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Review Article

Pharmacological Management of Dyslipidemia in Obese and Elderly Patients: Challenges, Current Therapies, and Emerging Treatments

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Abstract

Dyslipidemia, a state of abnormal blood lipid levels, contributes significantly to the development of atherosclerotic cardiovascular disease (CVD), especially in obese and elderly individuals. Lipid management is challenging in older adults because age is one of the key aspects leading to worsening of CVD, and other factors such as multiple comorbidities, polypharmacy, drug interactions, and patient functionality can further complicate the clinical picture. Likewise, management in obese patients is difficult because they often exhibit an adiposopathic lipid profile, with chronic inflammation and insulin resistance further exacerbating the abnormalities. Therefore, management in such high-risk patient populations requires a strategic plan, often combining non-pharmacological and pharmacological interventions. This review aims to summarize the recent evidence on the challenges and limitations associated with dyslipidemia management in obese and elderly patients, explaining the existing therapeutic options and focusing on the newer, emerging approaches. Current treatment guidelines recommend that physicians follow a therapeutic approach based on risk stratification and target lipid achievement. Traditional agents such as statins, ezetimibe, and fibrates remain the cornerstone, but their disadvantages, like limited efficacy and adherence issues, necessitate the development of innovative therapies. Despite evolving treatment, major literature gaps exist due to the lack of sufficient clinical evidence in obese and geriatric patients, who are underrepresented in clinical trials. Novel drugs result in significant reductions in different lipid components with improved dosing and patient compliance; however, more data needs to be generated to guide personalized treatments and incorporate them into routine regimens.

Keywords

Dyslipidemias, cardiovascular disease, polypharmacy, obesity, geriatric

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Introduction

Dyslipidemia is a major health issue affecting millions of people worldwide and increases the risk for a variety of cardiovascular complications, particularly atherosclerotic cardiovascular disease (ASCVD).[1] Cardiovascular disease (CVD) is considered to be the leading cause of death on a global scale[1,2] and, hence, more attention should be focused on the early prevention and prompt clinical management of dyslipidemia in all populations. Dyslipidemia refers to the abnormal or impaired levels of the circulating lipids in the bloodstream,

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including either high levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), or low levels of high-density lipoproteins (HDL) or both. High levels of LDL-C or TG can result in an increased risk of plaque formation and atherosclerosis, promoting inflammation of the arteries and reducing the blood flow to the heart. In fact, LDL-C was reported to be among the top three leading risk factors for CVD in 2019.[3] Dyslipidemia can be classified either as primary (genetic) or secondary, with the latter being more common. It can be modified by adequately addressing the underlying lifestyle factor or medical condition. In obese patients, dyslipidemia is more commonly secondary to metabolic disturbances such as insulin resistance, whereas in the elderly, it is frequently influenced by comorbid conditions and medication use.[1] However, primary dyslipidemia may also be present in both groups and should be considered during clinical evaluation. In clinical settings, differentiating between these forms is necessary to guide appropriate therapeutic strategies. The World Health Organization (WHO) has stated that approximately 39% of the adult population worldwide has elevated blood cholesterol levels,[4] and the prevalence of dyslipidemia continues to increase. Although dyslipidemia consists of multiple lipid parameter abnormalities, this review primarily focuses on LDL-C as it is considered the primary therapeutic target due to its well-established causal role in the development of ASCVD.[3]

Management of dyslipidemia is particularly important in obese and elderly populations because obesity and increasing age act as independent risk factors for the development of CVD, complicating the lipid profile in such patients. Obese and elderly individuals represent heterogeneous populations, with different clinical characteristics that may influence the type and severity of dyslipidemia as well as the therapeutic response.[1] Dyslipidemia tends to occur in around 60%–70% of obese patients, whereas 50%–60% of the overweight patients are usually dyslipidemic.[5] On the other hand, while the exact prevalence of dyslipidemia in elderly patients remains unclear, many studies, conducted to assess prevalence, have suggested a high percentage, roughly 60%–70%, of the elderly population has dyslipidemia.[6–8] A strong link exists between obesity and dyslipidemia. Obesity can be defined as a serious, chronic, yet treatable, multifactorial condition where the increased adiposity results in dysfunction of adipose tissue and abnormal fat masses, leading to negative health consequences.[9] Obese patients generally tend to exhibit a lipid pattern called adiposopathic or atherogenic dyslipidemia, comprising elevated blood TG levels, non-HDL cholesterol, Apolipoprotein B, reduced HDL and an increased proportion of small, dense LDL-C particles.[9]

The reduced LDL-C particle size and subsequent increase in small dense particle number pose a significant risk factor for ASCVD, because the smaller particles can easily cross the arterial wall and get trapped inside, activating an inflammatory response.[9] The adiposopathy in obese patients is also associated with insulin resistance, the most adverse consequence among other cardiometabolic risk factors.[9] Appropriate reduction of atherogenic lipoproteins and excess adiposity can be achieved through a proper implementation of non-pharmacological approaches, such as evidence-based dietary modifications and physical activity, as well as pharmacological measures, including hypolipidemic agents and anti-obesity medications.

Dyslipidemia in elderly patients remains a challenge since age is a key risk factor responsible for the development of ASCVD,[10] which can further be worsened by lipid abnormalities. Dyslipidemia also coexists with other comorbidities, thus contributing to an increased risk of cardiovascular morbidity and mortality. Aging causes a dysregulation in lipid metabolism, affecting both lipid digestion and absorption.[11] Lipid digestion may be reduced due to decreased gastric lipase activity, reduced pancreatic function, and decreased bile acid secretions, whereas in terms of lipid absorption, TG and cholesterol absorption decrease and increase with age, respectively.[11] Thus, aging seems to affect almost every regulatory component of lipid metabolism. The phenomenon of post-prandial lipemia (PPL) is also more exaggerated among older patients,[10,11] leading to an imbalance in circulating lipids. Evidence from several clinical trials suggests that statins are beneficial in both primary and secondary prevention of CVD in elderly patients.[10,12] However, research gaps still exist, and more data needs to be generated, especially for patients older than 80 years of age, and the ways to tackle the limitations of statin therapy in the elderly, such as frailty, adverse drug effects, and drug interactions.[12] The proportion of elderly individuals is rapidly increasing, with an expected rise to 1.5 billion by 2050.[10] Therefore, more personalized management strategies need to be implemented in this population.

This narrative review aimed to synthesize recent evidence on the specific challenges in the pharmacological management of dyslipidemia in obese and elderly patients, highlight current treatment options, identify gaps in the literature, and explore emerging approaches to optimize patient outcomes. This review contributes to a deeper understanding of the complexities in these high-risk patient populations. Although several reviews have explored the pharmacological management of dyslipidemia, most have focused on a single high-risk population—either the obese or the elderly. This review aims to bridge this gap by integrating the therapeutic challenges and pharmacological considerations in both populations. It provides insights into potential interventions that could deliver a more personalized therapy, thereby adequately addressing dyslipidemia and improving cardiovascular health.

Methods

A comprehensive literature search was conducted to select and retrieve studies related to the management of dyslipidemia in elderly and obese patients and their associated challenges.

Various electronic databases like PubMed, Google Scholar, Scopus, and Science Direct were utilized for the search using keywords like "dyslipidemia," "obesity," "aging," "geriatric," "statins," "PCSK9 inhibitors," "novel lipid-lowering treatment," "lifestyle modification for patients with dyslipidemia," and "challenges." The search was mostly restricted to English-language, full-text articles published within 2020–2026, but earlier studies and recent clinical guidelines were included where appropriate. Peer-reviewed original research articles, randomized controlled trials, observational and experimental studies, systematic reviews, meta-analyses, and guidelines were included. Case reports, conference abstracts, and studies with incomplete data or not focused on dyslipidemia or lipid management were ineligible. A total of 68 studies were retrieved and included after screening for relevance; data were extracted and synthesized narratively.

Results

Challenges and Obstacles Involved in Dyslipidemia Management

Lipid-lowering Therapies and Their Limitations in Obese and Elderly Patients

Statins are the first-line treatment of dyslipidemia.[13] Still, a proportion of patients tend to stop statin therapy either due to its adverse effects or because of the development of intolerance. Statin intolerance (SI) refers to the resolution of one or more adverse drug effects related to statin use after discontinuation or dosage reduction.[13] Although the development of SI remains unclear, several mechanisms have been proposed, including the following pathways: inhibition of cholesterol synthesis in skeletal muscles, disruption of the mevalonate pathway leading to impaired protein prenylation, mitochondrial dysfunction, depletion of coenzyme Q10, and oxidative stress.[14] These mechanisms lead to statin-induced muscle toxicity, thereby necessitating the appropriate management of SI, which may include switching to another statin, lowering the dose, alternating the dosing regimen, or adding a non-statin drug—SLAP strategy.[13] Other lipid-lowering therapies, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have their own benefits and risks in such patients when used alone or with statins. In obese patients, the published studies regarding these different hypolipidemic agents have reported mixed results. Some studies have demonstrated that statin therapy has resulted in a greater reduction in LDL-C in obese patients when compared to normal or overweight patients.[15–17] Despite receiving statin therapy, there was a more rapid progression of coronary atherosclerosis in obese patients as per a non-invasive imaging study,[17] indicating that the protective effect of statins may not occur in all individuals. Yet, the statin dose can be increased to reach the target LDL-C level if the patient can tolerate the drug dosing.[18] Based on the results of a study conducted to determine the effect of body mass index (BMI) on statin tolerance, only 6% of the obese patients reported adverse effects, and BMI was found to have an insignificant link.[19] However, the study was short-term and involved only a few patients with low BMI, so definitive conclusions about the impact of obesity cannot be drawn. PCSK9 inhibitors are monoclonal antibodies that are usually recommended when statin therapy becomes ineffective or when patients become statin-intolerant.[20] However, a retrospective study conducted to assess the impact of obesity on PCSK9 inhibitors found that the target LDL-C was more difficult to achieve in overweight or obese patients when compared to normal-weight patients.[21] Despite the fact that the drug use lowered LDL-C levels from baseline in obese patients, higher BMI had a negative impact on the achievement of the target LDL-C range in such patients.[21] Another cohort study conducted in Taiwan has also supported the finding that lower BMI is favorable toward the administration of PCSK9 inhibitors in target LDL-C achievement.[22] Further studies are necessary to clearly demonstrate the effect of BMI on the effectiveness of different lipid-lowering therapies and to guide strategic treatment plans in obese patients.

Statins and other lipid-lowering therapies should be monitored carefully in the elderly population due to multiple comorbidities, polypharmacy, increased vulnerability to adverse drug effects and a higher risk of drug interactions. Since statins are metabolized by the liver enzymes, particularly cytochrome P450, drugs that induce or inhibit the enzymatic activity may affect their bioavailability, leading to reduced efficacy or increased risk of adverse effects.[13,23,24] The most common adverse effect of statin therapy is mainly statin-associated muscle symptoms (SAMS) such as myalgia and myopathy.[13,23] Poor adherence and drug discontinuation due to statin-induced adverse effects and drug interactions have been linked to an increased risk of CVD.[13] As of now, older patients do not seem to have an increased risk of myopathy when compared to the general population.[25] When investigating the effects of statins on cognitive dysfunction in older patients, their use did not result in any dementia or mild cognitive impairment, but may exacerbate any existing cognitive disease.[26] Despite the fact that several studies have been conducted on patients aged greater than 60–65 years and statin therapy has been reported to be highly efficacious,[27,28] there seems to be limited evidence related to statin therapy for primary prevention in those aged greater than 75 years, as most randomized controlled trials underrepresent this specific population.[23,28,29] Nonetheless, it is important to understand that the prevalence of SI has been increasing, with age greater than 65 years and obesity accounting for a 31.2% and 30.6% increased risk, respectively.[30] Thus, SI is an increasingly recognized clinical problem that needs to be addressed through newer management strategies to possibly reduce the risk of ASCVD. The recent update of the Joint European Society of Cardiology (ESC)/European Atherosclerosis

Society (EAS) guidelines has suggested that the intensity of lipid-lowering therapy should be based on the person's estimated risk of having a cardiovascular event, and certain risk scores can be incorporated for risk estimation.[31] According to this new focused update, most of the patients above the age of 75 will probably fall under the category of high or very high risk due to the cumulative burden of aging, comorbidities, and atherosclerotic risk factors. The updated guidelines highlight the importance of individualized lipid-lowering therapy in older patients, with drug initiation or continuation based on careful assessment of the potential risk-benefit ratio.

Medication Adherence and Polypharmacy

Patients with dyslipidemia may often follow complex medication regimens, leading to medication adherence difficulties and exposing them to the various risks of polypharmacy. Growing evidence suggests that older patients with dyslipidemia receive several prescriptions for other comorbid conditions, frequently using more than 5–10 medications per day.[32] This leads to an increased risk for medication errors and potentially inappropriate medication (PIM) use.[32] Elderly patients tend to have comorbidities like diabetes, hypertension, and kidney disease, along with dyslipidemia, while obese patients have associated conditions like metabolic syndrome and non-alcoholic fatty liver disease, requiring long-term drug treatment. Long-term lipid-lowering therapy is thus considered an important determinant associated with non-adherence.[33] Increasing age is one of the most important risk factors leading to polypharmacy and medication adherence issues, and it has been reported that 60% of adults older than 65 years of age have at least three different concurrent medical conditions.[34,35] Especially in older adults with CVD, polypharmacy and its associated negative consequences are found to be higher, underscoring the need for proper medication reviews and appropriate prescribing. In a retrospective chart review conducted to assess the prevalence of polypharmacy in older adults with CVD, 385 patients out of a total of 404 received polypharmacy, and 278 received hyper-polypharmacy, with 313 patients experiencing at least one severe drug interaction due to multiple drug use.[35] Another study reported that approximately 80% of the older patients with dyslipidemia received polypharmacy, with 48.6% being administered at least one avoidable PIM.[32] A cluster randomized trial to assess the appropriateness of statin therapy in patients with multiple comorbidities found that there was both underuse and overuse of statins in such patients,[34] highlighting the need for clinicians to reassess statin therapy frequently at follow-up visits. Clinicians, especially in the family medicine setting, should evaluate the patient's prescriptions at each routine visit, identifying whether any medications have been prescribed inappropriately and prompting either a dose reduction or drug discontinuation. A higher number of prescribed drugs increases the chances for drug interactions, leading to adverse outcomes in elderly and obese patients. 98.1% of outpatients with dyslipidemia had at least one potential drug-drug interaction, underscoring the risk of drug interactions in dyslipidemia management.[36] On the other hand, direct evidence on medication adherence in obese patients with dyslipidemia remains limited; however, studies in obesity and other chronic diseases highlight that factors such as financial barriers, psychosocial behaviors, and limited understanding of obesity may impact long-term adherence.[37,38] Obese individuals may not feel motivated to lose weight and may consider themselves solely responsible for their weight management, which can lead to feelings of reduced medication worthiness.[38] Moreover, weight-related stigma and lack of recognition of obesity as a chronic, relapsing disease may prevent patients from seeking timely care,[37,38] thereby delaying initiation of lipid-lowering therapy.

Besides polypharmacy, several other factors contribute to a lack of medication adherence among elderly and obese patients. Statin adherence has been reported to be lowered due to patients' lack of knowledge about dyslipidemia and the role of statins in reducing cholesterol levels.[39] The patients who understood more about the mechanism, duration, and benefits of taking statins were more adherent to the treatment regimen compared to those who did not have a clear understanding.[39] Such modifiable influences can be avoided through proper patient counseling, because a better understanding leads to more informed decision-making. A telephone survey conducted in Greece revealed that almost 70% of the patients forget to take their medications as prescribed, indicating that forgetfulness was related to a decline in the health-related quality of life of patients with dyslipidemia.[40] Addressing forgetfulness can be challenging due to the complex regimens involved, but targeted interventions can help improve patient compliance. Furthermore, beliefs regarding the drug's side effects and disruption of daily activities have resulted in medication non-adherence and even discontinuation of drug treatment.[41] Discontinuing statin therapy was found to be linked with a higher risk of hospital admission and increased cardiovascular mortality,[42] and the patients who were highly adherent to the therapy had lowered LDL-C and total cholesterol levels.[43] Adherence in the elderly is further affected by visual or hearing impairment and over-reliance on caregivers, whereas in obese patients, the lack of immediate benefit from lipid-lowering therapies can cause them to be non-adherent. Healthy lifestyle modifications, such as regular exercise, weight management, and dietary patterns including low saturated fat and high fiber-rich foods, are imperative in reducing lipid-related ASCVD risk.[44] However, suboptimal adherence to these lifestyle factors has been identified in dyslipidemic patients due to multiple barriers such as lack of time and patient education, financial constraints, and low motivation.[45] Figure 1 outlines the key barriers involved in dyslipidemia management in obese and elderly individuals. Together, these challenges lead to poor lipid control and inadequate achievement of target cholesterol levels, making management more difficult in such high-risk patients.

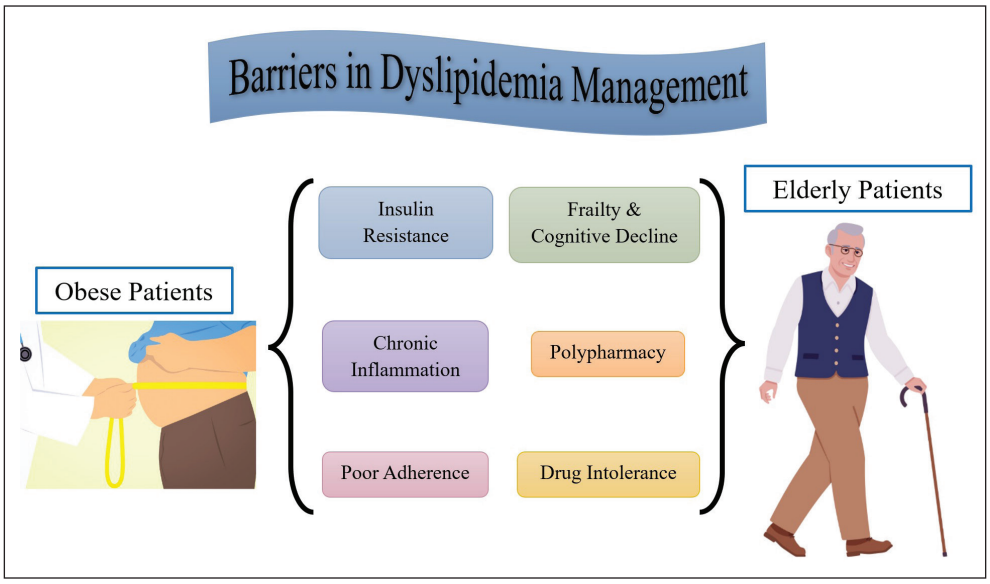

Figure 1. Different Barriers Associated with Obese and Elderly Patients in Dyslipidemia Management.

Current Standard of Care Treatment

Current clinical guidelines recommend following a structured approach to reduce cardiovascular risk in such patient populations. According to the ESC and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the management of dyslipidemia, the primary therapeutic goal is to lower the LDL-C to the target range, initiated through risk stratification.[44,46] Patients can be classified into four major categories based on the level of risk: low, moderate, high, and very high, and the LDL-C target has been defined as <116, <100, <70, and <55 mg/dL, respectively.[46] After stratifying the patient based on the estimated risk, the non-pharmacological and pharmacological therapy can be started to meet the individual clinical needs. For patients with a very low risk of developing ASCVD, lifestyle measures are considered to keep the patient's LDL-C levels under control, and a pharmacological agent is added when desired levels are not met.[44] In case of high-to-very high-risk patients, lifestyle changes with concomitant drug therapy should be immediately initiated.[44,46] The most commonly prescribed drug for the treatment of dyslipidemias is 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, such as atorvastatin and rosuvastatin. Statins inhibit the HMG-CoA reductase enzyme, blocking the rate-limiting step involved in the biosynthesis of cholesterol, making them the first choice in reducing the cholesterol levels and preventing CVD.[47,48] If patients are unable to tolerate statin therapy or require further disease control, then the second preferred agent is ezetimibe, which inhibits the intestinal absorption of cholesterol. Combination therapy has been found to be effective in enhancing cardiovascular outcomes,[47–49] but PCSK9 inhibitors can also be added to the regimen if goals are not achieved adequately.[44,46] Besides these classes of drugs, fibrates, bile acid sequestrants, and Omega-3 fatty acids are also involved in dyslipidemia management. Figure 2 represents the guideline-based treatment algorithm involved in the management of dyslipidemia.

Gaps in Literature and Limitations

Despite improvements, important evidence gaps still exist in high-risk populations. Current guidelines give general advice, but there is not enough strong data to guide the best drug treatments for age-related changes or the effects of obesity. Few studies compare how different groups respond to statins, ezetimibe, PCSK9 inhibitors, or combination treatments based on BMI or age. There is also limited real-world information about treatment complexity and its clinical impact, particularly in older patients. In addition, most clinical trials do not include enough obese or older adults, which makes it hard to know how to adjust doses, address adherence issues, manage lifestyle changes, or ensure long-term safety. These gaps make it difficult to create personalized treatment plans and show the need for future studies focused on specific populations to support evidence-based decisions. An increasing number of patients are experiencing SI, failing to achieve LDL-C targets, and discontinuing treatment prematurely. These challenges indicate that current lipid-lowering therapies are insufficiently effective for a substantial proportion of patients. Currently, two newer clinical trials, Statins in Reducing Events in the Elderly (STAREE) and Pragmatic Evaluation of Events and Benefits of Lipid-lowering in Older Adults (PREVENTABLE), are being conducted to assess the impact and role of statin therapy in primary prevention in older patients greater than 70–75 years of age.[50]

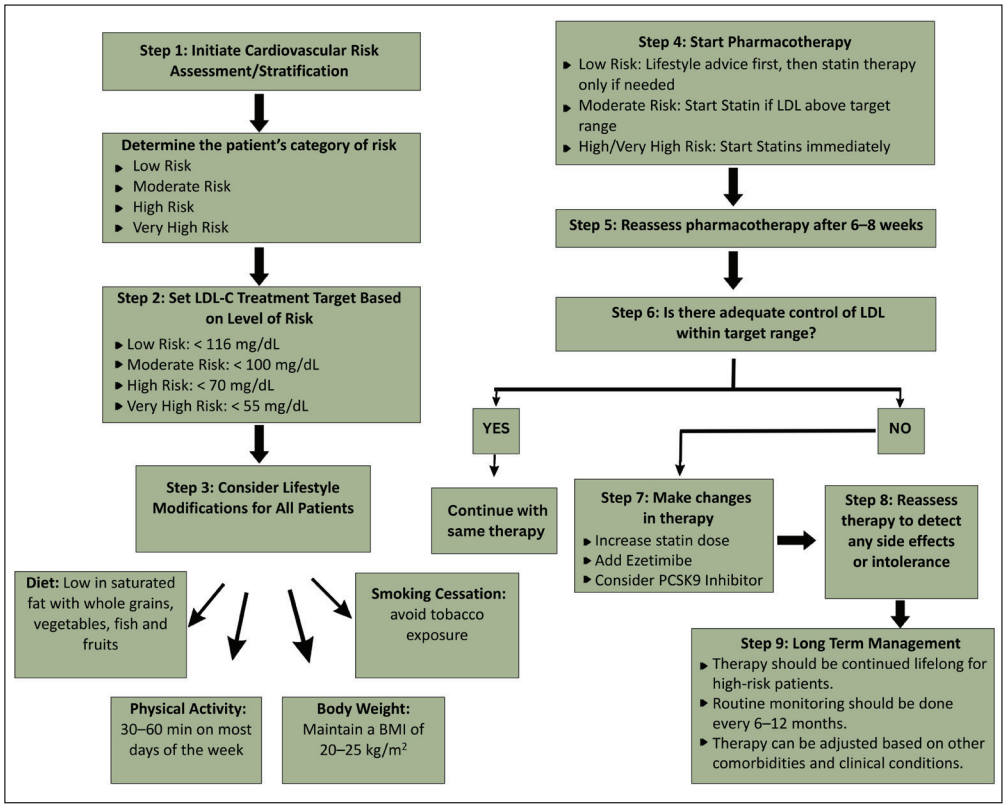

Figure 2. Guideline-based Treatment Algorithm for Dyslipidemia.

Source: Created by the authors based on ESC/EAS Guidelines for the management of dyslipidemias.[31,46]

Collectively, these gaps highlight the need to develop new lipid-lowering drugs with better tolerability, minimal drug interaction risk, mechanisms that do not rely on hepatic metabolism, and dosing schedules that improve adherence in such patients. Furthermore, personalized treatment strategies in both of these high-risk populations should consider the differences in their lipid profiles, risk factors, and treatment goals. Intensive, multi-targeted approaches, including dietary and lifestyle modifications, may be beneficial in obese individuals to address insulin resistance and metabolic syndrome, whereas in the elderly, the treatment plan often needs to be more conservative and safety-focused, balancing cardiovascular benefits with tolerability, comorbidities and quality of life. In fact, the coexistence of obesity and advanced age may further complicate the clinical picture and therapeutic decision-making, reinforcing the need for an integrated, patient-centric approach.

Novel and Emerging Approaches in Dyslipidemia Management

Recently, several newer drugs have been developed to improve cholesterol control and cardiovascular outcomes in dyslipidemia. Most of these novel agents are under investigation in randomized trials to determine their safety, efficacy, and real-world effectiveness. These emerging approaches have innovative mechanisms and also differ in terms of potency and dosing frequency. Incorporating these novel agents into the pharmacotherapy of dyslipidemia can not only transform the existing strategies but also address factors particularly relevant to obese and elderly patients, potentially creating a promising change. The different novel approaches involved in the management of dyslipidemia have been depicted in Figure 3.

PCSK9 Inhibitors

Two human Immunoglobulin G (IgG) monoclonal antibodies, namely Alirocumab and Evolocumab, have been designed to act as PCSK9 inhibitors by preventing PCSK9 protein from binding to the hepatic LDL-C receptors, thus blocking receptor degradation and leading to increased LDL-C clearance.[47,49] Several clinical trials and randomized studies have been performed to assess the safety and efficacy of these monoclonal antibodies in decreasing LDL-C levels in dyslipidemia patients. In the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) controlled trial, alirocumab was compared against placebo

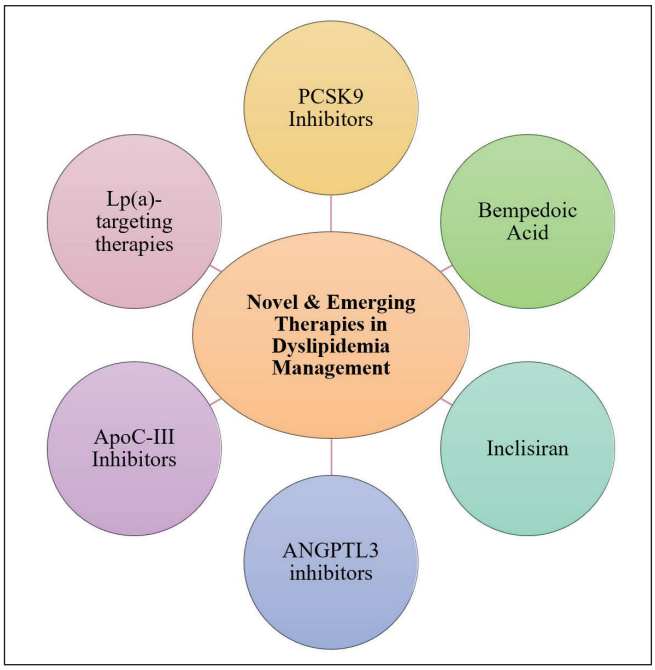

Figure 3. Novel and Emerging Therapies in Dyslipidemia Management.

treatment to determine its impact on dyslipidemia patients, especially those with known coronary disease risk factors and whose LDL-C levels were greater than 70 mg/dL despite maximum tolerated statin dose.[51] Alirocumab demonstrated a 61.9% reduction in LDL-C in the ODYSSEY LONG TERM trial, while the ODYSSEY OUTCOMES trial reported at least a 15% reduction in the risk of developing major adverse cardiovascular events (MACE), thereby decreasing cardiovascular morbidity but not mortality.[24,47,51] On the other hand, the Further Outcomes Research with PCSK9 In Subjects with Elevated Risk (FOURIER) trial was conducted to study the effectiveness of evolocumab in treating dyslipidemia, and the study reported a similar decrease of cardiovascular events by 15% in patients with existing CVD.[51,52] Likewise, an absolute risk reduction of 1.5%–1.6% was observed in both of these trials.[53] These antibodies have also demonstrated effects on reducing Apolipoprotein B, TG, and non-HDL cholesterol, thus potentially benefiting patients with lipid abnormalities. Interestingly, these antibodies have a low risk of immunological reactions, although rare hypersensitivity reactions and anti-drug antibodies may occur, and have other drawbacks like injection site reactions, myalgia, respiratory tract infections, and increased drug cost.[47,48,51,52] Current evidence regarding long-term safety concerns, such as potential neurocognitive effects and hyperglycemic disorders, however, remains inconclusive, necessitating clinical studies with longer follow-up periods.[54,55] Due to some positive evidence supporting its use, the updated guidelines now have established PCSK9 inhibitors as part of the treatment plan if there is a need to control lipid composition beyond administration of statin plus ezetimibe combination or even as a standalone drug in the treatment of statin-resistant patients.[24,51] PCSK9 inhibitors need to be administered only every 2 weeks or monthly once,[44] thus decreasing the frequency of dosing and acting as a strategy to deal with non-adherence due to administration reasons.[56] Although these clinical trials have demonstrated a favorable therapeutic profile for PCSK9 inhibitors, their widespread utilization in real-world clinical settings is further limited by their high cost and reduced accessibility. Studies conducted across several countries have mainly suggested that PCSK9 inhibitors are not cost-effective, and their high price can lead to difficult access in low or middle-income countries with constrained healthcare budgets.[55,57] Despite favorable, initial cost benefit ratios, the willingness-to-pay threshold per quality-adjusted life-year (QALY).[55]

Bempedoic Acid

Bempedoic acid, an adenosine triphosphate (ATP) citrate lyase inhibitor, is another agent for dyslipidemia management. Bempedoic acid is converted to its active form, bempedoyl coenzyme A, which inhibits ATP citrate lyase (ACL), an enzyme necessary for the conversion of citrate to acetyl CoA.[48,49,54] Thus, the drug blocks an important step of the cholesterol biosynthesis pathway, reducing LDL-C levels. Bempedoic acid is indicated in the treatment of adults with established ASCVD risk or those who are diagnosed with familial heterozygous hypercholesterolemia.[47–49] Bempedoic acid further leads to the activation of adenosine monophosphate-activated protein kinase (AMPK), inhibiting enzyme phosphorylation and decreasing liver fatty acids without a rise in circulating TG levels.[51,54] Furthermore, the drug acts on the inflammatory pathways to decrease the production of various pro-inflammatory mediators and regulates blood glucose levels.[54] This may be advantageous in both populations: preventing chronic inflammation and reducing the risk of atherosclerosis in obese patients and managing diabetes in elderly patients. In contrast to statin use, Bempedoic acid was found to reduce the incidence of musculoskeletal adverse effects because muscles lack the fatty acid transport protein necessary to convert the prodrug to its active form, and it mainly undergoes hepatic activation.[49,51] Several clinical trials under the name Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) have confirmed the safety and efficacy of the drug,[24] with around 15%–17% reduction in LDL-C after 12 weeks of therapy,[47,48,52] and reduced myopathy events, making it a useful option in selected patients. Despite being well tolerated among most patients, the drug has been associated with side effects like increased uric acid levels, gout, headache, and urinary tract infections.[48] Gout and cholelithiasis were the two major adverse effects found to occur in the trial participants, with a frequency of 3.1% and 2.2%, respectively.[24] The drug may also cause mild, reversible elevations in creatinine, blood urea nitrogen, liver

enzymes, and a decreased estimated glomerular filtration rate in some patients,[49,53] hence requiring caution in renal/hepatic impairment, which is more prevalent in elderly patients. Further studies are necessary to investigate its role and long-term safety in combination therapy.

Gene/RNA-based Therapies

Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) used for silencing gene expression and targeting PCSK9. Inclisiran consists of two different strands, an antisense and a sense strand, conjugated with N-acetyl galactosamine (GalNAc), which allows it to interact with the asialoglycoprotein receptor and further leads to the drug's endocytosis into the liver cells.[51,58] The antisense strand then dissociates from the sense strand to bind to messenger ribonucleic acid (mRNA), inhibiting translation in PCSK9[58] and blocking protein production. Reduced PCSK9 production leads to an upregulation of LDL-C receptors, enhancing LDL-C removal. The drug has been approved by the Food and Drug Administration (FDA) to treat ASCVD and primary or familial hypercholesterolemia, and by the European Medicines Agency (EMA) for mixed dyslipidemia.[47,48,52] A set of controlled trials was conducted to assess drug efficacy and safety, called ORION, which reported that Inclisiran resulted in almost a 50% drop in LDL-C levels in most patients and in patients with familial hypercholesterolemia, almost a 40% reduction.[24,51,58] Injection site reactions were the most commonly reported side effects,[52,53,58] with others like arthralgia and infections being comparable to placebo or existing drugs. No major drug interactions were observed, and the drug was considerably safer in patients with mild to moderate renal or hepatic impairment based on the generated data. An important feature that allows Inclisiran to improve adherence among patients is the fact that the subcutaneous dose only needs to be repeated at 3 months after the first dose, followed by 6 months thereafter.[32,56,58] Besides injection site reactions, the drug's high cost is yet another limitation to consider. In America, the cost per drug dose was reported to be $3,250 for patients lacking insurance coverage, with annual prices exceeding those of PCSK9 inhibitors.[58] Likewise, this translates to a few lakhs in Indian currency, limiting affordability for most patients. Currently, a trial assessing the effects of Inclisiran on clinical outcomes among people with CVD (ORION-4) is being conducted to determine the impact of Inclisiran on cardiovascular outcomes.[51,54,58] This trial is expected to be completed in 2026–2027[24,54] and will clarify its impact on cardiovascular morbidity and mortality.

Lerodalcibep is another third-generation small recombinant fusion protein that inhibits PCSK9, which has also been proven to effectively reduce LDL-C levels in patients with ASCVD after 24 and 52 weeks, with very modest reductions found in those with homozygous familial hypercholesterolemia.[48]

ANGPTL3 Inhibitors

Angiopoietin-like protein 3 (ANGPTL3) inhibitors function by blocking ANGPTL3, a hepatic protein that normally limits the activity of lipoprotein lipase (LPL) and endothelial lipase. Inhibition of ANGPTL3 increases the elimination of triglyceride-rich lipoproteins (TRL), thereby reducing circulating lipid levels.[48,51] Agents targeting ANGPTL3, such as the monoclonal antibody Evinacumab, have demonstrated reductions in LDL-C and TG concentrations, including in individuals unresponsive to conventional lipid-lowering therapies, such as those with homozygous familial hypercholesterolemia.[24,48,49,51] Recent developments in RNA-based therapies, including antisense oligonucleotides (ASOs) and siRNAs, have shown promising results in early-phase studies. These alterations show the potential for better-tolerated treatment choices for patients with comorbidities or SI.[59] Since ANGPTL3 inhibitors have been found to reduce both LDL-C/apoB particles and TRL, they may deal with a broader range of lipid disorders. Thus, these agents may be particularly useful in individuals with mixed dyslipidemia, refractory hypercholesterolemia, or persistent cardiovascular risk despite standard interventions.[60] However, further investigation is required to clarify their long-term safety, cost-effectiveness, and access.

ApoC-III Inhibitors

ApoC-III is a small apolipoprotein crucial to TRL metabolism. It causes atherogenic dyslipidemia by increasing the circulating levels of TG, blocking LPL activity, and lowering the liver's uptake of remnant lipoproteins.[48,61] Blocking ApoC-III may be a promising treatment, especially for people with severe hypertriglyceridemia or mixed dyslipidemia who do not respond to standard therapy.[62] Studies show that drugs like Volanesorsen and Plozasiran, which inhibit ApoC-III, can lower plasma TG by 50%–80% and reduce remnant lipoproteins such as chylomicrons, lowering non-HDL cholesterol and helping to reduce residual cardiovascular risk.[24,48,51,52] Since ApoC-III inhibitors do not rely on the LDL-C receptor pathway, they may still be effective for patients with LDL-C receptor problems or those who cannot take statins, making them useful in difficult cases.[63] Olezarsen is another agent in this class that was approved by the US Food and Drug Administration in December 2024 as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome. Olezarsen has been found to result in a 60%–70% reduction in ApoC-III levels, and when compared to Volanesorsen, it appears to have a more favorable platelet-safety profile.[24,48,52] However, long-term data on cardiovascular events, safety in older adults, and treatment adherence remain limited, warranting further research.

Lp(a)-targeting Agents

A newer target that has been found to be linked with the development of ASCVD is Lp(a), because it promotes inflammation through proatherogenic constituents, such as the presence of oxidized phospholipids.[64] In fact, Lp(a) acts as an independent risk factor for ASCVD. The novel pharmacological agents targeting Lp(a) include pelacarsen, olpasiran,

zerlasiran, and lepodisiran. These promising therapies are currently undergoing late-stage trials, and their confirmatory results are highly anticipated. Pelacarsen, a second-generation ASO, reduces the translation of Lp(a) mRNA, thus decreasing apolipoprotein(a) levels and further lowering the circulating amounts of Lp(a).[52,59,64] Lowering circulating Lp(a) may reduce and prevent lipid accumulation in arterial walls. Data from controlled trials have suggested that pelacarsen has resulted in a 70%–80% reduction in Lp(a) levels.[24,52,59] Similarly, next-generation siRNAs such as Olpasiran and SLN360/Zerlasiran have shown even more pronounced and sustained reductions—often exceeding 90%–99% after infrequent subcutaneous dosing.[52,59,64–66] Lepodisiran, another siRNA, has similar lipid-lowering characteristics, but its effects on adverse cardiovascular events can only be identified once the study is over in 2031.[59] These therapies offer a fundamentally different mechanism compared to LDL-C-based approaches, with potential to fill the "Lp(a)-gap" in cardiovascular risk management, especially in patients with high baseline Lp(a) or residual risk despite optimal LDL-C lowering.[65] These drugs tend to have very mild side effects, with injection site reactions being very common. There is no definitive cardiovascular outcome data yet, and future research should guide the implementation of these therapies in real-world clinical practice, particularly in obese and older adults. Table 1 summarizes the key comparative features of these novel therapies.

Discussion

This review delves into the challenges of managing dyslipidemia in obese and elderly patients, where metabolic abnormalities, comorbidities, and polypharmacy affect clinical outcomes. Unlike previous studies focusing on individual treatments, this review incorporates disease-specific challenges in high-risk populations and new pharmacological choices to provide a more clinically relevant insight into reducing cardiovascular risk, emphasizing MACE, cardiovascular mortality, myocardial infarction, and stroke.

Statins are considered first-line due to their established efficacy and safety, with strong data supporting reductions in MACE and cardiovascular mortality. However, SI and drug interactions may limit their use in susceptible populations. In comparison, PCSK9 inhibitors may achieve significant lipid-lowering effects and reduce non-fatal cardiovascular events, including myocardial infarction and stroke, but their clinical utilization is limited by high costs and low accessibility. Also, their effect on cardiovascular mortality is less evident. Thus, PCSK9 inhibitors are generally recommended when statins alone are insufficient and a more intense therapy is required in these high-risk populations. Bempedoic acid, on the other hand, may be considered as a practical alternative or adjunct, mainly in statin-intolerant patients. Inclisiran may help to improve patient adherence through its twice-yearly dosing schedule, whereas Evinacumab has been considered for rare, severe genetic dyslipidemias; ApoC-III inhibitors seem to address TG-driven disease, and the role of Lp(a) targeting agents in reducing residual cardiovascular risk is still being explored. These newer agents under investigation offer alternative choices with unique mechanisms and dosing improvements, though their long-term impact on cardiovascular outcomes remains under investigation.

In addition to these lipid-lowering therapies, recent clinical studies are also evaluating the role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in managing dyslipidemia and obesity, especially in patients with Type 2 diabetes mellitus and high cardiometabolic risk. GLP-1 RAs have demonstrated major effects on lipid metabolism, such as inhibiting fat synthesis, regulating lipolysis, fat differentiation, and stimulating adipose browning.[67,68] Several clinical trials have shown not only a greater mean weight loss with the use of these agents but also positive lipid outcomes, including significant decreases in total cholesterol, LDL-C, free fatty acids, TG, and elevations in HDL.[68] Furthermore, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial and the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) have reported a 13% and 26% reduced risk of MACE, respectively.[68] Despite these benefits, GLP-1 RAs seem to be controversial due to the higher incidence of gastrointestinal adverse effects, weight regain, reversal of lipid outcomes following cessation of treatment, and limited accessibility.[68] By promoting weight loss and reducing blood glucose levels, their dual action may help to address the underlying pathology inducing dyslipidemia and CVD. Although clinically relevant, an in-depth evaluation of these agents is beyond the scope of this lipid-focused review.

Based on the compiled evidence, no single therapy is considered universally optimal. The treatment should be designed based on individual risk and feasibility. Although newer agents show potential, their clinical use must be weighed against cost, accessibility, and long-term safety, especially in obese and elderly populations. Further research is necessary to optimize long-term outcomes and improve fair access.

Clinical Implications and Future Perspectives

To illustrate the practical application of the discussed evidence in dyslipidemia management, the following case scenarios highlight the crucial clinical considerations in obese and elderly patients.

Case Scenario 1: A middle-aged obese patient with elevated LDL-C levels and metabolic syndrome presents with poor

Table 1. A Comparative Evaluation of the Innovative Hypolipidemic Agents.

Novel Drug Class	Drug Examples	Mechanism of Action	Route(s) of Administration	Frequency	Cardiovascular Outcomes
PCSK9 inhibitors	Alirocumab Evolocumab	Binds to circulating PCSK9 protein, preventing LDL-C receptor degradation and increasing LDL-C clearance	Subcutaneous	75 mg every 2 weeks, or 300 mg every 4 weeks; the dosage can be adjusted to 150 mg every 2 weeks 140 mg every 2 weeks or 420 mg once a month	↓ MACE, ↓ MI, modest effect on cardiovascular mortality
ACL inhibitor	Bempedoic acid	Inhibits ACL in the cholesterol pathway, decreasing hepatic LDL-C production	Oral	180 mg orally once daily	↓ Incidence of non-fatal MI within MACE
PCSK9 siRNA	Inclisiran	Inhibits hepatic PCSK9 synthesis, causing increased LDL-C receptor upregulation	Subcutaneous	284 mg once at initiation, 3 months after initiation, then every 6 months	↓ MACE but limited cardiovascular outcome data
ANGPTL3 inhibitors	Evinacumab Zodasiran Solbinsiran	Inhibits ANGPTL3, increasing LPL activity and endothelial lipase	Intravenous Subcutaneous	15 mg/kg IV over 60 minutes every 4 weeks 50, 100, or 200 mg once every 12 weeks Dosing frequency still under investigation	Cardiovascular outcome data still under study
ApoC-III inhibitors	Volanesorsen Plozasiran Olezarsen	Inhibits ApoC, reducing its production, and increasing clearance of TRL	Subcutaneous	285 mg once weekly for 3 months, then down-titrated to once every 2 weeks 25 mg once every 3 months 80 mg once monthly	Cardiovascular outcome data not yet fully established
Lp(a) targeting Agents	Pelacarsen Olpasiran Zerlasiran Lepodisiran	Inhibits hepatic Apo(a) synthesis, decreasing Lp(a) particle production	Subcutaneous	Monthly Every 12 weeks 16–24 week intervals (in Phase II) Every 6 months	Cardiovascular outcomes still under investigation

Novel Drug Class	Drug Examples	Efficacy Data	Trial Names	Approval Status	Adverse Effects
PCSK9 inhibitors	Alirocumab Evolocumab	Reduction of LDL-C by 55%–65%, 15% reduced risk of MACE	ODYSSEY OUTCOMES, FOURIER	Approved	Injection site reactions, myalgia, respiratory tract infections
ACL inhibitor	Bempedoic acid	Reduction of LDL-C by 15%–22%	CLEAR outcomes	Approved	Hyperuricemia, gout, headache, urinary tract infections, mild GI disturbances
PCSK9 siRNA	Inclisiran	Reduction of LDL-C by 40%–50%, 26% reduced risk of MACE	ORION program	Approved (mainly for LDL-C lowering)	Injection site reactions, arthralgia, flu-like symptoms and infections
ANGPTL3 inhibitors	Evinacumab Zodasiran Solbinsiran	Reduction of LDL-C by 48%–49% from baseline	ELIPSE HoFH GATEWAY, ARCHES-2 PROLONG-ANG3	Approved Under clinical investigation (approval pending)	Injection site reactions, flu/cold, nasopharyngitis
ApoC-III inhibitors	Volanesorsen Plozasiran Olezarsen	Reduction of TG by 50%–80%, reduced ApoC-III levels by 60%–70%	APPROACH AROAPOC3-3001 BALANCE CORE and CORE-2	FDA approved for adults with familial chylomicronemia syndrome	Thrombocytopenia, bleeding, injection site reactions, musculoskeletal symptoms, respiratory infections
Lp(a) targeting agents	Pelacarsen Olpasiran Zerlasiran Lepodisiran	Reduced Lp(a) levels by 70%–90%	Lp(a) HORIZON OCEAN(a)-OUTCOMES OCEAN(a)-DOSE ALPACAR-360 ACCLAIM-Lp(a)	Not yet approved	Injection site reactions, fatigue

Note: PCSK9: Proprotein convertase subtilisin/kexin type 9, LDL-C: Low-density lipoprotein cholesterol, MACE: Major adverse cardiovascular events, MI: Myocardial infarction, ODYSSEY OUTCOMES: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab, FOURIER: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk, ACL: Adenosine triphosphate citrate lyase, CLEAR: Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen, GI: Gastrointestinal, siRNA: Small interfering ribonucleic acid, ANGPTL3: Angiopoietin-like protein 3, LPL: Lipoprotein lipase, IV: Intravenous, ELIPSE HoFH: Evinacumab LIPid StudiEs in patients with homozygous familial hypercholesterolemia, GATEWAY: A Phase 2 Open-Label Study to Evaluate the Efficacy, Safety, and Tolerability of ARO-ANG3 in patients with homozygous familial hypercholesterolemia (HoFH), ARCHES-2: A Randomized, Double-Blind, Placebo-Controlled Phase 2b Study, PROLONG-ANG3: A Study of Solbinsiran (LY3561774) in Participants with Mixed Dyslipidemia, ApoC: Apolipoprotein C, TRL: Triglyceride-rich lipoproteins, TG: triglyceride, APPROACH: A Study of Volanesorsen in patients with familial chylomicronemia syndrome, AROAPOC3-3001: A Phase 3 Study to Evaluate the Efficacy and Safety of ARO-APOC3 in adults with familial chylomicronemia syndrome, BALANCE: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Olezarsen in patients with familial chylomicronemia syndrome, CORE and CORE-2: Phase 3 Trial Investigating Olezarsen, Lp(a): lipoprotein(a), Apo(a): Apolipoprotein a, Lp(a) HORIZON: Assessing the Impact of Lipoprotein(a) Lowering with Pelacarsen on Major Cardiovascular Events in patients with CVD, OCEAN(a)-OUTCOMES and OCEAN(a)-DOSE: Olpasiran Trials of Cardiovascular Events and Lipoprotein(a) Reduction-Outcomes and Dose, ALPACAR-360: Assessment of Lipoprotein(a) Lowering in cardiovascular disease with Zerlasiran (SLN360), ACCLAIM-Lp(a): A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in adults with elevated lipoprotein(a) who have established atherosclerotic cardiovascular disease or are at risk.

response to initial statin therapy and low motivation for treatment and lifestyle adherence. In this case, management should primarily focus on switching to a non-statin agent based on guidelines, providing patient counseling to tackle the behavioral issues while reinforcing the need for lifestyle changes.

Case Scenario 2: An elderly patient with diabetes and mild osteoarthritis presents for a routine checkup, where laboratory results show high total cholesterol levels. The patient is worried about possible side effects from starting new medications. In this case, management should include risk assessment and evaluation, and a low-dose statin can be initiated to check tolerability while determining any other potential drug interactions.

In the future, dyslipidemia management should focus on transitioning from conventional drugs to other long-lasting, non-oral therapies to provide specialized care for both high-risk groups. The focus of future research lies in precision medicine and risk-based prescribing, targeting new pathways to address genetically oriented clinical factors in dyslipidemia. Integrating digital health tools like artificial intelligence-based models can further enhance treatment approaches by enabling earlier cardiovascular risk prediction and guiding individualized therapy.

Conclusion

While existing dyslipidemia therapies continue to play an important role, evolving clinical needs in the obese and elderly have led to the exploration of emerging, targeted approaches. This points to a shift toward a more precise, mechanism-based therapy. Advances in nanotechnology are also creating new avenues for delivering drugs, especially for patients with difficult-to-treat conditions. Continued research in such high-risk patients is important to bring these advances into routine clinical practice and help improve long-term cardiovascular outcomes.

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Authors' Contribution

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