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Commentary

Advances in Lipid-Lowering Therapies: Evolving Strategies in Cardiovascular Disease Prevention

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DESCRIPTION

Cardiovascular Disease (CVD) is a primary cause of death globally, largely driven by atherosclerosis, which is often accelerated by dyslipidemia condition marked by high levels of Low-Density Lipoprotein Cholesterol (LDL-C) and other lipoprotein abnormalities. Lowering lipid levels, particularly LDL-C, has long been a fundamental of CVD prevention. As our understanding of lipid biology and genetics has deepened, novel therapies have emerged to target cholesterol more effectively. Recent advances in lipid-lowering treatments aim to complement or improve upon traditional therapies, broadening options for patients who may not respond well to conventional treatments like statins. This article explores key innovations in lipid-lowering therapy, their mechanisms of action and their potential impact on cardiovascular outcomes.

The role of lipids in cardiovascular disease

Lipid abnormalities are among the most significant risk factors for atherosclerosis and related cardiovascular events. LDL-C is particularly harmful due to its propensity to accumulate in the arterial walls, leading to plaque formation, inflammation and, ultimately, arterial narrowing or rupture. High levels of triglycerides and low levels of High-Density Lipoprotein Cholesterol (HDL-C) are also associated with CVD, but LDL-C remains the primary therapeutic target. Traditional therapies, primarily statins, have proven effective in reducing LDL-C and lowering the risk of heart attacks, strokes and other CVD events. However, despite statin use, many patients fail to reach optimal lipid levels or suffer from residual risk, necessitating novel approaches.

Traditional therapies and their limitations

Statins are HMG-CoA reductase inhibitors that work by reducing the liver's production of cholesterol, effectively lowering LDL-C levels by approximately 20%-50%. Statins also offer anti-inflammatory benefits that contribute to cardiovascular protection. However, some patients are statin-intolerant or experience side effects like muscle pain, liver enzyme elevation, or increased diabetes risk. Additionally, statins may not sufficiently lower LDL-C in high-risk patients, such as those with Familial Hypercholesterolemia (FH) or in individuals at extreme risk due to other underlying conditions.

Ezetimibe, another traditional therapy, works by inhibiting cholesterol absorption in the intestine. When combined with statins, ezetimibe provides further LDL-C reduction but is generally less potent than newer agents. While these drugs form the foundation of lipid-lowering strategies, they have limitations that spurred the development of novel therapies.

PCSK9 inhibitors: A innovative advance

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) inhibitors represent one of the most significant advances in lipid-lowering therapy over the past decade. PCSK9 is a protein that binds to LDL receptors on the liver, leading to their degradation and reducing the liver's ability to remove LDL-C from the bloodstream. PCSK9 inhibitors, such as evolocumab and alirocumab, are monoclonal antibodies that bind to and inhibit PCSK9, thereby increasing LDL receptor levels and enhancing LDL-C clearance.

Inclisiran: A small interfering rna approach

Inclisiran is a novel lipid-lowering agent that employs small interfering RNA (siRNA) technology to reduce PCSK9 production in the liver. Delivered via injection, inclisiran silences the *PCSK9* gene, leading to a sustained reduction in PCSK9 levels and a corresponding drop in LDL-C. Unlike PCSK9 inhibitors, which require frequent administration, inclisiran is dosed only twice per year, making it a more convenient option for patients. The ORION clinical trials demonstrated inclisiran's efficacy in reducing LDL-C by around 50%, with a favorable safety profile. Given its unique mechanism and dosing regimen, inclisiran is a potential

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alternative for patients who require potent lipid-lowering but prefer less frequent treatment.

Bempedoic acid: An oral option

Bempedoic acid is a relatively recent addition to the lipid-lowering arsenal, targeting Adenosine Triphosphate Citrate Lyase (ACL), an enzyme upstream of HMG-CoA reductase in the cholesterol synthesis pathway. By inhibiting ACL, bempedoic acid reduces LDL-C production in the liver. Since bempedoic acid requires activation by the liver and not by muscle tissue, it has a lower risk of muscle-related side effects compared to statins, making it an appealing choice for statin-intolerant patients.

Novel approaches on the horizon: Gene therapy and antisense oligonucleotides

Gene therapy and Antisense Oligonucleotides (ASOs) represent the frontier of lipid-lowering therapies, targeting the genetic basis of hyperlipidemia. ASOs, such as mipomersen, work by binding to messenger RNA (mRNA) and inhibiting the production of specific proteins involved in lipid metabolism. Mipomersen, for example, targets Apolipoprotein B (ApoB), a key protein in LDL particle formation, reducing LDL-C levels in patients with severe forms of hypercholesterolemia.

Clinical implications and future directions

The evolution of lipid-lowering therapies has led to substantial improvements in cardiovascular risk reduction, especially for patients with complex lipid profiles or those at high risk for CVD. Combination therapies, which use statins alongside newer agents like PCSK9 inhibitors, inclisiran, or bempedoic acid, have become a favored approach to achieving optimal LDL-C targets. This multi-pronged strategy allows for more significant lipid reduction without necessarily increasing the dose of each individual drug, potentially minimizing side effects.

As lipid-lowering therapies evolve, questions regarding long-term safety, accessibility and cost-effectiveness continue to shape their clinical adoption. PCSK9 inhibitors and gene therapies, for example, have shown tremendous potential but are costly, limiting their use to specific high-risk populations. Future research aims to make these therapies more accessible and investigate whether lowering LDL-C to very low levels provides sustained benefits without adverse effects.

CONCLUSION

Advances in lipid-lowering therapies have transformed cardiovascular disease prevention, offering new hope for patients who struggle with traditional treatments or require more potent interventions. From PCSK9 inhibitors to inclisiran and gene-based approaches, these therapies represent a significant leap forward in managing cholesterol levels and reducing CVD risk. As these treatments become more refined and accessible, they hold the potential to improve outcomes for a broader range of patients, contributing to a decrease in the global burden of cardiovascular disease.