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Dyslipidaemia Management and Computational Intelligence Approaches for Synergistic Drug Prediction: A Comprehensive Review

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ABSTRACT

Dyslipidaemia, characterized by High levels of LDL cholesterol and triglycerides, combined with low HDL cholesterol, significantly increase the risk of heart disease, including atherosclerosis, heart attacks, and strokes. Although statins work well for many people, those at higher risk such as individuals with metabolic syndrome, diabetes, or inherited high cholesterol often don't achieve their target lipid levels with just one medication Combination therapies that leverage drug synergy, where the combined effect of medications exceeds their individual effects, offer a promising solution by improving efficacy and reducing side effects. Classical models like Bliss, Loewe, and ZIP help quantify these interactions, but experimentally testing multiple drug regimens can be complex and time-consuming. Advanced computational methods, such as machine learning, deep learning, and network-based pharmacology, offer a robust approach to identify the best drug combinations and dosages, taking into account individual patient characteristics. Combinations such as statin–ezetimibe or statin–PCSK9 inhibitors demonstrate both clinical and mechanistic synergy, highlighting the potential of multi-drug strategies. Despite challenges like data limitations, model transparency, and the need for clinical validation, integrating computational predictions with traditional methods enables personalized, safer, and more effective treatment plans. Overall, combining computational intelligence with drug synergy principles represents a forward-looking approach to dyslipidaemia management, offering tailored therapies that improve cardiovascular outcomes, enhance patient care, and advance precision medicine.

Keywords: Dyslipidaemia, Ezetimibe, Fibrates, PCSK9 inhibitors, Drug synergy, Bliss independence model, Loewe additivity model, Zero Interaction Potency (ZIP) model.

1. INTRODUCTION

The multifactorial metabolic disease known as dyslipidaemia is typified by elevated blood lipid levels. Elevated low-density lipoprotein cholesterol (LDL-C), increased total cholesterol (TC), elevated triglycerides (TG), and decreased high-density lipoprotein cholesterol (HDL-C) are its main symptoms. [1,2] Alterations in blood lipid levels are not merely lab findings—they play a direct role in triggering atherosclerosis and other heart-related conditions. The buildup of fatty deposits in arteries due to dyslipidaemia can lead to serious events like peripheral artery disease, heart attacks, and strokes. Globally, cardiovascular diseases remain one of the leading preventable causes of illness and death, claiming millions of lives every year. [1,3]

1.1 GLOBAL EPIDEMIOLOGY

In recent decades, the prevalence of dyslipidaemia has grown significantly around the world. Factors such as urban lifestyles, increased consumption of calorie-rich and fatty foods, lack of physical activity, and an aging population have all contributed to this trend. As a result, both developed and developing countries are experiencing high rates of this condition. [1,2]

Millions of people worldwide are affected by abnormal lipid levels, with some regions seeing prevalence rates as high as 30–40% among adults. Urban areas are particularly hard-hit due to diets rich in processed foods, high sugar intake, and sedentary lifestyles. Dyslipidaemia is also rising in middle- and low-income countries, driven largely by lifestyle changes and longer life expectancies. [2]

If dyslipidaemia goes unmanaged, it can have serious consequences for both individual health and public well-being. The risk of heart attacks, strokes, and sudden cardiac death rises sharply when abnormal lipid levels are left untreated. This underscores the

importance of early detection, routine screening, and population-wide prevention strategies to control and manage these risks effectively. [3]

1.2 RISK FACTORS

1.2.1 LIFE STYLE FACTORS

One of the most controllable causes of dyslipidaemia is lifestyle choices. Diets high in refined carbohydrates, trans fats, and saturated fats raise triglycerides and LDL-C while lowering HDL-C. [1,2] Obesity and insulin resistance are exacerbated by sedentary activity, which also exacerbates lipid abnormalities. In addition to changing lipid metabolism, long-term alcohol use raises triglyceride levels and increases the risk of cardiovascular disease.

1.2.2 GENETIC PREDISPOSITION

Dyslipidaemia is largely influenced by genetic factors. Familial hypercholesterolemia (FH) is a hereditary disorder characterized by very high levels of LDL cholesterol from birth. Individuals with FH have a greatly increased risk of developing cardiovascular complications, often experiencing heart problems before age 50, and are more prone to early-onset coronary artery disease. [3] Even without lifestyle-related risks, some people may inherit genetic variations in apolipoproteins, LDL receptors, or enzymes involved in lipid metabolism, making them naturally susceptible to dyslipidaemia.

1.2.3 CONCURRENT DISORDERS

Certain health conditions can worsen lipid imbalances. Mixed dyslipidaemia, marked by high LDL cholesterol, raised triglycerides, and low HDL cholesterol, is often associated with type 2 diabetes, metabolic syndrome, obesity, and high blood pressure. [3,19] In metabolic syndrome, insulin resistance plays a key role by boosting triglyceride production in the liver and reducing HDL cholesterol, further increasing the risk of cardiovascular complications.

1.3 CLINICAL IMPLICATIONS

Dyslipidaemia significantly raises the likelihood of cardiovascular problems, including peripheral artery disease, coronary artery disease, and stroke. [3] Low levels of HDL cholesterol impair the body's ability to remove excess cholesterol, while high LDL cholesterol contributes to damage of the blood vessel lining and encourages the buildup of fatty plaques. [3,19]

If dyslipidaemia remains uncontrolled over time, it can lead to the rupture of atherosclerotic plaques, triggering sudden cardiovascular events. Individuals with low HDL cholesterol are at higher risk of strokes, while those with elevated LDL cholesterol and triglycerides are more prone to heart attacks.

In high-risk populations, monotherapy with traditional cholesterol-lowering medications frequently fails to reach target lipid levels despite explicit guidelines emphasizing early intervention and lifestyle change. [7,8] In order to maximize patient outcomes, this problem emphasizes the necessity of combination therapy tactics, tailored interventions, and cutting-edge techniques like computer prediction of synergistic drug combinations.

Dyslipidaemia affects more than just the heart and blood vessels. Persistent lipid imbalances often lead to conditions like fatty liver, insulin resistance, and widespread inflammation, which increase overall health risks and complicate treatment. [1,3] Therefore, in order to avoid long-term problems and enhance quality of life, early detection and thorough management are essential.

1.4 ECONOMIC AND PUBLIC HEALTH IMPACT

Beyond its effects on individual health, dyslipidaemia poses a major challenge to public health systems worldwide and contributes substantially to economic burdens.Dyslipidaemia-related cardiovascular diseases (CVDs) are a major contributor to healthcare costs, lost productivity, and early mortality [1,2] Global health estimates indicate that CVD-related expenses, such as hospital stays, outpatient treatment, prescription drugs, and procedures, can surpass billions of dollars per year in high-income nations and put a growing burden on healthcare systems in low- and middle-income nations. [1]

The financial effect of dyslipidaemia is further compounded by its indirect expenses, which include missed workdays, incapacity, and a lower quality of life. Individuals who experience heart attacks or strokes often require ongoing medical treatment, rehabilitation, and adjustments to their daily routines, creating a lasting financial burden on both their families and healthcare systems. [1,2]

From the standpoint of public health, dyslipidaemia makes a substantial contribution to the burden of non-communicable diseases (NCDs) worldwide. The World Health Organization identifies high cholesterol as a key risk factor for non-communicable diseases that can be modified. Its occurrence is steadily rising in cities, driven by shifts in diet, sedentary lifestyles, and growing rates of obesity. [1,2] Screening and preventive initiatives offer cost-effective strategies to reduce the risk of heart disease, yet they remain underutilized in many regions, particularly where healthcare resources are limited. [2]

By averting expensive complications, early detection and treatment of dyslipidaemia can dramatically lower healthcare expenditures. Actively implementing cholesterol-lowering therapies, providing guidance on healthy eating, and promoting public health initiatives focused on regular physical activity and balanced nutrition can help reduce the occurrence of heart attacks, hospitalizations, and lasting health complications. [1,2] Population-level interventions, such as statin medication recommendations and lifestyle modification campaigns, could save a significant amount of healthcare expenditures each year and avoid millions of cardiovascular events. [1]

Health equity is also impacted by the growing incidence of dyslipidaemia. Disparities in cardiovascular outcomes are exacerbated by populations in low- and middle-income nations frequently having restricted access to screening, diagnostic services, and lipid-lowering drugs.[2] In contrast, sedentary lifestyles, processed foods, and aging populations continue to contribute to high prevalence of dyslipidaemia in high-income nations despite improved access to healthcare. [2,3] This suggests that the burden of dyslipidaemia is a global issue that transcends economic status.

1.5 PATHOPHYSIOLOGY AND MECHANISMS OF DYSLIPIDAEMIA

Disturbances in lipid metabolism that impact lipoprotein production, transport, and clearance in the plasma are the cause of dyslipidaemia. Genetic predisposition, nutritional factors, hormone regulation, and concomitant metabolic diseases are all part of the complex pathogenesis. [3,19] Designing targeted treatment approaches, such as combination therapy and computationally guided medication synergy, requires an understanding of the mechanisms driving dyslipidaemia.

1.5.1 LIPOPROTEIN METABOLISM

Lipoproteins are lipid-protein complexes that carry phospholipids, triglycerides, and cholesterol throughout the blood. The principal classes consist of:

• Chylomicrons: Move cholesterol and triglycerides from the colon to the peripheral tissues.

• The liver produces Very Low-Density Lipoprotein (VLDL) to carry endogenous triglycerides.

• Low-Density Lipoprotein (LDL) and Intermediate-Density Lipoprotein (IDL): LDL transports cholesterol to peripheral tissues by converting IDL. One of the main atherogenic factors is elevated LDL-C.[3]

• HDL: Transports extra cholesterol from tissues to the liver for elimination via mediating reverse cholesterol transport. [1,2]

1.5.2 CHOLESTEROL HOMEOSTASIS

Cholesterol levels stay healthy when there's a proper balance between dietary intake, the body's own production, cellular absorption, and elimination:

• Endogenous Synthesis: HMG-CoA reductase is the enzyme that limits the pace at which the liver produces cholesterol through the mevalonate route. By inhibiting this enzyme, statins lower the production of LDL-C. [4]

• Intestinal Absorption: The NPC1L1 transporter allows enterocytes to absorb dietary cholesterol, making it a target for ezetimibe treatment. [4,5]

• Cellular Uptake: To internalize cholesterol, LDL attaches to LDL receptors (LDLR) on peripheral and hepatocyte cells. Elevated circulating LDL-C is caused by impaired LDLR function, such as in familial hypercholesterolemia. [3,7]

• Excretion: Bile acid production and enterohepatic circulation regulate the excretion of cholesterol through bile. Lipid buildup may be exacerbated by disruption.[3]

1.5.3 TRIGLYCERIDE METABOLISM

The liver produces triglycerides, which are then carried by VLDL. Dysregulation is brought on by:

• VLDL overproduction: Frequently linked to obesity and insulin resistance.

• Impaired Lipolysis: Triglyceride clearance from chylomicrons and VLDL is decreased when lipoprotein lipase (LPL) is malfunctioning. [3,19]

• Secondary Causes: Hypertriglyceridemia can be made worse by alcohol usage, uncontrolled diabetes, and some medications.[3]

1.5.4 GENETIC AND FAMILIAL FACTORS

Dyslipidaemia is largely caused by genetic mutations:

• Mutations in LDLR, APOB, or PCSK9 cause familial hypercholesterolemia (FH), which is characterized by significantly increased LDL-C and poor LDL clearance. [3]

• Familial Combined Hyperlipidaemia: Due to polygenic impacts on lipid synthesis and clearance, this condition is characterized by increased LDL-C and triglycerides.[3]

The degree and type of dyslipidaemia are determined by the interaction of genetic predisposition with environmental and lifestyle factors, underscoring the necessity for individualized treatment.[3,19]

1.5.5 ROLE OF INFLAMMATION AND ENDOTHELIAL DYSFUNCTION

The main causes of atherosclerosis, endothelial dysfunction and persistent vascular inflammation, are exacerbated by dyslipidaemia:

• Oxidized LDL (oxLDL): When LDL particles undergo oxidative alteration, the endothelium experiences inflammatory reactions.

• Cytokine Activation: oxLDL promotes the production of foam cells and the development of plaque by stimulating macrophages and vascular smooth muscle cells.[3]

• HDL Dysfunction: Reverse cholesterol transport is hampered by low HDL-C, which exacerbates oxidative stress and lipid buildup. [1,3]

1.5.6 SECONDARY DYSLIPIDAEMIA

Lipid abnormalities can be made worse by acquired conditions:

• Diabetes Mellitus: Insulin resistance lowers HDL-C and raises VLDL production. [3,19]

• Hypothyroidism: Causes hypercholesterolemia and decreased LDL receptor activation.[3]

• chronic kidney disease: Alters how lipoproteins are processed in the body, which can increase the likelihood of developing heart and blood vessel diseases.[3]

2. THERAPEUTIC APPROACHES AND LIPID-LOWERING DRUGS

By restoring normal plasma lipid levels mainly by lowering LDL-C, triglycerides, and non-HDL cholesterol while raising HDL-C dyslipidaemia therapy seeks to lessen cardiovascular risk. Lifestyle changes, medication, and, in certain situations, sophisticated interventions are examples of treatment approaches. For individuals at elevated risk of heart disease, medication becomes crucial, especially when changes in diet and lifestyle alone fail to control risk factors. [4,5]

2.1 STATINS (HMG-COA REDUCTASE INHIBITORS)

Because of their strong LDL-C-lowering effects and proven cardiovascular benefits, statins continue to be the first-line treatment for dyslipidaemia:

• Mechanism of Action: Statins lower hepatic cholesterol synthesis by inhibiting HMG-CoA reductase, the enzyme that limits the rate of cholesterol biosynthesis. This improves the removal of LDL-C from the bloodstream by upregulating LDL receptors on hepatocytes.[4]

• Clinical Benefits: In patients with hypercholesterolemia and established cardiovascular disease, statins dramatically lower LDL-C, cardiovascular events, and all-cause mortality. [4,5]

• Restrictions: Adherence to statin therapy may be hampered by myopathy, hepatotoxicity, and, in rare cases, new-onset diabetes. Statins by themselves might not be able to reach the desired lipid levels in high-risk groups or familial hypercholesterolemia. [4,7]

2.2 EZETIMIBE

Ezetimibe works alongside statins to help lower cholesterol by specifically blocking its absorption in the intestines. It acts on the NPC1L1 transporter in the small intestine, which reduces the uptake of both dietary and bile-derived cholesterol. [4,5] On its own, ezetimibe can lower LDL-C levels moderately by about 15–20%, but when combined with statins, the effect is stronger, often producing an additive or synergistic reduction in LDL-C. This combination is especially beneficial for patients who cannot achieve their cholesterol targets using only statin therapy. [4,5,6] In addition, ezetimibe is usually easy to tolerate, causing minimal side effects and rarely interacting with other drugs.[5]

2.3 FIBRATES

Fibrates are primarily used to treat high triglyceride levels and low HDL cholesterol. They work by activating PPARα (peroxisome proliferator-activated receptor alpha), which helps the body break down fatty acids more efficiently, boosts the activity of lipoprotein lipase, and supports the production of HDL, the “good” cholesterol.[4] Clinically, Fibrates are effective at lowering triglycerides by 30–50% and can modestly raise HDL-C, which makes them particularly useful for individuals with mixed dyslipidaemia or metabolic syndrome. However, they have limited impact on LDL-C. When used alongside statins, there is a slight yet significant risk of muscle-related side effects, so close monitoring of patients is essential. [4,5]

2.4 PCSK9 INHIBITORS

PCSK9 inhibitors represent a newer, potent group of drugs for reducing LDL cholesterol. They act by inhibiting the PCSK9 protein, which normally degrades LDL receptors in the liver. By blocking this process, more receptors remain available to remove LDL from the bloodstream. PCSK9 inhibitors can lower LDL cholesterol by up to 60%, making them particularly valuable for individuals who cannot take statins or who have familial hypercholesterolemia, greatly reducing their risk of heart disease. However, their high price and the requirement for subcutaneous injections limit their broader accessibility. [5,6]

2.5 COMBINATION THERAPY

In many patients at high risk, using a statin or another lipid-lowering drug alone may not be enough to reach ideal cholesterol levels. Combining therapies can tackle different pathways in lipid metabolism, improving effectiveness while potentially reducing side effects. [9,12] For instance, pairing a statin with ezetimibe works by both blocking cholesterol production and limiting its absorption from the gut, leading to a stronger reduction in LDL-C.[9,10] Similarly, combining a statin with a PCSK9 inhibitor offers potent LDL-C lowering, which is especially useful for people with familial hypercholesterolemia or those who don’t achieve their targets with statins alone.[5,6] In certain cases, doctors may use a triple therapy of a statin, ezetimibe, and a PCSK9 inhibitor to reach very aggressive LDL-C goals, with careful monitoring to ensure safety.[5,9]

3. DRUG SYNERGY: CONCEPT AND MODELS

A pharmacological concept known as "drug synergy" refers to interactions between two or more medications in which the combined effect is greater than the anticipated additive effects of each treatment acting alone. Since many patients need multi-drug therapy to safely and efficiently attain lipid objectives, understanding synergy is crucial to managing dyslipidaemia. [9,17,18]

3.1 TYPES OF DRUG INTERACTIONS

Drug interactions can be broadly classified into synergistic, additive, and antagonistic effects:

- **Synergistic Interaction**: This happens when a drug's combined effect outweighs the sum of its individual effects. When a statin and ezetimibe together reduce LDL-C more than either medication alone, for instance, this is especially beneficial in the treatment of dyslipidaemia. [17,18] Lower dosages of each medication are possible with synergistic combinations, which lowers the possibility of side effects such myopathy or hepatotoxicity. [17,18]

- **Additive Interaction**: When the combined effect of two drugs is simply the sum of their individual effects, it is called additivity. This occurs when each medication works independently without influencing the other's mechanism. For instance, combining two drugs that reduce triglycerides through different pathways may produce additive effects, but not true synergy.[22] Even though additive effects don't achieve the enhanced benefits seen with true synergy, they still make it possible to target multiple pathways in treatment.

- **Antagonistic Interaction**: This happens when a drug interferes with another's effect, making the total effect less than anticipated. This could happen in dyslipidaemia if one medication changes the metabolism or pharmacokinetics of another, decreasing the effectiveness of lowering LDL-C. To guarantee therapeutic success, it is essential to recognize and steer clear of antagonistic combos. [22,23]

3.2 CLASSICAL MODELS TO QUANTIFY DRUG SYNERGY

Mathematical models offer structured ways to evaluate how drugs interact with each other. They are commonly applied in both preclinical research and clinical trials for dyslipidaemia treatments.

3.2.1 BLISS INDEPENDENCE MODEL

- **Overview:** Introduced by Bliss in 1939, this model assumes that drugs act independently via distinct mechanisms. [34]

- **Mathematical Formulation:**

$$E_{expected} = EA + EB - (EA \times EB)$$

EA is the fractional effect of **drug A** when used alone (e.g., as a decimal, 0.3 for 30% effect),

EB is the fractional effect of **drug B** when used alone.

- **Interpretation:**

- When the combined effect of two drugs exceeds what would be predicted from their individual effects, the interaction is classified as synergistic. ($E_{observed} > E_{expected}$)

- If the observed effect equals the expected effect, the interaction is additive.

($E_{observed} = E_{expected}$)

- If the observed effect is less than the expected effect, the interaction is antagonistic.

($E_{observed} < E_{expected}$)

3.2.2 LOEWE ADDITIVITY MODEL

The isobologram technique is a valuable approach for examining drug interactions, particularly when the medications are believed to act via similar mechanisms or can be measured in equivalent doses. [22,23] In this method, the dose of drug A is shown on the x-axis and drug B on the y-axis, illustrating the quantities required to achieve a particular outcome, such as a desired drop in LDL cholesterol. The straight line linking the individual drug doses indicates an additive effect, meaning a combination along this line produces the expected result without any stronger or weaker interaction. If a combination falls below this line, it indicates synergy,

showing that lower doses of both drugs together achieve the same effect more efficiently. Points on the line reflect simple additivity, while points above the line suggest antagonism, where the combination is less effective than predicted [22,23]. This method provides a clear and visual way to understand drug interactions, guiding the design of combination therapies that are bot. h effective and safe.

3.2.3 ZERO INTERACTION POTENCY (ZIP) MODEL

The Zero Interaction Potency (ZIP) model offers a detailed approach to assess how drugs interact, taking into account both their potency how much is needed to achieve a certain effect and their efficacy the greatest effect each drug can produce when two or more drugs are used together. [25,27] Unlike simpler models, the ZIP approach does not assume that drugs act entirely independently or through the same mechanism, making it well-suited for analyzing complex multi-drug treatments. One key benefit is its ability to detect even subtle synergistic or antagonistic interactions across a broad range of doses. This is particularly useful in managing dyslipidaemia, where combinations of medications such as statins, ezetimibe, and PCSK9 inhibitors are often employed to lower LDL-C effectively while minimizing adverse effects. [25,27]

Practically, the ZIP model has been implemented in computational tools like SynergyFinder, which allow researchers and clinicians to visualize synergy scores and identify the most effective dose ratios. By integrating dose-response data for each drug and evaluating how deviations from expected additive effects occur, ZIP helps in optimizing combination strategies and provides a quantitative basis for selecting doses that maximize therapeutic benefit while reducing toxicity. This makes ZIP a powerful tool for rational design of combination therapy in cardiovascular disease and other complex disorders. [25,27]

3.3 EXAMPLES OF DRUG SYNERGY IN DYSLIPIDAEMIA

Combining lipid-lowering therapies can achieve significantly greater reductions in LDL cholesterol by leveraging complementary mechanisms of action. For instance, statins plus ezetimibe work synergistically, with statins inhibiting cholesterol synthesis in the liver while ezetimibe reduces intestinal cholesterol absorption, resulting in a more pronounced decrease in LDL-C compared to either agent alone. [9,10] Similarly, the addition of a PCSK9 inhibitor to statin therapy provides substantial LDL-C lowering, particularly in patients with familial hypercholesterolemia, by enhancing the clearance of LDL particles through upregulation of hepatic LDL receptors [5,6] In high-risk populations, such as those with severe dyslipidaemia or existing cardiovascular disease, triple therapy combining statin, ezetimibe, and a PCSK9 inhibitor may be required to reach aggressive lipid targets and minimize cardiovascular risk. [9] This multi-pronged approach exemplifies the value of combination therapy in personalizing treatment and achieving optimal lipid control, particularly when monotherapy is insufficient.

3.4 LIMITATIONS OF CLASSICAL SYNERGY ASSESSMENT

Evaluating multiple drugs at different doses, whether in vitro or in vivo, is often a highly time-consuming and resource-intensive process, making experimental studies complex and challenging. [7,8] Moreover, traditional models frequently fall short in capturing the intricate, nonlinear interactions between drugs, as well as patient-specific variables like genetic background and coexisting health conditions, which can significantly influence therapeutic outcomes.[7,8] These challenges highlight the growing importance of computational intelligence approaches, which can efficiently and accurately predict synergistic drug combinations, reducing the experimental burden while offering more personalized insights into treatment strategies. [13,16]

4. COMPUTATIONAL INTELLIGENCE APPROACHES IN DRUG SYNERGY PREDICTION

As multi-drug treatments for dyslipidaemia become increasingly complex, advanced computational methods are needed to manage them. Techniques like machine learning, deep learning, and network-based models can help predict how drugs will work together, allowing researchers to anticipate synergistic effects without relying on extensive laboratory experiments. [13,14,16] To find the best drug combinations, these techniques combine pharmacological information, molecular characteristics, and clinical results.

4.1 OVERVIEW OF COMPUTATIONAL INTELLIGENCE

Computational intelligence (CI) refers to advanced techniques inspired by the way humans think and biological processes, allowing machines to detect patterns in complex, high-dimensional data. Machine learning (ML) methods, including Random Forest, Support Vector Machines, and Gradient Boosting, can analyse structured datasets to predict outcomes and uncover potential drug synergies based on past responses. Deep learning (DL), which is a branch of ML, uses neural networks to automatically identify intricate patterns from large datasets. Models like Convolutional Neural Networks (CNNs) and Graph Neural Networks (GNNs) are especially useful for representing molecular structures and understanding drug–target interactions to predict synergistic effects. Network-based approaches complement these methods by representing drugs, targets, and diseases as interconnected nodes, allowing the identification of synergistic combinations through analysis of network topology and interactions. Compared to classical

models, CI techniques offer the ability to handle large datasets, capture nonlinear relationships, incorporate patient-specific information, and predict synergy for novel drug combinations, making them invaluable for accelerating drug discovery and designing personalized therapies. [13,15]

4.2 MACHINE LEARNING APPROACHES

By using datasets of known drug pairings and their observed effects, machine learning models are trained to predict drug synergy. Important elements consist of:

4.2.1 FEATURE ENGINEERING

In computational drug synergy prediction, machine learning models rely on the integration of chemical, biological, and clinical features to capture complex patterns underlying drug interactions. Chemical features include molecular fingerprints, physicochemical properties such as molecular weight and lipophilicity, and structural descriptors that reflect three-dimensional arrangements and functional groups, providing insight into how drugs may interact at target sites. Biological characteristics include aspects like gene expression patterns, protein targets, pathway participation, and metabolic interactions. These features help models capture the underlying mechanisms of how drugs work together and predict synergistic effects based on complementary actions within cells. Clinical characteristics such as a patient's age, sex, existing health conditions, previous therapies, and medication history add a personalized dimension, allowing models to factor in individual differences that can influence how a patient responds to treatment. By integrating these diverse biological and clinical data, machine learning algorithms can identify patterns linked to drug synergy. This approach improves the ability to predict new effective drug combinations and aids in developing treatment plans tailored to individual patients. [14,15]

4.2.2 COMMON ML ALGORITHMS

Machine learning techniques, including Random Forest (RF), Support Vector Machines (SVM), and Gradient Boosting Machines (GBM), are widely used to predict drug synergy by analysing complex, multi-layered data. RF, which combines multiple decision trees, is particularly strong at managing large datasets and minimizing overfitting, and has been applied to identify synergistic pairs such as statins with ezetimibe. SVM, on the other hand, distinguishes synergistic from non-synergistic drug combinations by finding optimal boundaries in the data, efficiently capturing nonlinear relationships through kernel functions. Gradient Boosting Machines (GBM) construct models in a step-by-step manner, with each new model addressing the mistakes of the previous ones, which helps in capturing complex connections among chemical, biological, and clinical factors. These machine learning techniques are well-suited for datasets of moderate size and offer interpretable outputs, enabling researchers to pinpoint the critical features behind drug synergy and derive practical insights for developing new combination therapies. [13,14]

4.3 TECHNIQUES BASED ON DEEP LEARNING

Deep learning techniques are particularly strong at identifying intricate, nonlinear relationships among drugs, biological targets, and cellular pathways:

4.3.1 NEURAL NETWORK ARCHITECTURES

Deep learning (DL) techniques provide robust methods for forecasting drug synergy by uncovering complex patterns from large, diverse datasets. Feedforward Neural Networks (FNNs) link drug-related information—such as chemical properties, biological targets, and clinical data to continuous synergy measures like Bliss or ZIP scores, enabling accurate assessment of interaction strength. Convolutional Neural Networks (CNNs) are effective at recognizing spatial and structural patterns within molecular configurations and chemical fingerprints, highlighting specific atom arrangements or functional groups that drive synergy. Graph Neural Networks (GNNs) model drugs, proteins, and targets as interconnected nodes, with edges representing their interactions, allowing the system to learn the complex relationships and network structures underlying biological processes. By integrating these architectures, deep learning models can accurately predict drug combinations, leveraging FNNs for continuous score estimation, CNNs for structural feature extraction, and GNNs for network-level interaction modeling, thus providing a scalable framework for discovering novel synergistic therapies. [13,15]

4.4 NETWORK PHARMACOLOGY APPROACHES

Network pharmacology applies systems biology and network science to model the complex relationships among drugs, targets, and diseases. In this framework, drug target networks represent drugs and their molecular targets as nodes, with edges indicating interactions such as binding or inhibition, while disease networks map disease-associated genes or proteins as nodes, connected by

functional or regulatory relationships. By analysing the topology of these networks, researchers can predict synergistic drug combinations that act on complementary or overlapping pathways. For example, statins inhibit HMG-CoA reductase to reduce cholesterol synthesis, whereas ezetimibe targets NPC1L1 in intestinal cholesterol absorption; network models highlight that these drugs act on complementary pathways, explaining their synergistic effect in lowering LDL-C levels. This systems-level approach provides mechanistic insights and supports the rational design of effective combination therapies. [16]

4.5 INTEGRATION WITH CLASSICAL SYNERGY MODELS

Computational intelligence (CI) approaches complement classical drug synergy models, such as Bliss, Loewe, and ZIP, by overcoming key limitations in experimental evaluation. In contrast to traditional models that rely on extensive experimental testing of numerous dose combinations, computational intelligence (CI) techniques can estimate synergy scores virtually, allowing for rapid assessment across a broad spectrum of drug concentrations. This approach is especially valuable for multi-drug regimens, like triple therapy for high-risk dyslipidaemia patients, where conventional methods are hindered by the sheer number of possible combinations. Integrating CI predictions with classical models provides validation, ensuring that predicted synergy aligns with established pharmacological principles and known biological mechanisms. This complementary strategy allows scalable, accurate, and mechanistically interpretable identification of promising drug combinations. [25,27]

4.6 CHALLENGES AND LIMITATIONS

Despite their promise, computational intelligence (CI) approaches face several challenges in drug synergy prediction. Data quality remains a key limitation, as limited, inconsistent, or noisy datasets can reduce predictive accuracy and model generalizability. Another important challenge is interpretability, especially for deep learning models such as Graph Neural Networks (GNNs), which often operate as "black boxes," making it hard to decipher the biological mechanisms behind their predictions. Their generalizability can also be limited, as models trained on preclinical or in vitro datasets may not fully reflect human physiology or real-world clinical outcomes. Furthermore, applying these models in clinical settings demands thorough validation, strict compliance with regulatory requirements, and careful attention to patient safety and individualized treatment considerations. To address these limitations, researchers are developing hybrid strategies that integrate machine learning and deep learning methods with network pharmacology and traditional synergy scoring. This combined approach aims to improve prediction accuracy, provide clearer mechanistic insights, and increase translational relevance, helping to connect computational forecasts with practical clinical applications. [13,16,25,27]

5. APPLICATIONS IN DYSLIPIDAEMIA THERAPY

Under the guidance of insights from computational intelligence forecasts and traditional synergy models, the treatment of dyslipidaemia has progressed from monotherapy to multi-drug combinations. These strategies seek to minimize side effects, lower cardiovascular risk, and attain optimal cholesterol control. [7,8,16]

5.1 STATIN-BASED COMBINATIONS

Statins continue to be the mainstay of treatment for dyslipidaemia because they lower LDL-C levels by blocking HMG-CoA reductase. However, in high-risk individuals, especially those with metabolic syndrome or familial hypercholesterolemia, statin monotherapy frequently falls short of target lipid targets. [7,8]

5.1.1 STATIN + EZETIMIBE

The combination of statins and ezetimibe exemplifies a synergistic lipid-lowering therapy supported by mechanistic, clinical, and computational evidence. Statins inhibit HMG-CoA reductase to reduce endogenous cholesterol synthesis, while ezetimibe blocks intestinal cholesterol absorption via the NPC1L1 transporter, targeting complementary pathways in cholesterol metabolism. From a clinical perspective, using this combination has been found to reduce LDL-C levels by an additional 15–25% compared with statin alone, offering significant advantages for high-risk individuals [8,18]. Analyses based on Bliss and Loewe models indicate that the drugs work synergistically over a range of doses, aligning well with predictions from network pharmacology.[25] Computational studies, such as machine learning models built on drug–target interaction data, also indicate that simultaneously targeting both liver and intestinal cholesterol pathways promotes LDL clearance more efficiently than using either drug individually.[13,14] Together, these findings underscore the rational design and efficacy of statin–ezetimibe combination therapy.

5.1.2 STATIN + PCSK9 INHIBITORS

PCSK9 inhibitors are precision treatments that reduce LDL cholesterol by boosting the number of LDL receptors on liver cells, which increases the removal of LDL-C from the bloodstream. They work by preventing PCSK9 from breaking down these receptors,

which can enhance the effects of statins and produce additive or even synergistic lipid-lowering results. In clinical practice, they are especially beneficial for individuals who cannot tolerate statins, have familial hypercholesterolemia, or struggle with high cholesterol levels despite statin therapy. Using deep learning combined with network pharmacology, predictive models can analyze genetic, protein, and multi-omics information to pinpoint patients who are most likely to respond, supporting tailored and more effective cholesterol-lowering treatments. [16]

5.2 NON-STATIN COMBINATION THERAPIES

For individuals who have statin intolerance or residual risk, non-statin medications are becoming more and more crucial. These consist of omega-3 fatty acids, fibrates, niacin, and new drugs such obicetrapib. [21]

5.2.1 FIBRATES + STATINS

Fibrates work by activating PPARα, a receptor that controls genes responsible for fatty acid breakdown and lipoprotein metabolism, leading to reduced triglycerides and a modest rise in HDL-C. In clinical practice, they are especially useful as part of combination therapy for patients with mixed dyslipidaemia or high triglyceride levels, though regular monitoring is important to prevent potential muscle-related side effects. [18] Computational methods, such as machine learning models, help guide therapy by forecasting the most effective doses and drug pairings that lower triglycerides efficiently while reducing the risk of side effects, allowing for more individualized and effective treatment plans. [14]

5.2.2 OBICETRAPIB + EZETIMIBE

Obicetrapib, a CETP inhibitor, increases HDL-C and reduces LDL-C by blocking the transfer of cholesteryl esters from HDL to LDL and VLDL, while combination with ezetimibe targets complementary pathways in cholesterol metabolism by inhibiting intestinal absorption. Phase 2 clinical trials demonstrate that this combination significantly lowers LDL-C compared to placebo, with favourable safety and tolerability. [21] Synergy analyses using classical models such as Bliss and Loewe, along with machine learning-based predictions, indicate additive or synergistic effects across multiple dose ranges, highlighting the potential of obicetrapib–ezetimibe therapy for optimized multi-drug lipid-lowering strategies. [25,27]

5.3 MULTI-DRUG OPTIMIZATION STRATEGIES

In patients at high cardiovascular risk—such as those with metabolic syndrome, diabetes, or familial hypercholesterolemia—controlling dyslipidemia often needs three or four drugs, since a single therapy may not be enough. Computational intelligence helps in this scenario by fine-tuning drug doses to achieve maximum benefit with minimal side effects. It uses patient-specific information, including demographics, genetic data, and clinical history, to personalize treatment and can uncover new synergistic drug combinations by analyzing networks of interacting pathways with tools like Graph Neural Networks (GNNs). For instance, a triple therapy of statin, ezetimibe, and a PCSK9 inhibitor can be recommended for patients with LDL-C >190 mg/dL despite maximal monotherapy, with computational models predicting dose combinations that achieve target LDL-C levels without exceeding toxicity thresholds. [16]

5.4 CLINICAL INTEGRATION AND CHALLENGES

Although computational intelligence (CI) shows promise in predicting synergistic drug combinations, translating these predictions into clinical practice requires careful consideration. Predicted synergies must be validated through preclinical studies and clinical trials to ensure safety and efficacy, and regulatory approval is necessary for multi-drug regimens to confirm tolerability and pharmacokinetic compatibility. Patient adherence is another concern, as complex regimens increase pill burden; strategies such as fixed-dose combinations can help improve compliance. Additionally, the accuracy of CI models depends on high-quality preclinical and clinical datasets, as incomplete or inconsistent data can limit predictive reliability and generalizability. Integrating robust data, rigorous validation, and patient-centered strategies is therefore essential for realizing the clinical potential of CI-driven combination therapies. [13,16,25,27].

6. DRUG SYNERGY IN DYSLIPIDAEMIA MANAGEMENT

The idea of using drug synergy has become increasingly important in treating dyslipidaemia, especially for patients who do not reach their lipid goals with a single medication. Synergy happens when the combined impact of two or more drugs is greater than what each would achieve alone, which can allow for lower doses of each drug while still improving or sustaining therapeutic effects. [30,33] In managing dyslipidaemia, using combination treatments that act on different aspects of lipid metabolism has proven effective. For example, statins lower cholesterol production in the liver by inhibiting HMG-CoA reductase, while ezetimibe reduces

cholesterol absorption in the intestines. When used together, these drugs can produce additive effects or even greater synergistic reductions in LDL-C levels. [7,8] Similarly, the use of PCSK9 inhibitors alongside statins provides another example of synergistic lipid lowering, as these biologic agents enhance LDL receptor recycling, markedly increasing LDL-C clearance from the bloodstream. [12]

The rationale for exploring drug synergy extends beyond achieving lipid targets. Synergistic drug combinations can reduce the risk of adverse effects by allowing lower doses of individual agents, improve patient adherence through simplified regimens, and address multiple lipid abnormalities simultaneously, including elevated triglycerides, low HDL-C, and small dense LDL particles. [7,12,31] Preclinical studies using in vitro and in vivo models have demonstrated that combining drugs with complementary mechanisms can lead to improved modulation of lipid metabolism, reduced inflammation, and decreased progression of atherosclerosis.[30,32] Network pharmacology and systems biology approaches have further enhanced our understanding of these synergistic interactions, revealing how different molecular targets within lipid regulatory networks can be modulated concurrently to maximize therapeutic benefits. [31,33]

Even with these developments, applying drug synergy findings from laboratory studies to real-world clinical settings is difficult. Differences in patients' genetic makeup, existing health conditions, and environmental influences can affect both the strength and reliability of the combined drug effects. Moreover, clinical trials to validate synergistic combinations are often limited in size, duration, or population diversity, making it difficult to generalize results to broader patient groups. [31,32] Still, research that combines computational modeling with mechanistic pharmacology is actively uncovering drug combinations that could improve cardiovascular outcomes and offer more effective options for patients with resistant or high-risk dyslipidaemia.[30,33]

7. DRUG SYNERGY DATABASES AND RESOURCES

Drug synergy research is now supported by a number of specialist databases that offer curated datasets, scoring algorithms, and computational tools for identifying and analysing synergistic interactions. Researchers can systematically assess drug combinations and compare observed against projected effects by using resources like DrugComb and SynergyFinder, which provide access to high-throughput screening data. [30,33] Although these platforms have traditionally been used for oncology, efforts are being made to expand their usage in dyslipidaemia research by incorporating lipid-lowering drugs.

These databases give researchers access to data on synergy scores, combination indices, and dose-response relationships obtained from in vitro and in vivo investigations. Additionally, they offer computational pipelines that combine pharmacodynamic profiles, gene expression data, and molecular fingerprints to forecast possible synergistic combinations. [31, 32] Crucially, the availability of open-access synergy databases speeds up the conversion of computational predictions into experimental and clinical validation by promoting cooperation, reproducibility, and quick idea creation.

Despite their advantages, these resources have limitations. Data heterogeneity, incomplete coverage of lipid-lowering drugs, and variations in experimental design can reduce predictive reliability. Moreover, while databases can suggest potential synergistic combinations, they cannot replace rigorous experimental or clinical evaluation to ensure safety and efficacy. [30,33] Nonetheless, as these resources expand and integrate with computational intelligence tools, they provide a critical foundation for designing optimized combination therapies tailored to dyslipidaemia management.

8. APPLICATIONS AND CLINICAL IMPLICATIONS OF DRUG SYNERGY IN DYSLIPIDAEMIA

Leveraging drug synergy in dyslipidaemia management offers significant clinical benefits by improving patient outcomes and potentially lowering adverse effects. Combination therapies that target complementary mechanisms—such as statins paired with ezetimibe or with PCSK9 inhibitors—have been shown to more effectively reduce LDL-C, total cholesterol, and apolipoprotein B levels compared with single-drug treatments. [7,12] Synergistic combinations can reduce the overall burden of atherosclerotic disease by addressing multifactorial components of cardiovascular risk, such as oxidative stress, endothelial dysfunction, and inflammation, in addition to their effectiveness in lowering cholesterol.

Practically speaking, synergy-based therapy can improve adherence by lowering the requirement for high-dose monotherapy, which is frequently linked to side effects such myopathy, hepatotoxicity, or gastrointestinal distress. [30, 31] Fixed-dose combination formulations make regimens simpler, which may increase adherence, especially in older patients or those with several comorbidities. Additionally, patient-specific customization is made possible by artificial intelligence-guided synergistic combination selection, which takes individual lipid profiles, comorbid illnesses, and hereditary factors into account. This method ensures that each patient receives therapy that is both safe and effective, in line with the concepts of precision medicine.

However, potential dangers must be carefully considered before implementing synergistic regimens in clinical settings. Before starting combination therapy, drug-drug interactions, additive toxicities, and pharmacokinetic incompatibilities must be assessed. [31,33] To guarantee safety, it is crucial to regularly check muscle biomarkers, renal function, and liver enzymes. Despite these obstacles, the combination of mechanistic knowledge of lipid metabolism, high-quality clinical data, and predictive computational tools is gradually making it possible to rationally design synergistic regimens, which will ultimately improve cardiovascular outcomes and lessen the worldwide impact of dyslipidaemia.

9. CHALLENGES, LIMITATIONS, AND FUTURE DIRECTIONS

Combination therapy and computational intelligence have made promising progress in the treatment of dyslipidaemia, but a number of barriers still stand in the way of their widespread adoption and optimal application. One of the primary limitations is the data's quality and accessibility. Accurate predictions from AI and machine learning models rely on access to extensive, well-curated datasets. [13,16] Nevertheless, current dyslipidaemia datasets are often varied, insufficient, or biased, with limited representation of specific patient demographics, coexisting conditions, and real treatment outcomes. [13,14]

Lack of disease-specific data can reduce the predicted accuracy of computational models and produce recommendations that are less relevant to a range of demographics. [15,16] Furthermore, a number of synergy databases, including DrugComb and SynergyFinder, have historically focused on oncology or general pharmacology and offer very little information on lipid-lowering drugs, which hinders the development of AI models specifically suited to dyslipidaemia therapy. [30,33]

Another significant challenge is the actual application of computer forecasts. Experimental and clinical research must fully validate these predictions to ensure safety and efficacy. [7,8,15,16] Machine learning, deep learning, and network pharmacology can help identify optimal dose combinations and uncover drug pairs that may work synergistically. [15,16,28,29] Using high-dose combinations or multiple drugs can raise the likelihood of side effects such as muscle damage, liver toxicity, and interactions between medications, making close monitoring essential. [4,7,8] Moreover, deep learning models often act as "black boxes," making it challenging to comprehend why a particular medication combination is anticipated to be synergistic. This lack of transparency may further impede adoption in routine clinical practice, thereby undermining trust between doctors and regulatory agencies. [31, 32]

Patient adherence is another practical limitation. Multi-drug regimens can increase pill burden and complexity, which might reduce long-term treatment success and compliance even though they might be more effective. Fixed-dose combination formulations offer one solution, but they are not commonly accessible, and not all drug combinations can be mixed without compromising pharmacokinetics or stability.[7] Additionally, patient genetic, lifestyle, and comorbidity variability complicates the prediction of universal pharmaceutical synergies, necessitating tailored therapeutic approaches that may be resource-intensive to carry out without computational help. [13,14,28,29] Combining artificial intelligence with multi-omics and real-world clinical data holds considerable promise for overcoming these challenges in the future. [13,16] By combining genomic, transcriptomic, proteomic, and metabolomic data, AI models can generate patient-specific predictions, enabling truly personalized treatment. [13,14,28,29]

Machine learning and network-based approaches can predict long-term cardiovascular outcomes, such as a reduction in the incidence of myocardial infarction or the development of atherosclerotic plaque, as well as novel drug repurposing opportunities and dose ratio optimization. [9,11,12] Continuous input from clinical trials and electronic health records can also enhance predictive algorithms, creating a learning healthcare system where computer models improve over time as more patient data becomes accessible. [13,14,16]

Finally, future management of dyslipidaemia may be aided by the development of user-friendly clinical decision support systems that integrate medical knowledge with AI predictions. By providing real-time recommendations for medication selection, combination strategies, and dosage adjustments, these systems could support precision medicine while maintaining safety and efficacy standards. [13,16]. Despite existing limitations, the integration of high-quality clinical data, computational intelligence, and mechanistic understanding of lipid metabolism presents a revolutionary opportunity to improve the treatment of dyslipidaemia. [13,16,28,29]

CONCLUSION

A revolutionary approach to the treatment of dyslipidaemia is the combination of computational intelligence with medication synergy concepts. Treatment can move toward tailored, customized, and extremely successful regimens by utilizing new technology and resolving existing constraints. This strategy may improve long-term patient outcomes, lower the frequency of cardiovascular events, and enable more accurate, effective, and patient-centered care. In general, using computational insights to provide safer, more intelligent, and customized treatment approaches is the key to managing dyslipidaemia in the future.

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SL NO	ABBREVIATTIONS	FULL FORM
1	APOB	Apolipoprotein B
2	CI	Computational Intelligence
3	CNN	Convolutional Neural Network
4	CETP	Cholesteryl Ester Transfer Protein
5	CVD	Cardiovascular Disease
6	DL	Deep Learning
7	EA	Effect of Drug A
8	EB	Effect of Drug B
9	FH	Familial Hypercholesterolemia
10	FNN	Feedforward Neural Network
11	GBM	Gradient Boosting Machine
12	GNN	Graph Neural Network
13	HDL-C	High-Density Lipoprotein Cholesterol
14	HMG-CoA	CoA – 3-Hydroxy-3-Methylglutaryl-Coenzyme A
15	IDL	Intermediate-Density Lipoprotein
16	LDL-C	Low-Density Lipoprotein Cholesterol
17	LDLR	Low-Density Lipoprotein Receptor
18	LPL	Lipoprotein Lipase
19	ML	Machine Learning
20	NCDs	Non-Communicable Diseases
21	NPC1L1	Niemann-Pick C1-Like 1 Transporter
22	oxLDL	Oxidized Low-Density Lipoprotein
23	PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
24	PPARα	Peroxisome Proliferator-Activated Receptor Alpha
25	RF	Random Forest
26	SVM	Support Vector Machine
27	TC	Total Cholesterol
28	TG	Triglycerides
29	VLDL	Very Low-Density Lipoprotein
30	ZIP	Zero Interaction Potency

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