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European, Russian, and American Clinical Guidelines on dyslipidemia management – Where do we stand?

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ABSTRACT

Current clinical guidelines on lipid metabolism disorders are represented by the integration of relevant multicenter observational studies and registries aimed to identify the best strategies in cardiovascular risk stratification, diagnosis, and treatment of dyslipidemias. The approaches outlined in the European, Russian, and American guidelines look relevant to each other despite a range of slightly different postulates, as they all demonstrate a general tendency to the importance of accurate risk stratification of patients and timely action on low-density lipoprotein cholesterol (LDL-C) levels by using effective lipid-lowering therapies.

Keywords
Dyslipidemias;
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Dyslipidemia treatment

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Introduction

It is well known that cardiovascular diseases (CVDs) are one of the main causes of mortality and disability in all countries across the world. The development of CVDs is associated with both modifiable and unmodifiable risk factors, among which dyslipidaemia plays an essential role. There are specialized documents containing structured information based on scientific evidence on the prevention, diagnosis, and treatment of dyslipidemias, known as clinical guidelines. Many countries stick to the strategy of publishing national guidelines for the management of dyslipidemias, which may reflect some features conditioned by the healthcare system type and ethnic and geographic particularities, but share general concepts. The purpose of this paper is to summarize the key positions of European [1], Russian [2], and American [3] guidelines for the management of patients with dyslipidemias.

Cardiovascular risk stratification and target levels

Risk-based prediction is of strategic importance for choosing the best option for CVDs prevention. There are various charts for calculating cardiovascular risk. Physicians use the systemic coronary risk evaluation (SCORE) chart in Europe and Russia and the ACC/AHA ASCVD Risk Estimator Plus in America.

The ACC/AHA ASCVD Risk Estimator Plus includes a fairly large pool of measures such as sex, age, race, smoking, systolic and diastolic blood pressure, total serum cholesterol, LDL-C and HDL-C, the presence of diabetes mellitus, and information on ongoing therapies (particularly antihypertensive drugs, statins, and aspirin). According to the obtained index, we can define a group of people with low (<5%), borderline (5-7.4%), intermediate (7.5-19.9%), or high (≥20%) 10-year cardiovascular risk. In Europe and Russia, the SCORE chart is generally used, which takes into account five main indicators: sex, age, smoking, systolic blood pressure, and total serum cholesterol, allowing to identify people with low (<1%), moderate (1-5%), high (5-10%), or very high (>10%) 10-year cardiovascular risk. It is worth noting that the SCORE chart undergoes significant changes with each update of the clinical guidelines. Key changes in the most recent guidelines led to introduce an additional age group (from 65 to 70 years) and a decrease in the borderline total cholesterol level from 8 to 7 mmol/L, which is important to improve the screening of patients with clinical suspicion of heterozygous familial hypercholesterolemia. Two new cardiovascular risk charts - SCORE2 (for patients aged 40-69 years) and SCORE2-OP (for patients aged 70 years and older) have been introduced in the current European guidelines for the prevention of CVDs in clinical practice (**Figure 1**) [4].

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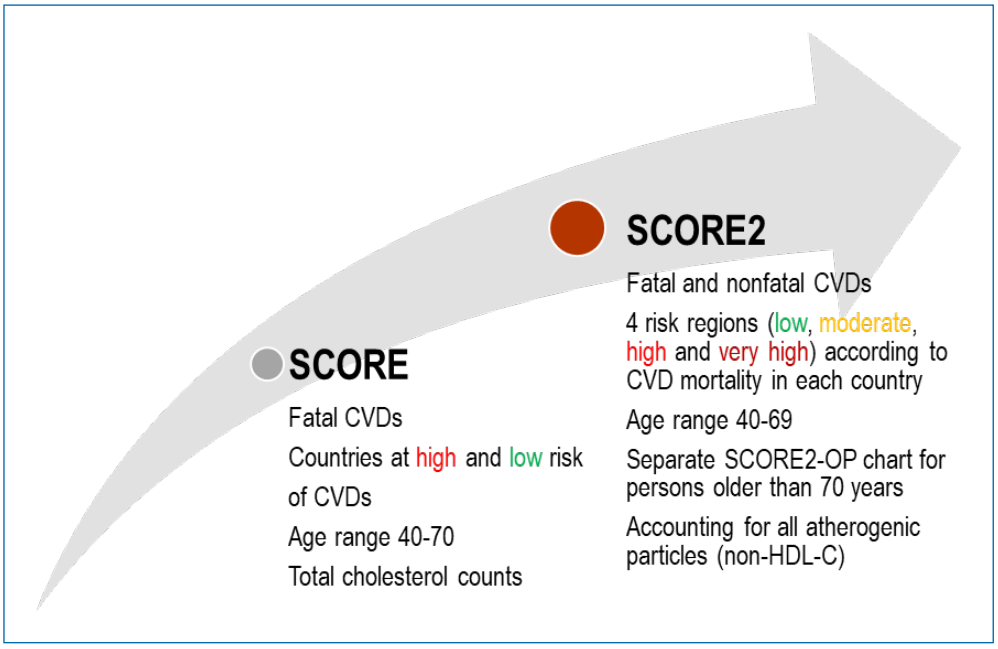

Figure 1 | **The main differences in the risk prevention approach.**

The most significant changes have affected the following items:

1) taking into account regional characteristics (in the SCORE chart, countries were divided into low-risk and high-risk categories only, in the updated charts SCORE2 and SCORE2-OP countries are divided into 4 risk zones: low, moderate, high, and very-high risk);
2) an assessment of the 10-year risk of aggregate fatal and nonfatal adverse outcomes (in the SCORE chart, an additional calculation was required to assess the risk of nonfatal cardiovascular events by multiplying the resulting index by 3 in men, and by 4 in women);
3) a paradigm shift has been implemented with regard to non-high-density lipoprotein cholesterol (non-HDL-C) levels instead of total serum cholesterol levels. In addition, the population was divided into three age groups, indicating the peculiarities of the primary prevention of CVDs. Reasonably, the level of risk by SCORE2 exceeds that obtained with SCORE for the same patient, as the first chart reflects the risk of fatal and non-fatal events while the second one considers only fatal events, unless not using a special index for risk recalculation to include both types of events. Definitely, there is a need for a discussion on how to standardize risk assessment procedures across all future guidelines to streamline work in clinical practice.

In 2018, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines on blood cholesterol control [3]. The updated guideline provides definitions of high- and very high-risk atherosclerotic CVDs with the corresponding recommended LDL-C levels. In 2019, the European Guidelines for the correction of lipid metabolism disorders were published [1] by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Compared with 2016 guidelines, there are still 4 categories of cardiovascular risk (all with lower LDL-C goals, except for individuals at low risk), but the concept of extreme risk was introduced, for patients with ASCVD who experience a second vascular event within 2 years (not necessarily the same as the first one) despite the background of the maximum tolerated dose of statin, and thus who may be recommended to reduce LDL-C levels <1.0 mmol/L (<40 mg/dL).

According to the VII revision of the Russian clinical guidelines on diagnostics and correction of lipid metabolism disorders to prevent and treat atherosclerosis [2], published in 2020, five categories of cardiovascular risk were identified: extreme (target level of LDL-C <1.0 mmol/L), very high (target level of LDL-C <1.4 mmol/L), high (target level of LDL-C <1.8 mmol/L), moderate (target level of LDL-C <2.6 mmol/L), and low CV risk (target level of LDL-C <3.0 mmol/L). Extreme cardiovascular risk refers to the combination of atherosclerotic CVD with type 2 diabetes mellitus (DM) or familial hypercholesterolemia plus two cardiovascular complications within 2 years despite an optimal lipid-lowering therapy and/or achieved LDL-C levels <1.4 mmol/L. This model likely derives from the clinical practice guidelines of the American Association of Clinical Endocrinologists/American College of Endocrinology, in which an extreme cardiovascular risk group appeared for the first time [5]. Despite variations in the categorization of this risk group, key strategies are similar, since both European and Russian guidelines recommend an LDL-C goal of less than 1.0 mmol/L (<40 mg/dL).

Imaging techniques as a tool for the improvement of cardiovascular risk assessment

An essential place in the clinical guidelines is given to additional methods of examination, allowing a more complete assessment of cardiovascular risk, since the precise estimation of a patient's cardiovascular risk is crucial for choosing an optimal prevention and treatment strategy, including timeline and type of intervention. Current guidelines refer to the use of non-invasive methods for subclinical atherosclerosis assessment in case of borderline cardiovascular risk to identify a risk group more precisely, i.e. to choose an optimal intervention strategy.

The importance of subclinical atherosclerosis diagnosis is conditioned by the absence of any clinical symptoms over a long period, however, it reflects the level of the atherosclerosis progression, and thus, very often reveals a necessity for intervention. Several non-invasive diagnostic tools are available, among which the most popular and accessible are duplex scanning of peripheral arteries, quantita-

tive assessment of coronary calcium index by Agatston, and coronary computed tomography angiography.

All clinical guidelines provide a comprehensive commentary on the choice of diagnostic approaches within specific chapters. The American Clinical Guidelines were the first that included coronary calcium testing as a risk assessment tool and paid special attention to a detailed algorithm to select candidates for the procedure, including cost-effectiveness data and its availability across the country. As for the duplex scanning of peripheral arteries, the intima-media thickness (IMT) measurement loses traction from a point of view of its predictive value [6], while atherosclerotic plaque presence is considered an important tool that may increase the level of cardiovascular risk in both European and Russian guidelines. Compared to IMT, atherosclerotic plaques have a stronger association with the development of cardiovascular events in patients without a previous history of coronary artery disease [7] and are stronger predictors of increased risk of major cardiovascular adverse event recurrence in a cohort of patients with a history of CVDs [8]. Reclassification is of value in people identified as being at moderate CV risk by using markers such as CAC score > 100 Agatston units, ankle-brachial index (ABI) < 0.9 or > 1.40, carotid-femoral pulse wave velocity > 10 m/s, or the presence of plaques at carotid or femoral ultrasonography based on the European guidelines. Russian guidelines suggest stratifying the risk of patients based on the percentage of stenosis due to the presence of atherosclerotic plaque, i.e. 25-49% and >50% for high and very-high risk, respectively. The CAC score index classifies patients as being at low (0), moderate (1-10), high (11-100), high/very high (101-400), or very high (>400) risk, based on the number of Agatston units. The ability to use the above-described reclassifiers can provide a more accurate evaluation of the cardiovascular risk category and perform the necessary timely interventions.

Dyslipidemia management

Lifestyle modification comprises the correction of key modifiable risk factors across all the guidelines.

Among drugs for the treatment of dyslipidaemias, statin therapy remains the first-line approach for reducing LDL-C levels. Data collected from large randomized clinical trials of statins (JUPITER (rosuvastatin 20 mg) [9], WOSCOPS (pravastatin 20-40 mg) [10], 4S (simvastatin 20-40 mg) [11], LIPID (pravastatin 40 mg) [12], HPS (simvastatin 40 mg) [13], ASCOT-LLA (atorvastatin 10 mg) [14], CARDS (atorvastatin 10 mg) [15], PROVE IT-TIMI 22 (pravastatin 40 mg and atorvastatin 80 mg [16] and TNT (atorvastatin 80 mg) [17]) have demonstrated a significant reduction in cardiovascular and overall mortality regardless of sex, age, and baseline total cholesterol level. In both European and Russian guidelines, algorithms for the management of lipid metabolism disorders include also cholesterol absorption inhibitors (ezetimibe) (SHARP [18]), fibrates (FIELD [19], Accord [20]), omega-3 PUFAs (GISSI-Prevenzione [21]), and PCSK9 inhibitors (FOURIER [22], ODYSSEY Outcomes [23]). Bile acid sequestrants and nicotinic acid (Coronary Drug Project [24], Stockholm Ischemia Heart Study [25], HDL Atherosclerosis Treatment Study [26]) are indicated in the European and American clinical guidelines, but not in Russian guidelines as these drugs are not currently registered and cannot be used for the treatment of patients with dyslipidemia.

To overcome the problem of achieving recommended LDL-C goals in patients with high pre-treatment levels of LDL-C, the option of using combination therapy is provided by all guidelines, including a moderate or high-intensity regimen of statin therapy combined with ezetimibe and/or a proprotein convertase subtilisin/kexin type 9 inhibitor. The very recent European consensus papers suggest considering a combination therapy as a first-line strategy in very-high risk patients [27, 28] to obtain a higher reduction in LDL-C levels in a shorter time, thus reducing the cumulative cardiovascular risk of these patients.

New approaches for lipid-lowering therapy are being actively introduced. Recently, the first and the only one in the class of lipid-lowering drugs based on small interfering RNA (siRNA) - Inclisiran - was registered in Europe, Russian Federation, and the USA. The registration was based on the results of phase III clinical trials ORION-9, -10 and -11 [29, 30]. Having in a toolbox an innovative drug for the treatment of dyslipidaemia that can be administered twice a year might allow to achieve and maintain LDL-C goals and rise patient compliance.

Conclusion

Despite some discrepancies in the European, Russian and American clinical guidelines, globally, there is a unidirectional vision in the strategy of dyslipidemia management (**Table 1**). The proper use in clinical practice can contribute to earlier detection of patients with lipid metabolism disorders, timely action on atherogenic lipid fractions, and prevention of CVDs and mortality.

Perspectives

There is a range of perspectives on dyslipidemia management related to new risk evaluation strategies and treatment options.

The approach of cardiovascular risk assessment and management based not only on the current 10-year risk scores but also on the concept of cumulative LDL-C burden, deriving from Mendelian randomization studies [31], might be considered as the tool for estimating the magnitude of the clinical benefit that can be achieved by maintaining recommended LDL-C goals and identifying the most effective timing for intervention.

Furthermore, several drugs targeting different lipid fractions, such as LDL-C, triglycerides, and lipoprotein (a) [Lp(a)] have been registered recently or are in phase III clinical trials, which seem very promising for the improvement of lipid disorder management in the near future [32]. Changing the treatment trajectory of atherosclerotic CVDs by reducing LDL-C levels is now possible with bempedoic acid, inclisiran, evinacumab, and the possibility of considering vaccines and genome editing is currently under discussion. Bempedoic acid inhibits the enzyme ATP-citrate lyase, which catalyses the synthesis of a precursor of cholesterol. Several studies have shown its favourable effect in lowering LDL-C and a satisfactory safety profile [33-35]. Inclisiran inhibits PCSK9 protein synthesis by RNA interference. This leads to increased uptake of circulating LDL-C by hepatic receptors and a decrease of LDL-C concentration in blood. The safety of inclisiran and its impact on the prognosis continues to be investigated as part of the ORION clinical research program. The development and research of the monoclonal antibody evinacumab, which specifically binds angiopoietin-like protein 3 (ANGPTL3), an inhibitor of lipoprotein lipase and endothelial lipase, thus reducing levels not only of LDL-C but also triglycerides. The main pool of studies on the efficacy and safety of this drug is concentrated in the group of patients with homozygous hypercholesterolemia and has already demonstrated significant results in reducing atherogenic lipid levels [36, 37]. Developing vaccines and genome editing technologies and investigating their clinical potential might be a promising step in the treatment strategy for patients with dyslipidemias, as confirmed by several studies [38-40].

Special attention to other atherosclerotic targets and reconsideration of the causal role of triglyceride-rich lipoproteins has ensured the de-

Table 1 | Key tools used for the risk assessment and dyslipidemias treatment according to European, Russian, and American clinical guidelines

Parameter	ESC/EAS for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk 2019	Russian guidelines on diagnosis and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis, 2020, VII revision	American guidelines on the Management of Blood Cholesterol 2018 AHA/ACC/AACVPR/AAPA/ ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA
CVD risk assessment	SCORE Cardiovascular Risk Chart Sex Age 40-70 years SPB 120-180 mmHg Total cholesterol 4-7 mmol/L	SCORE Cardiovascular Risk Chart Sex Age 45-70 years SPB 120-180 mmHg Total cholesterol 4-7 mmol/L	ACC/AHA ASCVD Risk Estimator Plus Sex Age 20-79 years Race Total cholesterol 130-320 mg/dL HDL cholesterol 20-100 mg/dL LDL cholesterol 30-300 mg/dL SPB 90-200 mmHg DPB 30-140 mmHg Personal history (diabetes, smoking, treatment for hypertension, statin, aspirin therapy)
Imaging in the assessment of cardiovascular risk	Peripheral arterial duplex scan Calcium score CT angiography Carotid–femoral pulse wave velocity	Peripheral arterial duplex scan Calcium score CT angiography	Peripheral arterial duplex scan Calcium score CT angiography
Cardiovascular risk categories	4 risk categories: very high, high, moderate and low However, there is a group of patients who had a second vascular event within 2 years (not necessarily the same as the first) on a maximum tolerated dose of statin	5 risk categories: extreme, very high, high, moderate and low	4 risk categories: very high, high, moderate and low However, 5 risk groups based on the guidelines of the American Association of Clinical Endocrinologists Also, for clinical decision-making in adults of different races/ethnicities, it is reasonable for clinicians to review race/ethnic features that can influence ASCVD risk to adjust the choice of statin or intensity of treatment
Target LDL-C levels based on the level of cardiovascular risk	For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-cholesterol goal of <1.0 mmol/L (<40 mg/dL) may be considered Very high - <1.4 mmol/L (<55 mg/dL) and decreased ≥50% from baseline; High - <1.8 mmol/l (<70 mg/dL) and ≥50% reduction from baseline; Moderate - <2.6 mmol/l (<100 mg/dL); Low - <3.0 mmol/L (<116 mg/dL)	Extreme risk - <1.4 mmol/L (<55 mg/dL), optimal <1.0 mmol/L (<40 mg/dL); Very high - <1.4 mmol/L (<55 mg/dL) and decreased ≥50% from baseline; High - <1.8 mmol/l (<70 mg/dL) and ≥50% reduction from baseline; Moderate - <2.6 mmol/l (<100 mg/dL); Low - <3.0 mmol/L (<116 mg/dL)	Very high - <1.8 mmol/L (<70 mg/dL); High - <2.6 mmol/l (<100 mg/dL) Reduce levels ≥50% in patients with DM and LDL-cholesterol ≥1.8 mmol/L (≥70 mg/dL) Moderate - clinician-patient risk discussion before starting a statin. Reduce LDL-cholesterol levels by ≥ 30% in patients without DM and LDL-cholesterol levels ≥1.8 mmol/L (≥70 mg/dL) Low - clinician-patient risk discussion
Dyslipidemias management strategies	Lifestyle modification, statins, ezetimibe, PCSK9 inhibitors, fenofibrate, n-3 fatty acids, monacolin, phytosterols, bile acid sequestrants, lomitapide, mipomersen, inclisiran*, lipoprotein apheresis	Lifestyle modification, statins, ezetimibe, PCSK9 inhibitors, fenofibrate, n-3 fatty acids, monacolin, inclisiran*, lipoprotein apheresis	Lifestyle modification, statins, ezetimibe, PCSK9 inhibitors, fenofibrate, n-3 fatty acids, bile acid sequestrants, lomitapide*, mipomersen*, inclisiran*, lipoprotein apheresis

Abbreviations: ASCVD - atherosclerotic cardiovascular disease, CT - computed tomography, DBP - diastolic blood pressure, DM - diabetes mellitus, HDL - high-density lipoprotein, LDL - low-density lipoprotein, PCSK9 - proprotein convertase subtilisin/kexin type 9, SBP - systolic blood pressure, SCORE - systemic coronary risk evaluation.
*- registered in the country, but not presented yet within the clinical guidelines

velopment of drugs aimed at reducing their concentrations and improving the cardiovascular profile of the patient [41]. These drugs include volanesorsen, vupanorsen, pemafibrate, and evinacumab. Volanesorsen, being an antisense oligonucleotide, prevents the translation of apolipoprotein C-III and inhibits lipoprotein lipase. Studies have shown a significant effect in reducing triglycerides [42, 43], however, reactions at the injection site and the possibility of developing secondary thrombocytopenia have been noted. Vupanorsen is also an antisense oligonucleotide, it inhibits ANGPTL3 and leads to improvement of the lipid profile [44]. No changes in platelet levels have been reported, but there remains the possibility of reactions at the injection site. The oral drug pemafibrate, a peroxisome proliferator-activated receptor alpha (PPARα) agonist, is being actively studied as part of the PROMINENT study [45]. This molecule aims to reduce triglyceride and apolipoprotein C-III levels, contributing to the prevention of cardiovascular events, particularly in patients with type 2 diabetes.
Another important lipid particle in terms of the development of atherosclerotic CVDs is Lp(a). Patients with premature, unexplained atherosclerotic cardiovascular events despite optimal LDL-C levels may have increased Lp(a) levels. Drugs aimed at reducing Lp(a) levels are represented by pelacarsen and olpasiran. Pelacarsen is an antisense oligonucleotide that inhibits Lp(a) synthesis. A study of this drug aims to evaluate efficacy, tolerability, and safety in the treatment of hyperlipoproteinemia. Published data demonstrate a sustained reduction in Lp(a) [46, 47], which is favourable for reducing residual cardiovascular risk. N-Acetylgalactosamine-conjugated siRNA, olpasiran, also reduces Lp (a) levels. The efficacy and safety of the drug in patients with Lp(a) >60 mg/dL are currently being evaluated [48]. The results obtained will contribute to the possibility of using targeted drugs in clinical practice.
Beyond that, combination lipid-lowering therapy has to be actively introduced into clinical practice, weighing the benefits versus the risks. The need to implement this approach is analysed in the recent EAS consensus documents [49, 50], and perhaps the future guidelines will convey this concept within the algorithms for the management of patients at high/very-high risk requiring combined lipid-lowering therapy right from the start.

Conflict of interest

The Authors declare that there is no conflict of interest.

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Credit authorship contribution statement

Alieva Asiiat: conception, review, and editing, Usova Elena: writing - original draft, responsible for literature search, Reutova Olga: writing - original draft, responsible for literature search.

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