Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 6 Issue 5 May 2022

Review Article

Management of Hypercholesterolaemia for Cardiovascular Risk Reduction: A Malaysian Perspective

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DOI: 10.31080/ASMS.2022.06.1260

Received: January 24, 2022

Published: April 29, 2022

Abstract

Cardiovascular disease (CVD) is a major health problem worldwide. Primary preventive population-based strategies aimed at improving global cardiovascular (CV) health is being advocated universally. In addition, specific CV risk factors need to be addressed. This paper focusses on the management of hypercholesterolaemia from a Malaysian perspective and also discusses the newer lipid lowering agents. In individuals at low and intermediate CV risk, lifestyle modification alone may suffice. This encompasses a pragmatic and healthy diet, weight management and increased physical activity. In individuals at high and very high CV risk however, in addition to lifestyle modification, drug therapy is almost always necessary to achieve the target Low Density Lipoprotein Cholesterol (LDL-C) levels which have been shown to improve CV outcomes. In clinical trials, very low LDL-C levels (< 1.4 mmol/l) have been shown to retard progression and sometimes even result in regression of atherosclerotic plaques. Statins are the first-line drugs because there is robust data that they are both effective and safe. Such low target LDL-C levels (< 1.4 mmol/l) however are sometimes not achievable despite maximally tolerated statin therapy and lifestyle modification. The addition of ezetimibe and/or Proprotein convertase subtilisin/kexin type 9 Inhibitors (PCSK9-i) to statins may be necessary to achieve these targets.

Keywords: Cardiovascular Disease; Hypercholesterolaemia; Statins; Familial Hypercholesterolaemia; Statin Intolerance; Ezetimibe; PCSK9-inhibitor

Abbreviation

ACL: ATP-citrate Lyase; ALT: Alanine Transminase; ARH: Autosomal Recessive Hypercholesterolaemia; Apo B: Apolipoprotein B; CHD: Coronary Heart Disease; CKD: Chronic Kidney Disease; CK: Creatine Kinase; CPH: Common Polygenic Hypercholesterolaemia; CRP: C-reactive Protein; CV: Cardiovascular; CVD: Cardiovascular Disease; EPA: Eicosapentaenoic Acid; FH: Familial Hypercholesterolaemia; FRS: Framingham Risk Score; GFR: Glomerular Filtration Rate; HDL-C: High Density Lipoprotein -Cholesterol; HMG CoA: 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase; IDL: Intermediate-Density Lipoprotein; IHD: Ischaemic Heart Disease; LDL-C: Low Density Lipoprotein -Cholesterol; LDL-R: LDL Receptor; LDLRAP1: Low-density Lipoprotein Receptor Adaptor Protein 1; Lp(a): Lipoprotein (a); NPC1L1: Niemann-Pick C1-like 1; PCSK9:

Proprotein Convertase Subtilisin Kexin Type 9; PPAR: Peroxisome Proliferator Activated Receptor; PUFA: Polyunsaturated Fatty Acids; SAMS: Statin-Associated Muscle Symptoms; SCORE: Systematic Coronary Risk Estimation; SFA: Saturated Fats; siRNA: Small Interfering RNA; SNPs: Single Nucleotide Polymorphisms; TC: Total Cholesterol; TFA: Trans Fats; TG: Triglycerides; UKPDS: United Kingdom Prospective Diabetic Study; ULN: Upper Limit Normal; VLDL: Very Low-Density Lipoprotein

Introduction

Non communicable diseases accounted for 7 of the 10 leading causes of deaths (74% of all deaths) globally in 2019 [1]. Ischaemic heart disease (IHD) was the major cause accounting for 16% of total deaths and accounted for the largest increase in deaths since 2000[1]. In general, mortality from cardiovascular disease (CVD) is significantly lower in developed countries. In Malaysia, ischaemic heart disease has remained the principal cause of medically certified deaths.

The most recent 2019 National Health and Morbidity Survey reported that among adults aged ≥18 years, the prevalence of some CV risk factors - diabetes and overweight/obesity - were on an increasing trend [2]. On the other hand, the prevalence of hypercholesterolaemia, hypertension and smoking, although still high, appeared to have stabilised and seemed to be on the downward trend [2]. The prevalence of hypercholesterolaemia was 38.1%. It was similar in both rural and urban populations [2]. Even in young adults aged 30-34 years, the prevalence was as high as 27.9% [2].

TC and LDL-C as CV risk factors

Total cholesterol and especially LDL-C (hypercholesterolaemia) is well documented to be linked to CVD. High LDL-C levels is an important causative factor for CVD and conversely, lowering TC and LDL-C has been shown to improve CV outcomes [3-6]. The relative risk reduction from LDL-C lowering is similar in all individuals but the absolute benefits is greater in individuals with high CV risk - i.e. those with pre-existing CVD and very high LDL-C levels [3-6]. Randomized clinical trials have consistently shown that the lower the on-treatment LDL-C achieved, the greater the CV benefits - both in terms of reduction in CV events and death [3,5].

In epidemiological studies, a low HDL-C and a high TG (especially post prandial TG) have also been associated with increased CV risk [7]. However, reducing TG and/or increasing HDL-C levels per se using pharmacological agents has not been shown to reduce CV events.

The addition of icosapent ethyl at a dose of 2 gm twice a day, to statin therapy in patients whose TG levels remained elevated despite near optimal LDL-C levels, has been shown to improve CV outcomes [8]. Currently there are ongoing trials of pure Eicosapentaenoic Acid (EPA) ethyl ester in combination with statin therapy and these will provide more information on the additional CV benefits of TG lowering in patients at optimal LDL-C targets.

Non-HDL-C measures the cholesterol concentration within all atherogenic lipoprotein particles. This includes chylomicron, very-low density lipoprotein (VLDL), LDL, intermediate density lipoprotein (IDL) and remnant particles. It has been shown to be a better predictor of CV risk than LDL-C especially in patients with diabetes and the metabolic syndrome [9].

Almost all guidelines recommend LDL-C as the primary target of therapy in the management of dyslipidaemia. After achieving LDL-C targets, Non-HDL-C is a secondary target of therapy to reduce residual CV risk.

Causes of Hypercholesterolaemia

Hypercholesterolaemia may be primary or secondary (Tables 1 and 2). Primary hypercholesterolaemia is due to genetic defects in lipoprotein metabolism leading to elevated LDL-C levels alone or both LDL-C and TG levels [10]. The TC and LDL-C levels are usually very high and the risk of developing premature CVD is also high. Secondary hypercholesterolemia, on the other hand, may be due to a variety of different aetiological factors. Treatment of the underlying disorder(s) alone may occasionally suffice without the need for lipid lowering pharmacotherapy. Most drugs cause elevations of both TC and TG levels rather than TC alone.

The commonest aetiology of Primary Hypercholesterolaemia is Common Polygenic Hypercholesterolaemia. It is usually due to multiple gene defects [10]. Familial Hypercholesterolaemia (FH) may be due to a single gene defect in 1 of 4 candidate genes or more often, from compound heterozygous mutations in either the LDL receptor (LDL-R) gene or Autosomal Recessive hypercholesterolaemia (ARH) gene [10,11].

Longitudinal family studies have shown that individuals with very high LDL-C levels from a young age (high lifetime exposure) have a CV risk that is magnified several fold when compared to the normal population [6]. Early treatment has been shown to slow down atherosclerosis and increase their CVD free survival [6,11,12]. Conversely, individuals who have genetically low levels of LDL-C have low CV risk and long CV event free survival [6].

Individuals with low LDL-C levels include those with loss of function of specific single nucleotide polymorphisms (SNPs) [13]. On example is the loss of function of the PCSK9 gene due to mutations on the R46L, L253F, and A443T alleles [13]. The PCSK9 gene is involved in the clearance of the LDL receptor from the surface of hepatocytes. Individuals with loss of function of this gene have more LDL receptors and this results in accelerated clearance of LDL-C from the blood [13]. Mutations on the R46L lowered LDL -C by about 0.5 mmol/l and resulted in a 50% reduction in CV risk [14]. Similarly, individuals with nonsense mutations in the PCSK9 gene had LDL-C levels that were lower by 1.0 mmol/l and a 88% reduction in their incidence of CHD [14]. Others with low LDL-C exposure throughout their lives include individuals with familial hypobetalipoproteinaemia.

The prevalence of FH is highly variable. From studies conducted in the West it has been estimated to be at 1:200 to 1:500, and that of the homozygous state to be less common at 1:160,000 to 1:1,000,000 [11,12].

In Malaysia, the prevalence of FH was found to be as high as 1:100 in the community [15].

An earlier study in patients with a clinical diagnosis of FH showed the presence of a significantly milder phenotype [16]. In the majority (73%) of those studied, there were no mutations in the genes coding for the LDL-R and apoB-100 detected [16]. The researchers postulated the possibility of a third gene in the Southeast Asian population contributing to a milder form of FH [16].

Common Polygenic Hypercholesterolaemia (CPH)	This is the commonest genetic disorder. It is usually due to mutations in multiple genes, each contributing to raising LDL-C levels. Occasionally it may be due to a single gene defect. Environmental factors such as obesity, an atherogenic diet rich in saturated fats and a sedentary lifestyle play an important role in the phenotypic expression [10]. Individuals with CPH may also have obesity and insulin resistance and thus high TG levels as well.

Familial Hypercholesterolaemia (FH) [10,11]	This is the commonest monogenic disorder.
	It is autosomal dominant.
	It may exist in the homozygous or heterozygous state. Homozygotes usually have about double the LDL-C levels of heterozygotes.
	
	FH may be due to mutations in four candidate genes all resulting in reduced clearance of LDL-C from the bloodstream:
	• Loss of function mutations of the:
	  • LDL receptor (LDL-R) gene (85%, most common)
	  • Apolipoprotein B-100 (Apo B-100) gene (5-10%)
	  • Low-density lipoprotein receptor adaptor protein 2 (LDLRAP-1)
	• Gain-of- function mutation of the PCSK9 gene

Autosomal Recessive hypercholesterolemia (ARH gene) [10]	The clinical presentation is similar to that of classical homozygous FH. It is however generally less severe, and more responsive to lipid-lowering therapy. It is found mainly in individuals of Sardinian or Middle Eastern origin.
Sitosterolaemia (ABCG5 or ABCG8 genes) [10]	This is a rare inherited autosomal recessive disorder. It is characterized by increased absorption and decreased biliary excretion of dietary sterols. It results from mutations in either the ABCG5 or ABCG8 gene which encode for a sterol half-transporter present in the intestine.
Cholesterol 7alpha-hydroxylase deficiency (CYP7A1 gene) [10]	This is a rare disorder of the enzyme cholesterol 7alpha-hydroxylase, which catalyzes the initial step in cholesterol catabolism and bile acid synthesis. The gene mutation leads to a loss of the enzyme function.

Table 1: Causes of Primary Hypercholesterolaemia.

Dietary factors
Nephrotic syndrome
Hypothyroidism
Obstructive liver disease
Drugs
• Cyclosporine and tacrolimus
• Antiviral therapy such as protease inhibitors
• Diuretics such as thiazides

Table 2: Causes of Secondary Hypercholesterolaemia.

Management of hypercholesterolaemia

Treatment targets

Lowering TC and LDL-C lowers CV risk. CV risk reduction is proportional to the degree of LDL-C lowering achieved independent of the type of therapy (pharmacotherapy, partial ileal bypass etc) used [3,5].

International guidelines recommended a LDL-C target of < 1.8 mmol/l in patients with CVD. Genetic studies and more recent randomized clinical trials, however, have shown that LDL-C levels lower than <1.8 mmol/L, provides additional clinical benefits without any safety signals [5,17-21].

LDL-C lowering to levels < 1.8 mmol/l has been shown in several coronary angiographic studies to be associated with less progression of the atherosclerotic plaque [22]. At levels of <1.6 mmol/L, regression of the plaque has been observed, the lower the LDL-C achieved, the greater the reduction in the atheroma volume [22,23].

For these reasons even lower LDL-C targets are being advocated in individuals who at Very High CV risk.

The European Society of Cardiology has presented its most recent 2021 Guidelines for the prevention of atherosclerotic CVD [24]. It has very comprehensive albeit elaborate CV assessment algorithms using the Systematic Coronary Risk Estimation 2 (SCORE-2) and Systematic Coronary Risk Estimation 2-Older Persons (SCORE 2-OP) risk charts for CVD - both fatal and non-fatal myocardial infarction and stroke [24].

In Malaysia, we advocate a simple and easy to remember CV Risk Stratification approach.

High and very high-risk individuals include those with pre-existing CVD, diabetes with and without target organ damage, chronic kidney disease and those with very high levels of individual CV risk factors [25,26] (Table 3). In all other individuals, (i.e. primary prevention), the CV risk should first be assessed [25].

Very High-Risk individuals are those with:
• Established CVD
• Diabetes with target organ damage eg proteinuria or with ≥3 major CV risk factors
• CKD with GFR <30 Ml/min^{-1}/1.73 m^2 (≥Stage 4)
High Risk Individuals include:
• Diabetes for ≥ 10 years without target organ damage and any other CV risk factor
• CKD with GFR ≥30- <60 Ml/min^{-1}/1.73 m^2 (Stage 3)
• Very high levels of individual risk factors (LDL-C >4.9 mmol/L, BP >180/110 mmHg)
• Multiple risk factors that confer a 10-year risk for CVD >20% based on the Framingham General (FRS) CVD Risk Score
Intermediate (Moderate) Risk Individuals:
• Have a FRS-CVD score that confer a 10-year risk for CVD of 10-20%
• Diabetes of < 10 years duration and < 50 years old and no additional CV risk factors
Low Risk Individuals:
• Have a FRS-CVD score that confer a 10-year risk for CVD <10%.

Table 3: Risk Stratification of Cardiovascular Risk (Adapted from [25,26]).

There are many CV risk calculators available. In Malaysia, the Framingham General CV Risk Score has been validated and is thus advocated [27,28]. In diabetic patients however, the UKPDS was found to be a better predictor of 10-year CVD risk compared with the Framingham CVD equation [29].

The target LDL-C depends on the individual's CV risk [4,24,25]. (Table 4) The higher the CV risk, the lower the LDL-C target level.

Individuals at Very High CV risk should aim for a LDL-C target < 1.4 mmol/l. In individuals with recurrent CV events despite achieving this target (Extremely High Risk), an even lower target of < 1.0 mmol/l has been shown to further reduce CV events [20]. In these individuals, all other modifiable CV risk factors should also be aggressively addressed.

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)	Non HDL-C Level corresponding to LDL-C targets in individuals with TG > 4.5 mmol/L
Low CV Risk*	Clinical judgement**	<3.0	<3.8
Intermediate (Moderate) CV Risk*	>2.6 **	<2.6	<3.4
High CV risk 20% 10-year CVD risk Diabetes for > 10 years without target organ damage and any other CV risk factor Very high levels of individual risk factors (LDL-C >4.9 mmol/L, BP >180/110 mmHg) CKD with GFR 30-<60 Ml/min^{-1}/1.73 m^2	> 1.8	≤1.8 or a reduction of >50% from baseline***	≤ 2.6 or a reduction of >50% from baseline***
Very high CV risk established CVD Diabetes with target organ damage eg proteinuria or with >3 major CV risk factors CKD with GFR <30 Ml/min^{-1}/1.73 m^2 but not dialysis dependent)	>1.8	<1.4 or a reduction of > 50% from baseline***	< 2.2 or a reduction of > 50% from baseline***

Table 4: Target LDL-C levels (Adapted from [25,26]).

*Low and Intermediate (Moderate) CV risk is assessed using the Framingham General CVD Risk Score

**After a therapeutic trial of lifestyle modification and following discussion with the patient of the risk: benefit ratio of drug therapy

***whichever results in a lower level of LDL-C. In patients who are "Extremely High Risk" with recurrent CV events, upon informed discussions with the patient on possible enhanced benefits of even lower LDL-C target, a target of <1.0 mmol/l may be reasonable.

In patients whose TG levels are > 4.5 mmol/l, the Friedewald equation underestimates LDL-C levels and is no longer reliable. LDL-C or apolipoprotein B has to be directly measured but these assays are not widely available in most laboratories. In these individuals, Non-HDL-C then becomes the primary target of therapy.

Following achievement of LDL-C target, Non-HDL-C is a secondary treatment target to reduce residual CV risk [25]. This applies especially to individuals with combined hyperlipidaemias, diabetes, cardio metabolic risk (metabolic syndrome) and chronic kidney disease.

Treatment strategies

Lifestyle modification

Lifestyle modification encompasses dietary changes, weight management and an increase in physical activity. In some

individuals especially those at Low and Intermediate (Moderate) CV risk, these lifestyle changes alone may be adequate to achieve target LDL-C levels.

Diet - cholesterol, saturated fats (SFA) and Trans-Fat

Early cohort studies suggested that dietary cholesterol and blood cholesterol levels had a linear relationship. These studies, however, had biases and confounding variables. It is now known that the relationship between cholesterol in the diet and that in the blood is more complex [30,31]. Blood cholesterol is mainly synthesized by the body especially in the liver. Dietary sources only contribute about 15-20% and there is, under normal circumstances, a balance between the 2 sources to maintain cholesterol homeostasis [30,31].

Studies have failed to show any significant association between dietary cholesterol intake and LDL-C levels [30,31]. Saturated fats (SFA) and especially trans- fats, on the other hand, have been shown to increase blood cholesterol levels and CV risk [32,33]. Most foods that are high in cholesterol are however also high in SFA, exceptions being shrimps and eggs. Low to moderate consumption of eggs is safe and does not increase CV risk [34]. However, the method of egg preparation (scrambled, fried or boiled) must also be taken into consideration.

A Cochrane review found that reducing SFA intake reduces CV events without any effect on CV or total mortality [35]. This benefit was seen when SFA was replaced with PUFA or starches. The greater the decrease in SFA intake, the lower the blood TC and greater the CV benefits seen [35].

Guidelines advise that SFA should constitute <10% of an individuals' total energy intake [24]. There is, however, no evidence that this arbitrarily set upper limits on SFA consumption will prevent CVD or reduce mortality. In fact, diet-induced LDL lowering is mainly due to a reduction in LDL large particles rather than the small dense LDL, which is more atherogenic [36]. These small dense LDL particles do not appear to be reduced by dietary fat restriction. Furthermore, fat restriction can also lead to a decrease in HDL-C levels [36].

Presently the emphasis is on healthy dietary patterns - emphasizing intake of fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and liquid vegetable oils rather than specifying dietary cholesterol targets [37].

Trans-fats (TFA) are produced either industrially by partial hydrogenation of unsaturated vegetable oils or naturally by bacteria (biohydrogenation) in the stomach of cows and sheep. Studies have shown TFA increases total CHD, all-cause mortality and CHD mortality [33]. Trans-fats should be kept at <1% of the total energy intake [25,30]. The European Union Commission has set the upper limit of trans-fats to 2g per 100g of fat [24]. TFA is best replaced by polyunsaturated fatty acids (PUFA) [32].

Exercise

There is robust data indicating that regular exercise is cardioprotective and reduces both all-cause and CVD mortality [38]. Regular exercise has a favourable effect on the traditional CV risk factors - body mass index, blood pressure, lipids and glucose metabolism- but these changes alone cannot explain all of the observed CV benefits.

The effect of exercise on lipid levels is small and dependent on exercise intensity and compliance to the protocol. Furthermore, the accompanying dietary changes make it difficult to quantify how much of the observed changes are purely due to exercise.

On average, regular exercise increases HDL-C levels by 3-10% (up to 0.16 mmol/L) and reduces TG by about 11% (up to 0.34 mmol/L) especially in those with high TG at baseline [39].

The effect on LDL-C levels is however small and inconsistent unless there is also accompanying weight loss [39].

Smoking

The association between smoking and CV risk is complex and multifactorial. Smoking cessation is associated with a significant reduction in CV morbidity seen within 6 months [40]. This cannot be explained by the observed changes in lipids alone.

Compared to non-smokers, HDL-C levels were about 6% lower and TG levels 11% higher in current smokers [41]. Smoking cessation increases serum levels of HDL-C. It, however, has no effect on TC, LDL-C, and TG levels [41].

Lipid modifying agents

Lipid modifying pharmacotherapy should be initiated simultaneously with lifestyle modification in patients at high and very high CV risk to achieve target LDL-C levels and improve their CV risk [24,25].

Statins

Statins are the lipid-lowering drugs of choice because they are evidence based to be both effective and safe. They have been shown in numerous randomized clinical trials in individuals with

both acute and chronic cardiac syndromes to improve long term CV outcomes by reducing both CV events and deaths [3,24]. The mechanism of action is by competitively inhibiting the enzyme, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), leading to an upregulation of the LDL receptor on the hepatocytes. This in turn leads to an increased clearance of LDL-C from the blood.

A 1 mmol/L reduction in LDL-C level with statins has been shown to result in a 22% relative risk reduction in major CV events [3,5]. They have also been shown to be safe [4,24].

In individuals at high and very high CV risk, it is advisable to attain LDL-C targets as quickly as possible so that the patient achieves the benefits of treatment early. This is currently preferable to the "starting low" and slowly up-titrating the dose to achieve LDL-C targets.

The baseline and the target LDL-C level will help determine the type and initial dose of statin. In clinical trials, it has been demonstrated that the observed CV benefits are greater with larger reductions in LDL-C levels [4]. Thus, in high and very high-risk individuals, high intensity statins that can result in >50% reduction in LDL-C levels are the preferred initial drugs (Table 5).

Statins are generally well tolerated. They may cause symptomatic adverse events (eg, muscle pain or weakness) in up to about 50-100 per 10 000 persons treated for 5 years [5]. How many of these adverse symptoms are real or due to the nocebo effect, remains unknown [42].

Common side effects include

Statin-associated muscle symptoms (SAMS) - These account for almost 72% of all reported statin adverse effects [43].

- In clinical trials the incidence is low but in registry reports, it may be as high as 10-30% [42].
- Muscle side effects are more common in the elderly (age > 80 years), women, low body mass index, Asian ethnicity, excessive exercise and in those with co morbidities and on multiple drugs [43].
- It usually presents bilaterally, affecting the large proximal muscles, especially of the legs. It can occur at rest or after exercise [42].
- A common manifestation is myalgia. In these cases, the enzyme creatine kinase (CK) is normal.
- A small percentage of patients experience [43]

1. Muscle symptoms and the CK is elevated but <10 times the upper limit of normal (ULN)
2. Myositis (CK is elevated but >10 times but < 40 times ULN or
3. Rhabdomyolysis (>40 x ULN) - This is very uncommon, but it is the most severe form of SAMS. The reported incidence is about 1-3 cases per 100,000 persons per year.

An increase in liver enzymes

- Statin therapy is associated with mild elevations of ALT in <3% of patients on statin treatment.
- Once the drug is discontinued, levels almost always return to normal and liver failure is rare[44].
- For these reasons, guidelines do not advocate routine monitoring of liver function tests during long term statin therapy [24,25].

New onset diabetes

- Statin therapy causes a small increase in the rate of new onset diabetes [45,46].
- This is more often seen in individuals who are pre-disposed to diabetes (e.g. those with a family history of diabetes, in the elderly, individuals who are obese, have the metabolic syndrome or insulin resistance [45,46].
- Statin use has also been associated with diabetes progression and the need for insulin therapy [47].
- Despite these observations, statin therapy is still recommended in these patients because its cardioprotective benefits far outweigh the risks of developing or worsening diabetes [4,24,45,46].

Neurological and neurocognitive function

- To date, statins have not been shown to impair neurocognitive function [48].
- A systematic review of 25 cohort studies showed that statins may reduce the risk of all-type dementia, Alzheimer disease, and mild cognitive impairment, with no apparent effect on vascular dementia [48].

There is individual variation in the response to statin therapy. For this reason, the "treat to target approach" is advocated over the "fire and forget approach", starting with the dose and type of statin that is most likely to achieve the LDL-C target. If targets are not achieved, the dose has to be up-titrated accordingly. Drug compliance and possible adverse effects of therapy need to be monitored and addressed [25]. At the same time, all other

modifiable CV risk factors should also be assessed and treated appropriately.

High-Intensity Statin Therapy*	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy**
Daily dose lowers LDL-C on average, by approximately ≥ 50%	Daily dose lowers LDL-C on average, by approximately 30% - < 50%	Daily dose lowers LDL-C on average, by < 30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

Table 5: Recommended Doses of Statin Therapy.

Adapted from: Stone NJ. Circulation. 2014; 129:S76-S99.
*High intensity statin therapy is for patients who are at very high and high CV Risk

**Low intensity statin therapy is generally used for primary prevention after lifestyle modification and following a discussion with the patient of the risk: benefit ratio.

Fibrates

Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists. They lower plasma TG and increase HDL-C levels.

In the statin era, fibrates have not been shown to reduce CV events. They may have a limited role in the reduction of residual CV risk in diabetic patients who are already at target LDL-C levels on statin therapy and still have low HDL-C (<0.88 mmol/L) and high TG (>2.3 mmol/L) [49]. There is however limited trial data to support this. Gemfibrozil should not be used in combination with statins due to an increased risk of rhabdomyolysis.

Fibrates are mainly indicated in patients with very high TG levels who are at risk of pancreatitis [25].

Bile acid sequestrants

Bile acid sequestrants bind bile acids and interrupt the enterohepatic circulation. This in turn, leads to a compensatory upregulation of LDL receptors on hepatocytes.

In primary prevention trials conducted in the pre statin era, bile acid sequestrants have shown modest benefits in the reduction of CV risk. They are associated with troublesome and unpleasant gastrointestinal side effects.

Nicotinic acid (Niacin)

Niacin decreases the mobilization of free fatty acids from adipose tissues. It increases HDL-C, reduces LDL-C and TG.

Despite its favourable effect on lipoproteins, niacin has not been shown to reduce CV events. It is thus not advocated for LDL-C lowering.

Challenges in the management of hypercholesterolaemia

Failure to achieve LDL-C targets is common. In the EUROASPIRE V survey only 29% of patients with CVD achieved an LDL-C <1.8 mmol/L [50]. The International ChoLesterol management Practice Study (ICLPS) found only 28.5% of their very high-risk patients achieved their target goal of LDL-C < 1.8 mmol/l [51].

The reasons for this failure to meet LDL-C target was multifactorial. A major reason was statin side effects (mainly SAMS). Other reasons included non-compliance to treatment and the continued use of suboptimal doses of statins because of the misconception of adverse effects with higher doses. This often leads to a reluctance by both the physician and the patient to up-titrate the dose despite non-achievement of targets. This was further compounded by the lack of awareness of the public of the CV benefits of lipid lowering drug therapy.

There was also underestimation of CV risk by physicians and sometimes a failure to use any risk scoring system, resulting in suboptimal targets. Simple CV risk stratification tables and a minimum number of target LDL-C levels according to the CV risk, could facilitate this process.

Statin discontinuation is another major problem. In one study, 50% of patients discontinued their statins, following initiation, at a mean of 3.4 years in secondary prevention and 3.7 years in primary prevention [52]. In another study from Denmark, statin discontinuation in persons> 75 years of age was associated with a higher rate of CV events than statin continuation [53].

The commonest causes for statin discontinuation were muscle symptoms, costs, and perceived lack of efficacy.

Statin intolerance

The Canadian Consensus Working Group has defined statin intolerance as a clinical syndrome characterized by significant symptoms and biomarker abnormalities that is documented by challenge/de-challenge/re-challenge using at least 2 statins (including atorvastatin and rosuvastatin) that is not due to drug-drug interactions or untreated risk factors for intolerance [54].

SAMS accounts for almost 72% of all reported statin adverse effects [54]. It typically occurs at 4-6 weeks following initiation of therapy though it could develop years later. It may also occur after the dose of statins has been increased [54].

If SAMS is suspected:

- Stop the statin for a period of 2-4 weeks.
- If symptoms persist, it is unlikely to be due to the statins, and statin therapy should be continued.
- If symptoms have resolved, it is possible that it is SAMS. The same or a different statin can be re-introduced at a lower dose as a challenge.
- Alternatively, using long-acting statins such as atorvastatin or rosuvastatin at less frequent dosing intervals such as every other day or twice a week may help alleviate symptoms and still achieve some degree of LDL-C lowering.

Individuals who are not at target despite maximally tolerated dose of statins

In EUROASPIRE V, only 32% of patients on statins achieved a target LDLC< 1.8 mmol/L [50]. Thus, there is a need for other lipid lowering agents besides statins.

Primary hypercholesterolaemia

Individuals with Common Polygenic Hypercholesterolaemia have only moderately high LDL-C levels. Lifestyle modification and statin therapy usually suffices to achieve LDL-C targets in most of these patients. Patients with FH however, especially the homozygous variants, have very high LDL-C levels and even maximal dose statin therapy is inadequate [10].

In these individuals and in those who have statin intolerance, the following treatment options can be considered.

Treatment Options in Individuals who do not achieve LDL-C targets

Ezetimibe

Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related plant sterols by selectively blocking the Niemann-Pick C1-like 1 (NPC1L1) protein in the jejunal brush border. Intestinal cholesterol transport to the liver is decreased leading to a cascade of reactions eventually resulting in an increased clearance of blood cholesterol.

When used as monotherapy, ezetimibe only lowers LDL-C modestly by 15-20% [55]. When used in combination with a statin there is significantly greater LDL-C reduction. This is because of dual cholesterol inhibition - liver production and absorption from the gut. When ezetimibe (10 mg) was administered with any dose of a statin, LDL-C levels was reduced by an additional 25%. This is far greater than the 6% obtained when the dose of statin is doubled [56].

Ezetimibe is well tolerated with hardly any side effects and no dose adjustment is necessary in patients with hepatic or renal insufficiency.

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE -IT) is a landmark study in that it is the first clinical trial to provide evidence for the LDL-C hypothesis - the lower the LDL-C, the better - rather than the statin intensity hypothesis [17]. Individuals who were on the statin-ezetimibe arm had a median LDL-C of 1.4 mmol/L versus 1.8 mmol/L in the statin monotherapy arm. Individuals with a lower LDL-C level had a significant additional reduction in major CV events [17].

Proprotein convertase subtilisin/kexin type 9 Inhibitors (PCSK9-i)

PCSK9 is a protein that binds to the LDL- receptor and degrades it. PCSK9-i are monoclonal antibodies that suppress the circulating PCSK9 protein. This leads to higher expression of LDL-receptors on the cell surface resulting in an increased clearance of LDL-C from the blood.

PCSK9-i are potent lipid lowering agents that can produce an additional >50% reduction in LDL-C levels when used as monotherapy or when used as add-on therapy to statins and/or ezetimibe. They are administered subcutaneously.

In clinical trials where PCSK9-i was added to a background of statin and ezetimibe therapy, LDL-C levels of < 1.0 mmol/l have been achieved. At these levels, there have been significant reductions in major CV events documented and regression of atherosclerotic plaques demonstrated [18,19,23]. These levels were also safe [20,21].

These agents were well tolerated and there were no significant differences in adverse effects (including new-onset diabetes and neurocognitive events) with the exception of injection-site reactions [18,19].

Based on these data, guidelines now recommend an LDL-C level of < 1.4 mmol/l in very high-risk patients [24].

Newer lipid lowering agents

Bempedoic acid

This is a class of non-statin LDL-lowering therapy that, like statins, targets the cholesterol biosynthetic pathway in the liver [57]. It is a prodrug that is converted to the active coenzyme A form by enzymes found only in the liver. It inhibits ATP-citrate lyase (ACL), two steps upstream of HMG CoA reductase, resulting in an upregulation of the LDL-C receptors. This in turn, leads to an increase in LDL-C clearance from the blood.

Bempedoic acid lowers LDL-C by about 23% as monotherapy and as much as 40% in combination with ezetimibe [57,58]. It also reduces C-reactive protein (CRP) levels by about 24% [58]. Patients who have no statins as background therapy appear to have greater LDL-C reductions [58]. Bempedoic acid was mainly intended for statin intolerant patients since it does not have any effects on muscle. Side effects include hyperuricaemia and gout and a slightly increased risk of tendon rupture [57].

CV outcome trials are ongoing and expected by end 2022.

Inclisiran

Inclisiran is a small interfering RNA (siRNA) molecule, which inhibits hepatic PCSK9 production, thus increasing the numbers of LDL receptors in the hepatocyte membranes and promoting LDL-C clearance from the bloodstream.

It has been shown to decrease LDL-C by as much as 51% when used in patients on background statin therapy and appears to have a consistent long-term effect on LDL-C lowering [59]. It has a favourable side effect profile and a convenient twice-a-year dosing regimen. Inclisiran has been approved in several European countries.

The results of the CV outcome trials are expected to be released in 2023.

Conclusion

In high- risk individuals with established CVD the current recommendation is an LDL-C target of < 1.4 mmol/l. This is based on trial evidence which have clearly demonstrated that there is additional reduction in CV events and possibly even regression of atherosclerotic plaques with lowering of LDL-C levels below the previously recommended < 1.8 mmol/l. In patients who continue to have recurrent CV events, an even lower target of < 1.0 mmol/l has been shown to be both effective and safe.

Statins are the initial drugs of choice. However, despite the use of high intensity statins, the recommended LDL-C targets are sometimes not achieved. With the use of ezetimibe and/or PCSK9-i and the newer lipid lowering therapy in combination with statins this is now possible. This reaffirms the LDL-C hypothesis - the lower, the better.

Statin non-adherence and discontinuation is a major problem. These can be overcome by efforts to educate both patients and physicians of the benefits and side effects of treatment, the use of effective cheaper generic formulations and using different

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