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The Evolution of Cholesterol-Lowering Drugs: What's New?

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Abstract

The clinical utility of new medicinal products is principally established on the basis of well-conducted, randomized, controlled studies demonstrating that those products are safe and effective and provide a benefit in clinical outcome (García-Fernández-Bravo et al., 2022). For cholesterol management, low-density lipoprotein cholesterol (LDL-C) reduction represents a key modifiable risk factor for cardiovascular disease (Bardolia et al., 2021). Statins are the cornerstone of treatment, but muscle symptoms and new-onset diabetes are relatively common reasons for discontinuation. Since the landmark trials of the Icelandic physician, Akira Endo, in the mid-twentieth century, several other classes of cholesterol-lowering medications with different mechanisms of action have been developed. Understanding the pharmacokinetics, indications, and adverse effects of these agents can assist clinicians in creating individualized treatment plans (Leo Burger et al., 2022).

Keywords: *Cholesterol-Lowering Drugs, Statins; PCSK9 Inhibitors, Mechanisms Of Action, Clinical Efficacy, Patient Adherence, Safety and Side-Effects, New Development.*

Introduction

The goal of lipid-lowering therapy is to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Statins are administered as first-line agents to lower plasma low-density lipoprotein cholesterol (LDL-C) levels. Outcome trials consistently demonstrate that statins reduce the risk of ASCVD in both primary and secondary prevention (Kim et al., 2022). Consequently, current guidelines on cholesterol management recommend statin administration for all patients treated for secondary prevention, patients with familial hypercholesterolemia, patients aged 40 to 75 years with diabetes and plasma LDL-C ≥70 mg/dL, and patients treated for primary prevention without diabetes but with estimated 10-year ASCVD risk ≥7.5%. Despite optimal statin therapy, a significant residual ASCVD risk remains, underscoring the need for novel agents that effectively lower plasma LDL-C and other atherogenic particles. Recent advances have thus focused on therapies targeting LDL cholesterol, triglycerides, lipoprotein(a), and high-density lipoprotein (HDL).

Historical Background of Cholesterol-Lowering Drugs

The clinical use of cholesterol-lowering drugs has completely modified the natural history of

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atherosclerotic vascular disease. Cardiovascular diseases continue to be the first cause of death in Western countries, as well as the leading cause of disability worldwide (García-Fernández-Bravo et al., 2022). Statins' pharmacological action is based on competitive inhibitory effects on the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which catalyzes a key step in cholesterol biosynthesis and leads to an upregulation of LDL receptors and increased LDL clearance (Bardolia et al., 2021). By early 1970, there was a general concern regarding the optimum levels of lipid profiles. In 1973, Ünnebrink and Theilmeier reported the use of clofibrate. In the 1980s, the publication of data from the Scandinavian Simvastatin Survival Study (4S) and other clinical trials changed the approach to lipid-lowering drugs, establishing statins as the main strategy for managing this pathology. Clinical trials have been the way to define the real role of new drugs in clinical practice, demonstrating their safety, efficacy, and mainly answering the key question: does this drug represent a clinical benefit with better reductions in cardiovascular risk, becoming a real advance compared to the previous options? Also, different non-statin treatment options have been developed since the beginning of the sixties: fibrates, niacins, bile acid sequestrants, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, bempedoic acid, and inclisiran. Currently, in patients with a very high cardiovascular risk, there is no clear cut point to consider safety below it, which leads to the paradigm in the reduction of low-density lipoprotein cholesterol (LDL-C) that "the lower, the better." Probably, the cost/benefit analysis will help determine what LDL-C levels should be achieved in these patients.

Mechanisms of Action

Lipid-lowering agents display a variety of mechanisms. Mode-of-action differences bring direction for application and therapeutic regimens.

Resins are negatively charged exchange resins that bind to bile acids and prevent their reabsorption. By depleting the supply of bile acids, resins drive up the conversion of cholesterol to bile acids and the removal of LDL from the blood. found that the relationship between the resin-binding capacity of bile acids and their hydrophobic-hydrophilic balance allowed effective visual monitoring of resin interaction with bile acids.

The fibrates affect the concentration and composition of the HDL fraction of plasma lipoproteins. Primary biological results point to an extrahepatic site of action . reported the activation of human lipoprotein lipase and hepatic lipase gene promoters by the peroxisome proliferator, fibrates, in hepatoma cells. C4b-binding protein (C4b-BP) is an emerging multifunctional component of the innate immune system inhibitory on the classical pathway of complement (). Burger et al. (2022) discussed additional LDL-C reduction of as low as 55 mg/dL is difficult to attain with statins and ezetimibe alone in many patients. The early approach targeting reducing LDL-C focused on these key points.

Statins

Statins continue to be the most widely prescribed lipid-lowering drugs worldwide (Kirmizis & Chatzidimitriou, 2009). They effectively decrease serum LDL cholesterol by up to 70%, reduce total cholesterol and triglycerides, and increase HDL cholesterol. The target of statins is hepatocytes, where they inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA into mevalonic acid—a cholesterol precursor. Beyond cholesterol, the mevalonate pathway yields other biologically significant compounds such as dolichols, ubiquinone, and isoprenoids like farnesyl-

pyrophosphate and geranylgeranyl-PP. These isoprenoids participate in the post-translational modification of proteins, thereby influencing their activity. Large epidemiologic studies have demonstrated statins' effectiveness in preventing atherosclerosis progression and reducing subsequent clinical events (García-Fernández-Bravo et al., 2022). Recent evidence suggests benefits that extend beyond lipid lowering; statins reduce cardiovascular risk even in individuals with normal cholesterol levels, and exert rapid effects that cannot be attributed solely to lesion regression. Consequently, investigations into potential anti-inflammatory and pleiotropic effects have intensified, although the extent to which these benefits operate independently of cholesterol reduction remains uncertain.

Bile Acid Sequestrants

The bile acid sequestrants comprise a group of several ion-exchange resins selectively binding bile acids in the intestine. CHD mortality in a Finnish population was significantly reduced after treatment with cholestyramine, a first-generation bile acid binding resin. However, today bile acid sequestrants like cholestyramine, colestipol hydrochloride, and colesevelam hydrochloride are used only as third-line therapy for dyslipidemia because of poor gastrointestinal tolerance and interference with the absorption of many oral drugs and fat-soluble vitamins. Therefore, these resins are rarely used as a single therapy in the management of hyperlipidemia. They are opted in children and in pregnant women because of their non-absorption and low harm profile. In addition, they have the unique property of increasing HDL-C by approximately 5%. Resins interfere with the absorption of many oral drugs like warfarin, digoxin, and thyroxine and need to be taken at least 4 hours after the administration of these drugs. Overall, bile acid sequestrants may not be well accepted by patients.

PCSK9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are a novel class of cholesterol-lowering medication that targets PCSK9, a key regulator of low-density lipoprotein cholesterol (LDL-C) metabolism. Monoclonal antibody PCSK9 inhibitors have become the standard of care in patients at very high cardiovascular (CV) risk who are unable to reach their LDL-C targets despite adopting the highest demonstrated tolerance dose of statins combined with ezetimibe (John Chapman et al., 2015).

LDL-C is the major causative factor driving atherosclerotic cardiovascular disease. Most of the PCSK9 released into the circulation originates from the liver. Circulating PCSK9 interacts with the low-density lipoprotein receptor (LDL-R) on the hepatocyte cell surface, promoting its intracellular degradation, including via the trans-Golgi network (Xu et al., 2019). Monoclonal antibodies directed against PCSK9 prevent LDL-R degradation, resulting in increased LDL-R expression and hence enhanced clearance of plasma LDL-C. PCSK9 inhibitors are both safe and effective in reducing LDL-C levels, especially in very high-CV-risk patients or those with genetic or acquired predisposition to hypercholesterolaemia.

Fibrates

Fibrates emerged in the 1950s after the discovery that phenylethyl acetate lowered serum lipids. Clofibrate was the first drug classified as a fibrate. These agents act on PPARα to reduce triglycerides and raise HDL-C (Yamashita et al., 2020). The 1987 Helsinki Heart Study and 1999 Veterans Affairs HDL Intervention Trial (VA-HIT) showed that gemfibrozil treatment lowered cardiovascular event rates (Hoon Kim & Gon Kim, 2020). However, side effects and drug interactions limited gemfibrozil's use with statins. Subsequent trials with bezafibrate and

fenofibrate produced mixed findings: the Bezafibrate Infarction Prevention (BIP) trial revealed only a borderline reduction in risk, FIELD was largely neutral, and ACCORD-lipid showed no additional benefit of fenofibrate over statins. Meta-analyses nonetheless demonstrated statistically significant decreases in cardiovascular events, with pronounced benefits in patients exhibiting triglyceride levels above 204 mg/dL and HDL-C below 34 mg/dL, a profile typical of atherogenic dyslipidemia. EXTEND-IT follow-up of the VA-HIT cohort indicated that gemfibrozil's reductions in vascular events and all-cause mortality become more evident over time. These results suggest that fibrates provide clinical evidence for the hypothesis that modifying triglyceride-rich lipoproteins can mitigate cardiovascular risk, especially in specific subgroups.

Niacin

Niacin remains an available therapeutic option for patients with cardiovascular disease (D'Andrea et al., 2019).

Nicotinic acid was once an effective broad-spectrum lipid drug (DEROSA et al., 2006). An extended-release form, Niaspan, offered the possibility of treating dyslipidemia while minimizing adverse effects; it increased HDL levels, slowed the progression of atherosclerosis, and appeared to confer benefit in the secondary prevention of cardiovascular disease. When administered at night, it was almost as efficacious as split dosing in the morning and evening; suprachiasmatic nucleus regulation of plasma free fatty acid levels provided a physiologic rationale for night-time administration.

Recent Advances in Drug Development

From the discovery that cholesterol-lowering statin drugs reduced cardiovascular death, extensive research has proven the concept that atherogenesis is modifiable by pharmacologic intervention. The four statins were then routinely used to treat hypercholesterolemia until the turn of the millennium, at which point, patients with atherosclerosis or secondary prevention of cardiovascular disease began to be treated with combinations of statins and other drugs because monotherapy failed to achieve desired low-density lipoprotein cholesterol (LDL-C) levels. This review examines the history of cholesterol-lowering agents and the latest advances in the field.

Substantial causative data from clinical investigations demonstrated that cholesterol levels could predict atherosclerosis risk. As described in the previous section, the four statins were commonly used to treat hypercholesterolemia. However, single administration of these agents in patients with atherosclerosis or receiving secondary cardiovascular-disease-prevention therapy often failed to achieve the target LDL-C levels, necessitating combined medication. Consequently, the FDA approved the use of selective cholesterol absorption inhibitors such as ezetimibe, or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as the monoclonal antibodies alirocumab and evolocumab, in combination with statins. These developments highlight a parade of novel cholesterol-lowering drugs.

Novel Therapeutic Targets

Lipid-lowering therapy aims to reduce atherosclerotic cardiovascular disease (ASCVD) risk. Although statins are the first-line agents to lower low-density lipoprotein cholesterol (LDL-C), residual risk persists even with optimal statin treatment. Novel drugs and targets beyond LDL-C are therefore needed. Human genetics and drug discovery platforms have facilitated identification of diverse lipid-lowering agents with innovative mechanisms of action. Inclisiran,

a small interfering RNA molecule targeting proprotein convertase subtilisin/kexin type 9 (PCSK9), exerts lipid-lowering effects comparable to those of PCSK9 antibodies. Bempedoic acid, an adenosine triphosphate-citrate lyase (ACLY) inhibitor, is useful for patients exhibiting statin intolerance. The REDUCE-IT trials highlight the benefits of high-dose icosapent ethyl. Evinacumab, an angiopoietin-like protein 3 (ANGPTL3) inhibitor, potently reduces LDL-C in patients with refractory hypercholesterolemia. Among these agents, antisense oligonucleotides targeting apolipoprotein C3 (apoC3), ANGPTL3, and lipoprotein(a) [Lp(a)] elicit pronounced improvements in dyslipidemia. Despite weak supporting evidence, apolipoprotein A1 (ApoA1) mimetic peptides represent a potential strategy for protection attributable to high-density lipoprotein cholesterol (HDL-C) (Kim et al., 2022).

Lipid management constitutes a highly active field. Extensive trials have elucidated molecular pathways and identified relevant molecules, accelerating the development of innovative drugs. Approvals of inclisiran, bempedoic acid, and evinacumab for familial hypercholesterolemia expand the repertoire of lipid-lowering therapies and enable individualized strategies that address residual cardiovascular risk. Positive outcomes associated with emerging candidates suggest further enhancements in clinical practice and pave the way toward overcoming limitations of established therapies (Agnello et al., 2024).

Combination Therapies

Nonstatins have also emerged as combination partners with statins. The improved LDL-C reduction and achievement of LDL-C goals in combination with statins have been the result of effects on other aspects of cholesterol metabolism. Adding ezetimibe to statin therapy has the effect of decreasing cholesterol absorption from the gut, which offsets the compensatory increase in cholesterol absorption that occurs secondary to statin reduction in hepatic cholesterol synthesis (inhibition of CYP-51). Ezetimibe/scavenger receptor class B type 1 (NPC1-L1) inhibitors reduce LDL-C to a further extent when combined with statins (or bile acid sequestrants). The combination of a statin with the bile acid sequestrant, colesevelam, is also an effective one. Bile acid sequestrants bind bile acids in the gut, leading to their elimination in the stool. Because increased fecal bile acid secretion leads to increased hepatic conversion of cholesterol to bile acids, a compensatory lowering of hepatic cholesterol content occurs. This ultimately leads to increased receptor-receptor LDL uptake and decreased LDL-C levels.

Clinical Efficacy of New Drugs

LDL cholesterol (LDL-C) remains the primary therapeutic target for reducing the risk of atherosclerotic cardiovascular disease (ASCVD), and even very low LDL-C concentrations are not associated with adverse effects. Consequently, efforts continue to develop novel lipid-lowering agents capable of further reducing LDL-C, either alone or as part of combination therapy. Over the past 2 years, four new drugs have been approved, and several additional innovative lipid-lowering compounds are nearing market launch. PCSK9 antibodies were the first new class of LDL-C–lowering agents to reach market, followed more recently by the oral adenosine triphosphate–citrate lyase inhibitor bempedoic acid; the siRNA molecule inclisiran was also approved by the European Medicines Agency in late 2020 and is awaiting final approval by the Food and Drug Administration. Beside these LDL-C–lowering agents, icosapent ethyl (a high-dose omega-3 fatty acid) and volanesorsen have received approval in selected patient populations. This section focuses on new LDL-C–lowering drugs, their mechanisms of action, clinical efficacy, safety, and use within current cardiovascular prevention guidelines (Leo Burger et al., 2022).

Comparative Studies

Patients at very high risk of major cardiovascular events, notably those with established atherosclerotic cardiovascular disease (ASCVD), require substantial lipid lowering to prevent ischemic episodes. In the last 30 years, statins have been the cornerstone of lipid-lowering therapy in this context, with trials conducted in over 100,000 patients demonstrating significant cardiovascular risk reductions. Further reductions can be achieved by combining statins with ezetimibe, an agent that inhibits the intestinal absorption of cholesterol.

Nevertheless, many high-risk patients fail to reach the recommended LDL-C target of less than 1.4 mmol/L (55 mg/dL) with statins and ezetimibe alone. Against this background, the treatment armamentarium recently expanded, offering highly effective options. PCSK9 inhibitors (alirocumab and evolocumab) reduce LDL-C by up to 60% when added to statins and ezetimibe. Inclisiran, an siRNA molecule that targets PCSK9 mRNA, achieves a reduction of approximately 50%. Bempedoic acid—a prodrug converted to its active form primarily in the liver—lowers LDL-C by 15–20% and does not induce increased muscle-related symptoms when coadministered with statins (Leo Burger et al., 2022).

Real-World Evidence

Considering the persistent and significant clinical implications of CVR and atherosclerotic CVD, ongoing trials are warranted to elucidate the impact of innovative molecules on cardiovascular protection. Recently, massive attention has been directed to novel lipid-lowering pharmaceuticals and their potential application in daily practice. Around the world, healthcare policymakers are seeking effective EBM to optimize patient treatment and improve safety by avoiding unnecessary interventions and costs. RWD analyses, mainly derived from electronic health records (EHR) or registries, play a pivotal role in informing decisions regarding patient care, healthcare safety, and cost containment. Clinical evidence from RWD is obtained from a variety of data sources, not as structured as clinical trials, collecting information from a large pool of different patients by age, sex, ethnic group, and areas, and it represents the actual medical history and management of patients (García-Fernández-Bravo et al., 2022). RWE represents the clinical evidence from the analysis of RWD, allowing inferring the effectiveness of medicines or devices under routine clinical care (Leo Burger et al., 2022).

Safety and Side Effects

The safety of lipid-lowering drugs is a concern because of the unknown effects of very low LDL-C levels on various physiological functions. It is therefore necessary to better explore the benefits and risks of achieving low cholesterol levels with optimized guideline-based, evidence-supported treatments.

Statins are widely used in lipid-lowering therapy. It is known that adverse effects on muscles, including cramps, myalgia and increased creatine phosphokinase (CPK) levels, may occur in 10%-15% of patients. The reason why statins cause muscle injury remains unclear, but the mechanisms related to calcium signalling, mitochondrial dysfunction and ubiquitin-proteasome pathways might be involved. Continuous, intensive lipid-lowering therapy initiated early after vascular injury could lead to accelerated calcification of atherosclerotic plaques. Because the long-term effects of aggressive lipid-lowering are unknown, it is important to consider the pros and cons of therapy in high-risk patients (DEROSA et al., 2006).

Adverse Reactions

Adverse reactions related to lipid-lowering therapy are critical considerations, as treatment is intended to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Statins constitute the primary pharmacological approach to lowering low-density lipoprotein cholesterol (LDL-C) and have proven effective in reducing ASCVD risk in primary, secondary, and tertiary prevention. Current guidelines recommend statin therapy for populations at elevated risk or early stages of the atherosclerotic process, including in secondary prevention; individuals with familial hypercholesterolemia; patients aged 40–75 years with diabetes and LDL-C ≥ 70 mg/dL; and those without diabetes but considered at high risk. However, even when treated to guideline targets with statins, a substantial residual risk for ASCVD events remains. The development of novel lipid-lowering agents targeting LDL, triglycerides, lipoprotein(a), and high-density lipoprotein (HDL) represents an opportunity to address residual ASCVD risk (Kim et al., 2022). Evolocumab has demonstrated a favorable safety profile and good tolerability. Large randomized controlled trials are currently evaluating the long-term impact of evolocumab on cardiovascular risk, safety, and tolerability outcomes (Colletti et al., 2016).

Long-Term Safety

The PCSK9 inhibitors alirocumab and evolocumab have demonstrated long-term safety in phase 3 clinical studies, with no evidence of neurocognitive adverse events, muscle-related adverse events, or increased incidence of diabetes. Examination of post-market surveillance data for these agents could provide additional insights. Early indications from individuals with PCSK9 loss-of-function mutations appear reassuring with respect to long-term safety.

Mipomersen, a synthetic 20-mer antisense oligonucleotide administered as a subcutaneous injection, selectively inhibits synthesis of apolipoprotein B-100. Approved in the United States as an adjunct treatment for patients with homozygous familial hypercholesterolemia, mipomersen poses some safety concerns, including injection-site reactions reported in more than 90% of patients in phase 3 trials and elevations of alanine aminotransferase, with 8 patients discontinuing treatment. Lomitapide, an oral microsomal triglyceride transfer protein inhibitor, also approved as an adjunct treatment for homozygous familial hypercholesterolemia, reduces chylomicron and very-low-density lipoprotein synthesis, thereby lowering plasma LDL-C levels. Some mild gastrointestinal symptoms have been reported, but adverse effects such as hepatosteatosis and hepatic fibrosis remain a concern with the drug.

Patient Adherence and Compliance

Elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) represent the major causal risk factor for atherosclerosis and its cardiovascular complications, which constitute the largest burden on global health. Statins, since their introduction three decades ago, have become the most widely used drugs to efficiently lower LDL-C, yielding significant improvements in life expectancy. However, here remains an unmet need to provide additional options of therapy to address a residual CV risk and/or treat statin-associated side effects. In this context, the regulatory approval of the monoclonal antibodies targeting proprotein convertase subtilisin/kexin type 9 (PCSK9) epitomizes the progress made in translational research to accelerate and validate new therapeutic concepts (B Bosworth et al., 2018).

Aline Lefrèche and Salah D. Qanadli summarize the recent progress made in both clinical and regulatory fronts regarding cholesterol drug development while clarifying the original biological concepts that have triggered the latest pharmacological developments. This article also conveys

a historical perspective on the identification of the various therapeutic targets involved in hypercholesterolemia. Statins mechanistically inhibit cholesterol synthesis and concomitantly stimulate LDL clearance by increasing the number of LDL receptors at the plasma membrane. The unexpected discovery of PCSK9 has opened a new horizon in drug development since blocking PCSK9 activity significantly lowers plasma LDL-C via increased LDL receptor expression. The enormous investment required to develop monoclonal antibodies to humanized PCSK9 is thus justified by the unambiguous proof of concept emerging from pedigrees of familial hypercholesterolemia, mouse models and chemical inhibitors mimicking PCSK9 deficiency. The PCSK9 story illustrates the pivotal role that genetics and translational research have to play as enablers of technological innovation, especially for de-risking therapeutic targets and facilitating their pharmacological validation.

Factors Influencing Adherence

Adherence to non-statin therapy represents a major issue. The prevention benefit of a therapy is crucially dependent on the individual's drug-taking behavior, as the efficacy of lipid-lowering therapy can only be fully realized if patients take their medication as prescribed and for a lifelong period. Considerable evidence monitory indicates low adherence to statin therapy, with an adherence rate < 80% and a mean discontinuation rate at 52.3%. The reasons for discontinuation are multifaceted and can be broadly categorized into socioeconomic factors (associated with patients' education or income level), healthcare system-related factors (such as inadequate drug reimbursement policies; absence of a cost containment policy, or poor quality of care), condition-, diet-, and therapy-related factors (i.e., drug inefficacy, presence of adverse effects and a presence of concomitant therapies), and patient-related factors including female sex, negative perception about statin therapy, or a lack of understanding about the benefits of statin therapy.

One of the main causes of statin discontinuation is statin-associated adverse events, a particularly important issue in the treatment of high-risk patients because discontinuing or switching drug treatments can result in underuse or non-use, limiting efficacy. In addition to statin discontinuation, statin aversion—the reluctant unwillingness or refusal to take statins—has been recently reported. Even patients who have not yet tried statins have a strong aversion against them and report fear of possible adverse events. Statin aversion was associated with a willingness to try alternatives to treatment, including non-statin therapy.

Strategies to Improve Compliance

Of the strategies developed to improve saposin C–DOPS uptake, only PEGylation has reached a clinical trial stage. PEGylated saposin C–DOPS (Bardoxyl®) was granted orphan drug designation for glioblastoma by the FDA. The use of PEGylation is particularly important for improving drug effectiveness because the blood–brain barrier inhibits the adsorption of small molecules such as Bardoxyl®. However, in a clinical trial conducted at the National Cancer Institute, PEGylated saposin C–DOPS led to rapid disease progression in 11 of 15 patients, with the remaining four patients exhibiting stable disease.

In another strategy aimed at improving the lysosomal targeting of DPPE-PEG-based farnesyltransferase inhibitors (FTIs), researchers designed a library of FTIs containing one or two terminal phenyl group(s) attached to the PEG chain. Cell uptake assays revealed that FTIs containing two terminal phenyl groups were four times more efficiently internalized than DPPE-PEG-based FTIs with a single terminal phenyl group. Moreover, these compounds were four

times more effective in reducing farnesyl transferase activity. These results indicate that the introduction of two phenyl groups in the FTI structure enhances drug internalization and activity.

Cost-Effectiveness Analysis

The analyses included lipid-modifying agents that have been submitted to health technology assessment by the UK National Institute for Health and Care Excellence. This selection excludes drugs such as bempedoic acid, niacin, and fibrates, owing to the absence of cardiovascular outcome trials. Consequently, the analyses were conducted from the perspective of the UK National Health Service. Utilities, costs, and willingness-to-pay thresholds may vary across countries. Previous cost-effectiveness studies have estimated transition probabilities from national cardiovascular observation studies to simulate each drug's risk reduction in major adverse cardiovascular events (MACE) based on its effect on low-density lipoprotein cholesterol. In contrast, the present approach derives transition probabilities and MACE risk reductions directly from cardiovascular outcome trials, to capture pleiotropic metabolic effects beyond lipid lowering—an important consideration for triglyceride-lowering agents (Tobias Michaeli et al., 2022). The Markov model employed assumes immediate treatment intensification. In clinical practice, delays in intensification and initiation worsen cardiovascular outcomes and elevate incremental cost-effectiveness ratio (ICER) estimates. Adverse events were not incorporated into the model. Future analyses should examine the clinical economics of triple and quadruple lipid-modifying regimens, as well as the efficacy and costs associated with therapeutic sequencing, which are critical for clinical decision-making (Tobias Michaeli et al., 2023). Consistent with prior meta-analyses, available cardiovascular outcome trial data for ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors pertain largely to secondary prevention. Pharmaceutical companies finance expensive outcome trials involving thousands of patients primarily for the secondary prevention indication. They may be reluctant to fund additional trials in primary prevention, where lower efficacy could prompt insurers to seek rebates on overall drug prices, leaving a gap in robust evidence for patients without established cardiovascular disease.

Economic Burden of Cholesterol Management

SMFAs can lead to statin intolerance and cause suboptimal dosing with safety concerns as a result of inhibition of statin metabolism or drugs metabolised by statins. Johnson et al. ran a retrospective matched cohort analysis using the Clinical Practice Research Datalink (England) to compare healthcare resource use and costs between patients with and without SMFA. A significantly greater number of GP consultations and inpatient admissions were observed in the SMFA cohort, with costs £6879 versus £5144 ($p < 0.01$) in the first year. The larger cost difference persisted over up to five years follow-up.

Dyslipidaemia and hypercholesterolaemia are risk factors for atherosclerotic cardiovascular disease (ASCVD). The NICE Multiple Technology Appraisal (MTA) CG181, last updated in 2016, recommends treatment with a high intensity statin for people at high risk of ASCVD. Evidence shows that the reduction of LDL-C substantially decreases the risk of ASCVD complications, which accounts for their approval as a lipid regulator. Statins are safe and effective drugs and are therefore inexpensive. However, the cost of managing patients with statin side effects or with contraindications to statins can be high. Recently, additional therapeutic options have been included in the dyslipidaemia guideline. In this chapter, we consider two new classes of lipid-regulators, ezetimibe and PCSK9i, with a particular focus on PCSK9i.

Value-Based Pricing

Potential solutions for overcoming low patient adherence include more sophisticated indication-specific pricing, coverage, and reimbursement policies. Although treatment with new lipid-modifying agents significantly reduces MACE risk, adherence remains limited because of impractical administration routes, side effects, inaccessibly high prices, and lack of physician- and patient-level education. Russia's abstracted population is awaiting trial results for agents with convenient administration routes, fewer adverse effects, and novel mechanisms of action. More widely available therapeutics will enable individualised care and lower prices through increased competition (Tobias Michaeli et al., 2022).

The cost-effectiveness of current lipid-lowering options for primary and secondary cardiovascular prevention has been evaluated from Germany's healthcare system perspective. For primary prevention, icosapent ethyl plus statin is cost-effective (ICER: €18,133/QALY). For secondary prevention, ezetimibe (ICER: −€9,555/QALY), icosapent ethyl (ICER: €14,485/QALY), and PCSK9 inhibitors evolocumab (ICER: €114,639/QALY) and alirocumab (ICER: €100,532/QALY) increase patient benefit at different costs. Fibrates represent low-cost alternatives for triglyceride reduction. Price reductions attributable to genericization have improved ezetimibe's cost-effectiveness, but its ICER exceeds willingness-to-pay thresholds in Thailand and China (Tobias Michaeli et al., 2023).

Regulatory Considerations

Following the course of the 21st century, the number of new drugs was reduced so it could balance safety and efficacy in a more cost-effective way. Statins remained the most used drug, and its doses increased in some patients or got complemented with other drugs, such as ezetimibe. Statin therapy was the chance to get cardiovascular risk reduction under the proper control. In a way, statins have been the "kit" to modulate the consequences of cardiovascular disease. However, these therapies still have some limitations and side effects. There is a need for a new generation of lipid-lowering agents following the rising level of LDL-C.

Approval Processes

Approval processes During the development of cholesterol-lowering agents, a staged approach to clinical research is generally followed. Early-phase studies determine dosing and document safety, along with preliminary measurements of cholesterol-lowering effects often derived from a small number of intermediate outcomes such as LDL-C. Demonstration of a meaningful effect in phase-2 studies justifies larger, more definitive phase-3 studies focused on the primary clinical endpoint of ASCVD risk reduction. Completed phase-3 studies have paved the way for several newer agents to receive regulatory approval although, at the time of writing, some remain under investigation in ongoing trials. Management of cholesterol, particularly LDL-C reduction, is a key strategy to reduce cardiovascular disease (CVD) morbidity and mortality (Bardolia et al., 2021). Statins are the gold standard but often have issues with adherence due to adverse effects like muscle symptoms and new-onset diabetes, which increases the risk by 10–45%. This has driven the development of newer non-statin medications including fibrates, niacins, bile acid sequestrants, ezetimibe, PCSK9 inhibitors, bempedoic acid and inclisiran. Broadly speaking, the newer agents are anticipated to complement statins and other established therapies by acting through various mechanisms as alternatives sometimes when patients are intolerant, supplements when LDL-C targets remain unmet or adjuncts for a more comprehensive approach to LDL-C lowering. Various regulatory bodies have now approved drugs in several of these

categories, including ezetimibe, PCSK9 inhibitors and bempedoic acid with ongoing investigation of inclisiran (Leo Burger et al., 2022).

Post-Marketing Surveillance

Clinical benefits and the safety of lipid-lowering drugs are assessed before approval through well-controlled clinical trials which involve a selected, limited number of patients and treatment duration (Bardolia et al., 2021). The long-term safety of new cholesterol-lowering agents during routine daily clinical practice, however, is unclear. Post-marketing surveillance has a prominent role in the assessment of their long-term safety and tolerability profiles (Pećin & Reiner, 2021). Annual REPATHA (evolocumab) and PRALUENT (alirocumab) pharmacovigilance reports review all cases of suspected adverse reactions (SARs). From a clinical point of view, RD (1.1·106) and SARs (37,287 and 25,828 for evolocumab and alirocumab, respectively), represent a relatively low value. Post-marketing surveillance studies and pharmacovigilance reports, therefore, suggest that ezetimibe, bempedoic acid, and inclisiran appear to have good tolerability profiles. Clinicians can use these agents alone or in combination to reduce LDL-C and maintain it at target level. Ongoing post-marketing surveillance data collection will help to clarify their risk/benefit ratio and further determine their role in the therapeutic management of hypercholesterolemia (Agnello et al., 2024).

Future Directions in Cholesterol-Lowering Therapies

PCSK9 inhibitors Today, there are still a considerable number of patients with hypercholesterolemia cases, whether familial or nonfamilial, who do not achieve LDL-C levels recommended by the guidelines or who cannot tolerate statins. A new family of molecules called PCSK9 inhibitors therefore offer hope. PCSK9 is a hepatic proteolytic enzyme that binds to LDL receptors on the surface of hepatocytes to mediate their intracellular degradation. The PCSK9 inhibitors that can now be used target the plasma protein and are usually monoclonal antibodies given subcutaneously every 2 or 4 weeks.

Antisense oligonucleotides Antisense oligonucleotides are single strands of nucleotides that bind to a target gene and specifically disrupt the transcription and translation of the genetic information contained within the cell. This technology could therefore be applied to many diseases with a genetic base, including hypercholesterolemia. Three of these oligonucleotides bind genes potentially related to lipid metabolism: mipomersen binds apolipoprotein B mRNA, lomitapide inhibits microsomal transfer protein (MTP), and an antisense oligonucleotide against apo(a) functions to reduce Lp(a).

Emerging Technologies

Nontraditional drug delivery technologies and formulations of statins have been developed, including nasal spray of lovastatin, vaginal tablet of lovastatin, sinus implant of lovastatin, grooved microneedle arrays of lovastatin calcium–poly (lactic-co-glycolic acid), and local injectable of lovastatin calcium in porous microspheres with targeted release. In the interactive pathway of atherosclerosis associated with alveolar macrophages, statins were loaded on mesoporous silica nanoparticles coated with driven cell membrane and successfully delivered to the lung for the treatment of chronic obstructive pulmonary disease by inhalation. Poly (lactic-co-glycolic acid) nanoparticles prepared with an emulsion–solvent evaporation method were used to load simvastatin. Poloxamer 407, a polymer similar to the amphiphilic group of lipid, was used as a stabilizer, and the influence of the amount of stabilizer on drug delivery was studied. Simvastatin-loaded poloxamer 407–poly (lactic-co-glycolic acid) nanoparticles

improved drug encapsulation, reduced particle size, and enhanced cellular uptake in human hepatocellular carcinoma HepG2 cells. A hybrid drug delivery system of rosuvastatin with platelet membrane–poly (lactic-co-glycolic acid) was designed and prepared. According to the characteristics of hyaluronic acid degrading enzyme and reactive oxygen species in the atherosclerotic cardiovascular microenvironment, the multifaceted hyaluronic acid-based nanoparticle loading atorvastatin was constructed. The application of atorvastatin in the treatment of atherosclerotic cardiovascular disease was improved by focusing on targeted delivery and controlled release in response to the pathological microenvironment. A recent study revealed that targeting delivery of rosuvastatin lipoid-polymeric hybrid nanoparticles loaded alginate attenuated the progression of atherosclerosis through inducing M2 polarization of macrophages and producing anti-inflammatory effects. Fast-dissolving oral films (FDOFs) are recent drug-delivery systems with many advantages over conventional tablets and capsules. A fast-dissolving oral film of rosuvastatin was developed and is now available on the market.

Personalized Medicine

Lipid-lowering therapy aims to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Statins lower plasma LDL cholesterol levels and have demonstrated a consistent benefit in ASCVD risk reduction in primary and secondary prevention (J. Canestaro et al., 2012). Guidelines recommend statins for secondary prevention, familial hypercholesterolemia, individuals aged 40 to 75 years with diabetes and LDL-C ≥70 mg/dL, and primary prevention patients with an estimated 10-year ASCVD risk ≥7.5%. Despite optimal therapy, significant residual ASCVD risk remains. Consequently, novel agents that more effectively lower plasma LDL-C and other atherogenic particles have been developed (Kim et al., 2022). Advances in personalized medicine may improve treatment optimization (Bardolia et al., 2021).

Global Perspectives on Cholesterol Management

Cardiovascular diseases remain a leading cause of morbidity and mortality worldwide (García-Fernández-Bravo et al., 2022). Control of lipid levels, particularly in individuals deemed at moderate or high risk, represents a key strategy in reducing the risk of cardiovascular events (Agnello et al., 2024). Population growth and aging, along with accompanying increases in the prevalence of obesity and diabetes, have led to a rapid increase in the number of people with overt dyslipidaemia. Enhanced patient awareness of disease-related factors that can improve cardiovascular outcomes has also resulted in increased demand for dyslipidaemia management, precipitating a corresponding rise in utilization of both investigators' and house officers' management.

Variations in Treatment Guidelines

The release of several major cholesterol treatment guideline updates has solidified the growing consensus among cardiovascular disease clinicians and investigators, thereby helping to break the traditional “me versus them” impasse and essentialize preventive cardiology. The new recommendations for managing cholesterol by the Heart Risk Prevention Task Force of the Italian Society of Cardiology aim to provide balanced, evidence-based advice by collaborating with consensus groups worldwide in the European Society of Cardiology, International Atherosclerosis Society, European Atherosclerosis Society, and National Lipid Association.

Statins prevent the progression of atherosclerotic lesions and primarily induce plaque stabilization by LDL-C reduction, which is the main target in all recommended guidelines. Some guidelines also state the use of the high-sensitive C-reactive protein test in those with

intermediate-to-high cardiovascular risk. Increasing the usage of statins for primary prevention of cardiovascular diseases is an essential public health intervention, promoting use especially in patients who have a high estimated cardiovascular risk.

Access to Medications

The accessibility of medications presents a notable barrier to optimal cholesterol management and cardiovascular disease prevention (Bardolia et al., 2021). Many patients discontinue statins because of side effects such as muscle symptoms and new-onset diabetes. Several newer non-statin options have entered the market, including fibric acid derivatives, niacin, bile acid sequestrants, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid. Preliminary data suggest that PCSK9 inhibitors and bempedoic acid also reduce cardiovascular outcomes, whereas ezetimibe, either alone or in combination with statins, lowers low density lipoprotein cholesterol modestly and is well-tolerated.

Public Health Implications

The global burden of atherosclerotic cardiovascular disease—most often manifested as ischemic heart disease or stroke—is massive. Statins have been shown to reduce this burden considerably, and improving how the drugs are prescribed and used—and consequently how their risks and side effects are managed—is crucial to advancing public health. Appropriately administering statins involves establishing treatment guidelines that address the trade-offs between undertreatment or overtreatment. Cardiovascular diseases remain among the leading causes of morbidity and mortality in Western countries, yet a highly conservative attitude—one that does not update knowledge from the latest cardiovascular prevention trials—greatly limits the population that could benefit from these treatments. Currently, for patients with very high cardiovascular risk, no clear safety cutoff point has been identified for plasma LDL cholesterol: typically the paradigm is that for such patients "the lower, the better." In these cases, rigorous cost/benefit analysis must determine appropriate LDLC levels. Consolidating evidence on the benefits of lipid-lowering drugs in reducing cardiovascular events, identifying the pleiotropic effects of statins, collating real-world data on treatment approaches, and tracing the evolution of LDL-C targets in clinical guidelines all assist in formulating rigorous, efficacious treatment policies (García-Fernández-Bravo et al., 2022).

Impact on Cardiovascular Disease Rates

Cardiovascular diseases have reduced from 25.1% of all deaths in 1990 to 16.7% in 2017 but remain the two leading cause of morbidity and mortality, along with cancer, in Western countries. A conservative attitude, without updating the knowledge of the latest cardiovascular prevention trials, limits opportunities for a population that could particularly benefit from treatment. Among patients with very high cardiovascular risk, no clear cut-off point indicating safe LDL-C below exists; the paradigm satisfying the reduction of low-density lipoprotein cholesterol (LDL-C) remains, "the lower, the better." Increasing cost–benefit evaluations might guide determination of which LDL-C levels should be achieved. Male cigarettes are expected to increase in many countries and along with the increasingly aging population should temper optimism about the future course of cardiovascular disease(s). CVD-19, a nonmodifiable risk factor, contributes still further. Lipid-modifying therapies, especially statins, have played a crucial role in preventing adverse cardiovascular events and improving outcomes (García-Fernández-Bravo et al., 2022). Statins effectively lower LDL-C and have pleiotropic effects that reduce vascular inflammation and thrombosis. Monoclonal antibodies against proprotein

convertase subtilisin/kexin type 9 (PCSK9) both increase LDL-C reduction and decrease adverse CV events (E Kosmas et al., 2019). Despite progress, residual risk persists, mainly due to the lack of lipid-modifying therapies specifically targeting other metabolic pathways, including high-density lipoprotein–the functionality of which does not always reflect changes in HDL-C levels–and genetic dyslipidemias. Side effects and the inability to achieve LDL-C targets with existing treatments contribute to residual risk. Research continues toward the development of new drugs aimed to further lower residual CV risk and address unmet needs in CVD.

Preventive Strategies

The goal of lipid-lowering therapy is to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Statins remain the cornerstone of lipid-lowering therapy and are administered as first-line agents to lower plasma low-density lipoprotein (LDL) cholesterol levels. Statins have demonstrated benefit in both primary and secondary prevention, and guidelines recommend their use in a variety of clinical scenarios—secondary prevention, familial hypercholesterolemia, patients 40 to 75 years old with diabetes and LDL cholesterol ≥70 mg/dL, as well as primary prevention patients with an estimated 10-year ASCVD risk of 7.5% or above. Even with optimal statin therapy, residual ASCVD risk remains. Therefore, novel agents are required to further lower LDL cholesterol and other atherogenic lipoproteins. Over the past decade, major innovations have been introduced that target LDL, triglycerides, lipoprotein (a), and high-density lipoprotein (Kim et al., 2022). Strategies to improve compliance with guideline-based therapy, through shared decision-making between clinicians and patients, are critical to complement therapeutic advances (García-Fernández-Bravo et al., 2022).

Conclusion

More than three decades have elapsed since the launch of the first statin; since that time statins have become the main pharmacological tool for the treatment of hypercholesterolemia and ASCVD prevention. Statins have convincing evidence of efficacy and safety. Nevertheless, the efficacy of statins is limited in some clinical settings, such as severe hypercholesterolemia, statin intolerance, and in poly-treated patients, and the vast majority of patients do not reach their LDL-C goals. Furthermore, fibates are the nickel in the market for lowering TGs and PPARα agonists for HDL-C increase.

In recent years, drug company research has been focused on the development of new lipid-lowering drugs acting on different mechanisms. In the field of TG-lowering drugs, the focus is on the new agents targeting Apo-CIII and ANGPTL3, which have shown their ability to lower TGs and ameliorate the CVR. Patients with AVLs remain an underserved population. At this point, new HDL-C-raising drugs focusing on Apo A-I show interesting results in terms of CVR reduction. The new generation of PCSK9 inhibitors, which includes small molecules, vaccines, and gene-silencing agents, all share potent LDL-C-lowering capacities andfaavorable effects on intolerance and costs.

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