Novel Lipid-Lowering Therapies Expand Treatment Options

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> Despite established guidelines and available pharmacotherapy, a substantial proportion of patients at high cardiovascular risk do not achieve optimal lipid targets. The emergence of novel therapeutic classes, such as small interfering RNA (siRNA) and oral proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, presents new avenues for more effective and convenient lipid management.

KEY TAKEAWAYS

- The Pivot: New drug classes, beyond statins and injectables, are entering the lipid control landscape, offering alternative mechanisms of action and administration routes.
- The Data: Clinical trials have demonstrated reductions in LDL-C of up to 50-60% with certain novel agents, often in patients inadequately controlled by existing therapies.
- The Action: Clinicians should familiarise themselves with the mechanisms, efficacy, and safety profiles of these emerging therapies to identify appropriate patient cohorts for their use.

Current lipid-lowering strategies primarily focus on statins, ezetimibe, and injectable PCSK9 inhibitors to reduce low-density lipoprotein cholesterol (LDL-C). While highly effective for many, challenges remain in patients with statin intolerance, very high baseline LDL-C, or those requiring more intensive reductions to meet guideline-recommended targets. These unmet needs have driven the development of therapies with distinct mechanisms of action.

Expanding the Therapeutic Horizon

One area of significant development is the emergence of small interfering RNA (siRNA) therapies. These agents work by targeting messenger RNA (mRNA) in hepatocytes, preventing the translation of specific proteins involved in lipid metabolism. For instance, inclisiran, an siRNA targeting PCSK9 mRNA, leads to sustained reductions in PCSK9 protein levels, thereby increasing hepatic LDL receptor expression and lowering circulating LDL-C. Clinical trials have shown that inclisiran administered subcutaneously twice yearly can achieve LDL-C reductions of approximately 50% in patients with atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolaemia (HeFH) who are already on maximally tolerated statin therapy.1 This sustained effect offers a significant advantage in terms of adherence compared to daily oral medications or more frequent injectable therapies.

Another promising class involves oral PCSK9 inhibitors. While injectable PCSK9 monoclonal antibodies (alirocumab, evolocumab) have demonstrated substantial LDL-C lowering and cardiovascular event reduction, their parenteral administration can be a barrier for some patients. Oral PCSK9 inhibitors, such as those targeting the interaction between PCSK9 and the LDL receptor, are under investigation. Early-phase studies have indicated that these oral agents can

achieve dose-dependent reductions in LDL-C, potentially offering a more convenient option for patients requiring intensive lipid lowering. The development of an oral formulation could broaden access and improve patient preference, particularly for long-term management.

Beyond PCSK9 inhibition, other novel targets are being explored. Angiopoietin-like 3 (ANGPTL3) inhibitors, such as evinacumab, target a protein that inhibits lipoprotein lipase and endothelial lipase, leading to reduced levels of triglycerides and LDL-C. Evinacumab is approved for homozygous familial hypercholesterolaemia (HoFH), a severe genetic disorder, where it has shown significant reductions in LDL-C, even in patients with defective LDL receptors.2

Olpasiran, an siRNA targeting lipoprotein(a) [Lp(a)], is also in advanced clinical development. Elevated Lp(a) is an independent, genetically determined risk factor for ASCVD, and current therapies have limited impact on its levels. Olpasiran has demonstrated substantial and sustained reductions in Lp(a) levels, potentially addressing a previously intractable risk factor.3

The safety profiles of these novel agents are a critical consideration. Inclisiran has generally been well-tolerated, with injection site reactions being the most common adverse event.1 Data on long-term cardiovascular outcomes for some of these newer agents are still accumulating, but the consistent and significant LDL-C reductions observed across various patient populations suggest a favourable impact on cardiovascular risk, consistent with the established relationship between LDL-C lowering and ASCVD event reduction. The expansion of the therapeutic armamentarium provides clinicians with more tools to individualise lipid-lowering therapy, addressing specific patient needs and genetic predispositions.

Another emerging area involves therapies targeting adenosine triphosphate-citrate lyase (ACL). Bempedoic acid, an oral ACL inhibitor, reduces cholesterol synthesis in the liver upstream of HMG-CoA reductase, the target of statins. It is approved for patients with HeFH or established ASCVD requiring additional LDL-C lowering, particularly those with statin intolerance. Clinical trials have shown that bempedoic acid can reduce LDL-C by approximately 18-28% when added to maximally tolerated statin therapy or as monotherapy. 4 Its unique mechanism of action makes it a valuable option for patients unable to tolerate statins due to muscle-related adverse events.

Future Directions and Clinical Integration

The evolving landscape of lipid-lowering therapies offers exciting prospects for improving cardiovascular outcomes. As more data emerge on long-term safety and cardiovascular event reduction, clinicians will gain further confidence in integrating these agents into routine practice. A key challenge will be to identify the optimal patient populations for each therapy, considering factors such as baseline lipid levels, genetic predispositions, comorbidities, and patient preferences. Cost-effectiveness will also play a significant role in determining widespread accessibility and adoption.

Future research will likely focus on combination therapies, exploring synergistic effects between different mechanisms of action to achieve even greater reductions in lipid parameters and cardiovascular risk. The development of precision medicine approaches, guided by genetic testing and advanced risk stratification, will further refine treatment selection, ensuring that patients receive the most effective and tolerable therapies tailored to their individual needs. This expansion of therapeutic options underscores a paradigm shift towards more comprehensive and individualized management of dyslipidemia.

CLINICAL IMPLICATIONS

The arrival of new lipid-lowering agents, particularly those with novel mechanisms and administration schedules, will necessitate a re-evaluation of current treatment algorithms. For clinicians, the challenge will be to integrate these therapies effectively into practice, identifying which patients stand to benefit most from a twice-yearly subcutaneous injection like inclisiran, or a potential future oral PCSK9 inhibitor, especially when statins and ezetimibe are insufficient or poorly tolerated. The sustained LDL-C reduction offered by inclisiran, for example, could significantly improve adherence in a patient population often burdened by polypharmacy and complex regimens. This is not merely about adding another drug; it is about optimising the patient journey towards guideline-recommended lipid targets.

From an industry perspective, the landscape is becoming increasingly competitive. While statins remain the bedrock of primary prevention, the market for secondary prevention and high-risk primary prevention is expanding. Companies developing these novel agents are vying for market share in a segment where unmet needs persist. The focus will shift towards demonstrating not just LDL-C reduction, but also hard cardiovascular outcomes, and crucially, cost-effectiveness. Payers will demand clear evidence of improved patient outcomes and reduced healthcare resource utilisation to justify the premium pricing associated with these innovative therapies. The success of these agents will depend on their ability to demonstrate a compelling value proposition beyond mere efficacy.

For patients, these developments offer renewed hope, particularly for those who have struggled to achieve their lipid goals with existing treatments. The prospect of an oral PCSK9 inhibitor could be a game-changer for individuals averse to injections, while a twice-yearly injection could simplify life for others. Addressing high Lp(a) with agents like olpasiran could also provide a sense of agency for patients with a previously untreatable genetic risk factor. However, patient education will be paramount. Understanding the benefits, potential side effects, and the importance of adherence, regardless of the administration route, will be key to maximising the real-world impact of these therapeutic advancements.

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