

## Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel

Abdullah Al-Ashwal<sup>1</sup>, Fahad Alnouri<sup>2</sup>, Hani Sabbour<sup>3</sup>, Abdulraof Al-Mahfouz<sup>4</sup>, Nasreen Al-Sayed<sup>5</sup>, Maryam Razzaghy-Azar<sup>6</sup>, Faisal Al-Allaf<sup>7</sup>, Khalid Al-Waili<sup>8</sup>, Yajnavalka Banerjee<sup>9</sup>, Jacques Genest<sup>10</sup>, Raul D. Santos<sup>11</sup> and Khalid Al-Rasadi<sup>8,\*</sup>



<sup>1</sup>Medical & Clinical Affairs, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; <sup>2</sup>Head of Cardiovascular Prevention, Rehabilitation and Patients Education Unit, Prince Sultan Cardiac Center, Riyadh, Saudi Arabia; <sup>3</sup>Consultant Cardiologist, Sheikh Khalifa Medical City, Abu Dhabi, UAE; <sup>4</sup>Head Section of Endocrinology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia; <sup>5</sup>Medical Director, Gulf Diabetes Specialist Center, Manama, Bahrain; <sup>6</sup>Tehran University of Medical Sciences, Tehran, Iran; <sup>7</sup>Department of Medical Genetics, Faculty of Medicine, Umm Al-Qura University, Makkah 21955, Saudi Arabia; <sup>8</sup>Department of Biochemistry, Sultan Qaboos University hospital, Muscat, Oman; <sup>9</sup>Department of Biochemistry, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman; <sup>10</sup>Faculty of Medicine, McGill University, Montreal, Quebec, Canada; <sup>11</sup>Cardiology, Lipid Clinic Heart Institute, University of Sao Paulo, Sao Paulo, Brazil



Khalid Al-Rasadi

**Abstract:** We present clinical practice guidelines for the diagnosis and treatment of homozygous familial hypercholesterolaemia (HoFH) in the Middle East region. While guidelines are broadly applicable in Europe, in the Middle East we experience a range of confounding factors that complicate disease management to a point whereby the European guidance cannot be applied without significant modification. Specifically, for disease prevalence, the Middle East region has an established epidemic of diabetes and metabolic syndrome that can complicate treatment and mask a clinical diagnosis of HoFH. We have also a high incidence of consanguineous marriages, which increase the risk of transmission of recessive and homozygous genetic disorders. This risk is further augmented in autosomal dominant disorders such as familial hypercholesterolaemia (FH), in which a range of defective genes can be transmitted, all of which contribute to the phenotypic expression of the disease. In terms of treatment, we do not have access to lipoprotein apheresis on the same scale as in Europe, and there remains a significant reliance on statins, ezetimibe and the older plasma exchange methods. Additionally, we do not have widespread access to anti-apolipoprotein B therapies and microsomal transfer protein inhibitors. In order to adapt existing global guidance documents on HoFH to the Middle East region, we convened a panel of experts from Oman, Saudi Arabia, UAE, Iran and Bahrain to draft a regional guidance document for HoFH. We also included selected experts from outside the region. This panel statement will form the foundation of a detailed appraisal of the current FH management in the Middle Eastern population and thereby provide a suitable set of guidelines tailored for the region.

**Keywords:** Homozygous familial hypercholesterolaemia, prevalence, diagnosis, treatment, genetics.

### INTRODUCTION

In the states of The Gulf Co-operation Council (GCC), cardiovascular disease (CVD) is the most common cause of death, accounting for up to 45% of all deaths [1]. The INTERHEART study showed that CVD risk factors like dyslipidaemia and smoking were prevalent in young populations in the region with a mean age of the first presentation of acute myocardial infarction (MI) 10 years younger in the Middle East countries than in other regions [2].

The Gulf Registry of Acute Coronary Events (Gulf RACE)-2 study showed that the Middle East also has a poor

record with treatment of elderly-at risk CVD patients, and that adherence to clinical practice guidelines could be much improved [3]. Recently, the Gulf Locals with Acute Coronary Syndrome Events Registry (Gulf COAST), including 3,188 regional patients admitted with a diagnosis of acute coronary syndrome (ACS) found that the Gulf ACS population is characterised as young with a very high-risk profile [4]. The projected future burden of CVD in the Middle East is set to exceed that of other global regions [5]. Therefore, conditions that overtly raise cardiovascular (CV) risk are of particular interest in the region, and clinical practice guidelines are needed.

Homozygous familial hypercholesterolaemia (HoFH) is a rare and serious genetic condition characterised by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels, and often (but not universally) cutaneous and tendon xan-

\*Address correspondence to this author at the Department of Clinical Biochemistry, Sultan Qaboos University Hospital, Muscat, Sultanate of Oman; Tel: +968 9678 0908; E-mail: [khalid77@squ.edu.om](mailto:khalid77@squ.edu.om)

thomas and/or corneal arcus caused by deposition of excess cholesterol [6, 7]. If untreated, most HoFH patients will develop overt atherosclerosis before the age of 20 years and are unlikely to survive the past 30 years [6]. In addition to atherosclerotic complications, HoFH patients can also develop aortic and supra aortic valve stenosis, conditions that significantly increase morbidity and mortality [7].

HoFH was originally characterised by its clinical features: plasma cholesterol levels  $>13$  mmol/L ( $>500$  mg/dL), extensive xanthomas, and premature progressive atherosclerotic CVD. Studies in cultured fibroblasts showed that patients with these clinical features had a severe impairment in their ability to bind and internalise LDL particles. Subsequently, this defect was shown to result from mutations in both alleles of the LDL receptor (LDLR) gene [6]. However, findings of recent studies suggest that HoFH can also be a result of mutations in other genes such as the apolipoprotein B (apo B) gene or the proprotein converting subtilisin/kexin type 9 (PCSK-9) gene [8] indicating that the disease is genetically heterogeneous.

### Prevalence of HoFH

HoFH is a highly under-recognised condition. In Oman where data are available, HoFH detection rates have been estimated at below 1% of the total population of patients likely to have the disease [9]. However, estimating diagnosis rates and prevalence is difficult. Data on the prevalence of HoFH in the Middle East are lacking, and there are no national registries currently collecting data. Therefore, we must rely mainly on data from outside the region to estimate prevalence and then apply some adjustment to acknowledge the unique family structures in the Middle East. In the past, the overall prevalence of HoFH was estimated to be around 1 in 1 million [6], but recent studies, particularly from The Netherlands, suggest that it may affect as many as 1 in 160,000-300,000 people [9, 10]. For the Middle East, HoFH may have a higher prevalence than in the Western world because consanguineous marriages are more common than in the West [11].

Rough estimates can be made by looking at the numbers of HoFH patients in key hospitals in the region. At the time of writing, the Sultan Qaboos University Hospital, Muscat, Oman, had 5 HoFH patients [12, 13]. If we take the population of Oman as 3.6 million persons, acknowledge 12 Omani hospitals capable of identifying and referring HoFH, and then consider that there may be other hospitals with unreported HoFH cases, then at least the Omani prevalence of HoFH will be higher than the historical estimates of 1 in 1 million. Published data from other countries are needed to complete the picture, and efforts are underway with a research group in the Middle East that includes the Oman Society of Lipid and Atherosclerosis (OSLA) to explore HoFH prevalence.

### The Importance of HoFH Awareness

The true prevalence of HoFH is important. Cardiologists, dermatologists, paediatricians, endocrinologists, plastic surgeons and general practitioners need to understand that they may well see a case during their clinical career. They need to be educated and equipped in terms of clinical criteria to rec-

ognise and respond to a case. In the Middle East in particular, there is an epidemic of type 2 diabetes mellitus (T2DM) [14]. This presents a particular problem for the diagnosis of HoFH in that patients who present with premature CVD typical of HoFH may be considered as diabetic or metabolic syndrome cases in the first instance, and hence not undergo appropriate lipid profiling and onward specialist referral. For example, along with high LDL-C levels, HoFH patients may present with high triglyceride levels, which may direct the clinician towards a diagnosis of metabolic syndrome. In contrast to all other hyperlipidaemias in which obesity, hypertension and T2DM are highly prevalent, these conditions are generally uncommon in FH [15]. If a delayed or wrong diagnosis is made, then a non-response to lipid-lowering therapies should trigger a re-evaluation for HoFH, including a detailed assessment of the family history.

### THE ORIGINS OF THE MIDDLE EAST PANEL

A recently published position paper from a consensus panel of the European Atherosclerosis Society (EAS) has highlighted the need for early identification of patients with HoFH, and the importance of prompt referral to specialist centres to enable appropriate treatment to be initiated as early as possible [8]. These recommendations are a useful guide to the diagnosis and treatment of HoFH. However, for the Middle East, there are clinical, genetic and practical factors specific to the region that need to be taken into account before we can apply the principles of the EAS guidelines. The Middle Eastern HoFH guidelines panel of regional HoFH experts was convened to discuss existing guidance on HoFH and to evaluate the considerations that need to be made to identify and treat the disease in Middle-Eastern hospitals and clinics.

### DIAGNOSIS OF HoFH

Recent European guidelines suggest that diagnosis can be made on the basis of LDL-C levels, physical signs, family history and, where available, genetic confirmation [8].

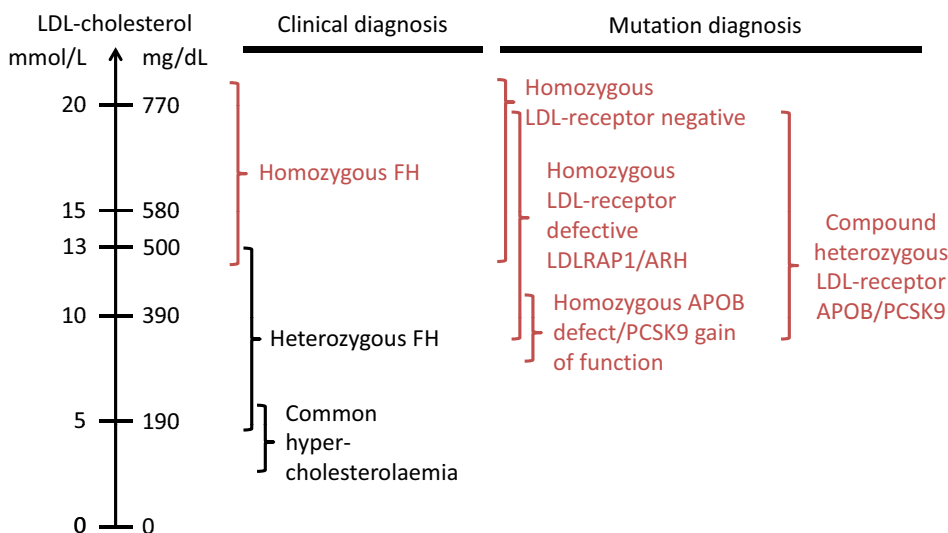
At present, it is understood that the diagnosis rate of HoFH in the Middle East is very low [16], which is a concern given the particular circumstances that put the population at elevated risk of inheriting the disease.

### LDL-C

Historically, HoFH has mostly been diagnosed on the basis of clinical and metabolic characteristics. Patients with HoFH have markedly elevated LDL-C levels [6, 7]. Importantly, the range of LDL-C levels observed in patients with HoFH is quite broad and can overlap with ranges found in other types of hypercholesterolaemia (Fig. 1) [8].

Typically HoFH can be suspected if a patient presents with an untreated LDL-C  $>13$  mmol/L (500 mg/dL) or treated LDL-C  $>8$  mmol/L (300 mg/dL) [8]. Recent data from clinical trials indicate that in some instances LDL-C levels may be as low as 4 mmol/L (155 mg/dL), so even in patients without classically high LDL-C, a diagnosis of HoFH can still be made [10].

Al-Rasadi *et al.* have published diagnosis criteria for the Omani FH population, which suggest using the Simon



**Fig. (1).** Low-density lipoprotein cholesterol (LDL-C) ranges in patients with familial hypercholesterolaemia (FH). Reproduced from Cuchel *et al.* *Eur Heart J* 2014; 35: 2146-57 [8], under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).

Broome criteria [17]. These criteria suggest diagnosis of FH at total cholesterol (TC) above 7.5 (290 mg/dL) or LDL-C levels >4.9 mmol/L (190 mg/dL) in adults and TC >6.7 mmol/L or LDL-C >4.0 mmol/L in children under 16 years, combined in both cases with a confirmed family history compatible with the diagnosis of FH [18]. However, these criteria are not specific to HoFH and should not be used in the HoFH setting. Similarly, guidance from the Dutch Lipid Clinic Network [9] and the Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria (USA) [19] use clinical parameters beyond LDL-C, but are also not specific to HoFH.

### Xanthomas

The high levels of cholesterol to which HoFH patients are exposed from birth, lead to accumulation of cholesterol in tendons, cutaneous tissues and cardiovascular tissues usually earlier than 10 years of age [7]. Thus, in addition to highly elevated LDL-C levels, other clinical characteristics of HoFH include early onset cutaneous and tendon xanthomas (Fig. 2), corneal arcus, widespread and severe atherosclerosis, aortic and supra aortic valve disease as well as early onset coronary heart disease [7].

Although xanthoma are a classic clinical sign of HoFH and are included in international guidelines for HoFH management, their appearance is not universal; therefore their absence does not preclude an HoFH diagnosis. Importantly, these xanthomas lead many HoFH patients to present in the first instance to dermatologists or plastic surgeons, thereby providing opportunities for prompt diagnosis.

### Family History

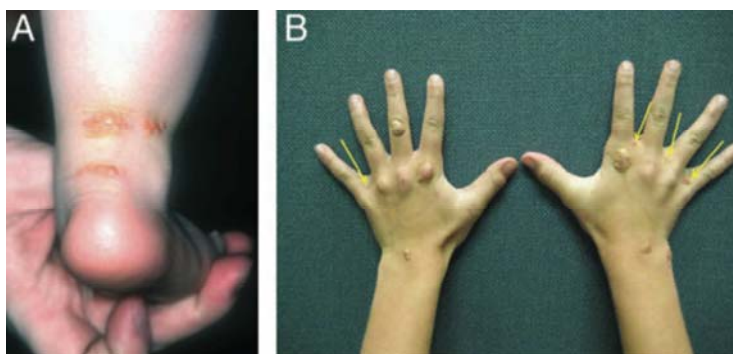
Family history can provide additional clues to aid the diagnosis of HoFH. Factors that can be taken into account include myocardial infarction at age ≤60 years in a first-degree relative (or ≤50 years in a second-degree relative), xanthoma, persistent and treatment-resistant elevated LDL-C

levels, and genetically confirmed heterozygous FH (HeFH) or HoFH. In the Middle East, tracing family histories may be easier than in some other regions because family trees are more clearly defined, and many individuals undergo medical examination as part of the requirements for marriage. Where there is a confirmed family history of FH, pre-natal counselling should be provided to ensure that prospective parents understand the likelihood of producing offspring with HoFH, and the risks and burdens that the disease can bring. As such, diagnostic teams should also establish if the parents of a patient are related. People marrying within a small town or village (*i.e.* a small genetic pool) create what is termed a ‘founder effect’ – a term derived from founding settlers of new communities (*e.g.* white South Africans), who multiplied within their own gene pool [20, 21].

### Genetic Testing

In cases where the LDL-C level is extremely high, a clinical diagnosis of HoFH can be quite clear cut. However, at the lower ranges, the situation is less certain, and genetic testing is important for an unequivocal FH diagnosis. The application of genetic testing for HoFH across the world is variable. Genetic testing is widespread in Europe, and relatively uncommon in the United States. In the Middle East, genetic testing is available in a limited number of specialist centres or referral units. Some units out-source genetic testing to Europe.

Once a case is identified, the testing centre will usually direct the genetic testing of siblings and parents. In some countries (*e.g.* The Netherlands and the UK), a positive genetic test triggers ‘cascade screening’ where all living relatives (parents, siblings, cousins, uncles, aunts *etc.*) are tested for FH-related mutations [22]. In the Middle East, cascade screening is not routinely performed, and is usually reserved for very severe HoFH cases. Application of cascade screening in the region is impeded by a complicated hospital system in which there are marked differences in treatment patterns and availability between military and non-military hospitals [23].



**Fig. (2).** Tendon xanthomas characteristic of homozygous familial hypercholesterolaemia (HoFH). Cutaneous and tuberous xanthomas in homozygous familial hypercholesterolaemia. Original photographs by Prof. Eric Bruckert and Prof. Frederick Raal. Reproduced from Cuchel *et al.* *Eur Heart J* 2014; 35: 2146-57 [8], under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).

Although genetic testing may provide a definitive diagnosis of HoFH, in some patients extensive testing may fail to yield genetic confirmation [6, 7]. This is because up to 20% of clinically defined FH patients will have a mutation that has not yet been identified [24]. HoFH is most commonly caused by mutations in both alleles of the LDLR gene, in individuals with parents who each have heterozygous FH. However, recently, mutations in genes coding for apo B, PCSK9 and LDL receptor adapter protein 1 (LDLRAP1), have been identified as causal in some patients with a severe phenotype resembling HoFH [8, 13, 25].

HoFH patients may be ‘true homozygotes’, with the same mutation in both alleles of the same gene, or ‘compound heterozygotes’ with different mutations in the two alleles of the same gene. Patients may also carry mutations in two different genes affecting LDL receptor function (Fig. 3). The severity of the mutation is a major factor governing the severity of the phenotype. Patients with mutations resulting in defective LDL-R usually have less elevated LDL-C than patients with mutations resulting in a complete absence of LDL-R activity [8]. Generally, the pattern of mean LDL-C levels by genotype increase as follows: HeFH < double heterozygote (*e.g.* LDL+PCSK9 gain-of-function or apo B mutation) < homozygous apo B or PCSK9 gain-of-function mutation < homozygous LDLRAP1 or LDLR-defective mutations < compound heterozygote LDLR-defective+LDLR-negative mutations < homozygous LDLR-negative mutations [8].

However, there is considerable overlap in the observed untreated LDL-C levels according to genotype [10], so an individual compound heterozygote for *LDLR*, for example, may have very severe hypercholesterolaemia, and equally, a simple *LDLR* homozygote may have lower untreated LDL-C levels. In many instances, a patient with a negative genetic test for HoFH may still have homozygous mutations, but these mutations have not been identified within the current panel of known HoFH-associated mutations. Therefore, if the spectrum of mutations causing FH in a certain population is not known/identified, genetic testing, while valuable, cannot yet be considered a 100% reliable means of identifying HoFH patients in such patients. Next-generation sequencing techniques may alleviate or eradicate this limitation.

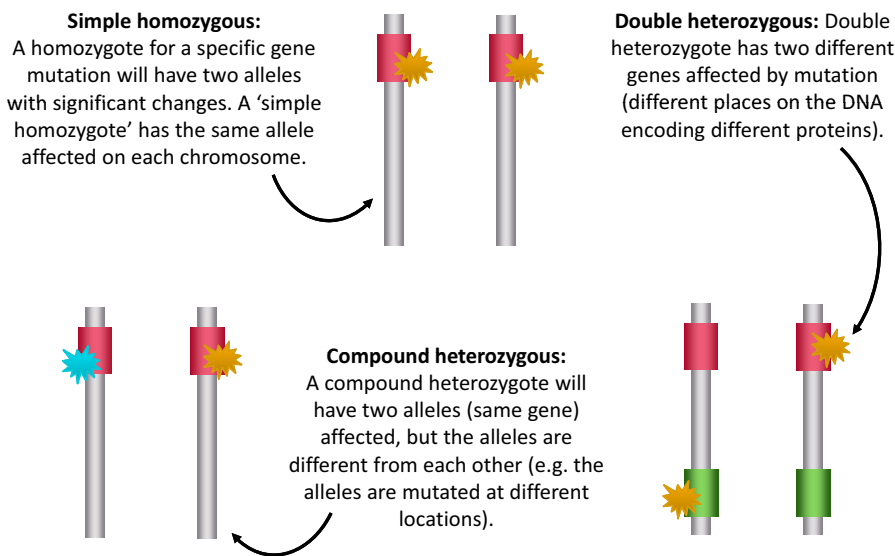
Genetic testing, where available still needs to be accompanied by comprehensive clinical and family history profiles [24]. A positive genetic test is definitive for HoFH. It is possible that cascade testing in the immediate family of an index patient may be made easier if the index mutation is known, and if the most common mutations in the Middle East region could be profiled.

Another disorder of lipid metabolism, sitosterolaemia (or phytosterolaemia), may have a similar clinical presentation to HoFH. A definitive diagnosis of sitosterolaemia can be confirmed by genetic analysis. In common with HoFH, any genetically determined metabolic disorder is likely to be more common in regions with lower genetic admixture than those with very few consanguineous marriages [26].

### Summary and Recommendations

Our recommendations for diagnosis of HoFH are similar to those set out in the European guidelines (Table 1) [8].

- HoFH can be suspected if LDL-C levels are >13 mmol/L (500 mg/dL) in untreated patients, or >8 mmol/L (300 mg/dL) in treated patients.
- Confirmation of diagnosis can be made if the elevated LDL-C is accompanied by either cutaneous or tendon xanthomas before the age of 10 years, or untreated elevated LDL-C levels consistent with HeFH in both parents.
- Genetic testing can independently confirm the diagnosis of HoFH, but a negative result does not rule out the possibility of FH.
- Detection rates for HoFH in the Middle East are low, and efforts must be made by the preventative cardiology and lipidology communities to educate dermatologists, general practitioners, plastic surgeons and cardiologists on the true prevalence and recognition of the disease.
- Genetic counselling should be given to couples where there is a risk of HoFH in their offspring, and patients should be advised to limit the number of pregnancies for reasons of both genetic transmission and maternal cardiovascular risk. Hormonal contraception should be avoided [8].



**Fig. (3).** Genetic diversity of homozygous familial hypercholesterolaemia (HoFH).

**Table 1. Summary recommendations for the diagnosis of homozygous familial hypercholesterolaemia (HoFH)**

Genetic confirmation of two mutant alleles at the <i>LDLR</i> , <i>APOB</i> , <i>PCSK9</i> , or <i>LDLRAP1</i> gene
Or
An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥8 mmol/L (300 mg/dL)*
Cutaneous or tendon xanthomas before age 10 years
Or
Untreated LDL-C consistent with heterozygous FH in both parents
*These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH

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- As standard of care, patients should be screened for other underlying problems that might cause hyperlipidaemia, such as diabetes, thyroid function disorders, impaired kidney function, drug treatments and sitosterolaemia (this is also probably under-diagnosed).

**NATURAL HISTORY AND CARDIOVASCULAR COMPLICATIONS OF HoFH AND THE IMPORTANCE OF SCREENING FOR SUBCLINICAL DISEASE**

In patients with HoFH, plasma levels of LDL-C are markedly elevated from birth and this high lipid burden underlies the development of atherosclerotic cardiovascular disease complications in these patients. HoFH is characterised by accelerated atherosclerosis, typically (but not exclusively) affecting the aortic root [8]. HoFH patients often experience their first major cardiovascular event during adolescence, and possibly even earlier if they are LDLR-negative and/or untreated [8]. In young children, early signs and symptoms are often those associated with aortic stenosis and regurgitation, as a result of cholesterol accumulation at valvular leaflets [8].

Even when cholesterol levels are reduced, valvular and supra-valvular aortic diseases may still progress due to haemodynamic stress and fibrosis [27], therefore regular screening for subclinical carotid, aortic and coronary heart disease is indicated. A number of screening methods may be considered including Doppler echocardiography, computed tomography coronary angiography, magnetic resonance imaging, trans-oesophageal echocardiography, stress testing, invasive coronary angiography [8] and genetic testing. At present, these methods are not routinely used in the Middle East to screen for aortic involvement in undiagnosed patients with a confirmed family history. A number of studies in children with FH has shown some evidence of endothelial dysfunction detected by flow-mediated dilation (FMD) [28, 29]. In addition, significant improvement of endothelial dysfunction was demonstrated by statins treatment in hypercholesterolaemic adults and in children with FH [30-32]. However, most of the guidelines underscore the value of non-invasive imaging of atherosclerosis in assessing and managing asymptomatic FH subjects [33, 34].

Should atherosclerotic CVD be present, then surgical procedures may be indicated in aortic valve replacement in cases of severe left ventricular outflow obstruction and re-

construction of the aortic root might also be necessary [35]. Coronary angiography should be reserved for those with symptoms or signs of ischaemia, because of the risk associated with catheterisation of patients with coronary ostial stenosis [35].

### Summary and Recommendations

- Screening for coronary calcium score should be conducted every 3 years [considering that the negative predicted value is low in young patients who have the usual risk factors for CVD (*e.g.* diabetes mellitus, hypertension and smoking)].
- Screening for plaque formation should be conducted every 5 years using low radiation computerised tomographic angiography (provided that radiation dose does not exceed 3-5 milliSievert). Use of carotid Doppler to image carotid plaque and velocity every 6 months is a reasonable surrogate in between computerised tomographic scans. If the initial computerised tomographic angiography at time of diagnosis is already abnormal with existing plaque, the time interval between scans can be reduced.
- Carotid intima media thickness should ideally be assessed every 6 months, but there is need for consistent technician/radiologist training to achieve this.
- Stress testing is not recommended for assessment of atherosclerotic plaques.
- If progression of subclinical disease is seen, intensification of treatment is warranted.

## TREATMENT

### Current Treatment Options for HoFH

#### Principles of Treatment

Reducing elevated LDL-C levels is the fundamental principle of the treatment of HoFH. Current guideline LDL-C targets in HoFH are <2.5 mmol/L (<100 mg/dL) [N.B. the target levels in children are somewhat higher, <3.5 mmol/L (<135 mg/dL)], or <1.8 (<70 mg/dL) in adults with atherosclerotic CVD [8, 9]. Importantly, the rarity of HoFH means that there is no prospect of robust therapeutic outcomes data [9]. In most studies the only data collected on cardiac events are reported as adverse events. Some trials are now looking at further surrogates for CVD effects other than LDL-C such as changes in atherosclerotic plaque size and morphology. In the meantime, reduction in LDL-C levels, which are firmly correlated with CV outcomes in other conditions [9, 36], need to be accepted as a marker for therapeutic activity.

Until the 1980s, the only available treatment options for patients with HoFH were adherence to a strict low-fat diet and use of minimally effective lipid-modifying drugs. These approaches have not demonstrated sufficient efficacy to control LDL-C to desired targets. Since the 1980s, and particularly with the advent of statins, a variety of different therapeutic strategies have been explored, including pharmacotherapy, apheresis and surgical approaches.

### Statins

Statins have been the mainstay of treatment of HoFH, and have been shown to reduce mortality [37]. In some instances, where permission is granted by the institute and insurer, statins may be used in children; the cut-off age may vary between countries (8, 10 or 12 years). Licensed treatment options for younger children are limited to dietary control, resins and apheresis. Recent European guidance on statin use in children with FH underscores the need to start therapy at 8 years of age [38], but in some instances this may be too late.

Statins work by in part increasing the expression of LDL-Rs *via* a feedback loop that detects reduced cholesterol levels caused by the inhibition of HMG-CoA reductase in the liver [39]. In HoFH, the LDL-R is either non-functional or severely impaired [6]; therefore, any drug with a LDL-R-dependent mode of action would be expected to have limited efficacy. Indeed, most HoFH patients achieve only modest reductions in plasma levels of LDL-C (10-25%) when receiving statins [8]. Further reductions in LDL-C levels can be achieved by the addition of other cholesterol-lowering medications, including ezetimibe, bile acid sequestrants, and niacin, but their use may be limited by tolerability and availability [8]. Additionally, a relatively large proportion of patients prescribed statins (estimates 10.5-23%) can exhibit intolerance to the drugs, manifested as muscle symptoms [40]. Statin intolerance has been recently defined as the inability to tolerate at least two low-dose statins with symptomatic or biomarker associations with dose titration or therapy withdrawal [41]. In these patients, alternative therapies should be sought. Statins have also been associated with the emergence of new onset T2DM [42], which may be a consideration, particularly in patients already suffering from, or at risk of, T2DM.

#### Statin Combination with Ezetimibe

Several studies have confirmed the efficacy of ezetimibe in combination with statin in patients with HoFH [43-49]. A study demonstrated at least 14.0% to 20.5% reduction in LDL-C when ezetimibe was co-administered with a moderate (40 mg) or maximal (80 mg) dose of statin therapy compared with maximal therapy with statins alone [44].

In patients with HoFH, the effect of statins can be significantly limited by the inability of these patients to effectively upregulate the LDL receptor. This seems not to be the case in ezetimibe, where the LDL-C lowering is mainly achieved through the inhibition of intestinal cholesterol absorption. The IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was the first trial to demonstrate incremental cardiovascular events reduction when adding ezetimibe to statin therapy. Over a 7-year period, the addition of ezetimibe to simvastatin 40 mg reduced the primary end point – a composite of cardiovascular death, MI, unstable angina requiring rehospitalisation, coronary revascularisation, or stroke – by 6.4% when compared with patients who received simvastatin alone ( $p=0.016$ ). The absolute reduction in risk over 7 years was 2.0%, with 32.7% in the ezetimibe/simvastatin arm experiencing an event in the primary end point set compared with 34.7% in the simvastatin arm [50].

### Apheresis

Where available, lipoprotein apheresis (LA) is an important adjunctive treatment for HoFH. There is evidence that in the long term it can contribute to plaque regression or stabilisation and improve prognosis [51]; however, it is time-consuming, costly [8], and can be an unpleasant experience for patients. Nevertheless, apheresis is an effective technique, and can be used in patients where licensed drugs are not available (*e.g.* children), where pharmacotherapy is contraindicated (*e.g.* pregnancy and breastfeeding) [52] or to limit statin-induced myopathy in those patients who show signs of statin intolerance.

If apheresis is being used in conjunction with other lipid-lowering therapies, and LDL-C levels are approaching the established targets, then physicians may consider adjusting the apheresis schedule or stopping the procedure in the interest of patient convenience. However, in doing so, the patient may lose some of the “pleiotropic” effects of apheresis, which include beneficial effects on lipoprotein a (Lp(a)), clotting factors, and possibly on circulating levels of pro-inflammatory cytokines [51].

LA that selectively removes apolipoprotein B100-containing lipoproteins from plasma, including Lp(a), is considered the current gold standard among apheresis therapies particularly when used alongside pharmacotherapy [51, 53]; however, in the Middle East, LA is largely inaccessible apart from in a few centres with access to advanced technology, and most centres that offer apheresis employ the older plasma exchange method (PEX), which is not selective for apoB-containing lipoproteins. Even for PEX, access may be limited, and patients may need to be prioritised for therapy. Despite its limitations, PEX, like LA, has been shown to improve the survival of patients with HoFH [54], and should ideally be initiated before the age of 5 years where available [8].

For both PEX and LA, LDL-C levels undergo rebound to baseline levels over 2-4 days [55], therefore apheresis should be applied weekly or biweekly [56].

Guidelines from the US National Lipid Association (NLA) that initiation of therapy in children is vital, and that although high dose statins may be somewhat effective, most patients will require LA; liver transplantation may also be considered and gene therapy is a potential new therapy in development [57].

### Liver Transplantation and Surgical Procedures

Liver transplantation can achieve a substantial improvement in LDL-C levels but it is associated with many drawbacks, including a high risk of post-operative complications and mortality and a need for lifelong immunosuppressive therapy [58]. Partial ileal bypass or portocaval shunting is not recommended but may be considered if there is limited access to more effective treatments or for patients with very severe disease [8].

### New Therapeutic Approaches for HoFH

Despite treatment with various types of lipid-lowering treatments, including lipoprotein apheresis, the majority of

HoFH patients do not achieve their LDL-C target treatment goals [9]. While statins have been the mainstay of therapy, the 10-25% reductions in LDL-C associated with using these drugs are not sufficient to achieve target LDL-C levels.

Efforts are underway to understand the cardiovascular benefits of ‘lower is better’ [59, 60]. Therefore, even in the face of very high baseline LDL-C, physicians should be seeking to achieve guideline targets of <2.5 mmol/L adult values; <1.8 mmol/dL in adults with atherosclerotic cardiovascular disease. This may appear to be ambitious for patients with HoFH. However, research into lipid-lowering therapies has not halted with the apparent success of statins and apheresis.

The introduction of lipid-lowering agents, with novel mechanisms of action, may result in improvements in the management of HoFH. Lomitapide, an oral inhibitor of the microsomal triglyceride transfer protein, and mipomersen, an injectable apolipoprotein B antisense oligonucleotide, are approved by the United States Food and Drug Administration as adjunctive therapy for HoFH [61, 62]. Lomitapide is also approved by the European Medicines Agency. After trying diet/lifestyle and statins, these novel agents, if licensed in the patient’s country, could be added in after apheresis or instead of apheresis for adult patients, and in accordance with the product label [61, 62]. Mipomersen is not licenced for use with apheresis in the US [62]. Theoretically, mipomersen will be available in the Middle East but its use is not currently supported through a compassionate use programme or clinical trials.

Certain factors may affect patients willingness to comply with treatments, *e.g.* for lomitapide, the need to adhere to a low-fat diet, to avoid steatorrhoea [61, 62], and for mipomersen the need to inject the drug and the onset of injection site reactions and flu-like symptoms [63]. Hepatic steatosis evident with lomitapide and mipomersen may be monitored *via* magnetic resonance imaging in patients considered to be at risk, on the understanding that in the Middle East in particular, non-alcoholic fatty livers are relatively common [64].

Other new approaches currently being studied for the treatment of HoFH include the use of PCSK9 inhibitors, cholesteryl ester transfer protein (CETP) inhibitors and gene therapy. There is virtually no experience of these agents in Middle Eastern patients at this time.

PCSK9 inhibitors work by binding to the LDL-R, and shortening the lifespan of this receptor, thereby decreasing LDL-R function [65]. Therefore, like statins, they rely on a functioning LDL-R, and may have limited efficacy in HoFH. Indeed, among HoFH patients in a trial of evolocumab (a PCSK9 monoclonal antibody), the drug resulted in a mean reduction in LDL-C levels from baseline of 23% after 12 weeks of treatment [66], which is considerably less than the 40-50% observed for lomitapide [67]. Current evidence on CETP inhibitors suggests that effectiveness of these agents are variable in HoFH, and that current trials used patient populations with lower baseline LDL-C values than commonly encountered in HoFH, making clinical efficacy difficult to evaluate [68].

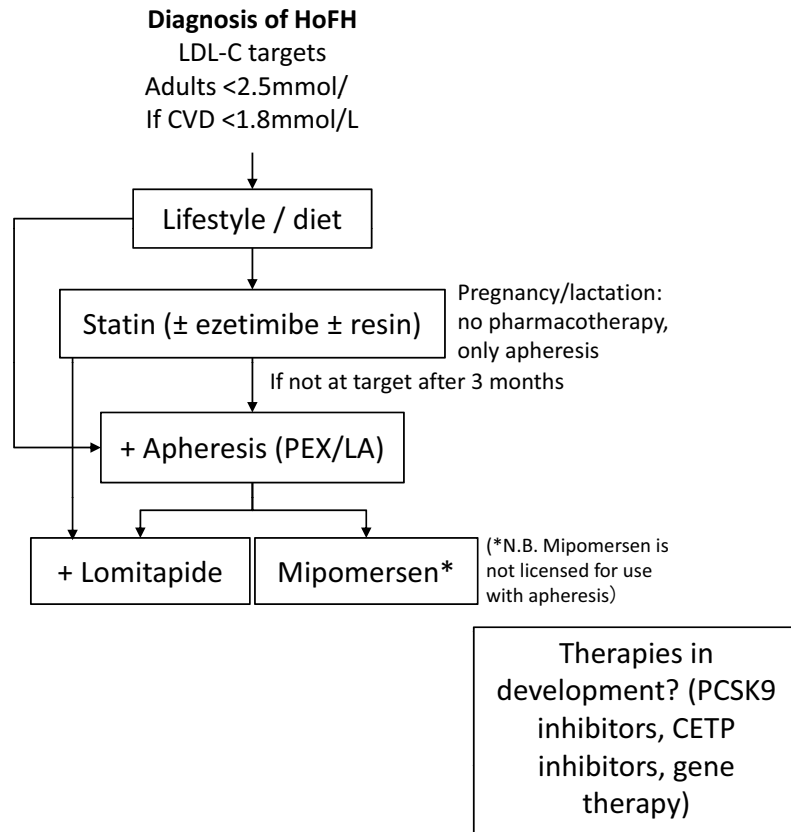
Despite 23 years of research [69], gene therapy for HoFH involving a single transfected vector is still some way off. Some initial successes have been observed with partial hepatectomy and re-infusion of engineered autologous hepatocytes; and particularly with *LDLR*-adenovirus-mediated transfer [69]. Cost may turn out to be a major limiting factor to adoption of these drugs.

**Summary and Recommendations**

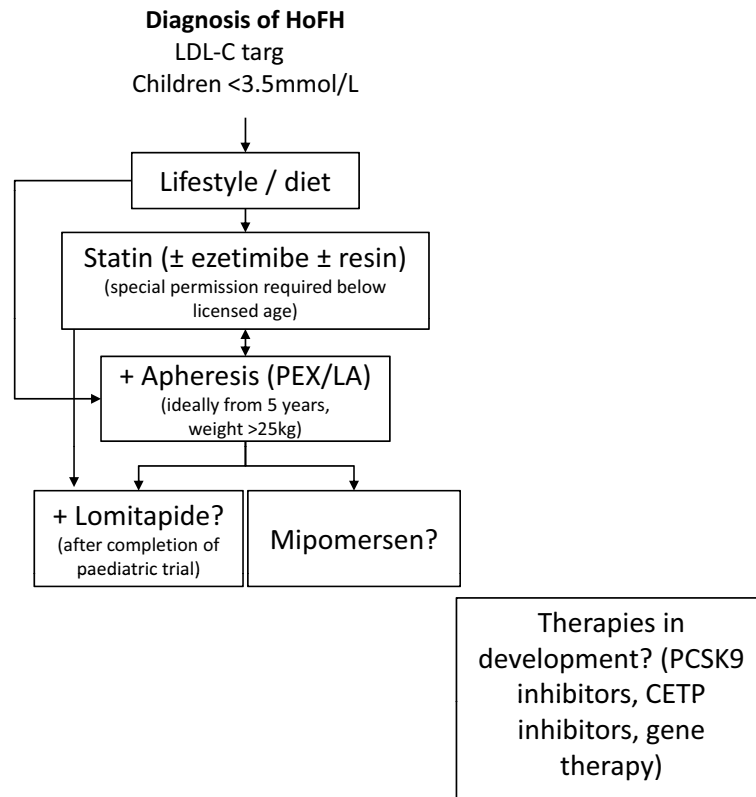
- Suggested LDL-C targets in HoFH are <2.5 mmol/L (<100 mg/dL) [N.B. the target levels in children are higher, <3.5 mmol/L (<135 mg/dL)], or <1.8 mmol/L (<70 mg/dL) in adults with atherosclerotic CVD [8, 9].
- First-line treatment: diet/lifestyle + maximum tolerated dose of high efficacy statins ± ezetimibe ± resin. Smoking should be avoided and exercise should be undertaken. If a genetic confirmation of HoFH is available, first-line treatment should be LA (preferred) or PEX (Fig. 4).
- If target is not achieved after 3 months (US National Lipid Association [NLA] guidelines recommend 6 months) apheresis is recommended; in the Middle East PEX is most widely available; however, LA is preferred, where available. PEX cannot be used in young children, below 25 kg in weight. Apheresis should be started by age of 5 years and no later than 8 years [8]. The Middle East Guidelines Panel recognises the difficulty in accessing apheresis therapy in the region, but apheresis is preferable to statins in the young, in whom they are not

licensed. A separate algorithm is provided for children (Fig. 4B).

- If target is not achieved, new lipid-lowering therapies, such as lomitapide could be added [with statins ± ezetimibe ± resin; also lomitapide (but not mipomersen) can be used with apheresis] (Fig. 4). Lomitapide and mipomersen are not yet approved in the Middle East but this can be expected in the future. A paediatric trial for lomitapide is planned, but the drug remains unlicensed in children in both the US and Europe.
- Pregnancy and breastfeeding
  - Pharmacotherapy is contra-indicated for pregnant and breastfeeding mothers.
  - Patients with HoFH should undergo thorough cardiovascular assessment before becoming pregnant.
  - It is advisable for HoFH patients to have apheresis during pregnancy to benefit both mother and baby. If a patient is not already on apheresis, the decision to start apheresis would depend on major cardiovascular risk factors and LDL-C level. If a patient has existing CVD they should be advised to undergo apheresis. If access to apheresis is an issue then the medical team should explore compassionate avenues.
  - Medical teams should be aware that exposure to high LDL-C commences *in utero*, and hence the cumulative LDL-C exposure over the lifetime of the offspring is increased both for the FH mother and FH child.







B

**Fig. (4).** Algorithm for the treatment of homozygous familial hypercholesterolaemia (HoFH). Caption: PEX, plasma exchange; LA, lipoprotein apheresis; PCSK9, proprotein convertase subtilisin/kexin type 9; CETP, cholesteryl ester transfer protein. Adapted from Cuchel *et al.* *Eur Heart J* 2014; 35: 2146-57 [8], under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>). Mipomersen licensed in US from age 12 years.

### RESEARCH RECOMMENDATIONS

Having evaluated the evidence to produce these guidelines, the Middle East HoFH guidelines panel can suggest a range of topics that are worthy of further examination to improve understanding, awareness and management of HoFH. These research suggestions are as follows:

- **Genetic counselling and neonatal screening.** This will be very important given the high prevalence consanguinity in the Middle East region. Pre- and neo-natal counselling are important in families with FH diagnoses.
- **Real world observational studies** are required to compare the clinical performance and pharmacoeconomics of all therapies used to treat HoFH, including apheresis. These studies will need to be designed to acknowledge the established difficulties in obtaining CV and survival outcomes data in rare diseases.
- **A Middle Eastern HoFH registry** is urgently needed to understand the true prevalence of HoFH across the region. A new initiative has recently been announced by the EAS, to try to set up a global registry of FH and HoFH; they are in discussion with other groups around the world, including the International Atherosclerosis Society (IAS), the FH Foundation in the US, and Prof. Gerald Watts in Australia. The initiative is being led by Prof. Kausik Ray, at Imperial College London, UK.

- **Screening programmes** are required to improve diagnosis and improve the quality of the data in the proposed registry.
- **Drug metabolism studies** are needed including covariate analysis, by age, ethnicity, *etc.* It may also be useful to understand the effects that lomitapide has on risks of non-alcoholic fatty liver disease, which is prevalent in the Middle East.

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