Reducing Cardiovascular Risk in Hypercholesterolemia

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Abstract

Hypercholesterolemia, characterised by elevated cholesterol levels, is a significant contributor to atherosclerosis and cardiovascular disease. This paper provides a comprehensive overview, exploring its genetic, lifestyle and metabolic intricacies. The cardiovascular risk factors associated with hypercholesterolemia, including age, family history, diabetes, smoking and low HDL-cholesterol levels, highlight the complexity of managing this condition.

Current treatments, particularly statins demonstrate effectiveness in lowering LDL cholesterol and reducing cardiovascular events. However, challenges bring up the need for alternative therapies, such as PCSK9 inhibitors and gene therapy, revealing the evolving landscape of hypercholesterolemia management. In summary, this review urges ongoing efforts and comprehending, managing and advancing hypercholesterolemia treatments. By combining existing knowledge with ongoing research and prioritising patient-centred approaches, we aim to improve outcomes and better address the challenges posed by hypercholesterolemia.

Keywords: Hypercholesterolemia, cardiovascular disease, atherosclerosis, risk factors, PCSK9 inhibitors, gene therapy, personalised medicine, patient adherence, integrated cardiovascular risk management

Introduction

Hypercholesterolemia is a prevalent and multifaceted medical condition, emerging as a focal point in discussions surrounding cardiovascular health. Characterised by elevated levels of cholesterol in the bloodstream, hypercholesterolemia significantly contributes to the development of atherosclerosis (1), a leading cause of cardiovascular disease, as well as the primary cause of death in the United States, with about 50% of Americans between the ages of 45 and 84 unknowingly having atherosclerosis (2). As a complex interplay of genetic predisposition, lifestyle factors and metabolic intricacies, this condition demands a comprehensive understanding to address its implications on public health. The significance of cardiovascular risk reduction lies in its pivotal role in mitigating the potential for life-threatening events, such as myocardial infarction and strokes (3), thereby fostering enhanced longevity, improved quality of life and a substantial reduction in healthcare burdens.

Methodology

A literature review was conducted across academic databases including PubMed and Science Direct, utilising keywords such as “hypercholesterolemia”, “LDL cholesterol”, “atherosclerosis”, “cardiovascular risk”, “treatment” and “patient adherence.

Articles were screened based on their titles and abstracts to identify potentially relevant studies. Full-text review was then performed for articles meeting the following criteria:

1. Relevance to preventing cardiovascular risk in hypercholesterolemia
2. Availability in the English language
3. Original research articles, reviews and clinical trials.

Key data points were extracted from selected studies, including study objectives, methodology employed, participant demographics and numbers, key findings and the conclusion drawn by the authors.

The extracted data was then synthesized according to theme to identify the common patterns, trends and gaps in the literature pertaining to reducing the cardiovascular risk in individuals suffering from hypercholesterolemia. This involved categorising the studies based on the focus areas mentioned above. Through this process, a comprehensive understanding of the current landscape of hypercholesterolemia research was achieved in this review, allowing for insights and implications for clinical practice and public health initiatives.

Hypercholesterolemia: A Brief Overview

Hypercholesterolemia is a hyperlipidaemia: a condition that describes a high level of lipids in the human body (4), primarily high serum level of Low Density Lipoprotein (1), also known as LDLs. Lipids are a group of naturally occurring molecules with a low water solubility and a high solubility in organic solvents. Circulating lipids, namely cholesterol, triglycerides and phospholipids are transported as plasma lipoproteins (3). These lipoproteins are divided into five distinct classes, according to their size. These are the following, from largest to smallest (5):

1. Chylomicrons
2. Very Low Density Lipoproteins (VLDL)
3. Intermediate Low Density Lipoproteins (IDL)
4. Low Density Lipoproteins (LDL)
5. High Density Lipoproteins (HDL

HDL is the only class that is anti-atherogenic (5) meaning that it prevents atherogenesis, which is the progression and development of a build-up of fatty deposits, cellular debris, cholesterol and other substances on the inner arterial walls. This accumulation then leads to plaque formation, restricting blood flow and contributing to the onset of cardiovascular disease (6). LDL is rich in cholesterol, with some derived from the liver by VLDLs or from circulating HDL. LDL formation rate is observed to be markedly higher in obesity and with a diet containing high amounts of saturated fat, such as the Western diet (7, 8).

There are two types of hypercholesterolemia: genetic (familial) and acquired, with familial hypercholesterolemia (FH) being the classical type. This results from a genetic mutation in the LDL-receptor gene, which accounts for over 85% of FH, causing high LDL-C levels – 3.7mmol/L (>145 mg/dl) in heterozygotes and even higher levels in homozygotes – 11.6mmol/L (>450 mg/dl) (1). Other genetic mutations in FH are defects in apolipoprotein B (apo-B) and proprotein convertase subtilisin / Kexin type 9 (PCSK9) (9).

Cholesterol, vital for cellular functions, undergoes meticulous control, with the endoplasmic reticulum (ER) serving to sense and regulate cholesterol levels (11). The ER houses inactive transcription factors that respond to cellular cholesterol levels. Cholesterol homeostasis is also regulated through sterol regulatory element-binding proteins (SREBPs) (11). SREBPs activate the expression of over 30 genes dedicated to synthesising and uptake of lipids including cholesterol, phospholipids, triglycerides and fatty acids, as well as the NADPH cofactor for the synthesis of these molecules (12). When cellular cholesterol rises, SREBPs do not reach the Golgi apparatus, and transcription of target genes declines (12). Furthermore, the ER-bound translation factor Nuclear Respiratory Factor 1 (NRF-1) plays a role in sensing heightened

cholesterol levels, leading to the activation of liver X receptor (LXR) and subsequent cholesterol excretion (11).

Cardiovascular Risk Factors Associated with Hypercholesterolemia

As previously discussed, elevated levels of cholesterol is a thoroughly documented risk factor for cardiovascular disease.

In Malta, hypercholesterolemia has been increasing since the 1980s (10), posing a growing challenge to public health initiatives and necessitating a comprehensive examination of contributing factors, lifestyle trends, and potential interventions to address and mitigate this concerning upward trajectory. The primary risk factors for hypercholesterolemia and cardiovascular disease include (13):

- Age

Males over the age of 45 and females over the age of 55 are at increased risk of hypercholesterolemia.

- A family history of premature atherosclerotic cardiovascular disease

Premature refers to <55 years in males and <65 years in females.

- Diabetes

According to the Heart UK website, diabetes damages the arterial wall. This makes it more likely that cholesterol binds to them, causing narrowing and blockage. Diabetes is also associated with a lower level of HDL cholesterol and a higher level of LDL cholesterol, further increasing the risk of atherosclerotic plaque (14).

- Smoking

Nicotine, an addictive compound found in tobacco, causes a decrease in HDL cholesterol levels and an increase in LDL cholesterol levels, also causing lipid adhesion and accumulation in the arterial wall (15).

- Low HDL-Cholesterol Levels

This is defined as <1mmol/L (40 mg/dl) in males and <1.4mmol/L (55 mg/dl) in females.

Other risk factors include lifestyle factors such as a diet rich in saturated (16) and trans fats (17), as well as an excessive intake of cholesterol-containing foods. A lack of regular physical activity can also lead to an impaired lipid metabolism and weight gain, ultimately leading to overall poor cardiovascular health (18). Hypertension also contributes to these risk factors by damaging arteries and accelerating the development of atherosclerosis, especially in individuals with hypercholesterolemia (19).

Atherosclerotic Plaque Formation

The formation of an atherosclerotic plaque is a multifaceted process involving (20):

1. Lipoprotein retention:

The central concept in atherogenesis is the sub-endothelial retention of apo-B-containing lipoproteins, serving as the key initiating event. This retention triggers a local chronic and maladaptive inflammatory reaction, leading to the development of atherosclerotic lesions. (21)

2. Inflammatory leukocyte recruitment

Pro-inflammatory leukocytes drive the progression of atherosclerosis by using soluble mediators and tissue-specific molecules. These act to influence the adhesion and transmigration of leukocytes. Multiple adhesion receptor-ligand pairs, such as selectins and integrins, guide the recruitment cascade. The plaque begins with a deposition of oxidised low-density lipoproteins (oxLDL) in the sub-endothelial space. The interactions between oxLDL and tissue-resident macrophages act to trigger a pro-inflammatory immune response, dominated by myeloid cells. The infiltrated leukocytes interact with stromal cells, secreting pro- or anti-inflammatory cytokines, influencing inflammation and tissue remodelling. The continuous accumulation of leukocytes in the plaque leads to its progression. (22)

3. Formation of Foam Cells

Foam cell development arises from elevated

oxLDLs internalisation and the increased lipid droplet accumulation within macrophages. This progression triggers fatty streak formation, evolving into primary atherosclerotic lesions. The integral role of foam cells in atherosclerosis pathogenesis becomes apparent, particularly in the sub-endothelial space of compromised arteries. This early sequence of events involving the creation and build-up of foam cells significantly contributes to atherosclerotic plaque formation (23)

4. Apoptosis of endothelial smooth muscle

Apoptosis is also known as programmed cell death (PCD) (24). It is a detrimental process when it comes to plaque stability, while when it comes to macrophages, it can be beneficial for plaque stability (25).

5. Necrosis

In contrast to apoptosis, necrosis is a more passive and unintentional cell death triggered by external disturbances, leading to the uncontrolled release of inflammatory cell contents (26). Necrotic cell death is marked by cell swelling, membrane rupture and the formation of a large necrotic core that characterises unstable plaques (27). In advanced plaques, increased necrosis results in the release of proinflammatory cytokines and Damage-Associated Molecular Patterns (DAMPs), intensifying inflammation and plaque destabilisation. (27)

6. Smooth muscle cell (SMC) proliferation

Triggered by endothelial cell damage, LDL accumulation prompts monocyte recruitment, transforming them into foam cell macrophages. SMCs then migrate to the tunica intima, proliferating and secreting extracellular matrix proteins. This process predisposes to plaque development. In advanced stages, SMCs play a role in stabilising lesions by forming a fibrous cap around the necrotic core. However, cap thinning increases rupture risk, leading to thrombus formation and potential complications. (28)

7. Matrix synthesis

SMCs migrate, proliferate and secrete extracellular matrix proteins, such as collagen, elastin, fibronectin and proteoglycans, forming the fibrous cap. (29)

8. Calcification

Micro-calcifications indicate and active stage linked to inflammation, while spotty calcifications associate with extensive atherosclerosis and increased disease progression. Large calcifications may contribute to stable plaques (30).

9. Angiogenesis

The formation of new blood vessels plays a dual role in atherosclerosis. In early stages, oxidative stress in the hyperplastic intima promotes neo-angiogenesis. In advanced plaques, chronic inflammation and oxidised lipids contribute to angiogenesis, resulting in leaky capillaries prone to injury. This leads to intra-plaque haemorrhages, cholesterol accumulation and plaque instability, increasing the risk of rupture (31).

10. Arterial remodelling

Arterial remodelling involves changes in vessel size in response the various triggers such as atherosclerosis and restenosis. Expansive remodelling prevents luminal narrowing, while constrictive remodelling accelerates it. (32)

11. Rupture of fibrous cap

A self-explanatory process, cap rupture is the leading cause of coronary thrombosis, leading to an infarction. In severe cases, this can lead to sudden cardiac death. (33)

12. Thrombosis

Described as the formation of blood clots in veins, thrombosis disrupts normal blood flow. Its complex diagnosis and management involves factors like location, acuity and underlying conditions, impacting treatment decisions (34).

Some plaques are asymptomatic, some are obstructive – leading to stable angina, and some can even lead to acute thrombosis, which can lead to an acute coronary syndrome (20).

Elevated LDL levels contribute to arterial injury, promoting endothelial dysfunction. Infiltration of LDL-containing lipoproteins triggers an inflammatory response, formation of foam cells and atherosclerotic development (35). On the other hand, HDL cholesterol efflux is consistently

associated with a reduced risk of cardiovascular disease (35).

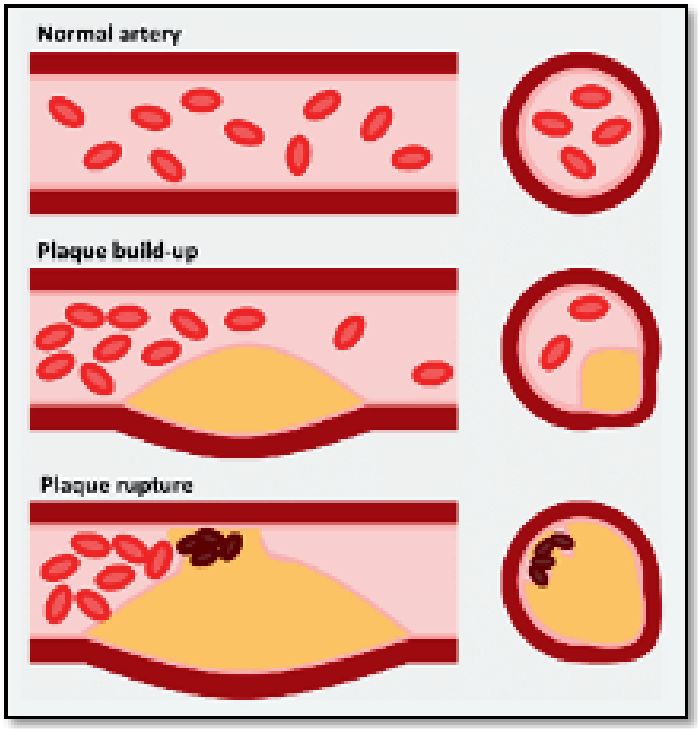

Figure showing the development of an atherosclerotic plaque. Retrieved from Ward, Liam. (2019). Sex differences in atherosclerosis and exercise effects.

Current Hypercholesterolemia Treatments and Efficacy of Statins

The primary approach for managing hypercholesterolemia involves lifestyle modifications such as maintaining a healthy weight and regular exercise (~150 minutes a week) (1). Furthermore, a diet high in vegetables, fruit, whole-grains, low-fat dairy, fish and omega-3 fatty acids is encouraged over one containing high levels of saturated and trans fats and refined carbohydrates (36).

Statins

Statins are the preferred drug class for treating hypercholesterolemia, able to lower LDL cholesterol by 22-50%, and reduce cardiovascular events (1). This is due to their inhibition of hydroxymethylglutaryl-CoA reductase enzyme (HMG-CoA), which is the enzyme that converts HMG-CoA to mevalonate in cholesterol synthesis (38). It also reduces apoB100 containing lipoproteins from the liver, which leads to a lower level in cholesterol concentrations (38). According to studies, statins have demonstrated effectiveness in preventing both mortality and cardiovascular morbidity among individuals with a low risk of cardiovascular events (39). The observed reductions in relative risk parallel those observed in patients with a known history of coronary arterial disease (CAD) (40). As such, existing recommendations for statin use rely on the anticipated risk of experiencing an atherosclerotic event rather than solely on the presence or absence of established CAD (39). Additional studies suggest that statin treatment for the primary prevention of cardiovascular disease in individuals with low or medium risk may have a beneficial effect if there is optimal treatment adherence (40).

However, they have side effects such as elevated transaminases, an indicator of liver dysfunction (37), myalgia and myopathy may occur. When monotherapy via statins proves insufficient, cholesterol absorption inhibitors such as ezetimibe, and bile acid sequestrants can be used (1).

PCSK9 inhibitors and other Novel Therapies including Gene Therapies

For patients with FH or those unable to achieve target LDL levels using the above approaches, new options like PCSK9 inhibitors have become available (1,37). PCSK9 regulates plasma LDL levels by influencing expression of LDL receptors (41). When cholesterol biosynthesis inhibitors like statins are administered, they can initially deplete hepatic cholesterol levels, therefore activating PCSK9. This leads to increased degradation of LDL receptors, attenuating effects of statins on LDL receptor expression. . Inactivating PCSK9 in mice has been shown to heighten sensitivity to statin treatment (42). Therefore, by blocking PCSK9 activity, these inhibitors help maintain higher levels of functional LDL receptors on the cell surface,

facilitating increased LDL clearance from the bloodstream. (41).

Additionally, combinations of medications may be necessary, and in extreme cases, LDL apheresis or liver transplantation could be considered (1). While lipoprotein apheresis effectively prevents atherosclerosis progression, using plasma exchange, double-membrane filtration and selective LDL adsorption – the latter of which is adopted globally, early initiation in crucial, especially in homozygous patients (42). Those starting apheresis in adulthood exhibited a poorer prognosis than those starting in childhood (42). Meanwhile, other studies state that liver transplantation is the only way to correct abnormal hepatic cholesterol metabolism in FH until now (43).

There have also been explorations in the applications of gene therapy in the FH field. Gene therapy involves inserting a functional gene into a human cell to correct genetic errors or introduce new functions (44). Current gene therapies that have undergone clinical trials for FH include:

1. Virus Vector-Mediated Gene Therapy

Adeno-associated virus (AAV) serves as a safe and effective gene-delivery system for treating hypercholesterolemia (45). Studies, including a clinical trial (NCT02651675, 2019), have highlighted the efficacy of AAV vectors in delivering the human LDLR gene, demonstrating a reduction in cholesterol levels. AAV8 has particularly shown superior hepatocyte transduction (46) and an improved lipid profile (47) when compared to AAV2. A phase 1 clinical trial reported successful reductions in serum cholesterol levels with AAV8-mediated LDLR gene therapy for Homozygous FH. The trial displayed safety and significant cholesterol reduction, setting the stage for further exploration of AAV-mediated gene therapy in hypercholesterolemia treatment.

2. Antisense Oligonucleotides (ASOs)

ASOs are short DNA strands designed to bind to specific mRNA sequences. Mipomersen, an ASO targeting apoB-100 mRNA reduces LDL-c levels in FH patients (45), with studies showing a 24.7% LDL-c reduction in a phase three trial (48). Another ASO, SISIS-APO(a)Rx, lowers Lipoprotein a levels by up to 89% (50). These ASOs offer potential in managing lipid disorders with promising efficacy and acceptable safety profiles (45).

3. Small Interfering RNAs (siRNAs) Targeting PCSK9 Synthesis

siRNAs like Inclisiran inhibit PCSK9 synthesis by subcutaneous administration. In the ORION-1 trial, 501 high-risk patients received single or two doses of Inclisiran, showing LDL-c reductions of 27.9% to 52.6% at 180-day follow-up. LDL-c and PCSK9 levels remained significantly lower at the 240-day follow-up. These promising results suggest siRNAs targeting PCSK9 may be beneficial for high-risk patients in lowering cardiovascular risk (50).

Potential Prospects in Novel Approaches in Pre-Clinical Development

Novel approaches in pre-clinical development for treating FH show promise. Mini-circle DNA vectors, which are compact non-viral plasmids, express therapeutic genes such as LDLR (51). In mouse studies, they controlled LDL-c levels effectively, but delivery challenges need addressing (51).

MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression, and according to results from animal studies, several of them influence the LDL-c pathway and delay atherosclerotic progression in mice (52). Numerous miRNAs regulate FH-associated genes, suggesting a potential novel therapy (45).

Long non-coding RSNs (lncRNAs), over 200nt RNA molecules, also regulate gene expression. In an AAV8 vector study, lncRNA targeting a specific sequence reduced cholesterol biosynthesis genes and atherosclerosis in mice (53).

The CRISPR/Cas9 system, a precise gene-editing tool, holds therapeutic potential. Using CRISPR/Cas9, researches knocked down PCSK9 expression, reducing plasma cholesterol levels (54).

The newer CRISPR/Cpf1 system shows promise for multiplex gene editing in vivo, and can repair mutations, providing potential treatment for monogenic inherited disease (35). Studies demonstrate its success in correcting genetic deficiencies related to FH, making it a promising therapeutic tool for the future (35, 46).

Challenges of Novel Approaches

While these approaches offer exciting prospects, some face challenges. Mini-circle DNA vectors, though effective, encounter delivery issues that need further exploration (35). miRNA-based therapies show potential but require additional research for clinical validation. lncRNA-based therapeutics show potential in mouse studies, but need more investigations for clinical validation (53). The CRISPR/Cas9 system, although powerful, necessitates ongoing research to address potential off-target effects and ensure its safety and efficacy for FH treatment (35).

Personalised Medicine

The aforementioned pre-clinical developments highlight diverse strategies for addressing FH, with each approach presenting unique advantages and challenges, emphasizing the need for continued research to refine and validate these novel therapeutic avenues for potential clinical use in the future. It is necessary to have multifaceted treatment approaches for personalised medicine as individuals exhibit unique genetic, environmental and lifestyle factors influencing their health. Certain medications diminish statin effectiveness by either reducing bioavailability or increasing metabolism, exemplified by rifampicin (56). Conditions affecting cholesterol metabolism, such as hypothyroidism, also impact statin efficacy (57, 58). Genetic variations within lipid metabolism-related genes also influence statin response (59). Moreover, a substantial proportion of treated patients (over 40%), fail to achieve target LDL-C levels (60). Barriers to reaching LDL-C goals encompass failure to start therapy, non-adherence, side effects, inappropriate drug/dose selection, and insufficient dose titration (55). Tailoring interventions to specific patient characteristics will allow for more precise and effective healthcare strategies.

Patient Adherence and Challenges in Treatment

Maintaining adherence to chronic disease treatment is crucial for its effectiveness and holds significant implications for public health and healthcare economics (61). Various factors contribute to low adherence, stemming from patients, physicians and healthcare systems. Widespread non-adherence to dietary recommendations and lipid-lowering drug therapies, especially for hypercholesterolemia, poses a significant challenge, limiting the potential benefits of serum lipid reduction in cardiovascular prevention. Many patients discontinue treatment, and adherence diminishes over time, highlighting the need for strategies to improve adherence (61).

The success of primary and secondary prevention strategies achieved through reducing LDL cholesterol, represents a milestone in medicine (62, 63). Notably, real-world adherence to lipid-lowering therapy, particularly with statins, falls below levels reported in controlled trials, contributing to reduced cardiovascular prevention efficacy. Therefore, translating the positive outcomes observed in clinical trials into real-world scenarios requires consistent adherence to prescribed therapies (64). Recognised as a major public health concern, poor adherence to chronic disease treatment compromises its effectiveness, influencing mortality, morbidity and healthcare costs (64).

Understanding the causes of poor adherence is crucial, with estimates suggesting that approximately half of patients not correctly follow long-term therapy prescriptions, saying that they were “no longer necessary”, “ineffective”, posing an “adverse reaction”, “too expensive” and even “inadequately covered by insurance” (65). Recognising physical-related barriers is imperative, emphasizing the need for efforts by scientific

societies to enhance physician awareness of their role in adherence improvement. Systematic strategies to reduce non-adherence should be advocated within healthcare systems.

Emphasizing the importance of dietary and lifestyle changes for cardiovascular risk reduction, guidelines recommend optimal dietary options and strategies in order to enhance patient adherence (61). Strengthening the cultural understanding of good adherence among patients and physicians is essential. Despite the recognised impact of good adherence on health outcomes, there remains a lack of knowledge on how modern technology could support both drug and dietary adherence. Further research in this area is deemed necessary to address this crucial aspect (61).

Impact of Cardiovascular Risk Reduction on Patient Outcomes

In a study by Smits et al (2023), the long-term outcomes of an integrated cardiovascular risk management program organised by a care group in the Netherlands was examined with the aim to understand changes in LDL cholesterol, systolic blood pressure (SBP) and smoking status among high-risk patients participating in the program from 2011 to 2018 (66).

The care group implemented a protocol for delegated practice nurse activities and utilised a multidisciplinary data registry for uniform registration. Annual education sessions were organised for general practitioners (GPs) and practice nurses on cardiovascular topics, along with regular meetings for practice nurses to discuss complex cases and implementation issues (66). Practice visitations were initiated in 2015 to support practices in organising integrated care. The study analyses data from 145 general practices affiliated with the Primary care group PoZoB (Praktijkondersteuning Zuidoost Brabant).

Results indicate positive trends for both primary and secondary prevention. Cholesterol-lowering and blood pressure-lowering medication prescriptions increased, accompanied by decreases in mean LDL cholesterol and mean SBP. The proportion of patients on target for LDL cholesterol and SBP also increased. The prevalence of smoking decreased and the percentage of non-smokers with both SBP and LDL cholesterol on target saw significant improvement (66).

The study emphasizes the importance of improved registration practices between 2011 and 2013, contributing to a sharp increase in patients meeting LDL cholesterol and SBP targets. The integrated care approach involved a comprehensive support system, including protocolled practice nurse involvement, a multidisciplinary registry, education, practice visitations and quarterly benchmark reports (66).

Strengths of this study include a large study population from routine clinical practice, standardized protocols and a real-life monitoring over an 8-year long period. Limitations include the lack of a reference group for comparison and some missing data between 2010 and 2013 (66). Comparisons with existing literature highlight the challenges of implemented structured care in randomised controlled trials, with carrying results (66). This study, focusing on real-world, long-term outcomes, contributes valuable insights into the effectiveness of integrated cardiovascular risk management in primary care.

Conclusion

In conclusion, this comprehensive exploration of hypercholesterolemia has provided valuable insights into its multifaceted nature, cardiovascular risk factors, current treatments and novel therapeutic approaches. The key findings of this review underscore the interplay between genetics, lifestyle and metabolic intricacies in the development of hypercholesterolemia, emphasizing the need for a holistic understanding to address its implications on public health.

The cardiovascular risk factors associated with

hypercholesterolemia shed light on the increasing challenge to public health initiatives. Factors such as age, family history, diabetes, smoking and low HLD-cholesterol levels contribute to the complexity of managing this condition. The detailed exploration of atherosclerotic plaque formation elucidates the intricate process involved, providing a foundation for the understanding of the progression of cardiovascular disease.

Current treatments, with a focus on statins, highlight the effectiveness of these drugs in lowering LDL cholesterol and reduce cardiovascular events. However, challenges such as side effects that lower quality of life, and the need for alternative therapies, including PCSK9 inhibitors and gene therapies, demonstrate the evolving landscape of hypercholesterolemia management.

The discussion on personalised medicine underscores the importance of tailoring interventions to individual characteristics, considering factors that may affect statin effectiveness. The exploration of patient adherence and challenges in treatment emphasizes the critical role of consistent adherence in achieving optimal outcomes, with a need for strategies to improve adherence in real word scenarios.

The impact of cardiovascular risk reduction on patient outcomes as evidenced by the study conducted in the Netherlands highlights the positive trends resulting from an integrated cardiovascular risk management program. This real-world evidence reinforces the importance of comprehensive support systems, education, and multidisciplinary approaches in primary care.

In conclusion, this review sets the stage for a continued and concerted effort in understanding, managing and advancing the treatment landscape for hypercholesterolemia. The synthesis of current knowledge, coupled with ongoing research and a focus on patient-centred approaches, will contribute to better outcomes and a more effective response to the challenges posed by this prevalent medical condition.

Declarations

Conflict of interest: N.A.
Ethical statement: N.A.

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List of Abbreviations

Abbreviation	Definition
AAV	Adeno-Associated Virus
ASO	Anti-Sense Oligonucleotides
CAD	Coronary Artery Disease
CAMPs	Damage Associated Molecular Patterns
ER	Endoplasmic Reticulum
FH	Familial Hypercholesterolemia
HDL	High Density Lipoproteins
HMG-CoA	Hydroxymethylglutaryl-CoA Reductase Enzyme
IDL	Intermediate Density Lipoproteins
LDL	Low Density Lipoproteins
lncRNA	Long non-coding RNA
LXR	Liver X Receptor
miRNA	Micro RNA
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NRF-1	Nucleotide Respiratory Factor-1
oxLDL	Oxidised Low-Density Lipoproteins
SBP	Systolic Blood Pressure
siRNAs	Small Interfering RNAs
SMC	Smooth Mucle Cell
SREBP	Sterol Regulatory Element Binding Proteins
PSCK9	Proprotein Convertase Subtilisin / Kexin type 9
VLDL	Very Low Density Lipoproteins

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