

EFFICACY OF NEW INJECTABLE CHOLESTEROL LOWERING MEDICATIONS
VERSUS STATIN DRUGS IN TREATING HYPERLIPIDEMIA: A RETROSPECTIVE
MIXED METHODS ANALYSIS OF CLINICAL OUTCOMES AND HEALTHCARE
PROVIDER PERCEPTIONS

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A Dissertation

Submitted to the Office of Graduate and Extended Studies

in Partial Fulfillment

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Health Science to the Office of Graduate and Extended Studies of East Stroudsburg University of Pennsylvania

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Title: Efficacy of New Injectable Cholesterol Medications versus Statin Drugs in Treating Hyperlipidemia: A Retrospective Mixed Methods Analysis of Clinical Outcomes and Healthcare Provider Perceptions

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Abstract

Introduction: Cardiovascular disease is the leading global cause of death, with elevated low-density lipoprotein cholesterol (LDL-C) as a major modifiable risk factor.

Purpose: The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on PCSK9 inhibitors, and statin drugs.

Methods: This retrospective mixed-methods study compared the effectiveness of statins with newer injectable lipid-lowering therapies. Data was drawn from 50 patient records and supplemented with semi-structured provider interviews to explore clinical decision-making.

Results: Injectable therapies reduced LDL-C by an average of 45.6%, exceeding the 39.5% reduction achieved with statins. Predictors for injectable use included elevated lipoprotein(a), high ASCVD risk scores, and significant coronary calcium scores.

Conclusion: Injectable lipid-lowering agents may offer greater benefits for high-risk patients or those intolerant to statins. Findings support individualized treatment strategies to improve hyperlipidemia management and reduce cardiovascular events.

Keywords

Cardiovascular disease, hyperlipidemia, statins, PCSK9 inhibitors, Praluent, Repatha, Leqvio, LDL-C reduction, lipoprotein(a), ASCVD risk, cholesterol-lowering therapy, provider perspectives, emerging lipid medications

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CHAPTER ONE

Introduction

Cardiovascular Disease (CVD) remains the leading cause of morbidity and mortality globally dating back to 1921. According to the American Heart Association (AHA), CVD accounts for approximately 17.9 million deaths annually (AHA, 2022). The accumulation of plaque within arterial walls leads to the narrowing and hardening of arteries thus disrupting blood flow and increasing the risk of CVD.

Atherosclerosis is characterized by the accumulation of lipid-rich plaques within arterial walls and contributes to the development of various CVD manifestations. Atherosclerotic plaque is comprised of lipid molecules which are made up of vitamins and cells in the body. However, increased cholesterol can bind with other blood substances to form hard deposits in the arteries, which causes narrowing and weakening of the vessels. This can eventually lead to a heart attack or stroke. Atherosclerosis plays a pivotal role in its pathogenesis (Nedkoff et al., 2023).

Cholesterol

Cholesterol is defined as a vital lipid molecule which exists in various forms in the bloodstream. This plays a central role in atherosclerosis by depositing cholesterol in arterial walls and promoting plaque formation (Libby, 2021). Cholesterol is categorized into three types. Low density lipoproteins (LDL-C) or bad cholesterol. High density lipoproteins (HDL-C) or good cholesterol and total cholesterol.

High-density lipoprotein cholesterol plays a role in helping remove excess cholesterol from the bloodstream and transporting it to the liver for excretion, thereby exerting a protective effect against atherosclerosis (Libby, 2021).

LDL-C

Low-density lipoprotein cholesterol (LDL-C) is the primary lipoprotein responsible for transporting cholesterol to peripheral tissues. Elevated LDL-C levels are strongly associated with the initiation and progression of atherosclerosis, as excess particles penetrate the arterial wall and contribute to the formation of lipid-rich plaques. Over time, this process leads to arterial narrowing, reduced blood flow, and heightened risk for coronary heart disease and stroke. Because of its central role in cardiovascular disease, LDL-C is often the primary target of lipid-lowering therapy. AHA (2022) recommends maintaining LDL-C levels below 100 mg/dL in the general population, with even lower thresholds (<70 mg/dL) for individuals at high risk.

HDL-C

High-density lipoprotein cholesterol (HDL-C) plays an essential protective role in cardiovascular health through reverse cholesterol transport, a process in which cholesterol is removed from arterial walls and returned to the liver for metabolism and excretion (AHA, 2022). Higher levels of HDL-C are generally associated with a lower risk of atherosclerosis, as HDL helps maintain vascular health by reducing lipid accumulation and exerting anti-inflammatory and antioxidant effects. Guidelines recommend HDL-C levels above 40 mg/dL in men and above 50 mg/dL in women to provide adequate cardioprotective benefits (AHA, 2022).

Luckily, cholesterol-lowering medications have emerged as essential tools in the management and prevention of CVD (Mach et al., 2019). Among these medications, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a recent advancement with promising outcomes (Chaudhary et al., 2017). Cholesterol alone is not predictive of cardiac risk. Other blood markers such as C-Reactive protein can impact the development of atherosclerosis.

C - Reactive Protein

C- reactive protein or CRP is a protein produced by the liver in response to inflammation. High levels indicate inflammation in the body which occurs from infection, autoimmune diseases, or chronic conditions. High levels of CRP increase the risk of heart disease and stroke. Atherosclerosis occurs due to plaque buildup in the arteries; inflammation leads to this overtime. Levels above 2–3 mg/L can suggest higher risk for cardiovascular events.

Triglycerides

As defined by AHA (2022), triglycerides are a fat source found in the bloodstream, that can increase risk of CVD if high numbers are diagnosed. Normal triglyceride profiles include <150mg/. dL, borderline high is 150-199 mg/dL, high is 200-499 mg/dL, and very high includes >500mg/dL. Therefore, when examining the current lipid profile of patients, healthcare providers will screen triglyceride levels as well as the traditional cholesterol markers (AHA,2022).

The goal is to keep LDL cholesterol under 100 mg/dL for most individuals, and to keep it at a more aggressive target of <70mg/dL for those at a higher risk if they have diseases such as diabetes or pre-existing CVD, (AHA,2022).

HDL assists in transporting cholesterol away from the arteries and towards the liver to be eliminated by the body. Higher HDL are correlated with better health outcomes. AHA guidelines recommend HDL to be >40mg/dL for men and >50mg/dL for women. Total cholesterol is a combination of HDL, LDL, and triglycerides, this number should be under 200 mg/Dl (AHA,2022).

LP(a)

Lipoprotein(a), or Lp(a) is a type of LDL-C particle with an additional protein component called apolipoprotein(a). It is largely determined by genetics and has been identified as an independent risk factor for CVD. Elevated levels of Lp(a) are associated with a higher risk of atherosclerosis, myocardial infarction, and stroke due to its pro-atherogenic and pro-thrombotic properties (Tsimikas, 2017). Unlike traditional LDL cholesterol, Lp(a) can promote inflammation and impair fibrinolysis, further contributing to plaque instability and thrombosis (Nordestgaard et al., 2010). Because lifestyle changes have minimal impact on Lp(a) levels, emerging therapies like PCSK9 inhibitors are being investigated for their potential to reduce Lp(a) and mitigate CVD risk (Lambert et al., 2021).

Cardiac Calcium Score

A cardiac calcium score is obtained through a non-invasive CT scan and is used to detect and quantify calcium deposits in the coronary arteries. These deposits are a marker of atherosclerosis, which can lead to CVD and other cardiovascular events. The purpose of this test is to improve cardiac risk stratification. Individuals may be asymptomatic but already have an intermediate risk due to age, cholesterol levels, and elevated blood pressure. A score of zero suggests a very low short-term risk of heart attack, whereas higher scores indicate an increased likelihood of coronary events. This information helps clinicians determine the need for

preventive strategies, such as initiating statin therapy or intensifying lifestyle changes (Nasir et al., 2018). A calcium score over 100 is typically seen as a sign of moderate to high risk for heart disease.

Atherosclerotic Cardiovascular Disease Score

The Atherosclerotic Cardiovascular Disease (ASCVD) risk score is a widely used tool to estimate the 10-year risk of cardiovascular events such as heart attacks or strokes in individuals. It incorporates various risk factors such as age, cholesterol levels, blood pressure, smoking status, and diabetes to provide a numerical estimate of risk. This score helps clinicians guide decision-making in terms of initiating preventive measures, such as statin therapy, for patients who are at elevated risk for cardiovascular events. Studies have shown that the ASCVD risk score is a reliable predictor of cardiovascular outcomes, making it an essential component of cardiovascular risk assessment (Nedkoff et al., 2023; Stone et al., 2014).

American Heart Association Cholesterol Guidelines

AHA guidelines as of 2022, recommend that total cholesterol should ideally be under 200 mg/dL, with LDL levels below 100 mg/dL for most people, or even lower for those at high risk of cardiovascular disease. HDL should be 40 mg/dL or higher for men, and 50 mg/dL or higher for women (AHA,2022).

For individuals with known heart disease, the guidelines suggest more aggressive management, including the potential use of non-statin therapies when LDL cholesterol remains elevated despite statin therapy. Statin drugs have been utilized for decades; however, this study explored the use of new drugs to lower cholesterol such as Praluent and Leqvio.

Purpose Statement

The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on PCSK9 inhibitors, and statin drugs. Trends in cardiovascular disease (CVD) prevalence, and the efficacy and safety of cholesterol-lowering therapies were evaluated. Understanding these aspects is crucial for optimizing cardiovascular health and reducing the burden of CVD worldwide. A secondary purpose was to gain perspective on the perceptions of prescribing injectable cholesterol lowering medications efficacy of healthcare providers. The study aimed to identify predictors of PCSK9 inhibitor use, such as statin intolerance and high baseline low density lipoprotein cholesterol (LDL-C) levels.

The following research questions were utilized in this study:

1. How did statins compare to PCSK9 inhibitors in terms of reducing LDL-C with patients with hyperlipidemia?
2. What were the predictors of usage for PCSK9 inhibitors versus statin drugs with individuals with hyperlipidemia?
3. What was the efficacy in prescribing non-statin drugs (Repatha, Praluent) to those with hyperlipidemia?
4. What were the perceptions of healthcare providers on the efficacy of PCSK9 inhibitors and statin drugs in the use of treating cardiovascular disease via hyperlipidemia?

Significance of Study

Cardiovascular disease encompasses a broad spectrum of conditions affecting the heart and blood vessels, including coronary artery disease, cerebrovascular disease, and peripheral artery disease. Nedkoff et al. (2023), indicated a concerning rise in the prevalence of CVD, driven by various factors such as aging populations, urbanization, sedentary lifestyles, and unhealthy dietary habits. Additionally, the increasing prevalence of obesity, diabetes, and metabolic syndrome further exacerbates the risk of developing CVD (Nedkoff et al., 2023).

Despite advances in medical technology and interventions, CVD remains a leading cause of morbidity and mortality globally. Efforts to address the rising prevalence of CVD require comprehensive strategies focusing on primary prevention, risk factor modification, early detection, and timely intervention (Nedkoff et al., 2023).

As of 2024, CVD continues to represent a major public health burden in the United States, affecting half of the adult population. An estimated 122.4 million U.S. adults, or approximately 47 percent, are living with a form of CVD, including coronary artery disease, heart failure, and stroke (AHA 2022). On average, one person dies from CVD every 34 seconds, accounting for 2,552 deaths each day across the country (AHA, 2022). This study explored the effectiveness of emerging lipid-lowering medications, which offer promising alternatives or adjuncts to traditional statin treatment in managing cardiovascular risk.

Operational Definitions:

Atherosclerosis: the buildup of cholesterol-rich plaques within arterial walls, leading to reduced blood flow and increased risk of cardiovascular events

For this study, atherosclerosis includes or is associated with the following clinical conditions:

- Coronary bypass artery graft (CABG): a surgical intervention used to bypass occluded arteries with severe coronary atherosclerosis (AHA, 2025)
- Diabetes Mellitus (DM): a metabolic disease characterized by chronically high blood sugar, accelerating the development of atherosclerosis (Baek, 2023)
- Myocardial Infarction (MI): heart muscle damage caused by blocked blood flow
- Percutaneous coronary intervention (PCI): a non-surgical procedure used to treat narrow or blocked coronary arteries caused by atherosclerosis
- Peripheral Vascular Disease (PVD): a condition involving atherosclerotic obstruction of peripheral arteries leading to chronic leg pain
- Sick Sinus Syndrome: a cardiac rhythm disorder caused by the malfunction of the heart's natural pacemaker (Dakkak & Doukky, 2023)
- Stroke: the sudden loss of brain functions due to interrupted blood flow or bleeding in the brain

Health Care Provider: An individual licensed or certified to deliver medical, diagnostic, or therapeutic services, including physicians such as cardiologists and primary care providers, or nurse practitioners.

Hypertension: chronic condition characterized by persistently elevated blood pressure requiring lifestyle modification or medication

Hyperlipidemia: chronic condition marked by elevated blood lipid levels, particularly cholesterol and triglycerides, requiring medical or dietary intervention

Inhibitors: biological active agents designed to bind and neutralize molecular targets, targeting PCSK9 and clearing LDL-C

Injectable Medications: Treatments administered via subcutaneous injection

Medication Compliance: Percentage of prescribed doses of a medication a patient takes within a specific time frame

Medication Side Effects: An unintended or adverse physiological or psychological response to a drug

PCSK-9 inhibitors: proprotein convertase subtilisin/kexin type 9 serine protease

(Chaudhary et al., 2017)

Plaque: a buildup of fatty deposits, cholesterol, calcium and other substances in the walls of the artery

Conceptual Framework

Statin intolerance along with hyperlipidemia is noticeably high among patients in clinical settings. The increased impact of hyperlipidemia and potential for reduced compliance to statins

due to side effects, places patients for accelerated atherosclerosis and thereby potentially compromised mortality.

The rationale behind prescribing cholesterol-lowering medications, such as statins, was grounded in their proven efficacy in reducing the risk of heart attack, stroke, and other complications related to atherosclerosis. Elevated levels of LDL cholesterol are a major contributor to the development of atherosclerosis. Over time, these plaques can rupture and trigger blood clot formation, leading to potentially life-threatening events like heart attacks and strokes.

Statins have been the most prescribed class of cholesterol-lowering drugs. They work by inhibiting HMG-CoA reductase, a key enzyme in the liver's cholesterol synthesis pathway. By reducing cholesterol production, statins effectively lower LDL cholesterol levels in the blood. Numerous large-scale clinical trials, such as the Heart Protection Study and the JUPITER Trial, have shown that statins can reduce LDL cholesterol by 30-50% and significantly lower the risk of cardiovascular events (Jupiter, 2008).

Methodological Overview

The current study investigated the efficacy and perceptions of cholesterol-lowering therapies, specifically PCSK9 inhibitors such as Praluent and Leqvio, versus traditional statins in managing hyperlipidemia and reducing CVD risk. The study included a mixed-methods approach, the research included a retrospective analysis of EHRs and qualitative interviews with healthcare providers. The study aimed to assess clinical outcomes, including LDL-C reduction, adherence, and associated barriers. Healthcare providers' perspectives and real-world effectiveness were utilized to understand drug treatments' roles in lowering CVD risk.

Limitations

For the present study, the following limitations applied:

- PCSK9 inhibitors were only passed by the FDA in 2015
- Statin drugs have been the first-line treatment since 1987; their widespread use may limit the ability to assess newer therapies or alternatives
- Patient adherence to these medications could not be assessed

Delimitations

The present study was delimited to:

1. Data only from one health network in Pennsylvania
2. Outcome measures (LDL reduction, risk of heart attack or stroke)
3. Medication type (Statin drugs, alternative injectable medication/PCSK9 inhibitors)

Overview of Study

Chapter two presents the relevant literature on cardiovascular disease, the atherosclerotic process, and current cholesterol lowering medications. Chapter three presented research design, subjects, instrumentation, procedures, and data analysis. Chapter four discussed findings via each research question. Finally, Chapter five synthesized the findings in the context of the literature, made recommendations for future research and provided a study conclusion.

Chapter 2

Literature Review

This chapter will outline the study's purpose and search strategy, discussed atherosclerosis and the prevalence of high cholesterol and heart disease, and reviewed cholesterol-lowering medications including statins, PCSK9 inhibitors, and alternatives. It also addressed statin intolerance, medication adherence, and the impact of diet and exercise.

Purpose Statement

The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on PCSK9 inhibitors, and statin drugs. Trends in cardiovascular disease (CVD) prevalence, and the efficacy and safety of cholesterol-lowering therapies were evaluated. Understanding these aspects is crucial for optimizing cardiovascular health and reducing the burden of CVD worldwide. A secondary purpose was to gain perspective on the perceptions of prescribing injectable cholesterol lowering medications efficacy of healthcare providers. The study aimed to identify predictors of PCSK9 inhibitor use, such as statin intolerance and high baseline low density lipoprotein cholesterol (LDL-C) levels.

The following research questions were utilized in this study:

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4. What were the perceptions of healthcare providers on the efficacy of PCSK9 inhibitors and statin drugs in the use of treating cardiovascular disease via hyperlipidemia?

Search Strategy

Key words and phrases to locate data points for this study included cholesterol, hyperlipidemia, Statin drugs, and cardiovascular disease. Several journals from the American Heart Association (AHA) were included. MedLine and PubMed were the primary databases utilized with dates of publication from 1990 to present day. A total of 29 research studies were analyzed, along with 3 case studies based on secondary data to evaluate cholesterol-lowering therapies and their outcomes.

Atherosclerosis: Pathophysiology and Mechanisms

Atherosclerosis is a complex, multifactorial process involving various cellular and molecular mechanisms (Dasagrandhi et al., 2021). It begins with endothelial dysfunction, characterized by impaired endothelial cell function and increased permeability to lipoproteins (Libby, 2021.) In response to endothelial injury or inflammation, circulating monocytes adhere to the dysfunctional endothelium and migrate into the subendothelial space, where they differentiate into macrophages and engulf oxidized low-density lipoprotein (LDL) particles, forming foam cells (Libby, 2021).

Foam cells form as an immune response to endothelial damage and lipid accumulation. Over time, lipids, foam cells, and other immune cells lead to the development of a more complex

atherosclerotic plaque. This plaque is made up of a lipid core, surrounded by a fibrous cap composed of smooth muscle cells and extracellular matrix proteins. The fibrous cap attempts to stabilize the plaque, but if the inflammation persists, the cap can become thin and vulnerable to rupture (Nedkoff et al., 2023).

Over time, these fatty streaks progress into more advanced lesions characterized by the deposition of the extracellular matrix, smooth muscle cell proliferation, and the formation of a fibrous cap (Dasagrandhi et al., 2021). When the fibrous cap breaks open, the lipid core and other substances are exposed to the bloodstream, triggering the formation of a blood clot (thrombus). If the clot becomes large enough, it can completely block blood flow through the artery, this can potentially lead to severe consequences such as heart attack or stroke (AHA, 2022). To an extent, this process is reversible, with diet and lifestyle changes. Inflammatory cytokines released by activated macrophages and other immune cells further contribute to plaque progression and destabilization (Libby, 2021). Inflammatory cytokines released by activated macrophages and other immune cells further contribute to plaque progression and destabilization (Libby, 2021).

Atherosclerosis can affect various arteries throughout the body, including coronary arteries (leading to CVD), carotid arteries (increasing the risk of stroke), and peripheral arteries (causing peripheral artery disease), as well as an increased risk of diabetes mellitus. Irrespective of the location of the atherosclerosis, the impact on one's health can be significant.

The rupture or erosion of vulnerable plaques can trigger thrombus (blood clot) formation, which can lead to acute cardiovascular events such as myocardial infarction (heart attack) or stroke. Moreover, chronic inflammation within the plaque microenvironment promotes

endothelial dysfunction, vasoconstriction, and thrombosis, exacerbating the progression of atherosclerosis (Libby, 2021). Understanding the pathophysiology of atherosclerosis is essential for developing effective strategies to prevent and treat CVD. By targeting key molecular pathways involved in plaque formation and inflammation, novel therapeutic approaches aim to mitigate the progression of atherosclerosis and reduce the risk of adverse cardiovascular events (Dasagrandhi et al., 2021).

Approximately 95 million American adults, or about 38% of the U.S. population have elevated cholesterol (CDC, 2023). Of these, nearly 29 million are currently taking cholesterol-lowering medications, primarily statins. Despite widespread treatment, CVD remains a leading cause of death, affecting over 20 million adults in the United States (AHA, 2023). These figures underscore the ongoing public health challenge of managing cholesterol and preventing cardiovascular disease.

Treatments for Hyperlipidemia

Elevated cholesterol is managed through a combination of lifestyle changes and medications. Statins are the primary treatment due to their effectiveness in lowering LDL-C and reducing cardiovascular risk (Grundy et al., 2019). For patients who cannot tolerate statins or require additional lipid-lowering, options include newer treatments such as Praluent and Repatha, provide alternatives for high-risk individuals (Robinson et al., 2015, Ray et al., 2020; Nissen et al., 2023). The choice of therapy depends on the patient's cholesterol levels, cardiovascular risk factors, and medication tolerance.

Role of Cholesterol-Lowering Medications

Cholesterol-lowering medications play a crucial role in the management and prevention of CVD, particularly in individuals with hyperlipidemia or elevated cholesterol levels (Mach et al., 2019). By reducing circulating levels of LDL-C, these medications help attenuate the progression of atherosclerosis and lower the risk of adverse cardiovascular events (Mach et al., 2019).

Statin Drugs

Statins have been a foundational therapy in lipid management and cardiovascular disease prevention for over three decades. The first statin compound, mevastatin (compactin), was discovered in the 1970s by Japanese biochemist Akira Endo. He identified its ability to inhibit HMG-CoA reductase, a key enzyme in cholesterol synthesis (Endo, 2010). Clinical use began with the FDA approval of lovastatin (Mevacor) in 1987, marking the first statin to enter the U.S. market (Lennernäs & Fager, 1997). Initially, statins were considered second-line therapy, used after diet and lifestyle modifications failed to adequately reduce cholesterol levels. However, due to their proven efficacy in lowering LDL-C and reducing cardiovascular events, statins soon became the first-line pharmacologic treatment for hyperlipidemia (Grundy et al., 2019). Over time, more potent statins such as atorvastatin and rosuvastatin were developed, further expanding their role in clinical practice. Today, while newer injectable lipid-lowering agents are available, statins, oral medications usually taken once daily in pill form, remain the standard initial pharmacologic intervention for managing elevated LDL-C due to their effectiveness, safety profile, and broad accessibility (Grundy et al., 2019).

Statins function by inhibiting HMG-CoA reductase, reducing the production of cholesterol within the liver, leading to an increased uptake of LDL-C from the bloodstream through upregulation of LDL receptors. As a result, statins effectively lower circulating LDL-C levels, which significantly reduces the risk of atherosclerotic cardiovascular disease. According to the CDC (2023), approximately 28% of U.S. adults aged 40 and older with elevated cholesterol are prescribed statins, making them the most widely used cholesterol-lowering medication. Common side effects include muscle pain (myalgia), elevated liver enzymes, and in rare cases, rhabdomyolysis. Additionally, some patients report cognitive symptoms and increased risk of diabetes, though these remain topics of ongoing research. Despite these concerns, statins' benefits in reducing cardiovascular events generally outweigh the risks, but side effects can impact patient adherence and necessitate alternative therapies for intolerant individuals (Grundy et al., 2019).

Statin drugs are classified as HM CoA reductase inhibitors which works in the liver to prevent cholesterol from forming, which in turn prevents the total amount of cholesterol circulating in the blood. Statin drugs also promote HDL cholesterol production and lower triglycerides.

Available statin drugs include Atorvastatin, Pravastatin, Rosuvastatin, and Simvastatin.

Bile Acid Sequestrates

These drugs may be used in conjunction with a Statin drug if a patient has known CVD. Bile acid sequestrants lower LDL-C by binding bile acids in the intestine, preventing their reabsorption (Chiang et al., 2020). This forces the liver to use more cholesterol to make new bile acids, which increases LDL receptor activity and removes more LDL -C from the blood. These

medications include Cholestyramine and Colestipol. These medications are usually taken orally in a tablet or powder form, taken multiple times per day to maximize effectiveness.

Omega-3 Fatty Acid Ethyl Esters

These specific medications derive from fish oil, which promote a healthy heart and are used in high doses to lower triglyceride levels. They reduce triglycerides by inhibiting the liver's production of triglycerides and increasing the activity of enzymes that break down triglyceride-rich lipoproteins, which together lower blood triglyceride levels. Omega-3 fatty acid ethyl esters are prescription oral medications typically taken as capsules, usually with meals, to help lower triglyceride levels in the blood. These medications include Lovaza, Vascepa, and Omtryg.

PCSK9 Inhibitors

Among the various classes of cholesterol-lowering medications, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have garnered significant attention for their potent lipid-lowering effects and cardiovascular benefits (Chaudhary et al., 2017). PCSK9 inhibitors, such as Praluent, Leqvio, and Repatha, inhibit the degradation of hepatic LDL receptors, thereby increasing the clearance of LDL-C from the bloodstream (Chaudhary et al., 2017).

Clinical trials have demonstrated the efficacy of PCSK9 inhibitors in reducing LDL-C levels by up to 60-70%, even in patients with familial hypercholesterolemia or statin intolerance (Chaudhary et al., 2017). Moreover, PCSK9 inhibitors have been shown to lower the risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death, in high-risk patient populations (Bandyopadhyay et al., 2018).

In addition to their LDL-C-lowering effects, PCSK9 inhibitors exhibit anti-inflammatory properties and may exert beneficial effects on plaque stability and endothelial function (Bandyopadhyay et al., 2018). Recent studies indicate that women may demonstrate a comparatively diminished reduction in LDL-C levels following treatment with PCSK9 inhibitors relative to men. This disparity is thought to be influenced by biological factors such as hormonal regulation, differences in lipid metabolism, and baseline variations in lipoprotein particle characteristics (Berro Rivera et al., 2023; Moriarty et al., 2022). Additionally, sex-specific differences in cardiovascular risk profiles, plaque composition, and inflammatory responses can impact the overall effectiveness of lipid-lowering therapies (Shah et al., 2021; Virani et al., 2020). These findings highlight the importance of incorporating sex as a biological variable in the development of personalized treatment plans to ensure optimal outcomes in cardiovascular disease management. Praluent and Repatha are typically injected every two weeks or once every four weeks, while Leqvio is administered initially, then after three months, and subsequently every six months.

Despite the promising benefits of PCSK9 inhibitors, their high cost and potential adverse effects, such as injection site reactions, have raised concerns regarding their widespread use and affordability (Chaudhary et al., 2017). Nevertheless, ongoing research efforts aim to address these challenges and further elucidate the role of PCSK9 inhibitors in cardiovascular risk reduction. These medications have only been researched since 2015; therefore, further research is indicated to show effectiveness.

Alirocumab

Praluent (alirocumab), produced by Sanofi, is a monoclonal antibody that lowers LDL cholesterol by inhibiting PCSK9, a protein that reduces the liver's ability to clear LDL-C from the bloodstream. Administered via subcutaneous injection every two weeks or once every four weeks, Praluent provides significant LDL-C reduction for patients who require additional lipid-lowering beyond statins or who are statin-intolerant (Robinson et al., 2015).

Evolocumab

Similarly, Repatha (evolocumab), developed by Amgen, functions through the same PCSK9 inhibition mechanism and is typically injected every two weeks or monthly. Both medications have demonstrated substantial efficacy in reducing LDL-C levels and lowering cardiovascular risk in high-risk populations (Sabatine et al., 2017). Their dosing schedules, while more frequent than newer agents like inclisiran, offer effective and well-tolerated treatment options for patients needing aggressive lipid management.

Inclisiran

Leqvio (inclisiran) is a cholesterol-lowering medication that targets LDL-C by utilizing small interfering RNA (siRNA) to reduce the production of PCSK9, a protein that hinders LDL-C clearance from the blood. This mechanism allows for substantial LDL-C reduction by dosing only twice per year after an initial dose and a three-month follow-up, making it a unique and convenient option for patients who struggle with adherence to more frequent dosing (Ray et al., 2020). While Leqvio primarily targets LDL-C, researchers are also exploring its potential effects on LP(a) (Tsimikas, 2019). Addressing this risk factor is particularly relevant for patients who

remain at high cardiovascular risk despite optimal LDL-C management (Nordestgaard & Langsted, 2016).

Statin Intolerance and Alternative Drug Therapies

Statin intolerance, characterized by adverse effects such as muscle symptoms or elevated liver enzymes, poses a significant challenge in the management of hyperlipidemia (Fitchett et al., 2015). Despite the proven efficacy of statins in reducing LDL-C levels and preventing cardiovascular events, a subset of patients may experience intolerable side effects, leading to treatment discontinuation or non-adherence (Fitchett et al., 2015.) Recognizing the prevalence of statin intolerance, healthcare providers must explore alternative lipid-lowering therapies to achieve optimal cholesterol control and cardiovascular risk reduction.

Several alternative drug therapies have been investigated for the management of high LDL cholesterol in statin-intolerant patients' Clinical trials have demonstrated the efficacy and safety of ezetimibe as monotherapy or in combination with statins for LDL-C lowering in statin-intolerant patients, providing a valuable treatment option for this population (Moriarty et al., 2015). Additionally, PCSK9 inhibitors, have emerged as promising therapeutic agents for statin-intolerant patients with familial hypercholesterolemia or elevated cardiovascular risk (Moriarty et al., 2015). PCSK9 inhibitors may be a better alternative in lowering LDL-C for those who suffer from statin intolerance.

Medication Compliance and Side Effects

The US food and drug administration oversees the approval process for medications, and is a rigorous process, requiring extensive preclinical and clinical trials to ensure safety and efficacy. This process can take several years and includes multiple phases of testing in diverse

populations before a drug is deemed suitable for public use (FDA, 2024). Despite the promise of new therapies, all medications, including cholesterol-lowering drugs, come with potential side effects that can significantly impact patient compliance. For instance, statins are associated with muscle pain and liver enzyme elevation, while PCSK9 inhibitors like Praluent and Leqvio may cause injection site reactions (Chaudhary et al., 2017; Ray et al., 2020). The high cost of these medications further complicates adherence, averaging \$5,800 and \$6,500 annually. These factors underscore the importance of balancing efficacy, side effects, and affordability to optimize treatment outcomes and patient adherence.

With over half of patients with chronic conditions failing to adhere to their prescribed regimens, medication noncompliance is a widespread issue in healthcare. This non-adherence leads to significant health and financial consequences, including approximately 125,000 preventable deaths annually and a \$300 billion burden on the U.S. healthcare system due to increased hospitalizations and emergency care (AHA, 2023). The reasons for non-adherence include forgetfulness, fear of side effects, high medication costs, and the complexity of treatment regimens (American Medical Association, 2023). Additionally, patients with asymptomatic conditions like hypertension may underestimate the importance of their medication, leading to inconsistent adherence. To address these challenges, healthcare providers can simplify treatment plans, address financial concerns, and improve patient education to ensure better adherence and improved health outcomes (American Medical Association, 2023).

Howard, et al (2021) with the Journal of American College of cardiology investigated experiences felt from Statin drugs and a placebo drug. The results showed that patient's felt similar symptomology with Statin drugs, and the placebo. Many of the symptoms were nocebo,

the pattern of symptoms is identical for placebo drugs. Placebo-controlled trials of >80,000 participants have found no evidence when looking at drug therapy versus placebo. The study in 2021 had over half of their participants discontinue drug therapy, twenty-six stopping Statin drugs and twenty-three stopping the placebo (Howard, 2021).

A European study demonstrated high levels of adherence and persistence among patients treated with PCSK9 inhibitors, with over 95% of participants achieving high adherence and persistence rates exceeding 97% at 18 months of follow-up. Discontinuation was uncommon, occurring in only 3.5% of patients, and was driven primarily by patient preference or clinical decisions related to perceived excessively low LDL-C levels rather than safety concerns. Adverse drug reactions were infrequent and generally mild, most commonly consisting of localized injection-site reactions that rarely led to treatment cessation (Gargiulo, 2023).

Diet and Exercise

Due to its association with CVD, diet and exercise play a critical role in reducing LDL-C. A diet low in saturated and trans fats, commonly found in processed and fried foods, can help lower LDL levels by reducing cholesterol intake and decreasing liver cholesterol production (Bazzano et al., 2019). Increasing fiber-rich foods, such as fruits, vegetables, and whole grains, further aids in reducing LDL. Soluble fiber binds cholesterol in the digestive tract, preventing its absorption into the bloodstream (Lamarche et al., 2020). Regular physical activity also has a beneficial impact on cholesterol by increasing the enzymes that help transport LDL from the blood to the liver, where it is processed and excreted (Durstine et al., 2018). These lifestyle changes can be particularly effective for individuals with mild to moderate hypercholesterolemia and are often recommended alongside medications to enhance lipid-lowering effects.

The Ornish and Mediterranean diets are two evidence-based dietary approaches shown to lower cholesterol levels and improve cardiovascular health. The Ornish diet emphasizes plant-based, low-fat eating with minimal animal products and no added fats, while prioritizing whole grains, fruits, vegetables, and legumes. This ultra-low-fat approach has been linked to significant reductions in LDL cholesterol and even reversal of atherosclerosis (Ornish et al., 1998). In contrast, the mediterranean diet is less restrictive and includes foods such as olive oil, nuts, fatty fish, and moderate consumption of wine, alongside fruits, vegetables, and whole grains. Its high monounsaturated fat content and anti-inflammatory properties have been shown to lower LDL cholesterol and increase HDL cholesterol, offering a cardioprotective effect (Estruch et al., 2018.) Both diets demonstrate the benefits of nutrient-rich, plant-based foods, but the Mediterranean diet is often more sustainable due to its flexibility and palatability (Martinez-Gonzalez et al., 2020).

Exercise

The American College of Sports Medicine (ACSM) emphasizes the role of structured physical activity in CVD risk. ACSM recommends aerobic exercise performed three to five days per week (frequency), with each session lasting between 30 to 60 minutes (time), depending on the individual's fitness level and goals. The type of exercise should primarily involve continuous activities such as walking, jogging, cycling, or swimming, which engage large muscle groups and elevate heart rate (type). Intensity depends on the individual's capacity and health status. To ensure ongoing improvement, it is important to gradually increase the duration, intensity, or frequency of exercise over time as the body adapts. This structured approach to physical activity has been shown to enhance cardiovascular function, lower LDL-C levels, and reduce overall risk

of atherosclerosis and other CVD outcomes, making it a key component of both prevention and management strategies for individuals with hyperlipidemia.

Summary

This chapter presented the relevant literature related to how high cholesterol contributes to heart disease and why managing cholesterol is important for overall health. Treatment for elevated lipids typically begins with diet and exercise, but when lifestyle changes are insufficient, statin drugs and newer injectable cholesterol-lowering medications are often prescribed. This chapter highlighted the need for personalized care to help people better manage their cholesterol and reduce the risk of heart problems, as well as the impact of diet and exercise. Chapter three will present the methodology and subjects utilized in this study.

Chapter 3

Methodology

Purpose Statement

The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on PCSK9 inhibitors, and statin drugs. Trends in cardiovascular disease (CVD) prevalence, and the efficacy and safety of cholesterol-lowering therapies were evaluated. Understanding these aspects is crucial for optimizing cardiovascular health and reducing the burden of CVD worldwide. A secondary purpose was to gain perspective on the perceptions of prescribing injectable cholesterol lowering medications efficacy of healthcare providers. The study aimed to identify predictors of PCSK9 inhibitor use, such as statin intolerance and high baseline low density lipoprotein cholesterol (LDL-C) levels.

The following research questions were utilized in this study:

1. How did statins compare to PCSK9 inhibitors in terms of reducing low density lipoprotein cholesterol (LDL-C) with patients with hyperlipidemia?
2. What were the predictors of usage for PCSK9 inhibitors versus statin drugs with individuals with hyperlipidemia?
3. What was the efficacy in prescribing non-statin drugs (Repatha, Praluent) to those with hyperlipidemia?
4. What were the perceptions of healthcare providers on the efficacy of PCSK9 inhibitors and statin drugs in the use of treating cardiovascular disease via hyperlipidemia?

This chapter will outline the methodology used in the study, including research design and data collection processes. It will explain the retrieval of quantitative and qualitative data from electronic health records and provider interviews. The interview questions used during the provider interviews will be presented, along with descriptions of the procedures followed and the data analysis methods employed.

Overview

CVD remains a leading cause of mortality worldwide, driven largely by high levels of LDL-C, a key modifiable risk factor (World Health Organization, 2021). To combat this, treatments such as Repatha and Praluent have emerged as powerful options for significantly reducing LDL-C, particularly in patients who do not respond adequately to traditional statins (Sabatine et al., 2015). These therapies, individually or in combination, have led to better patient outcomes, including lower rates of heart attack and stroke (Giugliano et al., 2017). In patients with high cardiovascular risk, these drugs provide essential tools to achieve and maintain LDL-C goals, ultimately improving quality of life and reducing mortality associated with CVD. This chapter will explain the subjects and procedures used in this study to conduct a retrospective, mixed method exploratory study.

Research Design

The present study employed a mixed-methods exploratory research design with a retrospective analysis of patient electronic medical records and included semi-structured interviews with health care providers on their perceptions on efficacy and patient compliance.

Subjects

Prior to data harvesting for dependent variables and conducting provider interviews, IRB approval was obtained. Fifty participants were included in this study as well as three providers with various expertise to gain insight into their medication prescribing habits. A snowball sampling technique was used to garner provider participation. Data from patients was selected based on inclusion criteria outlined below.

Quantitative Data

For this retrospective study, quantitative data was collected using secondary data from electronic health records (EHRs) to examine patient outcomes related to cholesterol-lowering treatments. A health network in the Northeast of the United States was utilized. The use of EHR data provided an efficient and rich source of patient information, including demographic details, medical history, treatment regimens, and clinical outcomes (see table 1.) The data allowed for a thorough analysis of these medications and their impact on LDL-C levels, cardiovascular events, and patient adherence.

Table 1

Data Retrieved from EHR

Age
Gender
Comorbidities
Medications
Hospitalizations
Total Cholesterol
HDL-C
LDL-C
TC/HDL ratio
Non-HDL cholesterol
Triglycerides
LDL Subtractions
Lipoprotein A
Family History of Hyperlipidemia (Yes or No)
ACVD Risk Score
Cardiac Calcium Score
Patient's Insurance
Alternative Medications
LDL-C pre and 6 months post medication therapy
Lipid Reduction Score-Change

Qualitative Data

For this study, qualitative data was gathered through virtual interviews with a nurse practitioner (NP), interventional cardiologist, and cardiologist to explore their perspectives on the efficacy and challenges of prescribing cholesterol-lowering drugs. The interviews focused on understanding the healthcare providers' decision-making processes when selecting lipid-lowering therapies, as well as their experiences with patient outcomes, adherence, and any barriers to treatment. The interviews included seven questions and were conducted via Zoom and telephone, then recorded for transcription across the healthcare providers' viewpoints. This approach provided contextual insights into the practical considerations involved in prescribing these medications, particularly in relation to other cholesterol-lowering options like statins and ezetimibe. By examining the different perspectives of these providers, the study aimed to deepen the understanding of how these drugs are integrated into treatment plans and the perceived effectiveness in managing high cholesterol, ultimately contributing to better patient care (Appendix A.)

Table 2

Provider Experience/ Specialty

Provider 1	Provider 2	Provider 3
Specialty: Primary Care	Interventional Cardiology	Cardiology
Years of Experience: 10	11	16

Procedures

This study included adult patients with cardiovascular risk factors such as high cholesterol, hypertension, and diabetes. Electronic medical records were harvested for patients from a health network in northeastern U.S. who were diagnosed with elevated lipids. For inclusion into the subject pool, lipid medication was prescribed for a minimum of six months. The patients were diagnosed with hyperlipidemia or were prescribed cholesterol lowering medications prior to the study. Both male and female patients were included to ensure diverse representation, as gender differences in cholesterol metabolism and cardiovascular risk factors can influence treatment outcomes. Gender-based analysis was important to explore potential disparities in medication responses, as research shows that men and women may have different lipid profiles, responses to treatments, and patterns of medication adherence.

Including a wide range of comorbidities, such as diabetes and peripheral vascular disease was vital for reflecting real-world clinical practice, where patients with multiple health conditions are the norm (AHA, 2022).

The study utilized retrospective data, based on available records, from a health network in Pennsylvania. This period, spanning February 2023 to December 2024, was selected to provide a balance between gathering sufficient data for meaningful analysis and maintaining a manageable study scope.

Data Analysis

The quantitative data were analyzed with descriptive statistics. In addition, nonparametric analysis was used to measure efficacy as treatment outcomes were placed in categories as responsive, unresponsive, and stable. Patient profiles were analyzed to develop prediction models on efficacy. A logistic stepwise regression analysis was used to evaluate predictors for PCSK9 usage. Change scores were calculated to show LDL-C at baseline and 6 months post beginning a medication regimen. Independent T-tests were used to evaluate statistical significance of dependent variables. SPSS 29.0 was utilized for all analyses.

The qualitative data was analyzed by coding interview transcriptions for thematic analysis. SPSS 29.0 was used for all quantitative analyses. Two independent content specialists coded the transcriptions to identify themes utilizing Taguette 4.0. The final list of themes was determined through consensus between coders, with inclusion based on thematic saturation, consistency across transcripts, and alignment with the study objectives.

Chapter 4

Results

Purpose Statement

The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on PCSK9 inhibitors, and statin drugs. Trends in cardiovascular disease (CVD) prevalence, and the efficacy and safety of cholesterol-lowering therapies were evaluated. Understanding these aspects is crucial for optimizing cardiovascular health and reducing the burden of CVD worldwide. A secondary purpose was to gain perspective on the perceptions of prescribing injectable cholesterol lowering medications efficacy of healthcare providers. The study aimed to identify predictors of PCSK9 inhibitor use, such as statin intolerance and high baseline low-density lipoprotein cholesterol (LDL-C) levels.

Cardiovascular disease remains a leading cause of morbidity and mortality worldwide, prompting an ongoing search for effective prevention and treatment strategies. Among these, cholesterol-lowering medications, particularly statins and the newer class of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, play a critical role in reducing LDL-C and associated cardiovascular risk. This chapter presents a comprehensive overview of patient demographics, followed by descriptive statistics, inferential statistics, and thematic analysis of qualitative work, and detailed analysis addressing all research questions.

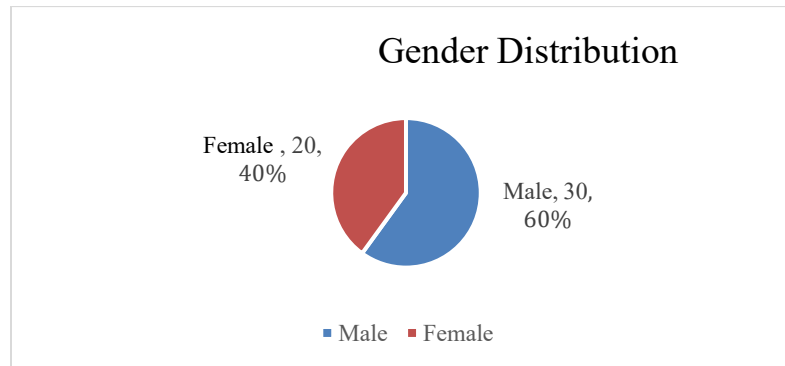
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4. What were the perceptions of healthcare providers on the efficacy of PCSK9 inhibitors and statin drugs in the use of treating cardiovascular disease via hyperlipidemia?

Descriptive Demographic Data

Figure 1

Gender Distribution



The study sample size included 50 patients harvested by secondary data analysis. 22 presented with comorbidities for this study. Figure 1 provides the gender breakdown for the sample. Sixty percent of the cohort were males, the remaining 40% were female.

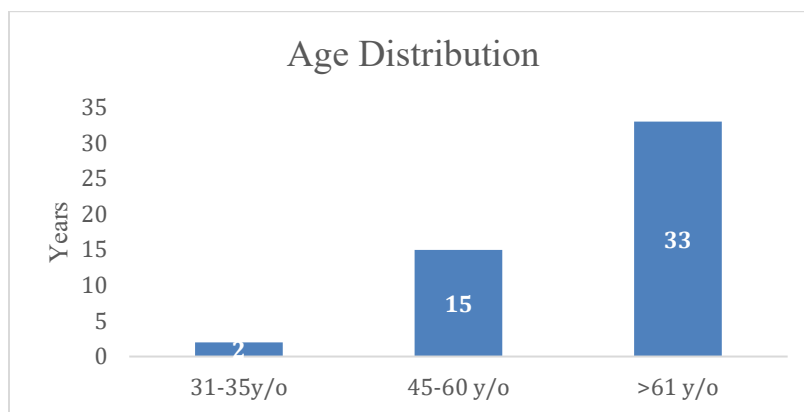
Figure 2*Age Distribution*

Figure 2 illustrates the age distribution of patients. Two participants were between 31 and 35 years old, 15 were between 45 and 60 years old, and the majority, 33 participants, were 61 years old or older. Overall, 66% of the study population fell into the 61 and older age group.

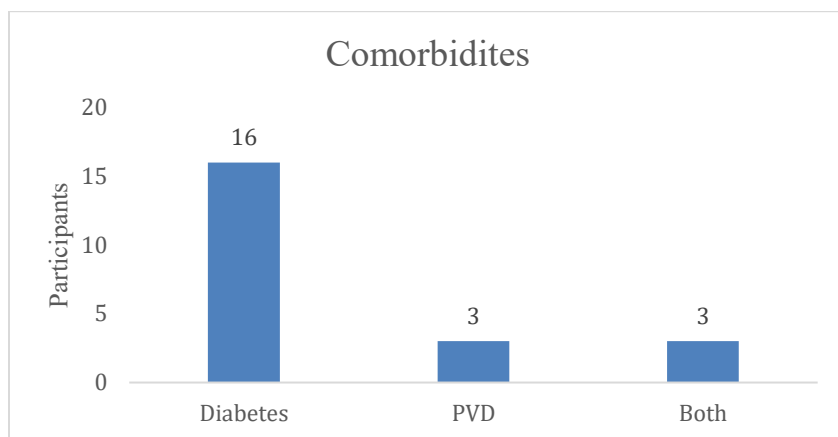
Figure 3*Comorbidities*

Figure 3 highlights comorbidities among the 50 patients. Sixteen patients had diabetes, three had peripheral vascular disease, and three had both.

Table 3*Descriptive Statistics of Lipid Profile Measures Before and After Treatment*

Dependent Variable	Mean	Standard Deviation	Highest Value	Lowest Value
LDL-C Statin Only	151.83 mg/dL	11.54	181 mg/dL	139 mg/dL
LDL-C in 6 months Statin Only	104.25 mg/dL	10.17	120 mg/dL	89 mg/dL
LDL-C PCSK9 Inhibitor	182.5 mg/dL	15.21	209 mg/dL	124 mg/dL
LDL-C in 6 months w/ PCSK9	96.17 mg/dL	11.58	148 mg/dL	78 mg/dL

Table 3 shows descriptive statistics of lipid profiles before and after treatment. The statin only group started with an average LDL-C before treatment of 151.83 mg/dL, which is lower compared to the 182.5 mg/dL, in the PCSK9 group. The statin-only group experienced an average LDL-C reduction of approximately 31.3% after six months of treatment. In comparison, patients receiving PCSK9 inhibitors showed a greater average reduction of about 47.3% over the same period.

Table 4*Descriptive Statistics of Lipid Profiles at Baseline*

Dependent Variable	Mean	Standard Deviation	Highest Value	Lowest
Total Cholesterol	218.88 mg/dL	20.49mg/dL	265 mg/dL	187 mg/dL
HDL-C	41.82 mg/dL	6.15 mg/dL	54 mg/dL	31 mg/dL
Triglycerides	207.45 mg/dL	99.63mg/ dL	402 mg/dL	78 mg/dL
TC/HDL Ratio	5.32 mg/dL	0.84 mg/dL	7.72 mg/dL	3.98 mg/dL

Table 4 provides an overview of lipid profile measurements, including total cholesterol, HDL-C, LDL-C, triglycerides and the total cholesterol to HDL ratio. For each variable, the table displays the mean, standard deviation, highest, and lowest values, offering a summary of the distribution and range of lipid levels in the study population. This study cohort had higher than recommended lipid values with some subjects demonstrating significant dyslipidemia.

Table 5
Cardiac Calcium Scores by Treatment Group

Assessment	Mean	SD	Highest Value	Lowest Value
Cardiac calcium score (Statin)	111.45	95.92	80	0
Cardiac calcium score (PCSK9 inhibitor)	181.35	80.45	360	75

Table 5 summarizes the mean and standard deviation of cardiac calcium scores among the participants. Of the 50 individuals in the study, 37 underwent this diagnostic testing. Notably, two participants recorded a calcium score of 0, indicating no detectable coronary arterial calcification at the time of measurement. Patients taking alternative medications had a higher average cardiac calcium score. Notably, participants with a score of zero were exclusively on statin therapy, suggesting that individuals at higher cardiovascular risk may benefit from additional or alternative lipid-lowering medications.

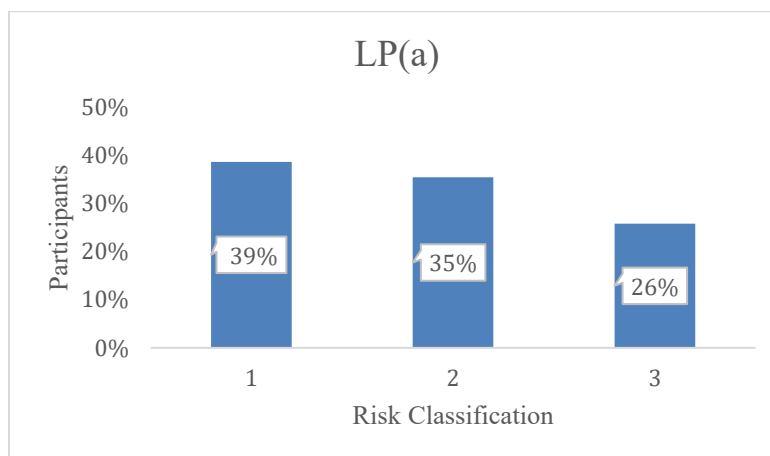
Figure 4*LP(a)*

Figure 4 illustrates the distribution of lipoprotein(a) levels, which were measured in 74% of the study sample (37 out of 50 participants). The values are categorized into three groups: (1) indicating normal levels, (2) indicating elevated levels, and (3) indicating high levels. Among the 37 participants tested, 12 had normal Lp(a) levels below 30 mg/dL, while 8 had high levels above 50 mg/dL, indicating that over 20% of those tested were at increased cardiovascular risk due to elevated Lp(a.)

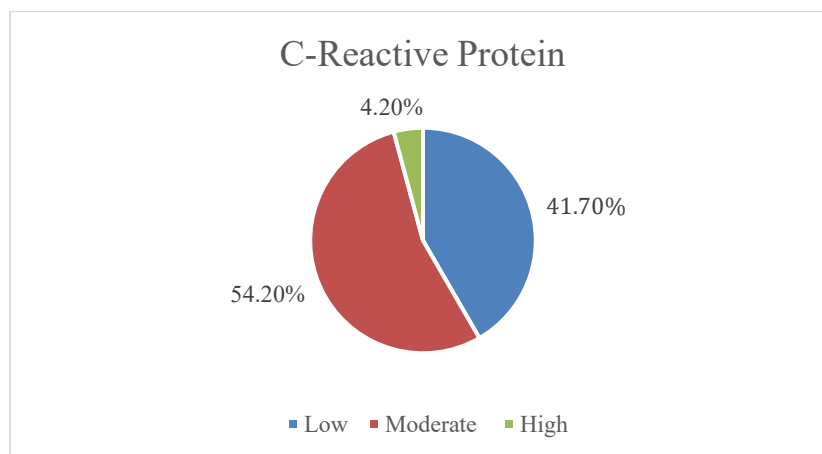
Figure 5*C-Reactive Protein*

Figure 5 shows the distribution of C-Reactive Protein (CRP) levels among 24 patients. Of these, 10 patients (41.7%) had low CRP levels, 13 patients (54.2%) had moderate levels, and 1 patient (4.2%) had a high CRP level. CRP levels below 1.0 mg/L are considered low risk, while levels above 3.0 mg/L indicate high cardiovascular risk; in this study, only one patient exceeded the high-risk threshold, while the majority (54.2%) fell into the moderate-risk range of 1.0–3.0 mg/L, suggesting a commonly observed mild inflammatory state.

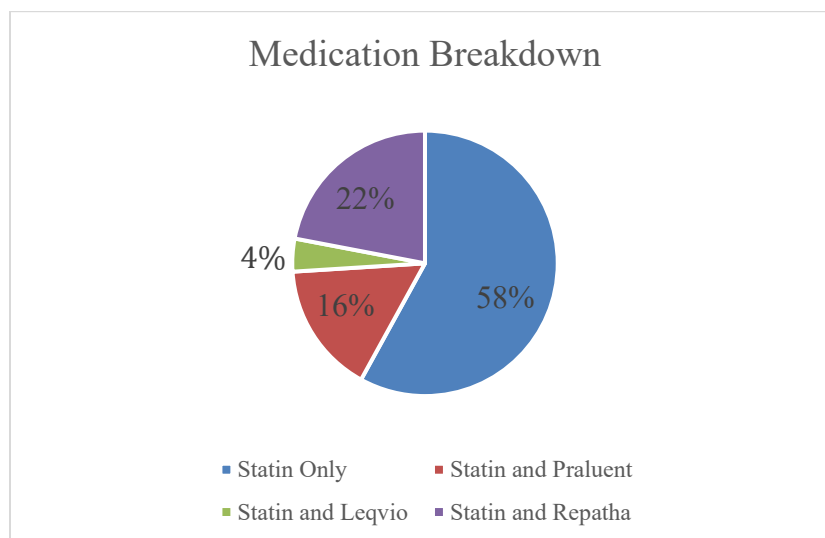
Figure 6*Lipid Medication Profile*

Figure 6 presents the breakdown of medications taken by study participants. All 50 patients were prescribed a statin, indicating universal use of this lipid-lowering therapy within the cohort. Additionally, 8 participants (16%) were taking a statin in combination with Praluent, 2 participants (4%) with Leqvio, and 11 participants (22%) with Repatha. This distribution highlights that while statin therapy was consistent across all patients, a significant portion also received adjunct lipid-lowering medications.

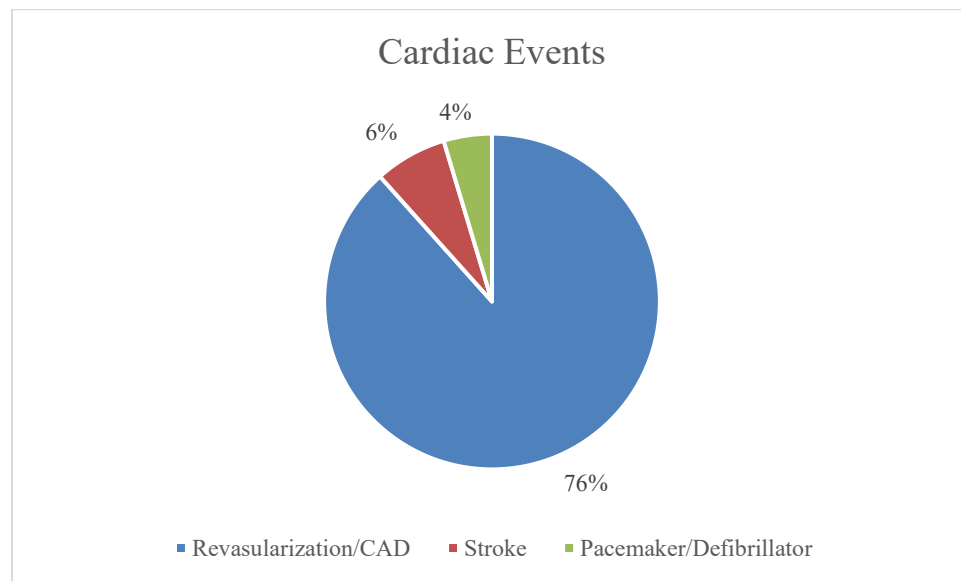
Figure 7*Cardiac Events*

Figure 7 illustrates the prevalence of cardiac events among 46 of the 50 participants in this study. Many of these individuals had experienced revascularization or occlusion-related events, including myocardial infarction (heart attack) with or without stent placement, as well as Coronary Artery Bypass Graft (CABG) surgery, which sometimes occurred alongside myocardial infarction. Specifically, twenty (20) participants had a history of myocardial infarction, four (4) underwent stent placement, and seven (7) received bypass surgery. Additionally, some participants experienced both myocardial infarction and revascularization procedures: (5) had both a myocardial infarction and stent placement, and two (2) had a heart attack followed by bypass surgery. Other cardiac events included three (3) cases of stroke and two (2) patients who required pacemaker or defibrillator implantation. These results underscore the high incidence of serious cardiovascular events and interventions within the study population.

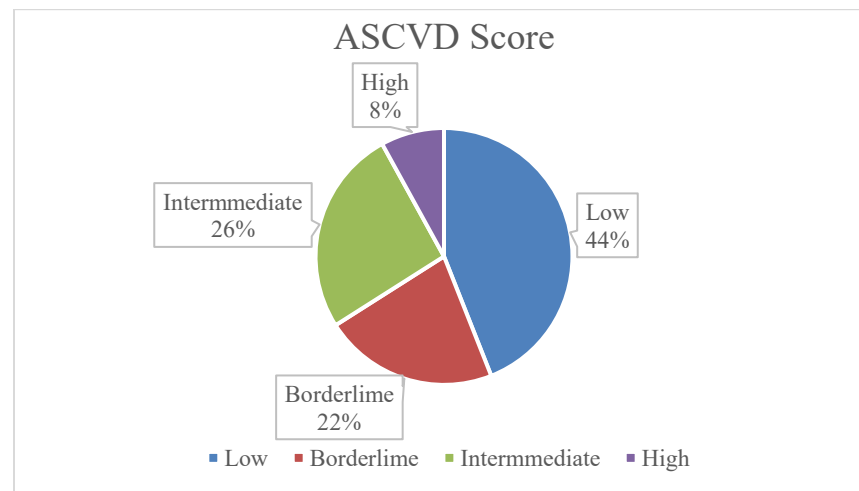
Figure 8*ASCVD Risk Score*

Figure 8 reveals that participants were distributed across all ASCVD risk categories, with a concentration in the intermediate and high-risk groups, indicating a population with generally elevated cardiovascular risk. Scores are measured as low, borderline, intermediate, and high.

Table 6*Lipid Reduction Score Change by Treatment Group*

Group	N	Mean	SD	SEM
Statin	29	47.65	5.83	1.08
Alternative medication	21	87.24	13.72	2.99

Table 6 indicates that alternative medications are nearly 50% more effective in reducing LDL-C levels compared to statin therapy alone. After six months of treatment, participants receiving alternative lipid-lowering medications demonstrated significantly greater reductions in LDL-C ($M = 87.24$, $SD = 13.72$) compared with those receiving statin therapy alone ($M = 47.65$, $SD = 5.83$), $p < .01$.

Table 7
Case Review Patient Characteristics and Lipid Measures

Patient demographics	Cardiac history	ASCVD	Medications	CAC	LDL-C	LDL-C (6 mo)	Triglycerides	Lp(a)
45-year-old male	Stent—proximal LAD	Intermediate	BB, aspirin, statin	75	167	101	285	1
65-year-old male	Sick sinus syndrome	Borderline	Statin	30	119	84	78	1
47-year-old male	Familial hyperlipidemia	Intermediate	Statin, Repatha	155	155	71	387	3

Table 7 presents a case study of three patients with differing metabolic profiles. Patient 1 was a 45-year-old male without familial hyperlipidemia who had a 90% blockage in the proximal left anterior descending artery treated with a stent. Medications included a beta-blocker, aspirin, and a statin. With an intermediate ASCVD risk score and a coronary calcium score of 75, he had moderate cardiovascular risk. His initial triglycerides were 285 mg/dL and LDL-C was 167 mg/dL. After six months, LDL-C decreased by 65 mg/dL (39.5%) to 101 mg/dL, showing effective lipid-lowering response.

Patient 2, a 65-year-old male without familial hyperlipidemia but with sick sinus syndrome was on statin therapy. He had a borderline ASCVD risk and a coronary calcium score of 30, indicating lower coronary disease burden. His LDL-C fell from 119 mg/dL to 84 mg/dL over six months, a 29.4% reduction (35 mg/dL). Triglycerides were 78 mg/dL, and lipoprotein(a) was normal at 1. This shows moderate LDL-C improvement in a lower-risk patient.

Patient 3 was a 47-year-old male with both hyperlipidemia and familial hyperlipidemia, treated with a statin and PCSK9 inhibitor, Repatha. He had an intermediate ASCVD risk and a high coronary calcium score of 155. Starting LDL-C was 155 mg/dL and triglycerides were

elevated, 387 mg/dL. After six months, LDL-C dropped by 85 mg/dL (45.6 %) to 71 mg/dL, demonstrating strong response to combined therapy in familial hyperlipidemia.

Table 8
Provider Interview Themes Codes and Frequencies

Theme	Frequency	Representative quotation
Lifestyle changes	15	Much of the American diet problem is too much processed food...
Family history	7	I urge patients with genetic risk to get treated even at a young age.
Cost	5	Insurance coverage is often the main barrier.
Compliance	2	We generally start low and increase as tolerated.
Misinformation	2	There is a ton of misinformation online.
Follow-up	2	Direct LDL may be ordered if calculations are unreliable.

Table 8 shows common themes among providers. Providers consistently highlighted lifestyle changes as the most critical factor, pointing to poor dietary habits, such as excessive processed food consumption. Family history was also a key consideration, with clinicians stressing the importance of early and aggressive intervention, especially in younger patients showing genetic risk factors for cardiovascular disease. Cost emerged as a significant barrier to treatment adherence, as insurance coverage limitations often restrict patient access to newer or more effective lipid-lowering therapies, necessitating providers to explore assistance programs to offset expenses. Finally, compliance was addressed as a practical challenge, with many providers adopting a strategy of initiating therapy at low doses to enhance patient tolerance and gradually increasing dosage to optimize treatment outcomes. These four themes underscore the complex

interplay of behavioral, genetic, financial, and clinical factors shaping effective hyperlipidemia management.

Common themes that emerged between the three providers include the following:

- Statin drugs are the first line therapy
- May be adjunct therapy in patients with known disease
- This is a shared decision-making process between provider and patient
- Those with documented statin intolerances are more likely to be able to be on injectable cholesterol lowering meds such as pcsk9 inhibitors
- Red yeast rice to be further researched
- Patient reluctance
- Insurance issues/ high cost of medications
- Bloodwork (8 weeks to 3 weeks after cholesterol lowering medication therapy begins)
- Genetics, family history
- Diet modifications

A logistic stepwise regression analysis identified seven primary predictors for the use of PCSK9 inhibitors over statins in individuals with elevated lipoproteins, each of which aligned with over 90% of the study population. Central to these predictors is a coronary artery calcium score greater than 100, indicating significant subclinical atherosclerosis and elevated cardiovascular risk. Additional factors include low-density lipoprotein cholesterol (LDL-C) levels exceeding 95 mg/dL, reflecting persistent hyperlipidemia despite standard therapy. An atherosclerotic cardiovascular disease (ASCVD) risk scores greater than 2 further signifies heightened risk for future cardiac events. Elevated lipoprotein (a) and high-density lipoprotein cholesterol (HDL-C) below 40 mg/dL contribute additional independent cardiovascular risk.

Male biological sex, a known non-modifiable risk factor, and a history of cardiovascular disease (CVD) were also strong predictors of PCSK9 inhibitor use. Together, these variables provide a comprehensive risk profile, guiding clinicians toward more aggressive lipid-lowering strategies in high-risk individuals.

Figure 9

Indicators for PCSK9 Inhibitor Usage

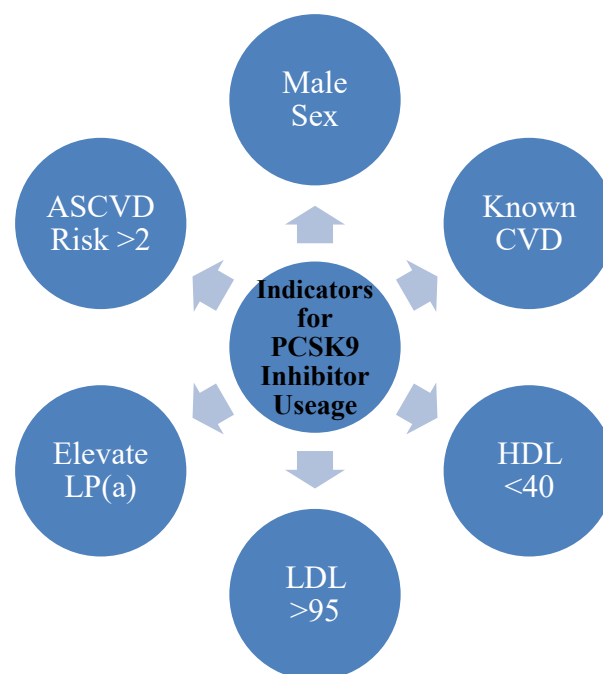


Figure 9 highlights the results of the secondary data analysis demonstrated the importance of multiple risk factors in guiding the use of alternative lipid lowering medication. Thematic analysis revealed that providers were consistent with suggesting the importance of early intervention with a collaborative decision-making process with the patient included.

Chapter 5

Discussion

This chapter addressed the four research questions related to the management of CVD. First, it compared the effectiveness of statins and PCSK9 inhibitors in reducing LDL-C levels, drawing on both clinical data and literature that highlight their relative benefits. Second, it explored the predictors that influence whether patients are prescribed PCSK9 inhibitors versus statins. Third, it examined the efficacy of non-statin drugs in patients with elevated cholesterol, referencing major clinical trials that have established their role. Lastly, it captured healthcare providers' perceptions of these therapies, connecting provider insights with existing research on adherence, patient outcomes, and treatment strategies.

Purpose Statement

The purpose of this study was to explore and compare the role of cholesterol-lowering medications, with a focus on proprotein convertase subtilisin/kexin type 9 inhibitors, and statin drugs. Trends in cardiovascular disease (CVD) prevalence, efficacy and safety of cholesterol-lowering therapies were evaluated. Understanding these aspects is crucial for optimizing cardiovascular health and reducing the burden of CVD worldwide. A secondary purpose was to gain perspective on the perceptions of prescribing injectable cholesterol lowering medications efficacy of healthcare providers. The study aimed to identify predictors of PCSK9 inhibitor use, such as statin intolerance and high baseline low density lipoprotein cholesterol (LDL-C) levels.

Cardiovascular disease has remained a leading cause of morbidity and mortality worldwide, which has prompted an ongoing search for effective prevention and treatment strategies. Among these, cholesterol-lowering medications, particularly statins and the newer class

of PCSK9 inhibitors, play a critical role in reducing LDL-C and associated cardiovascular risk. This chapter presents a comprehensive overview of patient demographics, followed by descriptive statistics and detailed analysis addressing all research questions. Both quantitative and qualitative data were examined to provide a multidimensional understanding of the current landscape of cholesterol-lowering therapy.

1. How did statins compare to PCSK9 inhibitors in terms of reducing low density lipoprotein cholesterol (LDL-C) with patients with hyperlipidemia?

In this study, analysis of patient records showed that PCSK9 inhibitors achieved LDL-C reductions of 60–70%, outperforming statins, which reduced LDL-C by about 30–50%. These findings were based on the retrospective comparison of lipid panel results pre- and post-treatment in individuals prescribed either therapy. Providers also emphasized PCSK9 inhibitors' value for familial hypercholesterolemia or statin intolerance cases during interviews. This aligns with clinical trials and meta-analyses reported by Chaudhary et al. (2017) and Sabatine et al. (2015), supporting the superior efficacy of PCSK9 inhibitors in high-risk populations, while affirming statins as the first-line treatment. Chaudhary et al. (2017) conducted a meta-analysis of more than 24 randomized controlled trials, demonstrating that PCSK9 inhibitors not only reduced LDL-C by up to 70% but also significantly decreased the incidence of major adverse cardiovascular events. This effect was especially notable in individuals with a history of cardiovascular disease or familial hypercholesterolemia, where statins alone often fail to achieve guideline-recommended LDL-C thresholds. Sabatine et al. (2015), through the FOURIER trial, found that evolocumab led to a 59% LDL-C reduction and a 15% relative risk reduction in cardiovascular events over a median follow-up of 2.2 years. The mechanism behind these

outcomes is related to PCSK9 inhibitors' ability to increase LDL receptor recycling and enhance hepatic clearance of LDL particles, offering a complementary pathway to statin therapy.

2. What were the predictors of usage for PCSK9 inhibitors versus statin drugs with individuals with hyperlipidemia?

Using regression analysis on patient demographic and clinical data, the study identified several significant predictors influencing the prescription of PCSK9 inhibitors over statins. Clinical variables such as male sex, elevated ASCVD score and LP (a), LDL >95, HDL <40, and known CVD were strongly associated with PCSK9 inhibitor use. These findings, drawn from both regression modeling and provider interviews, are consistent with prior research. Moriarty et al. (2022) emphasized that patients with multiple risk factors, such as low HDL-C and elevated Lp(a), were more likely to be escalated to PCSK9 inhibitor therapy in real world clinical settings. Similarly, Tariq et al. (2022) found that demographic variables like male sex, along with provider perception of cardiovascular risk severity, independently influenced the decision to prescribe PCSK9 inhibitors. These findings suggest that both objective clinical markers and subjective clinical judgment play a significant role in treatment selection.

3. What was the efficacy in prescribing non-statin drugs (Repatha, Praluent) to those with hyperlipidemia?

This study's review of patient outcomes showed that non-statin agents effectively lowered LDL-C to target levels in patients who were at high cardiovascular risk. Providers highlighted the essential role of these therapies in achieving rigorous lipid control in patients for whom statins alone were insufficient. They also emphasized that the combination of non-statin agents

with statins enables personalized treatment approaches tailored to the patient's unique lipid profile and associated cardiovascular risks. These observations, gathered through chart reviews and provider interviews, confirm findings from major trials such as ODYSSEY and FOURIER, as noted by Ray et al. (2020), reinforced the effectiveness of these therapies in lipid management.

4. What were the perceptions of healthcare providers on the efficacy of PCSK9 inhibitors and statin drugs in the use of treating cardiovascular disease via hyperlipidemia?

Provider interviews revealed strong confidence in statins as foundational therapy, but also growing recognition of PCSK9 inhibitors and other non-statin drugs as important adjuncts for specific patient populations. Providers reported using shared decision-making and regular lipid monitoring (every 8–12 weeks) to adjust treatment plans. These qualitative insights align with Howard (2021), described similar challenges with patient adherence, and emphasized personalized, evidence-based care. Providers are tasked with addressing the pressing issue of lipid management with the medication efficacy and potential side effects.

Clinical Recommendations

In assessing provider perceptions of these therapies, all three healthcare professionals recognized the central role of statins in primary and secondary prevention of CVD but also acknowledged the increasing importance of PCSK9 inhibitors and other non-statin therapies for certain populations. Their responses highlighted a shared commitment to personalized, evidence-based care. Such observations are reflected in the literature, including Howard (2021), which noted similar patterns of patient non-adherence due to perceived or actual side effects, many of which may be attributed to placebo effects. Providers reported that their decisions were

increasingly guided by shared decision-making and regular monitoring, including lipid panels at 8–12-week intervals and adjustments based on genetic risk markers, ASCVD scores, and patient lifestyle.

Practical Clinical Implications

Several potential clinical implications emerged from this analysis. First, increased education for both providers and patients are essential to improve understanding of the safety and efficacy of PCSK9 inhibitors and other emerging lipid lowering therapies. Clearer insurance guidelines and streamlined prior authorization processes could reduce delays in treatment initiation and improve access, especially for high-risk individuals who are most likely to benefit. Expanding coverage for injectable cholesterol lowering medications which offer convenience and improved adherence through twice-yearly dosing, may also support better long-term outcomes.

Future Study Recommendations

Future studies should explore the impact of emerging gene-editing therapies, such as VERVE-101 that could signify a fundamental change in how hyperlipidemia and atherosclerotic cardiovascular disease are treated. VERVE-101 is a CRISPR-based, single-dose investigational treatment designed to permanently switch off the PCSK9 gene in liver cells, leading to a lifelong reduction in LDL-C levels. Early-phase clinical trials have demonstrated promising results, including significant and sustained LDL-C reduction after a single administration, without the need for ongoing medication adherence (Basile, 2023.) If long-term safety and efficacy are established, this therapy could eliminate the barriers associated with daily oral regimens or costly injectable medications, such as poor compliance and access issues. The potential for a one-time, curative approach to hyperlipidemia makes VERVE-101/ 102 a potential gamechanger,

especially for patients with familial hypercholesterolemia or those at extremely high cardiovascular risk.

Future research should examine long-term outcomes, cost-effectiveness, patient acceptance, and how such therapies might be integrated into current lipid management guidelines. Additional research should further investigate the role of insurance coverage, out-of-pocket expenses, and overall treatment affordability to better understand how these financial barriers affect long-term management of hyperlipidemia and cardiovascular risk reduction.

Future research should focus on real-world effectiveness, cost-benefit analysis, and the long-term impact of combination therapies in diverse populations. Additionally, interventions that promote lifestyle changes, particularly physical activity, which have been shown to elevate HDL levels, should continue to be integrated into treatment protocols alongside medication. A multidisciplinary approach that combines pharmacologic therapy, lifestyle modification, and patient education will be essential in reducing the global burden of cardiovascular disease and improving the management of hyperlipidemia in real-world settings.

As of March 2026, The American College of Cardiology (ACC) and AHA has released new guidelines for cholesterol that align with the findings of the present study. Specifically, the inclusion of ASCVD risk scores, cardiac calcium scores, and LP(a) as part of routine assessments. Supporting the clinical relevance of these tests in risk stratification and decision making (AHA, 2026).

Future research should continue to build upon the updated recommendations from ACC which emphasize earlier screening and intervention in cholesterol management. A major focus of these guidelines is the implementation of early lifestyle modifications, including maintaining a

healthy weight, engaging in regular physical activity, alongside pharmacologic treatment when clinically indicated.

Limitations

A key limitation of this study was its sample size. Future research with a larger and more diverse sample could improve the generalizability of the results and provide deeper insights into treatment outcomes across different populations. This analysis was based on three years of retrospective data rather than the initially intended five years, due to constraints in available resources and access. This abbreviated timeframe may have limited the ability to capture long-term trends. Therefore, future research should aim to incorporate a larger and more demographically diverse sample across an extended period. Finally, the qualitative interview data involved subjective interpretation, which may limit consistency across analyses.

Conclusion

Pharmacological interventions remain effective in managing hyperlipidemia. However, newer injectable lipid-lowering agents, as examined in this study, have demonstrated greater efficacy in reducing LDL-C levels compared to traditional statin therapy. The decision to prescribe these medications should consider individual patient needs, potential side effects, and long-term implications. In this study, a 47.3% reduction in LDL-C was observed over a six-month period, supporting clinical effectiveness in lowering overall CVD risk. The continued impact of CVD on patient mortality presses the providers to examine all options of early and aggressive treatment of lipid management in a subset of patients. These findings further align with emerging recommendations from AHA and ACC reinforcing the shift towards earlier and individualized approaches to lipid management.

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Appendix A

Provider Interview Questions

1. When managing a patient's high cholesterol, at what point would you consider prescribing medication, and how do you decide if lifestyle changes alone are not enough?
2. In your experience, how effective are lifestyle modifications such as diet and exercise compared to prescribing a statin or PCSK9 inhibitor like Repatha?
3. Are there certain patient characteristics that make one approach more appropriate than the other?
4. When you prescribe cholesterol-lowering medication, how do you involve the patient in the decision-making process?
5. Have you encountered challenges with PCSK9 inhibitors such as Repatha, Leqvio, or Praluent, particularly related to patient cost or insurance coverage?
6. What strategies do you use to support patient adherence and ensure they stay on track with treatment? How do you measure medication compliance in your patients?
7. How do you evaluate the effectiveness of cholesterol-lowering medications or lifestyle interventions in your patients, and which clinical markers do you typically use?

Appendix B

Quantitative Code Book

Gender	Comorbidities	Age	Statin?	Hospitalizations	Total Cholesterol	HDL-C	LDL-C	
1= male 2= female	1= diabetes 2= PVD	1=<18 2= 18-30 3=31-45 4=45-60 5=61+	1=yes 2=no	1= Cardiac Related 2= non-cardiac related				
1		1	4	1	1	206	43	146
1			4	1	1	219	39	171
2		1	5	1	1	198	37	157
1	1,2		5	1	1	237	46	183
1		1	5	1	1	241	32	195
2		1	4	1	2	221	43	160
1		1	5	1	2	199	50	140
1			5	1	1	216	46	160
2		2	4	1	1	231	40	181
2			4	1	1	223	39	171
1			5	1	1	251	37	202
1	1,2		5	1	1	234	33	187
1			4	1	2	189	31	139
1			5	1	1	265	50	199
2			5	1	1	237	40	179
1			3	1	1	203	46	148
2		1	4	1	1	197	40	138
2		1	4	1	1	216	35	169
1		2	5	1	2	221	42	173
1	1,2		5	1	1	247	32	209
2			5	1	1	251	45	199
1			5	1	2	187	33	149
1			5	1	1	194	39	145
1		1	4	1	1	193	31	151
1		1	5	1	1	231	42	178
2			3	1	1	211	48	148
2		1	5	1	2	187	44	138
1			5	1	1	201	47	148

2		4	1	1	215	42	157
2	1	5	1	2	232	40	178
1	2	5	1	1	261	50	198
1		5	1	2	213	43	139
1		5	1	1	223	56	158
1		5	1	1	189	32	142
2	1	5	1	1	204	39	153
2		4	1	1	257	53	198
1		5	1	1	214	37	164
2		4	1	1	229	41	167
1	1	5	1	1	217	38	165
1		5	1	1	189	42	131
1		5	1	2	249	48	184
2	1	5	1	1	226	38	179
1		5	1	1	206	49	150
2		4	1	1	211	39	159
1		3	1	1	225	54	154
1	1	5	1	1	234	36	183
1	1,2	5	1	1	231	47	161
2		4	1	1	197	40	151
2	1	5	1	1	203	42	147
1		5	1	1	231	49	168
2		4	1	2	201	48	139

LP(a)	Family history of LDL?	ACVD Risk Score	Cardiac Calcium Score	Patient's Insurance	HX of Cardiac Event?	
1=normal	1= yes	low=1		1= Medicare	1= MI	
2=elevated	2= no	borderline=2		2= Medicaid	2= Stroke	
3=high		intermediate=3		3= BCBS	3= Stent Placement	
		high=4		4= Aetna	4= Pacemaker/Defib	
				5= other	5= CABG	
	1	1	2	15	3	1
	2	1	2	100	3	
	1	2	2		1	1,3
	2	2	1	75	1	5
	2	1	2	180	1	
	3	2	3	250	4	1
	1	2	1		1	3
	1	1	1	0	1	1
		2	2	50	5	1,5
	3	1	2	175	5	4
		1	3	204	1	
	2	2	1		1	1
		2	1	24	2	1
	3	2	3	275	1	1,3
	2	2	3	310	1	1,5
		2	1	15	5	1
		1	1		5	
		1	1		4	1
	1	1	3	75	1	2
	3	1	4	180	1	3
	2	2	4	360	1	3
	1	2	2		1	1
		2	2	25	1	1
		2	2	75	2	5
	2	1	3	100	1	4
	2	2	3	125	3	5
		2	1		1	3
		1	1	50	1	2
	1	1	2	75	3	1
	2	2	3	125	1	1,3
	3	1	4	290	1	1,3

1	1	1		1	1
	2	1	25	1	5
	1	1	10	1	
	2	1		1	1
3	1	3	160	4	5
	1	1	0	1	1
2	1	2	90	3	1
3	2	3	100	1	2
1	1	1		1	1
3	2	4	208	1	
	1	3	220	1	1
	2	1		1 1,3	
1	1	1	25	5	1
1	1	1	80	5	
2	1	3	100	1	5
1	2	1		1	5
	2	1		3	1
	1	3	70	1	1
	1	2	30	1	1
	2	1		2	

CRP	Other Medications	LDL-C 6 months
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Low=1

1=Beta Blocker

Moderate=2

2= Anticoagulant

3= Ca Channel

High=3

Blocker

4= Ace Inhibitor

5= Diuretic

1	1,9	101
		83
2	1,2,9	119
1	1,9,6,	89
2		101
	1,9	91
1		98
		112
		118

1	87
2	101
2	86
	89
	101
2	124
	97
2	89
2	114
1	120
	114
	89
	101
	96
	108
1	97
	85
2	101
2	103
1	111
	97
	108
	97
	111
2	98
	108
	112
2	107
	81
	92
3	86
	98
	87
	106
1	105
1	108
2	78
	111
	96
1	108
	121
2	89

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