Updates in the management of Dyslipidaemia in the high and very high risk individual for CV risk reduction

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ABSTRACT
Cardiovascular disease (CVD) has been the main cause of mortality and an important cause of morbidity in Malaysia for several years. To reduce global cardiovascular (CV) risk in the population, primary preventive strategies need to be implemented. Hypercholesterolaemia is one of the major risk factors for CVD. This paper is an expert review on the management of hypercholesterolemia focusing on high and very high risk individuals. In low and Intermediate risk individuals, therapeutic lifestyle changes (TLC) and a healthy lifestyle alone may suffice. In high and very high risk individuals, drug therapy in conjunction with TLC are necessary to achieve the target LDL-C levels which have been shown to slow down progression and sometimes even result in regression of atherosclerotic plaques. Statins are first-line drugs because they have been shown in numerous randomized controlled trials to be effective in reducing CV events and to be safe. In some high risk individuals, despite maximally tolerated statin therapy, target Low Density Lipoprotein Cholesterol (LDL-C) levels are not achieved. These include those with familial hypercholesterolaemia and statin intolerance. This paper discusses non-statin therapies, such as ezetimibe and the newer Proprotein convertase subtilisin/kexin type 9 Inhibitors (PCSK9-i).

KEY WORDS: Cardiovascular disease, hypercholesterolaemia, statins, familial hypercholesterolaemia, statin intolerance, ezetimibe, PCSK9-inhibitor

INTRODUCTION
The National Health and Morbidity Surveys have reported that the prevalence of the CV risk factors - hypertension, hypercholesterolaemia, smoking, diabetes and overweight/obesity - among adults aged ≥18 years are on an increasing trend. The prevalence of hypercholesterolaemia has increased by 46% from 2011 to 2015. This high prevalence of hypercholesterolaemia has also been documented both in the young and in rural populations.

Dyslipidaemia is defined as:
• Total cholesterol (TC) >5.2mmol/L and/or
• High Density Lipoprotein Cholesterol (HDL-C) (males <1.0mmol/L and females <1.2mmol/L) and/or
• Triglycerides (TG) >1.7mmol/L.

This review focuses on the management of TC and Low density Lipoprotein Cholesterol (LDL-C) in high and very high risk individuals. (See Table I for risk stratification)

TC and LDL-C as CV risk factors
The link between TC (especially LDL-C) and CVD is robust and well documented in numerous animal experiments, genetic (Mendelian) studies and prospective epidemiological studies. Randomized controlled clinical studies in individuals with and without pre-existing CVD, have shown that lowering TC and LDL-C reduces CV events and CV deaths. The risk of a recurrent CV event is greater in individuals with pre-existing CVD and thus the benefit seen from LDL-C lowering is also greater in these and other high risk individuals.

Epidemiological prospective studies have indicated that a low HDL-C and a high TG (especially post prandial TG) is associated with an increase in CV risk. Interventions to reduce TG and/or increase HDL-C levels have however, not shown a reduction in CV events. For this reason, LDL-C is the primary target of therapy in individuals with dyslipidaemia.

Causes of Hypercholesterolaemia
Hypercholesterolaemia may be due to primary or secondary causes.

Primary Hypercholesterolaemia is due to genetic disorders resulting in an isolated increase in LDL-C levels or a combination of elevation of LDL-C and TG. It is usually due to the complex interaction of multiple genes although occasionally it may be due to single gene defect. The commonest genetic disorder is Common Polygenic Hypercholesterolaemia which is caused by a combination of
multiple gene defects and environmental factors such as an atherogenic diet, sedentary lifestyle and obesity.\(^5\)

The commonest monogenic disorder is familial hypercholesterolaemia (FH). This is an autosomal dominant disorder characterised by severely elevated LDL-C levels and cutaneous manifestations such as xanthelasmas, tendon xanthoma and premature corneal arcus. At a younger age, the LDL-C level may not be high (around 4.0mmol/L) but rises with age.\(^6\)

The prevalence of the heterozygous state has been estimated from studies conducted in the West, at 1:200 to 1:500, and that of the homozygous state from 1:160,000 to 1:1,000,000.\(^7\,8\) About 3.6-9 million population of South-east Asia are estimated to have FH. At least 50% of FH patients in the world are likely to come from Asian countries including Western Pacific and South-east Asia.\(^9\)

Heterozygous individuals tend to develop premature CAD typically by the age of 40, while the homozygous variants, may develop it as early as childhood. The risk of developing premature CAD is estimated to be as high as 20 times that of the normal population. This is due to their lifelong exposure to elevated LDL-C levels. At any age, the cumulative LDL-C burden in these individuals are much higher than that of an individual without FH.\(^10\) Early long-term treatment has been shown to reduce this burden and to increase their coronary heart disease (CHD) - free survival.\(^11\)

Mutations in four candidate genes have been noted in FH patients: loss of function of the LDL receptor (LDL-R) gene (85%, most common), Apolipoprotein B-100 (Apo B-100) gene, low-density lipoprotein receptor adaptor protein 2 (LDLRAP-1) and gain-of- function mutation of the PCSK9 gene.\(^12\) In most cases, inheritance is autosomal co-dominant with homozygotes having about double the LDL cholesterol levels of heterozygotes.

The other causes of primary hypercholesterolaemia are rare and include autosomal recessive hypercholesterolaemia (ARH gene), sitosterolaemia (ABCG5 or ABCG8 genes) and cholesterol 7alpha-hydroxylase deficiency (CYP7A1 gene).\(^13\)

In Malaysia, a study was conducted on 86 Southeast Asian patients of multi-ethnic origin with a clinical diagnosis of FH to detect mutations in the genes coding for the LDL-R and apoB-100.\(^14\) A complete Deoxyribonucleic Acid (DNA) analysis of the LDL-R and apoB-100 genes by denaturing gradient gel electrophoresis (DGGE) and DNA-sequencing was performed. In the majority (73%) of the cohort studied, no mutations could be detected, even after extensive analysis of the LDL-R and apo B-100 genes.\(^15\) The fact that the majority of the FH patients studied had no detectable mutation and that this group had a significant milder phenotype, suggests the presence of a third gene in the Southeast Asian population, predominately leading to a disorder resembling a milder form of FH.\(^16\)

Conversely, individuals who have been exposed throughout their lives (life time exposure) to very low LDL- C levels, have very low risks of incident CVD and have long CV event-free survival. These very low levels of LDL-C may occur due to genetic loss of function of specific single nucleotide polymorphisms (SNPs). One example is the missense PCSK9 gene mutation (rs11591147) on the R46L allele resulting in a loss of function of this gene and thus reduced clearance of the LDL receptor from the surface of the hepatocytes. This results in a greater clearance of the LDL-C from the blood leading to lower LDL-C levels. These individuals have a 50-60% reduction in their CV risk.\(^17\,18\) Thus, the longer the exposure to lower circulating LDL-C levels, the lower the CV risk.

Secondary hypercholesterolaemia may result from dietary factors, diseases such as nephrotic syndrome, hypothyroidism, obstructive liver disease and drugs such as anabolic steroids.\(^19\) Treatment of the underlying aetiology can result in an improvement in the lipid profile.

A) Management of Hypercholesterolaemia

A1. Treatment Targets

Lowering TC and LDL-C lowers CV risk, the absolute benefit is greater in high risk individuals.\(^20\) The lower the LDL-C achieved, the greater the CV benefit. At levels ≤1.8mmol/L, less progression of the atherosclerotic plaque is seen and at levels ≤1.6mmol/L, regression of the plaque has been documented.\(^21\,22\)

Genetic studies and more recent randomized clinical trials show that LDL-C levels lower that the currently recommended targets of <1.8mmol/L, provide additional clinical benefits without any safety signals.\(^23\) CV risk reduction is proportional to the degree of LDL-C lowering achieved irrespective of the strategy used to achieve the reduction.\(^24\,25\)

High and very high risk individuals include those with pre-existing CVD, chronic kidney disease and diabetes.\(^26\) (Table I) In all other individuals, (i.e. primary prevention), the CV risk should first be assessed.\(^27\) The intensity of risk reduction efforts will depend on the individual’s CV risk.\(^28\) The higher the CV risk, the lower the LDL-C target level.\(^29\) (Table II)

There are many CV risk calculators available. The one that has been validated in the Malaysian population in two independent studies is the Framingham General CV Risk Score.\(^30\,31\)

Following achievement of LDL-C target, Non-HDL-C may be considered as a secondary treatment target to reduce residual CV risk.\(^32\) Non-HDL-C reflects the concentration of cholesterol within all lipoprotein particles considered atherogenic. Epidemiological studies have demonstrated that non-HDL-C is a better predictor of CV risk than is LDL-C and may be especially true in statin-treated patients.\(^33\) It has however not been used as a primary target of therapy in any randomized clinical trial.

Non-HDL-C is a primary target of therapy in individuals whose TG>4.5mmol/L. In these individuals, the Friedewald equation used in the calculation of LDL-C is invalid.

Non-HDL-C may be considered as a secondary target when treating patients with combined hyperlipidaemias, diabetes,
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Table I: Risk Stratification of Cardiovascular Risk

- **Very High Risk** individuals are those with:
  - Established CVD
  - Diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia
  - CKD with GFR <30 Ml/min−1.73 m² (≥Stage 4)

- **High Risk** Individuals include:
  - Diabetes without target organ damage
  - CKD with GFR ≥30- <60 Ml/min−1.73 m² (Stage 3)
  - Very high levels of individual risk factors (LDL-C >4.9mmol/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%

- **Low Risk** Individuals:
  - Have a FRS-CVD score that confer a 10-year risk for CVD <10%

Table II: Target LDL-C levels

<table>
<thead>
<tr>
<th>Global Risk</th>
<th>LDL-C Levels to Initiate Drug Therapy (mmol/L)</th>
<th>Target LDL-C Levels (mmol/L)</th>
<th>Levels (mmol/L) corresponding to LDL-C targets in individuals with TG &gt; 4.5 mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV Risk*</td>
<td>Clinical judgement** &gt;3.4 **</td>
<td>&lt;3.0</td>
<td>&lt;3.8</td>
</tr>
<tr>
<td>Intermediate (Moderate) CV Risk*</td>
<td>&gt; 2.6</td>
<td>≤2.6 or a reduction of &gt;50% from baseline***</td>
<td>≤ 3.4 or a reduction of &gt;50% from baseline***</td>
</tr>
<tr>
<td>High CV risk</td>
<td>&gt;1.8</td>
<td>&lt;1.8 or a reduction of &gt; 50% from baseline***</td>
<td>&lt; 2.6 or a reduction of &gt; 50% from baseline***</td>
</tr>
</tbody>
</table>

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

**After a therapeutic trial of 8-12 weeks of TLC and following discussion of the risk: benefit ratio of drug therapy with the patient

***whichever results in a lower level of LDL-C

cardio metabolic risk (metabolic syndrome) and chronic kidney disease.

B) Treatment Strategies

B1. Therapeutic Lifestyle Changes

In most individuals at Low and Intermediate (Moderate) risk, therapeutic lifestyle changes alone should suffice to reduce global CV risk and to achieve target LDL-C levels.43

**Diet – Cholesterol, Saturated Fats (SFA) and Trans-Fat**

The relationship between dietary cholesterol and blood cholesterol levels is complex and controversial. Recent studies suggest that eating foods high in cholesterol does not cause a significant rise in serum total TC and LDL-C level.31,52 It has also been shown that low to moderate consumption of eggs, which are high in cholesterol but not SFA, is not associated with an increased CV risk.35-37

Most guidelines advise that SFA should constitute <10% of an individuals’ total energy intake.43,51,52 Limiting the intake of SFA results in a decrease in cholesterol intake since the two often co-exist in the same food.43-46 SFA in the diet may be replaced with polyunsaturated fats (PUFA), monounsaturated fats (MUFA) and/or carbohydrates (CHO). When SFA is replaced with PUFA, it has been shown to improve lipoprotein profiles and reduce cardiac events and CV mortality.45 However, there is no clear evidence that replacing SFA with MUFA or CHO reduces CVD risk.41

Increased consumption of trans-fats has been associated with an increase in all-cause mortality, CHD mortality and total CHD.56 Trans-fats should be kept at <1% of the total energy intake.43,51,52 Replacing it with PUFA, MUFA or CHO helps improve the overall lipid profile, the best profile being seen with PUFA.47

**Exercise**

Regular exercise reduces the risk of all-cause and CVD mortality in both healthy individuals and those with pre-existing CVD.36-40

The effect of exercise on lipids is however small. Regular aerobic exercise increases HDL-C by 3–10% (up to 0.16mmol/L) and reduces triglycerides by about 11% (up to 0.34mmol/L).41,62
Smoking
Smoking is a strong and independent predictor of CVD.\textsuperscript{63,64} Smoking cessation is strongly encouraged. It leads to a significant reduction in CV morbidity seen as early as six months.

Smokers tend to have higher TG and lower HDL-C levels than non-smokers.\textsuperscript{65} Smoking cessation increases serum levels of HDL-C, especially in women, but has not been shown to have any effect on TC, LDL-C, and TG.\textsuperscript{66}

B2. Lipid Modifying Agents
In individuals at high and very high CV risk, lipid modifying therapy should be initiated at the same time as TLC to achieve target LDL-C levels and to reduce CV risk.\textsuperscript{67}

Statins
Statins are the lipid-lowering drugs of choice because they have been shown in numerous clinical trials to reduce the risk of CVD.\textsuperscript{18,20} They act by competitively inhibiting HMG-CoA reductase, the first and key rate-limiting enzyme of the cholesterol biosynthetic pathway. This leads to an upregulation of the LDL receptor and increased clearance of the LDL from the blood.

A 1mmol/L reduction in LDL-C level with statins has been shown to reduce CV mortality by 22%.\textsuperscript{18,67} They have also been shown to be safe.\textsuperscript{68}

The choice and initial dose of statin will depend on the baseline and the target LDL-C level. 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 to ensure that LDL-C targets are achieved. There are also greater CV benefits seen with greater percent reductions in cholesterol from statin therapy.\textsuperscript{18,69}

Statins are generally well tolerated. However, some individuals may experience statin-associated muscle symptoms (SAMS). In practice and from registry reports, the incidence is 10-30% although in clinical trials, it is much lower.\textsuperscript{70,72} The most common manifestation of SAMS is myalgia - pain, aches, weakness, or cramping. In these cases, the enzyme creatine kinase (CK) is normal. A small percentage of patients may experience myositis (CK is elevated but <10 times the upper limit of normal (ULN)) or rhabdomyolysis (>10 x ULN). Rhabdomyolysis is the most severe form of statin-induced myopathy but it is rare with only 1-3 cases per 100,000 patients per year.\textsuperscript{73,74} Muscle side effects are more common in the elderly, women and in those with co morbidities and on multiple drugs. (For management of SAMS, see section C1)

Other adverse effects are an increase in liver enzymes. Mild elevation of ALT is common, occurring in <3% of patients on statin treatment and almost always returns to normal once the statin is discontinued.\textsuperscript{75} It has not been shown to be associated with true hepatotoxicity or changes in liver function. Liver failure is rare and routine monitoring of liver function tests during long term statin therapy is no longer advocated.\textsuperscript{76}

There is also a small increase in the rate of new onset diabetes which is more common in those who are pre-disposed to diabetes (e.g. elderly, metabolic syndrome, obese, insulin resistance, family history of diabetes).\textsuperscript{77,78} This occurs with both hydrophilic and lipophilic statins. There is no evidence that statins cause any effect on neurocognitive function.\textsuperscript{79,80}

It is recommended that these high and very high risk individuals on long term statins be assessed on a regular basis to determine if target LDL-C levels have been achieved and to monitor for possible adverse effects.\textsuperscript{67} The frequency of monitoring would vary depending on whether target LDL-C levels are achieved. Individuals who tolerate statins without adverse effects and who are compliant and have stable LDL-C levels at target, can be monitored at yearly intervals. All other CV risk factors (blood pressure, glucose, and smoking cessation) should also be assessed and treated appropriately to target.

Fibrates
Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists. Their mechanism of action is postulated to be the induction of lipoprotein lipolysis leading to a reduction in the production of very low density lipoprotein (VLDL) in the liver.

Various trials have shown that fibrates are useful in lowering plasma TG and increasing HDL-C levels.\textsuperscript{27} However, the use of fibrates has not been shown to reduce CV events in the secondary prevention trials conducted in the statin era.\textsuperscript{79} Therefore, the use of fibrates is limited to patients with very high TG levels who are at risk of pancreatitis.\textsuperscript{45,82} It may have a role in CV risk reduction in diabetic patients who are already on maximally tolerated statins and still have low HDL-C (<0.88mmol/L) and high TG (>2.3mmol/L).\textsuperscript{45,82,83}

Bile Acid Sequestrants
Bile acid sequestrants, such as cholestyramine, colestipol and colestevaram, are a group of resins that bind bile acids and interrupt the enterohepatic circulation. This reduction of bile acids then leads to an upregulation of a key enzyme required for bile acid production, particularly CYP7A1. This results in a compensatory upregulation of hepatic LDL receptors and an increased LDL-C clearance from the blood.

Bile acid sequestrants have shown modest benefits in the reduction of CV risk in primary prevention trials.\textsuperscript{70,84} These studies were performed before newer treatment strategies were available. The use of bile acid sequestrants is often limited by gastrointestinal adverse effects e.g. flatulence, constipation, diarrhea and nausea.

Nicotinic Acid (Niacin)
Niacin decreases the mobilization of free fatty acids from adipose tissues. It increases HDL-C by up to 25%, and reduces LDL-C by 15-18% and TG by 20-40%. A common side effect of niacin which limits its use in clinical practice is flushing.

Recent trials have not shown niacin to reduce CV events. It is thus not advocated for LDL-C lowering.\textsuperscript{77,78}
C) Challenges in the Management of Hypercholesterolaemia

Failure to achieve LDL-C targets is common. In the EUROSPIRE IV survey only about 20% of patients with CVD achieved a LDL-C <1.8mmol/L. In Thailand, following an Acute Coronary Syndrome (ACS) >75% of patients did not attain treatment targets.87

The most common reasons for not meeting LDL-C targets were statin side effects (mainly SAMS), low adherence and the use of moderate to low intensity statins and a reluctance on the part of the physician and patient to up titrate the dose despite failure to reach targets.88

C1. Statin intolerance

Statin intolerance is characterized by the inability to tolerate statins or reach its optimal dose due to significant symptoms or biochemical abnormalities.89 In certain trials, ‘statin intolerant’ patients are defined as patients unable to tolerate at least two different statins because of unexplained skeletal muscle-related symptoms (pain, aches, weakness, or cramping) that began or increased during statin therapy and returned to baseline when statin therapy was discontinued.90

The onset of SAMS is typically at 4-6 weeks following initiation of therapy though it could develop years later. If SAMS is suspected, it is advisable to stop the statin for a ‘washout period’ of 2-4 weeks or longer. If symptoms persist, it is unlikely to be due to the statins, and statin therapy should be continued.

If symptoms have resolved, the statin can be re-introduced at a lower dose. Alternatively, dosing such as every other day or twice a week with long acting statins such as atorvastatin or rosuvastatin can be used.91

C2. Individuals who are not at target despite maximally tolerated dose of statins

There is individual variation in the response to statins. In EUROASPIRE IV, only 68% of patients on high intensity statins, achieved LDL-C <2.5mmol/L and only 27% achieved levels <1.8mmol/L.92

C3. Primary Hypercholesterolaemia

The commonest primary hyperlipidaemia is Common Polygenic Hypercholesterolaemia.93 Many of these individuals have moderately high LDL-C levels and can achieve target LDL-C with TLC and statin therapy. Individuals with FH however, have very high LDL-C levels despite maximal dose statin therapy.94

Patients presenting with premature CAD (aged <45) in first degree relatives, and any adult with TC of >7.0mmol/L should be screened for FH.95 This can be done using the validated US MEDPED, the UK Simon Broome or the Dutch Lipid Clinic criteria.96 Genetic studies help in confirming the diagnosis. Locally, genetic studies are not performed routinely because of costs constraints. An effective strategy of LDL-C lowering with TLC and statin therapy may be acceptable without genetic screening.97

In many of these individuals with FH, the response to current treatment modalities is usually only modest and it is difficult to achieve even a 50% reduction in their LDL-C levels. In these individuals and in those who have statin intolerance, the following treatment options can be considered.

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

D1. 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. This leads to a decrease in the delivery of intestinal cholesterol to the liver.

Ezetimibe when used alone lowers LDL-C by 15-20%.98 When combined with a statin, there is dual inhibition of both sources of cholesterol (liver production and absorption from the gut) resulting in significantly greater LDL-C reduction. When ezetimibe (10 mg) was administered with any dose of a statin, LDL-C levels was reduced by an additional 25%, compared with the usual 6% attained by doubling the statin dose.99,100

It is well tolerated with no major adverse effects.101 No dosage adjustment is necessary in patients with mild hepatic impairment or mild to severe 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 which showed CV benefits when a non-statin agent (ezetimibe) was added to a statin (simvastatin) as compared to statin monotherapy.102 Individuals in the statin- ezetimibe arm had a median LDL-C of 1.4mmol/L versus 1.8mmol/L in the statin alone arm.103 There was significant additional CV benefit seen in the arm on combination statin -ezetimibe which had achieved lower LDL-C level.104

This trial reinforces the LDL-C hypothesis – the lower is better– rather than the statin intensity hypothesis.

The ezetimibe-statin combination has also been shown to be beneficial in patients with CKD Stage 3-5 demonstrating a significant reduction (17%) in major atherosclerotic events.105

D2. Proprotein convertase subtilisin/kexin type 9 Inhibitors (PCSK9-i)

PCSK9 is a protein that binds to the LDL- receptor and stimulates its internalization and degradation. Thus, less LDL-receptors are available on the cell surface of hepatocytes for clearance of LDL-C.

PCSK9-i are newly developed monoclonal antibodies that suppress the circulating PCSK9 protein, preventing it from binding and leading to the degradation of the LDL receptor. This leads to higher expression of LDL-receptors on the cell surface resulting in an increased clearance of LDL-C from the blood.106
PCSK9-i are administered via subcutaneous injections at two weekly or monthly intervals. The half-life of these agents are long – alirocumab 6-7 days and evolocumab 11-17 days.97,98 These agents produce an additional >50% LDL-C level reduction when used as monotherapy or when used as add-on therapy to statins and/or ezetimibe. In individuals with severe primary hypercholesterolaemia, it is now possible to reduce the LDL-C to target levels or at least achieve a 50% LDL-C reduction with statin therapy in combination with ezetimibe and/or PCSK9-i. In phase III clinical trials conducted in individuals with FH or statin intolerance, these agents have been shown to significantly reduce pre specified CV end points.99-106

In the GLAGOV trial, a coronary angiographic study with intravascular ultrasound, regression of atherosclerotic plaques was demonstrated after 78 weeks of therapy with PCSK9-i in addition to standard statin therapy.10 The mean LDL-C levels achieved at 18 months in the arm with PCSK9-i/statin combination was 0.9mmol/L when compared to 2.4mmol/L in the statin alone arm. Greater plaque regression was seen at lower achieved LDL-C levels.93

The FOURIER trial is another landmark trial in which the PCSK9-i evolocumab (a fully human monoclonal antibody), was administered to high risk individuals who had failed to achieve an LDL-C <1.8mmol/L despite the use of high intensity statins. The mean LDL-C level with PCSK9-i was 0.78mmol/L as compared to 2.3 mmol/L in the placebo arm. There was a significant 15% reduction in the primary endpoints of CV death, MI, stroke, unstable angina and coronary revascularisation seen in the arm with the lower achieved LDL-C.10 The pre-specified secondary endpoints of major CV end points (CV death, myocardial infarction (MI) and stroke) was also reduced by 20%. This was largely driven by reductions in MI and stroke events.

There were no significant differences in adverse effects (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab. A sub study, the EBBINGHAUS trial also met its primary end point, demonstrating that evolocumab was non-inferior to placebo with regard to its effect on cognitive function.107

The SPIRE-1 and SPIRE-2108 trials which were published and announced at the same time as the FOURIER trial, reinforced the efficacy of another PCSK9-i, bococizumab, in lowering LDL-C between 55-60% at 14 weeks. However, this humanised monoclonal antibody evokes neutralising antibodies that caused 10-15% attenuation in LDL-C reduction with time. The higher risk patients in SPIRE-2 trial who had baseline LDL-C of > 2.6mmol/L had significant reduction (21%) in primary endpoints (Nonfatal MI, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death) with the lower LDL-C attained with this drug.

Based on these data, a recent guideline has recommended an LDL-C level of < 1.4 mmol/l in patients deemed to be at extremely high risk and this would include patients with recurrent coronary events and progressive CVD despite achieving current LDL-C targets of < 1.8 mmol/L.109 Individuals with FH and established CVD are also classified under this risk category.109

CONCLUSION

In managing high and very high risk individuals with hypercholesterolaemia, statins are the initial drugs of choice. However, many individuals fail to achieve recommended LDL-C targets despite the use of high intensity statins.

The more recent lipid trials conducted in high risk individuals with established CVD, have shown additional reduction in CV events at on-treatment LDL-C levels which are lower than the currently recommended targets.

These very low LDL-C levels is now achievable with the use of statins in combination with ezetimibe and/or PCSK9-i. These very low LDL-C levels have also been shown to be safe. This reaffirms the LDL-C hypothesis – the lower, the better.

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