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Review Article

Familial Hypercholesterolemia: A Call for Increased Awareness in the Asian Indian Population

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Abstract

Cardiovascular Disease (CVD) is the leading cause of death in India. Asian Indians have a high prevalence of CVD, with earlier disease onset, more severe clinical phenotype, and worse patient outcomes. Familial Hypercholesterolemia (FH) is an inherited disorder of lipoprotein metabolism, and affected individuals have a 10- to 20-fold increased risk of premature CVD. Early disease modification through lifestyle changes and lipid-lowering therapies is highly effective and potentially life-saving, yet FH remains poorly diagnosed and inadequately managed.There is an immense need foran increased awareness of FH in the Indian population. Studies to examine the potential contribution of FH to the alarming CVD trends in India are also urgently required.

Keywords: India; Familial hypercholesterolemia; Cardiovascular disease; Coronary heart disease

Introduction

Cardiovascular Disease (CVD) is a major and growing problem in India. It is the leading cause of death for both males and females in all regions of India [1]. In a 2001-2003 report, CVD accounted for 19% of deaths across all ages, and 25% of deaths in the 25 to 69 age category [1]. A more recent report, published by the World Health Organization in 2005, found 28% of all deaths in India to be attributed to CVD [2]. Asian Indians are known to have an increased prevalence of CVD compared to other ethnic groups [3,4]. Alarmingly, the average age of CVD onset is earlier among Asian Indians, who have a more severe disease course and a worse prognosis [3-7]. This has a significant economic impact as many affected are in their prime productive years. In the year 2000, deaths from CVD in the 35 to 64 age groupin India led to a loss of 9.2 million potentially productive years, a figure 570% higher than that of the United States. In the year 2030, the loss is expected to increase to 17.9 million years, or 940% greater than the projected United States percentage [8].

Although the excess cardiovascular risk may be partly explained by conventional and emerging risk actors [5] – particularly the high rate of metabolic syndrome and glucose intolerance in Asian Indians [9,10] – the contribution of monogenic hypercholesterolemic conditions, such as Familial Hypercholesterolemia (FH), to this phenomenon remains unclear. FH (Online Mendelian Inheritance in Man [OMIM] entry 143890) is an inherited disorder of lipoprotein metabolism, and is among the most common autosomal dominant diseases encountered in clinical medicine [11]. FH patients have significantly elevated plasma cholesterol levels since birth, and experience a 10- to 20-fold increased risk of premature Coronary Heart Disease (CHD) if not satisfactorily managed [12,13]. While14 to 34 million people worldwide are estimated to be affected by FH, most (>90%) remain undetected, with an unacceptable diagnostic rate of <1% in many countries [14]. Even though effective therapy is available, FH is often inadequately managed [15].

As one of the most populated countries in the world, India undoubtedly carries a significant burden of the disease. However, the true prevalence of FH in India remains unknown, although it is estimated to affect at least 2.5 million individuals. There is therefore an urgent need to raise awareness of this condition among both health care providers and the general public. It is vital that FH patients be identified in a timely manner and be initiated on lifelong lipid-lowering therapies, so as to attenuate the development of atherosclerotic CVD and to reduce premature morbidity and mortality. This review serves to provide information about FH, and to promote the dissemination of knowledge on FH, to Asian Indian physicians.

Background and prevalence

FH is caused by genetic derangements in the Low-Density Lipoprotein (LDL) clearance pathway, leading to diminished cellular uptake of LDL particles and increased plasma LDL-cholesterol (LDL-C) Concentrations. Although it is dominantly inherited, FH has a strong gene dosage effect. Patients with 1 mutant allele are heterozygotes; those with identical defects in both alleles are homozygotes, while still others with different mutations in the 2 alleles are compound heterozygotes. In most parts of the world, the prevalence of heterozygous FH (HeFH) is between 1 in 300 and 1 in 500 [16]. However, in certain populations, such as the French Canadians [17], the Christian Lebanese [18], the Tunisians [19], as well as the Afrikaners [20], Ashkenazi Jews[21], and Indians [22]of South Africa, HeFH may be much more common – up to 1 in 50 to 100 – due to founder effects [12]. In HeFH patients, the cumulative risk of a fatal or non-fatal CHD by the age of 60 is at least 50% in males and 30% in females [23,24]. By contrast, homozygous FH (HoFH) individuals usually present with the sequelae of severe and widespread atherosclerosis, including sudden death from acute myocardial infarction (MI), in the first 2 decades of life [25]. However, HoFH remains rare, with a reported occurrence of 1 in 1 000 000 [25].

Molecular defects

In humans, cholesterol is synthesized (or recycled) in the liver,

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Table 1: Genetic defects reported in Asian Indian patients with familial hypercholesterolemia.

Exon	cDNA Modification[a]	Mutation at Peptide Level[b]	Patient(s)' Region of Origin in India	Patient(s)' Country of Residence	Reference
***LDLR* Gene**					
1	c.1A>T	p.Met1Leu (M-21L)	N/A	South Africa	[93]
3	c.205A>C	p.Lys69Gln	N/A	India	[94]
3	c.232C>T	p.Arg78Cys (R57C)	N/A	South Africa	[95]
3	c.242_243insG	p.Arg81fsX49 (R60fsX49)	N/A	India	[96]
3	c.268G>T	p.Asp90Tyr (D69Y)	N/A	South Africa	[97]
3	c.301G>A	p.Glu101Lys	N/A	United Kingdom	[41]
4	c.397_398insG	p.Asp133GlyfsX47 (D112GfsX47)	N/A	India	[96]
4	c.418G>A	p.Glu140Lys (E119K)	N/A	South Africa	[97]
4	c.649_650insT	p.Asp217ValfsX110	N/A	United Kingdom	[41]
4	c.661G>T	p.Asp221Tyr (D200Y)	N/A	South Africa	[36]
4	c.682G>A	p.Glu228Lys (E207K)	Maharashtra	South Africa	[36]
5	c.709C>T	p.Arg237Cys	N/A	United Kingdom	[41]
5	c.736delG	p.Gly246GlufsX19 (G225EfsX19)	N/A	United Kingdom	[32]
6	c.829G>A	p.Glu277Lys (E256K)	N/A	Malaysia	[98]
8	c.1176C>A	p.Cys392X (C371X)	N/A	South Africa	[93]
9	c.1215C>G	p.Asn405Lys (N384K)	Gujarat/Surat	South Africa	[36]
9	c.1217G>C	p.Arg406Pro (R385P)	N/A	United Kingdom	[32]
9	c.1222G>A	p.Glu408Lys (E387K)	Gujarat	India	[99]
			N/A	United Kingdom	[38]
			N/A	South Africa	[32]
			N/A	United Kingdom	[41]
9	c.1241T>G	p.Leu414Arg (L393R)	N/A	India	[99]
10	c.1474G>A	p.Asp492Asn	N/A	United Kingdom	[41]
11	c.1681C>T	p.Gln561X (Q540X)	West India	United Kingdom	[100]
13	c.1855T>C	p.Phe619Leu	N/A	United Kingdom	[41]
14	c.2054C>T	p.Pro685Leu (P664L)	Gujarat/Surat	South Africa	[37]
			Gujarat	South Africa	[35]
			N/A	United Kingdom	[38]
			N/A	United Kingdom	[39]
			Gujarat	United Kingdom	[40]
			N/A	United Kingdom	[32]
			N/A	United Kingdom	[41]
16	c.2356A>T	p.Ser786Cys (S765C)	N/A	South Africa	[36]
17	c.2439G>A	p.Trp813X	N/A	United Kingdom	[41]
7-12	Deletion of exons 7-12	-	N/A	United Kingdom	[41]
7-14	Approx. 11-kb deletion of exons 7-14	-	N/A	United Kingdom	[101]
Other Genes					
LDLRAP1, Exon 1	c.70_71delGG[c]	p.Gly24ArgfsX9[c]	N/A	United Kingdom	[102]

N/A = not available

[a]Nucleotide numbering is according to the genomic reference sequence (http://www.ucl.ac.uk/ldlr/LOVDv.1.1.0/refseq/LDLR_codingDNA.html).

[b]Historical numbering of LDLR amino acid variants is shown in parentheses, where the first amino acid of the mature peptide is labelled as 1.

[c]Numbering has been changed to adhere to the reference sequence, and to recommendations from the Human Genome Variation Society (HGVS).

and subsequently packaged into Very Low-Density Lipoprotein (VLDL) particles. VLDL is released into circulation and provides a source of cholesterol for peripheral tissues. It subsequently returns to the liver as LDL, and is taken up via interaction of its surface ligand, apolipoprotein B100 (apoB100), with the LDL receptor and an adaptor protein termed LDL receptor adaptor protein 1 (LDLRAP1). The complex is internalized and transported to lysosomes, where LDL is hydrolyzed and the receptor recycled back to the cell surface [26].

FH has been attributed to mutations in the LDL receptor gene *(LDLR),* the apolipoprotein B gene (*APOB*), the proprotein convertase subtilisin/kexin type 9gene (*PCSK9*), and the LDL receptor adaptor protein 1 gene (*LDLRAP1*). *LDLR* defects account for the majority (85-90%) of FH cases, although the prevalence is region-dependent [27,28]. More than 1200 variants have been described, with about 79% being pathogenic [29]. The reported mutations affect all functional domains of the LDL receptor, and can be categorized into 5 major classes [30]: class 1, with complete absence of receptor synthesis (null alleles); class 2, with impaired receptor transport between the endoplasmic reticulum and the Golgi apparatus, and thus failure of receptor expression on the cell surface (transport-defective alleles); class 3, with receptors which are unable to bind to LDL particles on the cell surface (binding-defective alleles); class 4, with receptors which, once bound to LDL, fail to cluster in clathrin-coated pits and initiate receptor-mediated endocytosis of LDL (internalization-defective alleles); and class 5, with receptors which, once internalized, do not release LDL in lysosomes and recycle back to the cell surface (recycling-defective alleles).

Mutations in *APOB* and *PCSK9* are less common, and make up approximately 5-6% and 1-2% of FH cases, respectively [27,28]. A single amino acid substitution at position 3500, from arginine to glutamine, in exon 26 is the most common defect in *APOB*, and is responsible for 5-7% of FH cases in Europe [31,32], although it is less frequently reported in other populations [12]. Because mutations in the *APOB* allele do not have complete penetrance, affected individuals present with a similar clinical phenotype as classic FH, but with less severe LDL-C elevations. PCSK9 is a serine protease which binds to and targets LDL receptors for lysosomal destruction, thereby preventing their recycling to the cell surface [33]. Gain-of-function mutations in *PCSK9* lead to significant hypercholesterolemia, and >20 defects have been described [14].

Only a small number (<30) of genetic mutations have been reported in Asian Indians (Table 1), with the majority affecting *LDLR*. We did not come across any studies describing *APOB* or *PCSK9* defects in Indian FH patients. India is a highly heterogenous population with diverse ethnic groups, and this may potentially explain the paucity of common FH-causing mutations in Asian Indians [34]. It is possible that region- or community-specific

Table 2: Dutch Lipid Clinic Network (DLCN) Criteria for the diagnosis of familial hypercholesterolemia [44].

Criteria	Score
1. Family History	
a. First-degree relative with known premature coronary and/or vascular disease (men <55 years, women <60 years)	1
b. First-degree relative with LDL-C >95th percentile for age and sex	1
c. First-degree relative with tendon xanthomas and/or corneal arcus	2
d. Children age <18 years with LDL-C >95th percentile for age and sex	2
2. Clinical History	
a. Patient with premature coronary artery disease (ages as above)	2
b. Patient with premature cerebral or peripheral vascular disease (ages as above)	1
3. Physical Examination	
a. Tendon xanthoms	6
b. Corneal arcus age <45 years	4
4. Laboratory Analysis	
a. LDL-C ≥8.5 mmol/L	8
b. LDL-C 6.5-8.4 mmol/L	5
c. LDL-C 5.0-6.4 mmol/L	3
d. LDL-C 4.0-4.9 mmol/L	1
5. DNA Analysis	
a. Functional mutation in a FH-related gene (e.g.*LDLR*, *APOB*, or *PCSK9*)	8
Diagnosis	**Total Score**
Definite FH	>8
Probable FH	6-8
Possible FH	3-5
Unlikely FH	<3

Abbreviations: LDL-C = Low-Density Lipoprotein Cholesterol; FH = Familial Hypercholesterolemia

FH mutations do exist, especially in areas which have endured longstanding segregations due to religious or cultural practices [34]. One common genetic aberration is the Pro685Leu mutation (or Pro664Leu, if the historical numbering system is used) in exon 14 of *LDLR*, which was initially reported by Soutar *et al.* in a South African Indian [35]. It was later found to account for 50% of FH mutations in Indian immigrants residing in South Africa [36]. This molecular defect has since been described in other Indian FH individuals spanning a wide geographical distribution [32,37-41], most of whom have a common Gujarati ancestral origin [39].

Very rarely, defects in *LDLRAP1* (formerly known as *ARH*) lead to a complete loss of function in the accessory protein essential for LDL endocytosis [42]. Patients have an autosomal recessive hypercholesterolemia, with a clinical picture resembling HoFH [42]. One such case has been described in Asian Indians (Table 1).

Diagnosis

FH should be considered in patients with a personal or family history of marked hypercholesterolemia and/or premature CHD. Up to 20% of patients who present with an acute MI before the age 45 have FH [12]. HeFH individuals, with at least 50% residual function in their LDL clearance pathway, typically have untreated LDL-C levels 2-3 times above normal [26], corresponding to plasma LDL-C concentrations between 5 and 13 mmol/L [43]. In contrast, HoFH patients, with2-30% residual activity, will present with untreated LDL-C concentrations >13 mmol/L, or 4-8 times above average [26,43]. Triglycerides and high-density lipoprotein cholesterol (HDL-C) levels are typically normal and low, respectively [26].

On physical examination, cutaneous stigmata of FH may be observed, and are secondary to the infiltration of lipid-laden histiocytes, and/or deposits of cholesterol, in the tendons (xanthomas), in theeyelids (xanthelasmas), oralong the corneal margin (corneal arcus) [12]. Xanthomas are often found in the extensor tendons of the hands or in the Achilles, but may also occur in the patellar or triceps tendons [12]. Partial or complete corneal arcus is suggestive of FH if observed in a young patient (age <45). In general, physical findings of FH are insensitive but specific markers of the disease [12]; their absence does not exclude FH.

A number of validated algorithms are available to assist in the diagnosis of FH, including the Dutch Lipid Clinic Network (DLCN) Criteria (Table 2)[44], the Simon Broome Register Criteria in the United Kingdom (Table 3)[45], and the Make Early Diagnosis-Prevent Early Death (MEDPED) Criteria in the United States (Table 4)[46]. Due to biological variations, the average of at least 2 fasting LDL-C results should be used to make a diagnosis of FH [47]. Acute illnesses can lower both total cholesterol and LDL-C, and lipid testing should be deferred until at least 8 weeks post-recovery [48].Secondary causes of hypercholesterolemia (such as hypothyroidism, nephrotic syndrome, cholestatic liver disease, and certain medications), as well as familial combined hyperlipidemia, should be ruled out, although these pathologies would not present with the dermatological findings of FH.

Detection of a genetic mutation allows for an unequivocal FH diagnosis, even in the absence of other clinical manifestations. It is also helpful in identifying the disease in affected relatives, thereby increasing the accuracy and cost-effectiveness of family screening (see "Cascade Screening" below)[49]. However, the absence of a pathogenic mutation does not necessarily preclude a diagnosis of FH, especially if the clinical presentation is consistent with the condition [50]. In these patients (about 10-50% of cases [28,51,52]), it is possible that the mutation resides in a gene which has yet to be implicated. Alternatively, the hypercholesterolemic phenotype may be the result of polygenic [26,53], epigenetic [54], or acquired defects. Regardless, the consequences of severe dyslipidemia– that is, marked morbidity and mortality from early CVD – remain the same irrespective of the molecular etiology. Therefore, our focus should remain on the phenotypic identification and management of affected individuals, rather than on their genetic test results.

Cascade screening

Family cascade screening is the most cost-effective and efficient means to identify new FH cases [14,55,56].Once an index case (i.e. the first individual diagnosed with FH in a family) is discovered, his/her biological first-degree relatives (parents, siblings, offspring) are systematically screened for FH (via clinical history, physical examination, and lipid profile), preferably in conjunction with DNA testing, although this is not mandatory [14]. Screening is then further extended to second- and third-degree relatives.

Currently, the Netherlands, Spain, and Wales have nationwide screening programs. Australia, Brazil, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, and Slovenia have regional programs, while Austria, Germany, Ireland, Italy, Malaysia, Poland, Portugal, Switzerland, and Taiwan have local initiatives [15]. The widely successful cascade screening program in the Netherlands, which began in 1994, identifies 1500-2000 new cases of FH in relatives per year, and has made16 000 new FH diagnoses in total [15]. Family membersare started on lipid-lowering interventions at a relatively young age (average of 37 years) [57]. Following 8.5 years of statin therapy, patients identified by the program have a 76% reduced risk of CHD, to a similar risk level as the general population [58].

Management

Cardiovascular risk assessment tools commonly used in the clinical setting, such as the 10-year Framingham risk score, are not applicable to the FH population and should not be relied upon to guide management [43]. Ideally, FH patients should be identified at an early age and initiated on lifelong, aggressive lipid-lowering therapies. Guidelines for the management of FH are available from a number of professional bodies, including the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) [59], the United States National Lipid Association (NLA) [16,60,61], the FH Australasia Network [62], and the International FH Foundation [43].

Clinical management involves a combination of lifestyle modification and pharmaceutical agents. All other cardiac risk factors should be adequately addressed. Adherence to a heart-healthy diet, with regular intake of fruits and vegetables, fiber, whole grains, tree nuts, fish and lean meats, along with decreased consumption of trans fat, saturated fat, and refined sugars, are essential [63]. Supplementation with plant sterols or stanols should be considered [64]. Alcohol should be consumed in moderation, and avoidance or cessation of smoking is critical. Concurrent hypertension and/or diabetes should be managed according to their respective guidelines.

Table 3: Simon Broome Register Criteria for the diagnosis of familial hypercholesterolemia [45].

Criteria	
A. Plasma cholesterol measurement of: i. TC >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult ii. TC >6.7 mmol/L or LDL-C >4.0 mmol/L in a child<16 years	
B. Tendon xanthomas in the patient, or in a first-degree relative (parent, sibling, or offspring) or second-degree relative (grandparent, aunt, or uncle)	
C. DNA-based evidence of mutation in a FH-related gene (e.g.*LDLR*, *APOB*, or *PCSK9*)	
D. Family history of coronary artery disease: i. Below age 60 in a first-degree relative ii. Below age 50 in a second-degree relative	
E. Family history of hypercholesterolemia: i. TC >7.5 mmol/L in an adult first- or second-degree relative ii. TC >6.7 mmol/L in a child or sibling age <16 years	
Diagnosis	**Criteria**
Definite FH	A + B *or* C
Probable FH	A + D *or* A + E

Abbreviations: TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; FH: Familial Hypercholesterolemia

Table 4: The Make Early Diagnosis-Prevent Early Death (MEDPED) Criteria for the diagnosis of familial hypercholesterolemia [46].

Age (Years)	TC (LDL-C) Levels inmmol/L			
	First-Degree Relative with FH	Second-Degree Relative with FH	Third-Degree Relative with FH	General Population
<20	5.7 (4.0)	5.9 (4.3)	6.2 (4.4)	7.0 (5.2)
20-29	6.2 (4.4)	6.5 (4.6)	6.7 (4.8)	7.5 (5.7)
30-39	7.0 (4.9)	7.2 (5.2)	7.5 (5.4)	8.8 (6.2)
≥40	7.5 (5.3)	7.8 (5.6)	8.0 (5.8)	9.3 (6.7)

Abbreviations: TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; FH: Familial Hypercholesterolemia

Regular physical exercise, as well as weight control for those with an increased Body Mass Index (BMI), should be instituted. Assessment of cardiac function before the initiation of any intense exercise regimen is strongly advised. Lipoprotein(a) [Lp(a)] is a known risk factor for CHD independent of LDL-C [65], and Lp(a) levels are raised in FH patients [66,67]. A recently published study found Lp(a) to be an independent predictor ofCVD in FH patients, especially in those carrying the most severe *LDLR* mutations [68]. Measurement of Lp(a) is therefore recommended, and if found to be elevated, should prompt more aggressive lowering of LDL-C, including consideration for lipoprotein apheresis.

Even with lifestyle and dietary optimization, FH patients will still require intense LDL-modifying pharmacotherapies. Three-hydroxy-3-methylglutaryl–coenzyme A (HMG–CoA) reductase inhibitors (statins) remain the cornerstone of FH treatment, and are highly effective in inducing regression of atherosclerosis [69,70] and in decreasing CHD events [58,71-74]. Neil *et al.*, in a large HeFH cohort (n=3382), demonstrated that statin use can reduce CHD mortality by 48% and 25% in primary and secondary prevention, respectively [71]. In HoFH patients (n=149), Raal *et al.* noted that, even with a modest LDL-C reduction of 26.4%, the hazard ratio for benefit from statin therapy is 0.34 for mortalityand 0.49 for major adverse cardiovascular events [73].

Therapy in both HeFH and HoFH patients should first aim for a 50% reduction in LDL-C [16,43,50,75]. Once this is attained, a goal LDL-C of <2.5 mmol/L or <1.8 mmol/L in adults (if CHD or other major cardiovascular risk factors are absent or present, respectively), and <3.5 mmol/L in children, should be attempted [14,43]. Adult patients should be started on the highest tolerable dose of a potent statin, such as atorvastatin 80 mg or rosuvastatin 40 mg. High-dose simvastatin is associated with an increased risk of rhabdomyolysis, and is not recommended [14]. Statin monotherapy can decrease LDL-C by 55-60% [26]; adjunct treatment with other lipid-lowering agents, such as ezetimibe, bile acid sequestrants, fibrates, and niacin, can further reduce LDL-C by an additional 20-30% [26,43,76-79]. These alternatives should also be prescribed in patients refractory to or intolerant of statins.

Certain FH individuals, particularly those with HoFH, will not reach the stated therapeutic goals despite maximum pharmacotherapies [14,25]. In these patients, Lipoprotein Apheresis (LA) is required. LA is an extracorporeal technique which removes apolipoprotein B-containing lipoproteins from circulation. It has been shown to delay progression of atherosclerosis and improve CHD outcomes in FH individuals [80]. A single treatment can lead to an immediate decline in LDL-C of 49-76%, and Lp(a) of 19-74% [80]. LA may be used in HoFH persons and compound heterozygous FH individuals, as well as in treatment-resistant or statin-intolerant HeFH patients with CHD [14,43,61,80]. Regrettably, LA has several limitations: it is invasive, time-consuming, and not universally available or affordable. Further, its effects are transient, requiring repeated treatment every 1-2 weeks. Despite regular LA, cardiovascular manifestations continue to progress in most HoFHpatients [81]. In fact, the average life expectancy of a HoFH person is 33 years [73]. Clearly, more effective treatment–especially for HoFH–is desperately needed, and several novel agents are exhibiting promising results.

Upcoming Pharmacotherapies

Production of VLDL in the liver is a major determinant of plasma

LDL-C concentration. Emergent therapies which target hepatic VLDL synthesis, acting independently from the LDL receptor pathway, are believed to be of particular benefit to HoFH patients. Two new medications, mipomersen and lomitapide, work via this mechanism.

ApoB100 is an essential component of both VLDL and LDL. Mipomersen (Kynamro; Genzyme, Cambridge, MA) is a synthetic antisense oligonucleotide analog which binds to the messenger RNA encoding apoB100, and promotes its degradation by RNase H1 [82], thereby leading to decreased circulating levels of both VLDL and LDL. Several phase 3 clinical trials on mipomersen have been performed in both HoFH and HeFH populations. Raal *et al.* conducted a study involving 51 HoFH patients, 34 of which were randomized to receive mipomersen 200 mg Subcutaneous (SC) weekly, and 17 to receive placebo, for 26 weeks [83]. LDL-C was reduced by 25% from baseline in the mipomersen cohort, compared to 3% in the placebo group. Studies performed in the HeFH population, in which subjects received a similar dose of mipomersen (200 mg SC weekly) and were monitored for a similar time period (26 weeks), revealed mean LDL-C reductions from baseline between 28% and 37% [84-86].

Microsomal Triglyceride Transfer Proteins (MTPs) deliver neutral lipids, such as triglycerides, to the liver for assembly into VLDL, and to the intestine for assembly into chylomicrons [87]. **Lomitapide** (Juxtapid; Aegerion Pharmaceuticals, Cambridge, MA) is a MTP inhibitor. A recently published phase 3 study enrolled 29 HoFH patients, 23 of which completed 26 weeks of lomitapide at a median dose of 40 mg/day [88]. An intention-to-treat analysis showed a mean LDL-C reduction of 50% at the end of the 26 weeks (the efficacy phase). Impressively, 9 patients attained LDL-C levels of <2.6 mmol/L, and 1 of LDL-C <1.8 mmol/L, during this period. All 23 subjects subsequently went on to complete the safety phase (78 weeks), during which time they remained on loperamide, but changes to concurrent lipid-lowering therapies were allowed after week 26. LDL-C remained decreased by 38% at week 78 [88].

In contrast to the 2 medications discussed above, PCSK9 inhibitors (REGN727/SAR236553, AMG145) are subcutaneously administered human monoclonal antibodies directed against PCSK9. In phase 2 studies performed in HeFH patients, REGN727/SAR236553 (at doses of 150-300 mg SC every 2-4 weeks) decreased LDL-C from baseline by 29-68% at week 12 [89], and AMG145 (at doses of 350 mg or 420 mg SC every 4 weeks) reduced LDL-C by 43-55% at week 12 [90]. A study on HoFH found AMG 145 (at 420 mg SC every 2-4 weeks) to lower LDL-C by 19-26% in LDL receptor-defective patients (i.e. those with 2-25% residual LDL receptor function) [91]. However, no LDL-C decline was observed in receptor-negative patients (i.e. those with <2% residual receptor function). Phase 3 trials on PCSK9 inhibitors are ongoing.

Both mipomersen and lomitapide are approved for use in HoFH patients by the United States Food and Drug Administration (FDA); lomitapide has also been approved by the European Medicines Agency for the treatment of HoFH. However, as with any new pharmaceutical agent, the long-term safety and efficacy of these medications remain to be established.

Concluding Remarks

FH is a potentially lethal yet highly treatable condition which remains under diagnosed and undertreated in most parts of the world. Due to India's remarkable population size, it is home to a significant number of FH patients. The current indifference to a disease which prematurely terminates the lives of so many Asian Indians, often in their most productive years, must be transformed. To accomplish this, first and foremost, we believe education is the key. Knowledge of FH must be disseminated to health care providers at all levels and in various specialties, via seminars, conferences, and journals. Affected family members should be educated. Print and media campaigns, as well as social networking sites, are avenues to engage the public and to further raise awareness of FH. Laboratorians can also assist in the identification of FH individuals by flagging markedly elevated LDL-C results on laboratory reports, and alerting practitioners to the possibility of this pathology.

The MEDPED program (www.medped.org) is a non-profit organization founded more than 20 years ago by the late professor Roger R. Williams from the University of Utah. It has spearheaded international efforts to diagnose and treat hypercholesterolemic disorders in children and adults, and has garnered support from over 40 countries. However, participation rates from countries in the Asia-Pacific region remain low [92], and India has yet to be fully involved in the MEDPED program. Registration and collaboration with the MEDPED organization will undoubtedly be an important step forward.

Most of our current knowledge on FH stem from studies conducted in the West. At present, large trials in the Indian population are lacking. There is therefore a tremendous need for further research to be done, to determine the true prevalence of FH in India, and to evaluate how FH contributes to the CVD epidemic in India. Establishment of a network of lipid clinics will aid in such activities. Further, regional pilot studies can be started in local communities to ascertain best practices for cascade screening, and the principles ultimately applied to nationwide programs. As medications approach their patent expirations, the costs of lipid-lowering therapies, especially statins, will continue to decline. As well, the exponential rate at which DNA technology is advancing will lead to more economical genetic testing costs. Funding from various stakeholders, including government agencies, professional associations, non-profit foundations, individual donors, and industry members, should be sought to finance these endeavors. Policymakers at local, state, and national levels must be engaged in FH efforts, in order to ensure that affected individuals are diagnosed early, initiated on appropriate treatment, and monitored closely for the attainment of therapeutic targets. Such actions will most certainly have an immense impact on reducing the health care burden of FH in India.

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