



Emerging Role of PCSK9 Inhibitors in Lipid Management

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DESCRIPTION

PCSK9 inhibitors have introduced a transformative approach to lipid management, especially for patients who fail to achieve sufficient reductions in Low-Density Lipoprotein Cholesterol (LDL-C) levels with statin therapy alone. These agents, designed as monoclonal antibodies, specifically target Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), a protein that plays a critical role in lipid metabolism. PCSK9 binds to LDL receptors on hepatocytes, promoting their degradation. This reduces the liver's capacity to remove LDL-C from the bloodstream. By blocking the activity of PCSK9, these drugs increase the number of available LDL receptors on liver cells, thereby enhancing the clearance of LDL-C and lowering serum cholesterol levels more effectively. The development of PCSK9 inhibitors such as evolocumab and alirocumab has been underpinned by rigorous clinical trials. Two of the most influential studies FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) and ODYSSEY OUTCOMES have demonstrated significant reductions in major cardiovascular events among high-risk patients receiving PCSK9 inhibitors. The benefits were particularly evident in patients with established Atherosclerotic Cardiovascular Disease (ASCVD) and those with familial hypercholesterolemia, populations that often fail to reach LDL-C targets with statins and other conventional lipid-lowering therapies.

When added to background statin therapy, PCSK9 inhibitors have shown the ability to reduce LDL-C levels by up to 60 percent an effect that surpasses that of any currently available oral lipid-lowering medication. This profound LDL-C reduction correlates with a notable decrease in the incidence of myocardial infarction, stroke and cardiovascular death, reinforcing the role of PCSK9 inhibitors in secondary prevention. Additionally, these agents are generally well tolerated. The most frequently reported adverse effects are mild and include injection site reactions, nasopharyngitis and flu-like symptoms, making them a safe long-term option for most patients. Beyond LDL-C lowering, PCSK9 inhibitors also influence other lipid

parameters. One of the most significant ancillary effects is the reduction of lipoprotein an independent and genetically determined risk factor for cardiovascular disease. Elevated levels are associated with increased risk of atherosclerosis and are notoriously resistant to treatment with traditional lipid-lowering drugs. PCSK9 inhibitors offer a promising solution for this unmet clinical need, potentially broadening their utility among patients with elevated Lp.

Despite their therapeutic benefits, the high cost of PCSK9 inhibitors has limited their widespread adoption, particularly in low- and middle-income countries. Health systems globally continue to assess the cost-effectiveness of these agents, weighing their clinical advantages against economic constraints. However, as patents begin to expire and biosimilar versions enter the market, prices are expected to decline. This could significantly improve accessibility and allow broader implementation across various healthcare settings. Additionally, value-based pricing models and negotiations with pharmaceutical companies are being explored to facilitate more equitable access. Efforts to improve patient adherence have also led to the development of alternative drug delivery systems. Inclisiran, a Small Interfering RNA (siRNA) therapeutic, works by silencing the PCSK9 gene in hepatocytes, resulting in long-lasting suppression of PCSK9 production. Administered via subcutaneous injection just twice a year, inclisiran offers a more convenient option compared to the biweekly or monthly dosing of monoclonal antibodies. This could substantially improve treatment adherence, particularly in patients with chronic cardiovascular disease who require long-term lipid management.

Looking further ahead, gene-editing technologies such as CRISPR-Cas9 are being investigated as a means to achieve permanent reduction in PCSK9 expression. Preclinical and early-phase studies have shown promise, suggesting that a single intervention might provide lifelong cholesterol control. While still experimental, such approaches have the potential to revolutionize lipid management. Nevertheless, long-term safety, ethical considerations and regulatory challenges must be addressed before clinical application becomes feasible. In conclusion, the introduction of PCSK9 inhibitors represents a

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major advancement in cardiovascular pharmacotherapy. They offer an effective and safe option for lowering LDL-C and reducing cardiovascular risk, especially in high-risk populations who do not reach lipid targets with conventional therapy. While statins remain the cornerstone of lipid management, PCSK9 inhibitors have become an essential adjunct for patients

requiring more intensive therapy. As evidence continues to accumulate and accessibility improves, PCSK9-targeting therapies are poised to play an increasingly central role in global lipid-lowering strategies, ultimately helping reduce the burden of cardiovascular disease worldwide.