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# Solutions to Familial Hypercholesterolemia

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## ABSTRACT

FH or (Familial Hypercholesterolemia) is a genetic disease which passes on from one family member to another, and affects about 1/250 people around the world, but is untreated even though it has high risk with addition of increasing one's chances of getting coronary heart diseases. This disease causes plaques on the sides of blood vessels (over build up of cholesterol). There are 4 solutions worth mentioning are Lomitapide, Statins, Surgery, and Genetic engineering. Lomitapide is a pill to be taken by mouth and it takes action in the early processes of making triglycerides. Statins are used to reduce the level of LDL Proteins in the Liver. The surgical options are to be used in rare cases as not all situations are the same and may not be for anyone and everyone. The Genetic engineering solution is going to be used as a therapeutic method which has never been tried before, it may prevent future generation problems.

## Introduction

Familial Hypercholesterolemia is the disease which causes the unregulated production of cholesterol in our body of one's inherited genes. Which results in people who have Familial Hypercholesterolemia have a high risk of many heart diseases, as well as this can cause a massive impact on the person as well as their family because this disease is passed on through the family tree.

People with familial hypercholesterolemia have a high risk of developing a form of heart disease called coronary artery disease at a young age. This condition occurs when excess cholesterol in the bloodstream is deposited on the inner walls of blood vessels, particularly the arteries that supply blood to the heart (coronary arteries). The abnormal buildup of cholesterol forms clumps (plaques) that narrow and harden artery walls. As the plaques get bigger, they can clog the arteries and restrict the flow of blood to the heart. The buildup of plaques in coronary arteries causes a form of chest pain called angina and greatly increases a person's risk of having a heart attack.

In addition, there are two different types of Hypercholesterolemia. First of all homozygous familial hypercholesterolemia (HoFH) which is caused by two mutated alleles, it is known that this form carries a much worse effect compared to the heterozygous form. HoFH is a serious condition that poses a constant threat to the lives of affected individuals through the lifelong exposure to elevated LDL cholesterol levels in the blood, which greatly increases the risk of developing ASCVD, including coronary artery disease (CAD), valvular aortic stenosis, and supravalvular aortic stenosis (SVAS), which are associated with substantial calcium clusters and make surgical intervention challenging. And the second being HeFH (Heterozygous Familial Hypercholesterolemia), which has the part having a higher life expectancy, but it comes with almost all the same diseases like the first one stated before.

To tackle this issue we will be using 4 different treatments/therapies for FH. Surgical options, Lomitapide, Statins, and lastly a maybe more prominent solution which will be done using Crispr to edit the mutated gene out replacing them, prevent the incoming issues with this, as well as preventing the future spread of Familial Hypercholesterolemia in one's descendants.

- The LDLR gene provides instructions for making a protein called a low-density lipoprotein receptor. This type of receptor binds to particles called low-density lipoproteins (LDLs), which are the primary carriers of cholesterol in the blood.

Mutations in the LDLR gene that cause the high level of cholesterol level:

- **Missense mutations**. Missense mutations are the most numerous of the small DNA variations (58.5%, 821/1404) reported in the LDLR gene in association with Familial Hypercholesterolemia (FH).

The LDLR gene is located **on the short arm of chromosome 19 (19p13. 1–13.3)** with a length of approximately 45 kb encoding 18 exons and 17 introns. LDLR is a protein of 839 amino acids that is synthesized in the endoplasmic reticulum (ER), where it folds and is partially glycosylated.

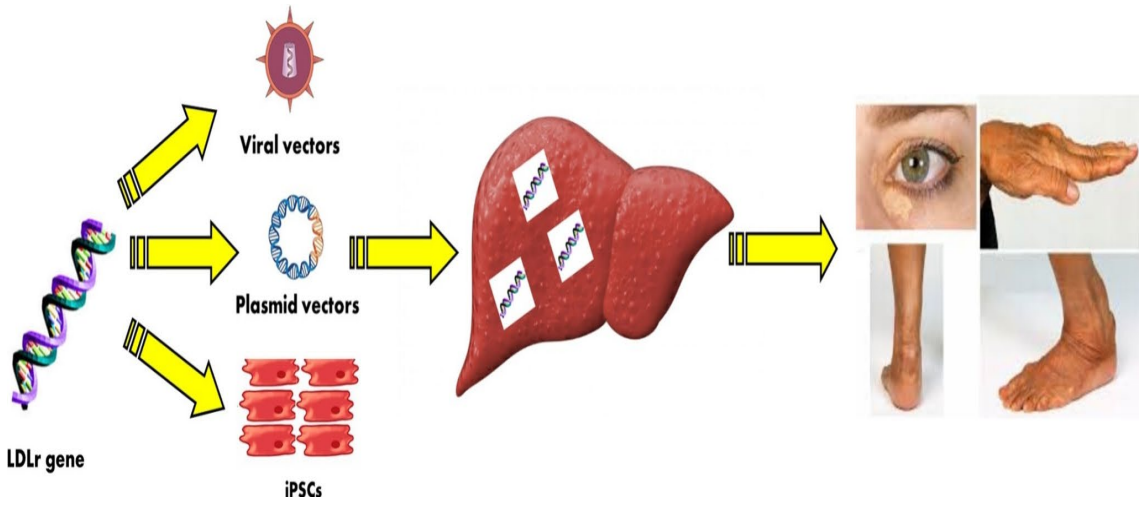



Fig. 1. Use and effect of Familial Hypercholesterolemia

## A Healthy Lifestyle is Key

A Healthy lifestyle is an important part of mitigating the risks of Familial Hypercholesterolemia.

- Eat a healthy diet rich in vegetables, fruits, fish and whole grains and low in saturated fat, trans fat, refined carbohydrates and salt
- Be physically active more often and sit less
- Maintain a healthy weight

## Treating FH

- FH is undertreated and underdiagnosed, even though they have excellent rate of recovery if treated on time, and identified on time.
- Exercising and eating healthy are important parts, but in fact when trying to reduce the high levels of fats in the body , medicines are needed.
- Treatment usually involves a statin drug, and other cholesterol-lowering medications such as Lomitapide may also be required. People with extremely high LDL cholesterol, such as those with homozygous familial hypercholesterolemia, may need to undergo a treatment called LDL apheresis. This is a dialysis-like procedure that's done every few weeks to remove cholesterol from the blood.
- If your cholesterol — particularly the LDL ("bad") type — stays high after you make healthy lifestyle changes, the solutions below might be an option for you.

# Lomitapide

## What is Lomitapide?

This enzyme is responsible for the synthesis of very low-density lipoproteins in the liver and chylomicrons in the intestine. Lomitapide has been approved by the US Food and Drug Administration, European Medicines Agency, and other regulatory agencies for the treatment of hypercholesterolemia in adult patients with homozygous familial hypercholesterolemia. Clinical trials have shown that lomitapide reduces low-density-lipoprotein cholesterol levels by around 40% in homozygous familial hypercholesterolemia patients on treatment with statins with or without low-density-lipoprotein apheresis, with an acceptable safety and tolerance profile. The most common adverse events are gastrointestinal symptoms that decrease in frequency with long-term treatment, and the increase in liver fat remains stable.

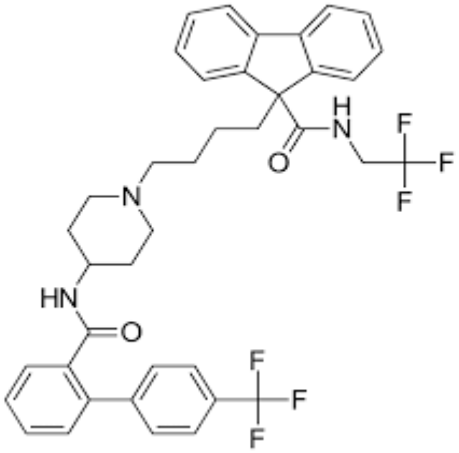



Fig. 2 - Lomitapide structure

Table-1: Impact summary of Lomitapide:
(Core evidence clinical impact summary for lomitapide)

| Outcome measure | Evidence | Implications |
|---|---|---|
| Disease-oriented evidence | | |
| LDL-C reduction in homozygous FH | Phase II and III, single-arm studies in HoFH ≥18 years old; real-world clinical experience (registries); clinical cases using lomitapide (dose up-titrated from 5 to 60 mg/day or to maximum tolerated every 4 weeks) in monotherapy (Phase II) or with statins with or without LDL-apheresis (Phase III and registries) | Dose-dependent LDL-C reductions between 25-51%; also, triglycerides were reduced by 35-65%. In Phase III trials, reduction was maintained after 26 weeks and in long-term extension studies. During the trial, 74% patients achieved an LDL-C level below 100 mg/dL at least once during the efficacy phase.<br>In those adult patients on LDL-apheresis, it is probable that one in three will reduce the frequency of the apheresis or even discontinue it. |
| Patient-oriented evidence | | |
| Tolerability and safety | Phase II and III, single-arm studies in HoFH ≥18 years old; real-world clinical experience (registries); clinical cases using lomitapide (dose up-titrated<br>from 5 to 60 mg/day or to maximum tolerated every 4 weeks) in monotherapy (Phase II) or with statins with or without LDL-apheresis (Phase III and registries) | All studies have demonstrated that gastrointestinal symptoms are the most frequent adverse events and are related to the dose, transient and related to a bad adherence to a low-fat diet.<br>Due to its mechanism of action, variable liver fat accumulation and an increase in transaminases occurs with lomitapide and return to baseline levels after 4 weeks of discontinuation of the drug. In the extension trials, the frequency of adverse events diminished compared to pivotal trials. |
| Net Benefit | | HoFH is a rare and severe disorder causing death and cardiovascular disease since childhood. These patients have few therapeutic options like LDL-apheresis (not available in all countries) or liver transplantation. Although there are some adverse events, few patients discontinued medication due to them, and LDL-C reduction is important depending on the dose. The up-titration every 4 weeks or more and a good adherence to a low-fat diet can improve the tolerability and maximize the efficacy. |
| Economic Evidence | | Lomitapide is an expensive medication, and there are no cost-effective studies. |

## How does Lomitapide Work?

Lomitapide is a microscopic molecule which binds directly to and inhabits MTp in the endoplasmic reticulum of hepatocytes and enterocytes. This enzymes plays a key role in the early stages of VLDL and chylomicron assembly, most likely by transferring triglycerides to nascent ApoB as it enters the lumen of the endoplasmic reticulum, controlling the number of ApoB-containing lipoprotein particles secreted to the bloodstream. Analysis of the rare recessive genetic disorder abetalipoproteinemia, produced by mutations in the MTP gene located in chromosome 4q22-24, has suggested that inhibit of the MTP could be a new target to reduce plasma-lipid levels. Clinically, abetalipoprotienamia is characterized by the absence of ApoB and ApoB-containing lipoprotiens n plama associated with systemic manifestations. These patients have very low plasma levels of cholesterol and triglycerides and undetectable levels of ApoB and LDL.

By inhabiting MTP in hepatocytes and enterocytes, lomitapide reduces plasma levels of all ApoB-containing lipoproteins, including VLDL, LDL and chylomicrons.The adverse events can be explained by the actions occurring. Liver steatosis can be explained by the intracellular increase in triglycerides associated with impaired assembly and secretion of ApoB-containing lipoprotein. In addition, studies in mice have shown that chemical inhibition of MTP decreases cholesterol ester synthesis and increases free-cholesterol levels in hepatic and intestinal cells. It has been suggested that this pile up of free cholesterol in the endoplasmic reticulum produces oxidative stress and increases some gene transcriptions, producing an increase in plasma transaminases.[15] On the other hand, the effect of lomitapide on the gastrointestinal tract is suspected to be driven by the increase of intracellular triglycerides in the enterocytes, reduction in chylomicron formation, and reduction in dietary fat absorption, causing steatorrhea and gastrointestinal symptoms.

## Side-effects of Lomitapide:

- diarrhea
- nausea
- vomiting
- stomach pain
- constipation
- bloating
- gas
- upset stomach
- weight loss
- headache
- dizziness
- sore throat
- runny nose
- back pain

## When and Why was Lomitapide Approved?

Lomitapide (Juxtapid, Aegerion Pharmaceuticals [US]; Lojuxta, Amryt Pharma [UK]) received the reputation of an orphan drug for the treatment of HoFH in 2007 and was approved by the US Food and Drug Administration (FDA) in 2012, “under special circumstances”by the European Medicines Agency (EMA) in 2013, and by other international agencies in Japan and key Latin America markets to treat adult patients with HoFH, associated with a low-fat diet and

other lipid-lowering medications or treatment (LDL apheresis is included in the FDA approval). As well as for the EMA, the patient's disease should be confirmed by genetic testing as soon as possible.

Lack of evidence of long-term lomitapide treatment in cardiovascular morbidity and mortality reduction was considered a limitation by the FDA and EMA at the time of approval, and needs to be confirmed in further studies. On the other hand, due to the increased risk of hepatotoxicity and considering the unknown long-term effect, regulatory agencies recommended that patients receiving lomitapide be closely monitored and managed. For this reason, in 2012 the FDA also approved lomitapide risk-evaluation and -mitigation strategies to mitigate the risk of hepatotoxicity with the participation of health-care providers, patients, and pharmacies.

## Statins

What are Statin?

This drug acts to reduce levels of fat, triglycerides, and cholesterol, in the blood. This is the first line of therapy in the long list which is used to lower a patients low-density lipoprotein (LDL) cholesterol in familial hypercholesterolemia (FH), particularly in heterozygous patients.

Statins work by blocking a key enzyme in the liver which produces cholesterol. Which leads to the liver sending a signal to clear up the cholesterol in the bloodstreams. The way by which the liver gets cholesterol is by making more LDL receptors to get cholesterol from the blood. In response the Liver receptor makes more healthy LDL receptors. Multiple studies have shown that statins can reduce LDL-cholesterol by 35 to 55 percent and can decrease the risk of cardiovascular disease (CVD) by 22 percent for each 40 mg/dL (1 mmol/L) reduction in LDL cholesterol. Statins are mainly prescribed to a elderly people but new studies are showing that they can be used for the younger population.

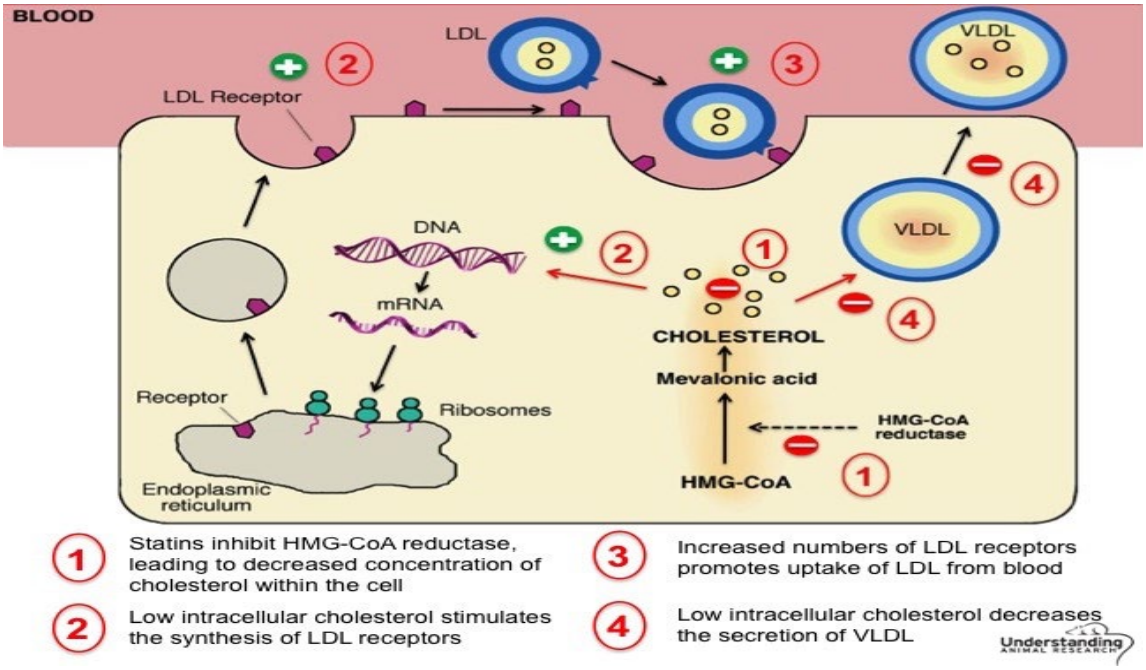



Fig. 3 - Process of Statins Help reduce cholesterol in a person's body.

The figure above shows the process by which Statins prevent the overproduction of cholesterol in the body.

1. The statins stop the HMG-CoA reductase, which leads to the decrease in concentration in cholesterol.

2. The low intracellular cholesterol increases the synthesis of LDL receptors.
3. The larger amount of LDL receptors boosts uptake of LDL from blood.
4. Lower intracellular cholesterol decreases the amount of production of VLDL.

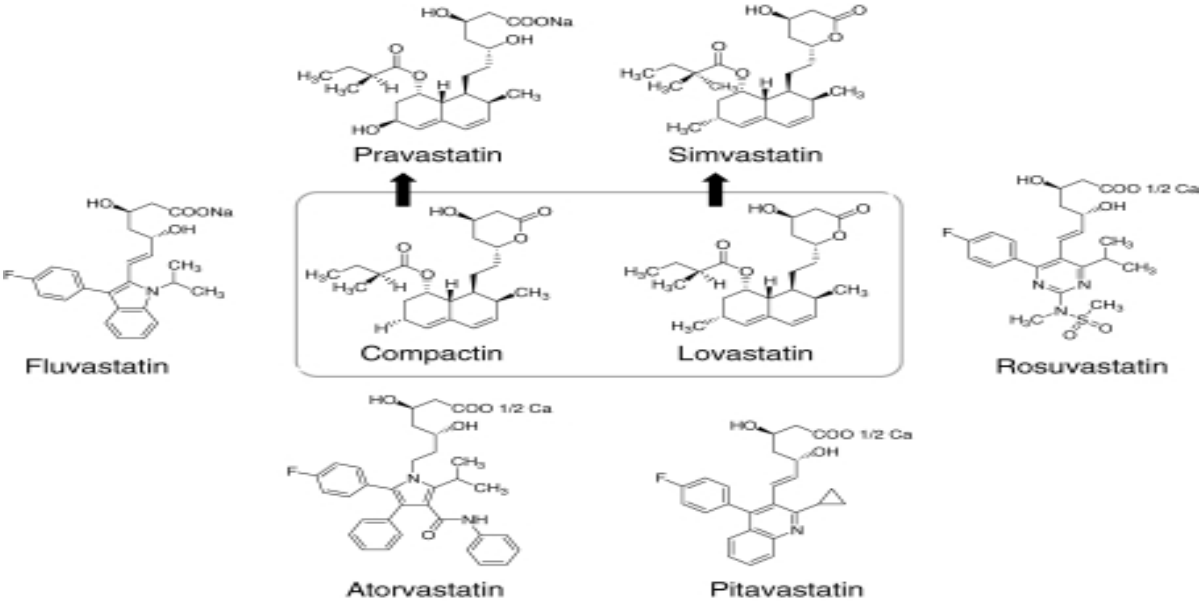



Fig. 4 -Structures of Different Statins

## Types of used statins

Currently 7 different types of high potency statins are used. Because of the very high levels of LDL, cholesterols are related to Familial hypercholesterolemia.

Table 2: Examples of High-,Moderate-, and Low-Intensity Statin Therapy (Adapted from 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults):

| High-intensity Statin Therapy | Moderate-Intensity Statin Therapy | Low-Density Statin Therapy |
|---|---|---|
| Daily dose lowers LDL-C on average by approx. ≥50%. | Daily dose lowers LDL-C, on average, by approximately 30% to <50%. | Daily dose lowers LDL-C, on average, by <30%. |
| Atorvastatin: (40-80 mg) | Atorvastatin: (10-20 mg) | Fluvastatin: (20-40 mg) |
| Rosuvastatina: (20-40 mg) | Fluvastatin: (40 mg twice daily) | Lovastatin: (20 mg) |
| | Fluvastatin: (XL 80 mg) | Pitavastatin: (1 mg) |
| | Lovastatin: (40 mg) | Pravastatin: (10-20 mg) |
| | Pitavastatin: (2-4 mg) | Simvastatin: (10 mg) |
| | Pravastatin: (40-80 mg) | |
| | Rosuvastatin: (5-10 mg) | |
| | Simvastatin: (20-40 mg) | |

## High Potency Statins

- Rosuvastatin (Crestor)-(8/13/2003)
- Atorvastatin (Lipitor)-(6/15/2001)
- Pitavastatin (Livalo)-(8/03/2009)
- Simvastatin (Zocor)-(3/31/1998)

## Statins

- Lovastatin (Mevacor, Altoprev) - (3/11/1999)
- Pravastatin (Pravachol)-(2/10/2000)
- Fluvastatin (Lescol, Lescol XL) -( 5/8/1999)

### Who are recommended to take Statins?

People who already have atherosclerotic cardiovascular disease. This includes people who have heart attacks, strokes caused by blockages in a blood vessel, mini-strokes(transient ischemic attacks), peripheral artery disease, or prior surgery to open or bypass coronary arteries.

People with very high LDL cholesterol. This group of people include adults who have LDL-cholesterol levels of 190 mg/dL (4.9 mmol/L) or higher. This group includes people with Familial Hypercholesterolemia, including children who have the ability to take statins between the ages of 8-10.

Furthermore, people who have diabetes. This group includes adults who have diabetes and an LDL-cholesterol between 70 and 189 mg/dL (1.8 and 4.9 mmol/L), especially if they have evidence of vascular disease.

People with a higher 10-year risk of heart attack. This group of people includes people who have an LDL-cholesterol between 70 and 189 mg/dL (1.8 and 4.9 mmol/L), and whose 10-year risk of a heart attack is 7.5 percent or higher.

### Common side effects of statins

Side effects can vary between different statins, but common side effects include:

- Headache
- Dizziness
- Feeling sick
- Feeling usually tired or physically weak
- Digestive system problems, such as constipation, diarrhea, indigestion or farting
- Muscle pain
- Sleep problems
- Low blood platelet count

### When and Why were statins approved?

The very first station was approved on September 1, 1987. And since then many more have been approved, as stated above these are used because of their success rate, in helping against Familial hypercholesterolemia. And since them many more have been approved, such as the one listed above, for the use to help people with HoFH and other such diseases.

# Surgical Options

## Overview

Using the paper (Surgical Management and Outcomes of Homozygous Familial Hypercholesterolemia in Two Cousins: A Rare Case Report) we will discuss the possibility of treating a some rare cases with surgeries which will help prevent the loss of life because of HoFH (Homozygous Familial HyperCholesterolemia). And it reports two cases of related patients with aortic stenosis and mitral regurgitation resulting from HoFH, who underwent the Bentall aortic root replacement, mitral valve replacement, and coronary artery bypass graft (CABG) surgery.

## Situation for patient 1 and 2:

Both the patients were first degree cousins. One being a 39 year old make non-smoker, and a 38 year old female non-smoker. Whole the make was diagnosed at the age of 14, the female was
diagnosed at the age of 17. Both had a history of family members with Hypercholesterolemia.

## Patient 1:

The 39-year-old was diagnosed with FH at age 14, and was initially taking oral simvastatin (80 mg) once daily. As the drug had gradually failed to maintain the total and the LDL cholesterol levels within the normal range, he had begun to undergo total plasma exchange and subsequent LDL plasma apheresis at 17 years of age. The combination of LDL plasma apheresis and statin therapy had been effective at that time. Moreover, at the age of he he was found with the symptoms with class II heart failure by the New York Heart Association (NYHA) functional classification of: angina and shortness of breath, and physical examination had been unremarkable apart from ejection systolic murmur over the second right intercostal space at the right sternal border.

The patient had been admitted at 25 years of age and undergone the Bentall procedure for SVAS, and he had tolerated the procedure very well. On postoperative day three, the patient had collapsed and had been intubated. Coronary angiography had shown stenotic ostial LAD and RCA. The patient had then undergone emergency CABG with the left internal mammary artery (LIMA) to LAD and saphenous vein graft (SVG) to RCA and obtuse marginal artery (OM). Three years after that, the patient had undergone mechanical mitral valve replacement and CABG reoperation (LIMA to diagonal and SVG to RCA and left circumflex artery), and he had tolerated the procedure very well.

At the most recent cardiac evaluation (November 18, 2019), the patient was found to be physically active with no significant cardiac symptoms on regular daily activities. The patient was vitally stable with minimal pulmonary congestion found on his chest X-ray.

## Patient 2:

Patient 2 was a 38-year-old female non-smoker, who was a known case of HoFH that had been diagnosed at 17 years of age. The patient had a positive family history of hypercholesterolemia in her father, sister, and brother. The patient also had a family history of valve replacement in her brother and sister and CABG in her father. Additionally, patient 1 was her first-degree cousin.

Timeline of the disease and treatment course for patient 2

| LDL: low-density lipoprotein; ECG: electrocardiography; CABG: coronary artery bypass graft | | | |
|---|---|---|---|
| **Date** | **Clinical Representation** | **Diagnostic findings** | **Interventions** |
| July 7, 1999 | Angina, dyspnea | Very high LDL cholesterol in serum | Statins |
| June 18, 2003 | Palpitation, dyspnea | Coronary angiography revealed blockage and echocardiography revealed aortic stenosis and mitral regurgitation. | Bentall procedure, mitral valve replacement, and CABG |
| January 9, 2020 | None | Lipid profile, ECG, Echo, chest X-ray | Statins, LDL apheresis, aspirin, evolocumab, ezetimibe, and warfarin |

### Discussion

Due to lipid infiltration and calcium deposition, HoFH is typically predisposed to CAD, valvular aortic stenosis, and SVAS from a lifetime of exposure to high levels of LDL and total cholesterol in the blood. In the report, patient 1 underwent two CABG procedures in addition to two procedures in which his aortic and mitral valves were replaced. Aortic and mitral valve replacements had already been performed on patient 2 during one CABG procedure. These two patients' requirement for surgical operations to keep them alive after being initially managed with high-dose statins and LDL apheresis implies that the development of their ASCVD was connected to protracted exposure to the high LDL and total cholesterol. Through the high risk invasive, and expensive treatment the patients had stabilized their output of Cholesterol in the body which would benefit in the long run while increasing their life expectancy. Which is why surgical options are useful options but it has to be used with the other provided solution.

## Genetic Engineering

### Overview

Genetic engineering has been used many times in mice to see if it is successful in mitigating the effects of FH. A mutation in the low-density lipoprotein (LDL) receptor (LDLR) is one of the main causes of familial hypercholesterolemia, which induces atherosclerosis and has a high lifetime risk of cardiovascular diseases. The clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 system is an effective tool for gene editing to correct gene mutations and thus to ameliorate disease.

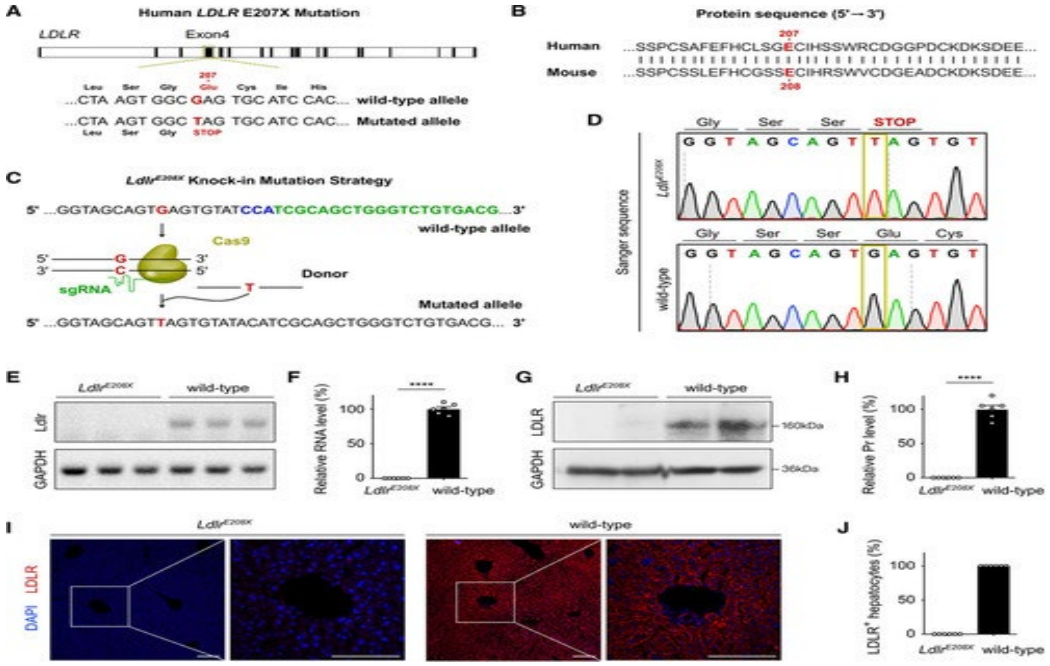
### Methods

The scientists provided both mice with a high fat diet. However, one received the AAV Crispr-Cas9 serum, and the other one did not. And these mice were both led through a 12 week high Fat diet, where both groups saw a significant increase in fats in theory, as the LDLR gene did not stop the LDL from producing and causing the Atherosclerosis plaques to build up in the blood vessels.

The goal of this work was to determine whether in vivo somatic cell gene editing through the CRISPR/Cas9 system delivered by adeno-associated virus (AAV) could treat familial hypercholesterolemia caused by the Ldlr mutant in a mouse model.The team of scientists produced a mouse with a nonsense mutation in the LDLR gene, based on a relevant familial hypercholesterolemia-related gene mutation. The AAV-CRISPR/Cas9 was designed to correct the point mutation in the Ldlr gene in hepatocytes and was delivered subcutaneously into Ldlr 208X mice.

## Results

The LDLR gene's fourth exon is where the majority of mutations take place. An individual with FH has been found to have the nonsense point mutation variant of LDLR known as E207X (a G-to-T point mutation, GAG -> TAG) (Figure 1A). To create a knock-in mouse line that expressed an E208X mutation (GAG -> TAG) in the LDLR gene via HDR, which was similar to the E207X mutation in the human LDLR gene, the research team used the CRISPR/Cas9 system to implant into fertilized eggs (Figure 1B and 1C). Additionally, a silent mutation (ATC -> ATA) was added to stop sgRNA from attaching to the sequence and recutting it (Figure 1C). A common mouse model for the study of atherosclerosis is the homozygous LdLr knockout mouse (LDLR-/-), whereas the heterozygous strain (LDLR+/-) has a heterozygous form of the gene.




## Discussion

The importance of genetic engineering solutions for this genetic disease is imperative. As could help the current as well as the future generations by almost removing the chance of someone having hypercholesterolemia. As in genetic engineering the tool with find the specific gene which in these conditions is the LDLR genes fourth exon, and it will delete the gene, which will cause a change in the body lower the rate of cholesterol in the body, which after a brief time period will return the person to a normal state. Even though there are some side effects of this therapy, the benefits outweigh the downfalls which is why this is of such importance.

## Conclusion

Familial Hypercholesterolemia is an Autosomal dominant, which occurs through inherited mutation in the LDLRAP1 Gene. It is characterized by very high levels of serum LDL-C with an increased risk for atherosclerosis and CVD, particularly coronary heart disease, the most important cause of mortality worldwide. Which is why it is of utmost importance for this disease to be cured. The solutions above are only some of the many solutions to Familial Hypercholesterolemia.

## Limitations

A limitation was how little amount of data there was on Genetic Engineering solutions for Familial Hypercholesterolemia.

## Acknowledgements

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