**The management of familial hypercholesterolaemia with statin-associated muscle symptoms**

N Schellack, BCur, BPharm, PhD (Pharmacy), Associate Professor, School of Pharmacy, Sefako Makgatho Health Sciences University (SMU)

G Schellack, BCur, Adv Univ Dipl Nurs Sc (HSM), Hons BSc (Pharmacology), Clinical research specialist in the pharmaceutical industry

E Bronkhorst, BPharm, MSc (Med) (Pharmacy), PhD Candidate, Senior Lecturer, School of Pharmacy, Sefako Makgatho Health Sciences University (SMU)

N van der Sandt, BPharm, MPharm*, J Schoeman, BPharm, MSc (Pharmacology)*

H de Klerk, BPharm, MPHarm Candidate, Sefako Makgatho Health Sciences University (SMU) *Pharmacist

Correspondence to: Prof Natalie Schellack, e-mail: natalie.schellack@smu.ac.za

**Keywords:** familial hypercholesterolaemia, dyslipidaemia, statins, PCSK9, hypercholesterolaemia, statin-associated muscle symptoms (SAMS), myopathy, HDL, LDL

**Abstract**

Hypercholesterolaemia and dyslipidaemia, marked by decreased levels of high-density lipoproteins (HDL) and elevated levels of low-density lipoprotein cholesterol (LDL-C), increase the risk of cardiovascular disease. By agreement, statin therapy constitute the agents of choice for the reduction of LDL-C. Despite being the most commonly prescribed lipid-lowering agents, with an exceptional safety profile and good tolerability, 10–25% of statin users experience muscle toxicity. This is known as the statin-associated muscle symptoms (SAMS), which range from myalgia to rare, life-threatening cases of rhabdomyolysis, in the presence of normal or elevated creatine kinase (CK). Familial hypercholesterolaemia (FH), diagnosed based on the clinical features seen in patients with a positive family history, constitutes a heritable disorder involving a single gene. FH can exist in either the heterozygous (HeFH), or the homozygous (HoFH) form, and may be differentiated based on clinical features and genetic studies. A novel drug target, namely proprotein convertase subtilisin/kexin type 9 (PCSK9), has resulted in the development and subsequent approval of new, targeted monoclonal antibodies in the treatment of hypercholesterolaemia. Targeting PCSK9 with such monoclonal antibodies (evolocumab and alirocumab) inhibits the degradation of LDL-receptors and, against a background of optimised statin therapy, increases the life expectancy of patients with hypercholesterolaemia by reducing the incidence and severity of coronary artery diseases. This article gives an overview on the management of hypercholesterolaemia in this setting.

© Medpharm

**Introduction**

Atherosclerotic cardiovascular disease has the highest mortality rate globally, with ischaemic heart disease being the leading cause of death worldwide.1,2,3 Atherosclerotic cardiovascular disease represents 28.2% of the global all-cause mortality.2 Estimates predict that, by the year 2020, cardiovascular diseases, and more notably atherosclerosis, will become the leading cause of the world’s total disease burden.1

Risk factors for cardiovascular disease (CVD) were introduced in 1961 by the Framingham Heart Study, which linked the presence of specific antecedent conditions (e.g. elevated cholesterol levels, arterial hypertension, diabetes mellitus and tobacco use) to future cardiovascular disease. These risk factors may be classified as being either traditional or non-traditional. The traditional risk factors include the constitutional factors, like a family history of atherosclerosis, age and gender, the behavioural or lifestyle factors, like nutrition, physical activity and tobacco exposure, and the physiological factors, such as blood pressure, lipids, obesity, as well as glucose metabolism including diabetes mellitus. In addition, medical diagnoses, such as diabetes mellitus and chronic kidney disease, are included.4

Conversely, the non-traditional risk factors—or novel biomarkers—that may be of value in predicting CVD include adipocyte dysfunction, mitochondrial dysfunction and oxidative stress, inflammation, haemostasis and thrombosis, as well as insulin resistance. The clinical utility of the non-traditional risk factors remains limited because of inconsistent associations with CVD, especially in children. The role of these biomarkers, especially in identifying childhood risk factors, is increasingly being studied.4

The pathogenesis of coronary heart disease (CHD) remains largely unknown, but it is generally accepted to be a polygenetic disease, resulting from several gene interactions, in addition to environmental and psychosocial factors.5 Two of the risk factors, which are consistently being recognised as contributors towards the development of CHD, are circulating blood lipid levels and atherosclerosis.5
Atherosclerosis as a risk factor

Atherosclerosis is an inflammatory disease associated with lipid and metabolic abnormalities, which cause alterations in the arteries and is considered to be the major cause of cardiovascular disease. Atherosclerotic plaques are initiated by the so-called fatty streak or initial lesion. These initial lesions arise from localised increases in the lipid content of lipoproteins and, in particular, of the fraction of lipoproteins pertaining to low-density lipoprotein, or LDL. These lipoproteins bind to constituents of the extracellular matrix in the intima of arteries, increasing the lipid-rich particles within the arterial wall. Lipoprotein particles in the extracellular space of the intima may undergo oxidative modifications, forming oxidised lipoproteins that support a pathogenic role in atherogenesis. Oxidative stress plays an important role in cholesterol metabolism. Oxidised low-density lipoprotein is toxic to the vascular network, whereas high-density lipoprotein (HDL) acts as an antioxidant. Oxidative stress is believed to be a major cause of plaque rupture and resultant thrombosis; both are late events in the progression of atherosclerosis.

Reduced levels of HDL-cholesterol is an important risk factor for CVD, because the so-called reverse cholesterol transport that is mediated by this high-density lipoprotein provides for an independent pathway for lipid removal, away from atheroma formation.

Familial hypercholesterolaemia

Familial hypercholesterolaemia (FH) is an autosomal dominant trait, with a mutation of the LDL-receptor gene on chromosome 19, which can often be identified by elevated levels of umbilical cord blood cholesterol. Familial hypercholesterolaemia is therefore characterised by defects of the LDL-receptors, and some individuals produce non-functional and kinetically impaired receptors.

FH may either present as homozygous familial hypercholesterolaemia (HoFH) or as heterozygous familial hypercholesterolaemia (HeFH). The latter has a 1-in-500 prevalence in most populations, with higher incidences described in Afrikaner South Africans and French Canadians. The underlying genetic disorder seems to be attributable to a loss-of-function mutation in the LDL-receptor alleles, with more than 1 600 mutations having been identified. Other causes that occur less frequently include defects in apolipoprotein B-100 (ApoB) and the gain-of-function mutation in proprotein convertase subtilisin/kexin type 9 (PCSK9) serine protease.

In the case of the HoFH form, affected children would inherit the abnormal gene from both their parents (i.e. both alleles would be pathogenic) and therefore suffer from the most severe form of this disease. Refer to Figure 1. The clinical manifestations of HeFH versus HoFH are listed and compared in Table I.

Table I. Comparison between the clinical manifestations of heterozygous versus homozygous familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Heterozygous (HeFH)</th>
<th>Homozygous (HoFH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon xanthoma</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Cutaneous xanthoma</td>
<td>–</td>
<td>Present</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>Older than 25 years of age</td>
<td>Younger than 25 years of age</td>
</tr>
<tr>
<td>LDL-cholesterol levels</td>
<td>&gt; 5 mmol/l; &lt; 12 mmol/l</td>
<td>&gt; 12 mmol/l</td>
</tr>
</tbody>
</table>

LDL-levels tend to increase throughout childhood, while triglyceride levels are usually normal. Tendon xanthomas may be present and arcus corneae and xanthelasma may appear in the third decade. Levels of cholesterol often exceed 25.8 mmol/l.

Adipocyte dysfunction

Pathophysiological and metabolic consequences of excess adiposity appear as central phenomena in the pathway to CVD. Excessive levels of circulating glucose and triglycerides cause energy imbalances, which lead to adipocyte hypertrophy and hyperplasia. The subsequent result is an inflammatory process within adipose tissue. Excesses of circulating nutrients can then not be absorbed and the capacity of the adipocyte to store triglycerides and glucose is overwhelmed, causing adipocyte dysfunction. This dysfunction is characterised by infiltration of inflammatory cells and elevated pro-inflammatory cytokines that activate additional inflammatory pathways.

Transport and metabolism of lipoproteins

The most important lipids in the body are phospholipids, cholesterol and the triglycerides, with the latter two also constituting the major plasma lipids. These lipids are transported in the bloodstream lipoprotein complexes. The liver is the primary organ responsible for the metabolism of lipoproteins. The latter complexes mostly may fall into one of three categories, namely

![Figure 1. The mode of inheritance of familial hypercholesterolaemia, showing both the heterozygous and homozygous forms of the disease](image-url)
HDL, LDL and VLDL (refer to Table II). The category of intermediate-density lipoprotein (IDL) is typically grouped with LDL in the clinical practice setting (IDL is also referred to as LDL₂ with the more characteristic connotation with LDL actually referring to LDL₁).9,10

<table>
<thead>
<tr>
<th>Term/Acronym</th>
<th>Definition/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>Low-density lipoprotein. LDL is sub-divided into LDL₁ (or intermediate-density lipoprotein) and LDL₂ (the typical LDL that constitutes the major component of low-density lipoprotein)</td>
</tr>
<tr>
<td>VLDL</td>
<td>Very-low-density lipoprotein</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein (sub-fractions of HDL also exist, namely HDL₂ and HDL₃)</td>
</tr>
</tbody>
</table>

The significance of dyslipidaemia

Dyslipidaemia refers to the combination of elevated levels of total and LDL-cholesterol (as well as the triglycerides), combined with decreased levels of HDL-cholesterol, and is considered to be a disorder of lipoprotein metabolism. There is an undisputed association between elevated levels of total and LDL-cholesterol, as a major modifiable risk factor, and coronary heart disease. LDL-cholesterol transports around two-thirds of all the circulating cholesterol in the human body. Elevated levels of LDL, in particular, are considered to constitute a primary risk factor for the occurrence of atherosclerosis and associated ischaemic coronary events.9,10,11,12

The pivotal role of the LDL-receptor and PCSK9

The protein constituents of lipoprotein complexes are referred to as apolipoproteins, which are grouped into four different classes, namely A, B, C and E. The most significant apolipoprotein associated with LDL-cholesterol, is apolipoprotein B-100 (ApoB). The latter provides for an attachment to the binding site for low-density lipoprotein on its LDL-receptor.9,10

When LDL binds to its receptor on the cell surface of selected tissue cells, especially hepatocytes, the resultant internalisation of LDL provides for its lysosomal degradation. This is subsequently followed by the so-called recycling of the LDL-receptor (LDL-r) back to the cell’s plasma membrane. Once repositioned, it is able to bind yet another molecule of LDL. This is an ongoing process. However, in an attempt to maintain normal, stable levels of LDL-cholesterol in the body, the uncontrolled recycling of the LDL-r may be counteracted by the effects of PCSK9 (i.e. by proprotein convertase subtilisin/kexin type 9), which promotes the

Figure 2. Simplified diagram of a prototypical hepatocyte, illustrating the production and release of PCSK9, with its subsequent role in the degradation of the LDL-receptor, and showing the site of action of the PCSK9-inhibiting monoclonal antibodies (mAbs)
breakdown of these receptors (refer to Figure 2). PCSK9, a serine protease that is expressed in particularly significant quantities within the liver (the main source of circulating PCSK9), intestines and kidneys, may therefore be regarded as a modulator of LDL-cholesterol levels in the plasma. It effectively acts to reduce the number of LDL-receptors on the cell surface of hepatocytes.\(^\text{11,12}\)

In turn, PCSK9 undergoes endogenous inactivation by two different proprotein convertases, referred to as furin and PCS5/6A, within hepatocytes.\(^\text{12}\)

**Treatment for hypercholesterolaemia**

The following options may be considered:

**Statins in the treatment of hypercholesterolaemia**

Statins have become the most commonly used lipid-lowering class since their introduction in 1987\(^\text{13,14}\) with a worldwide use of roughly 100 million prescriptions per year.\(^\text{13,15}\) This revolutionised the treatment of hypercholesterolaemia, a major CVD risk.\(^\text{15,16}\)

In South Africa, statins are still commonly prescribed after four decades and remain the lipid-lowering agents of choice. Here, the vast majority of statin prescriptions are attributed to simvastatin (64.6%), followed by atorvastatin (22.2%), rosuvastatin (10.9%), pravastatin (1.6%), fluvastatin (0.6%) and lovastatin (0.2%).\(^\text{17,18}\)

The main pharmacological effects of statins are to lower LDL-C levels used for both primary and secondary prevention of CVD.\(^\text{18}\) Statins lower LDL-C by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase reducing the production of endogenous cholesterol, in addition to other products of the mevalonate pathway.\(^\text{\text{10}}\) Decreased intracellular cholesterol levels trigger upregulation of LDL-specific receptor expression consequently accelerating removal of LDL-C from the blood, further reducing hyperlipidaemia.\(^\text{\text{14,18}}\) Furthermore, statins not only modestly reduce triglycerides, but also mildly increase HDL-C.\(^\text{\text{18}}\)

Statins are generally well tolerated\(^\text{\text{19}}\) with an acceptable risk-benefit ratio\(^\text{14}\) and an excellent safety record.\(^\text{19}\) Nonetheless, with its worldwide common use, two main adverse effects have come to light, respectively, hepatotoxicity with a transient increase in liver enzymes and muscle toxicity.\(^\text{\text{20,21}}\) With 10%–25% of patients complaining of statin-associated muscle symptoms (SAMS) (ranging from pain or aching to stiffness, tenderness, cramping and even weakness) the latter has received noteworthy attention.\(^\text{\text{22}}\) Studies have however indicated that SAMS complaints are more commonly found in observational cohort studies (11%–29%) compared to those in randomised clinical trials (1%–5%).\(^\text{\text{23}}\) Furthermore, no difference has been found in the measurements of muscle strength or exercise performance in statin-treated patients compared to those who received placebo.\(^\text{\text{23}}\)

This data possibly reflects the specific exclusion of patients with musculoskeletal complaints prior to randomisation.\(^\text{\text{24}}\) Thus clinical trial results are unlikely to accurately depict the true prevalence of muscle symptoms.\(^\text{\text{24}}\) Irrespective, owing to SAMS, up to 75% of patients discontinue the use of statins within two years of initiation.\(^\text{\text{15,21,25}}\) Moreover, in 65% of former statin users, the main reason for statin non-adherence or discontinuation was the onset of side-effects, of which SAMS was the predominant complaint.\(^\text{\text{23}}\)

SAMS not only affects a patient’s quality of life, but importantly adherence to potentially, life-saving treatment.\(^\text{\text{15}}\) Occurrence of serious muscle toxicity with currently marketed statins is fortunately rare\(^\text{\text{22}}\) and the majority of SAMS resolves within weeks to months of discontinuation.\(^\text{\text{19,23}}\)

Effort should be made to keep high-risk patients on a statin therapy, as these agents are the only lipid-lowering agents with comprehensive evidence proving clinical end-point reduction.\(^\text{\text{23}}\)

**Switching to an alternative statin**

There are two available treatment options if SAMS or CK abnormalities resolve after discontinuation of the causative statin, either re-initiation with lower dosing of the primary statin or the use of an alternative statin. The aim is to achieve the target LDL-C level with the maximum tolerable dose with minimal SAMS.\(^\text{\text{23}}\)

The use of fluvastatin is associated with less myopathy compared to the use of lovastatin, simvastatin, or atorvastatin. Furthermore, cases of fatal rhabdomyolysis with the use of fluvastatin have not yet been reported.\(^\text{\text{15}}\)

As high statin doses and drug-drug interactions are risk factors for SAMS, the use of rosuvastatin, metabolised by CYP2C9, in patients receiving multiple medication, has a theoretical benefit. Additionally, lower dosages are safe, effective in SAMS patients and reduction in LDL-C cholesterol comparable to that of atorvastatin have been shown.\(^\text{\text{15}}\)

**Non-daily dosing of statins**

If the above-mentioned options are not tolerated, the treatment strategy of choice to reduce LDL-C levels is to alternate day or twice-weekly dosing\(^\text{\text{18}}\) with long-acting statins, administered in low dosages or at a reduced frequency.\(^\text{\text{26}}\) Potentially suitable agents, with respectively 20 and 15 hour half-lives, both rosuvastatin and atorvastatin may decrease LDL cholesterol levels whilst possibly reducing adverse effects. Limited data exists on atorvastatin alternate day dosing. Non-daily dosing of rosuvastatin appears tolerable and may decrease LDL-C levels in SAMS. However, the reduction in CVD risk still has to be evaluated.\(^\text{\text{15}}\)

**Non-statin based lipid-lowering therapy**

In the presence of complete statin intolerance, persistent LDL-C levels above the targeted goal and high CVD risk patients despite maximally tolerated statin dosage to reduce LDL cholesterol,\(^\text{\text{23}}\) the addition of an alternative lipid-lowering agent should be considered.\(^\text{\text{26}}\)

Drug of choice to achieve targeted LDL-C levels is ezetimibe, followed by the use of bile acid sequestrates (BAS) or fibrate in combination with ezetimibe.\(^\text{\text{23}}\)
Ezetimibe decreases LDL cholesterol levels by targeting the NPC1L1 transporter and inhibiting intestinal cholesterol absorption. Compared to higher dosages of statin monotherapy, similar results in LDL cholesterol reductions have been achieved with the addition of ezetimibe to existing statin therapy. This combination is both safe and well tolerated, which may benefit patients with SAMS who do not achieve their targeted LDL-C levels. Although ezetimibe has been shown to reduce CVD events, comprehensive data on the risk reduction of CVD morbidity and mortality is lacking.

Bile acid sequestrants (BAS)

Despite reducing cholesterol absorption and CVD events, the extent of BAS LDL-C reduction is dose-dependent together with high rates of gastrointestinal intolerance. However, compared to previous formulations, colesevelam (not available in South Africa) may lead to enhanced patient compliance as it is easier to take, better tolerated with an improved adverse effect profile. Opportunely, greater decreases in LDL-C have been seen in the combination of ezetimibe and BAS.

Fibrates

Fenofibrate can lower LDL in patients with high baseline levels in the absence of hypertriglyceridemia. In addition, it is easy to take with a safety profile in diabetic patients with CVD risks. Regrettably, increased serum creatinine levels have been shown during treatment and no added CVD benefits have been demonstrated. Compared to gemfibrozil, combination use of fenofibrate with a statin showed no increased risk for rhabdomyolysis.

Niacin

Niacin reduces LDL-C levels and may be used in combination with BAS and ezetimibe in statin-intolerant patients that require a large reduction in LDL-C levels. The use of this agent is however limited by its significant adverse effect profile and although niacin monotherapy reduces CVD morbidity and mortality, no significant CVD benefit has been demonstrated.

Lastly, several complementary and novel treatment strategies have been proposed with differing levels of success. These strategies are presented in Table III.

Novel LDL therapies in the management of SAMS

Two novel therapies provide potential alternative treatment in the management of persistent SAMS, pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and cholesteryl ester transfer protein (CETP) inhibitors.

PCSK9-antibody therapy

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a member of the protease subfamily of subtilisin-related serine endoproteases and participates in the regulation of low-density lipoprotein cholesterol (LDL-cholesterol). PCSK9 has emerged as a target for preventing and treating CHD. Elevated serum levels of LDL-cholesterol have been implicated in various human genetic studies as gain-of-function mutations that can lead to premature incidences of CHD. The opposite holds true for reduced serum levels of LDL-cholesterol. The complete loss of PCSK9 results in very low serum LDL-cholesterol levels of less than 1.11 mmol/l in healthy subjects. PCSK9 targets the LDL-receptor (LDL-r) for degradation in the liver by lysosomes, thereby preventing expression of the receptor on the cell membrane. PCSK9 binds to the receptor on the cell membrane and the complex is then internalised and destroyed by the lysosomes.

Targeted monoclonal antibodies now have the ability to bind to PCSK9, thereby inhibiting its interaction with LDL-cholesterol receptors. Outcomes with regard to their efficacy indicate a reduction in LDL-cholesterol of greater than 50% and an elevation in HDL-cholesterol levels, especially when administered against a background of statin therapy. Other potential strategies that are currently under investigation include gene silencing and mimetic peptides.

The human monoclonal antibodies, evolocumab (IgG2 isotype) and alirocumab (IgG1 isotype), which target PCSK9, have been identified as treatment options, as an adjunct to diet, for patients diagnosed with HeFH and HoFH, where LDL-cholesterol levels could not be reduced to target using statins alone, or in combination with other agents, e.g. ezetimibe, newer bile acid sequestrants, and extended-release formulations of niacin. In addition, they may also be used in patients diagnosed with clinical atherosclerotic cardiovascular disease that requires additional lowering of LDL-cholesterol. Both of these agents received approval from the United States Food and Drug Administration in the latter half of 2015.
Following the introduction of the novel, injectable PCSK9-inhibitors, concerns were raised with regards to the potential for eliciting neurocognitive impairment. PCSK9 is involved in cortical regeneration and cholesterol is an important component of neurons. In the OSLER and OSYSSEY long-term studies, a low rate of neurocognitive-related adverse events was reported; however, still higher than on the matching placebo arm. The monoclonal antibodies and lipoproteins do not cross the blood-brain barrier and PCSK9 loss-of-function variants have not been associated with a decline in cognitive performance. Other reported adverse events include allergic reactions, which are inherent to the use of monoclonal antibodies and other forms of protein therapeutics.

The use of PCSK9-inhibitors against a background of statin therapy significantly reduces cardiovascular risk factors, by significantly reducing LDL-cholesterol.

**Cholesterol ester transfer protein inhibitors (CEPT)**

Both anacetrapib and evacetrapib equally lower LDL cholesterol and have shown significant increases in HDL-C by mediating the hetero-exchange of triglycerides and cholesteryl esters between lipoproteins. The molecular base for LDL-C reduction is still uncertain, however improved fractional removal rates for LDL apolipoprotein B from plasma is involved. Fortunately, no muscular toxicities have been identified.

**Conclusion**

Dyslipidaemia is a disorder associated with liver lipoprotein metabolism, which includes combined elevated levels of LDL-C and decreased HDL-C levels. In addition to adipocyte dysfunction, atherosclerosis is also a risk factor for CVD events. This article provided a brief introduction to lipoprotein metabolism and the genetic differences involved in the phenotypic expression of patients suffering from FH, treatment of dyslipidaemia and management of SAMS. The use of statin treatment for patients suffering from FH has greatly reduced the mortality rate by decreasing the incidence of coronary events. The use of the novel PCSK9-inhibitors has brought new hope for patients suffering from FH, as coronary incidences are greatly reduced when these monoclonal antibodies are used against a background of statin therapy and dietary modifications. In recent years great improvements have been made in the management of SAMS. Management is aimed at risk vs. benefit and in the discontinuation and reintroduction of statins, although novel drug development could greatly aid in providing additional treatment options. Fortunately, statins can be interchanged, discontinued and reintroduced in order to improve quality of life for SAMS patients as the condition is rarely a life-threatening condition.

**References**


