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REVIEW ARTICLE

Emphasize on combination drug therapy of poorly water soluble antilipemic drugs-Atorvastatin and fenofibrate with other novel treatment

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ABSTRACT
Combination drug therapy has gained significant attention in addressing hyperlipidemia, a major risk factor for cardiovascular diseases. This approach leverages the synergistic action of two or more drugs to enhance therapeutic efficacy and reduce adverse effects. Atorvastatin and fenofibrate are two widely prescribed antilipemic agents; however, their poor water solubility limits their bioavailability and therapeutic performance. Overcoming these challenges requires innovative strategies to improve solubility and dissolution rates, such as nanoparticle formulation, solid dispersions, and lipid-based drug delivery systems. Recent advancements in these techniques have shown promising results in enhancing the oral bioavailability of atorvastatin and fenofibrate, offering a more effective combination therapy. Emerging treatment strategies, such as fixed-dose combinations (FDCs) and co-amorphous systems, enhance patient compliance and therapeutic outcomes by reducing pill burden and improving drug solubility and stability. Additionally, advanced nanotechnology platforms, including polymeric nanoparticles, liposomes, and micelles, offer controlled and targeted drug delivery, further optimizing the effectiveness of combination therapies. This review emphasizes the potential of combination therapy with atorvastatin and fenofibrate for improved management of dyslipidemia and highlights novel formulation approaches to address solubility challenges. Future research should focus on clinical translation of these advanced systems to achieve better lipid profile management, reduce cardiovascular risks, and enhance patient adherence. These strategies represent a promising step towards more efficient and patient-friendly therapies for hyperlipidemia.
Keywords: *Combination drug therapy, Atorvastatin, fenofibrate, hyperlipidemia, bioavailability.*

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INTRODUCTION

Combination therapy, the use of two or more medications for the same condition, is often employed when a single agent is insufficient. Common examples include combining diuretics with calcium channel blockers for hypertension, multiple heart failure drugs targeting various pathways, or a glucocorticoid with a β2-adrenoceptor agonist for asthma. In oncology, combination therapies aim to target multiple pathways to improve cancer treatment outcomes. This approach also extends to functional urology, such as combining α1-adrenoceptor antagonists with 5α-reductase inhibitors for treating lower urinary tract symptoms in benign prostatic hyperplasia [1].

For combination therapy to be effective, co-administered drugs should not interact negatively, particularly in terms of pharmacokinetics, and should not have additive toxicity. Additionally, the drugs should ideally be compatible in a fixed-dose combination (FDC). This approach was initially pioneered in oncology in 1965, when combination chemotherapy was first used in pediatric acute leukemia. Since then, cancer research has focused on developing drugs that target multiple molecular pathways, increasing the range of potential combinations. Targeted therapies have expanded the scope of combination treatments, enabling the use of other chemotherapeutic agents alongside them.

Combination therapy offers several therapeutic benefits, including enhanced treatment outcomes, reduced clonal heterogeneity, and decreased drug toxicity by allowing lower doses of each drug. It also helps prevent drug resistance by simultaneously targeting multiple cancer cell pathways and overcoming adaptive resistance mechanisms. While combination therapies have traditionally been based on empirical trials, newer methods like the 'drug atlas' and the 'CombiPlex' platform are being used to predict synergistic pairings and optimize treatment strategies by identifying effective drug combinations and their optimal dosages for specific tissues [2].

Elevated LDL-C is a key risk factor for cardiovascular disease (CVD), and while statins effectively lower LDL-C and reduce CVD risk, significant residual risk persists, particularly in patients with metabolic syndrome. Statins have minimal effects on other lipid abnormalities, whereas fibrates improve triglycerides, HDL-C, and LDL-C, reducing cardiovascular events. Combining statins with fibrates may offer additional benefits for managing residual CVD risk in patients unresponsive to statin monotherapy.

The INTERHEART study highlights dyslipidemia as a major contributor to vascular risk, particularly in conditions like metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM). Atherogenic dyslipidemia, marked by high triglycerides, low HDL-C, and small, dense LDL particles, increases cardiovascular risk. While LDL-C reduction remains the primary goal, addressing other lipid imbalances is crucial. Statins lower LDL-C by inhibiting cholesterol synthesis, and fibrates, by activating PPARα, reduce triglycerides and raise HDL-C. Their complementary mechanisms make combining these agents an effective strategy for managing residual cardiovascular risk in patients where monotherapy is inadequate.

Fibrates and statins not only impact cholesterol metabolism but also offer pleiotropic benefits, including improved endothelial function, reduced inflammation, stabilized atherosclerotic plaques, and lowered thrombogenic risk. These effects, particularly with statins, may reduce cardiovascular morbidity and mortality. Fenofibrate's benefits extend to microvascular complications in T2DM and potentially lower CVD risk. However, further research is needed to determine if combining statins and fibrates enhances inflammatory marker reduction compared to monotherapy [3].

POOR WATER SOLUBILITY OF ANTILIPEMIC DRUGS – CHALLENGES AND LIMITATIONS

Antilipemic drugs often struggle with poor water solubility, leading to low bioavailability, unpredictable absorption, and suboptimal therapeutic outcomes. This necessitates higher doses, increasing side effects and reducing adherence. Formulating these drugs is challenging and costly, requiring advanced delivery systems to enhance solubility and efficacy.

Commonly used antilipemic drugs, including fenofibrate, atorvastatin, and simvastatin, struggle with these solubility issues. Strategies to address this include particle size reduction through micronization or nanonization to enhance dissolution, solid dispersion systems using hydrophilic carriers, and lipid-based delivery systems like self-emulsifying drug delivery systems (SEDDS) to improve absorption. Other approaches involve converting drugs into amorphous forms to increase solubility, cyclodextrin complexation to form soluble inclusion complexes, and prodrug development to enhance solubility while maintaining therapeutic efficacy [4].

Recent advancements in nanotechnology, such as nanocrystals and polymeric nanoparticles, have shown promise in improving the solubility and bioavailability of drugs like atorvastatin and fenofibrate. Emerging solutions, like lipid-polymer hybrid systems, offer enhanced drug delivery. However, these approaches face challenges, including stability issues like recrystallization in amorphous formulations, high development costs, regulatory barriers, and compatibility concerns with non-traditional excipients. Despite these hurdles, innovative delivery systems, including nanotechnology and cyclodextrin complexes, continue to evolve, offering improved solubility and therapeutic outcomes for antilipemic drugs [5, 6].

ATORVASTATIN AND FENOFIBRATE: MECHANISMS OF ACTION, INDIVIDUAL EFFICACY AND SIDE EFFECTS

Atorvastatin and fenofibrate are commonly prescribed antilipemic agents used to treat dyslipidemia, a significant risk factor for cardiovascular diseases. These drugs target distinct pathways in lipid metabolism, making them effective individually and complementary when used together.

Atorvastatin, a statin and HMG-CoA reductase inhibitor, blocks the enzyme responsible for cholesterol synthesis in the liver, reducing cholesterol production and increasing LDL receptor activity. This process enhances the removal of LDL cholesterol from the bloodstream, leading to significant reductions in LDL-C, total cholesterol, and triglycerides, along with a modest increase in HDL-C levels. Beyond lipid management, atorvastatin offers pleiotropic benefits, including improved endothelial function, reduced

inflammation and oxidative stress, and stabilization of atherosclerotic plaques, which collectively lower the risk of cardiovascular events.

Fenofibrate, a fibrate, activates PPAR-α, a nuclear receptor that regulates lipid metabolism in tissues such as the liver and muscle. This activation increases lipoprotein lipase activity, breaking down triglycerides in VLDL and chylomicrons, thereby lowering plasma triglyceride levels. Fenofibrate also alters LDL particle composition to reduce atherogenicity and raises HDL-C levels by promoting the production of apolipoproteins essential for reverse cholesterol transport. Additionally, fenofibrate offers anti-inflammatory effects by lowering C-reactive protein (CRP) levels, enhances insulin sensitivity, and reduces uric acid levels, benefiting patients with metabolic disorders or gout[7, 8].

Combining atorvastatin and fenofibrate effectively manages complex lipid profiles in conditions like metabolic syndrome or diabetes, reducing cardiovascular risk. However, careful monitoring is needed to manage potential side effects, including muscle or gastrointestinal issues[9, 10].

Rationale for Combination Therapy in Dyslipidemia Management

Combination therapy for dyslipidemia involves the use of multiple lipid-lowering medications with complementary mechanisms of action. The goal is to optimize lipid profiles, address various lipid imbalances, and lower cardiovascular risk while minimizing the side effects often seen with high-dose monotherapy.

Rationale for Combination Therapy:

Combination therapy effectively manages dyslipidemia by addressing high LDL-C, elevated TG, and low HDL-C, often inadequately controlled with monotherapy. Statins lower LDL-C, while fibrates target TG and HDL-C, creating a complementary approach with enhanced efficacy and fewer side effects. Clinical evidence supports adding fenofibrate to statins, particularly for diabetes or metabolic syndrome patients, and lower-dose statins with ezetimibe or fibrates offer alternatives for statin-intolerant individuals, improving lipid control and reducing cardiovascular risks.

Commonly Used Combinations:

Statins + Fibrates: Statins lower LDL-C, while fibrates reduce TG and raise HDL-C, effectively managing mixed dyslipidemia. Fenofibrate is safer than gemfibrozil due to a lower risk of myopathy.

Statins + Ezetimibe: Ezetimibe inhibits cholesterol absorption, complementing statins' cholesterol synthesis inhibition, ideal for patients needing additional LDL-C reduction.

Statins + Omega-3 Fatty Acids: Omega-3s (EPA, DHA) lower TG without increasing myopathy risk, benefiting severe hypertriglyceridemia management.

Statins + PCSK9 Inhibitors: PCSK9 inhibitors enhance LDL receptor recycling, significantly reducing LDL-C, suitable for familial hypercholesterolemia or statin-resistant cases.

Statins + Bile Acid Sequestrants: These drugs promote bile acid excretion, further lowering LDL-C when added to statin therapy.

Clinical Evidence Supporting Combination Therapy:

The ACCORD study found that combining statins with fibrates provided modest cardiovascular benefits in diabetic patients with high TG and low HDL-C levels. The IMPROVE-IT trial showed that adding ezetimibe to statins improved cardiovascular outcomes by further reducing LDL-C in high-risk patients after acute coronary syndrome. Similarly, the REDUCE-IT trial demonstrated that combining statins with omega-3 fatty acids significantly reduced major cardiovascular events in patients with elevated TG levels.

Safety Considerations:

Statin-fibrate combinations, especially with gemfibrozil, raise the risk of muscle toxicity, making fenofibrate a safer option. These therapies may also elevate liver enzymes and cause renal dysfunction, necessitating regular monitoring of liver and kidney function. Additionally, drug interactions between statins and other lipid-lowering agents may require dose adjustments to prevent adverse effects.**[11, 12].**

STUDIES ON ATORVASTATIN AND FENOFIBRATE COMBINATION THERAPY

The combination of atorvastatin and fenofibrate is commonly used for patients with mixed dyslipidemia, characterized by high LDL-C, elevated triglycerides (TG), and low HDL-C. This combination has been studied for its effectiveness, safety, and impact on cardiovascular health.

Rationale for Combination Therapy:

The combination of atorvastatin and fenofibrate works through complementary mechanisms, with atorvastatin lowering LDL-C by inhibiting HMG-CoA reductase, while fenofibrate activates PPAR-α to reduce triglycerides (TG) and increase HDL-C. This therapy is especially beneficial for patients with atherogenic dyslipidemia, such as those with metabolic syndrome or type 2 diabetes. It helps manage

residual cardiovascular risk, as statins alone may not sufficiently address high TG or low HDL-C levels, both of which contribute to ongoing cardiovascular risk.

Key Clinical Studies:

The ACCORD Lipid Trial (2005) found no significant cardiovascular benefit from combining simvastatin with fenofibrate in patients with type 2 diabetes, but a subgroup with high triglycerides and low HDL-C saw benefits, suggesting the combination may be effective for certain patient profiles. The FIELD Study (2005) showed that fenofibrate reduced triglycerides and non-HDL cholesterol but didn't significantly lower major cardiovascular events, though it helped reduce diabetic retinopathy, highlighting its value as an adjunct to statin therapy. The COMBOS Trial (2008) found that combining atorvastatin with fenofibrate led to greater reductions in triglycerides and non-HDL cholesterol and increased HDL-C, with similar LDL-C reductions as monotherapy. The REALIST Study (2011) showed that adding combination therapy improved triglyceride levels, HDL-C, and LDL particle composition, demonstrating its safety and efficacy for patients not fully responsive to statins. A 2014 study by Kashani et al. found that combination therapy improved lipid profiles in patients with mixed dyslipidemia and metabolic syndrome, with low risk of muscle toxicity, though caution was advised for certain patient groups.

Safety and Adverse Effects:

Muscle toxicity, including myopathy and rhabdomyolysis, is a rare but possible side effect, especially with improper dosing or renal issues. Fenofibrate is considered safer than gemfibrozil when used with statins. Mild liver enzyme elevations may occur, necessitating regular monitoring, and fenofibrate can raise serum creatinine levels, although this effect is typically reversible upon discontinuation.

Clinical Implications:

Combination therapy is suitable for patients with mixed dyslipidemia or persistent lipid abnormalities despite statin use, especially those with metabolic syndrome or type 2 diabetes. Regular monitoring of liver function, creatinine levels, and muscle symptoms is essential, particularly in older or renal-impaired patients. While the therapy offers significant lipid-lowering benefits, it requires careful management to balance efficacy and minimize risks [10, 13, 14].

Pharmacokinetics and Pharmacodynamics

The combination of atorvastatin and fenofibrate provides a synergistic approach to managing dyslipidemia by targeting various lipid abnormalities. Understanding their pharmacokinetics (PK) and pharmacodynamics (PD) is essential for optimizing their effectiveness and minimizing potential side effects.

Pharmacokinetics:

Atorvastatin is rapidly absorbed with a bioavailability of 12%, reaching peak plasma concentration within 1-2 hours. It is highly protein-bound (>98%) and metabolized in the liver by CYP3A4 into active metabolites, which prolong its inhibitory effect on HMG-CoA reductase for 20-30 hours. Atorvastatin is primarily excreted in the bile with minimal renal excretion. Fenofibrate is converted to its active form, fenofibric acid, in the intestine, with absorption enhanced by food. It is also >99% protein-bound and undergoes liver conjugation. With a half-life of about 20 hours, fenofibrate is eliminated mainly through urine, requiring dose adjustments in renal impairment.

Drug Interaction and PK Considerations:

Co-administration of atorvastatin and fenofibrate does not significantly affect the pharmacokinetics of atorvastatin. While fenofibrate may slightly increase atorvastatin levels through protein binding displacement, this effect is usually not clinically significant. However, fenofibrate can elevate serum creatinine levels, which may impact atorvastatin elimination in patients with kidney impairment. Therefore, renal function should be monitored, especially in individuals with pre-existing kidney issues.

Pharmacodynamics:

Atorvastatin lowers LDL cholesterol (LDL-C) by inhibiting HMG-CoA reductase, enhancing LDL receptor activity in the liver and increasing LDL clearance. It also modestly reduces triglycerides (TG) and raises HDL cholesterol (HDL-C), while offering cardiovascular benefits through its anti-inflammatory, antioxidative, and endothelial function-improving effects. Fenofibrate, on the other hand, activates PPAR-α to lower TG by boosting lipoprotein lipase activity and reducing liver TG production. It increases HDL-C levels by promoting apolipoproteins A-I and A-II synthesis, shifts LDL to a less atherogenic form, and reduces inflammation, collectively improving lipid profiles and lowering cardiovascular risks.

Combined Pharmacodynamics:

The combination of atorvastatin and fenofibrate offers synergistic effects, as atorvastatin primarily lowers LDL cholesterol (LDL-C), while fenofibrate reduces triglycerides (TG) and increases HDL cholesterol (HDL-C). This pairing effectively addresses mixed lipid abnormalities, particularly in conditions like atherogenic dyslipidemia. Fenofibrate complements atorvastatin by targeting residual

cardiovascular risk factors, such as high triglycerides and low HDL-C, which statins alone may not fully address, making the combination therapy valuable for reducing cardiovascular risk in patients with complex lipid profiles.

Clinical Implications:

Advantages:

The combination provides greater lipid-lowering benefits than monotherapy, with more significant reductions in triglycerides (TG) and non-HDL-C, and higher increases in HDL-C. It is especially effective for patients with mixed dyslipidemia, such as those with metabolic syndrome or diabetes.

Safety Considerations:

The combination of atorvastatin and fenofibrate slightly increases the risk of myopathy, though fenofibrate is safer than gemfibrozil. Renal function should be closely monitored, as fenofibrate can raise creatinine levels and impact atorvastatin metabolism in patients with kidney problems.

Dosing Recommendations:

Atorvastatin and fenofibrate can generally be co-administered at standard doses in most patients. Renal function should be assessed before starting therapy, particularly for fenofibrate [13, 15, 16].

Clinical Efficacy and Safety

Atorvastatin and fenofibrate combination are commonly used to treat mixed dyslipidemia, particularly in patients with high triglycerides, low HDL-C, and high LDL-C, effectively managing lipid abnormalities and reducing cardiovascular risk.

Clinical Efficacy

The combination of atorvastatin and fenofibrate offers significant lipid-lowering benefits by reducing LDL-C, lowering triglycerides, and increasing HDL-C, resulting in improved overall lipid profiles. It effectively reduces non-HDL-C, small dense LDL particles, and enhances the LDL-C to HDL-C ratio, a critical marker for cardiovascular risk. This therapy is particularly beneficial for patients with atherogenic dyslipidemia, including those with metabolic syndrome or type 2 diabetes, as evidenced by studies like the ACCORD Lipid Trial.

Key Clinical Studies

The COMBOS Trial (2008) showed that combination therapy significantly reduced triglycerides (47% vs. 29%) and increased HDL-C (19% vs. 9%) more than atorvastatin alone, with similar LDL-C reductions. The REALIST Study (2011) demonstrated that patients with residual dyslipidemia despite statin use experienced notable reductions in triglycerides and non-HDL-C, with a consistent safety profile. The ACCORD Lipid Trial (2010) found no overall cardiovascular benefits from combination therapy in patients with type 2 diabetes, but a subgroup with high triglycerides and low HDL-C showed a reduction in cardiovascular events.

Safety Considerations

Combination therapy with statins and fibrates may slightly increase the risk of myopathy, with fenofibrate being safer than gemfibrozil due to fewer interactions with statin metabolism. Regular liver function tests are recommended due to the potential for mild liver enzyme elevations. Fenofibrate may raise serum creatinine, though this is usually reversible after discontinuation, so renal function should be monitored, especially in elderly or renal-impaired patients. Mild gastrointestinal discomfort is a common side effect of fenofibrate.

Patient Selection

This combination therapy is suitable for patients with mixed dyslipidemia, atherogenic dyslipidemia from type 2 diabetes or metabolic syndrome, and those with residual lipid abnormalities despite statin use. It is not recommended for individuals with severe renal impairment, active liver disease, or a history of statin-induced myopathy.

Clinical Implications

Combination therapy offers enhanced lipid-lowering effects and potential cardiovascular benefits, especially for high-risk patients. However, it requires frequent monitoring for muscle toxicity and renal function, and its benefits are more pronounced in specific subgroups rather than the general population [10, 13, 15, 17].

Novel Treatment Approaches in Antilipemic Therapy

Recent advancements in lipid metabolism and atherosclerosis research have led to innovative therapies aimed at reducing residual cardiovascular risk and improving outcomes, especially for those unable to tolerate traditional treatments like statins and fibrates.

PCSK9 inhibitors, such as alirocumab and evolocumab, are monoclonal antibodies that enhance LDL-C clearance by preventing PCSK9 from degrading LDL receptors on liver cells. Clinical trials show they can lower LDL-C by up to 60% and reduce cardiovascular events, though their high-cost limits widespread use. Bempedoic acid works by inhibiting ATP-citrate lyase in cholesterol synthesis, providing LDL-C reduction similar to statins but without myopathy risk. It can reduce LDL-C by 17-28%, especially for statin-intolerant patients, though mild hyperuricemia or tendon issues may occur.

Inclisiran is a small interfering RNA (siRNA) that reduces PCSK9 production in the liver, offering long-term LDL-C reduction with biannual dosing. Clinical studies show it can lower LDL-C by 50%, with minimal side effects, mainly injection site reactions. Evinacumab, a monoclonal antibody targeting ANGPTL3, regulates lipid metabolism and is used to treat homozygous familial hypercholesterolemia. It can reduce LDL-C by 49% and is generally well-tolerated, though mild flu-like symptoms and gastrointestinal upset may occur.

Gene therapies like CRISPR-Cas9 and base editing are being explored to modify genes involved in lipid metabolism, such as PCSK9 and ANGPTL3, offering potential long-term solutions for genetic lipid disorders like familial hypercholesterolemia, though clinical use is still limited. Icosapent ethyl, a purified form of EPA, lowers triglycerides by reducing liver TG synthesis and enhancing clearance. The REDUCE-IT trial showed it significantly reduces cardiovascular events in high-risk patients with elevated triglycerides, and it is well-tolerated, with mild gastrointestinal issues and rare bleeding risks.

Cholesteryl Ester Transfer Protein (CETP) inhibitors, like anacetrapib, work by blocking CETP, which transfers cholesterol from HDL to LDL, leading to increased HDL-C and decreased LDL-C levels. Newer CETP inhibitors are more effective in lipid modulation and better tolerated than older drugs like torcetrapib. Apolipoprotein(a) inhibitors, such as pelacarsen, target lipoprotein(a) [Lp(a)], a cardiovascular risk factor independent of LDL-C or HDL-C, and have shown promising results in significantly reducing Lp(a) levels in early trials.

Clinical Implications:

These novel therapies offer valuable alternatives to traditional lipid-lowering treatments, especially for high-risk patients with residual cardiovascular risk. However, challenges remain in terms of cost, accessibility, and the need for long-term safety data before these therapies can be widely implemented[18-20].

Nanotechnology-Based Drug Delivery Systems

Nanotechnology is transforming antilipemic therapy by using nanoscale carriers to improve the solubility, stability, and bioavailability of lipid-lowering drugs. These systems address challenges like poor solubility in drugs such as statins and fibrates, enhance drug dissolution, and enable sustained release for longer therapeutic effects with fewer doses. Targeted delivery minimizes side effects and protects drugs from degradation, improving safety and efficacy.

Various nanotechnology-based drug delivery systems enhance lipid-lowering therapies. Lipid-based nanocarriers like Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) improve solubility and stability of drugs like atorvastatin. Polymeric nanoparticles, such as those made from PLGA, offer sustained release and targeted delivery to atherosclerotic plaques. Liposomes enhance bioavailability and reduce side effects for drugs like fenofibrate, while micelles improve absorption and tissue targeting. Dendrimers enable precise, controlled drug delivery, including for statins or siRNA. Functionalization with ligands and stimuli-responsive nanocarriers allow targeted delivery to specific tissues like the liver or plaques.

Recent advances in nanotechnology have shown promising results in antilipemic therapy. Atorvastatin nanocarriers, such as SLNs and NLCs, have improved bioavailability and targeted delivery to atherosclerotic plaques in animal models. Fenofibrate nanocrystals enhance solubility and absorption, while lipid nanoparticles are being explored for delivering small interfering RNA (siRNA) targeting PCSK9 and ANGPTL3 to reduce LDL-C and triglyceride levels.

Nanotechnology in drug delivery offers benefits such as improved solubility, targeted delivery, sustained release, and the potential for multi-drug systems, enhancing patient compliance and reducing side effects. However, challenges remain, including scalability, nanoparticle stability, high production costs, and regulatory issues due to a lack of standardized evaluation. Future advancements in multifunctional nanocarriers, using biodegradable materials, and integrating nanotechnology with diagnostic tools for cardiovascular diseases, hold great promise [18, 21, 22].

Gene Therapy

Gene therapy offers a promising approach for treating lipid disorders, particularly conditions like familial hypercholesterolemia and dyslipidemia. It works by modifying genes involved in lipid metabolism, such as PCSK9, LDL receptors, and ANGPTL3, to correct genetic defects or enhance lipid-lowering mechanisms. Gene editing technologies like CRISPR/Cas9 may offer permanent solutions for genetic lipid imbalances, aiming for long-term control of cholesterol and lipid levels rather than just symptom management.

Gene therapy for lipid disorders targets key genes like PCSK9, LDL receptor (LDLR), and ANGPTL3. Silencing the PCSK9 gene increases LDL receptor activity, improving LDL-C clearance, with therapies like siRNA (e.g., Inclisiran) showing promising results. CRISPR/Cas9 is also being explored for long-term LDL-C reduction by modifying the PCSK9 gene. For familial hypercholesterolemia (FH), gene therapies aim to restore LDLR function by delivering functional copies of the LDLR gene. Additionally, silencing or editing ANGPTL3 to boost lipoprotein lipase (LPL) activity could lower triglycerides and LDL-C, benefiting patients with hypertriglyceridemia or atherosclerosis.

Recent advances in gene therapy for lipid disorders show promising results. Inclisiran, a siRNA targeting PCSK9, has reduced LDL-C by 50% with biannual injections in clinical trials. Evinacumab, a monoclonal antibody targeting ANGPTL3, effectively lowers LDL-C and triglycerides in FH patients. CRISPR/Cas9 has shown lasting LDL-C reductions in animal models and early trials suggest potential for correcting genetic lipid disorders. Gene therapy offers long-term efficacy, targeting the root causes of lipid disorders, reducing reliance on lifelong medications, and potentially minimizing side effects compared to traditional lipid-lowering drugs.

Gene therapy faces challenges, including efficient delivery to the liver and targeted tissues, particularly for large systems like CRISPR. Long-term safety data is limited, with potential risks such as off-target effects and immune responses. Additionally, the high cost and accessibility issues hinder widespread use. Looking ahead, combining gene therapy with traditional treatments like statins could improve lipid control, and personalized medicine tailored to genetic profiles may enhance effectiveness. Expanding gene therapy to target other lipid pathways could offer broader solutions for complex dyslipidemia[18, 23-25].

CONCLUSION

In conclusion, the combination of poorly water-soluble antilipemic drugs like atorvastatin and fenofibrate offers a promising approach to effectively manage mixed dyslipidemia by addressing multiple lipid abnormalities. This combination enhances lipid-lowering effects, improving LDL-C, triglyceride, and HDL-C levels, thus reducing cardiovascular risk, especially in patients with atherogenic dyslipidemia. However, challenges such as poor solubility and potential side effects require innovative delivery systems. Novel treatments, including nanotechnology-based drug delivery, gene therapies targeting lipid metabolism pathways, and emerging treatments like PCSK9 inhibitors, bempedoic acid, and siRNA therapies, further expand the possibilities for improved lipid control. The integration of these approaches, particularly in combination with traditional therapies, holds great potential for personalized, more effective management of lipid disorders and cardiovascular risk.

ETHICS COMMITTEE APPROVAL AND PATIENT CONSENT

Not applicable as no animals or humans are used in this study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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REFERENCES

1. Michel, M.C., & Staskin, D. (2022). Study Designs for Evaluation of Combination Treatment: Focus on Individual Patient Benefit. Biomed.,10:270.
2. Ayoub, N.M. (2021). Editorial: Novel Combination Therapies for the Treatment of Solid Cancers. Front. Oncol.,11:708943.
3. Catherine, F., &Bart, S. (2009). Combination therapy of statins and fibrates in the management of cardiovascular risk. Curr. Opin. Lipidol.,20(6):505–511.
4. Huang, Y., & Dai, W.G. (2014). Fundamental aspects of solid dispersion technology for poorly soluble drugs. ***Acta.*** *Pharm. Sin. B.*,4(1):18-25.

5. Savjani, K. T., Anuradha, K, G., &Jignasa, K. S. (2012).Drug solubility: Importance and enhancement techniques. *ISRN. Pharm.*Article ID 195727.
6. Müller, R. H., Jacobs, C., &Oliver, K. (2000).Nanosuspensions for the formulation of poorly soluble drugs. *Int. J. Pharm*.,196(2):149-157.
7. Cesare, R. S. (2014). The pharmacology of statins. *Pharmacol. Res.*,88:3-11.
8. Staels, B., & Fruchart, J. C. (2005).Mechanisms of action of fibrates: Selective PPAR modulators (SPPARMs). ***J.** Lipid. Res.*,46(5):933-943.
9. Barter, P. J., & Rye, K.A. (2006).The rationale for using apoA-I as a clinical marker of cardiovascular risk. ***J.** Internal. Med.*,259(5):447-454.
10. Keech, A., Simes, R. J., Barter, P., Best, J., Scott, R., Taskinen, M. R., Forder, P., Pillai, A., Davis, T., Glasziou, P., Drury, P., Kesäniemi, Y. A., Sullivan, D., Hunt, D., Colman, P., d'Emden, M., Whiting, M., Ehnholm, C., &Laakso, M. (2005).Effects of long-term fenofibrate therapy on cardiovascular events. *The Lancet.*,366(9500):1849-1861.
11. Reiner, Ž. (2013). Combined therapy in the management of dyslipidemia. *Front. Cardiovas. Medicine.*, 67(2):185-192.
12. Robert, N. S., Philip, M. M., Ross, J. S. Jr. (2013).Beyond statins: lipid management to reduce cardiovascular risk. Pharmacotherapy.,33(7):754-764.
13. Després, J. P., Lemieux, I., Salomon, H., Delaval, D. (2002).Effects of micronized fenofibrate versus atorvastatin in the treatment of dyslipidaemic patients with low plasma HDL-cholesterol levels: a 12-week randomized trial. J Intern Med.,251(6):490-499.
14. Gissette, R. S., Carlos, R. C., Henry, N. G. (2011).Combination therapy with statin and fibrate in patients with dyslipidemia associated with insulin resistance, metabolic syndrome and type 2 diabetes mellitus. Expert. Opin. Pharmacother.,12(9):1429-1438.
15. Peter, H. Jones., Anne, C. G., Howard, R. K., Maureen, T. K., Carolyn, M. S., James, C. S., Darryl, J. Sleep. (2010).Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. Am. Heart. J.,160(4):759-766.
16. Davidson, M. H. (2001).Rosuvastatin and fenofibrate: Pharmacokinetics and drug-drug interactions. *Cardiovas. Drugs. Ther.*,15(3):287-294.
17. Ginsberg, H. N., Marshall, B. E., Laura, C. L., John, R. C., Lawrence, A. L., Peter, L., William, T. F., John, B. B., Hertzel, C. G., Jeffrey, P., Richard, H. G., Faramarz, I. B., Thomas, B. J., David, C. G., William, C. C., Denise, G. S. M., Robert, P. B. (2010).Effects of combination lipid therapy in type 2 diabetes mellitus. N. Engl. J. Med.,362(17):1563-1574.
18. Ray, K. K., Ulf, L., Lawrence, A. L., David, K., Robert, D., Mahir, K., Tim, H., Roland, P. T. T., Traci, T., Frank, L. J. V., Peter, W., Scott, W. R., John, J. P. K. (2017). Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N. Engl. J. Med.,376(15):1430-1440.
19. Bhatt, D. L., Gabriel, S. P., Michael, M., Eliot, A. B., Terry, A. J., Steven. B. K., Ralph, T. D. (2019).Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N. Engl. J. Med.,380(1):11-22.
20. Banach, M., & Penson, P. E. (2021). Bempedoic acid: A new era in lipid management. *Cardiovasc. Res.*,117(9):2012-2022.
21. Aziz, U., Muneeb, U., Sung, I. L. (2024).Recent advancements in nanotechnology based drug delivery for the management of cardiovascular disease. Curr. Probl. Cardiol.,49(4):102396.
22. Alexander, S. R. P., Tarini, D., Natalie, Y. L. P., Vishalli, D., Kimberley, Y. L. P., Cai, L. Y., Shawn, J. J. L., George, W. Y., Boon, H. B., Dinesh, K. S. (2024). Nanoparticles as Drug Delivery Systems for the Targeted Treatment of Atherosclerosis. Molecules., 29(12):2873.
23. Marcin, G., Himadri, R., Shalini, B., Seppo, Y. H. (2004).Gene therapy for cardiovascular diseases. Curr. Pharm. Des.,10(4):407-423.
24. Wei, S. S., Yin, Q. T., Chee, K. K., Bey-Hing, G., Serena, Z., Kamal, D, Dinesh, K. C., Acharaporn, D., Surasak, S., Pochamana, P., Wei, H. Y. (2021).Harnessing the Potential of CRISPR/Cas in Atherosclerosis: Disease Modeling and Therapeutic Applications. Int J Mol Sci. 22(16):8422.
25. Raal, F. J., Robert, S. R., Laurens, F. R., Kees, H. G., John, J. P. K., Paolo, R., Shazia, A. (2020). Evinacumab for homozygous familial hypercholesterolemia. N. Engl. J. Med., 383(8):711-720.