Minireview Article

Current Lipid Management Guidelines In Atherosclerotic Cardiovascular Disease

Abstract :

The use of coronary artery calcium (CAC) score to reclassify risk individuals at either borderline or intermediate risk, for whom the danger of statin therapy is unknown, is another significant addition to the 2018 recommendations. Increased risk of recurrent cardiovascular (CV) events is linked to having established atherosclerotic cardiovascular disease (ASCVD). Many modifiable risk factors for cardiovascular disease have been connected in the literature, including blood pressure, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose intolerance, and smoking. Statins with high dose and strict adherence to dietary and lifestyle changes have been shown to reduce the risk of coronary even events, with the advent of newer lipid lowering medications, statins my one day become obsolete.

Keywords: high-density lipoprotein, cardiovascular disease, coronary artery calcium, Atherosclerosis

Introduction

Cardiovascular disease is the main cause of death, an estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths [1,2]. Cardiovascular disease kills 5 individuals every hour in Saudi Arabia, accounting for 37% of all fatalities in the kingdom [3]. Due to an unstable or ruptured plaque obstructing blood flow and raising the risk of CV events, early and vigorous treatment of Atherosclerosis may lower the risk of CV events [4,5,6,7]. The underlying cause of CVD that develops early in childhood is atherosclerosis caused by elevated LDL-C.

Increased risk of recurrent cardiovascular (CV) events is linked to having established atherosclerotic cardiovascular disease (ASCVD). Many modifiable risk factors for cardiovascular disease have been connected in the literature, including blood pressure, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose intolerance, and smoking [8]. Total cholesterol is more than or equivalent to 240 mg/dL, which includes LDL, HDL, and triglycerides. Low HDL levels are defined as serum HDL concentrations of less than 40 mg/dL. Low HDL levels were seen in 18.4% of people in the United States [9]. 71 million (33.5%) of U.S. adults had an increased LDL level, with just 23 million (33%) of these people regulating their LDL levels, despite having a target LDL level of less than 100 mg/dL [10]. Low-density lipoproteins (LDL) induce ASCVD, according to evidence from genetic, epidemiologic, and clinical investigations [11]. Lowering LDL cholesterol (LDL-C) results in significant reductions in new ASCVD events, according to randomized clinical studies using cholesterol-lowering medications [12,13].

Elevated Lipids Have the Greatest Impact on MI Risk, according to the INTERHEART Study[14]. Low-density lipoprotein (LDL) is strongly linked to coronary heart disease; every 39 mg/dL (1 mmol/L) reduction in LDL-C reduces the relative risk of CHD by 20-25 percent [15,16,17]. However, despite awareness that lowering LDL-C levels in patients with acute coronary syndrome (ACS) provides benefits, few of these high-risk patients attain their LDL-C target goals [18]. Lipoprotein(a), often known as Lp(a), is a modified version of LDL-C that has long been recognized as a CVD risk factor. It's worth testing in individuals who have a familial history of early ASCVD or a personal history of ASCVD that can't be explained by other risk factors.

2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) Guidelines and 2018 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines.

Table 1 : Recommended treatment goals for LDL-lower therapy: main changes from 2016-2019

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Recommended treatment goals for LDL-lowering therapy: main changes from 2016 to 2019

Risk category	LDL goals (starting with untreated LDL-C)	
	2016	2019
Very-high-risk	<1.8 mmol/L (70 mg/dL) or >50% ↓ if LDL-C 1.8-3.5 (70 - 135 mg/dL)	<1.4 mmol/L (55 mg/dL) and >50% ↓
High-risk	<2.6 mmol/L (100mg/dL) or >50% ↓ if LDL-C 2.6-5.2 (100 - 200 mg/dL)	<1.8 mmol/L (70 mg/dL) and >50% ↓
Moderate-risk	<3.0 mmol/L (115 mg/dL)	< 2.6 mmol/L (100 mg/dL)
Low-risk	<3.0 mmol/L (115 mg/dL)	<3.0 mmol/L (115 mg/dL)

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

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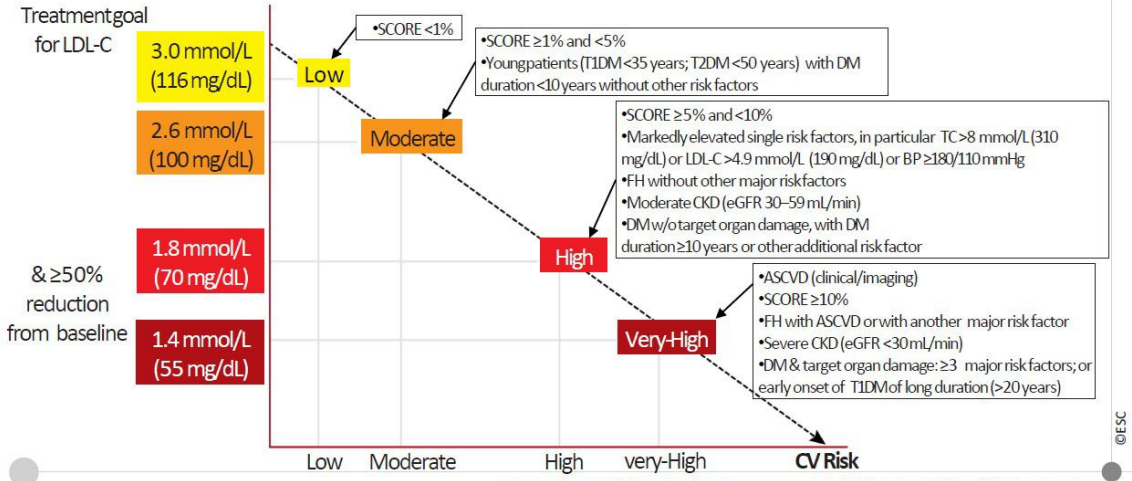
Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk



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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Table 2 : Treatment goals for low-density lipoprotein cholesterol(LDL-C) across categories of total cardiovascular disease risk.

Recommendations for treatment goals for low-density lipoprotein cholesterol (1)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
In secondary prevention patients at very-high risk[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	A
In primary prevention, for individuals at very-high risk but without FH[c], an LDL-C reduction of at least 50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C

[c]For definitions see Table 1.
[d]The term 'baseline' refers to the LDL-C level in a person not taking any LDL-C lowering medication. In people who are taking LDL-C-lowering medication(s), the projected baseline (untreated) LDL-C levels should be estimated, based on the average LDL-C-lowering efficacy of the given medication or combination of medications.

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2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Table 3 : Recommendations for treatment goals for low-density lipopritein cholestrol(1)

Any patient with confirmed ASCVD (e.g., past ACS, stable angina, coronary revascularization, stroke, transient ischemic attack, or peripheral artery disease) is deemed extremely high risk, according to the recommendations. In very high-risk individuals, the ultimate treatment objective for secondary prevention is a 50% decrease in LDL-C from baseline and a target LDL-C of 55 mg/dL. Patients who do not meet their LDL-C objectives on maximally tolerated statin medication should be given a statin plus ezetimibe combination therapy. A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is advised in individuals who have not met their LDL-C target while using a maximally tolerated statin in conjunction with ezetimibe [(19)].

A history of multiple major ASCVD events or one major ASCVD event plus multiple high-risk conditions (age 65 years, heterozygous familial hypercholesterolemia, prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD

event(s), diabetes mellitus, hypertension, chronic kidney disease, current smoker, persistently elevated LDL-C > or equal to100 mg/dL on a maximally tolerated statin and ezetimibe, and a history of congestive heart failure). High-intensity or maximally tolerated statin medication should be given to patients with ASCVD who are at very high risk. It is appropriate to add ezetimibe to maximally tolerated statin medication if LDL-C is not below 70 mg/dL. It is appropriate to add a PCSK9 inhibitor to people on a maximally-tolerated statin and ezetimibe medication who have not attained an LDL-C 70 mg/dL [12,13].

Pathophysiology

Dyslipidemias are characterized by clinically elevated cholesterol and/or triglycerides, as well as lower HDL levels. Genetic factors, high carbohydrate diets, excessive alcohol use, obesity, insulin resistance, and nephrotic syndrome can all contribute to increased hepatic VLDL production [20]. The absolute amount and cumulative length of LDL-C exposure have been directly linked to the risk of atherosclerotic cardiovascular disease (ASCVD) [21]. There is currently no evidence that HDL has a preventive effect in the prevention of atherosclerosis [22]. Increased cholesterol levels in the body can cause plaque to develop and build up in the vasculature, resulting in athero-sclerotic cardiovascular disease [23].

Clinical Presentation

Hypercholesterolemia is a substantial risk factor for cardiovascular disease despite the lack of obvious symptoms. Xanthomas and corneal arcus are symptoms of high cholesterol levels, which are most commonly found in familial hypercholesterolemia. Carotid artery disease, stroke, peripheral vascular disease, high blood pressure, and type 2 diabetes mellitus are all complications of poorly controlled hypercholesterolemia (T2DM). Psoriasis, Crohn's disease,

inflammatory bowel disease, chronic obstructive lung disease, depression, chronic pain, and chronic kidney disease are examples of systemic disorders that affect dyslipidemia [24].

According to 2017 observational research of 7,641 Europeans over 50, 1,591 (20.8 percent) of the participants had high triglyceride or low HDL values. These individuals were also more likely to be obese, have type 2 diabetes, and consume more alcohol than the recommended weekly limit. Patients with high T.G. and low HDL received no lipid treatment in 55% of cases [25]. When the ACC/AHA released the 2018 Guideline for the Management of Blood Cholesterol, it made more revisions to the 2013 lipid recommendations. It acknowledges that, while there is no optimum LDL-C blood level, it is critical to maintain those levels low, since people with LDL-C levels of 100mg/dL or less are less likely to suffer from heart disease and stroke. The 2018 guidelines recommend looking into risk-enhancing factors in older patients aged 40 to 75, such as family history and other factors of health conditions, in addition to risk factors that are commonly associated with cardiovascular diseases such as high cholesterol, high blood pressure, and smoking [26].

The use of coronary artery calcium (CAC) score to reclassify risk individuals at either borderline or intermediate risk, for whom the danger of statin therapy is unknown, is another significant addition to the 2018 recommendations [27]. Unless the patient has a very high risk of ASCVD, lifestyle changes such as reducing saturated fat consumption and exercising for at least 40 minutes three to four times per week are usually the initial step in therapy for high cholesterol [28]. With the emergence of non-statin medications like ezetimibe and bile acid sequestrants, the 2018 recommendations provide for more tailored care and treatment alternatives, but they also incorporate new risk-assessment tools to reduce inappropriate statin prescriptions.

Statins and Ezetimibe: Statins and healthy lifestyle changes are the first-line medication and healthy lifestyle modifications for lowering LDL-C to reduce CV risk, according to a large body of data from CV outcomes studies. In a review of many clinical studies, an ACC/AHA Expert Panel discovered that initiating moderate-intensity statin medication (to drop LDL-C by 30% to 50%) or high-intensity statin therapy (to lower LDL-C by 50%) is a crucial factor in reducing ASCVD occurrences. Ezetimibe is a selective cholesterol absorption inhibitor that reduces LDL-

C levels by preventing cholesterol absorption in the gut. When this medicine is added to a statin regimen, the amount of LDL-C that is reduced increases by 20% to 25% [12].

PCSK9 inhibitors: Monoclonal antibodies that attach to the PCSK9 protein are used in these treatments. PCSK9 normally blocks LDL receptor recycling by targeting the LDL receptor for destruction when it attaches to it, preventing the LDL receptor from returning to the hepatocyte's surface to bind new LDL particles.

On top of all types and dosages of statin medication and ezetimibe decrease in LDL-C by treatment and background therapy, evolocumab provides up to 75% additional LDL-C lowering [28,29,30]. A consistent decrease of LDL-C from a baseline of 60% was seen throughout all evolocumab clinical studies [30].LDL-C Lowering has been shown To reduce atherosclerotic burden, and percent atheroma volume [32]. Patients who had a recent MI were more likely to have serious unfavourable CV events than those who had a remote MI. Evolocumab decreased the risk of the main endpoint by 19% in recent MI patients, and the risk of CV mortality, MI, or stroke was lowered by 25% [32].

Inclisiran might be the first and only siRNA therapy to diminish LDL-C levels. It should be injected subcutaneously by a healthcare expert with an initial dosage, followed by a second dose three months later, and then every six months after that. Inclisiran promotes LDL-C absorption by hepatocytes and decreases LDL-C levels in the circulation by enhancing LDL-C receptor recycling and expression on the hepatocyte cell surface [33]. Inclisiran is a cholesterol-lowering small interfering RNA-based medication that got European Medicines Agency clearance in December 2020 for use as an addition to diet in individuals with primary hypercholesterolemia or mixed dyslipidemia**.**US food and drug administration (FDA) officially approved Inclisran add on therapy to lower cholesterol on December 22, 2021 [34,35]. Evinacumab inhibits angiopoietin-like 3,a lipoprotein and endothelial lipase inhibitor that increases triglyceride and other lipid levels [36]. Vupanorsen inhibits the formation of the ANGPTL3 protein, lowering LDL-C levels in the process. Vupanorsen has also been demonstrated to lower total cholesterol, triglycerides and non-HDL-C [37]. Through its liver-

directed downregulation of hepatic apolipoprotein C-III, Gemcabene can improve VLDL clearance in plasma and limit cholesterol and triglycerides synthesis in the liver [38]. Bempedoic acid inhibits ATP-citrate lyase, a component of the cholesterol synthesis pathway [39]. The United States Food and Drug Administration (FDA) has authorized bempedoic acid as an adjuvant to diet and maximally tolerated statin medication for treating persons with heterozygous familial hypercholesterolemia or established ASCVD who require further LDL-C reduction [40]. In adults with elevated triglycerides (150 mg/dL) who have either established CVD or type 2 diabetes (T2D) and 2 CVD risk factors, icosapent ethyl is approved as an adjunct to maximally tolerated statin therapy to reduce the risk of MI, stroke, coronary revascularization, and unstable angina requiring hospitalization [41]. Fibrates aid to reduce triglyceride levels by reducing VLDL synthesis in the liver and assisting in the removal of triglycerides from the blood. Fibrates can marginally enhance HDL-C levels and have varying effects on LDL-C levels, depending on the existence of other lipid disorders [42]. Niacin is a B-complex vitamin that decreases triglycerides by 20% to 50%, lowers LDL-C by 10% to 20%, and improves HDL-C by 15% to 35% [43]. Bile acid sequestrants bind to bile and prevent its absorption in the gut. Because bile is made up of cholesterol, these drugs lower total cholesterol and LDL-C levels in the body. Cholestyramine has been proven to decrease CV events in hypercholesterolemic males when given as monotherapy [17].

Lifestyle changes For ASCVD patients are an important aspect of secondary prevention. Smoking cessation, weight loss, and engaging in moderate-to-vigorous physical exercise 3–4 times per week for around 30-40 minutes per session are strongly advocated, in addition to participating in cardiac rehabilitation programs whenever possible [12,13].

Conclusion

Low-density lipoprotein is a good indicator of a patient's lipid profile. LDL levels should be less than 100 mg/dL in healthy people; however, in those with heart disease or diabetes, they should be less than 70 mg/dL. Patients with a larger than 7.5 percent ASCVD risk, those with a history of familial hypercholesterolemia, patients with a documented history of atherosclerotic disease,

and patients with diabetes mellitus all benefit from LDL reduction. Statins with high dose and strict adherence to dietary and lifestyle changes have been shown to reduce the risk of coronary even events, with the advent of newer lipid lowering medications, statins my one day become obsolete.

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