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Ministry of Health

DIAGNOSIS AND TREATMENT OF FAMILIAL HYPERCHOLESTEROLEMIA IN SAUDI ARABIA: Clinical Protocol

1. Introduction:

Familial hypercholesterolemia (FH) is an autosomal dominant inherited disorder of lipid metabolism (each child of a person with heterozygous FH has a 50% chance of inheriting the disorder). It is one of most common inherited metabolic disorders affecting people worldwide. FH is a life-threatening genetic disorder that causes high cholesterol starting at birth. There are many different forms of FH. But our aim is to emphasize the clinical approach to the most common two types of Familial hypercholesterolemia.

Heterozygous Familial Hypercholesterolemia (HeFH) = LDL-C is 2-3-fold higher than normal and can lead to Premature coronary Heart Disease in the second and third decade of life.

Homozygous Familial Hypercholesterolemia (HoFH) = LDL-C is 6-8-fold higher than normal and can lead to premature coronary heart disease in even 1st decade of life and hence premature death. Patients often have LDL-C above 400 mg/dL and as high as 800 mg/dL or more at birth.

Mutation in one of three genes identified as a cause of FH. The most common is the low-density lipoprotein cholesterol receptor (LDLR) gene that accounts for 79% of FH cases. Second common mutation is Apolipoprotein B gene (APOB) which accounts for 5% of FH cases and the least common is mutation in proprotein convertase subtilisin/kexin type-9 (PCSK9) gene that accounts for less than 1% of FH cases.

A rare form of FH, Autosomal recessive hypercholesterolemia (ARH) occurs when a patient inherits two pathogenic variants in the low-density lipoprotein adaptor protein 1 (LDLAP1) gene. The cause for remaining 15% of FH cases can be polygenic mutation or undiagnosed and less recognized monogenic mutations including APOE, APOB, SREBP2 and STAP1. In UK, 93% of patients have mutation in LDLR gene, 5% in APOB, and only 2% in PCSK9 gene.

Very limited data is available in Saudi Arabia on Genetics of FH. A systematic review Showed that 21 variants were mapped to 3 genes (LDLR, APOB and PCSK9). As expected, 80% of these variants were affecting the LDLR gene and only 2 mutations among these were found to be novel variants in the LDLR gene; as c.1332dup (p.D445*) and c.2026delG (p. G676Afs*33) . To date, there is no reported data for APOE, LDLRAP1 and other less common variant genes in FH in Saudi Arabia. Also reported that certain tribes from central, northern and western parts of Saudi Arabia have founder mutations. It seems that consanguinity plays a role in developing some types of FH particularly homozygous and some types of

heterozygous FH. Genetic counseling is advisable for families who have index case of FH.

It is crucial to treat HeFH properly in right time to prevent premature coronary heart disease (CHD) before the age of 55 in male and before age of 60 in females. In untreated FH men have 50% risk of having a cardiac event by age 50 and females have 30% risk by age 60. FH patients have a 2.5–10-fold increased risk of heart disease, but when FH is diagnosed and treated early in life, the risk is reduced by about 80%. Many individuals with HoFH will have xanthomas or xanthelasmas (cholesterol deposits under the skin or around the eyes). Individuals with HoFH have two copies of an FH-causing gene, one inherited from each parent. Each child of a person with HoFH has a 100% chance of inheriting FH.

Recent data from Saudi Arabia has shown that there is significant knowledge gap among physicians, in the awareness, knowledge, practice, and detection of FH. Among physicians, only 7.1% found to have acceptable knowledge and 92.9% of the physicians had poor knowledge of FH. Among other deficiencies, a significant issue was that physicians were unaware of clinical algorithms to diagnose patients with FH, what is cascade screening, what are specialist lipid services available and where are these facilities, and among treatments what are the alternatives to statins like proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Which raise the necessities to a clinical protocol for the management of FH.

1.2 Aim and scope:

is to develop a protocol that highlights the diagnosis and treatment of familial hypercholesterolemia to be followed by the physicians with different ranks in general pediatrics and pediatric endocrinology as well as internal medicine specialists and adult endocrinologists to deal with this disease.

1.3 Methodology:

To develop this protocol we have been through several steps as follows:

1- Extensive review of the literature using google scholar engine of search and pubmed as well as personal membership in some of the medical journals, we targeted the protocols, guidelines, and review papers all over the world.
2- Gather the best practice from different parts of the world and customize some protocols and adopt others as suitable to our situation
3- Form a task force from pediatric and adult endocrinologist as well as cardiologist to review the different guidelines, protocols and algorithms to

choose the most recent and applicable guidance for management of familial hypercholesterolemia

4- Expose the final version of the protocol to panel of experts to have their opinion and amend accordingly.

1.4 Conflict of interest: the task force panel herby declare no conflict of interest.

1.5 PREVALENCE:

The FH is a common disease worldwide but it is underdiagnosed and undertreated. The most common form of familial Hypercholesterolemia is Heterozygous FH (HeFH), which was reported as having prevalence of at least 1/500 in Europe and the second form, homozygous familial hypercholesterolemia (HoFH) affects 1/1 million people. Some populations have reported higher prevalence such as 1:300,000 in Netherlands. However, this can be different in different countries and different regions of same country. In USA data showed variable prevalence of Heterozygous FH (HeFH) ranging between 1 per 67 individuals to 1 per 300 individuals. The prevalence of FH (HeFH) in the other parts of the world ranging between 1 per 76 people to 1 per 350 people. A survey in Europe called EUROASPIRE IV has reported that the prevalence of HeFH in patients with MI is 8.3%, 10% in patients aged 70 years and above and 20% in those with premature (50 years) CHD.

Currently there are no epidemiological data for the frequency of FH in Saudi Arabia. This is due to lack of national registry for FH. One of recent studies by Alallaf et al in 2017 has predicted that based on the rate of 1: 200-500, the number of people with FH in Saudi Arabia can be expected in the range from 63,485 to 158,712 cases of HeFH. Similarly, based on rate of 1:300,00-600,000 there are 53 to 106 cases of HoFH in Saudi Arabia. latest data showed that about 80 patients with (HoFH) are being treated with LDL-apheresis every 2 weeks in Riyadh city.

2. Clinical approach and Lab Diagnosis:

FH is a clinical and laboratory criteria-based diagnosis which can be confirmed by genetic testing. To date, there have been four different widely used criteria for FH diagnosis. Some of these criteria use total cholesterol or LDL -C levels while others use personal history and family history of premature coronary artery disease, personal and family history of presence of signs of FH, examination for clinical features of FH and genetic testing. Because blood cholesterol levels vary as per different confounding factors like age, gender, race, certain medications

and some diseases, so we can't rely only on laboratory testing to confirm the presence of FH.

The most common diagnosis criteria summarized as follows:

1. The Dutch Lipid Clinic Network (DLCN) Criteria (Netherlands)
2. The Simon Broome Register (SBR) Group criteria (UK)
3. The Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria (USA).
4. The European Atherosclerosis Society criteria. (EU)

Every criterion has its own merits and different countries follow different criteria for diagnosis of FH. Nevertheless, DLCN criteria showed to have more sensitivity than others do in diagnosis of FH.

2.1 Differential Diagnoses:

Before the confirmation of FH by genetic testing and before starting family screening for FH, it is recommended to rule out secondary causes of hypercholesterolemia like hypothyroidism, nephrotic syndrome, cholestatic liver disease, diet rich in saturated fats and some medications like steroid and cyclosporin.

2.2 Cascade Screening:

Once the index case detected, the most cost-effective approach for detection of FH is cascade screening of family members. One index case can help detecting up-to 5 new cases of FH. Prevalence seen in cascade screening is around 50% in 1st degree relatives, 25% in 2nd degree relatives and 12.5% in 3rd degree relatives.

2.3 Diagnostic Criteria for Familial Hypercholesterolemia

There are currently three accepted resources for FH diagnosis: the Simon Broom Criteria, the MEDPED Criteria, and the FH Dutch Lipid Clinic Criteria. We recommend utilizing the Dutch Lipid Clinic Network (DLCN) method for clinical diagnosis of adult FH, which based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score attributed to each component; the higher the score, the higher the likelihood of the person having. If the DLCN score is >3, then the patient should be referred to a specialist. The DNA analysis used for research purposes when available. In addition to that, we accommodate also the diagnostic criteria of FH in children from Harada Shiba et al for more precision. Both incorporated in one table (table 1).

Table 1: Diagnostic criteria for adult FH and pediatric FH

Diagnostic Criteria for Adult FH from the Dutch Lipid Clinic Network	
Family history	**Score**
1. First-degree relative with premature coronary heart disease or	1
2. First-degree relative with LDL cholesterol >95th percentile by age and gender for country	1
3. First-degree relative with xanthoma and/or arcus cornealis or	2
4. Children <18 years with LDL cholesterol >95th percentile by age and gender for country	2
Clinical history	
1. Premature coronary heart disease	2
2. Premature cerebral or peripheral vascular disease	1
Physical examination	
1. Tendon xanthoma	6
2. Arcus cornealis <45 years	4
LDL cholesterol	
1. >8.5 mmol/l (>329 mg/dL)	8
2. 6.5-8.4 mmol/l (251-325 mg/dL)	5
3. 5.0-6.4 mmol/l (193-247 mg/dL)	3
4. 4.0-4.9 mmol/l (155-189 mg/dL)	1
DNA analysis	
1. Causative mutation in LDLR, APOB or PCSK9	8
Clinical diagnosis	
Definite	>8
Probable	6-8
Possible	3-5
Unlikely	<3
Diagnostic Criteria for Pediatric FH	
1. Hyper-LDL cholesterolemia: LDL-C level of ≥ 3.6 mmol/l (≥140 mg/dL) when untreated (If total cholesterol level is ≥ 5.7 mmol/l (≥ 220 mg/dL), measure the LDL-C level)	
2. Family history of FH or premature CAD (blood relative closer than the two parents)	
• Excluding secondary hyperlipidemia, if two items are satisfied, FH is diagnosed.	
• During the growth phase, there are fluctuations in LDL-C; therefore, careful observation is required.	
• In pediatric cases, there are few clinical symptoms such as xanthomatosis; therefore, it is important to investigate the family history for FH. Use the family survey results of those beyond the parents as a reference if necessary.	
• Early CAD is defined as CAD with an onset at < 55 years of age for males and < 65 years of age in females, respectively	
• If xanthoma is present, LDL-C is suspected to be extremely high (homozygote).	

Source: Adapted from Nordestgaard et al., 2018; Harada-Shiba et al., 2018

2.4 Management:

Multidisciplinary Team approach to manage patients with familial hypercholesterolemia is highly recommended as possible

The following clinical disciplines needs to see and follow FH patients to make decisions regarding recommended management plan:

1. Pediatric Endocrinology
2. Cardiology: for cardiac evaluation at baseline then every 6-12 months
3. Genetic: For genetic diagnosis, counseling, and cascade screening
4. Social worker
5. Clinical dietician for diet advice

2.4.1 Life style changes (Diet and Exercise help in 10-15% LDL-C reduction)

Low-fat diet has little effect in treatment of FH but still as a part of healthy lifestyle, it is part of FH management to prevent secondary increase in LDL-C. In addition to a low-fat diet, other healthy lifestyle choices include regular exercise and smoking cessation. Every patient should be encouraged to exert suitable and enough life style changed at the diagnosis and continue to do so ever after even with other modalities of treatments.

2.4.2 Statins: (35-55% LDL-C reduction)

Statins are the 1st line medication in treatment of hypercholesterolemia, both familial and non-familial and have proven efficacy in prevention and treatment of Atherosclerotic cardiovascular Disease) ASCVD.

There are many clinical trials on statin efficacy in primary and secondary prevention of coronary heart disease. A large meta-analysis showed that 21% reduction in coronary and stroke events occurs by lowering just by 1mmol/L of LDL-C and this also helps in reducing allcause mortality. Statins have variable efficacy and at maximum doses of simvastatin, atorvastatin, and rosuvastatin, reduce LDL-C 42%, 55% and 58% respectively. Another important point is that each step of doubling statin dose results in another 5-6% reduction in LDL-C and which showed reduction in CV diseases and all-cause mortality.

2.4.3 Ezetimibe: (18-25% LDL-C reduction)

A cholesterol absorption inhibitor, which work in the intestine to prevent cholesterol absorption. Even in HoFH, by Adding ezetimibe can lower LDL-C by 10–15%.

2.4.4 PCSK9 inhibitor: (40-65% LDL-C reduction)

This monoclonal antibody is new addition to arsenal for treatment of hypercholesterolemia.

It works only where some functional LDL receptors are present. So, it can work in HeFH and in some cases of HoFH with LDL residual activity .

Available medication in the formulary: Evolocumab

Privilege of prescription: only consultant Endocrinologist and Cardiologist

Eligible patients for this medication:

1- **HoFH (either by genetic testing or diagnostic score)**
2- **HeFH with established acute coronary syndrome (ACS)**

2.4.5 Indications of LDL apheresis (or lipoprotein apheresis):

1. HoFH
2. severe HeFH
3. pregnant FH patients.

LDL apheresis reduces the LDL-C by almost 70%. It is done fortnightly or once monthly for 2-3 hours depending on severity and response of patient. It is similar to dialysis except that the filter is different.

2.4.6 MTP inhibitor (microsomal triglyceride transfer protein) Lomitapide:

Lomitapide is an oral medication which is recommended only in cases of HoFH. In an open label trial, in addition to other oral medications and LDL apheresis, it helps in reducing LDL-C and apoB levels by up to 50% and Lp (a) by 15% at 26 weeks, with durable LDL-C lowering over a further 12 months follow up.

Privilege of prescription: only Adult and/or Pediatric consultant Endocrinologist.

2.4.7 Liver transplantation:

Liver transplantation works by bypassing the dysfunctional LDL receptors and replacing them with functional LDL receptors in transplanted liver, which helps in normalizing LDL metabolism. It is invasive but one of very effective treatment option reserved for HoFH. Although there are successful trials of liver transplantation to a HoFH patient, it is not recommended as treatment modalities due to massive complications except in a very limited indication.

2.4.8 Treatment Targets:

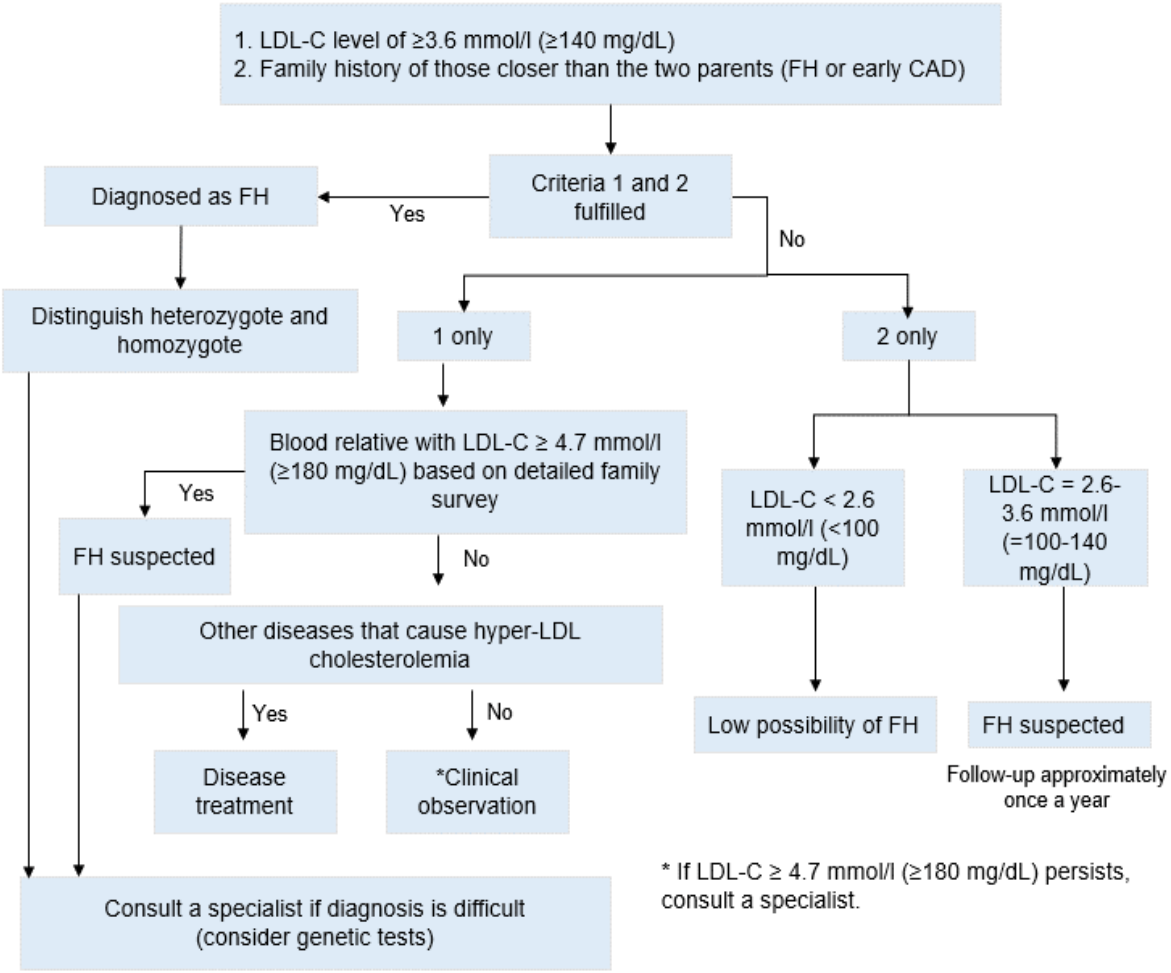
The NICE (national Institute of Health and Clinical Excellence) UK recommends that one should target LDL-C reduction of 50% and above from the baseline LDL-C in FH patients.

The European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) recommended in 2019 guidelines that FH patients with ASCVD should achieve an LDL-C reduction of more than 50% from baseline and LDL-C less than 1.4 mmol/L (55mg/dL). For Primary prevention in patients with FH without ASCVD but at very high risk, same targets as above should be considered. Target for FH without any other risk factors is 1.8 mmol/L (70mg/dL).The recommended target for FH children more than 10 years is LDL-C less than 3.5mmol/L (135mg/dL).

3. Approach to FH mitigation:

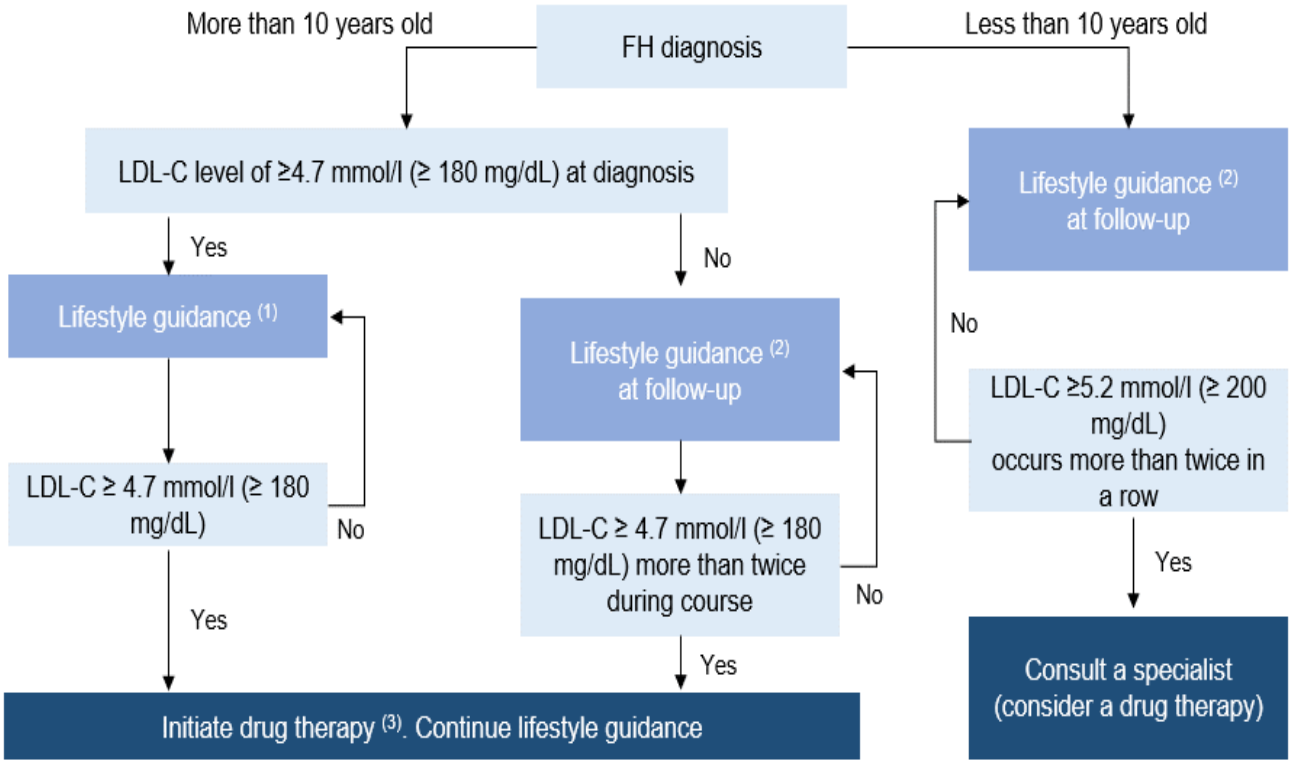
We agreed in our panel sessions to adopt the diagnostic approach algorithm as well as the algorithm of treatment approach reported by Harada shiba et al for pediatric age group, 2018. This guidance gives approach to the diagnosis of FH in children, when to consider referring to specialist, and how to mitigate the problem in the shadow of limited treatment varieties. For the adults 15 years and older we adopted the algorithm of treatment approach from Harada Shiba et al, 2018 for both heterozygous and homozygous Hypercholesterolemia, as shown below.

3.1 Diagnosis Algorithm for FH in children:



Source: Adapted from Harada-Shiba et al., 2017

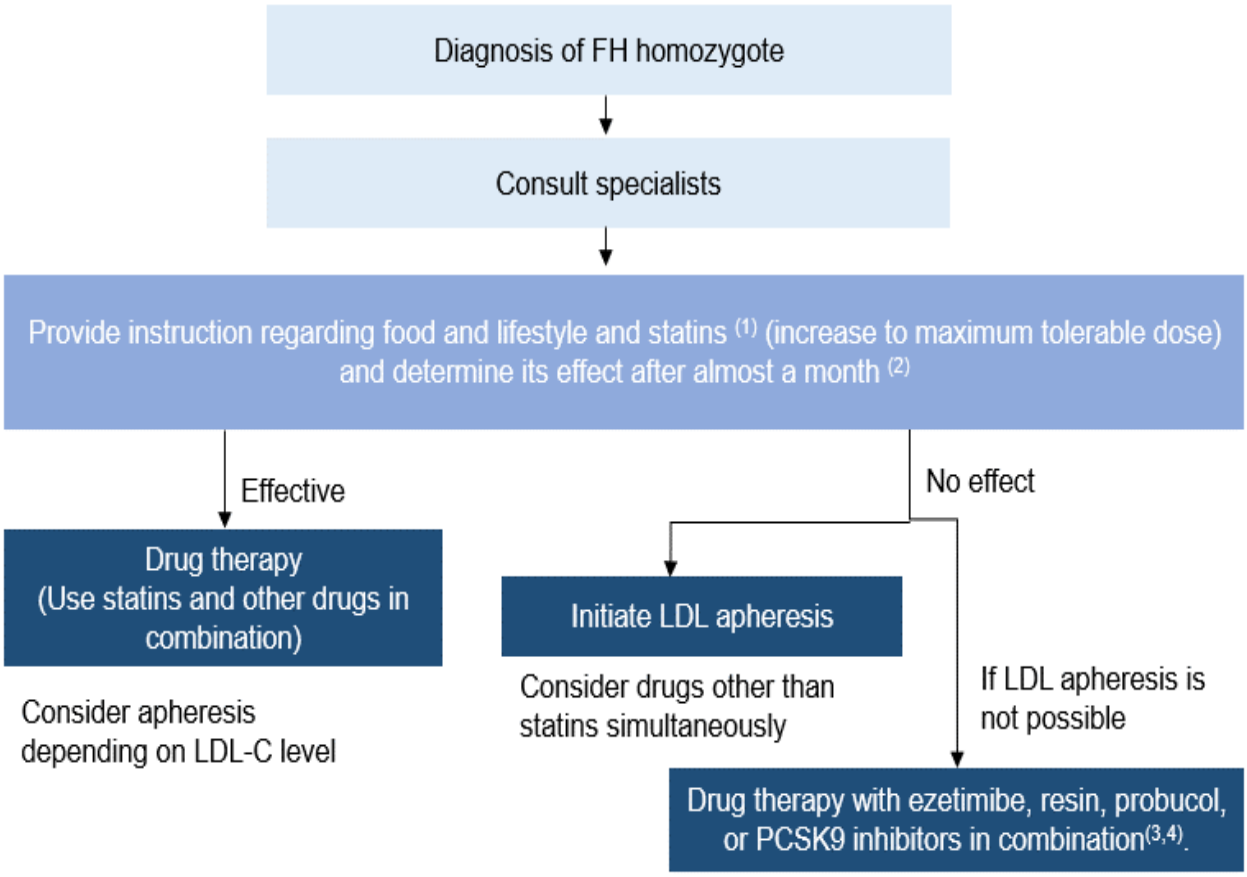
3.2 Treatment algorithm for heterozygous FH in children:



(1) Evaluate the LDL-C level after instruction of approximately a month. If the levels is < 4.7 mmol/l (<180 mg/dL), follow-up regularly.
(2) Continue lifestyle guidances and evaluate LDL-C levels thrice a year.
(3) First-choice drug should be statin. Start with a minimum dose. If there is complication of early CAD in the family history or diabetes, management target level of <3.6 mmol/l (<140 mg/dL) should be maintained.

Source: Adapted from Harada-Shiba et al., 2018

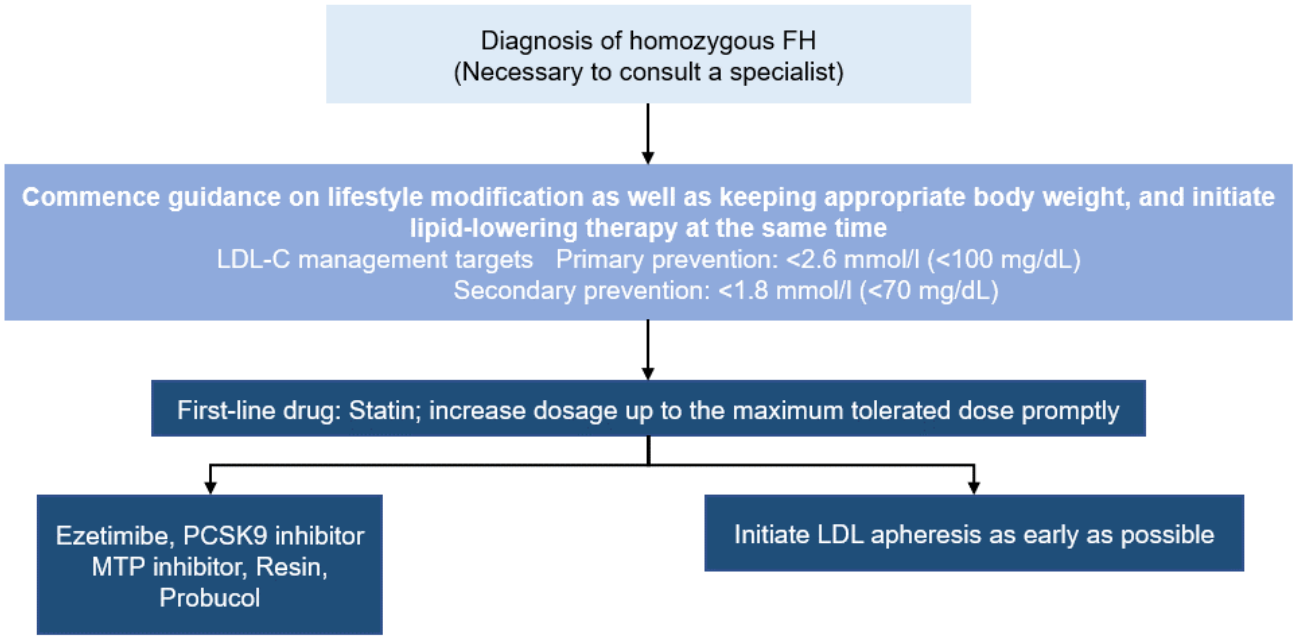
3.3 Treatment algorithm for homozygous FH in children:



(1) Strong statins are recommended.
(2) If LDL-C level reduces by approximately 25%, it is said to be effective and the drug therapy will need to be stabilized.
(3) PCSK9 inhibitors have not been used much in children aged <12 years. Discontinue if LDL-C levels do not reduce.
(4) MTP (Microsomal triglyceride transfer protein) inhibitors have not had their safety and efficacy confirmed in pediatric cases.

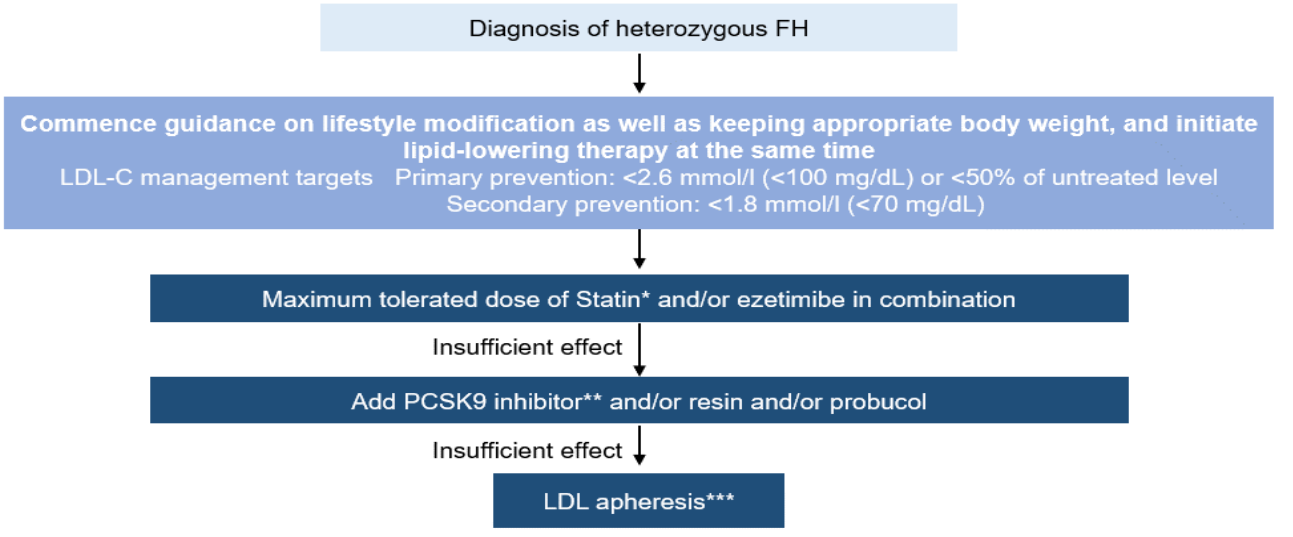
Source: Adapted from Harada-Shiba et al., 2018

3.4 Treatment algorithm for adult (15 years or over) homozygous FH:



Source: Adapted from Harada-Shiba et al., 2018

Figure 4: Treatment algorithm for adult (15 years or over) heterozygous FH



* In case of patient with statin intolerance, consider prescription of another statin or changing dosing interval and increase dose as much as possible
** Advisable to consult a specialist when initiating PCSK9 inhibitor
*** As PCSK9 inhibitor will be removed by LDL apheresis, injection should be administered after LDL apheresis

Source: Adapted from Harada-Shiba et al., 2018

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References:

1- Watts, G. F. et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation. Int J Cardiol 171, 309–325 (2014).
2- Wiegman et al. Eur Heart J 2015;10:157 2..
3- Slack J. Risks of ischemic heart disease in familial hyperlipoproteinemic states. Lancet 1969;2(7635):1380-2.
4- Goldstein JL et al. Familial hypercholesterolemia. In: Scriver Cet al. Editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001:2863-2913
5- Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment. Atherosclerosis 2012;223:262-8.
6- Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolemia 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. 34, 3478-90. (2013).
7- Hobbs, H. H., Brown, M. S. & Goldstein, J. L. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Human Mutation 1, 445–466 (1992).
8- Goldstein JL et al. Familial hypercholesterolemia. In: Scriver C et al. Editors. The Metabolic and Molecular Bases of Inherited Disease. 8th ed. New York: McGraw-Hill; 2001:2863–2913.
9- Marks D, Thorogood M, Neil HA et al. A review on the diagnosis, natural history, and treatment of familial hypercholesteremia. Atherosclerosis 2003;168: 1–14
10- Versmissen, et al. Efficacy of statins in familial hypercholesterolemia: a long-term cohort study. Bmj 2008; 337.
11- Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolemia from the International FH Foundation. International Journal of Cardiology 2013.
12- Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, et al. Homozygous familial hypercholesterolemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolemia of the European Atherosclerosis Society. Eur Heart J 2014;35(32)2146-57.
13- Brown MS, Goldstein JL, Receptor mediated control of cholesterol homeostasis. Science. 1986; 232 (4746): 34-47.
14- Wiegman A, Gidding SS, et al. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015; 36(36):2425-37.
15- Zuliani, G. et al. Characterization of a New Form of Inherited Hypercholesterolemia: Familial Recessive Hypercholesterolemia. Arteriosclerosis, Thrombosis, and Vascular Biology 19, 802–809 (1999).

16- Cenarro A, Etxabarria A, et al. The p.Leu167del mutation in APOE gene causes autosomal dominant hypercholesterolemia by down regulation of LDL receptor expression in hepatocytes. J Clin Endocrinol Metab. 2016; jc20153874.
17- Alves A, Etexbarria A, et al. Novel functional APOB mutation outside LDL binding region causing familial hypercholesterolemia. Hum Mol Genet. 2014; 23(7):1817-28.
18- Miserez R, Muller P, et al. Sterol regulatory element binding protein (SREBP)-2 contributes to polygenic hypercholesterolemia. Atherosclerosis. 2002;164(1):15-26.
19- Fouchier S, Dallinga-Thie G, et al. Mutations in STAP1 are associated with autosomal dominant hypercholesterolemia. Circ Res. 2014;115(6):552-5.
20- Humphries, S. et al. Genetic causes of familial hypercholesterolemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. Journal of medical genetics 43, 943–949 (2006).
21- Soutar, A. K. & Naoumova, R. P. Mechanisms of Disease: genetic causes of familial hypercholesterolemia. Nature Clinical Practice Cardiovascular Medicine 4, 214–225 (2007).
22- Alharbi KK, Kashour TS, Al-Hussaini W, Al-Nbaheen M, Mohamed S, Hasanato RM, et al. Association of angiotensin converting enzyme gene insertion/deletion polymorphism and familial hypercholesterolemia in the Saudi population Lipids Health Dis [Internet] 2013; 12(1): 177.
23- Al-Allaf FA, Athar M, Abduljaleel Z, Bouazzaoui A, Taher MM, Own R, et al. Identification of a novel nonsense variant c1332dup, p(D445*) in the LDLR gene that causes familial hypercholesterolemia Hum genome Var. 2014. 1:14021.
24- Alharbi KK, Kashour TS, Al-Hussaini W, et al. Screening for genetic mutations in LDLR gene with familial hypercholesterolemia patients in the Saudi population. Acta Biochim Pol 2015; 62(3): 559-62.
25- Al-Allaf FA, Athar M, Abduljaleel Z, et al. Next generation sequencing to identify novel genetic variants causative of autosomal dominant familial hypercholesterolemia associated with increased risk of coronary heart disease. Gene 2015; 565(1): 76-84.
26- Al-Allaf FA, Alashwal A, Abduljaleel Z, Taher MM, Siddiqui SS, Bouazzaoui A. Identification of a recurrent frameshift mutation at the LDLR exon 14 (c2027delG, p(G676Afs*33)) causing familial hypercholesterolemia in Saudi Arab homozygous children Genomics 2016; 107(1): 24-32.
27- Al-Allaf FA, Alashwal A, Abduljaleel Z, Taher MM, Bouazzaoui A, Abalkhail H, et al. Compound heterozygous LDLR variant in severely affected familial hypercholesterolemia patient. Acta Biochim Pol 2016.
28- Nordestgaard, B. G. Genetic testing for familial Hypercholesterolemia is essential in individuals withhigh LDl cholesterol: who does it in the world? Eur. Heart J. 38, 1580-1583 (2017).
29- Hobbs, H. H., Brown, M. S. & Goldstein, J. L. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Human Mutation 1, 445–466 (1992).

30- Sjouke, B. et al. Homozygous autosomal dominant hypercholesterolemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. European heart journal 36, 560 (2015).
31- Miller, P. E. et al. Screening and advanced lipid phenotyping in familial hypercholesterolemia: The Very Large Database of Lipids Study- 17 (VLDL-17). J. Clin. Lipidol. 9, 676-683 (2015).
32- Varvel, S. A. et al. Familial hypercholesterolemia prevalence of 1.5% in a clinical database of 542,214 patients: refined risk stratification using apoB: LDL-C ratio. J. Clin. Lipidol. 9. 103 (2015).
33- Walter, K. et al. The UK 10K project identifies rare variants in health and disease. Nature 526, 82–90 (2015).
34- Wald, D. S. et al. Child–Parent Familial Hypercholesterolemia Screening in Primary Care. New England Journal of Medicine 375, 1628–1637 (2016).
35- Benn, M., Watts, G. F., Tybjaerg-Hansen, A. & Nordestgaard, B. G. Familial Hypercholesterolemia in the Danish General Population: Prevalence, Coronary Artery Disease, and Cholesterol-Lowering Medication. The Journal of Clinical Endocrinology & Metabolism 97, 3956–3964 (2012).
36- Leitersdorf, E., V der Westhuyzen, D., Coetzee, G. & Hobbs, H. Two common low-density lipoprotein receptor gene mutations cause familial hypercholesterolemia in Afrikaners. Journal of Clinical Investigation 84, 954 (1989).
37- Steyn, K. et al. Estimation of the prevalence of familial hypercholesterolemia in rural Afrikaner community by direct screening for three Afrikaner founder low density lipoprotein receptor gene mutations. Hum. Genet. 98, 479-484 (1996)
38- Marais, A. D., Firth, J.C. &Blom, D.J. Familial hypercholesterolemia in South Africa. Semin. Vasc. Med. 4. 93-95 (2004).
39- Der Kaloustian, V. M., Naffah, J. &Loiselet, J. Genetic diseases in Lebanon. Am. J. Med. Genet. 7, 187-203 (1980).
40- Moorjani, S. et al. Homozygous familial hypercholesterolemia among French Canadians in Québec province. Arteriosclerosis, Thrombosis, and Vascular Biology 9, 211–216 (1989).
41- Nordestgaard, B. G. et al. Familial hypercholesterolemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of European Atherosclerosis Society. Eur. Heart J. 34, 3478-3490 (2013).
42- Sjouke, B. et al. Homozygous autosomal dominant hypercholesterolemia in the Netherlands: prevalence, genotype–phenotype relationship, and clinical outcome. European heart journal 36, 560 (2015).
43- Shi, Z. et al. Familial Hypercholesterolemia in China: prevalence and evidence of under detection and undertreatment in community population. Intl J. Cardiol. 174, 834-836 (2014).

44- Watts, G. F. et al. Prevalence and treatment of familial hypercholesterolemia in Australian communities. Intl J. Cardiol. 185, 69-71 (2015).
45- Do, R. et al. Prevalence and management of familial hypercholesterolemia in coronary patients: an analysis of EUROASPIRE IV, as study of the European Society of Cardiology. Atherosclerosis 241, 169-175 (2015).
46- Faisal Alallaf, Fatima Amanulla et al. The Spectrum of Familial Hypercholesterolemia (FH) in Saudi Arabia: Prime Time for Patient FH Registry. The Open Cardiovascular Medicine Journal, 2017, 11, 66-7.
47- Batais MA, Almigbal TH, Bin Abdulhak AA, Altaradi HB, AlHabib KF (2017) Assessment of physicians' awareness and knowledge of familial hypercholesterolemia in Saudi Arabia: Is there a gap? PLoS. ONE 12(8): e0183494. https://doi.org/ 10.1371/journal.pone.0183494.
48- Defesche JC, Lansberg PJ, et al. Advanced method for the identification of patients with inherited hypercholesterolemia. Semin Vasc Med. 2004;4(1):59-65.
49- Henderson R, O'Kane M, McGilligan V, Watterson S. The genetics and screening of familial hypercholesterolemia. J Biomed Sci 2016; 23: 39.
50- Scientific Steering Committee on behalf of the Simon Broome Register Group. Risk of fatal coronary heart disease in familial hypercholesterolemia. BMJ. 1991; 303(6807): 893-6.
51- Hsia SH,Connelly PW, et al. Genetic screening protocol for familial hypercholesterolemia in affected relatives using pedigree tracing. Clin Biochem. 1996;29(4):371-7
52- Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolemia 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(45): 3478-568.
53- Bruckert E. Recommendations for the management of patients with homozygous familial hypercholesterolemia: overview of a new European Atherosclerosis Society consensus statement. Atheroscler Suppl 2014; 15(2): 26-32.
54- Weng SF, Kai J, et al. Improving identification of familial hypercholesterolemia in primary care: Derivation and validation of familial hypercholesterolemia case ascertainment tool (FAMCAT). Atherosclerosis. 2015;238(2):236-43.
55- Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolemia 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. 34, 3478-90. (2013).
56- Gidding, S. S. et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation132, 2167-92 (2015).
57- Consensus statement of the EAS. Eur Heart J.2013 Dec. 34; (45): 3478-90.

58- Benn M et al. European Heart Journal (2016) 37, 1384–1394.
59- Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005; 366: 1267-78.
60- Law MR, Wald NJ, Rudnicka AR. Quantifying effects of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326: 1423-30.
61- Statins have proven efficacy in patients with HoFH also, even in those patients with receptor-negative
62- Raal FJ, Pilcher GJ, Illingworth DR, Pappu AS, Stein EA, Laskarzewski P, Mitchel YB, Melino MR. Expanded-dose simvastatin is effective in homozygous familial hypercholesterolemia. Atherosclerosis 1997; 135:244–256.
63- Raal FJ, Pappu AS, Illingworth DR, Pilcher GJ, Marais AD, Firth JC, Kotze MJ, Heinonen TM, Black DM. Inhibition of cholesterol synthesis by atorvastatin in homozygous familial hypercholesterolemia. Atherosclerosis 2000; 150:421–428.
64- Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Palmer M, Wilpshaarf W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolemia. Atherosclerosis 2008; 197:400–406.
65- Marais AD, Blom DJ, Firth JC. Statins in homozygous familial hypercholesterolemia. Curr Atheroscler Rep 2002;4: 19–25.
66- Yamamoto A, Harada-Shiba M, Kawaguchi A, Oi K, Kubo H, Sakai S, Mikami Y, Imai T, Ito T, Kato H, Endo M, Sato I, Suzuki Y, Hori H. The effect of atorvastatin on serum lipids and lipoproteins in patients with homozyous familial hypercholesterolemia undergoing LDL-apheresis therapy. Atherosclerosis 2000; 153:89–98.
67- Raal FJ, Pilcher G, Panz VR, van Deventer HE, Brice BC, Blom DJ, Marais AD. Reduction in mortality in subjects with homozygous familial hypercholesterolemia asso- ciated with advances in lipid-lowering therapy. Circulation 2011;124: 2202–2207.
68- Pahan K. Lipid-lowering drugs Cell Mol Life Sci 2006.
69- Familial hypercholesterolaemia: identification and management | Guidance and guidelines 27 August 2008.
70- Couture P, Lamarche B. Ezetimibe and bile acid sequestrants: impact on lipoprotein metabolism and beyond. Curr Opin Lipidol 2013; 24(3): 227-32.
71- Gagne C, Gaudet D, Bruckert E. Efficacy and safety of ezetimibe co-administered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002;105: 2469–2475.
72- Mullard A. 2013 FDA drug approvals. Nat Rev Drug Discov 2014; 13(2): 85-95
73- Sabatine MS, et al. "Evolocumab and clinical outcomes in patients with cardiovascular disease". *The New England Journal of Medicine*. 2017. epub 2017-03-17:1-10.

74- Sabina A. Murphy, Terje R. Pedersen, Zbigniew A. Gaciong et al. Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events in Patients with Cardiovascular Disease. A Prespecified Analysis from the FOURIER Trial. *JAMA Cardiol.* 2019;4(7):613-619.

75- Thompson GR, Barbir M, Davies D, Dobral P, Gesinde M, Livingston M, Mandry P, Matthews S, Neuwirth C, Pottle A, le Roux C, Scullard D, Stokes G, Tyler C, Watkins S. Recommendations for the use of LDL apheresis. Atherosclerosis 2008; 98:247–255.

76- Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, RossJ L, Ziajka PE; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5: S1–S8.

77- 40. Harada-Shiba M, Arai H, Oikawa S, Ohta T, Okamura T, Nohara A, BujoH, Yokote K, Wakatsuki A, Ishibashi S, Yamashita S. Guidelines for the management of familial hypercholesterolemia. J Atheroscler Thromb 2012;19: 1043–1060.

78- 42. Stefanutti C, Julius U. Lipoprotein apheresis: state of the art and novelties. Atheroscler Suppl 2013;14: 19–27.

79- Taylan C, Schlune A, Meissner T. A??ukaitis K, Udink ten Cate FEA, Weber LT. Disease control via intensified lipoprotein apheresis in three siblings with familial hypercholesterolemia. J Clin Lipidol 2016.

80- Hussain MM, Rava P, Walsh M, Rana M, Iqbal J. Multiple functions of microsomal triglyceride transfer protein. Nutr Metab (Lond) 2012;9:14.

81- Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du PlessisAM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ; Phase3 HoFH Lomitapide Study investigators. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolemia: a single-arm, open-label, phase 3 study. Lancet 2013;381: 40–46.

82- Crooke ST, Geary RS. Clinical pharmacological properties of mipomersen (Kynamro), a second-generation anti sense inhibitor of apolipoprotein B. Br J Clin Pharmacol 2013;76:269–276.

83- Raal FJ, Santos RD, Blom DJ, Marais AD, Charng MJ, Cromwell WC, Lachmann RH, Gaudet D, Tan JL, Chasan-Taber S, Tribble DL, Flaim JD, Crooke ST. Mipomersen, an apolipoprotein B synthesis inhibitor,for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolemia: a randomized double-blind, placebo-controlled trial. Lancet 2010;375: 998–1006.

84- Tonkin AM, Watts GF, Blom D, Rader D, Stein E. Into the future: diversifying lipid management Lancet (London, England) 2012; 380(9858): 1971-4.

85- Maiorana A, Nobili V, Calandra S, Francalanci P, Bernabei S, El Hachem M, Monti L, GennariF, Torre G, deVillede Goyet J, Bartuli A. Pre-emptive liver transplantation in a child with familial hypercholesterolemia. Pediatr Transplant 2011;15: E25–E29.

86- Ibrahim M, El-HamamsyI, Barbir M,Yacoub MH. Translational lessons from a case of combined heart and liver transplantation for familial hypercholesterolemia 20 years post-operatively. J Cardiovasc Transl Res 2012;5:351–358.

87- KucukkartallarT,KanmazT,TopaloglуS,AcarliK,KalayogluM. Liver transplantation as a treatment option for three siblings with homozygous familial hyper-cholesterolemia. Pediatr Transplant 2011;15:281–284. 50. MalatackJJ.Livertransplantationastreatmentforfamilialhomozygoushypercholes-terolemia: too early or too late. Pediatr Transplant 2011;15:123–125.

88- Page MM, Ekinci EI, Jones RM, Angus PW, Gow PJ, O'Brien RC. Liver transplantation for the treatment of homozygous familial hypercholesterolemia in an era of emerging lipid-lowering therapies. Intern Med J 2014; 44(6): 601-4.

89- Khalifeh M, Faraj W, Heaton N, Rela M, Sharara AI. Successful living-related liver transplantation for familial hypercholesterolemia in the Middle East. Transpl Int 2005; 17(11): 735-9.

90- National Institute of Health and Clinical Excellence (NICE). Familial hypercholesterolemia- costing report: Implementing NICE guidance. 2009. Pp. 1-42. http://www.nice.org.uk/guidance/cg71/resources/familial-hypercholesterolemia-costing-report2.

91- Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2019. Doi: 10. 1093/eurheartj/ehz455.