on these beneficial outcomes, a PCSK9 inhibitor should be added in the treatment of ACS patients not achieving LDL-C goal on a maximum tolerated dose of statin and ezetimibe after 4-6 weeks[1]. Furthermore, the latest ESC/EAS guidelines for the management of dyslipidemia recommend that in ACS patients with LDL-C levels not at target despite already on a maximally tolerated statin dose and ezetimibe, adding a PCSK9 inhibitor should be considered early after the event (even during hospitalization)[1] (**Table 20**).

In statin naïve ACS patients, atorvastatin 40-80 mg or rosuvastatin 20-40 mg must be immediately initiated at hospital admission. LDL-C must be measured within 48 h and if >110 mg/dL, ezetimibe must be administered during hospitalization (**Figure 4**)[361].

In statin-treated ACS patients, statin therapy must be uptitrated to atorvastatin 40-80 mg or rosuvastatin 20-40 mg at hospital admission. LDL-C must then be measured within 48 h and if ≥70 mg/dL, ezetimibe must be administered during hospitalization **(Figure 5**)[361].

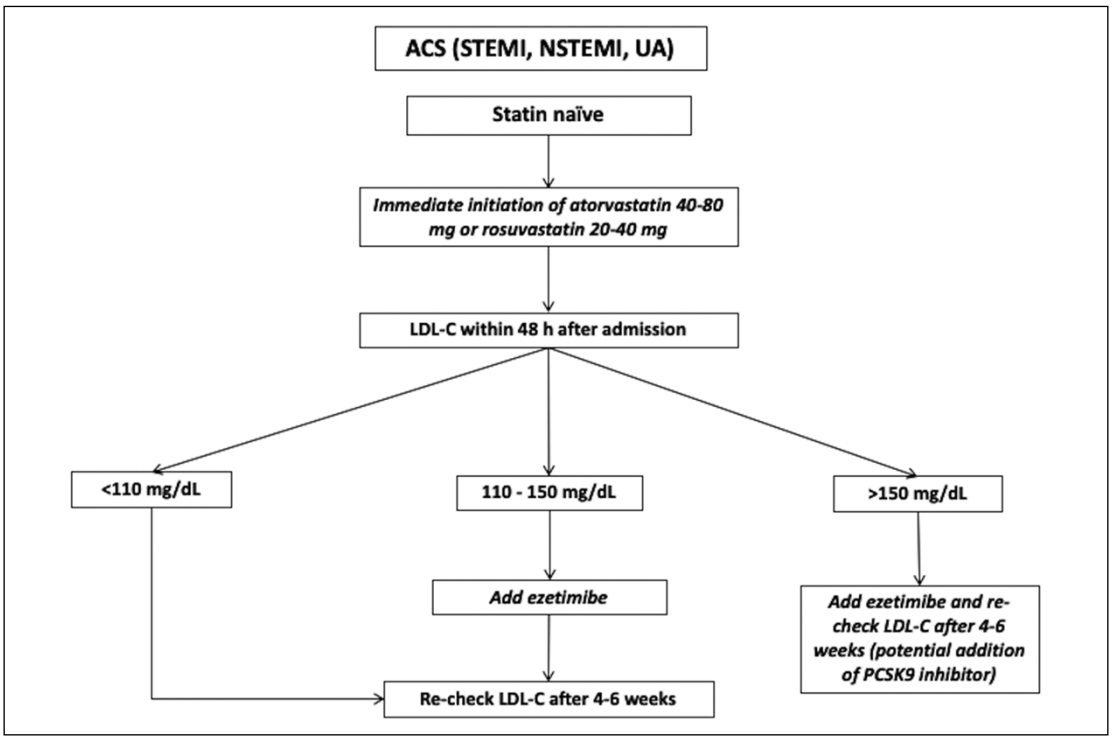

FIGURE 4. Management of dyslipidemia in statin naïve patients with ACS.

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: unstable angina; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

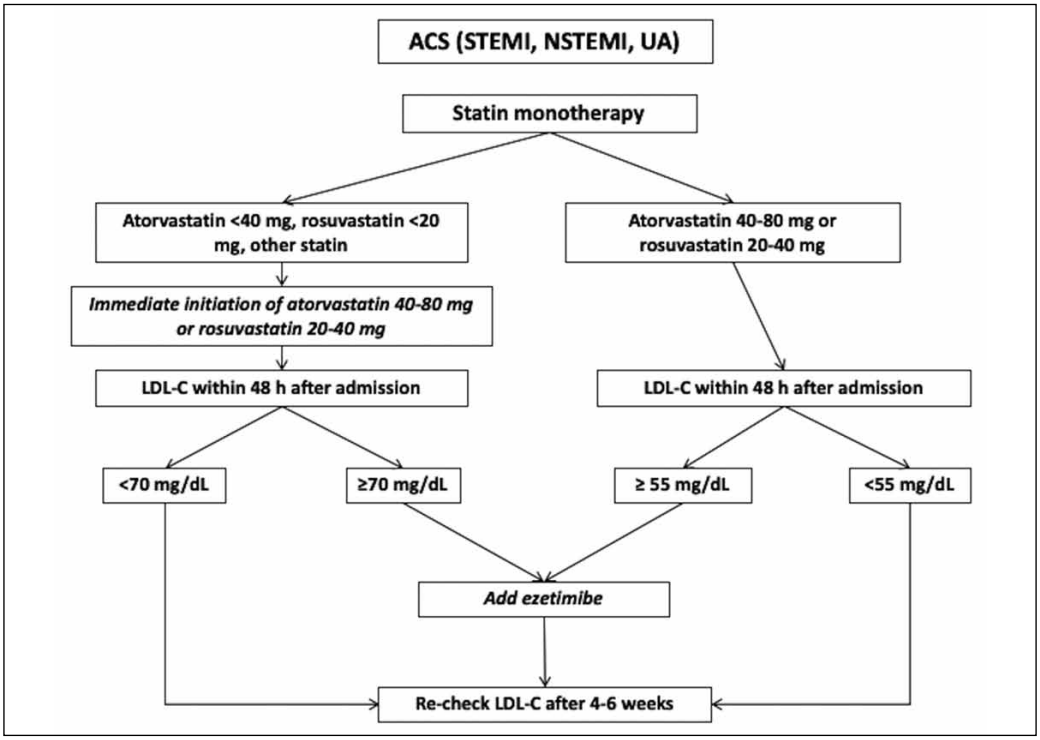

FIGURE 5. Management of dyslipidemia in statin-treated patients with ACS.

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: unstable angina; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

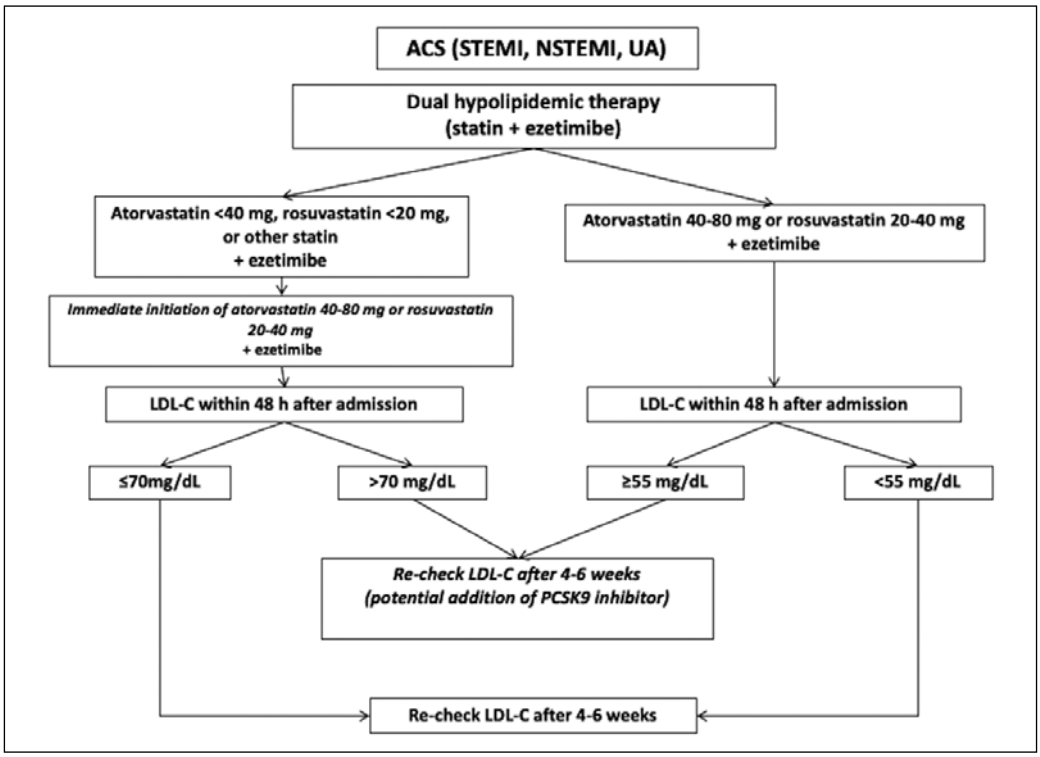

FIGURE 6. Management of dyslipidemia in statin plus ezetimibe treated patients with ACS.

ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: unstable angina; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

In ACS patients on atorvastatin 40-80 mg or rosuvastatin 20-40 mg, LDL-C must be measured within 48 h and if ≥55 mg/dL, ezetimibe must be administered during hospitalization (**Figure 5**). LDL-C must be re-checked at 4-6 weeks after hospital discharge and if still off-target, a PCSK9 inhibitor should be considered (**Figure 6**)[361].

13 Statin Use in Heart Failure

Heart failure (HF) has been recognized as a clinical condition characterized by debilitating symptoms, poor quality of life, frequent hospital admissions and reduced survival[362,363]. CHD seems to be the most common etiological factor for HF; it is the main cause of HF with reduced ejection fraction (HFrEF) and one of the main contributors for HF with preserved ejection fraction (HFpEF)[364,365]. Elevated LDL-C is uncommon in HFrEF; patients with advanced HFrEF frequently have low LDL-C levels that are related to a worse prognosis[365]. This is more obvious in the cases of advanced HF with deteriorated function of right ventricle and clinical appearance of malnutrition or cachexia[364,365].

HF as the final pathway of clinical conditions that cause ventricular pressure or/and volume overload, is accompanied by hypertrophy, inflammation, angiogenesis and apoptosis[366]. Statins may represent a potential treatment strategy for preventing cardiac hypertrophy and improving myocardial revascularization by decreasing NADPH oxidation activation and increasing NO bioavailability[367,368] (**Figure 7**).

Statin use has been linked with Q10 mitochondrial depletion and muscle fatigue[369]. Statins suppress the prenylation of Rho protein and its downstream inflammatory cytokine production through NF-kB[370]. Therefore, statins seem to act as immune-inflammatory suppressive agents and may have beneficial effects on those who have excessive immune-inflammatory reactions, such as in HF[371,372].

Statin use in HF may have other pleiotropic effects such as a change in myocardial action by modulation of Kv1.5 and Kv4.3 channels activity and inhibition of sympathetic nerve activity, consequently suppressing arrhythmogenesis[373]. On the other hand, there is some evidence that statins might exert prosarcopenic properties by reducing muscle strength and altering energy metabolism during aerobic exercise[374]. Advanced patient age and HF severity may minimize statin efficacy in terms of CV and HF outcomes[375]; statins might be beneficial in reducing CVD risk in patients with less advanced HF, whereas in severe HF, it could be too late for any potential benefits from statin therapy due to progressive loss of pump function[376].

LDL-C lowering with statins reduces the incidence of HF in patients with stable CHD or ACS without previous HF[1]. Similar statin-related benefits were reported in primary prevention settings[377]. Indeed, in a meta-analysis (17 trials, n=132,538 participants) over 4.3 years, statin therapy reduced non-fatal HF hospitalization by 10% [risk ratio (RR) 0.90, 95% CI: 0.84-0.97) and the composite HF outcome by 8% (RR 0.92, 95% CI: 0.85-0.99) but not HF death[377]. Statin efficacy in decreasing the rate of first non-fatal HF hospitalization was similar irrespective of the presence or absence of a prior myocardial infarction[377].

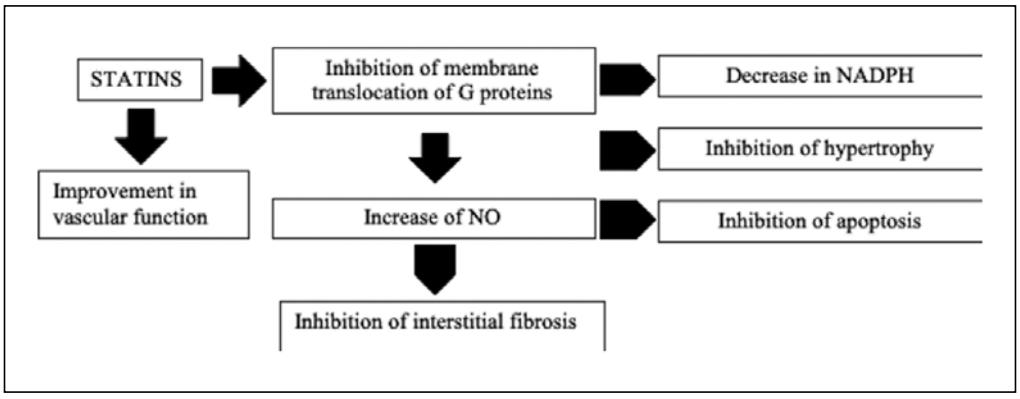

FIGURE 7 Molecular mechanisms of statin use in patients with heart failure.

NO: nitric oxide; NADPH: Nicotinamide adenine dinucleotide phosphate

TABLE 21. Main studies with statin use in heart failure patients with reduced and preserved ejection fraction.

Study	N	Ejection fraction (%)	Age (years)	Statin used	OR	CI	Year
Alehagen et al	9140	>50	78±12	Non specified	0.8	0.72-0.89	2015
Alehagen U et al.	21,864	<40	72±12	Non specified	0.8	0.76-0.86	2015
Coleman et al.	1144	<30	67±13	Non specified	0.67	0.53-0.85	2008
Fukuta et al.	137	>50	65±12	Atorvastatin vs simvastatin or Fluvastatin or pravastatin	0.32	0.10-1.02	2005
Go et al.	24,598	<40	70±12	Non specified	0.76	0.7-0.83	2006
Gomez Soto et al.	2573	>47	70±8	Non specified	0.71	0.59-0.85	2010
Horwitz et al.	450	<40	57±11	Non specified	0.52	0.30-0.90	2004
Huan et al.	479	<40	74±4	Simvastatin	0.5	0.30-0.83	2017
Kaneko et al.	1124	>50	66±11	Non specified	0.55	0.32-0.95	2013
Kjekshus et al.	5011	<40	73±7	Non specified	0.94	0.82-1.08	2007
Nochioka et al.	3124	>50	69±11	Non specified	0.72	0.63-0.82	2015
Roik et al.	146	>45	69±11	Simvastatin vs atorvastatin	0.24	0.07-0.82	2008
Sola et al.	416	<35	55±6	Atorvastatin vs simvastatin or Fluvastatin or pitavastatin	0.52	0.32-0.85	2005
Tavazzi et al.	4574	30-35	68±1	rosuvastatin	1.01	0.88-1.16	2008
Tsujimoto et al.	3378	>50	69±10	Non specified	0.83	0.67-1.03	2018
Yap et al.	750	>50	73±11	Non specified	0.57	0.37-0.88	2015

Odds ratio (OR) for total main outcome (cardiovascular death and hospitalization)

According to the 2021 ESC guidelines for acute and chronic HF, statin initiation is not generally recommended, except for patients already receiving a statin for CHD[362]. The recent reclassification of HF subtypes in heart failure with mildly reduced ejection fraction (HFmrEF) and HFpEF, defines a large group of patients with EF>40% where several clinical trials have shown beneficial effects from statin use[378,379]. In advanced stages of HF with severe cachexia, statin continuation may be reconsidered in the scope of personalized approach or palliative care.

There are no randomized controlled trials that evaluated the use of ezetimibe in HF patients. There is one ongoing trial with evolocumab in HFrEF patients [EVOlocumab in Stable Heart Failure With Reduced Ejection Fraction of Ischemic Etiology: EVO-HF Pilot (EVO-HF)][380].

TABLE 22. Recommendations for dyslipidemia management in patients with heart failure.

Recommendations	Class of recommendation
Lipid-lowering therapy initiation is not recommended in patients with heart failure in the absence of other indications	III

Table 21 summarizes the main studies with statin use in heart failure patients with reduced and preserved ejection fraction in relation to CV and hospitalization outcomes.

Table 22 summarizes the recommendations for management of dyslipidemia in HF patients.

14 Prevention of Stroke

14.1 Primary prevention of stroke

The use of statin therapy in adults at high risk of ASCVD reduces the risk of ischemic stroke or transient ischemic attack (TIA)[381]. Patients with high LDL-C, arterial hypertension, diabetes and patients with multiple ASCVD risk factors benefit most by statin treatment regarding the reduction of stroke risk[382–385]. Risk reduction for a first ischemic stroke per 1.0 mmol/L (39 mg/dL) LDL-C decrease is about 21%, and it is similar in men and women[357,386]. Furthermore, intensive lipid-lowering therapy reduces the risk of stroke in the setting of established ASCVD[381,387,388]. More intensive statin treatment is associated with a lower risk of stroke compared with less intensive regimens[357,386,389,390].

In the IMPROVE-IT trial, the addition of ezetimibe to simvastatin in post-ACS patients had an incremental beneficial effect for ischemic stroke and marginally for all strokes[359]. Similar results have been reported with PCSK9 inhibitors in the FOURIER (with evolocumab)[194] and the ODYSSEY OUTCOMES trial (with alirocumab)[195]. In particular, evolocumab added to a statin (± ezetimibe) significantly reduced the risk of ischemic stroke in patients with stabilized ASCVD, whereas alirocumab decreased the risk of ischemic stroke in patients with recent ACS[194,195]. Concerns for an increased risk of hemorrhagic stroke with statin treatment and achievement of very low LDL-C levels, whether on a statin alone or on combination of a statin with ezetimibe or/and a PCSK9 inhibitor, do not appear to be justified[391,392].

14.2 Secondary prevention of stroke

Following a stroke or TIA, patients are at a very high risk of major ASCVD events, including recurrent stroke[393]. Secondary prevention statin therapy significantly lowers the risk of recurrent stroke [by 12% per mmol/L (39 mg/dL) reduction in LDL-C], MI and vascular death[1,389,394]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial was the first randomized trial which enrolled 4731 patients at least a month following a stroke or TIA[394]. Aggressive treatment with atorvastatin (80 mg) significantly decreased the risk of recurrent total stroke (HR 0.84, 95% CI: 0.71-0.99, p=0.03), major coronary events (HR 0.65, 95% CI: 0.49-0.87, p=0.003), and fatal stroke (HR 0.57; 95% CI: 0.35-0.95, p=0.03)[394]. Of note, the reduction of total stroke was greater among patients achieving LDL-C concentrations lower than 70 mg/dL (HR 0.72, 95%CI: 0.59-0.89, p=0.0016). Statin-based therapy reduces the risk of recurrent ischemic stroke depending on achieved LDL-C levels[395]. In this context, the Treat Stroke to Target (TST) trial showed that aggressive LDL-C reduction with a goal of <70 mg/dL in patients with ischemic stroke/TIA and evidence of ASCVD results in a lower risk of subsequent CV events compared with a LDL-C target of 90-110 mg/dL[396].

The IMPOVE-IT trial included 641 patients (out of 18,144 post-ACS patients) with a prior stroke (82% with a history of ischemic stroke)[397]. In this population, the risk of any stroke was reduced by 40% (HR 0.60; 95%CI: 0.38-0.95, p=0.03) and for ischemic stroke by 48% (HR, 0.52; 95%CI, 0.31-0.86; p=0.011)[397]. These findings support the benefit on stroke prevention of LDL-C lowering through a non-statin drug.

The addition of a PCSK9 inhibitor on top of statin ± ezetimibe treatment provides a potent therapeutic option to achieve very low LDL-C target levels in stroke survivors. There is evidence from the FOURIER trial that evolocumab reduced the primary ASCVD composite endpoint, all strokes and ischemic strokes in patients with a history of previous stroke and stabilized ASCVD[398]. Similar results were reported for alirocumab in the ODYSSEY OUTCOMES trial[399].

In a pooled analysis, TIA (due to carotid stenosis) patients pretreated with a statin had a reduced risk of recurrent early stroke risk, thus denoting an as-early-as-possible initiation of statins after stroke[400]. Routine use of statins in the (hyper-)acute phase of stroke (first 2 days to one week) is not supported by solid evidence from randomized controlled trials[401,402]. However, based on observational data, in-hospital statin use is related to better functional outcomes and lower mortality, whereas statin withdrawal can lead to poor functional outcomes[403].

Statin use in secondary prevention of ischemic stroke

TABLE 23. Recommendations of treatment of dyslipidemia for the primary and secondary prevention of stroke.

Recommendations	Class of recommendation
Lipid-lowering treatment with statins in combination with lifestyle changes is recommended for primary prevention of ischemic stroke in patients who have high or very-high ASCVD risk	I
Prophylactic intensive statin-based lipid-lowering therapy is recommended in patients with a history of non-cardioembolic ischemic stroke or TIA for the secondary prevention of stroke	I
In patients with a history of stroke or TIA a treatment goal of LDL-C <55 mg/dL and a ≥50% reduction from baseline LDL-C levels is recommended	I
If LDL-C target is not achieved with the maximally tolerated dose of statin, ezetimibe must be added in both primary and secondary prevention settings	I
If LDL-C target is not achieved with the maximally tolerated dose of statin + ezetimibe, a PCSK9 inhibitor must be added in secondary prevention settings	I

ASCVD: atherosclerotic cardiovascular disease; TIA: transient ischemic attack; LDL-C: low-density lipoprotein cholesterol

caused by less frequent non-atherosclerotic etiologies, such as atrial fibrillation, arterial dissection, and patent foramen oval (PFO), requires further investigation. Patients should be treated according to global ASCVD risk.

An overview of the above recommendations is provided in **Table 23**.

15 Management of Dyslipidemia in Patients with CKD

CKD [eGFR <60 mL/min/1.73 m^2 and/or the presence of albuminuria (defined as urine albumin-to-creatinine ratio ≥30 μg/mg)] for at least 3 months] is independently associated with elevated ASCVD risk[404,405]. Detection of albuminuria in the context of reduced eGFR multiplies ASCVD risk[406,407]. The risk increases with severity of eGFR dysfunction[404]; a threshold of risk is set round 75 mL/min/1.73 m^2. Mendelian randomization analyses in patients with eGFR <60 mL/min/1.73 m^2 showed a 14% (95% CI 3-27%) higher CHD risk per 5 mL/min/1.73 m^2 lower genetically predicted eGFR[408]. Stage 3 CKD patients (eGFR 30-59 mL/min/1.73 m^2) are considered at high risk in whom an LDL-C reduction of ≥50% from baseline and an LDL-C goal < 70 mg/dL (1.8 mmol/L) are recommended[1,408]. Stage 4-5 CKD patients (eGFR <30 mL/min/1.73 m^2 not on dialysis) are at very high risk; LDL-C reduction of ≥50% from baseline and an LDL-C goal <55 mg/dL (1.4 mmol/L) are recommended[1]. In all CKD patients, a fasting lipid profile should be assessed to determine the need for initiation of lipid-lowering treatment, diagnose secondary causes of dyslipidemia (e.g., nephrotic syndrome) and identify hypertriglyceridemia, a frequent lipid abnormality in CKD patients[409].

Statin ± ezetimibe therapy was reported to significantly reduce major CV events in both primary and secondary settings in CKD patients (eGFR <60 mL/min/1.73 m^2)[410]. Several meta-analyses reported that the relative reduction in major CV events with statin therapy becomes smaller with eGFR decline, with little or no evidence of benefit in patients on dialysis[411]. Of note, only a few patients on dialysis or with renal transplants have been included in lipid-lowering trials; thus, further research is required in this field[411].

Statins were shown to decrease microalbuminuria and proteinuria in a previous meta-analysis[412]. Another statin-related renal benefit refers to the prevention of contrast-induced acute kidney injury (CI-AKI)[413–416].

In the Study of Heart and Renal Protection (SHARP) trial, simvastatin and ezetimibe combination therapy was related to a lower risk for major atherosclerotic events (coronary death, myocardial infarction, non-hemorrhagic stroke or any revascularization) compared with placebo in patients with stage 3A-5 CKD[417]. Adjusting for subgroup-specific reductions in LDL-C levels, the proportional effects on major atherosclerotic events were similar in patients on dialysis and those not receiving dialysis[417]. However, the trial did not have sufficient power to assess the effects in the primary outcome separately in dialysis and non-dialysis patients. Continuation of statin therapy after initiation of dialysis is supported by the fact that more than 30% of patients transitioned to dialysis[417].

Despite the highest absolute risk of ASCVD events among persons receiving dialysis, the proportion of deaths attributed to atherosclerotic complications is lower[418,419]. In adults with CKD that require dialysis, initiation of a statin is not recommended based on the findings of 2 large-scale randomized controlled trials, namely the 4D trial (Die Deutsche Diabetes Dialyse)[418] and the AURORA trial (A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events)[419], showing no effect of atorvastatin 20 mg and rosuvastatin 10 mg, respectively, on CV outcomes in this population. Whether lipid-lowering treatment benefits more patients on peritoneal dialysis than those on hemodialysis and vice versa remains unclear.

In a systematic review of 22 studies including 3465 patients with a functioning kidney transplant without ASCVD, statins reduced ASCVD events; nonetheless treatment effects should be interpreted in the light of heterogeneity of studies and different statin regimens used[420]. Importantly, dose adjustments may be needed in CKD patients depending on statin used, concomitant drugs (e.g., cyclosporin) and eGFR[421].

In a sub-analysis of the FOURIER trial, evolocumab was shown to significantly lower LDL-C levels and CV outcomes in CKD patients, and this effect was consistent across CKD groups[422]. Of note, absolute reduction in the composite of CV morbidity and mortality with evolocumab was numerically greater in patients with more advanced CKD[422]. Similarly, consistent LDL-C lowering effects were achieved with alirocumab in both patients with and with-

TABLE 24. Recommendations for dyslipidemia management in patients with CKD.

Recommendations	Class of recommendation
Stage 3 CKD patients (eGFR 30-59 mL/min/1.73 m^2) are considered at high risk. LDL-C reduction of ≥50% from baseline and LDL-C goal <70 mg/dL (1.8 mmol/L) are recommended	I
Stage 4-5 CKD patients (eGFR <30 mL/min/1.73 m^2) are at very high risk; LDL-C reduction of ≥50% from baseline and LDL-C goal <55 mg/dL (1.4 mmol/L) are recommended	I
The use of statins or statin/ezetimibe combination is indicated in non-dialysis dependent CKD patients	I
In patients already on statins, ezetimibe or a statin/ezetimibe combination at the time of dialysis initiation, lipid-lowering therapy should be continued	IIa
In patients with CKD without ASCVD who require dialysis, statin treatment should not be initiated	III
In adult kidney transplant recipients, statin treatment should be considered	IIa

eGFR: estimated glomerular filtration rate; LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

out CKD (defined by eGFR 30-59 mL/min/1.73 m^2 and ≥ 60 mL/min/1.73 m^2, respectively)[423]. Further research is needed to elucidate the clinical use of PCSK9 inhibitors in CKD patients.

Table 24 summarizes the recommendations for dyslipidemia management in patients with CKD.

16 Management of Dyslipidemia in Women

Although women are underrepresented in clinical studies evaluating the effect of lipid-lowering therapies in primary and secondary prevention of ASCVD, the benefit of statin treatment in CV risk seems to be similar in men and women.

16.1 Primary prevention

In a 2013 Cochrane analysis, the observed reductions in all-cause mortality, vascular events and revascularizations following statin therapy were similar in men and women[424]. Similarly, in a meta-analysis of statin trials from the CTT showed no significant gender differences for the relative risk of major coronary events, coronary revascularization and stroke, whereas significant decreases in vascular events were induced by statin therapy in primary prevention settings in both women and men[386]. Therefore, primary prevention of ASCVD events in women at high ASCVD risk should include statin use[1].

In women, adverse health conditions during pregnancy (such as preeclampsia, eclampsia and gestational diabetes)[425,426] and menopause have been shown to increase ASCVD risk[427]. Several characteristics during menopause may influence women ASCVD risk, such as the type of menopause, age at menopause, menopause stage, endogenous estradiol levels and menopause-related symptoms[427]. For example, early (between 40 and 45 years) or premature menopause (<40 years) may further increase ASCVD risk[425–427]. Iatrogenic menopause by bilateral oophorectomy during the premenopausal period is also associated with greater ASCVD risk[427]. In contrast, hysterectomy, regardless of ovarian status, does not affect ASCVD risk factors before or after menopause[427]. Such conditions are considered as risk-enhancing factors for statin therapy.

16.2 Secondary prevention

Accumulating data suggest that statin therapy reduces CV events in women with ASCVD. For example, a meta-analysis including >8000 women with known ASCVD, lipid-lowering therapy effectively reduced CHD events and mortality, nonfatal myocardial infarction and revascularization, without affecting total mortality[428]. Correspondingly, the CTT meta-analysis showed that statin-induced ASCVD benefit in secondary prevention does not differ by gender[386]. Thus, secondary prevention of ASCVD events in women should routinely include a statin regimen, with the same indications and therapeutic goals as in men[1].

16.3 Lipid-lowering combination therapy

In the IMPROVE-IT study, 24% of the study population were women[359]. In this study, simvastatin 40 mg and ezetimibe 10 mg combination significantly reduced the composite endpoint of CV death, myocardial infarction and stroke (HR 0.90, 95%CI 0.84-0.96), and this result was consistent in both genders[359]. The FIELD study showed that fenofibrate led to greater (non-significant) reductions in CV outcomes (CV death, fatal and non-fatal stroke and carotid and coronary revascularization) in women than men[429]. However, the ACCORD lipid study showed significantly less benefit for primary event reduction with statin/fenofibrate combination in women[222].

With regard to PCSK9 inhibitors, relative risk reductions in the primary and key secondary CV endpoints were similar in women and men with evolocumab in the FOURIER trial[430] as well as with alirocumab in the ODYSSEY OUTCOMES trial[431].

Overall, ezetimibe or fibrates, either alone or in combination with statins can be used. The addition of a PCSK9 inhibitor should be considered if LDL-C targets are not achieved with maximally tolerated statin dose and ezetimibe[1].

16.4 Pregnancy

All statins are contraindicated during pregnancy due to data linking their use with malformations[432] and miscarriages[433], mainly in animals. For this reason, when pregnancy is planned, statin therapy should be stopped 1 to 2 months before it is attempted. In case of an unexpected pregnancy, statins should be discontinued as soon as the pregnancy is confirmed. Statin therapy should be initiated only after the breastfeeding period. For statin-treated women of reproductive age that are sexually active, the

TABLE 25. Recommendations for the management of dyslipidemia in women.

Recommendations	Class of recommendation
Statin therapy is recommended for primary ASCVD prevention in women at high ASCVD risk. Pregnancy-associated adverse health conditions (such as preeclampsia, eclampsia, gestational diabetes) and menopause (especially early or premature) should be considered as risk-enhancing factors	I
Statins are recommended for secondary prevention in women with the same recommendations and therapeutic goals as in men	I
Lipid-lowering therapy should not be administered 1 to 2 months before pregnancy is attempted, during pregnancy and during the breastfeeding period	III

ASCVD: atherosclerotic cardiovascular disease

use of an effective contraception method is recommended.

It should be mentioned that recently the FDA has requested revisions to the information about use in pregnancy in the prescribing information of the entire class of statins[434]. These changes include the removal of the contraindication against using these medicines in all pregnant patients, because the benefits of statins may include prevention of serious or potentially fatal events in a small group of very high-risk pregnant patients, especially in patients with HoFH and those who have previously had a heart attack or stroke. Importantly, patients with high CVD risk who require statins during pregnancy should not breastfeed after giving birth and should use alternatives such as infant formula[434].

Table 25 summarizes the recommendations for dyslipidemia treatment in women.

17 Management of Dyslipidemia in the Elderly

In elderly patients, the same increase in LDL-C levels is associated with a smaller relative increase in ASCVD events than in younger individuals[435]. Indeed, in a meta-analysis of 61 prospective observational studies (n = 892,237), 39 mg/dL (1 mmol/L) lower TC was related to 56, 34 and 17% lower CHD mortality at ages 40-49, 50-69, and 70-89 years, respectively[435]. However, elderly patients have higher absolute ASCVD risk than younger ones and thus, the same increase in LDL-C levels is associated with greater increases in the absolute risk of ASCVD events[435]. Furthermore, statin treatment is similarly effective in reducing ASCVD risk in the elderly and younger patients. In the Pravastatin in elderly individuals at risk of vascular disease (PROSPER) trial, which included 5804 patients aged 70-82 years with a history of, or risk factors for, ASCVD, treatment with pravastatin 40 mg/day for 3.2 years reduced the incidence of the primary endpoint (coronary death, non-fatal myocardial infarction, and fatal or non-fatal stroke) by 15%[436].

TABLE 26. Recommendations for the management of dyslipidemia in the elderly.

Recommendation	Class of recommendation
Lipid-lowering treatment must aim at LDL-C levels <55, <70 and <100 mg/dL in very high, high, and moderate risk elderly patients (≤ 75 years old).	I
In very high- and high-risk elderly patients (≤ 75 years old), a reduction in baseline LDL-C levels by >50% is recommended	I
In very high- and high-risk elderly patients >75 years old, initiation of statin therapy should be considered	IIa
In the presence of renal impairment and/or drug interactions, statin therapy must be initiated at a low dose, and then titrated, if needed, to attain LDL-C target	I

LDL-C: low-density lipoprotein cholesterol

Another issue with the management of elderly patients is the risk of adverse effects of lipid-lowering agents due to the presence of comorbidities (particularly impaired renal function) and polypharmacy. Therefore, statins with minimal risks for interactions with other treatments (e.g., rosuvastatin) and minimal renal clearance (e.g., atorvastatin and pitavastatin) should be preferred in the elderly. In such cases, statin therapy should be started at a low dose and then titrated upwards to achieve LDL-C target.

Table 26 summarizes the recommendations for the elderly.

18 Lipid Management in Diabetes

Patients with T2D present with atherogenic dyslipidemia characterized by elevated TC and TG, low HDL-C and 'normal' or increased LDL-C levels[52,437]. sdLDL particles are also raised. This mixed dyslipidemia (high TG and low HDL-C) has been linked to increased ASCVD risk, although the evidence is not so strong as with high LDL-C[52,437]. Furthermore, there is growing evidence that non-fasting TG may predict ASCVD risk even better than fasting TG[33]. Postprandial hypertriglyceridemia following an oral fat tolerance test has been associated with ASCVD risk[34,35,438].

Regarding ASCVD risk classification (**Table 27**), patients with T2D and established ASCVD (ACS, stable angina, CHD, stroke, TIA and PAD), target organ damage (e.g., microalbuminuria, retinopathy or neuropathy), chronic kidney disease (eGFR< 30 mL/min/1.73 m^2) or with ≥3 major risk factors are considered at very high risk[1]. Young T2D patients (<50 years) with diabetes duration <10 years and without other risk factors are considered at moderate risk. All other T2D patients are considered at high risk[1].

Patients with T1D are at very high risk in the presence of ASCVD or long disease duration (>20 years)[1]. Young T1D patients (<35 years) with DM duration <10 years and without other risk factors are considered at moderate risk. All other T1D patients are considered at high risk[1].

18.1 Therapeutic goals

The primary therapeutic goal in T2D patients in relation to lipid disorders is LDL-C based on individual's ASCVD risk (**Table 28**). The only exception to this rule refers to cases with very high TG levels i.e., >400 mg/dL, when TG lowering is a priority to avoid acute pancreatitis[1]. For T2D patients at very high, high and moderate risk, LDL-C targets are: <55, <70 and <100 mg/dL, respectively[1].

Non-HDL-C (TC minus HDL-C) represents the secondary treatment target in T2D patients. Non-HDL-C goal is 30 mg/dL higher than LDL-C target i.e., <85, <100 or <130 mg/dL for patients at very high, high, or moderate ASCVD risk, respectively. ApoB may also be considered as a secondary therapeutic target in T2D patients with target levels <65, <80 or <100 mg/dL, respectively[1].

TG levels ≤150 mg/dL are considered optimal, whereas drug treatment should be considered when TG are >200 mg/dL despite statin treatment[1].

18.2 Treatment

T2D represents a secondary cause of dyslipidemia; thus, it is clinically important to achieve euglycemia, which will improve related lipid disorders, and especially TG levels. Lifestyle interventions (healthy diet, physical activity, weight management and smoking cessation) are recommended to improve both dyslipidemia and ASCVD risk (see **Table 29**). However, the majority of T2D patients will require pharmacotherapy to achieve lipid targets.

Statins represent the first-line drug choice [439]. Statins

TABLE 27. ASCVD risk classification in patients with type 2 diabetes.

Patients characteristics	ASCVD risk category	Class of recommendation
Patients with T2D and established ASCVD (ACS, stable angina, CHD, stroke, transient ischemic attack, and PAD)	Very high risk	I
Patients with T2D and target organ damage (e.g., microalbuminuria, retinopathy or neuropathy), chronic kidney disease (eGFR< 30 mL/min/1.73 m^2) or with ≥3 major risk factors	Very high risk	IIa
Patients with long-standing T1D (>20 years)	Very high risk	IIa
Patients with diabetes (duration >10 years) plus at least 1 major risk factor	High risk	IIa
Patients with diabetes (duration <10 years), age <50 years with no major risk factor	Moderate risk	IIa

T2D: type 2 diabetes, ASCVD: atherosclerotic cardiovascular disease, ACS: acute coronary syndrome, CHD: coronary heart disease, PAD: peripheral artery disease, eGFR: estimated glomerular filtration rate

TABLE 28. Therapeutic goals in patients with type 2 diabetes.

	Class of recommendation
The primary therapeutic goal in T2D patients in relation to lipid disorders is LDL-C	I
Non-HDL-C represents the secondary treatment target in T2D patients	IIa
TG levels ≤150 mg/dL are considered optimal	IIa
For T2D patients at very high, high and moderate risk, LDL-C targets are: <55, <70 and <100 mg/dL, respectively	I
Non-HDL-C goal is <80, <100 or <130 mg/dL for patients at very high, high, and moderate risk, respectively	IIa
ApoB may be considered as a secondary therapeutic target in T2D patients with target levels <65, <80 or <100 mg/dL	IIb

T2D: type 2 diabetes, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides, apoB: apolipoprotein B

TABLE 29. Lifestyle recommendations for lipid management in diabetes.

- Application of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) dietary pattern
- Reduction of saturated or *trans*-fat intake (e.g., cream, sweets, butter, cheese, processed meat)
- Preference of monounsaturated (extra virgin olive oil) and polyunsaturated fat (vegetable oils)
- Increased consumption of fruits, vegetables, legumes, nuts, whole-grain cereals, plant stanols/sterols and fish (especially oily)
- Moderate consumption of alcoholic beverages (i.e., <20 g/day for men and <10 g/day for women); patients with hypertriglyceridemia should abstain from alcohol drinking
- Limited intake of beverages and foods with added sugars
- Regular physical exercise for at least 30 min/day every day
- All forms of smoking should be avoided

have been shown to significantly lower ASCVD risk in both primary and secondary prevention settings. Statins have been shown to slightly (by 9%) increase the risk of new-onset diabetes (NOD)[440]. Several mechanisms have been implicated in statin-induced NOD, including insulin signaling and sensitivity, pancreatic beta-cell function and adipokine secretion[42,441]. This drug effect is dose, potency and time dependent; some patients may be more prone to NOD development such as those with a family history of T2D, gestational diabetes, obesity, menopause and Asian origin[442]. However, this minor risk does not outweigh the clinical benefits of ASCVD risk reduction induced by statins.

The type and dose of statin should be individually selected based on the required % reduction in LDL-C levels to attain LDL-C goal[1] (see **Table 55**). Intensification of statin therapy is recommended to achieve LDL-C targets.

If LDL-C goal is not reached with the maximum tolerated dose of statin dose, the addition of ezetimibe is recommended[1]. Indeed, in the IMPROVE-IT, ezetimibe addition to simvastatin led to significant reductions in ASCVD events in patients after an acute coronary syndrome[359]; the benefit was more evident in T2D patients[443].

If LDL-C remains off-target despite statin and ezetimibe therapy, a PCSK9 inhibitor should be considered. The FOURIER trial[194] showed that evolocumab significantly lowered the composite endpoint of ASCVD morbidity and mortality in patients with stable CHD, treated with a statin ± ezetimibe. Similar results were observed in the ODYSSEY OUTCOMES trial with alirocumab in statin ± ezetimibe treated patients after an ACS[195]. In sub-analyses of the FOURIER and the ODYSSEY OUTCOMES trials, the observed ASCVD benefit was even greater for T2D patients[444,445]. It should be noted that there are slightly different LDL-C threshold values for the administration of PCSK9 inhibitors in different countries based on economical and cost-effective analyses[446–448].

In the presence of complete statin intolerance, ezetimibe monotherapy is recommended, and if LDL-C goal is not attained, a PCSK9 inhibitor should be added[1].

Regarding TG, drug treatment should be initiated when TG are >200 mg/dL[1]. Statins are considered the first-line drug choice to reduce ASCVD risk in patients with hypertriglyceridemia. Fenofibrate may be combined with statins if TG remain >200 mg/dL despite statin monotherapy. Of note, the ACCORD Lipid study showed that only those T2D patients with mixed dyslipidemia (defined

TABLE 30. Recommendations for drug hypolipidemic treatment in patients with type 2 diabetes.

	Class of recommendation
Statins are the first-line drug choice	I
Intensification of statin therapy is recommended to achieve LDL-C targets	I
If LDL-C goal is not reached with the maximum tolerated dose of statin dose, the addition of ezetimibe is recommended	I
If LDL-C remains off-target despite statin and ezetimibe therapy, a PCSK9 inhibitor should be considered if risk high or above	IIa
In the presence of total statin intolerance, ezetimibe monotherapy is recommended.	I
In the presence of total statin intolerance, if LDL-C goal is not attained with ezetimibe monotherapy, a PCSK9 inhibitor should be added	IIa
Statins are considered the first-line drug choice to reduce ASCVD risk in patients with hypertriglyceridemia	I
Icosapent ethyl (at a dose of 2x2 g/day) should be considered in combination with a statin, if TG are between 135-499 mg/dL in statin-treated patients at risk high or above	IIa
Fenofibrate may be combined with a statin if TG remain >200 mg/dL despite statin therapy	IIb
Gemfibrozil co-administration with statins is not recommended	III
Highly purified omega-3 fatty acids (EPA+DHA) may be added if TG levels remain >500 mg/dL despite treatment with statins and/or fenofibrate	IIb

LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, ASCVD: atherosclerotic cardiovascular disease, TG: triglycerides, PCSK9: proprotein convertase subtilisin-kexin 9

as TG ≥204 mg/dL and HDL-C ≤34 mg/dL) benefited from adding fenofibrate to simvastatin[222,449]. Similarly, the FIELD study found that fenofibrate significantly decreased ASCVD events by 11% in the total T2D population, but this benefit was even greater (reduction by 27%) in those with elevated TG (>204 mg/dL) and low HDL-C (<40 mg/dL for men and <50 mg/dL for women)[450]. Furthermore, fenofibrate was reported to significantly reduce the risk of microvascular diabetic complications i.e., retinopathy, nephropathy and amputations[451,452]. These findings highlight the clinical importance of fenofibrate therapy in T2D patients[449]. Gemfibrozil co-administration with statins is not recommended.

Icosapent ethyl (at a dose of 2x2 g/day) should be added in combination with statins (and fenofibrate if needed) in patients with T2D and established ASCVD or with ≥1 major risk factor and TG >150 mg/dL based on the findings of the REDUCE-IT[134]. **Table 30** summarizes the recommendations for drug hypolipidemic treatment in T2D patients.

Patients with T1D also have increased ASCVD risk, and especially those with CKD and/or target organ damage. ASCVD risk classification is similar in T1D and T2D patients (see **Table 27**). Statins are recommended as the first-line choice to reduce LDL-C in T1D patients. Regarding ezetimibe and PCSK9 inhibitors, evidence for their use in T1D patients is lacking.

19 Dyslipidemia in Children and Adolescents

Pediatric dyslipidemia is a risk factor for atherosclerosis. Strong evidence indicates that atherosclerosis begins early in life and its severity is related to blood lipid levels. Dyslipidemia presented in youth is related to subclinical atherosclerosis and premature ASCVD in adulthood[453–455]. The first guidelines for the management of pediatric dyslipidemia were published 30 years ago[456]. Newer integrated guidelines were published by a National Heart, Lung, and Blood Institute (NHLBI) expert panel, in 2011[454]. Lipid levels in children vary depending on age, gender, and pubertal stage. Certain cut points for lipids/lipoproteins in childhood, derived from population distributions, have been determined[454,456] (**Table 31**).

With a few exceptions e.g., HoFH, children with dyslipidemia do not present with any manifestations and identification is based on lipid screening. Initially, a targeted screening of children at increased risk for early atherosclerosis was recommended and continues to be supported by the U.S. Preventive Services Task Force (USPSTF)[455–457]. The NHLBI expert panel, endorsed by the American Academy of Pediatrics, recommended universal screening of children, at 9-11 and 17-21 years, with a non-fasting non-HDL-C and selective screening of high-risk children older than 2 years, with a fasting lipid profile[439,454,458] (**Table 32** and **Table 33**).

In Greece, only targeted screening is recommended in high-risk children older than 2 years of age[459] (**Table 34**).

The diagnosis of pediatric HeFH is based either on clinical criteria or on a positive genetic testing, with the latter being the golden standard for diagnosis (**Table 35**).

The Dutch Lipid Network Criteria (**Table 18**), the UK Simon Broome system (**Table 12**) and the MEDPED (**Table 13**), are also used for the diagnosis of HeFH. Secondary

TABLE 31. Acceptable, borderline-high or -low, and high or low plasma lipid, lipoprotein and apolipoprotein concentrations for children and adolescents.

Category	Acceptable	Borderline[a]-High or Low	High[b]	Low[c]
TC (mg/dL)	<170	170-199	≥200	-
LDL-C (mg/dL)	<110	110-129	≥130	-
Non-HDL-C (mg/dL)	<120	120-144	≥145	-
ApoB (mg/dL)	<90	90-109	≥110	-
Triglycerides (mg/dL)				
0–9 years	<75	75-99	≥100	-
10–19 years	<90	90-129	≥130	-
HDL-C (mg/dL)	>45	40-45	-	<40
ApoA1 (mg/dL)	>120	115-120	-	<115
Lipoprotein (a) (mg/dL)	<30		≥30	

Adapted from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute 2011[454].

TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; apo: apolipoprotein; Non-HDL-C= Non-high-density lipoprotein cholesterol (TC - HDL-C).

[a]Borderline-High values represent the 75th percentile, and Borderline-Low values represent the 25th percentile.
[b]Abnormal high values represent the 95th percentile
[c]Abnormal low values represent the 10th percentile.

If abnormal, then repeat fasting lipid profile 2 weeks to 3 months apart.

TABLE 32. Selective screening for dyslipidemia in children and adolescents.

1. Children and adolescents with positive family history for dyslipidemia or early ASCVD* • Parent with total cholesterol (TC) ≥240 mg/dL or known genetic dyslipidemia • 1st or 2nd degree relatives with clinically established early ASCVD (men ≤55 years, women ≤65 years) • Children and adolescents with unknown family history 2. Children and adolescents with risk factors predisposing to dyslipidemia and/or ASCVD (see Table 35)	IIa

ASCVD: atherosclerotic cardiovascular disease

*Any of the following: myocardial infarction, stroke, angina, coronary artery bypass, stent, angioplasty, sudden cardiac death

causes of dyslipidemia must be excluded (**Table 33**). After confirming FH diagnosis in the screened child/adolescent ("index" case), a reverse cascade screening in family members is required[439,453,458,460].

HoFH, is not so rare as previously believed and should be suspected in cases were both parents have dyslipidemia. LDL-C levels may exceed 800 mg/dL since infancy and coronary events can occur in the 1st decade of life with lifespan being severely shortened. The diagnostic criteria include LDL-C levels, family history and DNA mutation (**Table 36**). Screening for complications is necessary[453,458,460] (**Table 36**). The discrimination between HeFH and HoFH is difficult when LDL-C levels are between 300-500 mg/dL[453].

Other rare genetic dyslipidemias (i.e., autosomal recessive form of FH, sitosterolemia, Wolman disease, cholesterol ester storage disease) should be included in the differential diagnosis of FH, especially in cases where parents have normal lipid levels[453]. FH patients may also have additional independent risk factors for atherosclerosis or co-exist with other diseases, which accelerate atherosclerosis[453] (**Table 37**). FCH is the most common genetic dyslipidemia, but diagnostic criteria are less clear, making the estimation of pediatric prevalence difficult[454].

Although there is agreement that early intervention in children with dyslipidemia is significant for the prevention of subclinical atherosclerosis, the most effective diagnostic and treatment approaches are yet unclear. FH children exert higher common carotid intima-media thickness (cIMT) associated with LDL-C levels, compared

TABLE 33. Causes of secondary dyslipidemia in children and adolescents.

Endocrine and Metabolic disorders • Hypothyroidism (even subclinic) • Diabetes type 1 or 2 • Hypopituitarism • Polycystic ovary syndrome • Overweight, obesity and metabolic syndrome • Lipodystrophy • Acute intermittent porphyria • Pregnancy	**Exogenous factors** • Smoking (active or passive) • Alcohol consumption • Unhealthy diets, specific diets e.g., ketogenic • Drugs: corticosteroids, isotretinoin, b-blockers, some oral contraceptives, antiepileptics chemotherapeutic agents and antiretroviral agents • Absence of physical activity
Renal disorders • Chronic kidney disease • Hemolytic uremic syndrome • Nephrotic syndrome	**Chronic inflammatory diseases** • Systemic lupus erythematosus • Juvenile idiopathic arthritis
Infections • Acute viral/bacterial infection • HIV infection • Hepatitis	**Liver disorders** • Obstructive liver disease • Cholestatic conditions • Biliary cirrhosis • Alagille syndrome
Other conditions • Anorexia nervosa • Kawasaki disease • Post-solid organ transplantation • Childhood cancer survivors • Low birth weight • Progeria • Idiopathic hypercalcemia • Klinefelter syndrome • Werner syndrome	**Storage diseases** • Glycogen-storage disease • Gaucher disease • Cystine-storage disease • Juvenile Tay-Sacks disease • Niemann-Pick disease • Sitosterolemia or phytosterolemia

Modified from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute 2011[454].

TABLE 34. Recommendations for lipid screening in children and adolescents aged 2 to 18 years.

Recommendations	Class of recommendation
Targeted screening* in children/ adolescents aged 2-18 years with risk factors for dyslipidemia/ASCVD (see **Table 37**) is recommended	IIa

ASCVD: atherosclerotic cardiovascular disease

*Screening should be avoided during acute infections, immobilization, or during the month following hospitalization.

TABLE 35. Diagnosis of heterozygous familial hypercholesterolemia in childhood and adulthood.

The probability is high if the child/adolescent has:	
• LDL-C ≥190 mg/dL (in 2 measurements with an interval of 3 months)	
• LDL-C ≥160 mg/dL or non-HDL-C ≥190 mg/dL (>95th percentile) with a family history of premature ASCVD in 1st or 2nd degree relatives and/or elevated cholesterol in one parent	IIa
• LDL-C ≥130 mg/dL if the parent has a genetic diagnosis of HeFH	
Confirmation of the diagnosis:	
• DNA testing establishes the diagnosis of HeFH	
• If another member of the family has genetic diagnosis of HeFH, the child/adolescent must undergo a DNA test	I
Reverse cascade screening of family members:	
• Cholesterol testing for 1st, 2nd -and when possible- 3rd degree relatives for detection of FH	IIa

ASCVD: atherosclerotic cardiovascular disease; HeFH: heterozygous familial hypercholesterolemia

with healthy controls or unaffected siblings[17,453,454,458]. Principles of management include lifestyle modification, lipid-lowering agents, and screening for ASCVD. Lifestyle changes are the first-line approach for all children/adolescents with dyslipidemia (**Table 38**). Existing evidence indicates that this is the most cost-effective approach to ASCVD prevention. Initiation of lifestyle changes early in life, where behavioral habits are being established, is essential for ensuring greater effectiveness and long-term adherence[453,454,458,461]. In obese children, the normalization of body weight is essential[454,460]. Two-step fat-modified healthy diet is recommended, while the Mediterranean diet exert several benefits for all pediatric populations[454,456,458,460]. The administration of PSS for children older than 5 years

TABLE 36. Diagnosis of homozygous familial hypercholesterolemia in childhood and adulthood.

HoFH is highly suspected in children with:	
• LDL-C ≥500 mg/dL	
• Clinical manifestations such as tendon xanthomas* (hands and Achilles tendons), corneal arcus, premature cardiovascular disease** and aortic valve disease	IIa
Hypercholesterolemia in both parents	
Confirmation of the diagnosis:	
• DNA testing establishes the diagnosis of HoFH	I
• CT angiography and/or MR imaging are recommended to evaluate coronary arteries and aorta	I
• Invasive coronary angiography may be indicated depending on clinical status and findings of non-invasive cardiac investigations	IIb

*Xanthomas in HoFH children appear from the first months of life until 10 years. The absence of xanthomas does not exclude the diagnosis of HoFH.

**Early cardiovascular symptoms due to aortic stenosis, regurgitation, and coronal ostial stenosis. Angina pectoris, myocardial infarction and death usually appear in adolescence, although they have been reported even in early childhood

HoFH: homozygous familial hypercholesterolemia

TABLE 37. ASCVD risk factors and co-morbidities.

A). High-Risk factors	B). Moderate-Risk factors
1. Hypertension (≥97th percentile + 5 mmHg) requiring drug therapy	1. Hypertension not requiring medication therapy
2. Obesity (BMI ≥97th percentile)	2. Obesity (BMI ≥95th, <97th percentile)
3. Current cigarette smoking	3. HDL-C <40 mg/dL
4. Presence of high-risk conditions	4. Presence of moderate risk conditions
• Diabetes type 1 and 2	• Chronic inflammatory disease: Systemic lupus erythematosus, Juvenile idiopathic arthritis, Kawasaki disease with regressed coronary aneurysms
• Chronic kidney disease	• HIV infection
• End-stage renal disease	• Nephrotic syndrome
• Post renal transplantation	
• Post orthotopic heart transplants	
• Kawasaki disease with current aneurysms	

Adapted from the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute 2011[454].

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol

TABLE 38. Lifestyle modification in children and adolescents 2-18 years with dyslipidemia.

A. Dietetic interventions	
Step-1 or CHILD-1 diet: Healthy diet for lowering cholesterol • Total fat 25-30% of daily Kcal intake • Saturated fat <10% of daily Kcal intake • Trans fats <1% of daily Kcal intake or < 2-3 g/day • Monounsaturated fat 10-15% of daily Kcal intake • Polyunsaturated fat up to 10% of daily Kcal intake • Daily cholesterol intake <300 mg/day ***Encourage***: • Low-fat dairy products • Fruit, vegetables, whole grains, beans • Fish and lean meat • High dietary fiber intake: child's age + 5 g for young children daily, up to 14 g per 1000 calories for older children and adolescents • Water instead of sugar sweetened beverages and 100% full juice • Daily breakfast • Eating meals as a family ***Limit or Avoid:*** • Sugar sweetened beverages • 100% full juice to ≤120 mL/day • Fast-foods	I
Mediterranean-style diets for lowering cholesterol	I
Step-2 or CHILD-2 diet for children/adolescents with dyslipidemia ***Main differences from Step-1, CHILD-1:*** • Saturated fat <7% of daily Kcal intake • Daily cholesterol intake <200 mg/day • Increase dietary fish to raise omega-3 fatty acids intake • Decrease sugar intake especially in case of hypertriglyceridemia • Consume complex instead simple carbohydrates	I
CHILD-2-TG: For children and adolescents with hypertriglyceridemia • Restrict fat as in CHILD-2 • Reduce sugar intake • Replace simple carbohydrates with complex ones • Avoid sugar sweetened beverages • Increase dietary fish to raise omega-3 fatty acids intake	I
For children and adolescents with hypertriglyceridemia • Omega-3 fatty acid supplementation can be added at 2-4 g/day if TG >500 mg/dL	IIa
For children and adolescents with elevated LDL-C levels: • Plant sterols/stanols esters supplementation: 2.0-2.5 g daily ◦ Encourage children to consume foods rich in vitamins A, E, and carotenes • Dietary intake of water-soluble fiber: age in years plus 5 g for children 2-10 years, up to 14 g / 1000 kcal for children >10 years • Other dietary nutrients and supplements such as yeast red rice, polycosanols, garlic extract, rapeseed oil and soy protein are not recommended (poorly evaluated in children)	IIa
B. Physical activity	
Pre-school children (1-4 years) • Active play should be encouraged ***School-aged children (5-17 years)*** • Moderate- to vigorous-intensity aerobic physical activity of ≥1 hour daily • Exercise should be of vigorous-intensity at least 3 days a week • Muscle-strengthening physical activity: as part of their 60 min or more of daily physical activity, at least 3 days a week • Bone-strengthening physical activity: as part of their 60 min or more of daily physical activity, at least 3 days a week	I
C. Avoiding unhealthy heart habits	
• Smoking cessation in adolescents • Decrease children's environmental smoke exposure • Discontinuation of alcohol intake in adolescents • Limit total media time to ≤2 hours per day	IIa

is also recommended, while water-soluble fiber psyllium has been poorly evaluated in children[453,454,458] (**Table 38**).

Increased physical activity is advised in all children/adolescents, especially in those with dyslipidemia and overweight/obesity. There is strong evidence that physical activity beneficially affects several metabolic risk factors, including lipid profile, whereas it may also improve subclinical atherosclerosis. Thus, all children should be encouraged for daily physical activity, given that there is no evidence of any harm[453,454,462] (**Table 38**). Unhealthy habits, such as cigarette smoking and alcohol consumption, should be discouraged[453,454]. Other ASCVD risk factors, e.g., hypertension, should be monitored and treated if indicated[454,458,461]. In several HeFH patients, the above-mentioned measures are insufficient in LDL-C-lowering to desirable levels and thus, pharmaceutical therapy will be required. The decision for drug therapy is based on LDL-C levels, family history and the presence of ASCVD risk factors (**Table 37** and **Table 39**). Since clinical trials on the use of lipid-lowering drug therapy and potential long-term effects in children are few, evidence-based recommendations are limited and children who require drug treatment should be carefully identified by lipid specialists[17,439,453,454,458].

Statins are considered as first choice drugs for the management of children/adolescents with genetic dyslipidemia (**Table 40**).

Although long-term studies are scarce, statins are thought to be safe and effective with increasing evidence supporting their use in high-risk children older than 8-10 years[17,439,453–455,458,461]. Restoration of endothelial dysfunction and regression of cIMT have been reported with statins. However, more research is needed, to confirm the exact age of statin initiation and its long-term safety. Statin administration is considered only after therapeutic lifestyle changes have been applied for 6-12 months and have failed to effectively lower LDL-C levels. Although there are currently no evidence-based recommendations, LDL-C<130 mg/dL is considered as the optimal LDL-C goal, necessary to prevent early atherosclerosis and ASCVD[439,453,454,458,461] (**Table 41**). If this target is not achieved, a more intense statin is administered, or ezetimibe is added. Recently, the FDA has approved evolocumab, a PCSK9 inhibitor, for use as an add-on treatment for children ≥

TABLE 39. Recommendations for initiation of statin therapy in children with dyslipidemia.

Recommendations	
Children ≥8-10 years with*:	
Persistently increased LDL-C ≥190 mg/dL **or** LDL-C: 160-189 mg/dL and a positive family history for early ASCVD** or presence of 1 high-risk ASCVD factor or ≥2 moderate-risk ASCVD factors (see **Table 39**) **or** LDL-C: 130-159 mg/dL and 2 high-level ASCVD risk factors or 1 high- and 2 moderate-level ASCVD risk factors	IIa

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol

*Therapeutic lifestyle changes should be applied for 6-12 months and if they fail to effectively lower LDL-C levels, then statin therapy should be initiated

**Any of the following: myocardial infarction, stroke, angina, coronary artery bypass, stent, angioplasty, sudden cardiac death

Note. In females, statin initiation post menarche (at least 1 year) is recommended

TABLE 40. Statins approved for treating children/adolescents with heterozygous familial hypercholesterolemia.

Type of statin	Age of initiation	Dosing	Comments
Atorvastatin	10 years	10-20 mg	Australia: Approved for children older than 6 years
Fluvastatin	10 years	20-80 mg	USA: Approved for children older than 8 years
Lovastatin	10 years	10-40 mg	
Pitavastatin	8 years	1-4 mg	
Pravastatin	8 years	<14 years: 20 mg ≥14 years: 40 mg	
Rosuvastatin	8 years	5-20 mg	Europe & Australia: Approved for children older than 6 years
Simvastatin	10 years	10-40mg	

TABLE 41. Low-density lipoprotein cholesterol (LDL-C) goals in children and adolescents.

• An absolute target for LDL-C does not exist • LDL-C goal is <130 mg/dL (ideally <110 mg/dL) in children aged ≥10 years, especially in those with additional CV risk factors, including increased Lp(a) levels • For children aged 8 to 10 years, a 50% decrease from pre-treatment levels is suggested	IIa

LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease; Lp(a): Lipoprotein (a)

TABLE 42. Follow-up and monitoring of children and adolescents on statins.

Recommendations	
Initiation and up-titration of statin therapy: • Statins should be initiated at the minimum dose and up-titrated according to the LDL-C lowering response and tolerability • If statin is not sufficient to achieve the LDL-C target: a) change to a more potent statin or b) add another lipid-lowering drug e.g., ezetimibe • Statins are received once daily	IIa
Lipid status assessment: • Lipid status should be reassessed 4-6 weeks after the initiation and again at 6 weeks interval until treatment goal is achieved • If adherence is a concern or the lipid profile is unstable, the individual will likely benefit from bi-annual assessment. • A full fasting lipid panel, including TC, LDL-C, HDL-C and TG should be part of each follow-up assessment	IIa
Liver and Muscle enzymes evaluation: • Check ALT, CK and creatinine levels before initiation of treatment • Check ALT and CK after 4-8 weeks of treatment initiation or change • If a liver disease exists, transaminases should be measured every 3 months • Plasma CK should be assessed whenever an individual reports clinically significant myalgias or muscle weakness • If abnormal transaminases ≥3 times or CK ≥10 times upper the normal limits, then withhold statin and repeat the blood work in 2 weeks • Children and adolescents with hypothyroidism or vitamin D deficiency are at higher risk to present statin-associated muscles symptoms	IIa
Fasting plasma glucose and/or random glycated hemoglobin (HbA1c): • Should be measured every 6 months only in children on higher doses of statins who are obese or have impaired glucose intolerance • Statins may increase the risk for diabetes in adults	IIa
Growth, sexual maturation, and development: • Should be followed up once or twice per year • Advise females adolescents for appropriate contraception	IIa
Myositis and Influenza: • In children, myositis is a common complication during influenza infection • Statins increase the risk for myositis • The vaccination against influenza in children under statin therapy must be discussed	IIa

LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; CK: creatine kinase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase

10 years with HeFH to achieve the LDL-C target.

Follow-up of children and adolescents on statin treatment is necessary[17,439,453,454,458] (**Table 42**).

The latest ESC/EAS guidelines for the management of dyslipidemia recommend that FH diagnosis should be considered in children with LDL-C levels >155 mg/dL (>4 mmol/L) and testing for FH could be performed from the age of 5 years, or earlier if HoFH is suspected[1]. Furthermore, FH children should adopt a heart-healthy diet and be treated with a statin from the age of 8-10 years with a LDL-C goal of <135 mg/dL (3.5 mmol/L) at >10 years of age (and a ≥50% LDL-C reduction at younger ages)[1]. Functional foods with PSS (≥2 g/day with the main meal) may also be considered in children (aged >6 years) with FH[1].

In HoFH patients, a very aggressive LDL-lowering treatment should be initiated at diagnosis, to prevent or delay

TABLE 43. Management of children and adolescents with homozygous familial hypercholesterolemia.

Recommendations	
• Early diagnosis is significant • Therapeutic lifestyle changes should be implemented	I
Drug Therapy • Initiation of aggressive therapy immediately after diagnosis • Initial therapy includes high intensity statin combined with ezetimibe • Co-administration of other hypolipidemic drugs e.g., colesevelam can be considered • Novel hypolipidemic agents, e.g., PCSK9 inhibitors*, evinacumab**, lomitapide, for older children/adolescents are being tested	IIa
LDL-apheresis • LDL-apheresis is recommended to begin early, even at 2 years of age: once or twice a week, measuring LDL-C levels before and after treatment	IIa
Target of LDL-C lowering • A reduction of 50% from baseline levels • LDL-C <100 mg/dL • In patients with a history of ASCVD: LDL-C<70 mg/dL	IIa
Surgical Therapy • Liver transplantation should be considered in severe, resistant to other measures, disease before CVD is established	IIa

*They are ineffective in individuals with double-null LDL receptor defects. Among PCSK9 inhibitors, evolocumab has been approved, in combination with other LDL-C lowering therapies, for use in children ≥10 years.

**Evinacumab, an ANGPTL3 (angiopoietin-like 3) inhibitor, is indicated as an adjunct to other LDL-C lowering therapies for use in children ≥12 years.

ASCVD: atherosclerotic cardiovascular disease; PCSK9: proprotein convertase subtilisin-kexin type 9; LDL-C: low-density lipoprotein cholesterol

TABLE 44. Management of hypertriglyceridemia in children and adolescents.

Recommendations	
Therapeutic lifestyle changes (see **Table 40**) and weight reduction, if overweight/obese • Consumption of foods rich in omega-3 fatty acids and poor in simple sugars and saturated fat • If fasting TG are 100-199 mg/dL (in those aged <10 years) or 130-199 mg/dL (in those aged >10 years) after lifestyle modification for 6-12 months, an increase in the intake of foods rich in omega-3 fatty acids is recommended	I
• If fasting TG are 200-499 mg/dL, after lifestyle modification for 6-12 months, supplementation of omega-3 fatty acids* may be considered	IIa
• If fasting TG are >500 mg/dL, without abdominal pain, supplementation of omega-3 fatty acids* and/or pharmacotherapy** is recommended	
• If fasting TG are >500 mg/dL with abdominal pain/pancreatitis or fasting TG are >1000 mg/dL, rapid lowering of TG is necessary • If fasting TG are >1000 mg/dL, fasting (nothing by mouth) and intravenous fluids may be needed	I
• If fasting TG are >500 mg/dL with abdominal pain/pancreatitis or fasting TG are >1000 mg/dL, continuous insulin infusion of 0.1-0.3 U/kg/h along with intravenous dextrose to maintain euglycemia may be needed	IIb
• Plasmapheresis has been applied in a few cases of children with severe hypertriglyceridemia and acute pancreatitis, complicated by lactic acidosis and multiple organ failure	IIb

TG: triglycerides

*Limited data is available about omega-3 fish oils in pediatric populations and they have not received US Food and Drug Administration (FDA) approval.

**Note: Fibrates are not approved for use in children/adolescents.

ASCVD. Delay in treatment may result in acute myocardial infarction, even before the age of 5 years. The combined statin/ezetimibe therapy is almost never sufficient to lower LDL-C at goal and prevent atherosclerosis development and progression. Most patients will need to undergo LDL-apheresis, which should be started before the age of 5.

Novel hypolipidemic agents are being tested as well. In severe cases, liver transplantation may be required[17,453,454] (**Table 43**).

There are no guidelines for managing low HDL-C levels in children. For hypertriglyceridemia, the first-line approach is lifestyle modification and body weight control. In more severe cases, omega-3 fatty acids, fibrates or other treatments may be required[454,458,463] (**Table 44**).

20 Dyslipidemia in Patients with HIV Infection

Patients with HIV infection have also a high ASCVD risk[464]. Importantly, patients with HIV who are receiving antiretroviral therapy (ART) have approximately 1.5-2.0 times higher risk for ASCVD events than HIV-uninfected people[464,465]. Moreover, dyslipidemia is more prevalent in patients with HIV infection, partly due to the adverse metabolic effects of most classes of ART[466]. In general, patients with HIV infection on ART should be treated as at least high-risk[1]. However, the optimal risk stratification tool in patients with HIV infection without established ASCVD, diabetes or CKD remains unknown. In this population, the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equation has been developed for ASCVD risk estimation, and incorporates both traditional and HIV-related CV risk factors, namely ART and CD4 count[467]. Limited data suggest that this equation has better discrimination and calibration than the HEART SCORE.

In patients with HIV infection, statins are as effective in lowering LDL-C levels as in the general population[468]. However, there are no randomized controlled studies that evaluated the effects of statins on ASCVD morbidity and mortality in patients with HIV infection[1]. Statins were reported to reduce non-calcified plaque volume and improve high-risk coronary plaque features in HIV-infected patients with subclinical coronary atherosclerosis[469]. In observational studies, treatment with statins was also associated with a trend for lower all-cause mortality and CV morbidity in patients with HIV[470]. The ongoing placebo-controlled Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) will evaluate whether pitavastatin will reduce CV morbidity in 6500 patients with HIV infection on ART, with a CD4 cell count >100/μl and without established ASCVD[471].

Statins are generally well-tolerated in patients with HIV infection[468]. Among antiretroviral agents, protease inhibitors (PIs) inhibit CYP3A4 whereas most non-nucleoside reverse transcriptase inhibitors (NNRTIs) induce CYP3A4[472]. Statins metabolized in the liver via the CYP3A4 (simvastatin and lovastatin) are susceptible to drug interactions with these antiretroviral agents[473]. Atorvastatin undergoes a lesser amount of CYP3A4 metabolism as one of its minor metabolic pathways[473]. In contrast, pravastatin

TABLE 45. Recommendations for the management of dyslipidemia in patients with HIV infection.

Recommendation	Class of recommendation
A fasting lipid profile must be assessed in HIV-infected patients annually as well as before and after changing ART regimens	I
Patients with HIV infection on ART should be treated as at least high-risk	IIa
In patients with HIV infection but without established ASCVD, CKD or diabetes, the Data collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study equation may be considered instead of the HEART SCORE for CV risk estimation	IIb
Atorvastatin, rosuvastatin, pravastatin, fluvastatin and pitavastatin are less susceptible to drug interactions with antiretroviral treatment	IIa
Starting and maximal doses of statins may be based on the background antiretroviral treatment	IIb
Ezetimibe, fenofibrate and PCSK9 inhibitors are safe and effective in patients with HIV infection	IIa
If LDL-C targets are not achieved despite maximally tolerated combination lipid-lowering therapy, change of antiretroviral treatment should be considered	IIa
Lipid-lowering therapy (mostly statins) should be considered in HIV patients with dyslipidemia to achieve LDL-C goal as defined for high-risk patients. The choice of statin should be based on potential drug-drug interactions	IIa

ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; LDL-C: low-density lipoprotein cholesterol

is not significantly metabolized via the CYP isoenzyme system, and fluvastatin, pitavastatin and rosuvastatin are metabolized via the CYP2C9 isoenzyme[473]. Therefore, in patients treated with ritonavir-boosted PIs, atorvastatin and rosuvastatin should be started at a low dose and the maximal doses are 40 and 20 mg/day, respectively; higher doses of pravastatin should be considered in these patients (except in patients treated with darunavir, where pravastatin should be started at a low dose), whereas simvastatin is contraindicated. In patients treated with NNRTIs, higher doses of atorvastatin and pravastatin should be considered, whereas rosuvastatin should be started at a low dose.

Among other lipid-lowering agents, ezetimibe and fenofibrate are safe in patients with HIV infection and affect lipid levels in a similar way with the general population[474]. There are also data supporting the use of PCSK9 inhibitors in combination with other lipid-lowering drugs in HIV patients to achieve LDL-C targets[475,476]. The ongoing Effect of PCSK9 Inhibition on Cardiovascular Risk in Treated HIV Infection (EPIC-HIV) study will provide more evidence for the effects of PCSK9 inhibitors on arterial inflammation and endothelial function in HIV patients[477].

Regarding the effect on ART on lipids, nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), NNRTIs and PIs can adversely affect lipid profile but these effects differ between members of these drug classes[478]. Interestingly, treatment with PIs increases the risk of myocardial infarction and this increase is partly mediated by PIs-induced dyslipidemia. On the other hand, integrase inhibitors do not alter the lipid profile[479,480]. Therefore, if LDL-C targets are not achieved despite maximally tolerated hypolipidemic drug therapy, a change of ART should be considered (i.e., replacing ritonavir-boosted PIs with NNRTI, integrase inhibitor or another PI known to cause less metabolic disturbances, replacing zidovudine or abacavir with tenofovir, or use an NRTI-sparing regimen).

Overall, fasting lipids should be measured in HIV-infected patients annually, as well as before and after changing ART regimens[1].

Table 45 summarizes the above recommendations.

21 Dyslipidemia in Autoimmune Diseases

Systemic inflammation is considered as a pivotal link between autoimmune diseases [such as rheumatoid arthritis (RA), systematic lupus erythematosus (SLE), psoriasis, antiphospholipid syndrome and inflammatory bowel disease (IBD)] and ASCVD risk since it plays a crucial role in the pathogenesis of atherosclerosis and vascular disease. Soluble inflammatory mediators (e.g., C-reactive protein, CRP) and autoimmune elements (e.g., autoantibodies, autoantigens) may accelerate the atherosclerotic process. Previous meta-analyses support the associations of RA, SLE, psoriatic arthritis and IBD with increased ASCVD risk[481–484]. Taking into consideration that these patients can develop inflammatory vasculitis and endothelial dysfunction, particular attention should be paid to the management of traditional ASCVD risk factors, such as dyslipidemia, in these settings[485–487].

TABLE 46. Recommendations for the management of dyslipidemia in autoimmune diseases.

Recommendations	Class of recommendation
In patients with autoimmune diseases, a fasting lipid profile should be measured to assess ASCVD risk and the need for statin therapy	IIa
Lipids should be measured 2-4 months after starting or altering inflammatory disease-modifying therapy	IIa
Patients with autoimmune or inflammatory disease should be treated as at least high-risk	IIa

LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

Early risk factor intervention and effective control of systemic inflammation should be incorporated into the management of autoimmune diseases. Apart from lipid-lowering, statins also exert immunomodulatory and anti-inflammatory actions, and they provide clinical benefit by protecting patients against accelerated atherosclerosis. These pleiotropic effects of statins may also beneficially affect disease activity, as in patients with RA[488]. In general, patients with autoimmune or inflammatory disease should be treated as at least high-risk[1].

It is worth mentioning that the assessment of ASCVD risk factors often leads to an underestimation of actual risk and, consequently, to undertreatment of these patients[489–491]. Patients with autoimmune diseases, especially those with RA, who are undertreated or who have high disease activity, ordinarily have low lipid levels due to the high inflammatory load leading to an increased cholesterol catabolism[492]. Treatment with anti-inflammatory regimens can affect (and even increase) lipid levels[492–495]. Therefore, it is more secure to re-estimate ASCVD risk 2 to 4 months after inflammatory disease has been controlled.

Table 46 summarizes the above recommendations.

22 Dyslipidemia in Patients with Non-Alcoholic Fatty Liver Disease

NAFLD is the hepatic manifestation of metabolic syndrome[496] and it is associated with abdominal obesity, T2D, dyslipidemia, arterial hypertension, and ASCVD[497]. Patients with NAFLD and non-alcoholic steatohepatitis (NASH) are at an increased risk for ASCVD morbidity and mortality[498]. Moreover, ASCVD has been established as the most common cause of death among patients with NAFLD/NASH[498]. For this reason, the treatment of dyslipidemia should be considered of great importance for the ASCVD risk reduction in those patients.

Lifestyle changes, such as diet and exercise, are important for NAFLD treatment[499], even though long-term compliance with lifestyle changes is rarely achieved. Statins are well established in the treatment of dyslipidemia and the prevention of ASCVD events. However, due to their potential deleterious effects on liver, their use in patients with increased (> 3xUNL) liver enzymes have been restricted[500]. Despite this, over the last decade, accumulating data demonstrated the beneficial effects of statins in patients with NAFLD, concluding that they are safe in this setting. Several studies showed statin-induced improvements, not only in liver histology, but also in ASCVD outcomes in NAFLD patients[501]. Although there are no prospective RCTs to examine the effect of statins on NAFLD, there are post-hoc analyses of large survival studies and some smaller studies with statins, including biopsy-proven NASH patients, supporting the beneficial effect of statins on both liver histology and ASCVD risk[501].

Particularly, a post hoc analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study was the first to show that statins significantly reduced ASCVD events especially in patients with NAFLD (defined by ultrasound and liver enzymes)[502]. Three years later, the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study[503] compared the effects of atorvastatin (80 mg/day) or simvastatin (20-40 mg/day) in a large Scandinavian population with established ASCVD and verified results of GREACE trial; atorvastatin normalized liver enzymes among patients with elevated levels and resulted in a greater reduction in the risk for major ASCVD events compared with simvastatin. Similarly, the sub-analysis of the ATTEMPT study[504], which was a primary ASCVD prevention study among patients with metabolic syndrome, showed that atorvastatin normalized liver enzymes and ultrasonographic findings. The impact of statins on the liver has been investigated in a few small studies with liver biopsies, showing a protective statin-induced effect on steatosis, steatohepatitis and fibrosis[505–507].

Based on the lack of evidence that statins increase the risk for hepatic injury, as well as data supporting their beneficial effects on NAFLD, statins are suggested for dyslipidemia treatment and ASCVD risk prevention in NAFLD patients[508,509]. LDL-C goals should be defined based on individual's ASCVD risk classification. Nevertheless, RCTs with histological endpoints are needed to prove statin-related favorable effects on liver histology and establish their role in the management of NAFLD.

Table 47 summarizes the recommendations for the management of nonalcoholic fatty liver disease.

TABLE 47. Recommendations for the management of dyslipidemia in non-alcoholic fatty liver disease.

Recommendations	Class of recommendation
Statins should be used to treat dyslipidemia and reduce ASCVD risk in NAFLD/NASH patients	IIa
Statins should not be used to specifically treat NASH until RCTs with histological endpoints prove their efficacy on liver histology	III

NAFLD: non-alcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; ASCVD: atherosclerotic cardiovascular disease; RCT: randomized controlled trial

23 Statin Intolerance - Statin-Associated Muscle Symptoms

SAMS are the most frequent (>70%) clinically relevant adverse events of statin therapy, potentially leading to drug discontinuation and higher risk of recurrent cardiac events[510]. Therefore, it is mandatory for the clinicians to use strategies to treat SAMS and maintain patients on lipid-lowering treatment. Most experts suggest that the definition of statin intolerance requires intolerance, either complete or partial, to at least 2 different statins, one given at a low dose[448,511].

23.1 Incidence of statin-associated muscle symptoms

The exact incidence is unknown, and this is mainly due to the lack of objective criteria for the diagnosis of SAMS. **Table 48** presents the definitions of SAMS proposed by the EAS consensus panel[512].

RCTs have reported very low incidence of SAMS, while in observational studies the incidence ranges from 7 to 29%[513,514]. The high rates of SAMS in observational studies may be partly attributed to the nocebo effect (inverse of placebo effect) due to the negative influences of media regarding the exaggeration of adverse effects of statins[515]. A series of n-of-1 trials, including statin-intolerant participants, showed that frequency and intensity of muscle symptoms did not differ between statins and placebo, suggesting that muscle symptoms were due to negative expectations during statin treatment (nocebo effect)[516,517]. The Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study, a double-blind, placebo-controlled study, which randomized 420 statin-naïve healthy individuals to atorvastatin 80 mg daily or placebo for 6 months, reported that 9.4% of the statin-treated and 4.6% of the controls met the study definition of myalgia[518]. These data suggest that the incidence of SAMS is considerably less than that reported in observational trials. Therefore, the incidence of SAMS in the daily clinical practice probably ranges between 5-10%[519,520]. A meta-analysis of individual participant data from 19 double-blind trials of statin versus placebo (n=123,940) and 4 double-blind trials of a more intensive versus a less intensive statin regimen (n=30,724) showed that statin treatment was associated with a 7% relative increase in muscle pain or weakness during the first year, corresponding to an absolute excess rate of 11 (6-16) events per 1000 person-years, which suggests that only one in 15 of these muscle-related complaints were really produced by the statin[521]. The analysis of all years of treatment showed that more intensive statin regimens (i.e.,

TABLE 48. Definitions of statin-associated muscle symptoms proposed by the EAS consensus panel.

Symptoms	CK levels	Incidence	Terminology	Comments
Muscle symptoms	Normal	3-5%	Myalgia	Causality is uncertain
Muscle symptoms	CK >ULN and <10 x ULN	3-5%		Commonly due to exercise or physical activity, but also may be statin-related
Muscle symptoms	CK >10 x ULN and <40 x ULN	0.1-0.2%	Myositis or myopathy	May be statin-related but may be associated with underlying muscle disease
Muscle symptoms	CK >40 x ULN	1 per 10,000 person-years	Rhabdomyolysis when associated with creatinine elevation and/or myoglobinuria	Referral for hospital admission
None	CK >ULN		Asymptomatic CK increase	Raised CK may be incidental finding. Consider checking thyroid function or may be exercise-related

CK: creatine kinase; ULN: upper limit of normal

40-80 mg/d atorvastatin or 20-40 mg/d rosuvastatin) were associated with a higher rate ratio of muscle symptoms than less intensive or moderate-intensity regimens [1.08 (1.04-1.13) vs 1.03 (1.00-1.05)][521].

23.2 Clinical manifestations of statin-associated muscle symptoms

The clinical spectrum of SAMS is highly heterogeneous and ranges from mild weakness, cramps and muscle pains to fulminant rhabdomyolysis requiring hospitalization. The most common type of SAMS (>80%) are muscle pains with or, most frequently, without mild CK elevation. Muscle pain is usually symmetrical and involves large proximal muscle groups including the thighs, buttocks, calves, and back muscles. They typically occur within 4-6 weeks after initiation of statin treatment and usually regress within 2-4 weeks after statin cessation[1,522]. SAMS are class effect, dose-dependent and appear independent of LDL-C reduction[523]. A score system has been developed to identify the probability of muscle symptoms to be statin-related[524] (**Table 49**).

23.3 Risk factors for statin-associated muscle symptoms

Table 52 presents the factors associated with a higher risk of SAMS. This risk can be minimized by identifying the "vulnerable" patients and the predisposing conditions. Gemfibrozil is the medication most associated with rhabdomyolysis when given with statins and should never be co-administered. In contrast, fenofibrate is safer and can be given with statins in case of mixed hyperlipidemias.

23.4 Management of patients with statin-associated muscle symptoms

It is important to exclude secondary causes of myalgias, such as hypothyroidism, low vitamin D levels, polymyalgia rheumatica, or increased physical activity, and review all concomitant drugs (i.e., CYP3A4 inhibitors, use of alcohol, etc.) that may interact with statins and increase the risk of SAMS[512] (**Table 50**).

The management of a patient for whom SAMS are likely is based on the severity of symptoms and the magnitude of CK elevation. **Figure 8** presents the algorithm for the management of patients with SAMS. It should be mentioned that routine measurements of CK are not recommended but only when muscle symptoms appear.

The management of the statin intolerant patient due to muscle symptoms is described in more details in **Table 51**. It should be noted that certain nutraceuticals (at certain doses) may represent an alternative therapeutic option in statin-intolerant patients[145,146,525].

TABLE 49. Proposed score system that assesses the probability of muscle symptoms to be statin-related.

Parameter	Score
Distribution of symptoms	
• Symmetric, hip flexors or thighs	3
• Symmetric, calves	2
• Symmetric, upper proximal extremities	2
• Not specific to any area, asymmetric or intermittent	1
Timing of symptom onset	
• <4 weeks	3
• >4-12 weeks	2
• >12 weeks	1
Timing of muscle symptoms improvement after statin withdrawal (de-challenge)	
• <2 weeks	2
• 2-4 weeks	1
• No improvement >4 weeks	0
Re-challenge with a statin	
• Same symptoms recur in <4 weeks	3
• Same symptoms recur in 4-12 weeks	1
• Same symptoms recur in >12 weeks or symptoms do not recur	0
Likelihood that patient's muscle symptoms are due to statin use	
• Probable	9-11
• Possible	7-8
• Unlikely	<7

23.5 Effectiveness of non-statin lipid-lowering therapy in LDL-C reduction

a) Ezetimibe: Ezetimibe in the dose of 10 mg daily reduces LDL-C by 15-20% and usually does not trigger muscle symptoms. The combination of ezetimibe with low-dose statins can reduce LDL-C by 40-50%.

b) BAS: Colesevelam (has more favorable tolerability than cholestyramine and colestipol) can be combined with ezetimibe or/and statin. The maintenance dose is 3 x 625 mg tablets, twice daily, taken with meals. Colesevelam lowers LDL-C by 10-16% in combination with other lipid-lowering drugs.

c) PCSK9 inhibitors: The two PCSK9 inhibitors that have been approved, evolocumab and alirocumab, lower LDL-C by ~60%. In studies that enrolled statin intolerant patients (≥2 statins) (GAUSS-3), the majority (~80%) of these patients tolerated PCSK9 inhibitors and remained free of muscle symptoms[526]. According to a consensus of Greek experts on the rational clinical use of PCSK9 inhibitors, very high risk (patients with established

TABLE 50. Conditions that increase the risk of statin-associated myopathy.

Patient-related risk factors
1. Age >80 years
2. Hypothyroidism
3. Impaired renal or liver function
4. Female sex
5. Low body mass index
6. Diabetes
7. Polypharmacy
8. Strenuous exercise
9. Vitamin D deficiency
10. Acute infection
11. Heavy alcohol consumption (alcohol is a direct muscle toxin)
12. Drug abuse (cocaine, amphetamines, heroin)
13. Impaired renal or hepatic function
14. Biliary tract obstruction
15. Inflammatory or inherited metabolic muscle defects (McArdle disease, carnitine palmityl transferase II deficiency)
16. Surgery with high metabolic demands
17. History of pre-existing/unexplained muscle/joint/tendon pain
Risk factors predisposing to statin interactions
Co-administration with:
1. Cytochrome P-450 3A4 inhibitors including:
• Macrolide antibiotics: azithromycin, clarithromycin, erythromycin
• Cyclosporine
• Antifungals: fluconazole*, itraconazole, ketoconazole*
• Antivirals (protease inhibitors): amprenavir, indinavir, nelfinavir, ritonavir
• Amiodarone
• Calcium antagonists (diltiazem, verapamil) [weak inhibitors]
• Warfarin*
• Colchicine
• Grapefruit juice (if >1 L/day)
2. Glucuronidation inhibitors: gemfibrozil
3. Nicotinic acid

*also metabolized through the cytochrome P-450 2C9

ASCVD) or high-risk (HellenicSCORE II 5-10%[15], **Figure 2**), patients who are intolerant to statins and have LDL-C ≥130 or ≥100 mg/dL, respectively, are eligible to receive a PCSK9 inhibitor[448].

d) Bempedoic acid: The CLEAR Tranquility study involved 269 patients (181 on bempedoic acid, 88 on placebo) with a history of statin intolerance (mean age 63.8 years; 61.3% women; mean baseline LDL-C 128 mg/dL; 25% had ASCVD)[527]. Overall, 44.8% of patients (39.1% placebo, 47.5% bempedoic acid) were on concomitant lipid-lowering therapy, including 31% (28.4% placebo, 32.6% bempedoic acid) on a statin (mainly a low dose of atorvastatin 10 mg/day). At week 12, LDL-C was decreased by 23.5% in the bempedoic acid group, whereas it increased by 5.0% in the placebo group, thus resulting in a placebo-corrected reduction of 28.5% from baseline ($p<0.001$)[527]. Bempedoic acid was safe and well tolerated. The CLEAR Serenity trial randomized 345 hypercho-

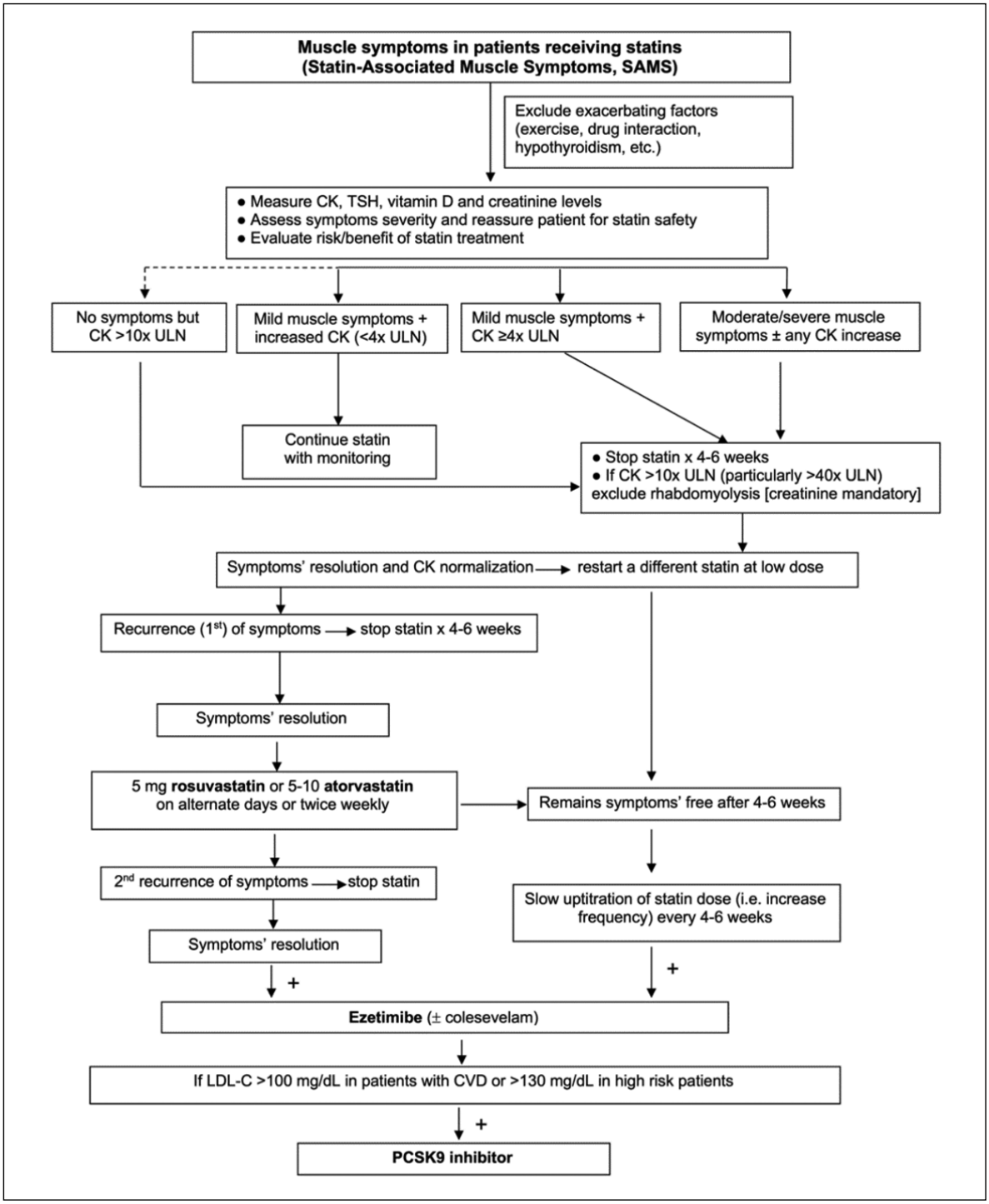

FIGURE 8. Algorithm for the management of patients with statin-associated muscle symptoms

CK: creatine kinase; ULN: upper limit of normal; TSH: thyroid-stimulating hormone; LDL-C: low-density lipoprotein cholesterol; CVD: cardiovascular disease; PCSK9: proprotein convertase subtilisin/kexin type 9

lesterolemic patients with a history of intolerance to ≥2 statins to receive either bempedoic acid 180 mg or placebo once daily for 24 weeks[528]. Of note, almost 8.4% of the patients continued their tolerated low-dose statin therapy. At week 12, bempedoic acid led to a 21.4% reduction in LDL-C compared with placebo (95%CI -25.1 to -17.7%; p<0.001). Based on pooled data analysis from 4 phase III trials, involving statin-intolerant patients with hypercholesterolemia, bempedoic acid (n=394) reduces LDL-C by 26.5% (95%CI -29.7 to -23.2%; p<0.001) com-

TABLE 51. Managing the patient with statin-associated muscle symptoms (SAMS).

1. Reassess the benefit of statin therapy
2. Reassure patient that statins are very safe and effective drugs and that muscle symptoms are reversible
3. Aggressive health-diet changes
Eliminate contributing factors (e.g., hypothyroidism, vitamin D deficiency, other drugs that may interact with statins [**Table *52***])
Confirm the diagnosis
a) dechallenge: discontinue statin and wait (usually 4-6 weeks) until complete resolution of symptoms + normalization of CK
b) rechallenge: try a second (usually different) statin at low dose (after dechallenge). If this is tolerated:
b1) statin can be up-titrated to achieve LDL-C goal, or as much LDL-C reduction can be achieved with minimal muscle complaints, or
b2) statin remains at low or moderate dose and ezetimibe ± colesevelam are added
4. If a second statin causes recurrence of muscle symptoms, try low dose of atorvastatin (5-10 mg) or rosuvastatin (5 mg) on alternate days or twice weekly. This approach lowers LDL-C by 25-35% and is tolerated by the majority (~80%) of intolerant to statin patients. For further LDL-C reduction, statin should be combined with ezetimibe ± colesevelam
5. If alternate low dose of statin is not tolerated (i.e., the patient is intolerant to 3rd introduction of statin), then no other attempt with statin should be tried
6. In statin-intolerant patients ("totally" or "partially") consider:
a) ezetimibe or combination of ezetimibe with colesevelam (in totally intolerant patient) and
b) a PCSK9 inhibitor (alirocumab or evolocumab) if despite low statin dose (in partially intolerant patients) + ezetimibe ± colesevelam, LDL-C remains >100 mg/dL in patients with established cardiovascular disease or >130 mg/dL in high-risk patients
c) bempedoic acid is a promising alternative to statin treatment in patients with SAMS

CK: creatine kinase; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9

pared with placebo (n=192) at week 12[529]. Furthermore, bempedoic acid+ezetimibe fixed-dose combination led to significantly lower LDL-C by 39.2% (95% CI -51.7 to -26.7%; p<0.001) compared with placebo. Bempedoic acid was well-tolerated with less muscle-related adverse events than placebo[529]. Such findings strongly support the clinical usefulness of bempedoic acid±ezetimibe in the presence of statin-intolerance.

e) Coenzyme Q10 administration and vitamin D supplementation in SAMS

Up-to-date studies evaluating the administration of coenzyme Q10 or vitamin D supplementation among statin intolerant patients have given controversial results[530,531]. Therefore, the existing data do not clearly support supplementation of coenzyme Q10 or vitamin D in patients with SAMS.

24 Therapeutic Targets and Treatment Algorithm in Patients with Dyslipidemia

24.1 Introduction

Serum TC and its lipoprotein carriers (LDL, VLDL, and HDL) are known to be related to ASCVD. LDL-C is the dominant form of atherogenic cholesterol. VLDL is the chief carrier of TGs, and VLDL cholesterol (VLDL-C) is also atherogenic. HDL-C is seemingly not atherogenic. Chylomicrons transport dietary fat; chylomicron atherogenicity is uncertain. The sum of LDL-C, Lp(a) and VLDL-C is called non-HDL-C and is more atherogenic than either lipoprotein alone. The main protein embedded in LDL and VLDL is apoB, and like non-HDL-C, apoB is a stronger indicator of atherogenicity than LDL-C alone.

24.2 Treatment targets - Therapeutic algorithm

In both the 2019 EAS/ESC guidelines for the management of dyslipidemias and the 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the treatment of blood TC to reduce athero-

TABLE 52. Treatment targets in dyslipidemia.

Recommendations	Class of recommendation
LDL-C lowering is the main treatment target in almost all patients	I
Non-HDL-C is a secondary treatment target in patients with TGs >200 mg/dL. Non-HDL-C target=LDL-C target + 30 mg/dL	IIa
TG lowering is a treatment priority in patients with TGs>500 mg/dL	IIa
HDL-C is not a treatment target	III

TABLE 53. ASCVD risk groups.

ASCVD Risk group	Patient characteristics
I. Very high ASCVD risk	1. Established CHD 2. Ischemic stroke/TIA 3. Atherosclerotic arterial stenosis >50% 4. Abdominal aortic aneurysm 5. Familial hypercholesterolemia with ≥1 major risk factor 6. Diabetes type 2 with target organ damage or ≥3 major risk factors (age, smoking, atherogenic dyslipidemia, hypertension, obesity) or diabetes type 1 >20 years duration 7. Chronic kidney disease stage 4 (eGFR <30 mL/min/1.73 m^2) 8. HELLENIC SCORE II ≥10%
II. High ASCVD risk group	1. HELLENIC SCORE II ≥5-<10% 2. At least one severe risk factor (stage 3 hypertension, extreme smoking, LDL-C>190 mg/dL) 3. Familial hypercholesterolemia without any major risk factor 4. Diabetes >10 years duration with 1-2 major risk factors (age, smoking, atherogenic dyslipidemia, hypertension, obesity) 5. Chronic kidney disease stage 3 (eGFR 30-60 mL/min/1.73 m^2) 6. Autoimmune diseases/HIV infection
III. Moderate ASCVD risk group	1. HELLENIC SCORE II ≥1-<5% 2. Diabetes <10 years duration in persons <45 years (type 2) or <35 years (type 1) without any major risk factors
IV. Low ASCVD risk group	HELLENIC SCORE II <1%

ASCVD: atherosclerotic cardiovascular disease; CHD: coronary heart disease; TIA: transient ischemic attack; LDL-C: low-density lipoprotein cholesterol

TABLE 54. LDL-C treatment goals for different ASCVD risk groups.

ASCVD Risk group	LDL-C treatment target	Initiation of lipid-lowering drug treatment	Class of recommendation
I. Very high ASCVD risk	<55 mg/dL AND >50% LDL-C reduction from baseline	Immediate + therapeutic lifestyle changes	I
II. High ASCVD risk	<70 mg/dL AND >50% LDL-C reduction from baseline	Immediate + therapeutic lifestyle changes	I
III. Moderate ASCVD risk group	<100 mg/dL	3 months following therapeutic lifestyle changes	I
IV. Low ASCVD risk group	<116 mg/dL	3-6 months following therapeutic lifestyle changes	IIa

LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease

sclerotic CV risk in adults, the importance of LDL-C lowering to prevent ASCVD is strongly emphasized.[1,439] Results from recent studies and systematic reviews have confirmed the dose-dependent reduction in ASCVD with LDL-C lowering; the greater the LDL-C reduction, the greater the ASCVD risk reduction, i.e. lower is better.[194,195,359,386] Of note, the benefits related to LDL-C reduction are not specific for statin therapy. Thus, non-statin treatments should be considered in very high- or high- risk patients not achieving their LDL-C target with a statin[532]. No level of LDL-C below which benefit ceases or harm occurs has been defined. Therefore, it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high ASCVD risk.

In patients with elevated TGs (>200 mg/dL) there are increased levels of circulating TG-rich lipoproteins that are also associated with increased ASCVD risk. In this case, non-HDL-C (TC minus HDL-C) captures all atherogenic lipoproteins [LDL-C, TG-rich lipoproteins and Lp(a)] and can be calculated in the non-fasting state. Non-HDL-C is a secondary treatment target for these patients. In patients with TG levels >500 mg/dL, TG lowering is the priority due to the increased risk of acute pancreatitis (**Table 52**).

We suggest 4 ASCVD risk groups (**Table 53**) and respective LDL-C treatment goals (**Table 54** & **Figure 9**). Proposed treatment algorithm is depicted in **Figure 10**.

Statins are the mainstay of treatment. The intensity of statin treatment is shown in **Table 55**. Initiation of high

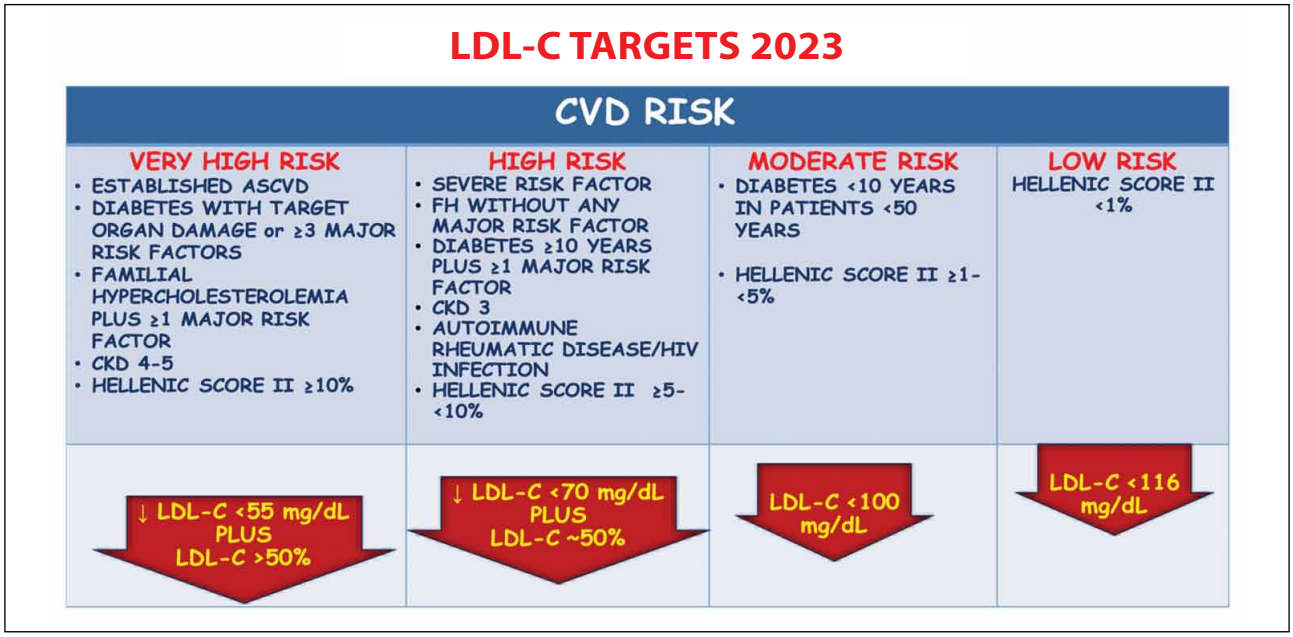

FIGURE 9. ASCVD risk groups and LDL-C targets.

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia

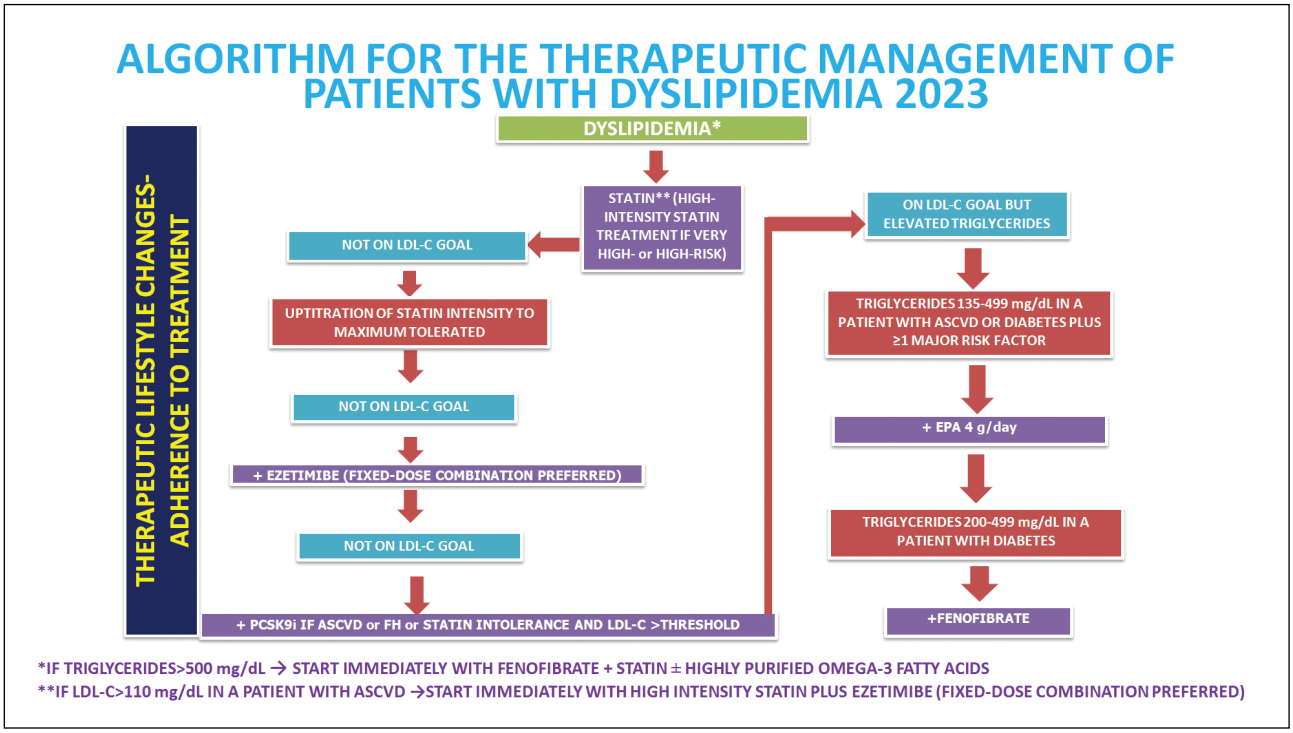

FIGURE 10. Proposed treatment algorithm.

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia

TABLE 55. Intensity of statin treatment.

High intensity (LDL-C reduction >50%)	Moderate intensity (LDL-C reduction 30-50%)	Low intensity (LDL-C reduction <30%)
Atorvastatin 40-80 mg	Atorvastatin 10-30 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 20 mg
	Simvastatin 20-40 mg	Lovastatin 20 mg
	Pravastatin 40 mg	Fluvastatin 40 mg
	Lovastatin 40 mg	
	Fluvastatin XL80 mg	
	Pitavastatin 1-4 mg	

LDL-C: low-density lipoprotein cholesterol

TABLE 56. Laboratory follow-up in patients on hypolipidemic drug treatment.

At diagnosis: TC, TGs, HDL-C, LDL-C, Lp(a), glucose, eGFR, AST, ALT, CK, TSH

↓

8 ± 4 weeks following treatment initiation or intensification: TC, TGs, HDL-C, LDL-C, glucose, eGFR, ALT, CK (if myalgias are reported)

↓

Every 12 months when on treatment target: TC, TGs, HDL-C, LDL-C, glucose, eGFR, ALT (if evidence of liver injury), CK (if myalgias are reported)

LDL-C: low-density lipoprotein cholesterol

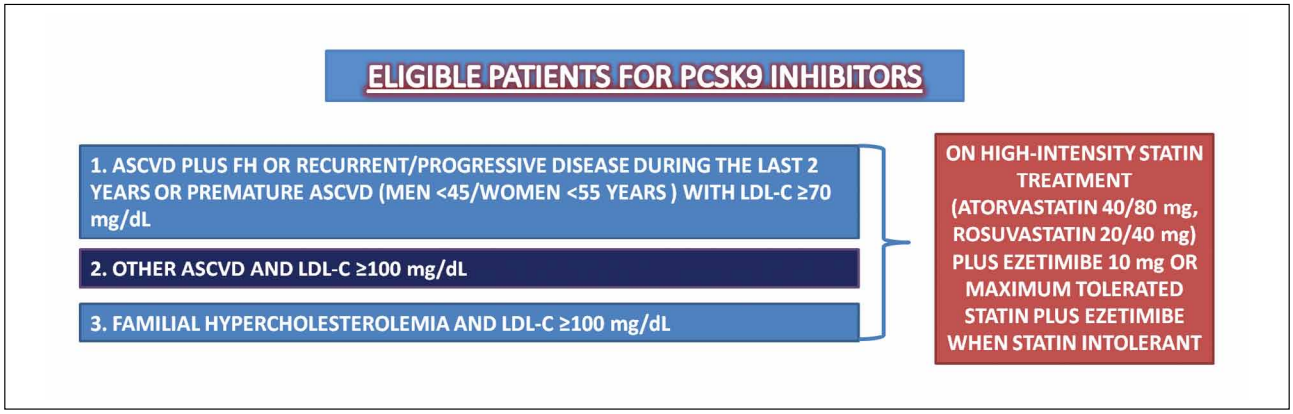

FIGURE 11 Proposed thresholds for PCSK9 inhibitor initiation

PCSK9: proprotein convertase subtilisin/kexin type 9; ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; CKD: chronic kidney disease; FH: familial hypercholesterolemia

TABLE 57. Proposed reporting of lipid test in adults.

Lipid parameter	Result	Target values*
TOTAL CHOLESTEROL (mg/dL)		<170 (DEPENDING ON LDL-C TARGET)
LDL CHOLESTEROL (mg/dL)**		<55 FOR VERY HIGH-RISK PATIENTS <70 FOR HIGH-RISK PATIENTS <100 FOR MODERATE RISK PATIENTS <116 FOR LOW-RISK PATIENTS
TRIGLYCERIDES (mg/dL)		<150
HDL CHOLESTEROL (mg/dL)		>40 FOR MEN >50 FOR WOMEN
NON-HDL CHOLESTEROL (mg/dL)		<85 FOR VERY HIGH-RISK PATIENTS <100 FOR HIGH-RISK PATIENTS <130 FOR MODERATE RISK PATIENTS
ApoB (mg/dL)		<65 FOR VERY HIGH-RISK PATIENTS <80 FOR HIGH-RISK PATIENTS <100 FOR MODERATE RISK PATIENTS
Lp(a) (mg/dL)***		<30

*TARGET VALUE IS DEFINED BY THE PHYCISIAN BASED ON CVD RISK
**IF LDL-C>190 mg/dL, FH SHOULD BE EXCLUDED
**Lp(a) >180 mg/dL IS ASSOCIATED WITH VERY HIGH CVD RISK

TABLE 58. Proposed reporting of lipid test in children and adolescents.

	Acceptable, mg/dL	Bordeline, mg/dL	Abnormal, mg/dL
TOTAL CHOLESTEROL	<170	170-199	≥200
TRIGLYCERIDES (0-9 years)	<75	75-99	≥100
TRIGLYCERIDES (10-19 years)	<90	90-129	≥130
HDL CHOLESTEROL	>45	40-45	<40
LDL CHOLESTEROL*	<110	110-129	≥130
Non-HDL CHOLESTEROL	<120	120-144	≥145

*IF LDL CHOLESTEROL >160 mg/dL, FH SHOULD BE EXCLUDED

intensity statin treatment is recommended in patients at very high and high risk. In patients with established ASCVD and baseline LDL-C>110 mg/dL, combination therapy with high intensity statin treatment + ezetimibe (preferably in a single pill) should be started immediately.

Recent findings of PCSK9 inhibitor trials indicate that very low achieved LDL-C levels are associated with improved outcomes, a reduced risk of CV events, and regression of atherosclerotic lesions in the vascular system.[194,195,533] Proposed thresholds for PCSK9 inhibitor initiation are shown in **Figure 11**.

Many practitioners still believe that very low cholesterol levels pose a health risk for the patient and call for a reduction of the intensity of lipid-lowering therapy. These concerns are exaggerated by the fact that some laboratories mark low values as abnormal, using ranges of acceptable values. In some cases, this approach may prompt patients to discontinue treatment, leading to worse outcomes. Data indicates that achieving even very low LDL-C levels is safe for patients. An analysis of patients who achieved LDL-C levels below 25 mg/dL or even below 15 mg/dL during treatment with PCSK9 inhibitors showed that even with these values, no increased risk of adverse drug effects or adverse events related to neurocognitive disturbances is observed[392].

Following initiation of lipid-lowering therapy, lipid levels should be evaluated every 8 ± 4 weeks to adjust therapy until target lipid levels are reached. In patients with adequate on-treatment lipid levels, annual lipid profile testing is recommended. In addition, CK and ALT levels should be evaluated prior to the initiation of lipid-lowering therapy. Single ALT level retesting is indicated at 8-12 weeks after lipid-lowering therapy initiation or dose escalation. Further routine CK and ALT level retesting is not necessary unless prompted by clinical symptoms (**Table 56**).

There is an imperative need for laboratories not to mark low values as abnormal, using ranges of acceptable values. In some cases, this approach may prompt patients to discontinue treatment, leading to worse outcomes. For that reason, these guidelines suggest a recommendation to standardize laboratory report forms so as they indicate target ranges in accordance with the most recent recommendations and medical knowledge and do not generate a risk of potential errors by patients or physicians. **Table 57** and **Table 58** depict proposed way of reporting lipid test in adults and children.

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Conflicts of interest

Assist Prof Katsiki has given talks, attended conferences and participated in trials sponsored by Amgen, Astra-Zeneca, Boehringer Ingelheim, Elpen, Meranini, Novartis, Novo Nordisk, Sanofi, Servier, Vianex and Viatris, outside the submitted work.

Assist Prof. Filippatos reports participation in advisory board for Lilly and personal fees from Boehringer Ingelheim, Mylan, Astra-Zeneca, Lilly, Recordati, Bausch Health, Servier, Innovis, Perrigo, outside the submitted work.

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