Familial Hypercholesterolaemia: An Updated Overall Management

Noor Alicezah Mohd Kasim[1, 2], Chua Yung An[1], Hapizah Nawawi[1, 2]

1 Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia.
2 Department of Pathology, Faculty of Medicine, Universiti Teknologi MARA, Selangor, Malaysia.

Corresponding author:
Professor Dr Hapizah Mohd Nawawi,
Institute of Pathology, Laboratory and
Forensic Medicine (I-PPerForM),
Level 4 Academic Block,
Universiti Teknologi MARA,
Sungai Buloh Campus,
Selangor, Malaysia
Email: hapizah.nawawi@gmail.com;
hapizah@uitm.edu.my
Tel: +603-61267480/7469

ABSTRACT

Familial hypercholesterolaemia (FH), the commonest and serious but potentially treatable form of inherited dyslipidaemias, is characterised by severely elevated plasma low-density lipoprotein-cholesterol (LDL-C) level, which subsequently leads to premature coronary artery disease (pCAD). Effectiveness of FH early detection and treatment is supported by the outcome of several international cohort studies. Optimal FH management relies on prescription of statins either alone or together with other lipid-lowering therapies (LLT). Intensive lifestyle intervention is required in parallel with LLT, which should be commenced at diagnosis in adults and childhood. Treatment with high intensity statin should be started as soon as possible. Combination with ezetimibe and/or bile acid sequestrants is indicated if target LDL-C is not achieved. For FH patients in the very-high risk category, if their LDL-C targets are not achieved, despite being on maximally tolerated statin dose and ezetimibe, proprotein convertase subtilisin/kexin type1 inhibitor (PCSK9i) is recommended. In statin intolerance, ezetimibe alone, or in combination with PCSK9i may be considered. Clinical evaluation of response to treatment and safety are recommended to be done about 4-6 weeks following initiation of treatment. Homozygous FH (HoFH) patients should be treated with maximally tolerated intensive LLT and, when available, with lipoprotein apheresis. This review highlights the overall management, and optimal treatment combinations in FH in adults and children, newer LLT including PCSK9i, microsomal transfer protein inhibitor, allele-specific oligonucleotide to ApoB100 and PCSK9 mRNA. Family cascade screening and/or screening of high-risk individuals, is the most cost-effective way of identifying FH cases and initiating early and adequate LLT.

KEYWORDS: familial hypercholesterolaemia, premature coronary heart disease, lipid-lowering therapies, statin, ezetimibe, PCSK9i, lipoprotein apheresis, HoFH, ApoB100

INTRODUCTION

The natural history of Familial Hypercholestrolaemia (FH) has changed with the use of statins, such that proper identification and treatment of FH subjects through cascade screening (NICE 2018) has resulted in normalisation of disease-free survival almost approaching that of an age- and gender-matched population [1]. Furthermore, coronary artery disease (CAD) risk may be significantly attenuated, if diagnosed early and properly treated.

Genetic analysis of a Northern European general population has recently discovered approximately 1/200 of the people were with heterozygous FH (HeFH). Less than 1% of HeFH are detected in most countries, taking into account a theoretical estimated global prevalence of 1/500. Albeit

FH individuals have increased CAD risk by at least 10-fold, many studies reported failure to achieve recommended LDL-C targets in a large proportion of these patients. Based on the prevalence of 1/200 and 1/500 [2, 3], it is estimated that about 14 - 35 million individuals worldwide are affected by FH [4, 5]. If left untreated, HeFH individuals may develop premature CAD (pCAD) at ages of <55 and <60 years, in men and women respectively [5].

Therefore, individuals are recommended for FH screening, if a person or family member presents with either (i) FH, (ii) total plasma cholesterol level (TC) of ≥8 mmol/L (≥ 310 mg/dL), and/or LDL-C ≥ 5 mmol/L (≥ 195 mg/dL), in an adult; or TC ≥ 6 mmol/L (≥ 230 mg/dL) and/or LDL-C ≥ 4 mmol/L (≥ 155 mg/dL), in a child, (iii) tendon xanthoma(s) and/or (iv)

19

pCAD or sudden premature cardiac death. Family cascade screening and/or screening of high-risk individuals, is the most cost-effective way of identifying FH cases and initiating early and adequate LLT.

This review highlights an updated overall management of FH, comprising of treatment targets, lifestyle measures, optimal treatment combinations in adults and children, as well as an overview on newer LLT including PCSK9i, microsomal transfer protein inhibitor, allele-specific oligonucleotide to ApoB100 and PCSK9 mRNA.

RISK ESTIMATION

Recently confirmed new evidence suggests that retention of LDL-C and apolipoprotein B (ApoB) within the arterial wall is the key factor of atherogenesis [6]. Besides, lowering LDL-C and ApoB-containing lipoproteins reduces CV events. Furthermore, it has also been well documented that hypercholesterolaemia causes and is strongly linked to atherosclerotic cardiovascular disease (ASCVD). In tandem with these new findings, new targets for LDL-C and a revision of the CV risk stratification have been proposed by the new guidelines, particularly relevant to patients in the very-high and high- risk categories. For FH individuals, it is unnecessary to perform total risk estimation as they are already categorised as high or very-high risk individuals. Presence of ASCVD or one other major risk factor in FH patients, renders them to be in the very-high risk category, whilst those without are considered to be at high-risk (Figures 1, 2).

While the calculation for risk estimation scores is not needed for individuals who are already in proactive management for their risk factors, several groups of individuals have been identified to be in the high and very-high total CV risk categories. These include those with type 1 and type 2 DM, documented ASCVD, chronic kidney disease (CKD) or other high-level individual risk factors such as severe hypercholesterolaemia.

Figure 1 CV Categories

Reproduced from: Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al.: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk - The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal, 2019; 41: 111-88. [41]

Recommendations	Class[a]	Level[b]
It is recommended that a diagnosis of FH is considered in patients with CHD aged <55 years for men and <60 years for women, in people with relatives with premature fatal or non-fatal CVD, in people with relatives who have tendon xanthomas, in people with severely elevated LDL-C [in adults >5 mmol/L (>190 mg/dL), in children >4 mmol/L (>150 mg/dL)], and in first-degree relatives of FH patients.	I	C
It is recommended that FH should be diagnosed using clinical criteria and confirmed, when possible, via DNA analysis.	I	C
Once the index case is diagnosed, family cascade screening is recommended.	I	C
It is recommended that FH patients with ASCVD or who have another major risk factor are treated as very-high-risk, and that those with no prior ASCVD or other risk factors are treated as high-risk.	I	C
For FH patients with ASCVD who are at very high risk, treatment to achieve a ≥50% reduction from baseline and an LDL-C <1.4 mmol/L (<55 mg/dL) is recommended. If goals cannot be achieved, a drug combination is recommended.	I	C
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
Treatment with a PCSK9 inhibitor is recommended in very-high-risk FH patients if the treatment goal is not achieved on maximal tolerated statin plus ezetimibe.	I	C
In children, testing for FH is recommended from the age of 5 years, or earlier if HoFH is suspected.	I	C
Children with FH should be educated to adopt a proper diet and treated with a statin from 810 years of age. Goals for treatment should be LDL-C <3.5 mmol/L (<135 mg/dL) at >10 years of age.	IIa	C

ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolaemia; HoFH = homozygous FH; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
[a]Class of recommendation.
[b]Level of evidence.

Figure 2 Recommendations for the detection and treatment of patients with HeFH.

Some individuals, without requiring risk scoring, are categorised in the high- or very-high cardiovascular disease (CVD) risk groups, demanding the immediate attention of all risk factors. These include individuals with known FH, CVD, chronic kidney disease (CKD), diabetes mellitus (DM) of long duration, as well as the presence of coronary artery calcium score (>100 Agatston), carotid or femoral plaques, or severely elevated serum Lp(a) levels. Lp(a), an LDL-C-like particle that contains a highly variable apolipoprotein(a), has been associated with increased CV risk [7]. Elevated Lp(a) has also been reported as an independent determinant for CVD risk [8]. Therefore, a single Lp(a) measurement may assist in identifying individuals who inherit very high Lp(a) levels, resulting in enhanced ASCVD lifetime risk. Subsequent risk stratification of some groups of patients such as those with high risk of ASCVD and a strong family history of premature CVD, can be further assisted by high Lp(a) level. Furthermore, Lp(a) may be useful in ascertaining treatment strategies among patients with borderline estimated risk categories.

TREATMENT TARGETS: LDL-C

The recent European guidelines on management of dyslipidaemia, have suggested the following recommendations for LDL-C targets in FH: (1) Children: <3.5 mmol/L (<135 mg/dL), (2) Adults: <1.8 mmol/L (<100 mg/dL), and <1.4 mmol/L (<70 mg/dL) for adults in the very-high-risk category with ASCVD or one other major risk factor (Figures 2, 3).

In the presence of ASCVD or one other major risk factor, FH patients are considered to be at very-high risk, therefore, the recommended LDL-C targets are at

Global Risk	LDL-C Levels to Initiate Drug Therapy (mmol/L)	Target LDL-C Levels (mmol/L)	Non HDL-C Level corresponding to LDL-C targets in individuals with TG > 4.5 mmol/L
Low CV Risk*	clinical judgement**	< 3.0	< 3.8
Intermediate (Moderate) CV Risk*	> 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⁻¹/1.73m²	> 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⁻¹/1.73m² 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
**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
****In dialysis dependent patients,drug therapy is not indicated for primary prevention of CVD.

Figure 3 Target LDL-C levels according to risk categories.

Reproduced from: Ministry of Health Malaysia, Management of Dyslipidaemia 2017, MOH Malaysia, Editor. 2017, Ministry of Health: Malaysia. [71].

least 50% reduction from baseline and to achieve <1.4 mmol/L (<55 mg/dL). In contrast, FH patients without ASCVD or another major risk factor, are grouped in the high-risk category, with LDL-C targets suggested at least 50% reduction from baseline and <1.8 mmol/L (<70 mg/dL). Similarly, using the Framingham Risk Score (FRS)-General CVD risk stratification tool, FH with and without ASCVD are classified as very-high and high-risk categories respectively. However, with this tool, the recommended LDL-C targets for those risk categories are higher at <1.8 and <2.6 mmol/L (Figure 3).

Regardless of age, these targets are relevant for both HeFH and homozygous FH (HoFH). However, these targets are very challenging to accomplish in HoFH with current treatment, both in children and adults. Based on a community study in Malaysia, lipid-lowering therapies (LLT) are prescribed to only 56.6% of potential (Definite and Probable) HeFH, according to the Dutch Lipid Clinic Network (DLCN) criteria [9]. Still, none of them achieved the therapeutic LDL-C

target for high or very-high risk individuals as recommended by the Malaysian National Clinical Practice Guidelines for Management of Dyslipidaemia [9]. However, in a hospital-based FH cohort, an overall of 95.9% of the FH patients received statins, of whom only 9.8% achieved the LDL-C target of <1.8 mmol/L (Chua et al., 2019, unpublished).

Furthermore, our group reported that about 31% of the hypercholesterolaemic adults in the Malaysian community are in the high or very-high risk category according to the FRS-General CVD risk assessment tool. Of those, only 24.7% were on lipid-lowering medication, of whom only a mere 16.3% achieved target LDL-C for the high and very-high risk categories [10].

Due to ethical reasons, randomised clinical trials of LLT against placebo in FH subjects have not been organised, thus, the lack of reports on the benefits of LLT. Nonetheless, treatment goals and benefits have been well reported in large-scale clinical trials among non-FH individuals [11]. It has been clearly established

that with LDL-C as the main goal of treatment, its degree of decrement is proportional to the decline in both CV and all mortality. For every 1 mmol/L of decrement in LDL-C level, there is a corresponding decline in CV mortality and total mortality by 20% and 12% respectively, over 5 years [11]. Hence, all untreated FH individuals above 40 years of age, have been proposed to be regarded as very-high CV risk category, due to exposure to elevated LDL-C levels since birth [12].

LIFESTYLE MEASURES

In parallel with lowering the elevated LDL-C levels, lifestyle intervention has to be intensified and all other major risk factors have to be diligently managed according to expert recommendations (Figure 4). A healthy diet needs to be emphasised, consisting of low cholesterol, saturated fats, trans-fat and carbohydrates whilst focussing on whole grain products, fish, vegetables and fruits, gearing towards ideal body weight and waist circumference. Intensive health education focussing on lifestyle intervention including smoking, physical activity and diet, need to be given to all FH patients and their families [13]. A healthy diet should be implemented and individualised, with the involvement of the whole family and support by a certified dietitian. Plant sterols and stanols have been reported to lower LDL-c levels to a certain extent, hence can be considered as functional foods.

Smoking	No exposure to tobacco in any form.
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish.
Physical activity	3.5 - 7 hours moderately vigorous physical activity per week or 30 - 60 min most days.
Body weight	BMI 20 - 25 kg/m^2, and waist circumference <94 cm (men) and <80 cm (women).
Blood pressure	<140/90 mmHg.[a]
LDL-C	**Very-high risk in primary or secondary prevention:**
	A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL). No current statin use: this is likely to require high-intensity LDL-lowering therapy. Current LDL-lowering treatment: an increased treatment intensity is required.
	High risk:
	A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline[b] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL).
	Moderate risk:
	A goal of <2.6 mmol/L (<100 mg/dL).
	Low risk:
	A goal of <3.0 mmol/L (<116 mg/dL).
Non-HDL-C	Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively.
ApoB	ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively.
Triglycerides	No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.
Diabetes	HbA1c: <7% (<53 mmol/mol).

Apo = apolipoprotein; BMI = body mass index; HbA1c = glycated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
[a]Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.
[b]The term 'baseline' refers to the LDL-C level in a person not taking any lipid-lowering medication, or to the extrapolated baseline value for those who are on current treatment.

Figure 4 Treatment targets and goals for CVD prevention
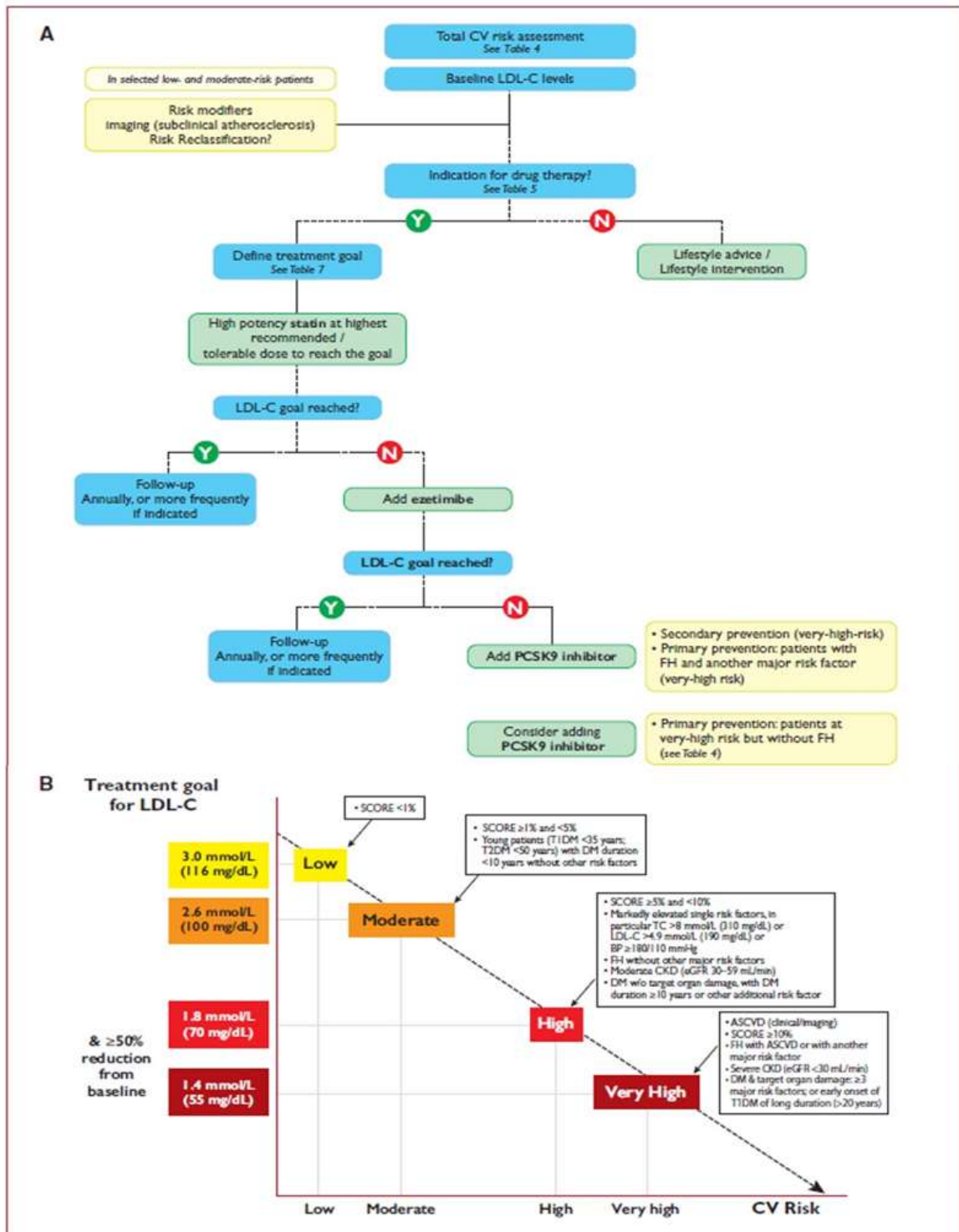
Reproduced from: Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al.: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk - The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal, 2019; 41: 111-88. [41].

Recommendations	Class^a	Level^b
It is recommended that a high-intensity statin is prescribed up to the highest tolerated dose to reach the goals set for the specific level of risk.	I	A
If the goals^c are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very-high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor may be considered.	IIb	C
For secondary prevention, patients at very-high risk not achieving their goal^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	A
For very-high-risk FH patients (that is, with ASCVD or with another major risk factor) who do not achieve their goal^c on a maximum tolerated dose of a statin and ezetimibe, a combination with a PCSK9 inhibitor is recommended.	I	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), ezetimibe should be considered.	IIa	C
If a statin-based regimen is not tolerated at any dosage (even after rechallenge), a PCSK9 inhibitor added to ezetimibe may also be considered.	IIb	C
If the goal^c is not achieved, statin combination with a bile acid sequestrant may be considered.	IIb	C

ASCVD = atherosclerotic cardiovascular disease; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.
^aClass of recommendation.
^bLevel of evidence.
^cFor definitions see Table 8.5.

Figure 5 Recommendations for pharmacological LLT

Smoking cessation is extremely important for smokers, and where necessary such patients should be referred to a specialised anti-smoking programme. It is imperative to advise children and young adults to abstain from smoking and not be subjected to passive smoking. Implementation of regular physical activities is crucial. However, assessment of CV function is advisable in adults with FH, before starting any strenuous exercise programme. Despite the benefits of lifestyle intervention, including healthy diets, almost all FH patients require LLT to reduce elevated LDL-C.

PHARMACOTHERAPY

In adults, treatment with LLT should be started as soon as possible, after a diagnosis of FH has been made, in tandem with lifestyle intervention. The utilisation of imaging techniques such as coronary calcium scoring and carotid/femoral plaques assessment is recommended to detect asymptomatic atherosclerosis, for subsequent improvement of risk assessment.

The priority of pharmacotherapy for adults is as follows: (i) maximal potent statin dose, (ii) ezetimibe, (iii) bile acid sequestrant, (iv) PCSK9i, (v) lipoprotein apheresis in HoFH and treatment-resistant HeFH with CAD. Treatment with high-intensity statin, in combination with ezetimibe in most instances, should be initiated as soon as possible. For FH patients in the very-high risk category (presence of ASCVD or one other major risk factor), if the LDL-C targets are not reached despite being on maximally tolerated statin dose and ezetimibe, proprotein convertase subtilisin/kexin type1 inhibitor (PCSK9i) is recommended. If the LDL- target is still not achieved, combination of statin with a bile acid sequestrant may be considered (Figure 5 and Figure 6). For patients with statin intolerance at any dosage (even after rechallenge), either ezetimibe alone, or in combination with a PCSK9i should be considered.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol.

Figure 6: (A) Treatment algorithm for pharmacological LLT. (B) Treatment goals for LDL-C across categories of total CVD risk.
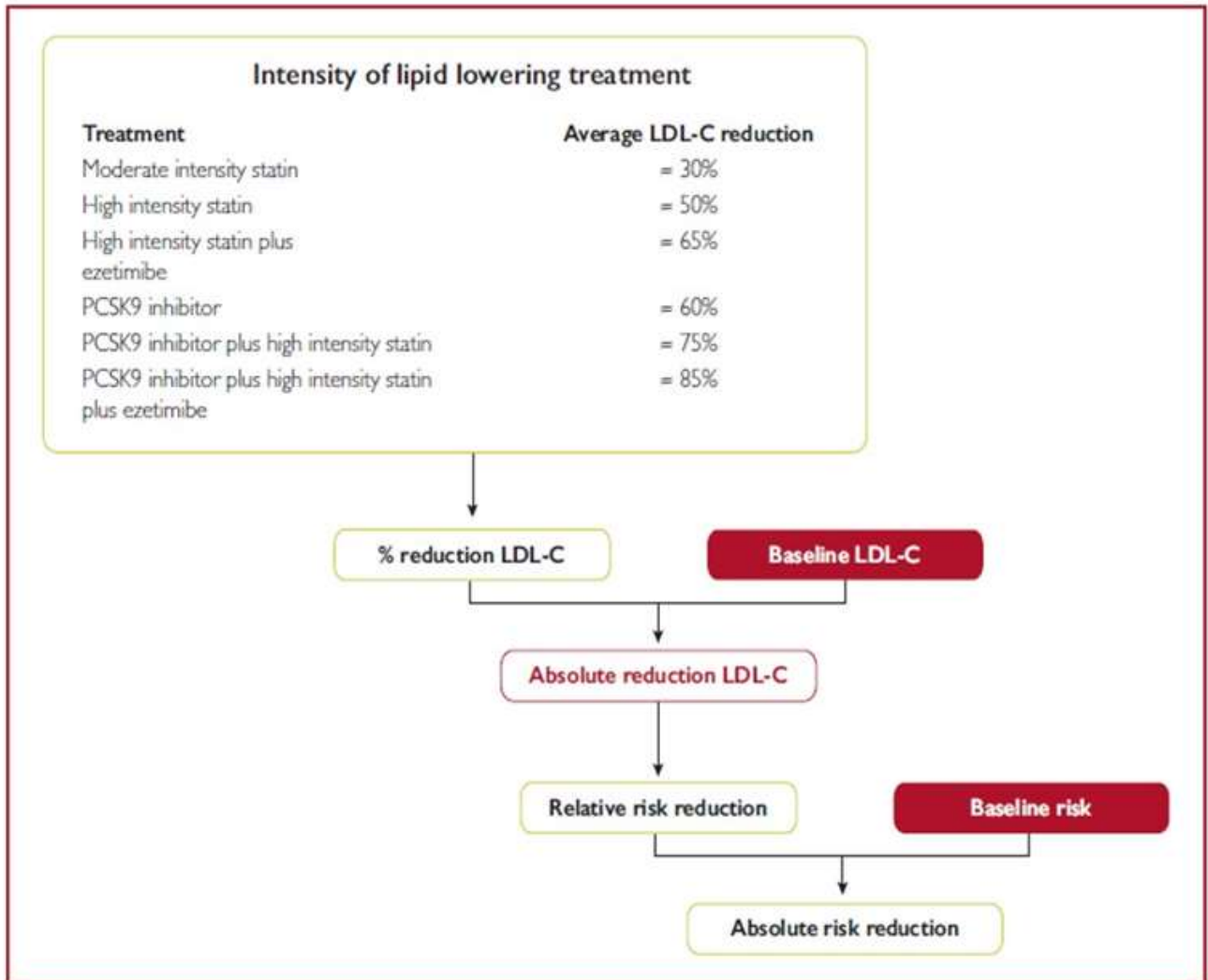
The expected clinical benefits of treatment to lower low-density lipoprotein cholesterol for any person can be estimated; it depends on the intensity of therapy, the baseline low-density lipoprotein cholesterol level, the expected absolute achieved reduction in low-density lipoprotein cholesterol, and the baseline estimated risk of atherosclerotic cardiovascular disease. The intensity of therapy should be selected to achieve the recommended proportional reduction in low-density lipoprotein cholesterol based on the person's estimated risk of atherosclerotic cardiovascular disease. Multiplying the proportional reduction in low-density lipoprotein cholesterol by a person's baseline low-density lipoprotein cholesterol level estimates the expected absolute reduction in low-density lipoprotein cholesterol that is likely to be achieved with that therapy. Because each 1.0 mmol/L absolute reduction in low-density lipoprotein cholesterol is associated with a 20% reduction in the risk of cardiovascular events, larger absolute reductions in low-density lipoprotein cholesterol lead to larger proportional reductions in risk. Multiplying the proportional reduction in risk expected for the achieved absolute reduction in low-density lipoprotein cholesterol by a person's estimated baseline risk of atherosclerotic cardiovascular disease determines the expected absolute risk reduction for that person. LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Figure 7 Expected clinical benefits of LLT.

Reproduced from: Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al.: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk - The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal, 2019; 41: 111-88. [41].
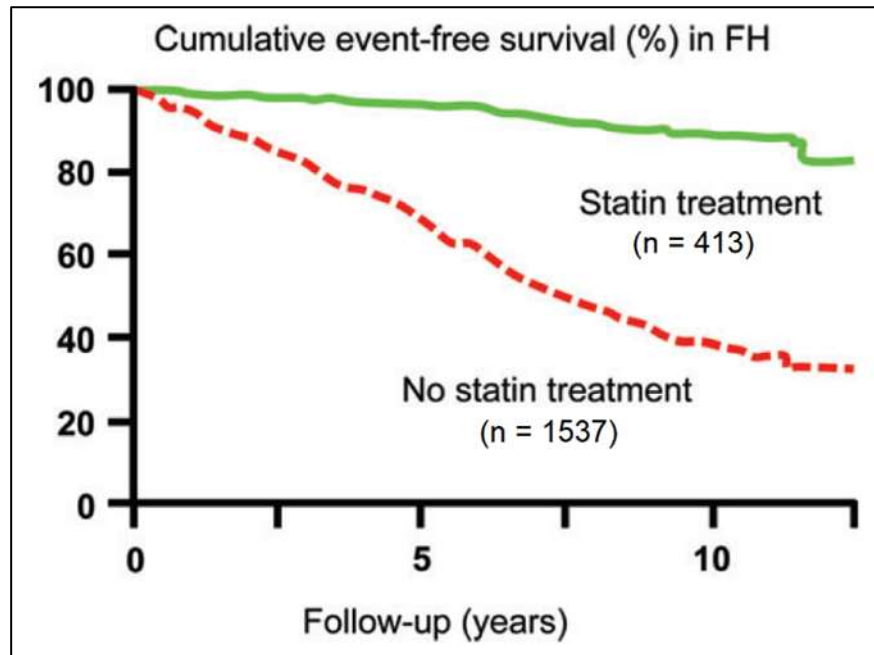
Figure 8 Kaplan Meyer Survivor curve of CAD-free life between FH individuals who received and not received FH treatments.

Reproduced from: Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al.: Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. European Heart Journal, 2013; 34: 3478-3490.[5].

High-intensity statin at maximal dose, including either rosuvastatin 40 mg, atorvastatin 80 mg, or pitavastatin 4 mg, should be commenced in adults at the first consultative visit (Figure 7). However, due to the association with elevated risk for myositis and rhabdomyolysis, simvastatin 80 mg is not recommended as this dose. There are several justifications for the recommendation to initiate treatment with maximal dose of a high intensity statin. Firstly, while most FH patients need at least 50% LDL-C reduction, only less than 5% (1/20) of FH individuals achieve the targeted LDL-C levels. Secondly, high percentage FH patients receive inadequate doses to reach LDL-C goals. Thirdly, many clinicians despite not achieving treatment targets, fail to increase statin doses.

In children, it is highly recommended to initiate LLT at about the age of 6 -10 years, in parallel with lifestyle intervention. The priority for pharmacotherapy in children is as follows; (i) statin, (ii) ezetimibe, (iii) bile acid sequestrant, and (iv) lipoprotein apheresis in HoFH. For children, statins to be used should only be amongst those licensed statins in this age group, usually simvastatin or pravastatin [14, 15].

Clinical evaluation of response to treatment and safety are recommended to be done about 4-6 weeks following initiation of therapy. Numerous evidences have shown substantial reduction in major CV events with statin treatment in observational studies. Thus, statins are the main drugs of choice [11, 16, 17]. Furthermore, the introduction of statin treatment has also resulted in the decline of CAD events in FH patients [18, 19]. Moreover, FH individuals who have had treatment initiated prior to onset of CAD, have the potential benefit of CAD event-free period as good as those in the general population (Figure 8).

Statins are first-line drugs for patients in the high and very-high risk categories, as they have been overwhelmingly proven to reduce CV events and safe to use by numerous randomised controlled trials.

However, in some high-risk individuals such as FH patients or those with statin intolerance, the targeted LDL-C levels are not achieved despite maximally tolerated statin. The use of non-statin therapies, such as ezetimibe and the newer PCSK9i have been previously reviewed [20]. Most FH patients are unable to achieve the targeted LDL-C level with statin alone, albeit commencement of the maximal doses of high intensity statin. In such situation, ezetimibe can be combined with statin therapy with high compliance and minimal side effects. Generally, statin–ezetimibe combination will result in 60–70% LDL-C reduction. Bile acid sequestrants such as cholestyramine, colestipol, or colesevelam, is suggested as a third drug for very-high risk patients when the LDL-C levels exceeding recommended targets of <1.8 mmol/L (<70 mg/dL). Addition of pure niacin (up to 3 g/day) on top of the above-mentioned medications, in some FH patients, as practised in some countries, is another possible option to reduce LDL-C and Lp(a) further. Combination of maximal dose of high-intensity statin with fibrates can be considered in FH patients with hypertriglyceridaemia and low HDL-C, or TG >5.7 mmol/L (>500 mg/dL). This statin combination is particularly with fenofibrate, due to its favourable drug interaction report [21] and effect on LDL-C reduction in FH [22]. Fenofibrate is also an option if there is intolerance or unavailability to other LLT, as it is capable of reducing LDL-C levels even when TG is normal. Further information on management, safety, as well as efficacy of LLT have been previously eluded [23].

Specialised clinical management is needed for statin intolerance in FH patients. This is to ascertain that wherever possible, the FH patients have been challenged with the various types of statins, in addition to considering, depending on appropriate cases, combination therapy of low dose of statin, ezetimibe, and resins.

LIPOPROTEIN APHERESIS

For severely hypercholesterolaemic individuals with very-high CV risk despite already under LLT, lipoprotein apheresis (LA) is recommended, especially for HoFH children. Up to 50-75% of LDL-C and Lp(a) reduction can be achieved with weekly or biweekly lipoprotein apheresis session [24-27]. LA is available at specialised lipid clinics, haemodialysis centres and blood transfusion centres. Different countries may have different clinical criteria for initiation of lipoprotein apheresis.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA

HoFH is rarer (1:160 000 – 1:320 000) than HeFH, and almost certainly cause early ASCVD death (<30 years old) if not treated. Clinical manifestations include xanthomata, premature and progressive CVD which usually develop before the age of 20 years, and TC level of more than 13 mmol/L (>500 mg/dL).

It is important to identify the HoFH in young age, and critical to initiate intensive LLT by lipid specialists, and, when available, with lipoprotein apheresis. These early and extensive treatment can lead to a 5 - 70% decrement in plasma LDL-C levels, if maximally tolerated pharmacological therapy is maintained [28]. The detailed guidelines on HoFH management is discussed in EAS consensus statements [28, 29].

Case 1 – Homozygous FH with severe xanthelasma

Our group has previously reported 3 cases of HoFH. The first case was a rare case of HoFH in a 22-year-old Malay woman with severe hypercholesterolaemia (LDL-C 13.9 mmol/L) and the presence of gross xanthelasma [30]. Upon her referral to a Specialist Lipid Clinic, she was clinically diagnosed as FH, but without personal history of CAD or other major risk factors. However, three of her siblings died due to sudden cardiac death at young age (20 - 40 years old). Her parents have marital consanguinity, where they are related (cousins). Genetic testing was done and she was confirmed to inherit a homozygous pathogenic variant, C255S (c.763T>A) in Exon 5 of the her LDLR gene. Family cascade screening was performed on her affected family members and confirmed the presence of the same disease-causing variant. She was treated with high-intensity statins (atorvastatin 40 – 80 mg) and ezetimibe, which managed to reduce her LDL-C by more than 50% from baseline, although targeted LDL-C of <2.6 mmol/L was not achieved.

Case 2 – Homozygous FH with successful pregnancy outcome

Our second case of HoFH, was first seen with complications of severe ASCVD including supravalvular aortic stenosis. Despite genetic counselling, she decided to proceed on with the pregnancy, with subsequent successful pregnancy outcome [31]. Pregnancy in HoFH may pose the risk of early coronary morbidity and mortality to both foetus and mother. Hence, the combination of HoFH and pregnancy can be a potentially fatal condition. The difficulty of her LDL-C management was exacerbated by the fact that statins are contraindicated in pregnancy, thus, the choice of LLT was limited. In contrast, LA is an alternative effective treatment to control cholesterol level during pregnancy. However, the procedure is not widely available in the Asian region, especially in economically deprived countries. Despite being counselled, this patient refused to undergo LA, hence, was continued on LLT. Her LDL-C level peaked to above 20 mmol/L in the second trimester, during which she developed angina symptoms and underwent angioplasty. To date, there are scarce documented case reports of HoFH in pregnancy, the majority of whom underwent LA through-out their pregnancy. This case report illustrates a rare but successful pregnancy outcome of a HoFH patient, managed by a multi-disciplinary team, treated with LLT during pregnancy.

Case 3 – Homozygous FH with good response and unique legacy effect of PCSK9 Inhibitor

In this third case of HoFH, our group report a good response and a unique prolonged effect of short-term alirocumab treatment on a clinically and genetically confirmed young HoFH patient, who suffered from ACS. The patient was initially treated with a combination of high intensity statin and ezetimibe for 12 weeks. Subsequently, alirocumab was added to the lipid-lowering regime, which managed to achieve guideline recommended LDL-C target within 10 weeks. However, due to financial constraints, alirocumab was stopped after 32 weeks of the triple drug combination therapy. Interestingly, despite cessation of PCSK9 inhibitor therapy for period of subsequent 30 weeks, LDL-C level only increased slightly, but not returning to pre-alirocumab baseline level, and more importantly, managed to maintain target LDL-C levels [32]. This suggests HoFH patients with residual LDL receptor expression as in this case, can benefit from PCSK9 inhibitor therapy. This case illustrates the hypothesised legacy effect of PCSK9 inhibitor, where LDL-C reduction may persist for a long time even after cessation of the medication. However, the long-term clinical benefit is still unclear.

FAMILIAL HYPERCHOLESTEROLAEMIA IN CHILDREN

Children with FH can be effectively diagnosed based on clinical features such as severe hypercholesterolaemia, a positive family history of hypercholesterolaemia, pCAD, and/or genetically confirmed FH mutations [33]. LDL-C in childhood can be used for optimal discrimination between FH and non-FH due to the lack of exposure to secondary causes of hyperlipidaemia. The threshold limit of hypercholesterolaemia in children with a positive family history of hypercholesterolaemia and pCAD is LDL-C of >4.0 mmol/L (>155 mg/dL). If FH gene mutation is detected in a parent, the child LDL-C threshold level is >3.5 mmol/L (>130 mg/dL). Genetic analysis in children can be initiated at 5 years old or even at younger age in suspected HoFH cases. Children of mutation-confirmed parents have 50% chance of inheriting the gene mutation, hence are also recommended to undergo genetic testing. [34].

Several observational studies in FH children have suggested that earlier initiation of LLT can lead to LDL-C reduction and improvement in endothelial function, better than starting the LLT in later age, where the early reduction of LDL-C will subsequently reduce coronary outcomes in later years [15, 33, 35, 36]. Therapeutic lifestyle changes and statin treatment are therapies for FH children, which should be initiated at the age of about 6 -10 years. Ten years old children should be screened for FH and treated with statins such as simvastatin or pravastatin, which are licensed for this age group. [14, 15]. The LLT can be started with low-dose statin, and gradually increased until the LDL-C goal is achieved [37]. For proven FH cases, on a suitable diet and LDL >4.0 mmol/L on two occasions, the initial

aim of the LLT is to achieve a reduction in plasma LDL-C by 50%, and subsequent target LDL of <4.0 mmol/L in children between the ages of 8 and 10 years. For children older than 10 years, an LDL-C goal of <3.5 mmol/L (<135 mg/dL) should be targeted.

Our group has recently reported a rare case of FH in a pair of 8-year old identical twins, who were identified in a family cascade screening [38]. Their baseline LDL-C levels were 8.8 mmol/L and 8.6 mmol/L respectively, with absence of lipid stigmata manifestation. Their father was the index case who initially presented with severe hypercholesterolaemia, pCAD, positive family history of pCAD, and subsequently clinically diagnosed and molecularly confirmed as FH. Besides the twins and the father, the family cascade screening also managed to clinically identify the paternal grandfather, another elder brother, aged ten years, a paternal uncle and a cousin as FH patients. Genetic analysis by targeted next-generation sequencing (NGS) revealed that all these individuals were carrying a heterozygous *LDLR* gene variant which was previously described as pathogenic missense mutation (c.530C>T). The twins and their elder brother were counselled on lifestyle intervention, including healthy diet and were started on low dose statin to target for at least 50% LDL-C reduction.

NEW TREATMENT MODALITY

i. PCSK9 Inhibitors

PCSK9 monoclonal antibodies (mAbs) are the newly approved medications for FH therapy which are recommended in FH patients in the very-high-risk category, if the targeted LDL-C goal is not acquired by statin and ezetimibe. Currently, there are only two mAbs approved by the Food and Drug Administration (FDA): alirocumab and evolocumab. PCSK9i can minimise LDL-C levels by up to 60% when co-administered with statin. Two randomised controlled trials recorded promising therapeutic effect of PCSK9 treatment in non-FH ASCVD patients [39, 40]. PCSK9i. PCSK9i monotherapy is also indicated for FH patients who are unable to tolerate statin [29, 41, 42] (Figure 6 A).

Mechanism of Action

PCSK9i exert their therapeutic effect by targeting PCSK9 protein which is involved in the control of the LDL receptor [43]. Physiologically, PCSK9 in plasma binds to the LDL receptor and decreases the expression of the LDL receptor by fostering lysosomal catabolism of the LDL receptor. Consequently, the plasma LDL-C level increases. Therefore, a decrease in PCSK9 concentration or would reduce plasma LDL-C levels [44]. PCSK9i reduces the amount of PCSK9 in plasma, which in turn decreases its ability to bind to LDL receptors. As this association causes intracellular degradation of the LDL receptor, reducing circulating PCSK9 will increase LDL receptor expression on the cell surface. Thus, more circulating LDL-C levels will be absorbed by the cells [44]. The optimal effects of PCSK9i has been reported when administered together with statins, as serum level of PCSK9 is elevated with statin treatment [45].

Effects on Lipids

Low-density lipoprotein cholesterol

Alirocumab and evolocumab, either alone or in combination with statins and/or other LLTs, in several clinical trials, have been reported to dramatically result in reduction in LDL-C levels by an average of 60 percent. If combined with high-intensity or maximally tolerated statins, alirocumab and evolocumab lead to 46-73 percent LDL-C reduction, compared to placebo, and 30 percent more than ezetimibe. PCSK9i plus ezetimibe decreased LDL-C, even in patients who do not tolerate statins [46]. Alirocumab and evolocumab have also been reported to attenuate LDL-C levels in patients at increased CV risk, especially those with DM. [47]. PCSK9i is effective in lowering LDL-C in a wide variety of hypercholesterolaemic patients, due to its primary action on LDL receptor, as long as patients are capable of producing LDL receptors. Patients who may benefit from PCSK9i are those with HeFH, and to a lesser degree, HoFH patients with residual LDL receptor expression. HoFH with receptor deficiency responds poorly to therapy [48].

Triglycerides and high-density lipoprotein cholesterol

In addition to being potent in LDL-lowering, PCSK9i also decrease TG levels and elevate both HDL-C and ApoA-I levels. Treatment with evolocumab results in 26 percent TG reduction, and 9 percent and 4 percent increment in HDL-C and ApoA respectively, in phase II studies; similar results have been reported for alirocumab [23, 49]. However, the TG lowering effect must be confirmed.in populations with higher initial blood TG concentrations.

Lipoprotein(a)

Contrary to statins, anti-PCSK9 mAB also lowers plasma levels of Lp(a) Pooled findings from phase II studies have demonstrated that PCSK9i treatment resulted in 30-40% reduction in Lp(a) [50, 51]. Whist recent research has attempted to understand the different mechanisms, the underlying process remains unclear. However, it seems to be dissimilar to statins, which also enhance the activity of the LDL receptor but do not reduce the levels of circulating Lp(a) in humans. Furthermore, in properly designed experiments, the relative input of this effect to reduction in cardiovascular risk continues to be discussed.

Effect on Cardiovascular Morbidity and Mortality

Phase III studies preliminary results showed that CV events reduction was accomplished in tandem with LDL-C reduction [52-54]. Two important trials have been recently completed: More Cardiovascular Outcomes Study on PCSK9 Inhibition in Elevated Risk Subjects (FOURIER) and Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY Outcomes) studies [39, 40]. The two trials were comparable with respect to the study design of secondary prevention and background treatment. However, the cohorts recruited had either stable CAD, peripheral arterial disease (PAD), or stroke; or a recent (median 2.6 months) ACS. The relative advantage was demonstrated in terms of primary endpoints risk reduction by 15-20 percent. The follow-up duration of both studies was relatively brief, hence, taking into account data from previous statin

studies showing that LDL reduction could occur only after approximately one year [11], suggesting possible benefit of longer-term therapy may have been underestimated in these studies [40, 54].

In the FOURIER study [39], 27,564 patients with atherosclerotic CVD, and LDL-C levels of > 1.8 mmol/L (70 mg/dL), who were on statin therapy, were randomly allocated to receive either evolocumab or placebo. Evolocumab at 48 weeks post-treatment, lowered the LDL-C median from 2.38 mmol / L (92 mg/dL) at baseline to 0.78 mmol / L (30 mg/dL). Evolocumab therapy decreased the primary outcome risk (composite CV mortality, MI, stroke, hospitalisation for unstable angina, or coronary revascularization) significantly, after a median follow-up period of 2.2 years, by 15%, [hazard ratio (HR) 0.85, 95 % CI 0.79-0.92]. The analysis conducted on the period to benefit also revealed a smaller benefit in the first year of trial compared to subsequent years, in parallel with the meta-analysis statin results reported in the Cholesterol Therapy Trialists [6]. The randomisation to evolocumab did not reduce CV mortality nor all-cause mortality risk in the FOURIER study.

The ODYSSEY Outcomes trial randomised 18,924 statin-treated patients, with LDL-C levels > 1.8 mmol / L (> 70 mg dL), non-HDL cholesterol > 2.6 mmol/L (> 100 mg dL) or ApoB > 80 mg/dL, following hospitalisation with acute MI or dysfunctional angina, to alirocumab or placebo injections. Alirocumab allocation lowered the baseline mean LDL-C at 12 months from 2.38 mmol/L (92 mg/dL) to 1.24 mmol/L (48 mg/dL). After a median follow-up of 2.8 years, there was a relative decline in the primary outcome (composite of CAD mortality, non-fatal MI, ischaemic stroke, or unstable angina involving hospitalisation) by 15% (HR 0.85, 95 percent CI 0.78-0.93) [40]. Although the ODYSSEY trial demonstrated a substantial decline in all-cause mortality, this was an exploratory result and was not accompanied by a significant impact on CV death.

Adverse Effects and Interactions

Anti-PCSK9 mAbs as PCSK9i are administered via subcutaneous injection, fortnightly or monthly, at different doses depending on the types of agent used.

There is absence of potential interaction with medications taken orally, as they do not exhibit pharmacokinetic or pharmacodynamic interference. Itching at the injection site and flu-like signs are among the most common reported side effects [55]. Increased patient-reported neurocognitive effects have been identified in several studies [56]. However, the results of a study specifically designed to monitor neurocognitive activity, the EBBINGHAUS trial [57], has been encouraging, as were the safety findings of both the FOURIER and ODYSSEY studies. Mendelian randomisation trials have also shown that inhibition of PCSK9 can increase the risk of LDL-C-related DM, as in the case with statins [58]. However, no signals have arisen from clinical trials to date [39, 59, 60]. While major long-term PCSK9i studies are essential to exclude these and other possible side effects of PCSK9i [61], the 7-year results from the IMPROVE-IT research showed that chronic low LDL-C levels are not correlated with any apparent adverse effects [62]. The occurrence of autoantibodies is a possible issue for long-term antibody therapy.

Evolocumab and alirocumab are both fully humanized antibodies and, therefore, theoretically are unlikely to activate autoantibodies. Up to now, very few anti-drug antibodies have been described, and there has been no diminished LDL-C lowering effect. However, long term treatment needs to be closely monitored. Recently, development for the third anti-PCSK9 mAB, a humanised antibody, bococizumab, was ceased due to presence of increased neutralizing antibodies resulting in diminished LDL-C-lowering effect over time, in addition to higher incidence of injection site reactions [42]. Furthermore, albeit PCSK9i are effective in attenuating LDL-C levels and CV events, in addition to statin and/or ezetimibe treatment, taking into account financial issues and limited long-term safety data, these medications are only probably likely to be considered cost-effective in patients in the very-high risk category. Hence, their utilisation in economically deprived countries may be limited.

ii. Lomitapide

In very low-density lipoprotein (VLDL) formation, the microsomal triglyceride transfer protein (MTP) transmits TGs and phospholipids from the endoplasmic reticulum to ApoB. The inhibition of MTP thus inhibits both VLDL formation in the liver, as well as chylomicrons in the intestines. Lomitapide. an inhibitor of MTP is an oral medication for HoFH. Lomitapide was evaluated as a supplementary treatment for statins with or without apheresis and a reduced-fat diet, in an open-label one-arm titration trial, [63]. At 26 and 56 weeks, LDL-C was reduced from baseline by 50% and 44% respectively. Lomitapide treatment has been demonstrated to reduce frequency of LDL-apheresis in patients with HoFH. However, the effect lomitapide on CV outcomes has not yet been determined.

Lomitapide is associated with elevated levels of aminotransferase due to its mechanism of action, which most likely represents high liver fat and poor gastrointestinal tolerability [63, 64]. The most prominent reason for inhibiting dosage increment of lomitapide in clinical trials, is the gastrointestinal side effects [63]. However, it has been reported that the incidence and severity of gastrointestinal side effects diminish with time. Therefore, lomitapide treatment requires proper patient education and counselling, in addition to close monitoring of liver function.

iii. Mipomersen

Mipomersen, an antisense oligonucleotide capable of binding to ApoB-100 messenger RNA (mRNA), hence resulting in selective degradation of the mRNA molecules, is preferentially transferred to the liver after subcutaneous injection. This results in inhibition of ApoB protein translation, leading to diminished synthesis of atherogenic lipids and lipoproteins, including LDL-C and Lp(a) [65]. Mipomersen, clinically indicated for LDL-C lowering in HoFH patients, is a supplementary therapy to LLT and diet. Albeit officially approved by the US Food and Drug Administration (FDA), mipomersen is still not registered with the European Medicines Agency (EMA). The most frequent adverse effect reported in patients on mipomersen therapy is injection site reactions [66]. The key safety issues of mipomersen is associated with liver toxicity. In addition, mipomersen has also be reported to contribute to the development of liver steatosis. Mipomersen-treated patients have demonstrated greater liver fat from baseline, compared

to placebo. [65]. Long-term mipomersen therapy in terms of efficacy and safety are currently being investigated in patients with statin intolerance and serious HeFH.

iv. Inclisiran

Inclisiran, an experimental drug for LLT, is a chemically engineered double-stranded small interference ribonucleic acid (RNA) conjugated with triantennary N-acetylgalactosamine (GalNAc) to promote uptake by hepatocytes. In the hepatocytes, the antisense strand is integrated into the ribonucleic acid (RNA)-induced silencing complex (RISC) and guides the catalytic breakdown of mRNA for PCSK9, hence, preventing the translation of the protein PCSK9. The decreased intrahepatic PCSK9 increases the recycling and expression of LDLR on the hepatocyte cell surface, increases LDL-C absorption and reduces circulating LDL-C levels [67]. Inclisiran tends to have more benefits over PCSK9-directed monoclonal antibodies, including its infrequent administration (2 injections/year vs. 12-26 PCSK9i injections/year) and the fact that anti-PCSK9 monoclonal antibodies is a challenge at plasma level. Inclisiran, on the other hand, acts to mitigate LDL-C and PCSK9 levels at the intracellular level of hepatocytes [68].

Recently, a post-hoc review of inclisiran from the Phase III, ORION-10, and ORION-11 trials revealed an average 54.1 percent decline in LDL-C levels after 17 months treatment compared to placebo. The data also supported reassuring safety profile and efficacy data of inclisiran, with 99 percent of inclisiran-treated patients exhibiting LDL-C reduction (placebo-adjusted) of around 30 percent [69]. Inclisiran is currently under review by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of primary hyperlipidaemia (including HeFH) in adults who have elevated LDL-C while being on a maximally tolerated dose of statin therapy [70].

CONCLUSION

This review highlights the overall management, and most optimal treatment combinations in HeFH and HoFH in adults and children, newer lipid lowering medications including PCSK9i, MTP inhibitor, ASO to mRNA of ApoB100 and PCSK9. Screening high-risk individuals, or cascade family screening, is the most cost-effective way of identifying FH cases and initiating adequate statin therapy alone or in combination with other LLT. In the case of severe FH, where plasma LDL-C levels remain high despite maximally-tolerated statin and ezetimibe treatment, PCSK9i should be considered.

Conflict of Interest

Hapizah Nawawi is an Amgen Advisory Board Member on Evolocumab for treatment of FH, while Noor Alicezah Mohd Kasim and Chua Yung An declared no conflict of interest with regards to this article preparation.

Acknowledgement

Authors' Contribution

Noor Alicezah Mohd Kasim and Hapizah Nawawi are clinicians who have managed the FH patients and prepared the manuscript. Hapizah Nawawi is the Principal Investigator who is the recipient of the research grants, initiated and conceived the study, and coordinated the overall patient management and research projects. Chua Yung-An is a post-doctoral researcher who have assisted in managing the patients' data and preparing the manuscript.

REFERENCES

1.   Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al.: Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ, 2008; 337: a2423.

2.   Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al.: Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ open, 2017; 7: e016461.

3.   Vallejo-Vaz AJ, De Marco M, Stevens CaT, Akram A, Freiberger T, Hovingh GK, et al.: Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis, 2018; 277: 234-255.

4.   De Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, and Sheldrick RC: Prevalence of familial hypercholesterolemia in the 1999 to 2012 United States national health and nutrition examination surveys (NHANES). Circulation, 2016; 133: 1067-1072.

5.   Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al.: Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. European Heart Journal, 2013; 34: 3478-3490.

6.   Ference BA, Graham I, Tokgozoglu L, and Catapano AL: Reprint of: Impact of lipids on cardiovascular health: JACC Health Promotion Series. Journal of the American College of Cardiology, 2018; 72: 2980-2995.

7.   Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, et al.: Lipoprotein (a) as a cardiovascular risk factor: current status. European Heart Journal, 2010; 31: 2844-2853.

8.   Alonso R, Andres E, Mata N, Fuentes-Jiménez F, Badimón L, López-Miranda J, et al.: Lipoprotein (a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. Journal of the American College of Cardiology, 2014; 63: 1982-1989.

9.   Chua YA, Razman AZ, Ramli AS, Mohd Kasim A, and Nawawi H: Familial hypercholesterolaemia in the Malaysian community: Prevalence, under-detection and under-treatment. Journal of Atherosclerosis and Thrombosis, 2020; In press.

10.   Razman AZ, Ismail SF, Amirah Mohd Ariff, Nazli SA, Noorjamal NA, Abu Bakar NA, et al.: Hypercholesterolaemia in an Asian population: prevalence, risk categorisation, lipid lowering therapy and achievement of control targets. in 11th Congress of the Asia-Pacific Society of Atherosclerosis & Vascular Diseases. 2018. Ilo-Ilo.

11.   Baigent C: Cholesterol Treatment Trialists'(CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 2005; 366: 1267-1278.

12.   Horton JD, Cohen JC, and Hobbs HH: PCSK9: a convertase that coordinates LDL catabolism. Journal of Lipid Research, 2009; 50: S172-S177.

13.   Broekhuizen K, Gm JJ, Van Poppelnm M, Lj LK, Brug J, and Van Mechelen W: Is the process of delivery of an individually tailored lifestyle intervention associated with improvements in LDL cholesterol and multiple lifestyle behaviours in people with Familial Hypercholesterolemia? BMC Public Health, 2012; 12: 348.

14.   Ramaswami U, Humphries SE, Priestley-Barnham L, Green P, Wald DS, Capps N, et al.: Current management of children and young people with heterozygous familial hypercholesterolaemia-HEART UK statement of care. Atherosclerosis, 2019.

15.   Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, De Groot E, et al.: 20-Year follow-up of statins in children with familial hypercholesterolemia. New England Journal of Medicine, 2019.

16.   Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, et al.: European Guidelines on cardiovascular disease prevention in clinical practice (version 2012) The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular

Prevention & Rehabilitation (EACPR). European Heart Journal, 2012; 33: 1635-1701.

17.   Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen M-R, Wiklund O, et al.: ESC/EAS Guidelines for the management of dyslipidaemias. European Heart Journal, 2011; 32: 1769-1818.

18.   Cooney M-T, Dudina A, Whincup P, Capewell S, Menotti A, Jousilahti P, et al.: Re-evaluating the Rose approach: comparative benefits of the population and high-risk preventive strategies. European Journal of Cardiovascular Prevention & Rehabilitation, 2009; 16: 541-549.

19.   Townsend N, Nichols M, Scarborough P, and Rayner M: Cardiovascular disease in Europe—epidemiological update 2015. European Heart Journal, 2015; 36: 2696-2705.

20.   Rajadurai J, Wan Ahmad WA, Nawawi H, Choo GH, Ng WK, Mohd Ali R, et al.: Updates in the management of dyslipidaemia in the high and very high risk individual for CV risk reduction. Medical Journal of Malaysia, 2018; 73: 154.

21.   Chapman MJ, Ginsberg HN, Amarenco P, Andreotti F, Borén J, Catapano AL, et al.: Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. European Heart Journal, 2011; 32: 1345-1361.

22.   Weisweiler P: Low-dose colestipol plus fenofibrate: Effects on plasma lipoproteins, lecithin: cholesterol acyltransferase, and postheparin lipases in familial hypercholesterolemia. Metabolism, 1989; 38: 271-274.

23.   Robinson JG and Goldberg AC: Treatment of adults with familial hypercholesterolemia and evidence for treatment: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of Clinical Lipidology, 2011; 5: S18-S29.

24.   Fernández-Fuertes LF, Tapia MM, Nieves PI, Novoa MF, and Díaz CJ: Low-density lipoprotein apheresis using double filtration plasmapheresis: 27-month use in a child with homozygous familial hypercholesterolemia. Therapeutic apheresis and dialysis: official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy, 2010; 14: 484.

25.   Küçükçongar A, Yenicesu İ, Tümer L, Kasapkara ÇS, Ezgü FS, Paşaoğlu Ö, et al.: Apheresis-inducible cytokine pattern change in children with homozygous familial hypercholesterolemia. Transfusion and Apheresis Science, 2013; 48: 391-396.

26.   Schuff-Werner P, Fenger S, and Kohlschein P: Role of lipid apheresis in changing times. Clinical Research in Cardiology Supplements, 2012; 7: 7-14.

27.   Stefanutti C and Julius U: Lipoprotein apheresis: state of the art and novelties. Atherosclerosis Supplements, 2013; 14: 19-27.

28.   Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al.: Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European Heart Journal, 2014; 35: 2146-2157.

29.   Landmesser U, John Chapman M, Farnier M, Gencer B, Gielen S, Hovingh GK, et al.: European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. European Heart Journal, 2017; 38: 2245-2255.

30.   Mohd Kasim A, Razali R, Rahman T, Hoh B, Hamzan NS, Muid S, et al.: Homozygous familial hypercholesterolemia. The Malaysian Journal of Pathology, 2014; 36: 131.

31.   Mohd Kasim A, Al-Khateeb A, Chua YA, Sanusi AR, and Nawawi H: Case Report of a Successful Pregnancy Outcome of Homozygous Familial Hypercholesterolaemia Patient on Statin Therapy. The Malaysian Journal of Pathology, 2020; In press.

32.   Muhamad Hamidi MH, Kasim S, and Nawawi H: Legacy effect of short term alirocumab in familial hypercholesterolaemia: A case report. in 12th Congress of the Asia-Pacific Society of Atherosclerosis & Vascular Diseases. 2019. Taipei, Taiwan.

33.   Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al.: Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and

treatment. European Heart Journal, 2015; 36: 2425-2437.

34.   Pang J, Martin AC, Bates TR, Hooper AJ, Bell DA, Burnett JR, et al.: Parent–child genetic testing for familial hypercholesterolaemia in an Australian context. Journal of Paediatrics and Child Health, 2018; 54: 741-747.

35.   Braamskamp MJ, Langslet G, Mccrindle BW, Cassiman D, Francis GA, Gagne C, et al.: Effect of rosuvastatin on carotid intima-media thickness in children with heterozygous familial hypercholesterolemia: the CHARON study (hypercholesterolemia in children and adolescents taking rosuvastatin open label). Circulation, 2017; 136: 359-366.

36.   Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, et al.: Statins for children with familial hypercholesterolemia. Cochrane Database of Systematic Reviews, 2017.

37.   Reiner Ž, Treatment of children with homozygous familial hypercholesterolaemia. 2018, SAGE Publications Sage UK: London, England.

38.   Mohd Nor NS, Al-Khateeb AM, Chua Y-A, Mohd Kasim NA, and Nawawi H: Heterozygous familial hypercholesterolaemia in a pair of identical twins: a case report and updated review. BMC Pediatrics, 2019; 19: 106.

39.   Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al.: Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. The Lancet Diabetes & Endocrinology, 2017; 5: 941-950.

40.   Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al.: Alirocumab and cardiovascular outcomes after acute coronary syndrome. New England Journal of Medicine, 2018; 379: 2097-2107.

41.   Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al.: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal, 2019; 41: 111-88.

42.   Ridker PM, Revkin J, Amarenco P, Brunell R, Curto M, Civeira F, et al.: Cardiovascular efficacy and safety of bococizumab in high-risk patients. New England Journal of Medicine, 2017; 376: 1527-1539.

43.   Abifadel M, Varret M, Rabès J-P, Allard D, Ouguerram K, Devillers M, et al.: Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genetics, 2003; 34: 154-156.

44.   Norata GD, Tibolla G, and Catapano AL: PCSK9 inhibition for the treatment of hypercholesterolemia: promises and emerging challenges. Vascular Pharmacology, 2014; 62: 103-111.

45.   Nozue T: Lipid lowering therapy and circulating PCSK9 concentration. Journal of Atherosclerosis and Thrombosis, 2017RV17012.

46.   Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, et al.: Clinical profile of statin intolerance in the phase 3 GAUSS-2 study. Cardiovascular Drugs and Therapy, 2016; 30: 297-304.

47.   Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, and Casas JP: PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews, 2017.

48.   Thedrez A, Blom DJ, Ramin-Mangata S, Blanchard V, Croyal M, Chemello K, et al.: Homozygous Familial Hypercholesterolemia Patients With Identical Mutations Variably Express the LDLR (Low-Density Lipoprotein Receptor) Implications for the Efficacy of Evolocumab. Arteriosclerosis, Thrombosis, and Vascular Biology, 2018; 38: 592-598.

49.   Stein EA and Turner TA: Are the PCSK9 inhibitors the panacea of atherosclerosis treatment? Expert Review of Cardiovascular Therapy 2017; 15.

50.   Gaudet D, Kereiakes DJ, Mckenney JM, Roth EM, Hanotin C, Gipe D, et al.: Effect of alirocumab, a monoclonal proprotein convertase subtilisin/kexin 9 antibody, on lipoprotein (a) concentrations (a pooled analysis of 150 mg every two weeks dosing from phase 2 trials). The American journal of cardiology, 2014; 114: 711-715.

51.   Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, et al.: Reduction in lipoprotein (a) with PCSK9 monoclonal antibody evolocumab

(AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. Journal of the American College of Cardiology, 2014; 63: 1278-1288.

52. Navarese EP, Kołodziejczak M, Kereiakes DJ, Tantry US, O'connor C, and Gurbel PA: Proprotein convertase subtilisin/kexin type 9 monoclonal antibodies for acute coronary syndrome: a narrative review. Annals of Internal Medicine, 2016; 164: 600-607.

53. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al.: Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. New England Journal of Medicine, 2015; 372: 1489-1499.

54. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al.: Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. New England Journal of Medicine, 2015; 372: 1500-1509.

55. Cicero AF, Tartagni E, and Ertek S: Safety and tolerability of injectable lipid-lowering drugs: a review of available clinical data. Expert Opinion on Drug Safety, 2014; 13: 1023-1030.

56. Lipinski MJ, Benedetto U, Escarcega RO, Biondi-Zoccai G, Lhermusier T, Baker NC, et al.: The impact of proprotein convertase subtilisin-kexin type 9 serine protease inhibitors on lipid levels and outcomes in patients with primary hypercholesterolaemia: a network meta-analysis. European Heart Journal, 2016; 37: 536-545.

57. Giugliano RP, Pedersen TR, Park J-G, De Ferrari GM, Gaciong ZA, Ceska R, et al.: Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. The Lancet, 2017; 390: 1962-1971.

58. Schmidt AF, Swerdlow DI, Holmes MV, Patel RS, Fairhurst-Hunter Z, Lyall DM, et al.: PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. The Lancet Diabetes & Endocrinology, 2017; 5: 97-105.

59. Cao YX, Liu HH, Dong QT, Li S, and Li JJ: Effect of proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies on new-onset diabetes mellitus and glucose metabolism: a systematic review

and meta-analysis. Diabetes, Obesity and Metabolism, 2018; 20: 1391-1398.

60. De Carvalho LSF, Campos AM, and Sposito AC: Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and incident type 2 diabetes: a systematic review and meta-analysis with over 96,000 patient-years. Diabetes Care, 2018; 41: 364-367.

61. Zhang L, Song K, Zhu M, Shi J, Zhang H, Xu L, et al.: Proprotein convertase subtilisin/kexin type 9 (PCSK9) in lipid metabolism, atherosclerosis and ischemic stroke. The International Journal of Neuroscience, 2016; 126: 675.

62. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalán R, Špinar J, et al.: Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). Circulation, 2018; 137: 1571-1582.

63. Cuchel M, Meagher E, and Du Toit Theron H: Lomitapide reduces LDL-C in homozygous familial hypercholesterolaemia. Lancet, 2013; 381: 40-6.

64. Cuchel M, Bloedon LT, Szapary PO, Kolansky DM, Wolfe ML, Sarkis A, et al.: Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. New England Journal of Medicine, 2007; 356: 148-156.

65. Agarwala A, Jones P, and Nambi V: The role of antisense oligonucleotide therapy in patients with familial hypercholesterolemia: risks, benefits, and management recommendations. Current Atherosclerosis Reports, 2015; 17: 467.

66. Li N, Li Q, Tian X-Q, Qian H-Y, and Yang Y-J: Mipomersen is a promising therapy in the management of hypercholesterolemia: a meta-analysis of randomized controlled trials. American Journal of Cardiovascular Drugs, 2014; 14: 367-376.

67. Fitzgerald K, White S, Borodovsky A, Bettencourt BR, Strahs A, Clausen V, et al.: A highly durable RNAi therapeutic inhibitor of PCSK9. New England Journal of Medicine, 2017; 376: 41-51.

68. Bandyopadhyay D, Hajra A, Ashish K, Qureshi A, and Ball S: New hope for hyperlipidemia management: Inclisiran. Journal of Cardiology, 2018; 71: 523-524.

69.	Clinicaltrialsarena. ESC 2020: Novartis' inclisiran continues to impress with post-hoc analysis. 2020 [accessed 1 October, 2020]; Available from: https://www.clinicaltrialsarena.com/comment/novartis-inclisiran-post-hoc-analysis.

70.	Novartis. Novartis new analysis shows high consistency in lowering LDL-C in individual response with investigational inclisiran. 2020 [accessed 1 October, 2020]; Available from: https://www.novartis.com/news/media-releases/novartis-new-analysis-shows-high-consistency-lowering-ldl-c-individual-response-investigational-inclisiran.

71.	Ministry of Health Malaysia, Management of Dyslipidaemia 2017, M.o.H. Malaysia, Editor. 2017, Ministry of Health: Malaysia.