Familial Hypercholesterolemia (FH) is one of the most common autosomal dominant disorders which exist in either heterozygous form or a homozygous form. These two forms are prevalent in 1 in 500 and 1 in a million population respectively. FH results in premature atherosclerosis; as early as childhood in case of homozygous (HoFH) form and in adults in case of heterozygous (HeFH) form. In case of HoFH both the alleles for LDL-receptor are defective, whereas the mutation in the single allele is the cause for HeFH. Both the forms of the disease are associated with high levels of LDL-C and lipoprotein (a) in plasma, with high morbidity and mortality rate caused by cardiovascular disease. In several past years, different lipid-lowering drugs like Statins (HM-Coenzym-A reductase inhibitor), MTTP inhibitor, CETP inhibitors, PCSK9 inhibitor, thyroid mimetics, niacin, bile acid sequestrants and lipid apheresis were administered to patients with FH, to achieve the goal of reducing plasma LDL-C and lipoprotein (a). However, such drugs proved inefficient to achieve the goals because of several reasons. Mipomersen is a 20 nucleotide antisense oligonucleotide; a novel lipid-lowering therapeutic drug currently enrolled in the treatment of patients with HoFH, HeFH and other forms of hypercholesterolemia. It arrests the synthesis of ApoB100 by targeting ApoB100 mRNA and thus inhibiting the synthesis and release of all Apo B-containing lipoproteins, such as very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low-density lipoprotein (LDL), and non-high-density lipoprotein. It also lowers lipoprotein (a), and ultimately reduces the severity of coronary artery disease and cardiovascular disease.

**ABSTRACT**

Familial Hypercholesterolemia (FH) is one of the most common autosomal dominant disorders characterized by increased plasma LDL-C and lipoprotein (a). The most common underlying defect of FH is the mutation in low-density lipoprotein receptor (LDLR). However, a mutation in two other genes-Apo B100 gene and PCSK9 (proprotein convertase subtilisin/kexin 9) gene can also cause FH.

FH is the first genetic disease of lipid metabolism which was clinically and molecularly characterized. The mutation in LDLR gene, located on chromosome number 19 results in the high level of plasma LDL-C due to reduced function of LDL-R pathway (which removes LDL-particles from the blood circulation), increasing the risk of premature CAD/CVD. Till date, over 100 different types of mutation in LDLR gene have been identified [1], which includes: (1) premature stop codon, (2) mutation affecting the promoter region, (3) point mutation[single amino acid substitution], (4) large rearrangement, (5) mutations affecting splicing of pre-mRNA which may be characterized by abnormal ligand binding, transport, internalization, recycling or total lack of receptor [2]. The most severe form of FH occurs due to the total lack of LDL-R.

FH can also be caused by two mutations in Apo B gene, both affecting ARG 3500 and the gain of function mutation in the PCSK9 gene [3-5]. PCSK9 is a serine protease which promotes the degradation of LDL-R on binding to it.

FH, if untreated, results in increased risk of atherosclerosis; and along with other risk factors such as smoking, hypertension, diabetes, obesity, can increase the morbidity and mortality rate.

**INTRODUCTION**

FH is an autosomal dominant genetic disorder characterized by increased plasma LDL-C and lipoprotein (a). The most common underlying defect of FH is the mutation in low-density lipoprotein receptor (LDL-R). However, a mutation in two other genes-Apo B100 gene and PCSK9 (proprotein convertase subtilisin/kexin 9) gene can also cause FH.

FH is the first genetic disease of lipid metabolism which was clinically and molecularly characterized. The mutation in LDLR gene, located on chromosome number 19 results in the high level of plasma LDL-C due to reduced function of LDL-R pathway (which removes LDL-particles from the blood circulation), increasing the risk of premature CAD/CVD. Till date, over 100 different types of mutation in LDLR gene have been identified [1], which includes: (1) premature stop codon, (2) mutation affecting the promoter region, (3) point mutation[single amino acid substitution], (4) large rearrangement, (5) mutations affecting splicing of pre-mRNA which may be characterized by abnormal ligand binding, transport, internalization, recycling or total lack of receptor [2]. The most severe form of FH occurs due to the total lack of LDL-R.

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FH, if untreated, results in increased risk of atherosclerosis; and along with other risk factors such as smoking, hypertension, diabetes, obesity, can increase the morbidity and mortality rate.

**Strategies for the treatment of FH**

For the past several years, various strategies have been employed to treat the patients with FH to achieve the desired goal of limiting LDL-C content in blood to less than 100 mg/dl. These strategies included lifestyle modifications and drugs used either as monotherapy or in combination with other drugs. Statins, ezetimibe, bile acid sequestrant, nicotinic acid and fibrates are commonly used [6].
hypercholesterolemia, and hyperlipidemia. Using these agents the goal of reducing LDL-C to ≤100 mg/dl was not achieved in patients with FH, not even with less fat intake in diet (particularly in HoFH) [15]. To achieve the goal of reducing plasma LDL-C in patients with FH, numbers of new strategies have been developed. These strategies include PCSK9 inhibitors, Thyroid mimetics, MTP inhibitors, CETP inhibitors and Mipomersen.

PCSK9 inhibitors

PCSK9 (proprotein convertase subtilisin/kexin type 9) serine proteases expressed at the highest level in liver and intestine are responsible for the degradation of LDL-C receptors. Generally, two different kinds of mutations are seen in PCSK9 i.e. rare loss of function mutations and very common gain of function mutations. Loss of function mutations leads to a reduction in LDL-C level and on the other hand, the gain of function mutations promotes degradation of hepatic LDL-R in the lysosome, rather than recycling it to the plasma membrane. PCSK9 can also bind to LDL-R intracellularly, so there is no removal of LDL-C from blood leading to its accumulation in the blood [16]. Due to its major role in inhibition of LDL-R, it is a new target to treat hypercholesterolemia and CHD. Drugs used to inhibit PCSK9 include: A peptide which mimics LDL-R, that binds to the PCSK9 and inhibit its binding to LDL-R to prevent degradation [17]. Anti-PCSK9 antibody, an anti PCSK9 antigenic fragment, inhibits translation of protein of PCSK9 by targeting its mRNA using ASO [18]. All these PCSK9 inhibitors allow the LDL-R to express on the surface of hepatic cells to lower down LDL-C level from the blood. LDL-C receptor function is required for the function of PCSK9 inhibitor; thus, it is functional only in HeFH and HoFH with reduced LDL-R. PCSK9 inhibitor is nonfunctional in the absence of LDL-R [19].

MTPP inhibitors

MTPP (Microsomal Triglyceride Transfer Protein) is required for the assembly of LDL-C. Hence, it plays an important role in the incorporation of triglyceride and Apo B to form VLDL. The loss of function mutation in MTPP protein (which normally lipilated Apo B) results in the degradation of Apo-B [20]. Mutations in the MTPP lead to hypertriglyceridemia, characterized by hypercholesterolemia. As MTP is essential for the formation of VLDL, it’s inhibition leads to low LDL-C level in the blood [21]. Lonipatide is one of the drugs which is used as an antagonist to MTPP. It is taken orally once a day, and its use was granted by Food and Drug Administration (FDA) in March 2012. This drug significantly reduces LDL-C level in blood, but it also promotes hepatic steatosis due to the accumulation of TG in liver cells, limiting its long-term application [22].

CETP inhibitor

CETP (cholesterol ester transfer protein) is a plasma protein, which facilitates the natural transfer of cholesterol ester from HDL-C to Apo B-containing lipoproteins. CETP inhibitors block the action of CETP which results in decreased Apo B-containing lipoproteins and an elevation of plasma HDL-C, reducing the chances of CVD and morbidity and mortality rate [23,24].

Till date, three different CETP inhibitors (Torcetrapib, Dorcetrapib, and Anacetrapib) are studied in various trials. Among these, Torcetrapib development has been stopped due to off-target side effects, which includes elevation in systolic blood pressure and an increase in plasma aldosterone, sodium, and bicarbonate levels with reductions in plasma potassium [25], and Dorcetrapib use was stopped because of low clinical efficacy. Anacetrapib is currently under trial due to its efficacy to reduce plasma LDL-Cholesterol by 40% in combination with statins [26].

Thyroid mimetics

Thyroid hormones are associated with regulation of LDL-C level in blood. Hyperthyroidism causes low LDL-C and hypothyroidism leads to hypercholesterolemia. An agonist to thyroid receptor, which is expressed in the liver, has been developed, which has shown to reduce the LDL-C level. An example is epiretroim which decreases LDL-C by approximately 30% when given with statins [15].

Mipomersen: a second generation antisense oligonucleotide

Mipomersen (Kynamro, Genzyme Corp, MA, USA) is the first antisense Oligonucleotide, which arrests the synthesis of Apo B100 by targeting Apo B100 mRNA and inhibiting the synthesis and release of all Apo B-containing lipoproteins, such as VLDL, IDL, LDL, and non-High Density Lipoprotein (non-HDL-C) [27]. Isis Pharmaceuticals have had the license for the production and development of mipomersen which now works in collaboration with Genzyme Corporation. They had an exclusive worldwide licensing and agreement for the development of mipomersen in June 2008 [28,29]. Mipomersen was approved by US FDA in January 2013 for the treatment of HoFH, as an adjunct to lipid-lowering medications and diet to minimize Apo B-containing lipoprotein [30,31]. However, the approval was declined in March 2013 by the EMA Committee for Medical Products for human use after analyzing the study in HoFH patients, and in patients with severe hypercholesterolemia [32,33].

Structure and chemical nature

Mipomersen (ISIS 301012, ISIS 301012, mipomersen-sodium and ISIS 447764 as mice specific ASO) is a 20 nucleotide antisense oligonucleotide having the following sequence: 5’-GCCUCA GCTCTGCTTTGACC-3’ [34]. Five 2’-O-(2-methoxyethyl) nucleosides are present, each on the 5’ and the 3’ ends of the nucleotide, with 10 internal 2’-deoxynucleosides.

Sodium mipomersen has a molecular weight of 7594.9 g/mole with a molecular formula C21H30NaO10PS5N3. It contains three main parts: A modified oligonucleotide strand with a phosphorothioate backbone, a 5’-phosphate and 3’-phosphate, and a 20-mer ASO; thus, it is functional only in HeFH and HoFH with reduced LDL-R. PCSK9 inhibitor is nonfunctional in the absence of LDL-R [19].

Drug modification

Unlike other second-generation ASOs, the oligonucleotides used in mipomersen are designed to eliminate nonspecific binding, increased binding efficacy, stability, and RNase H mediated degradation of Apo B gene. Mipomersen is a 20-mer that uses gap based techniques where 2’ methoxyethyl (MOE)-modified bases flank the 5’ and 3’ ends with ten internal nucleotides placed between the modified ends. All 20 nucleotides are modified by phosphorothiate backbone (replacement of one oxygen molecule of normal phosphate backbone by one sulphur molecule). The modified wings makes it easy for ASO to enter the lipid bilayer membrane and reach the target cell and also maintain its effective lifetime in the cytosol with richcytoplasm within the cell. The non-modified ends i.e. internal sequence retains RNase H activity [35].

Mechanism of action of mipomersen

Mipomersen is a second-generation antisense oligonucleotide (ASO), a novel therapeutic drug for the treatment of hypercholesterolemia, hyperlipidemia, and familial hypercholesterolemia.

Mipomersen consists of a 20-nucleotide that is complementary to a sequence present within the coding region of human Apo lipoprotein-B mRNA (exon 22, position 3249-3269 base pairs) [36-38]. Apolipoprotein B is an important structural component of all atherogenic lipoproteins i.e. very-low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), low-density lipoprotein (LDL) and Lipoprotein (a). It exists as Apo-B 100 (4536 amino acids) and Apo-B 48 (2152 amino acids) which is formed as a result of post-transcriptional edition. Apo-B48 is a component of intestinal chylomicron [39,40]. Apo-B100 is responsible for the recognition of LDL-receptors, promoting endocytosis of LDL-C in the extrahepatic tissue [41-43]. Apo-B100 is thus an important target for prevention of atherosclerosis [44]. The most recent strategy under trials is the use of second generation ASO mipomersen which prevents the synthesis of Apo-B100.

On administration, 20-mer ASO enters the nucleus of hepatocytes, binds specifically to the complementary sequence in the Apo-B mRNA and forms a hybridized sense-antisense duplex. The duplex formation induces RNase-H activity, which cleaves the target mRNA and prevents translation of Apo-B protein [45-47]. The outcome is the reduction of all apo-B100 containing lipoprotein, LDL-C, VLDL.
and Lp(a) in a dose and time-dependent manner [47], thus minimizing cholesterol accumulation and reducing the risk of atherosclerosis and CVD.

![Mode of Action of Mipomersen in liver cell](image)

**Fig. 1: Inhibition of Apo B synthesis by Mipomersen (ASO):** (1) entry of single-stranded DNA oligonucleotide to the cytoplasm through plasma membrane; (2) ASO after reaching nucleus targets the Apo B mRNA; (3) ASO hybridizes to a target mRNA by Watson and Crick hybridization technique; (4) hybridization leads to the release of enzyme RNase H1; (5) RNase H degrades the target mRNA; (5) Thus protein expression is inhibited; (6) Assembly of LDL-C particles is thus effected which leads to the low levels of LDL-C production.

### Pharmacokinetics of mipomersen

Pharmacokinetics studies have revealed that mipomersen is completely absorbed and has a rapid and extensive distribution to tissues (volume of distribution in humans 48.3 L/Kg). Studies have also shown that greater than 85% of mipomersen in plasma is bound to plasma proteins. An animal study showed the maximum concentration of mipomersen is found in liver and kidney [46]. Plasma clearance of modified ASOs occurs in a polyphasic manner with an initial rapid distribution phase in which uptake of mipomersen in kidneys and liver takes place [46, 47]. The rapid distribution phase is followed by a prolonged activation phase, which is followed by urinary excretion of mipomersen. Oligonucleotides metabolites are present along with mipomersen in urine. Clearance of mipomersen takes place in a time and dose-dependent manner [47]. The half-life of mipomersen is calculated to be approximately 30 d [46].

A limitation to the use of ASO is that it cannot be administered orally. ISIS has announced a preclinical testing of oral formulation of mipomersen in phase I study, but the development of this formulation has been discontinued [48]. Intravenous injections, though efficacious cannot be used for long-term drug delivery. All these studies suggest that the preferred route for administration of mipomersen is subcutaneous, and the proposed dose is 200 mg/ml once a week.

Mipomersen does not show any potential pharmacokinetic interaction with another lipid–lowering drugs, such as simvastatin or ezetimibe, and does not have any dependency on cytochrome P450 metabolism (CYP1A2, CYP2C9, CYP2C19, and CYP3A4 [49]). The previous clinical studies showed no evidence of intestinal fat malabsorption [50] such as that observed with MTTP inhibitors [51].

### Safety and tolerability

Mipomersen is well tolerable and has demonstrated a fair degree of safety. The most common adverse effects observed in patients treated with mipomersen as revealed by various studies are injection site reactions (ISRs). Flu-like symptoms were also observed in very few cases.

In a study where 34 patients were assigned to mipomersen and 17 to placebo, a total of 45 individuals completed the 26-week treatment period (28 mipomersen, 17 placebos). Various characteristics of injection site reactions noted in patients are tabulated below [52].

<table>
<thead>
<tr>
<th>Characteristics: injection site reactions (&gt;10%)</th>
<th>Mipomersen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema</td>
<td>19 [56%]</td>
<td>1 [6%]</td>
</tr>
<tr>
<td>Hematoma</td>
<td>12 [35%]</td>
<td>2 [12%]</td>
</tr>
<tr>
<td>Pain</td>
<td>12 [35%]</td>
<td>1 [6%]</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 [29%]</td>
<td>1 [6%]</td>
</tr>
<tr>
<td>Discoloration</td>
<td>10 [29%]</td>
<td>None</td>
</tr>
<tr>
<td>Macule</td>
<td>5 [15%]</td>
<td>None</td>
</tr>
<tr>
<td>Papule</td>
<td>4 [12%]</td>
<td>None</td>
</tr>
<tr>
<td>Swelling</td>
<td>4 [12%]</td>
<td>None</td>
</tr>
</tbody>
</table>

Influenza-like symptoms were found to be the second most common adverse event; although the number of events was similar in the two treatment groups, more events per patient were noted in the mipomersen group than in the placebo group. Mipomersen use results in a high serum alanine transaminase level (more than three times the upper limit from baseline) in the mipomersen group (6-15%) but not in the placebo group. Another serious safety consideration in mipomersen-treated patient is hepatic steatosis. Proton magnetic resonance spectroscopy (H-MRS) has shown an increase in hepatic fat from baseline levels in mipomersen-treated patient but not in placebo group which resulted in stopping of the dose in such patients. However, the serum ALT (alanine transaminase) and hepatic steatosis are reversed and resolved after discontinuation of the treatment.

The high discontinuation rate in patients due to injection site reactions and flu-like symptoms along with high serum ALT levels and hepatic steatosis have lead EMA to withhold approval of the drug, although it was approved for use by the US-FDA [53].

### Efficacy of mipomersen

**Phase I trial**

Kastelein et al. were the first scientist who conducted a study of mipomersen on 36 double-blind randomized placebo-controlled individuals with mild dyslipidemia. All were administrated with a subcutaneous dose of mipomersen ranging from 50-400 mg/week up to 4 w. It showed 50% and 35% reduction in Apo B and LDL-C levels respectively.

Both LDL-C and Apo B levels remained below baseline up to three months after the last dose of mipomersen. Common side effects were erythema at the site of injection in 72% subjects and elevated ALT in 14% patients after 2 w of administration [54]. The study concluded that only subcutaneous dose is to be given and may be injected into areas such as the abdomen, thigh, or upper outer arm regions. To minimize the risk of injection-site reactions all the patients should be pre-instructed about how to give an injection. [55].
Phase II trials

Phase II trial was conducted by Akdim et al. on a different group of patients with mild dyslipidemia, HeFH, and hypercholesterolemia with stable statins therapy. 44 patients with mild dyslipidemia and stable statins therapy were subcutaneously injected with 50-300 mg/week dose of mipomersen for 13 w. It showed dose-dependent reduction in LDL-C (21% and 34%), Apo B (23% and 33%), TG (23% and 22%) and lipoprotein (a) (17% and 24%) in 200 and 300 mg/week dose group [56]. The placebo group showed very negligible reduction in LDL-C and Apo B as shown in table 2. In another study with 74 patients of hypercholesterolemia on statin therapy, 59 were injected with mipomersen and 15 received dose of placebo. Dose ranges from 100–400 mg/week and was continued up to 13 w. LDL-C reduced by 24.7%, Apo B by 26.8%, lipoprotein (a) by 31.1% and TG up to 17% in mipomersen group. Placebo group showed very less reduction in the LDL-C (-3.3%), Apo B (-2.5%), lipoprotein (a) (-7.9%) and negligible rise in TG (0%).

Phase III trials

First published phase III trial was performed by Raal et al. on 51 maximally lipid lowering drug tolerated patients with HoFH who were on low-fat diet. Out of them, 34 were assigned to mipomersen and rest 17 to placebo with a standard dose of 200 mg/week for 26 w. It led to a reduction in LDL-C by 24.7%, Apo B by 26.8%, lipoprotein (a) by 31.1% and TG up to 17% in mipomersen group. Placebo group showed very less reduction in the LDL-C (-3.3%), Apo B (-2.5%), lipoprotein (a) (-7.9%) and negligible rise in TG (0%). Similar to phase II, about 76% patient of mipomersen group and 24% patients of Placebo group showed ISR (Infection Site Reactions) [59]. Reason for withdrawal from mipomersen group was ISR in 2 patients, rash in 1 patient, rise in ALT 1 patient, one was noncompliance, and one was consent withdrawn. Two phase III trials presented at the 79th European Atherosclerosis Society (EAS) Congress showed almost similar results. Second study by same author on 58 statins tolerated patients with severe FH on 200 mg/week subcutaneous injection of mipomersen and placebo also showed significant reduction in LDL-C and Apo B. The most common adverse effect was ISR due to which one patient was discontinued, one patient left because of FLs, and another left because of hepatic steatosis. Two patients left the treatment due to increasing in ALT and rest all continued till 26th week [60].

Table 2: It shows the efficacy of mipomersen in different trails phase

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Phase</th>
<th>Subject Type</th>
<th>Dose</th>
<th>Follow-up</th>
<th>Mipomersen outcome (mean result)</th>
<th>Placebo outcome (mean result)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kastelein et al. 2006 [54]</td>
<td>I</td>
<td>Double blind placebo controlled, 36 volunteer with mild dyslipidemia</td>
<td>Weekly dose of 50–400 mg subcutaneously</td>
<td>4 w</td>
<td>Apo B reduced up to 50% LDL-C up to 35%</td>
<td></td>
<td>Erythema at the site of injection in 72% subjects and elevated ALT level in 14% patients two week after administration. ISR, Flu like symptoms and elevated ALT level</td>
</tr>
<tr>
<td>Akdim et al. 2010 [56]</td>
<td>II</td>
<td>44 patients with HeFH, on statins therapy</td>
<td>50–300 mg/week subcutaneously</td>
<td>13 w</td>
<td>Apo B reduced by 23% and 33%, LDL-C reduced by 21% and 34%, TG reduced up to 23% and 22%, Lipoprotein (a) -17% and 24% in 200 and 300 mg/week dose and Apo B (-46% and 61% in respective mipomersen dose) reduced significantly [58].</td>
<td>Apo B (-1%) LDL-C (0%) TG (-16%) Lipoprotein (a) (+8%)</td>
<td>Erythema in 90% Patient at injection site. Increase in hepatic transaminase in 17% patients</td>
</tr>
<tr>
<td>Akdim et al. 2010 [57]</td>
<td>II</td>
<td>74 Patients with hypercholesterolemia receiving stable statins therapy</td>
<td>59 on mipomersen and 15 on placebo treatment 100–400 mg/week</td>
<td>13 w</td>
<td>Apo B reduced by 24% and 54%, LDL-C reduced by 27% and 52% in 200 mg and 300 mg/week dose respectively. In 200 &amp; 300 mg/week group Apo B reduced up to 46% and 61% LDL-C Reduced by 45% and 61%</td>
<td></td>
<td>All individuals show injection site reaction, 19% shown 3 times elevated transaminases</td>
</tr>
<tr>
<td>Akdim et al. 2011 [58]</td>
<td>II</td>
<td>50 subjects with mild to moderate hyperlipidemia</td>
<td>50–400 mg/week</td>
<td>13 w</td>
<td>Reduction in Apo B was 26.8% in LDL-C (24.7%) &amp; in lipoprotein (a) and TG by 31.1% and 17%</td>
<td>Apo B: (-2.5%) LDL-C: (-3.3%) TG: (+0.4%) Lipoprotein (a): (-7.9%) LDL-C (+12.5%)</td>
<td></td>
</tr>
<tr>
<td>RaalF et al. 2010 [59]</td>
<td>III</td>
<td>51 Patients with HoFH on low fat diet and maximum tolerated lipid-lowering drugs.</td>
<td>34 patients assigned for mipomersen and 17 patients for placebo. Dose was 200 mg/week</td>
<td>26 w</td>
<td></td>
<td></td>
<td>Injection site reaction 76% in mipomersen group and 24% in placebo group.</td>
</tr>
<tr>
<td>McGowan MP et al. 2012 [60]</td>
<td>III</td>
<td>58 patients with severe FH Statins tolerated</td>
<td>200 mg/week</td>
<td>26 w</td>
<td>LDL-C (-35.9%), and Significant reduction in Apo B and Lipoprotein (a)</td>
<td></td>
<td>Erythema at site of injection and elevated Transaminases</td>
</tr>
</tbody>
</table>
CONCLUSION
Recent trials and studies have shown Mipomersen can be a promising drug for the treatment of FH which may achieve the goal of reducing the LDL-c to a greater degree in comparison to those used earlier. The increased specificity and half-life of this drug overcomes the drawback shown by first generation ASOs. Also this drug can be used as monotherapy or as an adjunct with Statins in high-risk patients who are statin intolerant and unable to reach the target. Furthermore, lipoprotein (a) is a major cause of CVD, which can be treated effectively with mipomersen. FDA has approved this drug due to its tolerability and efficacy.

The potentiality of this drug is promising. However its long-term safety needs to be minded before it can be used as a sole drug for the management of Familial Hypercholesterolemia.

CONFLICT OF INTERESTS
The authors do not have any conflict of interest to declare.

REFERENCES


