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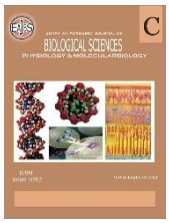
Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 17(1) pp163-177 (2025)*
DOI: 10.21608/EAJBSC.2025.432425

Egypt. Acad. J. Biolog. Sci., 17(1):153-177 (2025)

Egyptian Academic Journal of Biological Sciences
C. Physiology & Molecular Biology
ISSN 2090-0767
www.eajbsc.journals.ekb.eg



Revolutionizing Hypercholesterolemia Management: Integrating Genetics, Novel Therapies, and Public Health Strategies

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REVIEW INFO
Review History
Received:5/5/2025
Accepted:10/6/2025
Available:14/6/2025

Keywords:
Hypercholesterolemia; Lipid Metabolism; Low-Density Lipoprotein Cholesterol (LDL-C); PCSK9 Inhibitors; Atherosclerosis; Medical Genetics.

ABSTRACT

Hypercholesterolemia is a physiological condition in which there is an increase in the blood cholesterol. This condition is a genetic risk factor along with being modified by the environment as well as lifestyle factors. The disease is one of the major global issues which is found more in the low- and middle-income countries (LMICs) owing to their lifestyle diseases. It is estimated that approximately 39%-60% of adults worldwide are affected by elevated cholesterol levels, contributing significantly to the global burden of cardiovascular disease, which accounts for over 17 million deaths annually. Other common diseases accompanied by this undocumented medical condition include a stroke, coronary artery disease, and atherosclerosis. A majority identified cause of this disease is high levels of low-density cholesterol lipoproteins which lead to increased formation of vascular plaque. Effective strategies for treatment of the disease include genetic experiments and lipid profiling, some imaging tools were also effective. This is coupled with defining better stratification of risks and treatment options, PCSK9 inhibitors and statins have been common prescriptions due to their efficiency. Even though strides have been made, overcoming challenges such as lipid metabolism complexity, treatment accessibility while focusing on the patients is needed.

INTRODUCTION

High blood cholesterol levels, or hypercholesterolemia, are a severe and growing global health concern. In addition to being a lipid, a material that resembles fat, cholesterol also plays a role in the manufacture of hormones, bile acids, and cell membranes (Fleishman and Kumar, 2024). Nevertheless, the body's elevated cholesterol levels are mostly caused by low-density lipoproteins (LDL-C), which are one of the riskiest variables because they are known to promote atherosclerosis and cardiovascular illnesses (CVDs). With 17.9 million fatalities per year, CVDs continue to be the world's top cause of death. Since hypercholesterolemia is controllable, immediate action is needed to lessen the severe health and financial consequences this condition imposes (Ghodeshwar and Khobragade 2023). Although its prevalence varies by region according to age, gender, and socioeconomic level, hypercholesterolemia affects people on every continent. According to WHO estimates, diets high in cholesterol cause 4.4 million deaths per year, or 7.6 percent of all deaths (Ramírez *et al*., 2020). High-income nations have a well-established prevalence of hypercholesterolemia, which is linked to sedentary lifestyles and diets high in saturated fats (Ghazwani *et al*., 2023).

However, urbanization, dietary changes toward processed foods, and decreased physical activity are also contributing to the condition's sharp rise among LMICs. There are significant regional variations in the frequency of hypercholesterolemia. According to studies, prevalence rates among adults in North America and Europe range from 30% to 50%. On the other hand, the prevalence rate was low in places like Southeast Asia and Sub-Saharan Africa (Groenewegen *et al*., 2020).

However, as these areas adopt Western lifestyles and eating habits, they are catching up to the rest. In contrast to the extremely low rates among rural people, studies conducted in metropolitan India reveal that adult rates of hyper-cholesterolemia can reach around 25% (Chandra *et al*., 2024). In a similar vein, over the past three decades, hypercholesterolemia has become much more common in China, which is indicative of the larger dietary and lifestyle changes occurring in quickly growing nations (Li *et al.,* 2023). The prevalence of hypercholesterolemia is closely correlated with age due to changes in metabolism, a decrease in physical activity, and long-term exposure to risk factors. Actually, about 60% of adults over 60 have excessive cholesterol in the majority of nations. Another important factor is gender: premenopausal women often have lower LDL-C levels than men due to the preventive impact of estrogen (Witting *et al*., 2022). These levels, however, are higher in postmenopausal women, which raises their risk of cardiovascular problems later in life. A combination of environmental, nutritional, and hereditary variables can lead to hypercholesterolemia. Mechanisms that balance dietary intake and hepatic production against circulatory clearance strictly regulate cholesterol homeostasis (Song *et al*., 2024). The most atherogenic component of cholesterol, LDL-C, is increased when these mechanisms are disturbed. The circulating low-density lipoprotein cholesterol readily penetrates the artery endothelium. LDL-C experiences oxidative alteration as it enters the artery walls, which starts the inflammatory cascade. After that, macrophages consume oxidized LDL-C to produce foam cells, which aid in the formation of atherosclerotic plaques (Lu *et al.,* 2022). These plaques cause artery lumens to constrict over time, which lowers blood flow and raises the possibility of ischemic episodes. Acute consequences including myocardial infarction or ischemic stroke can arise from plaque rupture, highlighting the crucial connection between hyper-cholesterolemia and CVDs. By promoting reverse cholesterol transport, which involves removing extra cholesterol from peripheral tissues and returning it to the liver for excretion, high-density lipoprotein provides protection. Heart disease risk is further increased by low HDL levels, which typically coexist with excessive LDL-C (Alloubani *et al.*, 2021).

Triglycerides, the other lipid component, contribute to the pathogenesis of hypercholesterolemia when they rise, highlighting the complex nature of dyslipidaemia. In actuality, its influence extends far beyond issues of personal health; it has socioeconomic significance for families, communities, and even countries (Brett *et al*., 2021) . In addition, the financial burden of managing this illness and its repercussions is particularly heavy in environments where healthcare expenses are quite high. Given the costs of cholesterol-lowering medications, routine exams, and treating consequences like heart attacks and strokes, managing hypercholesterolemia can be very expensive (Ferrara *et al*., 2021). The treatment of disorders linked to hyper-cholesterolemia accounts for a sizable share of the more than $200 billion that cardiovascular diseases cost the US healthcare system each year. Due to limited access to reasonably priced healthcare and drugs, many people in LMICs are forced to forgo necessary treatment, which further exacerbates the financial strain. Significant production losses as a result of disability,

absenteeism, and early mortality are caused by hypercholesterolemia. Employees with cardiovascular issues frequently miss extended periods of work or retire early, which puts a financial strain on the family and lowers economic output overall (Ozawa *et al*., 2019).

Moreover, family members may be obliged to give up work in order to take care of individuals with advanced CVDs, further increasing the economic burden. Hypercholesterolemia presents a particularly compelling opportunity for intervention because it is a modifiable risk factor (Xiao, *et al*., 2024). Prevention, early detection, and management of hypercholesterolemia through lifestyle modifications and policy interventions are cornerstones of public health strategies. Heart-healthy behaviours are also a cornerstone of managing hypercholesterolemia. It follows those dietary changes, including the reduction of saturated fat and cholesterol intake with an increased consumption of fruits, vegetables, and whole grains, can significantly lower LDL-C levels (Rippe, 2018). Regular physical activity improves lipid metabolism and prevents cardiovascular diseases. It is also necessary to avoid smoking and control body weight to minimize the risks of hypercholesterolemia. Governments and public health organizations contribute a lot to creating supportive environments for a healthy lifestyle. This includes food labelling regulations, restriction of trans fats, and taxation of sugar-sweetened beverages (Wanjohi *et al*., 2021). In many countries, these policies have yielded positive results in reducing the risk factors related to hypercholesterolemia. Prohibition on trans fats, for example, resulted in striking decline rates of cardiovascular incidence, which pointed out huge potential regulatory policies could unleash. Community-based interventions proved efficient in spreading the knowledge and behavioural changes (Downs *et al*., 2017). Some interventions against hypercholesterolemia address the issue on a population basis such as workplace wellness programs, school-based nutrition education programs, and community physical fitness campaigns. These collaborations among governments, NGOs, and private sectors amplify their efforts in outreach and impact (Barnes *et al*., 2012). Hypercholesterolemia has traditionally been regarded as a disease of high-income countries, but there is an increasing awareness that this is an important public health problem in LMICs. The double burden of infectious and non-communicable diseases facing many countries in these regions adds complexity both for healthcare systems and policymakers (Gaziano *et al*., 2010). Urbanization has become one of the main drivers of rising rates of hypercholesterolemia in LMICs. As populations become more urbanized, diets shift toward processed foods that are high in saturated fats, sugars, and sodium (Anand *et al*., 2015). At the same time, lifestyles become more sedentary as physical activity is reduced and motorized transport becomes more common. The result is a rapid increase in hypercholesterolemia, along with other lifestyle-related diseases (Anand *et al*., 2021).

Limited access to healthcare services and medications poses significant obstacles to managing hypercholesterolemia in LMICs. Many individuals remain undiagnosed due to inadequate screening programs, while those diagnosed often face financial barriers to treatment (Li *et al*., 2024). Cultural factors, including stigma and traditional beliefs about illness, further complicate efforts to address hypercholesterolemia in these settings. Addressing hypercholesterolemia in LMICs requires innovative and context-specific approaches. Task-shifting strategies, where non-physician healthcare workers are trained to provide basic care, have been promising in expanding access to services (Coales *et al*., 2023). Figure 1 shows high cholesterol as a major modifiable risk factor for cardiovascular diseases, which are the leading cause of global mortality.

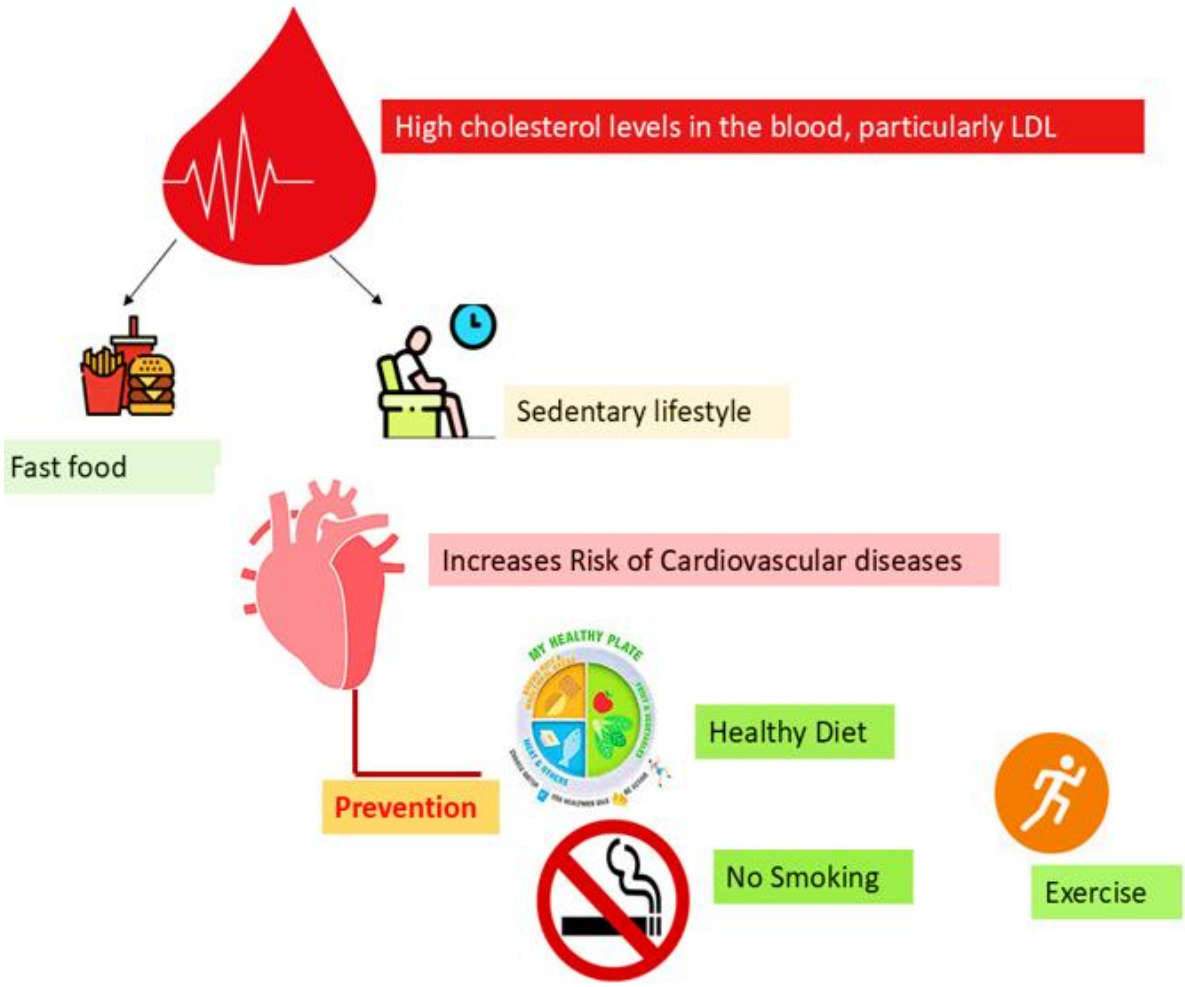

Fig. 1: Key Facts and Prevention of High Cholesterol.

Other alternatives include the mHealth technologies, which will educate the people, remind them on the use of medications, as well as provide them with tools for tracking their diet through mobile devices. The global menace of hypercholesterolemia has seen various international campaigns focus on its reduction and the health risks emanating from it (Abaza and Marschollek, 2017). In these calls, collaboration among governments, health care providers, and civil society is emphasized. The WHO's Global Action Plan for the Prevention and Control of Non-Communicable Diseases has set an ambitious target to reduce, by 25%, premature mortality from NCDs by 2025. The major components of this plan include promoting healthy diets, improving access to essential medicines, and integrating non-communicable disease management into primary healthcare systems (Peykari *et al*., 2017). Hypercholesterolemia is a vital point of this wide-ranging agenda. Regional organizations such as the European Heart Network and the Pan American Health Organization have targeted programs to address hypercholesterolemia (Thongtang *et al*., 2022). Many of these initiatives merge research, advocacy, and education in their approach to the improvement of cholesterol management and reduction in the burden of cardiovascular disease. In addition, such collaborative frameworks allow countries to share their knowledge and then adopt the best practices. Technological changes are the face of managing hypercholesterolemia. Digital health tools, such as mobile apps and wearable devices, put the power of knowing one's cholesterol levels and making informed lifestyle choices in the hands of the

individual. Telemedicine platforms increase access to specialized care, especially in underserved areas, by allowing remote consultations and follow-ups (Haleem *et al*., 2021).

Precision medicine approaches, including genetic testing and pharmacogenomics, offer personalized treatment strategies based on individual risk profiles.These innovations hold great promise for enhancing the effectiveness of hypercholesterolemia interventions and reducing its global burden (Downs *et al*., 2017). Hypercholesterolemia is a pressing problem in world health with wide-ranging repercussions for individuals and societies. As the major modifiable risk factor for cardiovascular diseases, its prevention, detection, and management need a comprehensive approach. It requires cooperation among governments, health systems, and communities in order to reduce the global burden of hypercholesterolemia and improve cardiovascular health outcomes (Tash and Al-Bawardy , 2023).

Genetic Basis of Hypercholesterolemia:

Atherosclerosis, coronary artery disease (CAD), heart attacks, and strokes are among the cardiovascular disorders that are greatly exacerbated by hypercholesterolemia, a condition marked by increased blood cholesterol levels (Libby, 2021). Hypercholesterolemia is recognized to be caused by environmental variables including diet and lifestyle decisions, but hereditary factors are equally important and frequently have a greater influence on the condition's development (Vrablik *et al*., 2020). Hyper-cholesterolemia, a condition characterized by elevated blood cholesterol levels, significantly aggravates a number of cardiovascular conditions, including atherosclerosis, coronary artery disease (CAD), heart attacks, and strokes. Although environmental factors, such as diet and lifestyle choices, are known to contribute to hypercholesterolemia, genetic factors are just as significant and often have a bigger impact on the condition's development (Ibrahim *et al*., 2025). The main molecular cause of hypercholesterolemia is an imbalance between the production, absorption, and elimination of cholesterol (Song *et al*., 2021). Cholesterol is an essential lipid that is necessary for the formation of bile acids, vitamin D, steroid hormones, and cell membrane structure and function. In order to prevent the negative consequences of both low and high cholesterol, the body needs to carefully control its cholesterol levels (Song *et al*., 2021). The genes that influence lipid transport and metabolism have the greatest direct influence on cholesterol levels, even though numerous genes play a role in this control. Familial hypercholesterolemia (FH), the most prevalent genetic cause of hypercholesterolemia, is an autosomal dominant disorder, meaning that a person will only be afflicted if they inherit one copy of the faulty gene from a parent (Pejic, 2014). LDL receptor (LDLR) gene mutations are usually the cause of FH. A protein called the LDL receptor, which is encoded by this gene, is found on the surface of the liver and other cells and is crucial for removing low-density lipoprotein cholesterol (LDL-C) from the blood. After attaching itself to blood LDL particles, the LDL receptor internalizes the cholesterol and sends it to the liver for processing and elimination (Wang *et al*., 2001).

When the LDLR gene is mutated, the receptor may become completely or partially dysfunctional, making it more difficult for the liver to eliminate LDL-C from the blood. Higher cholesterol and a higher risk of cardiovascular disease result from the accumulation of LDL-C in the bloodstream (Ibrahim *et al*., 2025). A person with heterozygous FH has one normal allele and one mutant allele, which causes a 50% decrease in LDL receptor function. As a result, LDL-C values become somewhat increased, frequently between 190 and 400 mg/dL. Heterozygous FH patients who receive no treatment eventually develop atherosclerosis and other early-onset cardiovascular disorders (Goldstein *et al*., 1976). Functional LDL receptors are almost entirely absent in homozygous FH, a

condition in which both alleles of the LDLR gene are altered. LDL-C values in this severe form of FH can surpass 600 mg/dL, and those who are afflicted frequently suffer from potentially fatal cardiovascular events before the age of 20 (Nohara *et al*., 2021). The pathophysiology of FH emphasizes how important the LDL receptor is to the metabolism of cholesterol. Hypercholesterolemia is caused by mutations in the LDLR gene as well as other genes that control the quantity and functionality of LDL receptors. The proprotein convertase subtilisin/kexin type 9 (PCSK9) gene is a crucial gene in this context. A serine protease that PCSK9 encodes controls the LDL receptor by encouraging its breakdown (Soutar and Naoumova, 2007).

The number of LDL receptors on the cell surface is reduced when PCSK9 binds to the LDL receptor and promotes the internalization and destruction of the receptor. This raises plasma cholesterol levels and decreases the blood's ability to remove LDL-C. LDL-C levels are markedly raised by gain-of-function mutations in PCSK9, which result in increased degradation of the LDL receptor (Peterson *et al*., 2008). However, PCSK9 loss-of-function mutations result in more functional LDL receptors, which improves LDL-C clearance and lowers plasma cholesterol levels. Given that PCSK9 inhibitors have been developed as a therapy method for hypercholesterolemia and have demonstrated considerable reductions in LDL-C levels and cardiovascular risk, these findings have major clinical implications (Liu *et al*., 2022).

Encoding the protein apolipoprotein B-100 (ApoB-100), the apolipoprotein B (APOB) gene is another gene linked to hypercholesterolemia. Atherogenic lipoproteins, such as LDL, VLDL, and IDL, are primarily composed of the protein ApoB-100. ApoB-100 is primarily involved in mediating lipoprotein binding to the LDL receptor and facilitating cell uptake (Kounatidis *et al*., 2024). Mutations in the APOB gene that alter ApoB-100's structure can hinder LDL particle binding to the LDL receptor, decreasing the effectiveness of LDL clearance and raising LDL-C levels. Familial faulty apoB-100 (FDB), a well-characterized mutation, causes a defective ApoB-100 protein that is unable to attach to the LDL receptor effectively. Like people with FH, those with this mutation have elevated cholesterol and a higher risk of cardiovascular disease (Tybjaerg-Hansen and Humphries, 1992).

Hypercholesterolemia is caused by mutations in a number of genes that impact lipid metabolism in addition to those that directly control LDL-C metabolism. For instance, a protein involved in the efflux of cholesterol from peripheral tissues, such the walls of arteries, to high-density lipoproteins (HDL) is encoded by the ATP-binding cassette transporter A1 (ABCA1) gene (Brunham *et al*., 2015). Reverse cholesterol transport is the term for this procedure. Atherosclerosis risk is increased by mutations in ABCA1 that affect cholesterol efflux and lower HDL-C levels. One important risk factor for cardiovascular disease is low HDL-C levels. Another receptor implicated in lipoprotein metabolism is encoded by the LDL receptor-related protein 1 (LRP1) gene. LRP1 plays a part in the removal of VLDL and chylomicron remnants as well as the endocytosis of lipoprotein particles (Au *et al.*, 2017). Familial mixed hyperlipidaemia (FCHL), a lipid condition marked by increased levels of both LDL-C and triglycerides, is linked to mutations in the LRP1 gene. A complicated genetic illness impacted by both genetic and environmental factors, FCHL usually manifests as early cardiovascular disease (Au *et al.*, 2017).

Another protein implicated in lipid metabolism is cholesterol ester transfer protein (CETP), which is encoded by the CETP gene. The distribution of cholesterol among various lipoproteins is impacted by the process by which CETP mediates the transfer of cholesterol esters from HDL to VLDL and LDL (Oestereich *et al.*, 2022). Changes in cholesterol levels have been linked to variations in the CETP gene that affect the protein's function. Atherosclerosis and

hypercholesterolemia are exacerbated by some genetic variations that cause elevated CETP activity, which lowers HDL-C and raises LDL-C levels. On the other hand, it has been discovered that certain forms of CETP decrease CETP activity, which is linked to increased HDL-C levels and a decreased risk of cardiovascular disease (Nurmohamed *et al.*, 2022).

Understanding the genetic basis of hypercholesterolemia requires knowledge of genetic variables affecting the production, absorption, and transport of cholesterol in addition to these well-characterized genes. The mevalonate route, which comprises the enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) converting acetyl-CoA to mevalonic acid, is the main way that cholesterol is produced in the liver (Friesen and Rodwell, 2004). Statin medications, which are frequently used to decrease cholesterol levels in people with hypercholesterolemia, target HMGCR. The activity of the enzyme can be changed by mutations in the HMGCR gene, which can lead to either increased or decreased synthesis of cholesterol. The intestinal Niemann-Pick C1-like 1 (NPC1L1) transporter facilitates the absorption of cholesterol from the diet in addition to its production (Dayar and Pechanova, 2022). Differences in cholesterol levels and vulnerability to hyper-cholesterolemia can result from variations in the NPC1L1 gene, which can impact the effectiveness of cholesterol absorption. Table 1, summarizing the genetic factors and associated proteins involved in hypercholesterolemia and cardiovascular diseases.

Table 1: Genetic Factors and Associated Proteins Involved in Hypercholesterolemia and Cardiovascular Diseases.

Gene/Protein	Role/Function	Associated Condition	Mechanism/Impact	Clinical Implications
LDLR (LDL Receptor)	Removes LDL-C from the blood	Familial Hypercholes-terolemia (FH)	Mutations in LDLR lead to dysfunctional receptors, resulting in decreased LDL-C clearance and increased plasma cholesterol levels.	Elevated risk of early-onset cardiovascular disease (atherosclerosis, CAD, heart attacks).
PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9)	Regulates LDL receptor degradation	FH, Hypercholes-terolemia	Gain-of-function mutations increase degradation of LDL receptor, raising LDL-C levels. Loss-of-function mutations improve LDL-C clearance.	PCSK9 inhibitors are used to lower LDL-C levels and cardiovascular risk.
APOB (Apolipoprotein B-100)	Involved in LDL, VLDL, and IDL lipoprotein structure and function	Familial defective apoB-100 (FDB)	Mutations alter ApoB-100, preventing efficient binding to LDL receptor, resulting in reduced LDL-C clearance.	Elevated cholesterol levels and cardiovascular disease risk similar to FH.
ABCA1 (ATP-Binding Cassette Transporter A1)	Mediates reverse cholesterol transport	Atherosclero sis, CAD	Mutations hinder cholesterol efflux from tissues to HDL, reducing HDL-C levels and increasing cardiovascular risk.	Decreased HDL-C levels increase atherosclerosis risk.
LRP1 (LDL Receptor-Related Protein 1)	Involved in lipoprotein particle endocytosis and clearance	Familial Mixed Hyperlipidae-mia (FCHL)	Mutations lead to increased levels of both LDL-C and triglycerides, raising cardiovascular disease risk.	A complicated genetic condition with early cardiovascular disease onset.
CETP (Cholesterol Ester Transfer Protein)	Transfers cholesterol esters between lipoproteins	Hypercholes-terolemia, Atherosclero sis	Mutations in CETP lead to altered cholesterol distribution, with some variations increasing LDL-C and lowering HDL-C, exacerbating cardiovascular risk.	Some CETP variants decrease CETP activity, linked to higher HDL-C and reduced cardiovascular risk.
HMGCR (3-Hydroxy-3-Methylglutaryl-CoA Reductase)	Converts acetyl-CoA to mevalonic acid in cholesterol biosynthesis	Statin therapy target	Mutations may increase or decrease cholesterol synthesis, affecting overall cholesterol levels.	Statin drugs target HMGCR to reduce cholesterol levels in hypercholesterolemia patients.
NPC1L1 (Niemann-Pick C1-Like 1)	Facilitates intestinal cholesterol absorption	Hypercholes-terolemia	Variations in NPC1L1 affect cholesterol absorption, influencing plasma cholesterol levels and susceptibility to hypercholesterolemia.	Impacts the effectiveness of cholesterol-lowering therapies and absorption inhibition (e.g., ezetimibe).

The intricate interaction of these genetic variants results in differences in plasma cholesterol levels and cholesterol metabolism. The development of hypercholesterolemia is influenced by disturbances to the equilibrium of cholesterol production, absorption, and elimination. Heart disease, atherosclerosis, stroke, and other cardiovascular disorders can be considerably increased by genetic

abnormalities that impact the LDL receptor, ApoB-100, PCSK9, ABCA1, and other important proteins involved in lipid metabolism (Burnett and Hooper, 2008). To treat hypercholesterolemia and lower the risk of cardiovascular disease, more focused and efficient treatments must be developed. This requires an understanding of these genetic pathways. The diagnosis, prevention, and treatment of lipid problems are also affected by genetic insights into hypercholesterolemia, which lays the groundwork for customized therapy in the care of patients with high cholesterol.

Diagnostic Implications:

One of the main risk factors for cardiovascular diseases (CVD), such as atherosclerosis, coronary artery disease, and stroke, is hypercholesterolemia, a condition characterized by high blood cholesterol levels. In order to identify those who are at high risk for cardiovascular events, it is essential to diagnose hypercholesterolemia as soon as possible (Bianconi *et al.,* 2021). This enables early intervention to stop the course of these disorders. Using a combination of sophisticated biomarkers, genetic testing, imaging methods, and conventional lipid testing, the diagnostic approach to hypercholesterolemia has undergone significant change. These diagnostic instruments not only assist in determining cholesterol levels but also offer crucial information on subclinical atherosclerosis, underlying genetic predispositions, and general cardiovascular risk (Medeiros *et al.,* 2023).

Triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) are all measured as part of the lipid profile, which is the main technique for detecting hypercholesterolemia. The lipid profile is the primary tool used to evaluate lipid abnormalities that lead to atherosclerosis, which is the pathological accumulation of plaque in the artery walls (Oh *et al.,* 2022).

The main cause of cholesterol buildup in artery walls, which results in plaque development, is LDL particles, which is why elevated LDL-C levels are an important diagnostic indicator for hypercholesterolemia (Wazir *et al.,* 2023). HDL-C, on the other hand, is frequently referred to as "good cholesterol" due to the fact that it makes it easier for cholesterol to be recycled from peripheral tissues to the liver. The risk of atherosclerotic cardiovascular disorders is thus increased by low HDL-C levels (Morin *et al.,* 2018). The risk of atherosclerosis is further enhanced by elevated triglycerides because they can cause lipoprotein particle sizes to rise, which may encourage atherogenesis. In order to diagnose hypercholesterolemia, blood tests are usually performed following an overnight fast. The gold standard for precise cholesterol readings is the fasting lipid profile, which captures the baseline lipid levels unaffected by recent food consumption. The lipid profile results are evaluated using predetermined thresholds specified by the National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) (Berberich and Hegele , 2022).

These recommendations classify LDL-C readings above 160 mg/dL as increased and total cholesterol levels above 200 mg/dL as high. It is considered low when HDL-C levels are less than 40 mg/dL for males and 50 mg/dL for women, and high when triglyceride levels are greater than 150 mg/dL (Wen *et al.,* 2019). Following that, the levels of these lipids are used to categorize people into different cardiovascular disease risk groups.

Lipid profiles, however, are not always adequate for determining the entire range of cardiovascular risk or identifying the underlying causes of hypercholesterolemia. For example, tests other than the lipid profile may be necessary to diagnose familial hypercholesterolemia (FH), a genetic disorder marked by abnormally high cholesterol levels (Shabana and Sarwar, 2020). Usually, FH is linked to significantly higher LDL-C levels, which frequently surpass 190 mg/dL in adolescents and 220 mg/dL in adults. Genetic testing may be used to find mutations in lipid metabolism-related genes in order to validate

a diagnosis of FH. The LDL receptor (LDLR) gene, which codes for a protein that eliminates LDL-C from the bloodstream, is impacted by the most prevalent genetic abnormalities linked to FH (Suryawanshi and Warbhe, 2023). Elevated cholesterol levels are caused by mutations in the LDLR gene, which decrease the quantity of functioning LDL receptors. The proprotein convertase subtilisin/kexin type 9 (PCSK9) and apolipoprotein B (APOB) genes, which are also important regulators of cholesterol metabolism, may be affected by further mutations (Suryawanshi and Warbhe, 2023).

The use of genetic testing to diagnose hypercholesterolemia has grown in importance, especially for those with a family history of early-onset cardiovascular disease or those whose excessive lipid levels cannot be explained by lifestyle choices alone (Ontario Health, 2022). When FH is suspected, genetic testing can verify whether LDLR, APOB, or PCSK9 gene variants are present. In addition to aiding in the diagnosis of FH, the discovery of these mutations gives family members who could be at risk for the illness vital information (Ontario Health, 2022). Genetic testing can also be used to diagnose other inherited lipid disorders, such as familial combined hyperlipidaemia (FCHL), which is linked to elevated levels of both LDL-C and triglycerides, or familial defective apoB-100, which is caused by mutations in the APOB gene and results in defective LDL particles that are ineffectively removed from the bloodstream (Patni *et al.*, 2023).

A number of sophisticated diagnostic techniques have been developed to better evaluate cardiovascular risk and identify those who are more likely to experience adverse events, even if their lipid levels are normal. These techniques go beyond conventional lipid testing and genetic analysis (Upadhyay, 2015). A genetically determined variation of LDL that has been demonstrated to be an independent risk factor for cardiovascular disease is lipoprotein(a) [Lp(a)], which may be measured. Particularly in those with hypercholesterolemia, elevated Lp(a) levels are linked to an increased risk of atherosclerosis and thrombosis (Reyes-Soffer *et al.*, 2022). Figure 2, represents the various diagnostic approaches used to identify hypercholesterolemia and assess cardiovascular risk.

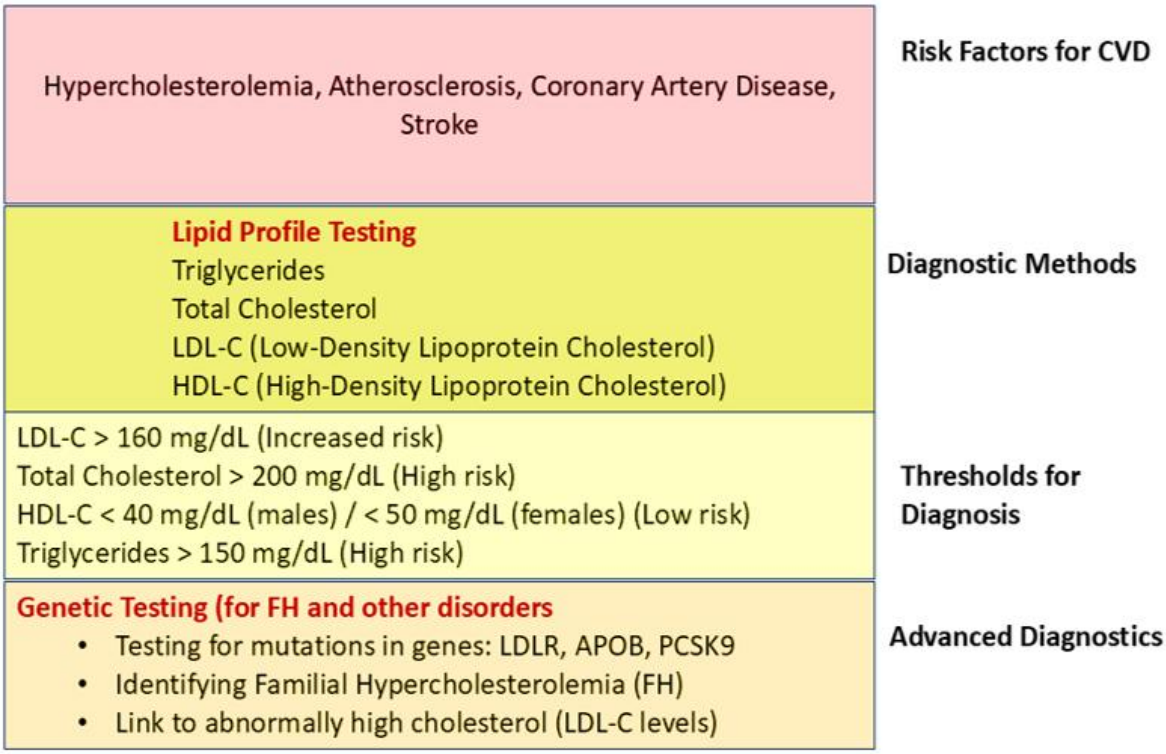

Fig. 2: Diagnostic Approaches to Hypercholesterolemia and Cardiovascular Risk.

The measurement of Lp(a) can help identify individuals who may be at higher risk for cardiovascular events, even if their LDL-C levels are within the normal range. Elevated levels of Lp(a) aid in the formation of atherosclerotic plaques and may stabilize them, increasing their vulnerability to rupture and subsequent cardiovascular events including heart attacks and strokes (Vinci *et al.*, 2023). A significant biomarker in the thorough evaluation of hypercholesterolemia and cardiovascular risk, elevated Lp(a) levels are also linked to other illnesses, such as valvular heart disease and chronic kidney disease (Vinci *et al.*, 2023).

In the assessment of cardiovascular risk and hypercholesterolemia, high-sensitivity C-reactive protein (hs-CRP) is another sophisticated biomarker with diagnostic utility. The systemic inflammatory response to atherosclerotic plaque accumulation in the arteries is reflected by the inflammatory marker hs-CRP. Atherosclerosis progresses mostly due to inflammation, which is indicated by elevated hs-CRP levels (Koenig, 2013). When hypercholesterolemia is present, raised hs-CRP levels may suggest subclinical atherosclerosis or a higher risk of plaque rupture. A more thorough evaluation of cardiovascular risk is possible when hs-CRP measurement is combined with lipid profile testing, particularly in people with borderline lipid levels. People with higher hs-CRP and high LDL-C levels, for instance, can benefit from more aggressive treatment approaches, such as statin therapy or other anti-inflammatory drugs. Non-invasive imaging methods are also crucial for identifying and evaluating the effects of hyper-cholesterolemia on cardiovascular health. Imaging techniques that offer important information about the existence and severity of atherosclerosis include magnetic resonance imaging (MRI), coronary computed tomography angiography (CTA), and carotid ultrasound. It is common practice to assess carotid intima-media thickness (CIMT) using ultrasound in order to identify subclinical atherosclerosis (Poznyak *et al.*, 2023).

It has been demonstrated that CIMT is a good indicator of upcoming cardiovascular events and correlates with the existence of coronary artery disease. Peripheral artery disease, heart attack, and stroke are all linked to elevated CIMT (Kabłak-Ziembicka and Przewłocki, 2021). The capacity to predict cardiovascular risk is improved when CIMT measurement is added to lipid profiles and genetic testing, especially for people who may have acceptable cholesterol levels but are at risk because of things like family history or elevated hs-CRP levels. MRI and coronary CTA can provide give detailed pictures of plaque accumulation and coronary artery blockages in addition to CIMT (Kabłak-Ziembicka and Przewłocki, 2021). In patients with hypercholesterolemia, these imaging methods can be used to measure the extent of coronary stenosis, spot high-risk plaques, and track the development of atherosclerosis. More individualized risk assessment is made possible by imaging, which can also help with the decision-making process when starting more invasive operations like coronary artery bypass grafting or angioplasty or statin therapy (Syed *et al.*, 2019).

Accurately diagnosing hyper-cholesterolemia, identifying people at increased cardiovascular risk, and tracking the progression of atherosclerosis are all made possible by the combination of genetic testing, lipid profile testing, sophisticated biomarkers, and imaging techniques (Ontario Health, 2022). Confirming a diagnosis of familial hypercholesterolemia or other hereditary lipid disorders requires genetic testing for patients with a family history of cardiovascular disease or those who come with severe lipid abnormalities. Apart from genetic and metabolic tests, biomarkers like hs-CRP and Lp(a) offer more insights into plaque stability and inflammation, which can help guide therapy choices. When subclinical atherosclerosis is detected by advanced imaging methods including MRI, coronary CTA, and CIMT assessment, patients who

might benefit from earlier intervention can be identified (Koenig, 2013). The diagnostic implications of hypercholesterolemia extend beyond the simple identification of elevated cholesterol. By using comprehensive diagnostic tools and methodologies, healthcare providers can better estimate the cardiovascular risk of each patient, monitor the progression of the disease, and tailor interventions to prevent adverse cardiovascular outcomes. This makes it possible to provide patient treatment that is more tailored to each patient. Better outcomes for people with hypercholesterolemia are anticipated as the diagnostic landscape for the condition develops with the discovery of additional biomarkers and imaging methods.

Therapeutic Interventions:

An important risk factor for the onset of atherosclerotic cardiovascular diseases (CVD), such as peripheral artery disease, coronary artery disease, and stroke, is hypercholesterolemia, which is characterized as having high blood cholesterol levels. The range of treatment options available to manage and treat hypercholesterolemia has expanded along with our understanding of its aetiology. Reducing low-density lipoprotein cholesterol (LDL-C) levels is the main objective of treatment for hyper-cholesterolemia since elevated LDL-C plays a significant role in the development and advancement of atherosclerosis (Surma and Banach, 2021). Additionally, the goal of therapeutic interventions is to lower triglyceride levels, increase HDL-C (high-density lipoprotein cholesterol), and alter the underlying environmental and genetic factors that affect lipid metabolism. There are several different approaches to treating hyper-cholesterolemia, including pharmaceutical treatments, lifestyle changes, and even surgery. Therapy can be customized to a patient's unique lipid profile, genetic predispositions, and overall cardiovascular risk as personalized medicine develops (Kirkpatrick *et al.*, 2023).

Adopting lifestyle changes is the cornerstone of managing hyper-cholesterolemia, and for best results, it should be used in conjunction with pharmaceutical therapy. Smoking cessation, weight control, physical exercise, and dietary modifications are the initial lines of care for hypercholesterolemia (Mannu *et al.*, 2013).These alterations in lifestyle can enhance the lipid profile overall by raising HDL-C levels and lowering LDL-C levels. Cholesterol levels can be lowered by increasing consumption of foods high in fiber, monounsaturated fats (like olive oil), and omega-3 fatty acids (found in walnuts, flaxseeds, and fatty fish). A diet low in saturated fats, trans fats, and cholesterol is advised. In particular, studies have demonstrated that the Mediterranean diet, which prioritizes plant-based foods, whole grains, and healthy fats, improves lipid profiles and cardiovascular health (Feingold, 2024). Table 2, represents mechanisms and outcomes of cholesterol management strategies.

Table 2: Therapeutic Interventions for Hypercholesterolemia: Strategies, Mechanisms, and Clinical Implications.

Intervention	Description	Mechanism of Action	Key Benefits	Potential Side Effects
Lifestyle Changes	Dietary modifications, exercise, smoking cessation, and weight management.	Improves lipid metabolism by reducing LDL-C and increasing HDL-C through healthy practices.	Enhances overall lipid profile, reduces cardiovascular risk, and supports general health.	Minimal (e.g., temporary discomfort from increased activity levels).
Statins	First-line pharmacological therapy for lowering LDL-C.	Inhibits HMG-CoA reductase, reducing cholesterol synthesis and increasing hepatic uptake of LDL.	Significantly lowers LDL-C, reduces cardiovascular events like heart attacks and strokes.	Myalgia, liver enzyme abnormalities, rare rhabdomyolysis.
Bile Acid Sequestrants	Medications like cholestyramine and colesevelam used as adjuncts to statins or standalone in some cases.	Binds bile acids in the intestine, prompting the liver to use cholesterol to produce more bile acids.	Lowers LDL-C, useful in statin-intolerant patients.	Gastrointestinal issues (bloating, flatulence, constipation).
Fibrates	Used to manage hypertriglyceridemia and mixed dyslipidemia.	Activates PPAR-α, enhancing lipoprotein lipase activity to reduce triglycerides and modestly raise HDL-C.	Reduces triglycerides, raises HDL-C, effective in hypertriglyceridemia.	Increased risk of muscle-related side effects when combined with statins.
Niacin	Vitamin B3 used to lower LDL-C and triglycerides and raise HDL-C.	Inhibits hepatic VLDL production and enhances reverse cholesterol transport.	Raises HDL-C, lowers LDL-C and triglycerides.	Flushing, itching, gastrointestinal discomfort, potential liver toxicity.
Cholesterol Absorption Inhibitors	Medications like ezetimibe used as an adjunct to statins or standalone therapy.	Blocks cholesterol absorption in the small intestine, reducing LDL-C in circulation.	Lowers LDL-C, reduces cardiovascular events, well tolerated.	Rare gastrointestinal discomfort.
PCSK9 Inhibitors	Monoclonal antibodies like alirocumab and evolocumab for severe hypercholesterolemia or familial cases.	Inhibits PCSK9, increasing LDL receptor availability for cholesterol clearance.	Reduces LDL-C by >60%, lowers cardiovascular risk in high-risk patients.	High cost, requires subcutaneous injections.
Emerging Therapies	Gene therapy and RNA-based treatments in development.	Targets genetic mutations (e.g., CRISPR-Cas9) or inhibits gene expression (e.g., siRNA).	Potential for long-term or permanent correction of hypercholesterolemia.	Still under research, long-term safety and efficacy unknown.

It has also been demonstrated that regular exercise, especially aerobic exercise, raises HDL-C and decreases LDL-C. At least 150 minutes a week of vigorous exercise, such as swimming, cycling, or brisk walking, can significantly enhance cardiovascular health and lipid metabolism (Franczyk *et al.*, 2023). Additionally, losing weight is linked to better lipid levels, and even small weight loss can have a good impact on cholesterol levels and lower the risk of CVD. Because tobacco use lowers HDL-C levels, speeds up the course of cardiovascular illnesses, and contributes to the formation of atherosclerosis (Franczyk *et al.*, 2023). Pharmacological treatment may be required in certain situations when lifestyle changes alone are not enough to reach acceptable cholesterol

levels. The severity of hypercholesterolemia, risk factors, and the patient's lipid profile all influence the medication selection (Chhetry and Jialal, 2023). Statins, bile acid sequestrants, fibrates, niacin, and, more recently, PCSK9 inhibitors and cholesterol absorption inhibitors are the drugs most frequently used for hypercholesterolemia (Chhetry and Jialal, 2023). The most popular family of drugs for reducing LDL-C levels are statins, sometimes referred to as HMG-CoA reductase inhibitors. Statins function by blocking the HMG-CoA reductase enzyme, which is necessary for the liver's manufacture of cholesterol (Schonewille *et al.,* 2016). Statins lower circulating LDL-C levels by blocking this enzyme, which lowers cholesterol synthesis and encourages the liver to absorb more LDL particles from the blood. It has been demonstrated that statins dramatically lower the risk of cardiovascular events, such as heart attacks, strokes, and cardiovascular disease-related deaths (Schonewille *et al.,* 2016). Statins are the first-line treatment for patients with hypercholesterolemia, especially those who are at high risk of atherosclerotic cardiovascular events, due to their effectiveness in lowering LDL-C and lowering cardiovascular risk. Statins do have certain adverse effects, though (Taylor *et al.,* 2013). The most frequent adverse effects include abnormal liver enzymes, myalgia (pain in the muscles), and, in rare instances, rhabdomyolysis. For the majority of individuals with hypercholesterolemia, statins continue to be the most effective pharmaceutical choice despite these possible side effects (Ramkumar *et al.,* 2016).

Another class of drugs used to reduce LDL-C levels are bile acid sequestrants, which include cholestyramine, colestipol, and colesevelam. In order to stop bile acids from being reabsorbed and to encourage their evacuation, these drugs attach to them in the intestine. This lowers the quantity of cholesterol in the bloodstream because the liver uses cholesterol to make more bile acids (Scaldaferri *et al.,* 1999). When statins are not tolerated by a patient, bile acid sequestrants are usually given as an adjuvant. Although these drugs are good in reducing LDL-C, they can have negative effects on the gastrointestinal tract, such as flatulence, bloating, and constipation (Scaldaferri *et al.,* 1999). Although they are mainly used to reduce triglyceride levels, fibrates like gemfibrozil and fenofibrate can also slightly raise HDL-C levels. The activation of peroxisome proliferator-activated receptor-alpha (PPAR-α) by fibrates raises the activity of the enzyme lipoprotein lipase, which breaks down triglycerides (Fruchart *et al.,* 1999). In individuals with hypertriglyceridemia, which is frequently found in association with hyper-cholesterolemia, fibrates are especially helpful. They can be used in concert with statins to offer a more thorough approach to lipid control. When taken with statins, fibrates can raise the risk of side effects relating to the muscles, hence their usage is usually limited to people with mixed dyslipidaemia or high triglyceride levels (Fruchart *et al.,* 1999).

Another medication used to treat hypercholesterolemia is niacin (vitamin B3), especially in those with low HDL-C levels. Niacin lowers LDL-C and triglyceride levels by preventing the liver from producing VLDL (very-low-density lipoprotein) (Zeman *et al.,* 2015). By improving the reverse cholesterol transport pathway, it also raises HDL-C levels. Despite its advantages, niacin's extensive use is restricted due to its negative effects, which include flushing, itching, gastrointestinal distress, and liver damage. Furthermore, niacin's use as a first-line treatment has decreased as a result of new research casting doubt on its cardiovascular advantages, particularly when combined with statins (Zeman *et al.,* 2015). Ezetimibe and other cholesterol absorption inhibitors function by preventing the small intestine from absorbing cholesterol. This lowers the quantity of cholesterol that enters the bloodstream and encourages the liver to absorb more LDL particles (Nutescu and Shapiro, 2003). For individuals who need more LDL-C lowering or who are unable to handle larger dosages of statins, ezetimibe is

frequently used as an adjuvant to statin therapy. When used with statin medication, it has been demonstrated to lower the risk of cardiovascular events and is generally well tolerated with a low incidence of adverse effects (Nutescu and Shapiro, 2003). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have completely changed the way hypercholesterolemia is treated in recent years, especially for patients with familial hypercholesterolemia or high-risk individuals who do not get enough LDL-C reduction from statins and other drugs (Ortega Martínez de Victoria, 2017). Monoclonal antibodies known as PCSK9 inhibitors, such alirocumab and evolocumab, attach to and block PCSK9, a protein that typically breaks down LDL receptors in the liver. These medications dramatically lower LDL-C levels by blocking PCSK9, which increases the amount of LDL receptors accessible to remove LDL particles from the bloodstream (Liu *et al.,* 2022).

PCSK9 inhibitors have been demonstrated in clinical trials to dramatically reduce the risk of serious cardiovascular events, such as heart attack, stroke, and death from cardiovascular disease, and to reduce LDL-C levels by 60% or more. Despite their high effectiveness, PCSK9 inhibitors are often only used in patients with severe hypercholesterolemia or a history of cardiovascular events due to their high cost and requirement for subcutaneous injections (Shapiro *et al.,* 2018). Apart from pharmaceutical treatments, the advancement of more recent methods like gene therapy and RNA-based therapeutics shows promise for the management of hypercholesterolemia in the future. Genetic mutations causing familial hypercholesterolemia may be corrected by gene editing methods like CRISPR-Cas9, which could give a long-term remedy for the illness (Abifadel and Boileau, 2023). The goal of RNA-based treatments, like small interfering RNA (siRNA) molecules, is to inhibit the expression of genes that raise cholesterol. Although they are still in the early phases of development, these strategies present promising opportunities for tailored, focused treatments of hypercholesterolemia (Abifadel and Boileau, 2023). Overall hypercholesterolemia has a wide range of therapeutic implications. The lipid profile, cardiovascular risk, and therapeutic response of the patient all influence the course of treatment for hypercholesterolemia. Pharmaceutical treatments, such as statins, bile acid sequestrants, fibrates, niacin, PCSK9 inhibitors, and cholesterol absorption inhibitors, offer efficient ways to manage high cholesterol levels, although lifestyle changes continue to be the mainstay of care. Future therapeutic options may be significantly improved by developments in genetics and biotechnology, such as the creation of gene therapy and RNA-based medicines. Reducing cardiovascular risk and enhancing general health outcomes are the ultimate goals of effective hypercholesterolemia care, which calls for a customized strategy that considers each patient's particular traits and risk factors.

Challenges and Future Directions:

Despite recent major advancements, managing hypercholesterolemia still presents a number of difficulties. A significant percentage of patients with hypercholesterolemia still do not reach optimal cholesterol levels and are at high risk for cardiovascular events, even with the availability of various therapeutic approaches, such as pharmacological treatments, lifestyle modifications, and new biologic therapies (Arnold and Koenig, 2023). A number of issues, including patient adherence, drug efficacy, the intricacy of underlying systems, and the requirement for individualized treatment plans, contribute to these difficulties (Arnold and Koenig, 2023).

Furthermore, as research advances, new understandings of the genetic causes of hypercholesterolemia and advancements in medication development could offer fresh strategies for dealing with these issues (Fu *et al.,* 2022). Improving patient outcomes and lowering the worldwide burden of cardiovascular illnesses require an understanding of these obstacles and an investigation of potential future paths in the

treatment of hypercholesterolemia (Fu *et al.*, 2022).

Patient adherence to recommended treatments is one of the biggest obstacles in the management of hypercholesterolemia. Long-term adherence to statins and other lipid-lowering medications is still an issue, despite their demonstrated effectiveness in lowering cholesterol and cardiovascular risk. Research continuously demonstrates that a significant portion of patients either stop taking their prescriptions or do not take them regularly, particularly when using therapy like statins that call for a lifetime commitment. Poor adherence can be caused by a number of factors, such as patient attitudes about the necessity of cholesterol-lowering drugs, the complexity of polypharmacy in people with many comorbidities, adverse effect worries, and the absence of fast symptom relief. One of the main causes of therapy cessation is muscle-related adverse effects, especially statin-induced myopathy (Maningat *et al.*, 2013).

Despite being uncommon in most cases, these side effects are severe enough to deter some patients from adhering to their treatment plans. Furthermore, many people still find it difficult to obtain pharmaceuticals, especially those in low- and middle-income nations, due to their high cost, especially those of more recent drugs like PCSK9 inhibitors.

The underdiagnosis and undertreatment of hypercholesterolemia further aggravates the problem of inadequate adherence. Since hypercholesterolemia is frequently asymptomatic, many people with high cholesterol levels are ignorant of their illness (Arnold and Koenig, 2023). Not all routine cholesterol screenings are carried out, and when they are, patients might not get the proper care or prompt follow-up. Effective management of the illness may be further hampered in some areas by restricted access to healthcare and lipid-lowering drugs.

Furthermore, there is variation in how treatment guidelines are applied, especially in primary care settings where doctors might not always start or intensify medication in line with suggested guidelines. The underutilization of existing medicines and the inability to attain effective cholesterol management are both caused by this inconsistent care.

The efficacy of existing pharmaceutical treatments in specific patient populations presents another difficulty. Even while statins are quite good at lowering LDL-C and avoiding heart attacks, not every patient reacts to treatment in the same way (Maningat *et al.*, 2013). To achieve adequate cholesterol reduction, individuals with familial hypercholesterolemia or other hereditary lipid disorders, as well as those who are statin-resistant or statin-intolerant, may need additional or alternative therapy.

Although PCSK9 inhibitors are a major improvement in lipid-lowering treatment, their use and accessibility are restricted by their high cost and requirement for frequent injections (Liu *et al.*, 2022). Combination treatments that can treat excessive LDL-C as well as other lipid abnormalities, such low HDL-C and high triglycerides, which are common in individuals with metabolic syndrome, are also becoming more and more necessary (Jacobson and Zimmerman, 2006). Even while combination treatments, such statins with ezetimibe or fibrates, have been demonstrated to offer further advantages, more potent, well-tolerated combination medications that can target several cholesterol pathways at once are still required (Jacobson and Zimmerman, 2006).

Furthermore, the development of universally effective treatments is hampered by the intricacy of the pathophysiology of hypercholesterolemia. A complex interplay of lifestyle, environmental, and hereditary variables frequently results in hypercholesterolemia rather than being a single disorder (Wazir *et al.*, 2023). It may occasionally be an indication of underlying metabolic conditions that call for specialized genetic testing and tailored treatment, such as familial dysbetalipoproteinemia, familial mixed hyperlipidaemia, or familial hypercholesterolemia (Wazir *et al.*, 2023).

Because lipid metabolism, genetic mutations, and other cardiovascular risk factors interact, treatment plans need to be customized for each patient based on their specific genetic profile, family history, and concurrent medical conditions. Even while this individualized approach is perfect, it poses serious problems with accessibility, cost, and genetic testing availability, especially in environments with limited resources (Ordovas, 2009).

One of the most potential research options for the future is the creation of innovative lipid-lowering medications that target unidentified mechanisms. Familial hypercholesterolemia and other inherited lipid disorders may be treated by correcting genetic abnormalities caused by the emergence of gene-editing technologies like CRISPR-Cas9 [92]. Such treatments could provide a long-term cure to hypercholesterolemia by directly altering the genes involved in cholesterol metabolism, obviating the need for long-term pharmaceutical intervention. The cost, safety, and ethical ramifications of these therapies, however, continue to be major obstacles to their broad use in clinical practice.

The creation of RNA-based treatments, including small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), which can specifically target the expression of particular genes involved in cholesterol metabolism, is another fascinating area for further study. For instance, clinical trials have previously demonstrated the potential of using siRNA to quiet the PCSK9 gene, which has resulted in notable drops in LDL-C levels (Zhang *et al.*, 2021). By providing a more focused and maybe more successful method of treating hypercholesterolemia, these therapies may supplement or even replace current ones. But there are still many obstacles to overcome, especially when it comes to delivering RNA-based treatments to the liver, which is where cholesterol metabolism takes place.

The management of hyper-cholesterolemia may be improved by developments in personalized medicine. Clinicians can now customize treatment plans based on a patient's genetic composition, family history, and therapeutic response because to the growing availability of genomic data. Patients who have inherited mutations in important lipid metabolism genes, such as the LDLR, APOB, and PCSK9 genes, can be identified through genetic testing as being at increased risk for hypercholesterolemia (Brautbar *et al.,* 2015). Furthermore, by reducing the possibility of side effects and maximizing therapeutic performance, pharmacogenomic investigations may help determine which treatment is best for each patient. Personalized medicine, while still in its early stages, has the potential to revolutionize the management of hypercholesterolemia, providing more effective and individualized treatment strategies (Brautbar *et al.*, 2015). Alongside improvements in pharmaceutical treatments, lifestyle modifications continue to be a key component of managing hypercholesterolemia. Lifestyle changes should continue to be the main focus, even when pharmacological treatments are necessary for many individuals, especially those with familial hypercholesterolemia or those at high cardiovascular risk (Abbasi *et al.,* 2024). It has been demonstrated that dietary interventions that emphasize cutting back on saturated fats, boosting fibre consumption, and including heart-healthy fats lower cholesterol and enhance cardiovascular health (Hooper *et al.,* 2020). Treatment still includes exercise, controlling weight, and quitting smoking, and efforts should be made to increase public knowledge and accessibility to these lifestyle changes. Given the increasing global burden of obesity and metabolic disorders, these preventive measures must be incorporated into public health strategies to reduce the incidence of hypercholesterolemia and its associated cardiovascular risks.

The use of biomarkers to more accurately determine cardiovascular risk and direct treatment choices represents yet another possible development. Although conventional cholesterol measurements like

LDL-C and HDL-C levels offer important information about lipid metabolism, new biomarkers like oxidized LDL, lipoprotein (a), and apolipoprotein B (apoB) provide more information about the risk of atherosclerosis (Mancini *et al.,* 2024). More precise risk assessment and more focused treatment approaches may result from the discovery of new biomarkers that more accurately represent the underlying pathophysiology of atherosclerosis and hypercholesterolemia. In conclusion, even though hypercholesterolemia therapy has advanced significantly in recent years, there are still obstacles in the way of attaining the best possible treatment results for every patient. To improve care, obstacles such low patient adherence, the intricacy of lipid metabolism, and the shortcomings of existing treatments must be addressed. The creation of innovative treatments that focus on the underlying genetic and molecular mechanisms of lipid metabolism and the incorporation of personalized medicine techniques that customize care for each patient are key to the future of managing.

Overall Conclusion and Perspectives:

Hypercholesterolemia is one of the major health burdens around the world, being amongst the major contributors to the cardiovascular disease burden. Its prevalence has continued to rise with modernization in diagnostic and therapeutic approaches because of changes in lifestyle, urbanization, and genetic predisposition. Management involves a multidimensional approach that includes lifestyle modifications, pharmacological intervention, and the use of advanced diagnostic modalities. While statins remain the cornerstone of treatment, newer agents such as PCSK9 inhibitors and RNA-based therapies expand the therapeutic landscape and offer hope for patients with severe or refractory hypercholesterolemia. However, significant challenges persist, including suboptimal patient adherence, the high cost of innovative therapies, and disparities in healthcare access, particularly in LMICs. The complexity of hypercholesterolemia's etiology encompassing genetic, environmental, and metabolic factors—further necessitates personalized treatment strategies. Looking ahead, advances in precision medicine and gene-editing technologies such as CRISPR-Cas9 may eventually revolutionize the treatment of hypercholesterolemia at its very genetic roots. Besides, digital health through telemedicine and wearable devices empowers patients in the better monitoring and management of their cholesterol levels. Public health strategies that emphasize prevention through dietary education, physical activity, and policy measures, such as trans-fat restrictions, will continue to be crucial in reducing the global burden of this condition. Thus, the struggle against hypercholesterolemia is one that is holistic in nature: it requires both innovative scientific breakthroughs and practical interventions at the population level. It requires health providers, researchers, policy makers, and communities to fight this growing health challenge and improve cardiovascular health outcomes worldwide.

Declarations:

Ethical Approval: Not applicable.

Conflict of interests: The author declare no conflicts of interest.

Authors Contributions: This work was solely conducted by a single author.

Funding: The author declare that no funds, grants, or other support were received during the preparation of this manuscript.

Availability of Data and Materials: All data supporting the described findings of the study is included within the manuscript.

Acknowledgements: The author gratefully acknowledges the support and assistance provided by the College of Applied Medical Sciences, Al-Baha University.

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