CONTEMPORARY DIAGNOSTICS, CLASSIFICATION, AND TREATMENT OF DYSLIPIDEMIAS ACCORDING TO INTERNATIONAL GUIDELINES 2025–2026

Silvana Babić (1), Mila Bastać (2), Pavle Nešović (3)

(1) CLINIC FOR OTORHINOLARYNGOLOGY, UNIVERSITY CLINICAL CENTER OF SERBIA, BELGRADE; (2) MEDSCAN TADIĆ DIJAGNOSTIKA, ZAJEČAR; (3) INTERNAL MEDICINE PRACTICE "DR BASTAĆ" ZAJEČAR

Summary: Dyslipidemias represent one of the key modifiable risk factors for atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease, cerebrovascular ischemia, and peripheral arterial disease. Epidemiological data show a clear linear relationship between low-density lipoprotein cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis. In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors, which forms the basis for assessing and managing overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after early menopause. Risk estimation systems such as SCORE2 and SCORE2-OP (used to calculate the 10-year risk of fatal and non-fatal cardiovascular events, with OP referring to older persons) can contribute to rational therapeutic decisions in order to avoid under- or overtreatment. Certain individuals classified as high or very high cardiovascular risk do not require SCORE risk assessment but instead require immediate management of all risk factors. This applies to patients with established cardiovascular disease, diabetes, or chronic kidney disease (CKD). In the last decade, and particularly in the period 2023–2026, significant changes have occurred in international guidelines. According to recommendations of the European Society of Cardiology (ESC), European Atherosclerosis Society (EAS), American College of Cardiology (ACC), American Heart Association (AHA), and American Diabetes Association (ADA), there has been a clear shift toward more aggressive LDL-cholesterol lowering, personalized therapy, and broader use of combination treatment strategies. Early diagnosis and aggressive lipid control remain central components of ASCVD prevention. All these guidelines emphasize the need for earlier, more intensive, and combination therapy to achieve very low levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C (total cholesterol minus HDL cholesterol; includes all atherogenic fractions: LDL, VLDL, IDL, lipoprotein(a)), and apolipoprotein B (ApoB). Advances in understanding lipid metabolism and the availability of new therapies have significantly improved treatment options. This review systematically presents modern principles of diagnosis, classification, treatment, and prognosis of dyslipidemias, along with a comparison of key guideline recommendations. Special attention is given to novel therapeutic modalities, including proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Particular emphasis is also placed on RNA interference gene therapy, where cells can “silence” specific genes via small interfering RNA (siRNA), which represents the mechanism of action of inclisiran.

Key words: dyslipidemia, LDL cholesterol, PCSK9 inhibitors, atherosclerosis, guidelines.

INTRODUCTION

Dyslipidemias encompass disorders of lipid metabolism that significantly contribute to the development of atherosclerotic cardiovascular disease (ASCVD). Elevated low-density lipoprotein cholesterol (LDL-C) represents the main causal factor of atherogenesis. Dyslipidemias are a heterogeneous group of lipid metabolism disorders characterized by increased or decreased concentrations of plasma lipoproteins. They are a key modifiable risk factor for ASCVD, including coronary heart disease, cerebrovascular disease, and peripheral vascular disease. Epidemiological data demonstrate a clear linear relationship between LDL cholesterol (LDL-C) levels and the incidence of cardiovascular events, confirming LDL-C as the primary causal factor in atherogenesis [1–7].

In apparently healthy individuals, the risk of developing ASCVD is most often the result of the interaction of multiple risk factors. This forms the basis for assessment and management of

overall cardiovascular (CV) risk. Risk factor screening should include lipid profiling in men over 40 years of age and in women over 50 years of age or after menopause. The updated electronic risk assessment system HeartScore (www.heartscore.org
), including SCORE2 and SCORE2-OP, supports clinical decision-making in order to avoid under- or overtreatment with lipid-lowering therapy. Certain individuals presenting with high, very high, or extreme cardiovascular risk do not require formal risk scoring but instead require immediate management of all risk factors. This applies to patients with established ASCVD, diabetes mellitus (DM), or chronic kidney disease (CKD) stage G3b–G4 or overt chronic renal failure. It should be noted that all risk scoring systems are relatively rigid and require additional clinical judgment when making final therapeutic decisions. Additional risk modifiers are included in electronic systems such as HeartScore (www.heartscore.org
). This comprehensive approach allows flexibility, as failure to achieve optimal risk reduction through one factor can be compensated by more intensive control of other risk factors.

According to current global, American, and European guidelines (ADA, AHA/ACC, ESC/EAS 2023–2026), early diagnosis and aggressive lipid control remain central components of ASCVD prevention [3–5].

In the period 2023–2026, new versions of major international dyslipidemia guidelines were published, including those of the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS), the American Heart Association (AHA), the American College of Cardiology (ACC), and the American Diabetes Association (ADA).

All these guidelines emphasize the need for earlier, more intensive, and combination therapy in order to achieve lower levels of atherogenic lipoproteins, with special focus on LDL-C, non-HDL-C, and apolipoprotein B (ApoB) [3–5] (Table 1).

Table 1. Comparative overview of key ADA vs ESC/EAS recommendations (2023–2026)

ADA (2024–2026)	ESC/EAS (2023–2026)
LDL-C targets for diabetic patients: more stringent (often <1.4 mmol/L)	LDL-C targets based on risk: very strict (<1.4 mmol/L for high risk; <1.0 mmol/L for extreme risk)
Recommends measurement of ApoB in most patients with type 2 diabetes	ApoB and non-HDL-C levels are considered equally important therapeutic targets
Inclisiran recommended in cases of poor adherence	Inclisiran included in standard therapeutic algorithms
Favors early combination therapy	Emphasizes a "stepwise + combination" approach
Personalized therapeutic approach	Matrix-based risk stratification approach

AIM OF THE STUDY

The aim of this review article is to comprehensively present contemporary principles of diagnosis, classification, early screening, assessment of 10-year cardiovascular risk using SCORE2 and SCORE2-OP tools, and therapeutic management of dyslipidemias in accordance with the latest international standards and guidelines (ESC/EAS, ADA, AHA, ACC).

CLASSIFICATION OF DYSLIPIDEMIAS

Primary dyslipidemias

Familial hypercholesterolemia (FH)

Familial combined hyperlipidemia

Polygenic hyperlipidemia

Secondary dyslipidemias

Most commonly caused by:

Diabetes mellitus

Obesity and metabolic syndrome

Chronic kidney disease

Hypothyroidism

Liver diseases

Medications (corticosteroids, antipsychotics, retinoids, immunosuppressants) [15–17]

DIAGNOSIS OF DYSLIPIDEMIAS

Standard diagnostic approach

Diagnosis includes measurement of the standard lipid profile: total cholesterol, LDL-C, HDL-C, and triglycerides; calculation of non-HDL-C and ApoB; assessment of secondary causes; evaluation of global cardiovascular risk; and review of family history.

Dyslipidemia screening is always indicated in patients with clinical manifestations of cardiovascular disease (CVD), in clinical

conditions associated with increased cardiovascular risk, and whenever risk factor screening is warranted. In several clinical conditions, dyslipidemia may contribute to an increased risk of developing CVD. Chronic autoimmune inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis are considered conditions associated with increased cardiovascular risk. In addition, in women, gestational diabetes and hypertension during pregnancy are important risk indicators, while in men, erectile dysfunction is considered a risk marker. Patients with chronic kidney disease and overt renal failure also have increased cardiovascular risk, and dyslipidemia screening is indicated in these individuals.

It is always necessary to identify clinical manifestations of genetic dyslipidemias, such as xanthomas, xanthelasmas, and early corneal arcus (before the age of 45), as these are indicators of severe lipoprotein disorders, primarily familial hypercholesterolemia (FH), which is most often a monogenic disorder associated with premature ASCVD. Screening for dyslipidemia is also indicated in patients with peripheral arterial disease (PAD) or in the presence of increased carotid intima-media thickness (IMT) or carotid plaques.

Screening should also be considered in all adult men aged ≥40 years or women aged ≥50 years or in early postmenopause, especially in the presence of additional risk factors. Screening is also indicated in the offspring of patients with severe dyslipidemia, with follow-up in specialized clinics if necessary. Furthermore, screening of family members of patients with premature ASCVD is recommended [2].

Evaluation of Lipid and Apolipoprotein Laboratory Parameters [2]

The proposed lipid analyses used for assessment include total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C. Blood samples collected in the fasting state and those collected after meals provide similar results for total cholesterol (TC), LDL cholesterol, and HDL cholesterol. Triglycerides (TGs), however, are influenced by food intake.

There is significant intra-individual variability in serum lipid levels. Variations of 5–10% for TC and >20% for TG, particularly in patients with hypertriglyceridemia (HTG), are not uncommon. This is partly due to analytical variation, but also to external factors such as diet, physical activity level, and seasonal variation, including higher TC and HDL cholesterol levels during winter.

LDL cholesterol

In most clinical studies, LDL cholesterol is calculated using the Friedewald formula [2]:

LDL-C = TC − HDL-C − TG / 2.2 (mmol/L)
LDL-C = TC − HDL-C − TG / 5 (mg/dL)

Methodological errors may accumulate because this calculation is based on three parameters: total cholesterol (TC), triglycerides (TG), and HDL cholesterol. Direct methods for LDL-C measurement are available and are now widely used. In general, direct and calculated LDL-C values show good agreement.

New LDL-C estimation formulas, such as the Martin/Hopkins and Sampson equations, are particularly recommended in ADA and AHA/ACC guidelines [3–4]. Direct methods for measuring HDL-C and LDL-C are widely used and are reliable in patients with normal lipid profiles. However, in hypertriglyceridemia (HTG), they may be unreliable, and results can vary between commercial assays.

Lipoprotein(a) [Lp(a)]

Lipoprotein(a) [Lp(a)] has been identified in several studies as an independent risk factor in the pathophysiology of atherosclerotic cardiovascular disease and aortic stenosis. Lp(a) shares similarities with LDL but contains a unique protein, apolipoprotein(a) [apo(a)], which is structurally homologous to plasminogen.

Lp(a) measurements are relatively stable over time. Statins do not reduce Lp(a) levels; however, a reduction of approximately 30% has been observed with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors and nicotinic acid. However, a clear reduction in cardiovascular outcomes through direct Lp(a) targeting has not yet been conclusively demonstrated. Emerging therapies targeting the Lp(a) gene can reduce circulating Lp(a) levels by more than 80%.

Lipid parameters in cardiovascular risk estimation

Most cardiovascular risk assessment systems use TC and LDL-C, while other markers such as apoB and non-HDL-C, although physiologically logical, are mainly supported by post-hoc analyses. TC and LDL-C remain primary therapeutic targets, while non-HDL-C and apoB

are considered secondary targets. In patients with elevated triglycerides, additional risk is contributed by triglyceride-rich lipoproteins, which must be taken into account.

Total cholesterol (TC) is recommended for cardiovascular risk estimation using the SCORE system. However, in individual cases, TC may be misleading. This is particularly relevant in women, who often have elevated HDL-C levels, and in patients with diabetes or elevated triglycerides, who frequently have reduced HDL-C levels.

Overall risk assessment is not required in individuals with familial hyperlipidemia (including FH) or in those with TC >7.5 mmol/L (290 mg/dL), as these patients are always considered high risk and require special clinical attention.

Non-HDL cholesterol

Non-HDL cholesterol is used to estimate the total amount of atherogenic lipoproteins in plasma, including VLDL, VLDL remnants, intermediate-density lipoproteins (IDL), LDL, and Lp(a), and it shows a strong correlation with ApoB levels. It is easily calculated as:

non-HDL-C = TC − HDL-C

According to the updated ESC dyslipidemia guidelines [3], SCORE2 and SCORE2-OP recommend non-HDL-C as a better risk indicator than LDL-C. In several analyses, non-HDL-C has shown superiority over other measures, while in others it provides similar information to LDL-C. Compared with LDL-C, non-HDL-C has the advantage of simplicity and does not require additional testing. It also includes triglyceride-rich atherogenic lipoproteins (VLDL, IDL, and remnants), which are increasingly recognized as important in atherogenesis based on genetic (GWAS) evidence.

LDL-C remains the primary treatment target; however, non-HDL-C is recommended as a secondary target once LDL-C goals are achieved. The non-HDL-C target can be estimated by adding 0.8 mmol/L (30 mg/dL) to the LDL-C target value.

High-density lipoprotein cholesterol (HDL-C)

Low HDL-C is an important independent cardiovascular risk factor and is included in most risk scoring systems, including HeartScore. Very high HDL-C levels are not necessarily protective. Epidemiological studies define increased risk thresholds as:

Men: HDL-C < 1.0 mmol/L (40 mg/dL)

Women: HDL-C < 1.2 mmol/L (48 mg/dL)

The protective role of HDL-C has been questioned in several Mendelian randomization studies. Recent evidence suggests that dysfunctional HDL particles may be more relevant to atherosclerosis development than absolute HDL-C levels.

Triglycerides (TG)

Triglycerides are measured using enzymatic methods. Rare analytical errors may occur in patients with extreme hypertriglyceridemia, particularly at very high TG levels. Elevated TG levels are often associated with low HDL-C and increased numbers of small dense LDL particles.

Multiple meta-analyses suggest that TG may represent an independent cardiovascular risk factor. Genetic studies further support the role of triglycerides in directly contributing to cardiovascular disease. Recent data also suggest that non-fasting TG levels may provide important information regarding remnant lipoproteins associated with increased cardiovascular risk.

APOLIPOPROTEINS

There are reliable immunochemical methods for the determination of apolipoproteins using conventional autoanalyzers. Analytical performance is generally good, and these assays do not require fasting conditions and are not affected by elevated triglyceride (TG) levels.

Apolipoprotein B (ApoB)

Apolipoprotein B (ApoB) is the main apolipoprotein of the atherogenic lipoprotein family (VLDL, IDL, and LDL). ApoB is useful for estimating the total number of these particles in plasma. This feature is particularly important in cases of elevated low-density lipoprotein (LDL) concentrations. Several prospective studies have shown that ApoB performs similarly to LDL cholesterol and non-HDL cholesterol in predicting cardiovascular risk. Although ApoB has not been established as a primary treatment target in clinical trials, several post-hoc analyses suggest that it may be used not only as a risk marker but also as a potential therapeutic target.

Apolipoprotein A1 (ApoA1)

Apolipoprotein A1 (ApoA1) is the main protein component of HDL cholesterol and provides a reliable estimate of HDL particle concentration. However, each HDL particle may carry between one and five ApoA1 molecules.

Apolipoprotein CIII (ApoCIII)

Apolipoprotein CIII (ApoCIII) is recognized as a potentially important emerging

cardiovascular risk factor. ApoCIII is a key regulator of triglyceride metabolism, and elevated serum ApoCIII levels are associated with increased concentrations of VLDL and serum triglycerides. In addition, loss-of-function mutations in ApoCIII are associated with low triglyceride levels and reduced cardiovascular risk.

GENETIC DIAGNOSTICS [4]

Genetic testing is recommended in cases of suspected familial hypercholesterolemia (FH), extremely elevated LDL-C levels (>4.9 mmol/L or >190 mg/dL), and a family history of premature ischemic heart disease.

THERAPEUTIC APPROACHES

The treatment of dyslipidemias is based on a combination of non-pharmacological and pharmacological strategies, primarily aimed at reducing LDL cholesterol, but also at controlling triglycerides, increasing HDL cholesterol, and reducing overall atherogenic burden. Contemporary guidelines are consistent with the key principle: "the lower, the better" for LDL-C, especially in patients at high and very high cardiovascular risk [1–9].

1. Non-pharmacological approaches

Lifestyle modification

These interventions represent the foundation of therapy in all patients with dyslipidemia, regardless of risk level. The most important measures include:

Reduction of saturated fat and trans fat intake

Mediterranean or DASH dietary pattern

Increased intake of dietary fiber and plant sterols

Aerobic physical activity ≥150 minutes per week

Weight reduction of ≥5–7% in overweight and obese patients

Smoking cessation

Reduction of alcohol intake in hypertriglyceridemia

Although lifestyle changes can reduce LDL-C by approximately 5–15%, they are usually insufficient as monotherapy in patients at high cardiovascular risk [16–22].

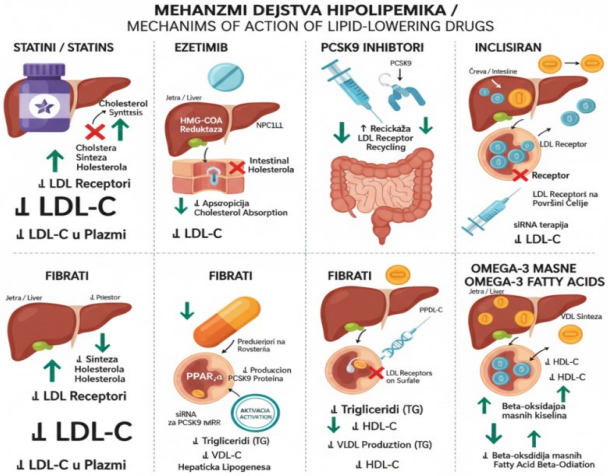
2. Pharmacological treatment of dyslipidemia

(Table 2 and Figure 1)

Table 2. Therapeutic Drug Classes — Comparison of Guideline Recommendations

Therapy	ADA	AHA/ACC	ESC/EAS
Statins	Mainstay of therapy; aim for the lowest possible LDL-C	First-line therapy	First and essential line of therapy
Ezetimibe	Second-line or add-on therapy	Add-on to statins	Mandatory in high-risk patients
PCSK9 inhibitors	Used when targets are not achieved	Preferred after ACS	Required in high and very high risk
Inclisiran	For poor adherence	Alternative to PCSK9 inhibitors	Integrated into treatment algorithms
Fibrates	For TG > 5.6 mmol/L	For severe hypertriglyceridemia	For TG > 5.6 mmol/L
Omega-3 (EPA)	For residual cardiovascular risk	REDUCE-IT population	Additional therapeutic option

Scheme 1. Graphical representation of the mechanism of action of lipid-lowering drugs



Statins (HMG-CoA reductase inhibitors)

Statins remain the first-line therapy in most patients. They are classified into high-intensity statins (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) and moderate-intensity statins (simvastatin, pravastatin, lovastatin, pitavastatin). Effects include LDL-C reduction of 30–60% depending on dose and a reduction in the risk of myocardial infarction, stroke, and cardiovascular (CV) mortality by 25–40% [8–10].n

Adverse effects include myopathy, elevated liver enzymes, and very rarely rhabdomyolysis.

Ezetimibe (cholesterol absorption inhibitor)

Ezetimibe inhibits the NPC1L1 transporter in the small intestine, thereby reducing cholesterol absorption.

Its clinical importance lies in its recommendation as second-line therapy in patients whose LDL-C remains above target despite maximal statin therapy. It provides an additional LDL-C reduction of 20–25% and is safe and well tolerated [13].

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors

PCSK9 inhibitors are monoclonal antibodies, including evolocumab and alirocumab. They block the PCSK9 protein, thereby increasing LDL receptor recycling and reducing LDL-C levels by 50–65%.

Indications include:

Patients at very high risk (previous myocardial infarction, polyvascular disease)

Patients with familial hypercholesterolemia (FH)

Patients who do not achieve target LDL-C levels despite maximal statin + ezetimibe therapy [10–11]

Major clinical trials (FOURIER, ODYSSEY Outcomes) demonstrated a significant reduction in cardiovascular mortality and myocardial infarction.

Inclisiran (siRNA therapy)

Inclisiran is a small interfering RNA (siRNA) that inhibits hepatic synthesis of PCSK9 in hepatocytes.

Advantages include administration only twice yearly and sustained LDL-C reduction of approximately 50%, making it particularly suitable for patients with poor adherence.

Guideline integration: ESC/EAS 2023–2026 includes inclisiran in standard treatment algorithms for very high-risk patients, while ADA recommends it in cases of poor therapeutic adherence [5–7].

Fibrates

Fenofibrate and bezafibrate are used in specific lipid disorders.

Indications include:

Triglycerides >5.6 mmol/L (>500 mg/dL)

Prevention of pancreatitis

Residual hypertriglyceridemia in type 2 diabetes mellitus (DM2)

Omega-3 fatty acids (EPA formulations)

High-dose EPA (2–4 g/day) is used to reduce triglyceride levels and stabilize atherosclerotic plaque.

The REDUCE-IT trial demonstrated a reduction in cardiovascular outcomes in patients with elevated triglycerides [39].

NEW DEVELOPMENTS IN THE 2023–2026 GUIDELINES (ADA, ESC/EAS, AHA/ACC)

In the past three years, several important changes have occurred that significantly impact everyday clinical practice. (Table 3 and Scheme 2).

Scheme 2. Graphical representation of the therapeutic algorithm and comparison of guidelines

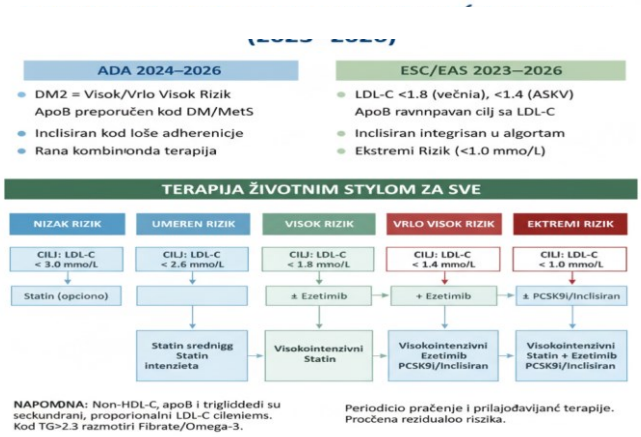


Table 3. Comparative LDL-C targets according to guidelines (ADA, AHA/ACC, ESC/EAS)

Risk category	ADA 2024–2026	AHA/ACC 2023–2025	ESC/EAS 2023–2026
Moderate risk	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L	LDL-C < 2.6 mmol/L
High risk	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L	LDL-C < 1.8 mmol/L
Very high risk	LDL-C < 1.4 mmol/L	LDL-C reduction as much as possible (often <1.4 mmol/L)	LDL-C < 1.4 mmol/L
Extreme risk	—	—	LDL-C < 1.0 mmol/L
FH (heterozygous)	≥50% LDL-C reduction target	≥50% LDL-C reduction	<1.8 mmol/L; if ASCVD <1.4 mmol/L
FH (homozygous)	specialized centers	PCSK9 + lomitapide	PCSK9 + lomitapide/evinacumab

1. ADA 2024–2026 – Diabetes and dyslipidemia

Patients with type 2 diabetes mellitus (DM2) are automatically classified as having high or very high cardiovascular risk. The LDL-C target in most diabetic patients is <1.8 mmol/L, while in patients with ASCVD the target is <1.4 mmol/L. Measurement of apoB is recommended in individuals with obesity, metabolic syndrome, and high triglycerides. Inclisiran is recommended in cases of poor adherence. The emphasis is on early initiation of combination therapy.

2. AHA/ACC 2023–2025 – Personalized therapeutic approach

PCSK9 inhibitors are increasingly used even after the first myocardial infarction. The LDL-C goal is "the lower, the better," although in some situations there is no strict numerical target. Lifelong LDL-C monitoring is emphasized in patients with familial hypercholesterolemia (FH). Non–HDL-C has an important role in patients with elevated triglycerides.

3. ESC/EAS 2023–2026 – Most aggressive LDL-C approach

A new "extreme risk" category has been introduced (e.g., polyvascular disease, recurrent ACS). LDL-C targets are: high risk <1.8 mmol/L, very high risk <1.4 mmol/L, extreme risk <1.0 mmol/L. LDL-C, non–HDL-C, and apoB are considered equal target parameters. Inclisiran is formally included in the therapeutic algorithm. There is a stronger focus on reduction of remnant lipoproteins and triglycerides.

The comparative therapeutic algorithm according to cardiovascular risk level is shown in Tables 4 and 5.

Table 4. Comparative therapeutic algorithm according to cardiovascular risk level

Risk	ADA	AHA/ACC	ESC/EAS
Low risk	Lifestyle ± statin	Lifestyle	Lifestyle ± statin
Moderate risk	Moderate-intensity statin	Statin based on clinical judgment	Moderate-intensity statin

Risk	ADA	AHA/ACC	ESC/EAS
High risk	High-intensity statin	High-intensity statin	High-intensity statin + ezetimibe
Very high risk	Statin + ezetimibe; PCSK9 if needed	High-intensity statin + early ezetimibe + PCSK9	Statin + ezetimibe + mandatory PCSK9
Extreme risk	—	—	Statin + ezetimibe + PCSK9 ± inclisiran
FH	Maximal combination therapy	Statin + ezetimibe, PCSK9	Statin + ezetimibe + PCSK9

Table 5. Recommendations for specific populations

Population	ADA	AHA/ACC	ESC/EAS
Diabetes	Automatically high risk	Most patients at high risk	Strict LDL-C targets (<1.4 mmol/L)
CKD	LDL-C <1.8 mmol/L	Caution with statins when GFR <30	Focus on apoB and non–HDL-C
Elderly	Benefit proportional to absolute risk	Individualization	Statins recommended up to age 75
FH	Statin + ezetimibe + PCSK9	Early family screening	Most aggressive approach
Post-ACS	Rapid LDL-C reduction <1.4 mmol/L	PCSK9 after first ACS	PCSK9 as first-line after ACS

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, it was shown that each reduction of LDL-C by 1 mmol/L (~39 mg/dL) reduces the risk of major vascular events by approximately 22% [23]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C reduction is beneficial in almost all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [6–8]. In addition to LDL reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [24].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016) [11]. This supports the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [10]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [11]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include dosing every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still ongoing, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

LATEST AMERICAN RECOMMENDATIONS FOR THE MANAGEMENT OF DYSLIPIDEMIA (2026)

The new American recommendations [40] reintroduce a focus on LDL cholesterol target values: for patients with borderline or intermediate risk, the target is <2.6 mmol/L; for high-risk patients <1.8 mmol/L; and for very high-risk patients (i.e., in secondary prevention), LDL-C should be reduced to <1.4 mmol/L.

The PREVENT-ASCVD calculator has been adopted, which estimates both 10-year and 30-year risk of adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular mortality). Key patient characteristics used for risk estimation include age, sex, systolic blood

pressure, antihypertensive therapy, presence of diabetes, smoking status, and laboratory markers (total and LDL cholesterol). These variables are required for the basic model. The expanded model additionally includes body mass index (BMI) and kidney function, while the full model also incorporates albuminuria and HbA1c [40].

A notable innovation is the assessment of both 10-year and 30-year cardiovascular risk in individuals aged 30 to 59 years. The new recommendations also strengthen the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), which is recommended to be measured at least once in a lifetime, and apolipoprotein B, which is particularly useful in patients with diabetes and hypertriglyceridemia.

Greater emphasis is placed on the assessment of coronary artery calcium (CAC) score [40], especially in situations where the decision to initiate statin therapy is uncertain—most commonly in patients with borderline or intermediate risk.

An important aspect of the new recommendations is earlier and more intensive LDL-C reduction. This is based on the concept that cumulative exposure to elevated LDL-C determines cardiovascular risk. Therefore, earlier initiation of therapy reduces lifetime exposure to high LDL-C levels and leads to a greater reduction in cardiovascular risk.

Accordingly, a complementary recommendation is universal lipid screening and lifelong prevention. Rather than waiting for cardiovascular events to occur, periodic assessment of lipid status is advised, with particular attention to screening in patients with diabetes, cardio-renal-metabolic syndrome, and in children [40].

PROGNOSIS

Dyslipidemias, if not properly diagnosed and treated, significantly increase the risk of atherosclerotic cardiovascular disease, premature disability, and mortality. However, contemporary therapeutic approaches allow for a substantial improvement in prognosis.

1. Prognosis

Prognosis depends on baseline LDL-C levels, the presence of comorbidities, degree of adherence, genetic factors (especially in familial hypercholesterolemia), and the timeliness of therapy initiation. In patients who achieve LDL-C target levels according to ESC/EAS guidelines (<1.4 mmol/L for high-risk patients), the risk of new cardiovascular events can be reduced by up to 50% [5].

2. Clinical implications

Recent guidelines (2023–2026) emphasize the following principles: LDL-C is the primary therapeutic target; lower LDL-C equals better prognosis. Combination therapy is the rule rather than the exception (statin + ezetimibe + PCSK9 inhibitor / inclisiran). ApoB and non–HDL-C are equally important as LDL-C, particularly in patients with elevated triglycerides and diabetes. Personalization of therapy is essential, with different targets for different risk categories..

CARDIOVASCULAR BENEFITS AND OUTCOMES

Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy in the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and decreased risk of major cardiovascular events [8–12,25–34].

1. Effect of LDL cholesterol reduction on cardiovascular outcomes

In a large meta-analysis by the Cholesterol Treatment Trialists' Collaboration, including over 170,000 patients, each 1 mmol/L (~39 mg/dL) reduction in LDL-C was associated with approximately a 22% reduction in major vascular events [25]. This effect is consistent across men and women, younger and older individuals, patients with diabetes, those with prior myocardial infarction, and in both primary and secondary prevention. LDL-C lowering is beneficial in nearly all clinical populations.

2. Statins – evidence from clinical trials

High-intensity statins have been shown to reduce myocardial infarction by 25–35%, ischemic stroke by 20–30%, and cardiovascular mortality by 15–20% [8–10]. In addition to LDL-C reduction, statins exert pleiotropic effects, including plaque stabilization, anti-inflammatory action, and improvement of endothelial function [26].

3. Ezetimibe – clinical outcomes

The IMPROVE-IT trial (ezetimibe + statin) demonstrated an additional LDL-C reduction of ~23% and a 6% relative reduction in primary cardiovascular outcomes (p=0.016)

[11], supporting the importance of combination therapy.

4. PCSK9 inhibitors – greatest benefit in highest-risk patients

The FOURIER trial (evolocumab) showed LDL-C reduction to ~0.8 mmol/L, a 15% reduction in cardiovascular events, and a 27% reduction in myocardial infarction risk [8]. The ODYSSEY Outcomes trial (alirocumab) demonstrated a significant reduction in cardiovascular mortality after acute coronary syndrome [9]. The key principle is: the lower the LDL-C, the greater the benefit.

5. Inclisiran – a new era of long-term lipid control

Inclisiran, as an siRNA-based therapy, provides sustained and stable LDL-C reduction. Its advantages include administration every 6 months, improved adherence, and approximately 50% LDL-C reduction [12]. Large outcome trials are still awaited, but current data are promising.

6. Triglycerides and residual risk

Elevated triglycerides and remnant lipoprotein particles significantly increase cardiovascular risk, particularly in patients with diabetes and metabolic syndrome [19–20]. The REDUCE-IT trial (EPA 4 g/day) demonstrated a 25% reduction in major cardiovascular events and a 20% reduction in cardiovascular mortality [39]. This confirms that residual risk is important and that LDL-C reduction alone is not sufficient.

GENE THERAPY AND FUTURE PERSPECTIVES [41]

In vivo gene or base editing represents a novel therapeutic strategy currently being investigated for the treatment of dyslipidemia, targeting genes such as PCSK9 and ANGPTL3. VERVE-101 is an experimental CRISPR-based therapy that includes mRNA encoding an adenine base editor targeting the PCSK9 gene, with the aim of permanently "silencing" (inactivating) this gene [42].

In non-human primates, a single infusion of VERVE-101 resulted in a 69% reduction in LDL-C, with sustained effects lasting up to 476 days post-dose, without significant adverse events. Following confirmed efficacy in primates, the first human study included 10 patients with heterozygous familial hypercholesterolemia (HeFH) and a mean LDL-C level of 201 mg/dL. A single intravenous infusion of CRISPR-based gene therapy delivered via targeted lipid nanoparticles resulted in up to a 55% reduction in LDL-C [43].

A next-generation therapy, Verve-102, represents an improved PCSK9 base-editing approach with enhanced liver targeting and redesigned lipid nanoparticles, and is currently in clinical development.

Today, numerous effective strategies are available to manage lipid-related cardiovascular risk factors. Even more promising innovations suggest continued progress in this field. However, the implementation of proven therapies, patient acceptance, adherence to treatment, and ensuring equitable access to modern therapeutic advances remain key challenges that must be addressed [4]..

CONCLUSION

Dyslipidemias remain one of the most important risk factors for atherosclerosis and cardiovascular mortality. Reduction of atherogenic lipoproteins, particularly LDL cholesterol, represents the most effective pharmacological strategy for the prevention of atherosclerotic cardiovascular disease (ASCVD). Numerous randomized clinical trials, genetic analyses, and meta-analyses demonstrate a clear causal relationship between LDL-C reduction and a decreased risk of major cardiovascular events.

Advances in the understanding of lipid metabolism and the availability of novel therapies have significantly improved treatment options. The integration of recommendations from ADA, AHA/ACC, and ESC/EAS enables an optimal and individualized approach, particularly in patients at high and very high risk.

A key novelty of the 2026 ACC/AHA guidelines is the assessment not only of 10-year cardiovascular risk (fatal and nonfatal), but also of 30-year risk in individuals aged 30 to 59 years. The new recommendations further emphasize the use of additional biomarkers for assessing residual cardiovascular risk, such as lipoprotein(a), apolipoprotein B, non–HDL cholesterol, coronary artery calcium score, body mass index, and HbA1c. Apolipoprotein B is particularly useful in patients with diabetes and hypertriglyceridemia.

Continued research in lipidology, the development of new therapeutic agents, and

advances in genetic diagnostics will contribute to even more effective prevention of ASCVD in the future..

REFERENCE:

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR /AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guidel ine on the Management of Blood Cholesterol. *Circulation.* 2019; 139(25):e1082–1143.
2. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to r educe cardiovascular risk. *Eur Heart J.* 2020;41(1):111–188.
3. Farkouh KE, Srivatsa S, Farkouh EM. The limitations of biomar kers in addressing bias in alcohol and cardiovascular disease re search. *Eur Heart J.* 2025;46(48):5296–5297.
4. Tokgözoğlu L, Libby P. Lipoprotein disorders and cardiovascul ar diseases. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bha tt DL, Solomon SD, et al., editors. *Braunwald's Heart Disease: A T extbook of Cardiovascular Medicine.* 12th ed. Philadelphia: Else vier; 2027.
5. American Diabetes Association. Standards of Medical Care in Di abetes – 2024. *Diabetes Care.* 2024;47(Suppl 1):S1–S221.
6. Virani SS, Morris PB, Agarwala A, et al. AHA/ACC Guideline on t he Management of Lipids – 2023 Update. *J Am Coll Cardiol.* 2023;81:184–218.
7. Visseren FLJ, Mach F, Smulders YM, et al. 2023 ESC/EAS Guideli nes on cardiovascular disease prevention. *Eur Heart J.* 2023;44: 1–111.
8. Ference BA, Ginsberg H, Graham I, et al. Low-density lipoprotei ns cause atherosclerotic cardiovascular disease. *JAMA.* 2017;31 8:1655–1663.
9. Collins R, Reith C, Emberson J, et al. Interpretation of the evide nce for the efficacy and safety of statin therapy. *Lancet.* 2016;3 88:2532–2561.
10. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and cli nical outcomes in patients with cardiovascular disease (FOURI ER). *N Engl J Med.* 2017;376:1713–1722.
11. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiova scular outcomes after acute coronary syndrome (ODYSSEY Out comes). *N Engl J Med.* 2018;379:2097–2107.
12. Ray KK, Wright RS, Kallend D, et al. Two phase 3 trials of inclisi ran in patients with elevated LDL cholesterol. *Lancet.* 2020;396 :797–806.
13. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). *N Engl J Med.* 2015;372:2387–2397.
14. Nicholls SJ, Lincoff AM, Garcia M, et al. Effects of high-dose eico sapentaenoic acid on coronary plaque. *Eur Heart J.* 2022;43:10 16–1024.
15. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA Guid eline for the management of high blood pressure. *Hypertension.* 2018;71:e13–e115.
16. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guideline s on cardiovascular disease prevention. *Eur Heart J.* 2016;37:2 315–2381.
17. Toth PP, Banach M. Statin intolerance. *J Clin Lipidol.* 2021;15:4 15–431.
18. Ganda OP, Bhatt DL, Mason RP. Clinical utility of reducing trigly cerides in patients with diabetes. *Diabetes Care.* 2021;44:2185 –2195.
19. Miller M, Cannon CP, Murphy SA, et al. Triglycerides and cardio vascular disease: A scientific statement from the AHA. *Circulati on.* 2011;123:2292–2333.
20. Borén J, Chapman MJ, Krauss RM, et al. Triglyceride-rich lipopr oteins and atherosclerotic cardiovascular disease. *Eur Heart J.* 2020;41:99–109.
21. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS G uideline for the management of overweight and obesity. *Circul ation.* 2014;129:139–143.
22. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics – 2021 update. *J Am Coll Cardiol.* 2021;77:159–240.
23. Kahn R, Cooper ME, Del Prato S. Pathophysiology and treatmen t of insulin resistance. *Diabetes Care.* 2022;45:188–199.
24. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association r ecommendations for patient-centered management of dyslipid emia. *J Clin Lipidol.* 2022;16:394–427.
25. Silverman MG, Ference BA, Im K, et al. LDL-cholesterol reductio n and the impact on cardiovascular outcomes: A systematic rev iew and meta-analysis. *Lancet.* 2016;388:643–651.
26. Ridker PM, Everett BM, Thuren T, et al. Anti-inflammatory ther apy with canakinumab (CANTOS). *N Engl J Med.* 2017;377:111 9–1131.
27. Brown MS, Goldstein JL. A receptor-mediated pathway for chol esterol homeostasis. *Cell.* 1986;46:1–10.
28. Tavori H, Fan D, Blakemore J, et al. PCSK9 and LDL receptor reg ulation. *Circulation.* 2015;132:164–176.
29. Laufs U, Parhofer KG, Ginsberg HN. Contemporary lipid-loweri ng strategies. *Eur Heart J.* 2021;42:2215–2223.
30. Ademi Z, Park H, Lee J. Cost-effectiveness of PCSK9 inhibitors. *P harmacoeconomics.* 2021;39:981–994.
31. Lloyd-Jones DM, Braun LT, Ndumele CE, et al. Lifetime risk asse ssment and its significance. *Circulation.* 2022;145:e1085– e1143.
32. Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA Guideline on the primary prevention of cardiovascular disease. *Circulati on.* 2019;140:e596–e646.
33. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associat ed with lipids and coronary disease. *N Engl J Med.* 2009;361:13 83–1392.
34. Holmes MV, Asselbergs FW, Palmer TM, et al. Mendelian rando mization of apoB. *Eur Heart J.* 2018;39:3389–3396.
35. Reiner Ž, Guardamagna O, Nair D, et al. Diagnosis and manage ment of familial hypercholesterolaemia. *Clin Lipidol.* 2018;13:1 –12.
36. Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial h ypercholesterolaemia – screening and diagnosis. *Eur Heart J.* 2013;34:3478–3490.
37. Santos RD, Gidding SS, Hegele RA, et al. Lipid management in cli nical practice. *J Am Coll Cardiol.* 2020;76:1397–1414.
38. Wiviott SD, Raz I, Bonaca MP, et al. SGLT2 inhibition and cardio vascular outcomes (DECLARE-TIMI 58). *N Engl J Med.* 2019;38 0:347–357.
39. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl (REDUCE-IT). *N Engl J Med.* 2019;380:11– 22.
40. Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, et al. 2026 ACC/AHA/AACVPR/ABC/ACPM/AD A/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia. *Circulation.* 2026;153:e00– e00. doi:10.1161/CIR.0000000000001423.
41. Rosenthal N, Ylä-Herttuala S. Gene therapy and future perspect ives. In: Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, S olomon SD, et al., editors. *Braunwald's Heart Disease: A Textboo k of Cardiovascular Medicine.* 12th ed. Philadelphia: Elsevier; 20 27.
42. Lee RG, Mazzola AM, Braun MC, et al. Efficacy and safety of an i nvestigational single-course CRISPR base-editing therapy targe ting PCSK9 in nonhuman primates and mouse models. *Circulati on.* 2023;146(3):242–253.
43. Naddaf M. First trial of base editing in humans lowers cholester ol – but raises safety concerns. *Nature.* 2023;623(7988):671– 672.