A Review of Lipid Management Guidelines

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Received: December 2023. Accepted: December 2023; Published: January 1, 2024.
Citation: Mohsin Younas, Mohammed Saliem. A Review of Lipid Management Guidelines. World Family Medicine. December 2024; 22(1): 54-62. DOI: 10.5742/MEWFM.2024.95257007

Abstract

Introduction: Comprehensive analysis was conducted on available guidelines to identify gaps in the available evidence for effective approaches to lipid management. The four guidelines included in the review are NICE, ESC, CCS and AHA/ACC/MS.

Method: Multiple databases were explored to locate relevant guidelines published within the past decade, until June 17, 2023. A qualitative comparison was made regarding recommendations on testing frequency, lipid-lowering therapies, risk stratification and target cholesterol levels.

Results: All the guidelines unanimously advocated for statins as the primary therapy for reducing lipid levels. Noteworthy disparities were observed in the recommended cholesterol targets across the various guidelines. Each guideline provided a specific target for the level of low-density lipoprotein cholesterol (LDL-C) and risk stratification. For long-term patient monitoring, many of the guidelines (n=2) recommended annual reviews, although some variations were noted, suggesting intervals ranging from 3 weeks to 12 months.

Conclusion: All the guidelines have the same scope, despite a few disparities, future research should focus on resolving these differences and on optimizing the preventive measures for lipid management.

Keywords: lipid management, guidelines, review

Introduction

The recent discovery regarding the relationship between apolipoprotein B (ApoB)-containing lipoproteins, particularly LDL-C, and their impact on dyslipidaemia management has prompted updates to the guidelines. The aim of this article is to perform a comprehensive comparative analysis of the lipid management guideline proposed by the American Heart Association/American College of Cardiology/Multi-Society (AHA/ACC/ MS) [15], the guidelines for prevention of atherosclerotic cardiovascular disease (ASCVD) by the European Society of Cardiology (ESC) [32], the 2014 National Institute for Health and Care Excellence (NICE) modification of blood lipids for the primary and secondary prevention of cardiovascular disease [14], and the dyslipidaemia management guidelines for cardiovascular disease by the Canadian Cardiovascular Society (CCS) [25]. The focus is to evaluate the fundamental approaches to dyslipidaemias outlined in these guidelines.

Materials and Methods

Literature Search

Thorough search was conducted across various databases to identify guidelines that were published in the decade preceding June 17, 2023, using the following search term: Lipid Guidelines. Guidelines published in English or at least have an English version were reviewed. Furthermore, various databases specific to guidelines were explored, including the guidelines used in Europe, United Kingdom, America and Canada for lipid management and the prevention of cardiovascular disease in adults with dyslipidaemia.

Following the systematic search, a manual search was carried out in order to find the most up-to-date versions of the guidelines. Additional articles were obtained by reviewing the references cited within the papers identified through the electronic search. The analysis conducted did not include meeting abstracts and unpublished papers.

Inclusion and Exclusion Criteria

The inclusion criteria for papers encompassed adherence to the definition given by the Institute of Medicine in 2011[16] for clinical guidelines. This definition delineates guidelines for clinical practice as comprising recommendations that aim to optimize patient care. The recommendations need to be founded on rigorous evidence-based systematic review and thorough evaluation of potential benefits and risks associated with various alternative treatments. Since this systematic review focused on lipid management, only guidelines providing specific management strategies for patients with any disease were included. We retained only the latest version of each guideline while excluding any previous versions.

Data collection and Analysis

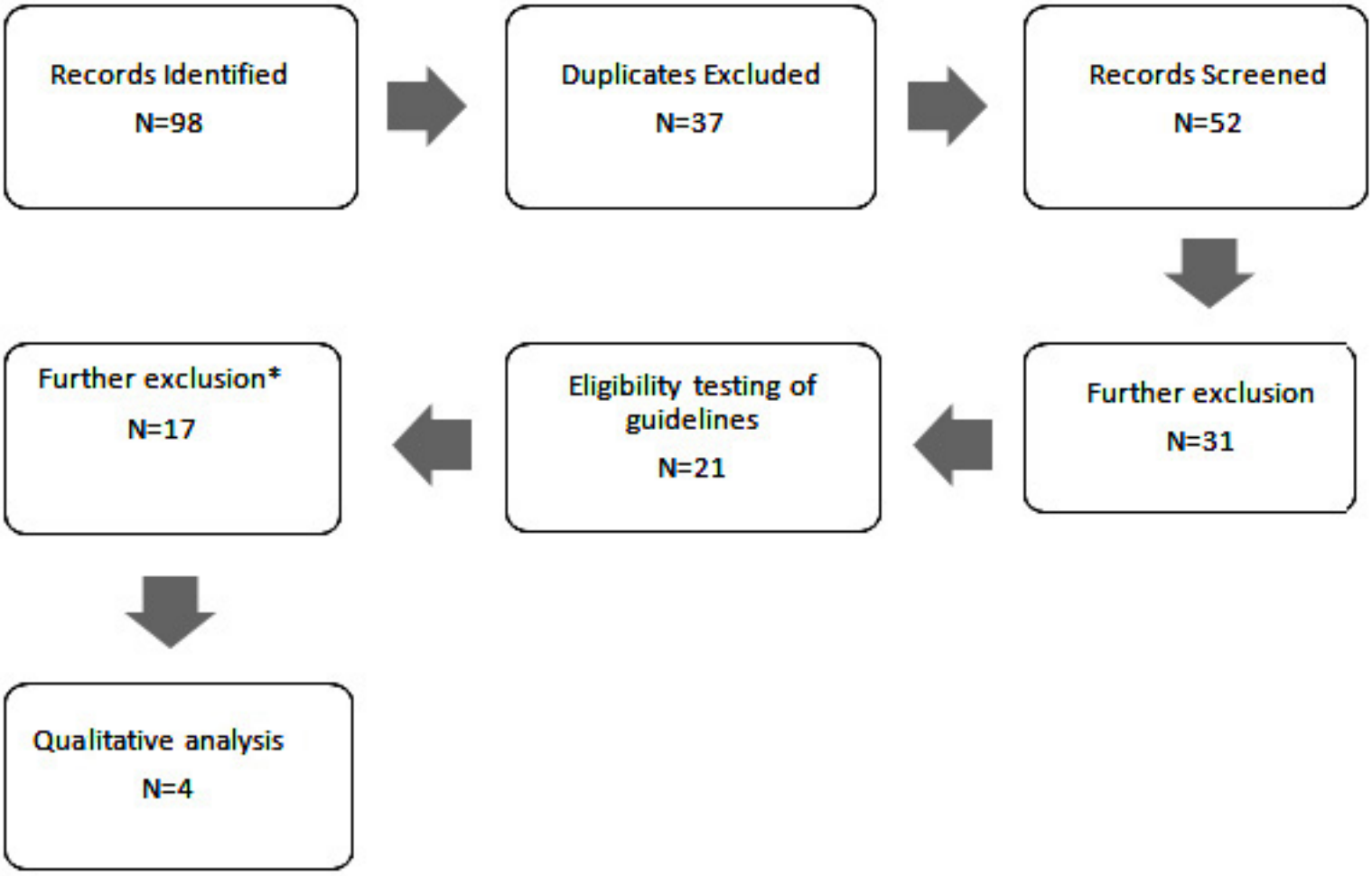
The extracted data encompassed the geographical scope of the guideline and its publication year. Furthermore, the guideline was utilized to extract recommendations for the optimal frequency of plasma lipid monitoring for the purpose of both primary and secondary prevention, as well as any particular lipid target level. The authors also assessed the robustness of each recommendation and the associated level of evidentiary support. Following this, all of the authors conducted a comparison of the extracted recommendations.

Results

Literature Search

Out of the initial 89 results obtained from the literature search (see Figure i), 37 were recognized as duplicates and removed. After a comprehensive evaluation of the titles and abstracts, a total of 31 out of the remaining 52 distinct outcomes were discarded. After conducting a thorough assessment of the complete content of the remaining 21 records, an additional 17 records were deemed ineligible for inclusion. The primary factors contributing to exclusion were the failure of the records to satisfy the established requirements for guideline status (n=4) and the presence of duplications of already existing guidelines (n=6).

Figure 1: Selection process of guidelines. *Not the recent version (N=2), not a guideline (N=4), guidelines were duplicates (N=6), English version unavailable (N=2), merged with another guideline (N=3).



The guidelines selected, categorized into 4 major regions, are summarised (see Table i). Two of the guidelines are for USA, one from Europe and one for Canada that is applicable globally. The guidelines have been published in 2014 (n=2), 2019 (n=1) and 2021 (n=1).

Table 1 Summary of included guidelines

Abbreviation	Development group	Title	Region	Year
ACD [15]	American College of Cardiology, American Heart Association, American Association of Cardiovascular and Pulmonary Rehabilitation, American Association Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurse	2018 AHA/ACC/AACVPR/AAPA/ ABC/ACPM/ADA/AGS/APhA/ ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol	USA	2018
CCS [36]	Canadian Cardiovascular Society	2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidaemia for the Prevention of Cardiovascular Disease	Canada	2021
ESCEAS[1]	European Society of Cardiology, European Atherosclerosis Society	2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk	Europe	2019
NICE [22]	National Institute for Health and Clinical Excellence	NICE Cardiovascular disease: risk assessment and reduction, including lipid modification	USA	2014

Summary of the Guidelines

Lipid Measurement

All the guidelines share the recommendation that the primary method for lipid analysis is to measure LDL-C levels, and suggest employing random rather than fasting blood lipid profiles for the purpose of screening. However, it should be noted that measurements done while patients are not fasting may result in false raised level of LDL-C, particularly in individuals with elevated triglyceride (TG) levels. Therefore, it is recommended to conduct fasting measurements of LDL-C in patients with hypertriglyceridemia [20]. The guidelines under AHA/ACC/MS emphasize the importance of fasting lipid profile measurements, particularly in cases where TG levels exceed 400 mg/dL [3] whereas NICE guidelines suggest complete lipid profiling that includes total cholesterol (TC), TG, and high-density lipoproteins-cholesterol (HDL-C). Additionally, the recommendations are that fasting samples are not required any longer unless the initial TG levels exceed 10 mmol/L. It is essential to pay attention to situations where TG levels are above 9 mmol/L, TG levels exceed 20 mmol/L or non-HDL cholesterol levels are higher than 7.5 mmol/L [18].

Patients experience lingering risks related to lipids that can be assessed through measuring ApoB and non-HDL-C [29]. In case of hypertriglyceridemia, the ESC guidelines recommend measuring non-HDL-C and ApoB. On the other hand, the AHA/ACC/MS guidelines do not regularly endorse ApoB measurement, primarily due to cost-effectiveness concerns. Nevertheless, these guidelines underscore the significance of ApoB measurement, particularly if triglyceride (TG) levels are equal to or greater than 200 mg/dL. Moreover, if LDL-C levels are equal to or greater than 1.5 mmol/L, the CCS guidelines suggest measuring ApoB or non-HDL-C[1].

Lipoprotein a (Lp(a)) levels are guided by genetic factors and are considered a common risk factor for ASCVD [17,31]. When Lp(a) levels surpass 180 mg/dL (430 nmol/L), they have been recognized as posing a similar risk for ASCVD events as individuals with heterozygous familial hypercholesterolemia. The CCS and ESC guidelines suggest the measurement of Lp(a) at least only once, particularly in individuals with a history of early ASCVD in their families. Similarly, the guidelines under AHA/ACC/MS suggest the same considering Lp(a) level greater than or equal to 50 mg/dL (125 nmol/L) as high risk.[34]. Moreover, Lp(a) levels aid in defining and classifying patients as moderate or high-risk categories [33].

Risk assessment and stratification

Different risk assessment methodologies are employed by various guidelines to determine the long-term cardiovascular risk associated with illnesses connected to dyslipidaemia. There is a widely accepted consensus that the implementation of preventative methods should be customized to suit specific countries and individuals.

The risk assessment techniques employed by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) utilize the Systematic Coronary Risk Estimation (SCORE) approach. The analysis employs extensive European cohort datasets that encompass a wide range of individuals. The changes of the SCORE (Systematic Coronary Risk Evaluation) instrument for all European nations can be accessed at the website www.heartscore.org. The utilization of the SCORE model has been employed in order to assess and approximate the categorization of Europe's regions into low-risk and high-risk zones.

The utilization of the SCORE system is employed for the evaluation of cardiovascular disease risk in individuals who are in good health, with the exception of those who have atherosclerotic cardiovascular disease, diabetes, chronic renal illness, or other chronic ailments that elevate the risk of cardiovascular disease. The scope of risk assessment may encompass fatal events only or encompass both fatal and non-fatal cardiovascular events, which is commonly referred to as total risk. The SCORE model is utilized to assess the aggregate risk of experiencing a fatal first cardiovascular event within a span of ten years. This methodology can be employed for the purpose of risk estimation. According to the cumulative SCORE data, there is a three-fold increased chance of death among men. Females face heightened vulnerability, whereas the elderly experience reduced susceptibility. A 5% individual SCORE risk corresponds to a 15% cumulative risk of experiencing a cardiovascular event.

The National Institute for Health and Care Excellence (NICE) in the United Kingdom supports the utilization of QRISK3 as a tool for classifying risks. The utilization of the QRISK3 assessment tool is recommended for individuals aged 25 to 84, including those diagnosed with type 2 diabetes, in order to ascertain their 10-year probability of developing cardiovascular disease (CVD). QRISK3-lifetime represents a viable alternative risk assessment technique. Doctors can utilize a risk assessment tool known as QRISK3-lifetime to engage in conversations regarding the risk of cardiovascular disease (CVD) while encouraging lifestyle modifications among those below the age of 40 who possess a QRISK3 score of less than 10% over a span of a decade, or exhibit indicators of CVD risk. The American College of Cardiology (ACC) and the American Heart Association (AHA) use The ASCVD Risk Estimator Plus. Atherosclerotic cardiovascular disease includes both stroke and coronary disease. This tool uses various demographic and risk factors, including ethnicity, sex, age, total cholesterol levels, HDL cholesterol levels, systolic pressure, usage of blood pressure medication, presence of diabetes, and cigarette use. This statistical measure provides an estimation of the probability of experiencing a cardiovascular incident within the upcoming decade.

The Framingham Risk Score (FRS) and Cardiovascular Life Expectancy Model (CLEM) are used in Canada. It predicts the risk over the span of the next decade. It uses similar factors as ASCVD. It is based on data from the Framingham Heart Study.

Guidelines for Primary Prevention

The significance of adopting a healthy diet and lifestyle is underscored by all sets of guidelines as the initial preventive measure for everyone. All the guidelines underscore the importance of engaging in regular physical activity and avoiding an idle lifestyle. It is recommended for individuals to engage in physical exercise multiple occasions throughout the week [4]. Moreover, all the guidelines presented recommend statins as the primary preventive measure. Additionally, the ESC guidelines propose the inclusion of resistance exercises 2 to 3 days per week to lower the risk of overall mortality.

LDL-C is widely considered as a causal factor for ASCVD, that's why all the guidelines take it as the primary focus in management of dyslipidaemia[7]. For primary prevention, in case of the "apparently healthy" individuals, the ESC guidelines take a personalized approach to therapy, considering the patient's age, SCORE2 risk, and risk modifiers. According to these guidelines, the recommended objectives are to achieve a ≥50% reduction in LDL-C from baseline and maintain an LDL-C level below specific thresholds. These thresholds are set as <1.4 mmol/L (55 mg/dL) for very high-risk groups, <1.8 mmol/L (70 mg/dL) for high-risk groups, <2.6 mmol/L (100 mg/dL) for moderate-risk groups, and <3.0 mmol/L (116 mg/dL) for low-risk groups[32]. The initial treatment of choice should involve prescribing a statin of high-intensity at the maximum tolerable dosage to obtain the LDL-C level established for the corresponding group. The guidelines under ESC suggest escalating the intervention intensity with the goal of achieving target outcomes. It is worth noting that the targeted level of LDL-C set by the guidelines under ESC are lower than the suggested threshold of intervention provided in the guidelines under CCS and AHA/ACC/MS.

The ESC guidelines do not provide specific targets for TG levels but offer secondary aim for non-HDL-C level (<2.2, 2.6, and 3.4 mmol/L or <85, 100, and 130 mg/dL) based on the degree of risk associated with atherogenic triglyceride-rich lipoproteins. Similarly, the secondary goals for ApoB level are 100 mg/dL, 80 mg/dL and <65 mg/dL for moderate to very high-risk individuals [9].

Based on the recommendations provided by NICE guidelines, if the individual's 10 year risk of cardiovascular diseases (CVD) exceeds 10%, including those with type 2 diabetes and significant chronic kidney disease, they should be prescribed a daily dosage of atorvastatin 20 mg for primary prevention. This modification replaces the previous practice of administering simvastatin 40 mg daily. The decision is supported by a careful assessment of drug costs, as well as an analysis evaluating the safety and cost-effectiveness of more intensive treatment [13].

The guidelines under AHA/ACC/MS also recommend lifestyle modifications and healthy habits for individuals at low and borderline-risk levels. Assessing treatment response and adherence is recommended within 4 to 12 weeks and 3 to 12 months following the initiation of statin therapy. Based on this evaluation, treatment intensity should be increased if necessary. When considering cost-effectiveness and making decisions together with patients, it is suggested to consider the use of Ezetimibe or Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) [21]. The guidelines under AHA/ACC/MS prioritize promoting healthy dietary habits and encourage lifestyle modification as the initial step. This is followed by the evaluation of secondary causes and considering statin therapy for individuals with moderate hypertriglyceridemia. As per the ACC 2021, the management of high-risk hypertriglyceridemia patients may involve considering the use of icosapent ethyl [31]. Moreover, the 2022 ACC offers additional recommendations regarding more recent non-statin therapies aimed at reducing levels of LDL-C[35]. Even with the maximum dosage of statin therapy, LDL-C levels remain at or above 190 mg/dL. In such cases, the initial approach to treatment is to use other treatment options such as PCSK9i and ezetimibe as the primary method of prevention aiming for ≥50% reduction in non-LDL-C <130 mg/dL or HDL-C <130 mg/dL. Ezetimibe can also be considered in individuals without ASCVD and non-diabetics, with LDL-C levels between 70-189 mg/dL, and a risk of at least 20%, and in diabetics with no ASCVD and LDL-C levels below 190 mg/dL, if statin therapy proves ineffective in achieving a reduction of at least 50% in LDL-C levels.

The CCS guidelines classify patients into three groups based on their Framingham risk score (FRS) for primary prevention. In the low-risk group, the initial recommendation is to make lifestyle changes without initiating statin treatment. For individuals in the intermediate-risk category (FRS 10-19%) with LDL-C levels of ≥ 3.5 mmol/L and high-risk patients (FRS ≥ 20%), statin therapy is recommended alongside lifestyle modifications. If, despite the use of the maximum tolerable dose of statin, the levels of LDL-Cholesterol stay at ≥ 2.0 mmol/L and for non-LDL-C at > 2.6 mmol/L, or if ApoB levels are ≥ 0.8 g/L treatment intensification with ezetimibe is advised[13]

The CCS guidelines suggest the utilization of higher potential of icosapent ethyl as a means to reduce the likelihood of cardiovascular events among patients diagnosed with ASCVD or diabetes along with at least one risk factor for cardiovascular disease. This recommendation applies to individuals who exhibit increased levels of fasting triglyceride ranging from 1.5 to 5.6 mmol/L, even after receiving the maximum tolerated dosage of statin therapy[2].

As per the guidelines from ESC, the primary course of treatment for individuals at high risk involves the use of statins, even if they have fasting TG levels above 2.3 mmol/L, after lifestyle modifications have been implemented. For high-risk patients who have attained their LDL-C targets but the TG level remains above 2.3 mmol/L, the addition of fibrates to the statin therapy can be considered[12]. Furthermore, it is suggested to contemplate the utilization of a combined therapy involving n-3 polyunsaturated fatty acids (PUFAs) (specifically, icosapent ethyl) alongside statins for high risk patients, who possess triglyceride levels ranging from 1.5 to 5.6 mmol/L[10].

Guidelines for Secondary Prevention

All guidelines emphasize prompt initiation of lipid-lowering intervention for secondary preventive measure. The guidelines under ESC identify ASCVD patients as very high-risk, recommending a minimum 50% reduction in LDL-C from baseline, targeting levels below 55 mg/dL. Recurrent ASCVD events within 2 years may prompt a level ≤ 40 mg/dL. After initiating a highly potent statin, patients will be assessed for treatment response within 4–6 weeks [4]. If LDL-C remains higher than 55 mg/dL regardless of maximum statin dose, along with ezetimibe or PCSK9i, the guidelines of ESC suggest low-dose colchicine for anti-inflammatory benefits in ASCVD patients who still have higher risk or experience recurring cardiovascular incidents[23].

According to the AHA/ACC/MS guidelines, high-intensity statin therapy is recommended for high-risk ASCVD patients, aimed to reduce 50% of LDL-Cholesterol levels. In cases where high-intensity statin therapy is not well-tolerated, an alternative is intermediate intensity statin intervention that results in 30-49% reduction. Still if the targeted level is not attained, adding ezetimibe is the initial choice. For LDL-C levels ≥70 mg/dL or non-HDL-C levels ≥100 mg/dL despite statin and ezetimibe combination, considering PCSK9i is suggested[8].

The guidelines under CCS also advocate high potential statin therapy as a secondary preventive measure. At maximum bearable statin dosage, PCSK9i and or ezetimibe should be used if LDL-C or non-LDL-C levels stays ≥1.8-2.2 mmol/L or ≥2.4-2.9 mmol/L, respectively, or ApoB level ≥0.7-0.8 g/L[2].

In NICE guidelines, to initiate treatment for secondary prevention in individuals with confirmed CVD, administration of a daily dosage of 80 mg of atorvastatin is needed. However, if there is a possibility of drug interactions, a heightened risk of negative effects, or the individual expresses a preference, a reduced dose should be considered. This evaluation should involve a thorough assessment of the individual during yearly medication review, potentially necessitating a switch to atorvastatin 80 mg [11].

All the guidelines; ESC, CCS AHA/ACC/MS, and NICE share the basic tenets of prioritizing LDL-Cholesterol reduction as a crucial approach for preventing cardiovascular events and statins as recommendation for dyslipidaemia as first line therapy. While there may be variations in treatment recommendations due to different interpretations of the evidence, the fundamental principles align[5]. All the guidelines emphasize LDL-Cholesterol as the initial goal and advocate for intensified treatment based on patient risk levels. The ESC guidelines, supported by recent trials like FOURIER-OLE, set more rigorous LDL-C targets for patients with higher risk, considering combination therapy and imaging evidence[24]. Establishing LDL-C goals promotes patient and physician motivation. The AHA/ACC/MS and CCS guidelines promote shared decision-making and risk assessment through imaging, representing important advancements. Instead of emphasizing disparities, our objective should be to fully implement the guidelines. For individuals requiring secondary prevention, an LDL-C threshold of ≥70 mg/dL has been set, and considering the incorporation of a non-statin lipid-lowering medication in conjunction with statin therapy is advised[1].

Monitoring

All the guidelines outlined detailed suggestions for continuous monitoring, which can be classified into three main categories: monitoring post-treatment initiation, observation beforehand achieving constant lipids, and continuous follow-up. Some guidelines provided suggestions that spanned multiple categories.

According to the guidelines from ESC/EAS, an important aspect in mitigating liver and muscle deterioration is the capability to determine high risk individuals and the possible exacerbating factors. The risk factors encompass various elements such as small stature, older age, experiencing hepatic and renal problems, female gender, having multiple systemic diseases, hypothyroidism, and engaging in alcohol abuse[27,28]. Similarly, the guidelines under ACC/AHA have also taken into account comparable exacerbating factors which include stroke, or intolerance to statin or the concurrent medications use that affect metabolism of statin [30]. All the mentioned guidelines recommend monitoring transaminase levels in every patient before initiating statin treatment. Furthermore, all the guidelines endorse tracking the creatine kinase (CK) biomarker. The guidelines under ESC/EAS suggest tracking CK in every patient[6,10]. However the guidelines under ACC/AHA recommend merely baseline tracking in patients who have muscular symptoms or have minor risk [30]. As per guidelines of NICE, monitor CK levels in specific conditions prior to statin therapy, with the consideration of factors such as smoking, BP, body mass index, alcohol intake, renal functioning, TC, non-HDL-C, HDL-C, TG, HbA1c, eGFR, transaminase levels and thyroid stimulating hormone[22]. Regarding the continuous checking of treatment, the ACA/AHA guidelines[30] recommend measuring CK and transaminase levels only if symptoms arise, such as jaundice (indicating hepatotoxicity) or symptoms suggestive of myotoxicity. As per ESC/EAS CK levels need to be measured merely when muscle symptoms appear after starting statin therapy [27,28]. Unlike the ACC/AHA guidelines transaminases need to be monitored eight weeks after commencing statin treatment and then annually when the values are lowered by 1/3 of the normal[30]. Whereas according to NICE guidelines (2014) transaminase levels should always be measured prior to statin treatment and after third and twelfth months. The elevated levels of CK to 5 times and transaminase to 3 times may necessitate treatment discontinuation.

The recommendations from different guidelines vary regarding the rationale for monitoring lipid profiles. The ESC/EAS guidelines emphasize the measurement of plasma lipids as they serve as treatment targets [27,28].

On the other hand, the guidelines under ACC/AHA suggest monitoring to verify the decrease in LDL-C levels and assess the adherence of individuals undergoing treatment[30]. NICE guidelines (2014) also recognize pharmacological adherence as a crucial aspect of managing cardiovascular risk but does not provide specific and effective strategies to enhance statin treatment adherence. Notably, NICE deviates from the other guidelines by not recommending a fasting blood sample.

Regarding the frequency of monitoring, the guidelines under ACC/AHA suggest testing after 4 to 12 weeks of statin treatment, followed by subsequent assessments every 3 to 12 months[29]. Additionally, testing is suggested after 1 to 12 weeks of statin treatment, 3 to 4 weeks following a medication switch, and annually once the treatment objective is achieved[27,28]. According to NICE guidelines (2014) lipid profiles should be determined three months after initiating lipid-lowering treatment and then annually. However, for acute coronary cases, testing needs to be conducted after 4 weeks of lipid-lowering treatment initiation. Interestingly, a meta-analysis proposed that yearly testing provides the most accurate and efficient timeframe for checking lipids [26].

Conclusion

The aforementioned guidelines predominantly emphasize LDL-C as the primary aim for lipid-lowering medication. The guidelines consistently suggest therapy intensification for individuals with an elevated risk. However, the risk assessment methods differ between the guidelines. There is a consensus among all guidelines that treatment should be intensified as the level of risk increases in patients.

The European guidelines, in particular, differ in targeting more stringent levels of LDL-C in high-risk individuals. All guidelines concur on statins being the recommended initial treatment, while non-statin options such as PCSK9i and ezetimibe are considered secondary choice for intervention. There are certain variations in suggestions and recommendations of the guidelines, while the fundamental principles remain consistent.

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