



Original Article

Addressing Residual Cardiovascular Risk: Contemporary Advances in Lipid Management

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ABSTRACT

Dyslipidemia is a major modifiable driver of atherosclerotic cardiovascular disease (ASCVD). Although statins and established lipid-lowering therapies have substantially reduced cardiovascular events, a significant proportion of high-risk patients continue to experience recurrent events despite achieving guideline-recommended LDL-C targets. This residual cardiovascular risk arises from multiple pathways including triglyceride-rich lipoproteins, remnant cholesterol, lipoprotein(a), inflammation, and metabolic dysregulation. This narrative review examines the pathophysiology of residual risk, evolving biomarkers, contemporary management strategies, and emerging precision therapies. Special emphasis is given to real-world challenges in low- and middle-income countries (LMICs) and South Asia. A personalized, multi-targeted approach is essential to further reduce the global burden of ASCVD.

Keywords: Dyslipidemia, Residual cardiovascular risk, PCSK9 inhibitors, Inclisiran, Bempedoic acid, Lipoprotein(a), Precision lipidology, LMICs.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality worldwide.¹ Dyslipidemia is one of its most powerful modifiable risk factors.² Intensive LDL-C lowering has dramatically improved outcomes over the past three decades.³ However, many patients continue to experience recurrent cardiovascular events despite achieving optimal LDL-C targets — a phenomenon known as residual cardiovascular risk.⁴

This residual risk reflects the multifactorial nature of atherosclerosis and involves triglyceride-rich lipoproteins, remnant cholesterol, lipoprotein(a) [Lp(a)], chronic inflammation, endothelial dysfunction, and metabolic dysregulation.⁵⁻⁷ The emergence of precision lipidology represents a paradigm shift from uniform LDL-C reduction toward individualized, biomarker-guided, and mechanism-specific interventions.⁸ Novel agents such as PCSK9 inhibitors, inclisiran, bempedoic acid, and therapies targeting ApoC-III, ANGPTL3, and Lp(a) have broadened the therapeutic landscape.⁹⁻¹² This review synthesizes current evidence and discusses practical implementation, with particular attention to LMIC settings.¹³

METHODS

A structured narrative review was performed. Literature was searched in PubMed, Embase, and Cochrane Library from January 2015 to June 2026. Priority was given to randomized controlled trials, meta-analyses, systematic reviews, and major international guidelines.

Pathophysiology and Key Lipid Biomarkers

The pathogenesis of atherosclerosis is fundamentally driven by the retention and oxidative modification of apolipoprotein B-containing lipoproteins within the arterial intima. LDL particles play a central causal role in this process. Once retained in the subendothelial space, LDL undergoes oxidation and other modifications that trigger an inflammatory cascade, leading to endothelial dysfunction, monocyte recruitment, foam cell formation, and progressive plaque development.¹⁴

While LDL-C has traditionally been the main therapeutic target, it has important limitations as a marker of atherogenic risk. Each atherogenic lipoprotein particle (LDL, VLDL, IDL, and Lp(a)) contains exactly one molecule of apolipoprotein B (ApoB). Therefore, **ApoB** concentration provides a more accurate assessment of the total number of atherogenic particles

in circulation. This becomes particularly relevant in patients with diabetes, obesity, metabolic syndrome, and hypertriglyceridemia, where LDL particles are often small and dense, and LDL-C levels may significantly underestimate the true atherogenic burden.¹⁵ Non-HDL-C, which represents the cholesterol content of all atherogenic lipoproteins, serves as a simple, widely available, and practical alternative to ApoB in routine clinical practice.

Beyond LDL-C and ApoB, several other lipid fractions contribute importantly to residual cardiovascular risk. **Triglyceride-rich lipoproteins** (TRLs) and their remnants promote atherosclerosis through multiple mechanisms, including direct endothelial toxicity, induction of inflammation, and generation of highly atherogenic remnant particles.¹⁶ Elevated remnant cholesterol has emerged as an independent predictor of cardiovascular events, even when LDL-C is well controlled.

Lipoprotein(a) [Lp(a)] is a unique, genetically determined lipoprotein that combines structural elements of LDL with those of plasminogen. It exerts pro-atherogenic, pro-thrombotic, and pro-inflammatory effects. Elevated Lp(a) levels are associated with premature ASCVD, calcific aortic valve stenosis, and increased risk of thrombosis.^{17,18} Importantly, Lp(a) levels are largely unaffected by conventional lipid-lowering therapies such as statins.

Chronic low-grade **vascular inflammation** also plays a critical role in plaque progression and instability. The landmark CANTOS trial demonstrated that targeted anti-inflammatory therapy (canakinumab) could reduce cardiovascular events independent of lipid lowering, highlighting inflammation as a key driver of residual risk.¹⁹

Finally, **insulin resistance and metabolic dysregulation** constitute a major contributor to residual risk. This cluster includes hypertriglyceridemia, low HDL-C, increased small dense LDL particles, and systemic inflammation. These abnormalities are particularly prevalent in South Asian populations, who often develop metabolic syndrome and premature ASCVD at lower body mass indices compared to Western populations.^{13,20}

Understanding these diverse pathophysiological pathways is essential for moving beyond simplistic LDL-C reduction toward a more comprehensive, precision-based approach to lipid management.

Risk Stratification and Treatment Targets

Accurate cardiovascular risk stratification is the cornerstone of effective and individualized lipid management. It allows clinicians to determine the intensity of therapy, set realistic targets, and allocate healthcare resources efficiently. Without proper risk assessment, both undertreatment of high-risk patients and overtreatment of low-risk individuals can occur, leading to suboptimal outcomes and inefficient use of limited resources.

Two widely validated tools are commonly used in clinical practice: the **SCORE2** system (recommended by the European Society of Cardiology) and the **ASCVD Risk Estimator** (widely used in the United States and many other regions).^{2,21} These calculators integrate multiple risk factors including age, sex, smoking status, blood pressure, diabetes, and lipid levels to estimate 10-year risk of fatal or non-fatal cardiovascular events. Based on this assessment, patients are categorized into low, moderate, high, or very high-risk groups.

Current major international guidelines advocate progressively stringent LDL-C targets according to the patient's risk category. Very high-risk patients (e.g., those with established ASCVD, familial hypercholesterolemia, or diabetes with target organ damage) have the most aggressive targets, while moderate-risk individuals have comparatively less stringent goals. In addition to LDL-C, **ApoB** and **non-HDL-C** are increasingly recognized as valuable secondary targets. These markers are particularly useful in patients with metabolic syndrome, diabetes, or hypertriglyceridemia, where LDL-C may underestimate the true atherogenic burden due to the presence of small, dense LDL particles.¹⁵

The following table summarizes the currently recommended LDL-C targets along with additional markers:

Risk Category	LDL-C Target	Additional Targets
Very High Risk	< 55 mg/dL	ApoB < 65 mg/dL
High Risk	< 70 mg/dL	ApoB < 80 mg/dL
Moderate Risk	< 100 mg/dL	Non-HDL-C < 130 mg/dL

Treatment Algorithm

The management of dyslipidemia should follow a structured, stepwise, and patient-centered approach that integrates lifestyle interventions with pharmacological therapy, guided by the patient's global cardiovascular risk category and LDL-C (or alternative targets) response. This algorithm is designed to achieve evidence-based targets while balancing efficacy, safety, tolerability, and cost-effectiveness.

Step 1: Foundation – Intensive Lifestyle Modification

Lifestyle interventions form the cornerstone of dyslipidemia management and should be emphasized at every stage. This includes adoption of a Mediterranean-style or heart-healthy diet rich in fruits, vegetables, whole grains, and healthy fats;

regular aerobic and resistance exercise (at least 150 minutes per week); achievement and maintenance of healthy body weight; and complete smoking cessation. These measures not only improve lipid profiles but also favorably influence multiple cardiometabolic risk factors, including blood pressure, glucose metabolism, and inflammation. Patient education, behavioral counseling, and regular follow-up are essential to improve long-term adherence.

Step 2: First-Line Pharmacotherapy – High-Intensity Statin For most patients at moderate to very high cardiovascular risk, high-intensity statin therapy (e.g., atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily) is recommended as the initial pharmacological intervention. Statins remain the most evidence-based, cost-effective, and widely available option, with proven benefits in both primary and secondary prevention.³

Step 3: Add Ezetimibe If the LDL-C target is not achieved despite maximally tolerated statin therapy, ezetimibe should be added as the preferred second-line agent. Ezetimibe inhibits intestinal cholesterol absorption and provides an additional 15–25% LDL-C reduction when used in combination with statins.²² This combination is generally well-tolerated and represents a rational, cost-effective escalation step before considering more expensive therapies.

Step 4: Escalation in Very High-Risk Patients In patients classified as very high risk (e.g., recent acute coronary syndrome, multiple prior events, or familial hypercholesterolemia) who remain above target despite statin plus ezetimibe, addition of a PCSK9 inhibitor (evolocumab or alirocumab) or inclisiran is recommended. These agents provide substantial additional LDL-C reduction (50–70%) and have demonstrated cardiovascular outcome benefits in large trials.^{9–11} Inclisiran offers the advantage of twice-yearly dosing, which may significantly improve long-term adherence.

Step 5: Statin Intolerance Pathway For patients who are truly statin-intolerant (confirmed after careful evaluation, including trial of multiple statins at lower doses), bempedoic acid, with or without ezetimibe, serves as an important oral alternative.¹² This agent inhibits cholesterol synthesis upstream of HMG-CoA reductase and is associated with a lower risk of muscle-related adverse effects compared to statins.

Step 6: Management of Persistent Hypertriglyceridemia In patients with elevated triglycerides despite optimal statin therapy (typically ≥ 135 –150 mg/dL in high-risk individuals), addition of icosapent ethyl (high-dose purified eicosapentaenoic acid) should be considered, based on the significant cardiovascular risk reduction demonstrated in the REDUCE-IT trial.²³

This stepwise algorithm allows clinicians to escalate therapy rationally according to individual risk, treatment response, tolerability, and affordability, thereby optimizing both clinical outcomes and resource utilization.

Pharmacological Therapy

Comparative Overview of Major Lipid-Lowering Agents

Drug Class /	Mechanism	LDL-C Reduction	Key Outcome Trials	Major Advantages	Key Limitations / Side Effects	Preferred Clinical Setting
Statins	HMG-CoA reductase inhibition	30–60%	Multiple meta-analyses ³	Robust evidence, pleiotropic effects, low cost	Muscle symptoms (~5–10% true intolerance), adherence	First-line for nearly all patients
Ezetimibe	NPC1L1 inhibitor	15–25% (add-on)	IMPROVE-IT ²²	Safe, oral, well-tolerated	Modest additional reduction	Add-on to statin when target not achieved
PCSK9 Inhibitors	Prevent LDL receptor degradation	50–70%	FOURIER, ⁹ ODYSSEY ¹⁰	Highly potent, proven CV benefit	High cost, subcutaneous injections	Very high-risk, familial hypercholesterolemia
Inclisiran	siRNA inhibiting hepatic PCSK9	~50%	ORION program ¹¹	Twice-yearly dosing, excellent adherence	Cost, injection-site reactions	Patients with poor long-term adherence
Bempedoic Acid	ATP-citrate lyase inhibitor	15–25%	CLEAR Outcomes ¹²	Oral, lower muscle-related side effects	Hyperuricemia, rare tendon rupture	Statin-intolerant patients
Icosapent Ethyl	Anti-inflammatory & TG effects	Minimal on LDL	REDUCE-IT ²³	CV risk reduction in	Cost, mild bleeding risk	Elevated triglycerides despite statin

				high-TG patients		
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Residual Cardiovascular Risk

Despite significant reductions in LDL-C achieved with current best therapies, many patients continue to face a clinically meaningful residual risk of future cardiovascular events. This residual risk is driven by elevated triglyceride-rich lipoproteins and remnant cholesterol,¹⁶ raised levels of lipoprotein(a),^{17, 18} persistent vascular inflammation (as convincingly demonstrated by the CANTOS trial with canakinumab),¹⁹ and multiple metabolic abnormalities including insulin resistance. These mechanisms appear especially relevant in South Asian populations, who often exhibit a constellation of metabolic disturbances and a markedly higher incidence of premature ASCVD.^{13, 20}

Lp(a) Lowering Strategies Lipoprotein(a) [Lp(a)] is minimally responsive to conventional lipid-lowering agents. While PCSK9 inhibitors offer modest reduction (approximately 20–30%),⁹ novel RNA-targeted therapies such as pelacarsen and olpasiran have achieved dramatic reductions of 80–95% in Phase 2/3 clinical studies. These agents are currently undergoing large-scale cardiovascular outcome trials.^{17, 26, 27} In patients with extremely elevated Lp(a) levels and recurrent events, lipoprotein apheresis remains a therapeutic option in specialized centers where it is available.

Emerging Therapies

The therapeutic pipeline for lipid disorders is rapidly expanding. ApoC-III inhibitors have shown potent triglyceride-lowering effects and may prove transformative in patients with severe hypertriglyceridemia and familial chylomicronemia syndrome.²⁴ ANGPTL3 inhibitors demonstrate the ability to lower both LDL-C and triglycerides independently of LDL receptor activity, making them particularly valuable in homozygous familial hypercholesterolemia.²⁵ Lp(a)-targeted therapies, including pelacarsen²⁶ and olpasiran,²⁷ have produced impressive reductions in circulating Lp(a) levels. In the longer term, gene editing technologies and advanced RNA-based platforms hold the potential for more durable modulation of atherogenic pathways.²⁸

Special Populations

Dyslipidemia management must be carefully tailored to specific patient populations. In **diabetes mellitus**, a highly atherogenic lipid profile characterized by elevated triglycerides, reduced HDL-C, and increased small dense LDL particles is frequently observed. In this setting, ApoB and non-HDL-C often serve as superior markers of risk compared to LDL-C alone.¹⁵ Patients with **chronic kidney disease** carry markedly elevated cardiovascular risk and generally require aggressive lipid-lowering therapy, with careful attention to dose adjustments based on renal function.²⁹ In **elderly individuals**, treatment decisions should be individualized after thorough assessment of frailty, comorbidity burden, life expectancy, and potential for polypharmacy-related adverse effects.³⁰ Finally, **familial hypercholesterolemia** continues to be significantly underdiagnosed worldwide. Early identification and prompt initiation of intensive LDL-C-lowering therapy are critical to preventing premature cardiovascular complications.³¹

Cost-Effectiveness and LMIC Perspective

The economic sustainability of lipid-lowering strategies is a critical consideration when translating evidence generated primarily in high-income countries into real-world practice in low- and middle-income countries (LMICs). Statins and ezetimibe continue to represent the most cost-effective foundation of dyslipidemia management.³² Generic statins are widely available at very low cost and have demonstrated excellent long-term cost-effectiveness across multiple health economic analyses. When added to statins, ezetimibe provides additional LDL-C reduction at a relatively modest incremental cost, making statin-ezetimibe combination therapy a highly attractive and practical option in resource-constrained healthcare systems.

In contrast, newer agents such as PCSK9 inhibitors, inclisiran, and bempedoic acid, while highly efficacious, come with substantially higher acquisition costs. Although these therapies have shown favorable cost-effectiveness ratios in selected very high-risk populations in high-income countries, their widespread use in LMICs remains severely limited by affordability concerns. In countries like India, where a large proportion of healthcare expenditure is out-of-pocket, the high cost of injectable biologics and novel agents poses a major barrier to equitable access and widespread adoption.

The LMIC perspective adds considerable complexity to lipid management. South Asia, and India in particular, faces a unique epidemiological transition marked by a rising burden of premature ASCVD, early-onset metabolic syndrome, diabetes, and atherogenic dyslipidemia, often occurring at relatively lower body mass indices compared to Western populations.^{13, 20} Despite this growing epidemic, healthcare resources are limited, advanced lipid profiling (such as ApoB or Lp(a) measurement) is not universally available, and long-term adherence to chronic therapy remains suboptimal due to socioeconomic factors, low health literacy, and fragmented healthcare delivery systems.

To bridge this gap, several pragmatic and context-specific approaches are necessary. First, there must be greater emphasis on optimizing the use of affordable, proven therapies — ensuring high-intensity statins are appropriately prescribed and that adherence is improved through patient education, simplified dosing regimens, and community-based follow-up

programs. Second, robust health technology assessment (HTA) and locally conducted cost-effectiveness studies should guide the selective introduction of newer agents, prioritizing those patients who are likely to derive the greatest absolute clinical benefit (e.g., individuals with familial hypercholesterolemia, recurrent events, or extremely high residual risk). Third, policy-level interventions — including price negotiation with manufacturers, inclusion of essential cardiovascular drugs in national essential medicine lists, and promotion of local manufacturing of biosimilars — could significantly improve affordability. Finally, innovative financing models, such as expanded health insurance coverage and public-private partnerships, need to be strengthened to ensure broader access to effective lipid-lowering therapies.

In summary, while novel lipid-lowering therapies represent exciting scientific progress, their successful integration into LMIC healthcare systems must be guided by careful consideration of cost-effectiveness, health equity, and local epidemiological realities. A balanced, tiered approach — maximizing the potential of affordable foundational therapies while strategically deploying newer agents for the highest-risk patients — offers the most practical and sustainable path forward in resource-limited settings.^{13, 20, 32}

DISCUSSION AND FUTURE DIRECTIONS

Precision lipidology offers significant promise but must overcome barriers of cost, accessibility, and long-term safety data. Future research should prioritize cardiovascular outcome trials of RNA-based therapies, cost-effectiveness studies in LMIC populations, AI-driven risk prediction, polygenic risk scores, and implementation science.

CONCLUSION

Dyslipidemia management is evolving from a LDL-C-centric approach to a comprehensive, precision-based strategy addressing residual cardiovascular risk. Successful integration of novel therapies alongside traditional agents, guided by appropriate biomarkers and individualized assessment, will be key to further reducing the global burden of ASCVD.

Declarations

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Conflicts of Interest: None

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