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

Jeyamalar Rajadurai, FRCP[1], Wan Azman Wan Ahmad, FRCP[2], Hapizah Nawawi, FRCPath[3], Choo Gim Hooi, FNHAM[1], Ng Wai Kiat, FRACP[4] , Rosli Mohd Ali , FAsCC[5], Al Fazir Omar, MRCP[5], Sazzli Kasim, FNHAM[6], Oteh Maskon, MRCPI[7], David Quek Kwang Leng, FRCP[4]

[1]Subang Jaya Medical Centre, Subang Jaya, Selangor, [2]Faculty of Medicine,University Malaya Medical Center, Kuala Lumpur, Malaysia, [3]I-PPerForM and Faculty of Medicine, Universiti Teknologi MARA, Sg Buloh Campus, Selangor, Malaysia, [4]Pantai Hospital, Kuala Lumpur, Malaysia, [5]Institut Jantung Negara, Kuala Lumpur, Malaysia, [6]Faculty of Medicine, Universiti Teknologi MARA, Sg Buloh Campus, Selangor, Malaysia, [7]Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

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.[1-3] The prevalence of hypercholesterolaemia has increased by 46% from 2011 to 2015.[2,3] This high prevalence of hypercholesterolaemia has also been documented both in the young and in rural populations.[4,5]

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.[6-17] 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.[18-20] 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.[18-20]

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.[21-24] Interventions to reduce TG and/or increase HDL-C levels have however, not shown a reduction in CV events.[25-29]

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

This article was accepted: 25 January 2018
Corresponding Author: Jeyamalar Rajadurai
Email: rjeyacardio@gmail.com

multiple gene defects and environmental factors such as an atherogenic diet, sedentary lifestyle and obesity.[30]

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 xanthelasma, 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.[31]

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.[31,32] 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.[32]

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.[32] Early long-term treatment has been shown to reduce this burden and to increase their coronary heart disease (CHD)- free survival.[32]

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.[32] 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 hypercholesterolemia (ARH gene), sitosterolaemia (ABCG5 or ABCG8 genes) and cholesterol 7alpha-hydroxylase deficiency (CYP7A1 gene).[30]

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.[33] 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.[33] 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, predominantly leading to a disorder resembling a milder form of FH.[33]

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.[34,35] 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.[30] 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.[19-21] 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.[36-39]

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.[40-42] CV risk reduction is proportional to the degree of LDL-C lowering achieved irrespective of the strategy used to achieve the reduction.[19,42]

High and very high risk individuals include those with pre-existing CVD, chronic kidney disease and diabetes.[43] (Table I) In all other individuals, (i.e. primary prevention), the CV risk should first be assessed.[43] The intensity of risk reduction efforts will depend on the individual's CV risk.[43] The higher the CV risk, the lower the LDL-C target level.[42] (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.[44,45]

Following achievement of LDL-C target, Non-HDL-C may be considered as a secondary treatment target to reduce residual CV risk.[43] 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.[46-49] 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,

Table I: Risk Stratification of Cardiovascular Risk[43]

- **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}/1.73 m^2 (≥Stage 4)
- **High Risk** Individuals include:
  - Diabetes without target organ damage
  - CKD with GFR ≥30- <60 Ml/min^{-1}/1.73 m^2 (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[43]

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)	Levels (mmol/L) 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*	>3.4 **	<3.0	<3.8
High CV risk			
• 20% 10-year CVD risk • diabetes without target organ damage • CKD with GFR 30-<60 Ml/min^{-1}/1.73 m^2	> 2.6	≤2.6 or a reduction of >50% from baseline***	≤ 3.4 or a reduction of >50% from baseline***
Very high CV risk			
• established CVD, • diabetes with proteinuria or with a major risk factor such as smoking, hypertension or dyslipidaemia • CKD with GFR <30 Ml/min^{-1}/1.73 m^2 but not dialysis dependent)	>1.8	<1.8 or a reduction of > 50% from baseline***	< 2.6 or a reduction of > 50% from baseline***

*Low and Intermediate (Moderate) CV risk is assessed using the Framingham General CVD Risk Score[50]
**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.[51,52] 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.[53-55]

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.[43,51] 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.[51] However, there is no clear evidence that replacing SFA with MUFA or CHO reduces CVD risk.[51]

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.[57]

Exercise

Regular exercise reduces the risk of all-cause and CVD mortality in both healthy individuals and those with pre-existing CVD.[58-60]

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).[61,62]

Smoking
Smoking is a strong and independent predictor of CVD.[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.[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.[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.[43]

Statins
Statins are the lipid-lowering drugs of choice because they have been shown in numerous clinical trials to reduce the risk of CVD.[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%.[18,67] They have also been shown to be safe.[67]

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.[68,69]

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.[70-72] The most common manifestation of SAM 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.[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.[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.[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).[77,78] This occurs with both hydrophilic and lipophilic statins. There is no evidence that statins cause any effect on neurocognitive function.[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.[43] 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.[29] However, the use of fibrates has not been shown to reduce CV events in the secondary prevention trials conducted in the statin era.[29] Therefore, the use of fibrates is limited to patients with very high TG levels who are at risk of pancreatitis.[43,82] 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).[43,82,83]

Bile Acid Sequestrants
Bile acid sequestrants, such as cholestyramine, colestipol and colesevelam, 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.[84,85] 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, diarrhoea 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.[27,28]

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.[86] 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.[59] 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.[43]

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.[89]

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.[86]

C3. Primary Hypercholesterolaemia

The commonest primary hyperlipidaemia is Common Polygenic Hypercholesterolaemia.[30] 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.[30]

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.[31] This can be done using the validated US MEDPED, the UK Simon Broome or the Dutch Lipid Clinic criteria.[90] 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.[31]

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%.[91] 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%[92] attained by doubling the statin dose.[91-93]

It is well tolerated with no major adverse effects.[94] 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.[40] Individuals in the statin- ezetimibe arm had a median LDL-C of 1.4mmol/L versus 1.8mmol/L in the statin alone arm.[40] There was significant additional CV benefit seen in the arm on combination statin -ezetimibe which had achieved lower LDL-C level.[40]

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.[95]

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.[96]

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.[39] 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.[39]

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 with or without ezetimibe.[41] 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.[41] 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.

ACKNOWLEDGEMENT

This expert review was supported by an unrestricted grant from Sanofi-Aventis (Malaysia) Sdn. Bhd.

REFERENCES

1. Institute for Public Health (IPH). The Third National Health and Morbidity Survey (NHMS III) 2006. Executive Summary. Malaysia: Ministry of Health; 2008.
2. Institute for Public Health (IPH). National Health and Morbidity Survey 2011 (NHMS 2011). Vol. II: Non-Communicable Diseases. 2011; 188.
3. Institute for Public Health (IPH). National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors & Other Health Problems. 2015.
4. Hazreen MA, Su TT, Jalaludin MY, Dahlui M, Chinna K, Ismail M, et al. An exploratory study on risk factors for chronic non-communicable diseases among adolescents in Malaysia: overview of the Malaysian Health and Adolescents Longitudinal Research Team study (The MyHeART study). BMC Public Health 2014; 14(3): S6.
5. Nawawi HM, Nor IM, Noor IM, Karim NA, Arshad F, Khan R, Yusoff K. Current Status of Coronary Risk Factors Among Rural Malays in Malaysia Eur J Prev Cardiol 2001; 9: 17-23.
6. Wissler RW, Vesselinovitch D. Studies of regression of advanced atherosclerosis in experimental animals and man. Ann N Y Acad Sci 1976; 275: 363-78.
7. Anitschkow N, Chalatow S. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung fuer die Entstehung einigerpathologischer Prozesse. Zentrbl Allg Pathol Pathol Anat 1913; 24: 1-9.
8. Friedman M, Byers SO, Rosenman RH. Resolution of aortic atherosclerotic infiltration in the rabbit by phosphatide infusion. Proc Soc Exp Biol Med 1957; 95: 586-8.
9. Armstrong ML, Warner ED, Connor WE. Regression of coronary atheromatosis in rhesus monkeys. Circ Res 1970; 27: 59-67.
10. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med 1961; 55: 33-50.
11. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA 1995; 274: 131-6.
12. Kannel WB, Neaton JD, Wentworth D, Thomas HE, Stamler J, Hulley SB, et al. Overall and coronary heart disease mortality rates in relation to major risk factors in 325,348 men screened for the MRFIT. Multiple Risk Factor Intervention Trial. Am Heart J 1986;112: 825-36.
13. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma Cholesterol Concentration and Mortality: The Whitehall Study. JAMA 1992; 267: 70-6.

14. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004; 364: 937-52.
15. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 2000; 284: 311-8.
16. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, et al for the Prospective Studies Collaboration,. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829-39.
17. Strong A, Rader DJ. Clinical Implications of Lipid Genetics for Cardiovascular Disease. Curr Cardiovasc Risk Rep 2010; 4: 461-8.
18. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalla N et al for the Cholesterol Treatment Trialists' (CTT) Collaboration,. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376: 1670-81.
19. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA 2016; 316: 1289-97.
20. Taylor F, Huffman MD, Macedo AF, Moore THM, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;:CD004816.
21. Assmann G, Schulte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis 1996; 124 Suppl: S11-20.
22. Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, et al for the Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. JAMA 2009; 302(18): 1993-2000.
23. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007; 298: 299-308.
24. Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting Compared With Nonfasting Triglycerides and Risk of Cardiovascular Events in Women. JAMA 2007; 298: 309-16.
25. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJP, Komajda M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357: 2109-22.
26. Cannon CP, Shah S, Dansky HM, Davidson M, Brinton EA, Gotto AM, et al. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010; 363: 2406-15.
27. The HPS2-THRIVE CollaborativeGroup.Effects of Extended-Release Niacin with Laropiprant in High-Risk Patients. N Engl J Med 2014; 371: 203-12.
28. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011; 365: 2255-67.
29. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010; 375: 1875-84.
30. Rader DJ. Chapter 5: Lipid Disorders. In: Textbook of Cardiovascular Medicine. 3rd Ed. Lippincott Williams & Wilkins; 2007.
31. France M, Rees A, Datta D, Thompson G, Capps N, Ferns G, et al. HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis 2016; 255: 128-39.
32. Norgestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L et al. Familial Hypercholesterolaemia is underdiagnosed and undertreated in the general population: Guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. Eur Heart J 2013; 34: 3478-90
33. Khoo KL, van Acker P, Defesche JC, Tan H, van der Kerkhof L, Heijnen-van Eijk SJ et al,. Low-density lipoprotein receptor gene mutations in a Southeast Asian population with familial hypercholesterolemia. Clin Genet 2000; 58(2): 98-105
34. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006; 354: 1264-72.
35. Guella, I., R. Asselta, D. Ardissino, P. A. Merlini, F. Peyvandi, S. Kathiresan, P. M. Mannucci, M. Tubaro, and S. Duga. Effects of PCSK9 genetic variants on plasma LDL cholesterol levels and risk of premature myocardial infarction in the Italian population. J. Lipid Res 2010; 51: 3342-9.
36. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291: 1071-80.
37. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295: 1556-65.
38. Tsujita K, Sugiyama S, Sumida H, Shimomura H, Yamashita T, Yamanaga K, et al. Impact of Dual Lipid-Lowering Strategy With Ezetimibe and Atorvastatin on Coronary Plaque Regression in Patients With Percutaneous Coronary Intervention: The Multicenter Randomized Controlled PRECISE-IVUS Trial. J Am Coll Cardiol 2015 ; 66: 495-507.
39. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJP, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA 2016; 316: 2373-84.
40. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372: 2387-97.
41. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376: 1713-22.
42. McCormack T, Dent R, Blagden M. Very low LDL-C levels may safely provide additional clinical cardiovascular benefit: the evidence to date. Int J Clin Pract 2016; 70: 886-97.
43. Ministry of Health. Clinical Practice Guidelines on Management of Dyslipidemia, 5th Ed [Internet]. 2017. Available from: www.acadmed.com.my
44. Chia YC, Gray SYW, Ching SM, Lim HM, Chinna K. Validation of the Framingham general cardiovascular risk score in a multiethnic Asian population: a retrospective cohort study. BMJ Open 2015; 5: e007324.
45. Selvarajah S, Kaur G, Haniff J, Cheong KC, Hiong TG, van der Graaf Y, et al. Comparison of the Framingham Risk Score, SCORE and WHO/ISH cardiovascular risk prediction models in an Asian population. Int J Cardiol 2014; 176: 211-8.
46. Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, Grundy SM. Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabetes Care 2005; 28: 1916-21.
47. van den Berg MJ, van der Graaf Y, de Borst GJ, Kappelle LJ, Nathoe HM, Visseren FLJ, et al. Low-Density Lipoprotein Cholesterol, Non-High-Density Lipoprotein Cholesterol, Triglycerides, and Apolipoprotein B and Cardiovascular Risk in Patients With Manifest Arterial Disease. Am J Cardiol 2016; 118: 804-10.
48. Mora S, Glynn RJ, Boekholdt SM, Nordestgaard BG, Kastelein JJP, Ridker PM. On-Treatment Non-HDL Cholesterol, Apolipoprotein B, Triglycerides, and Lipid Ratios in Relation to Residual Vascular Risk after Treatment with Potent Statin Therapy: The JUPITER Trial. J Am Coll Cardiol 2012; 59: 1521-8.
49. Arsenault BJ, Rana JS, Stroes ESG, Després J-P, Shah PK, Kastelein JJP, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol 2009; 55: 35-41.
50. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.
51. United States Department of Agriculture. Scientific Report of the 2015 Dietary Guidelines Advisory Committee [Internet]. 2015 [cited 2016 Dec 23]. Available from: https://health.gov/dietaryguidelines/2015-scientific-report/pdfs/scientific-report-of-the-2015-dietary-guidelines-advisory-committee.pdf
52. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315-81.
53. Shin JY, Xun P, Nakamura Y, He K. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. Am J Clin Nutr 2013; 98: 146–59.
54. Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of egg consumption and risk of coronary heart disease and stroke. J Am Coll Nutr 2016; 35: 704–16.
55. Díez-Espino J, Basterra-Gortari FJ, Salas-Salvadó J, Buil-Cosiales P, Corella D, Schröder H, et al. Egg consumption and cardiovascular disease according to diabetic status: The PREDIMED study. Clin Nutr 2017; 36(4): 1015-21.
56. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Trans Fatty Acids and Cardiovascular Disease. N Engl J Med 2006; 354: 1601-13.

57. Brouwer IA. Effect of trans-fatty acid intake on blood lipids and lipoproteins: a systematic review and meta-regression analysis. Geneva. World Health Organization. 2016.
58. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee I-M. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation 2011; 124: 789-95.
59. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol 2011; 40: 1382-400.
60. Löllgen H, Böckenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med 2009; 30: 213-24.
61. Kelley GA, Kelley KS, Franklin B. Aerobic Exercise and Lipids and Lipoproteins in Patients With Cardiovascular Disease. J Cardpulm Rehabil 2006; 26: 131-44.
62. Kelley G, Kelley K, Tran ZV. Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials. Int J Obes 2005; 29: 881-93.
63. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US). How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General [Internet]. Atlanta (GA): Centers for Disease Control and Prevention (US); 2010 [cited 2017 Apr 25]. (Publications and Reports of the Surgeon General). Available from: http://www.ncbi.nlm.nih.gov/books/NBK53017/
64. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General [Internet]. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014 [cited 2017 Apr 25]. (Reports of the Surgeon General). Available from: http://www.ncbi.nlm.nih.gov/books/NBK179276/
65. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Prev Med. 2003; 37: 283-90.
66. Gepner AD, Piper ME, Johnson HM, Fiore MC, Baker TB, Stein JH. Effects of Smoking and Smoking Cessation on Lipids and Lipoproteins: Outcomes from a Randomized Clinical Trial. Am Heart J 2011; 161: 145-51.
67. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet 2015; 385: 1397-405.
68. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, et al. Very Low Levels of Atherogenic Lipoproteins and the Risk for Cardiovascular Events. J Am Coll Cardiol 2014; 64: 485-94.
69. Ridker PM, Mora S, Rose L, JUPITER Trial Study Group. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J 2016; 37: 1373-9.
70. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, et al. Effect of statins on skeletal muscle function. Circulation. 2013; 127: 96-103.
71. Finegold JA, Manisty CH, Goldacre B, Barron AJ, Francis DP. What proportion of symptomatic side effects in patients taking statins are genuinely caused by the drug? Systematic review of randomized placebo-controlled trials to aid individual patient choice. Eur J Prev Cardiol 2014; 21: 464-74.
72. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes 2013; 6: 390-9.
73. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J 2015; 36: 1012–22.
74. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006; 97: 52C–60C.
75. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc 2010; 85: 349-56.
76. Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. Am J Geriatr Pharmacother 2012; 10: 264-71.
77. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, Craen AJ de, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735-42.
78. Preiss D, Seshasai SRK, Welsh P, Murphy SA, Ho JE, Waters DD, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305: 2556-64.
79. Strom BL, Schinnar R, Karlawish J, Hennessy S, Teal V, Bilker WB. Statin Therapy and Risk of Acute Memory Impairment. JAMA Intern Med 2015; 175: 1399-405.
80. Swiger KJ, Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. Mayo Clin Proc 2013; 88: 1213-21.
81. Stone NJ, Robinson J, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation 2014; 129(25 Suppl 2): S1-45.
82. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016; 37: 2999-3058.
83. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, Leiter LA, Linz P, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010 ;362:1563–74.
84. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–64.
85. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251: 365-74.
86. Reiner Ž, De Backer G, Fras Z, Kotseva K, Tokgözoglu L, Wood D, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. Atherosclerosis 2016; 246: 243-50.
87. Chinwong D, Patumanond J, Chinwong S, Siriwattana K, Gunaparn S, Hall JJ, et al. Statin therapy in patients with acute coronary syndrome: low-density lipoprotein cholesterol goal attainment and effect of statin potency. Ther Clin Risk Manag 2015; 11: 127-36.
88. Munkhaugen J, Sverre E, Otterstad JE, Peersen K, Gjertsen E, Perk J, et al. Medical and psychosocial factors and unfavourable low-density lipoprotein cholesterol control in coronary patients. Eur J Prev Cardiol 2017 ;2047487317693134.
89. Keating AJ, Campbell KB, Guyton JR. Intermittent nondaily dosing strategies in patients with previous statin-induced myopathy. Ann Pharmacother 2013; 47: 398-404.
90. Hovingh GK, Davidson MH, Kastelein JJP, O'Connor AM. Diagnosis and treatment of familial hypercholesterolaemia. Eur Heart J 2013; 34: 962–71.
91. Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res 2006; 3(2): 93–102.
92. Ambegaonkar BM, Tipping D, Polis A, Tomassini J, Tershakovec A. Achieving goal lipid levels with ezetimibe plus statin add-on or switch therapy compared with doubling the statin dose. A pooled analysis. Atherosclerosis 2014; 237: 829-37.
93. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002; 90: 1092-7.
94. Battaggia A, Donzelli A, Font M, Molteni D, Galvano A. Clinical Efficacy and Safety of Ezetimibe on Major Cardiovascular Endpoints: Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS ONE 2015; 10(4): e0124587.
95. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–92.
96. Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 2012 ;366: 1108–18.
97. Amgen. REPATHA (evolocumab) injection, for subcutaneous use. Initial U.S. Approval: 2015 [Internet]. 2015 [cited 2016 Dec 27]. Available from: http://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/repatha/repatha_pi_hcp_english.ashx.
98. Regeneron P. Regeneron and Sanofi announce FDA approval of Praluent® (alirocumab) injection, the first PCSK9 inhibitor in the U.S., for the treatment of high LDL cholesterol in adult patients [Internet]. 2015 [cited 2016 Nov 11]. Available from: http://investor.regeneron.com/releaseDetail.cfm?releaseid=923788.
99. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 385:341-50.
100. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015; 385: 331-40.

101. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 2014; 311: 1870-82.
102. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014; 63: 2541–8.
103. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014; 63: 2531-40.
104. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Am Heart J 2015; 169: 906–915.e13.
105. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J 2015; 36: 1186–94.
106. Kastelein JJP, Robinson JG, Farnier M, Krempf M, Langslet G, Lorenzato C, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther 2014 ;28: 281-9.
107. Giugliano RP, Mach F, Zavitz K, Kurtz C, Schneider J, Wang H, et al. Primary results of EBBINGHAUS, a cognitive study of patients enrolled in the FOURIER trial. Abstract 17-LB-16161-AC presented at: American College of Cardiology 2017 Scientific Sessions; March 18, 2017; Washington, DC.
108. Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al. Cardiovascular Efficacy and Safety of Bococizumab in High-Risk Patients. N Engl J Med 2017; 376: 1527-39.
109. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidaemia and Prevention of Cardiovascular Disease. Endocr Pract 2017; 23: (Suppl 2); 1-87.