Residual Cardiovascular Risk Despite Statin Therapy: Mechanisms, Clinical Evidence, and Emerging Therapeutic Strategies

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Abstract

Statins have fundamentally transformed the prevention and management of cardiovascular disease by effectively lowering low-density lipoprotein cholesterol (LDL-C) and reducing the incidence of major adverse cardiovascular events (1,2). Despite these benefits, a substantial proportion of patients continue to experience cardiovascular events even after achieving recommended LDL-C targets, a phenomenon commonly referred to as residual cardiovascular risk (3,4). This persistent risk reflects the complex and multifactorial nature of atherosclerosis, which extends beyond LDL cholesterol to include inflammation, triglyceride-rich lipoproteins, lipoprotein(a), and metabolic dysfunction (3–5).

Recent clinical trials have provided important insights into the mechanisms underlying residual risk and have demonstrated that targeting non-LDL pathways can yield additional reductions in cardiovascular events (6–8). At the same time, emerging therapies directed at lipoprotein(a) and inflammatory pathways are redefining the landscape of cardiovascular prevention. This review provides a comprehensive and critical evaluation of residual cardiovascular risk, integrating pathophysiological mechanisms, clinical evidence, and evolving therapeutic strategies.

Keywords

Residual cardiovascular risk; statins; inflammation; triglycerides; lipoprotein(a); cardiovascular disease

1. Introduction

Cardiovascular disease (CVD) continues to be the leading cause of death worldwide, accounting for nearly one-third of all global mortality (1). Over the past three decades, statins have emerged as the cornerstone of lipid-lowering therapy, with robust evidence demonstrating their ability to reduce LDL cholesterol levels and prevent cardiovascular events across diverse patient populations (2). Landmark trials such as the Scandinavian Simvastatin Survival Study (4S) and subsequent large-scale meta-analyses have consistently confirmed the benefits of statins in both primary and secondary prevention (2, 9).

However, despite intensive statin therapy and significant reductions in LDL-C levels, many patients continue to experience myocardial infarction, stroke, and other cardiovascular events (3,4). This observation has led to increasing recognition of residual cardiovascular risk, which represents the portion of risk that remains after optimal LDL lowering (3). Importantly, this residual risk is not negligible; in some high-risk populations, it accounts for a substantial proportion of recurrent events (4).

The persistence of cardiovascular events despite adequate LDL control challenges the traditional lipid-centric view of atherosclerosis and highlights the involvement of additional biological pathways (5). Factors such as chronic inflammation, triglyceride-rich lipoproteins, lipoprotein(a), and metabolic abnormalities have been increasingly recognized as contributors to residual risk (3–5). Understanding these mechanisms is essential for developing more comprehensive and effective strategies for cardiovascular prevention.

2. Pathophysiology of Residual Cardiovascular Risk

Residual cardiovascular risk is driven by a complex interplay of lipid and non-lipid factors that continue to promote atherosclerosis even in the presence of optimal LDL-C levels (3–5). These mechanisms often overlap and amplify one another, making residual risk a multifaceted clinical problem.

Major contributors to residual cardiovascular risk are illustrated in Figure 1.

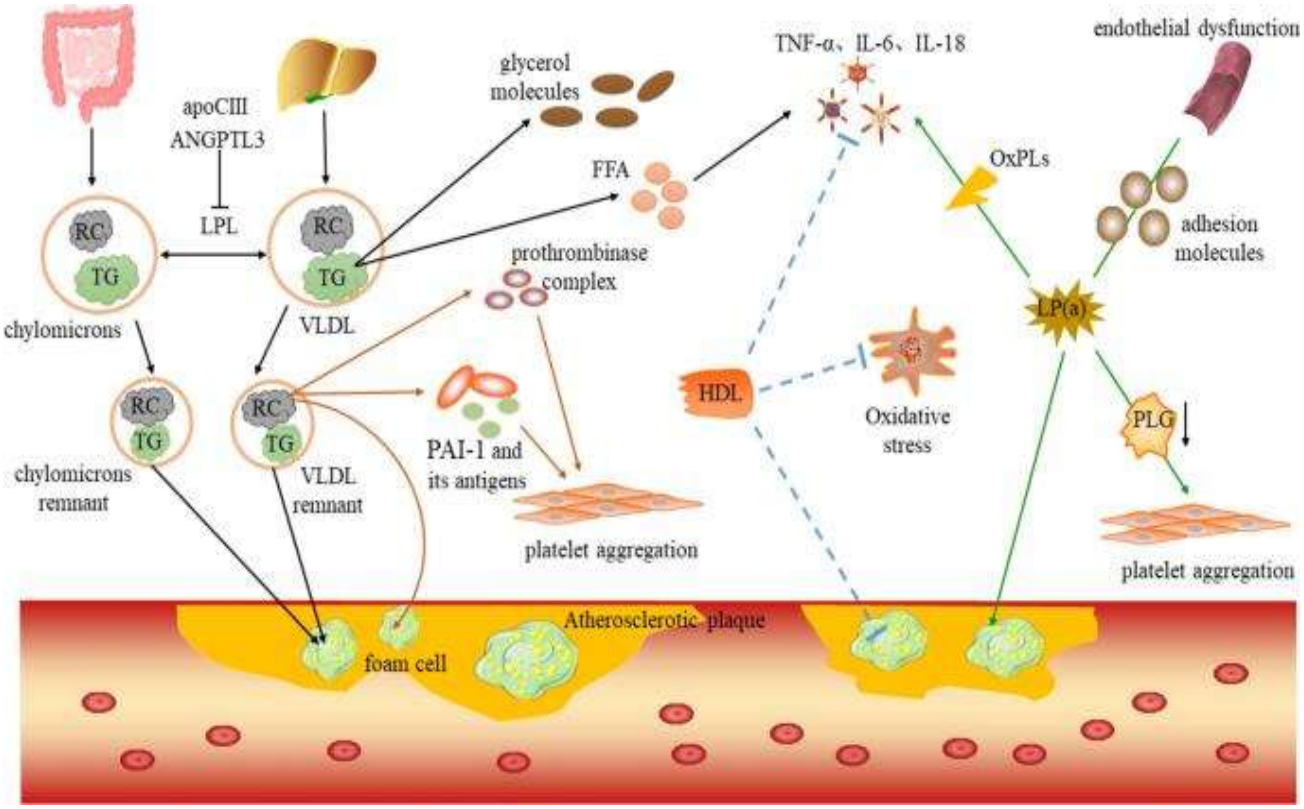
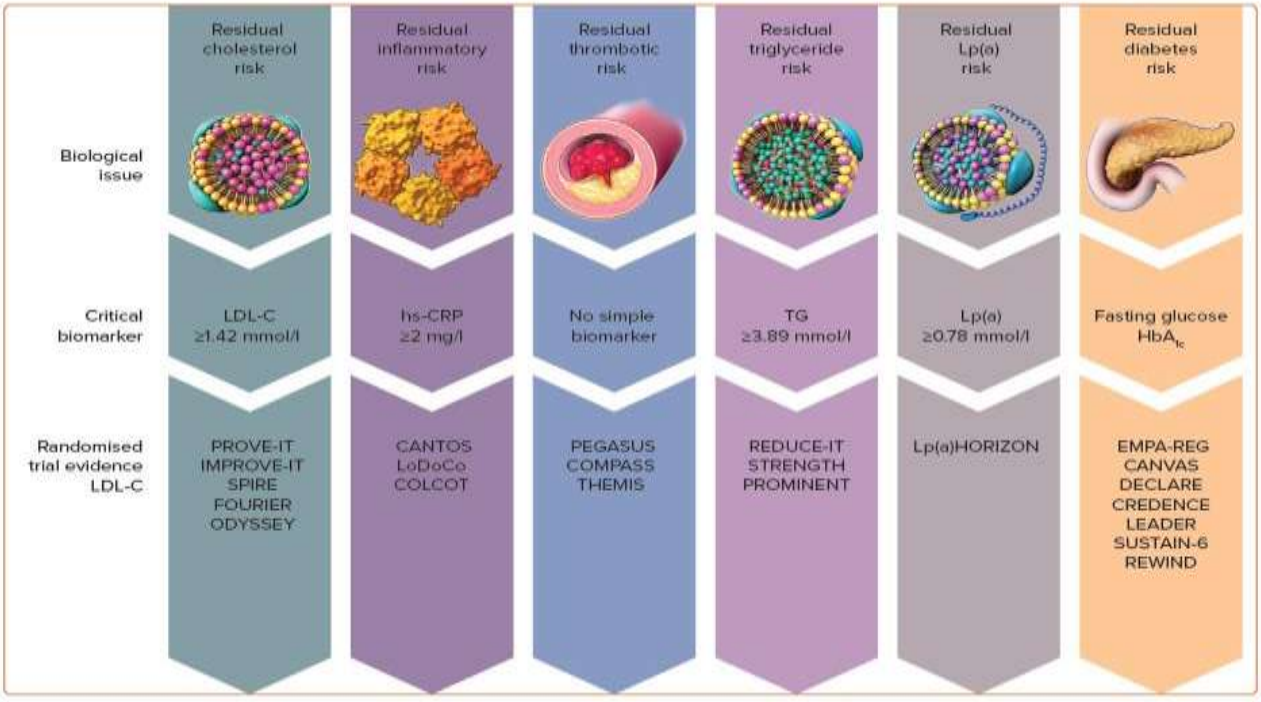


Figure 1: Key Contemporary Residual Risk Pathways in Secondary Prevention



hs-CRP = high-sensitivity C-reactive protein; LDL-C = LDL cholesterol; Lp(a) = lipoprotein (a); TG = triglyceride. Source: Lawler et al. 2020.[19] Adapted with permission from Oxford University Press.

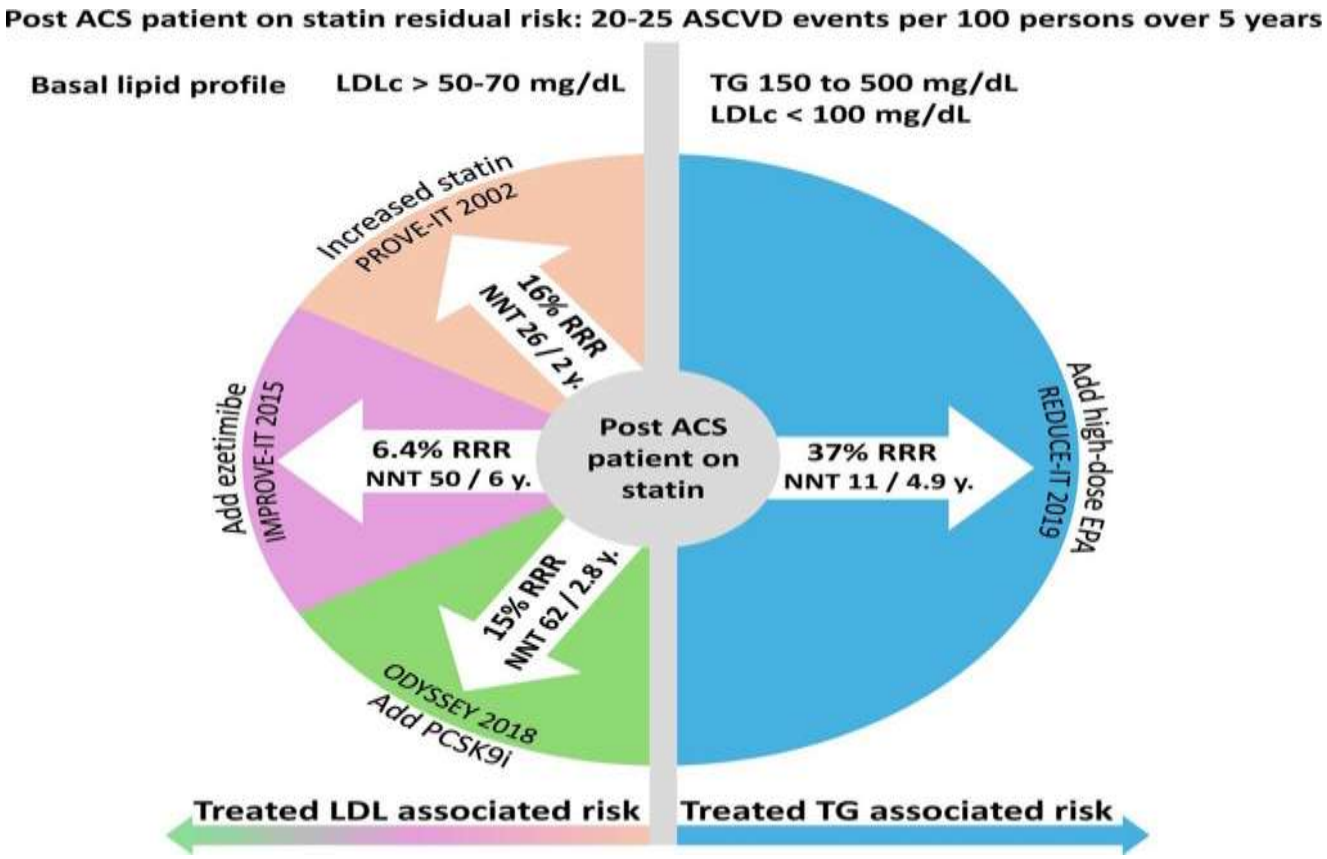


Figure 1: Major contributors to residual cardiovascular risk, including persistent inflammation, triglyceride-rich lipoproteins, lipoprotein(a), and metabolic dysfunction.
Conceptually adapted from contemporary atherosclerosis models. (3-5)

2.1 Persistent Inflammation

Inflammation is now widely recognized as a central driver of atherosclerosis, contributing to plaque initiation, progression, and eventual rupture (10). Even in patients with well-controlled LDL-C levels, elevated inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) are associated with increased cardiovascular risk (10,11).

The importance of inflammation in residual risk was clearly demonstrated in the CANTOS trial, which evaluated the effects of canakinumab, a monoclonal antibody targeting interleukin-1β (11). The study showed a significant reduction in cardiovascular events without any change in lipid levels, providing direct evidence that inflammation represents an independent therapeutic target (11).

However, the relationship between inflammation and cardiovascular risk is complex. The CIRT trial, which investigated low-dose methotrexate, failed to show a reduction in cardiovascular events, suggesting that not all anti-inflammatory strategies are effective (11). These findings highlight the need for precise targeting of specific inflammatory pathways rather than broad immunosuppression.

2.2 Triglyceride-Rich Lipoproteins and Remnants

Triglyceride-rich lipoproteins, including very low-density lipoproteins (VLDL) and their remnants, play an important role in atherosclerosis and are increasingly recognized as contributors to residual cardiovascular risk (12). These particles can penetrate the arterial wall, where they undergo modification and trigger inflammatory responses that promote plaque formation (12, 13).

Epidemiological studies have consistently demonstrated that elevated triglyceride levels are associated with increased cardiovascular risk, even after adjusting for LDL cholesterol (12). This association has been further supported by genetic studies indicating a causal role for triglyceride-rich lipoproteins in atherosclerosis (12).

The REDUCE-IT trial provided strong clinical evidence for the role of triglycerides by showing that high-dose icosapent ethyl significantly reduced cardiovascular events in patients with elevated triglyceride levels despite statin therapy (13). These findings suggest that targeting triglyceride-rich lipoproteins can meaningfully reduce residual risk.

2.3 Lipoprotein(a)

Lipoprotein(a), or Lp(a), has emerged as one of the most important genetically determined contributors to residual cardiovascular risk (14). Structurally similar to LDL but containing apolipoprotein(a), Lp(a) exhibits both pro-atherogenic and pro-thrombotic properties (14,15).

Elevated Lp (a) levels are associated with increased risk of coronary artery disease, stroke, and aortic stenosis (14). Importantly, Lp(a) levels are largely determined by genetic factors and are not significantly reduced by statin therapy (15). In some cases, statins may even modestly increase Lp (a) levels, further emphasizing its role in residual risk (15).

Recent advances in therapeutic development have led to the emergence of targeted treatments for Lp (a), including antisense oligonucleotides such as pelacarsen, which have shown substantial reductions in Lp (a) levels in early clinical trials (15). Ongoing outcome trials will determine whether these reductions translate into improved cardiovascular outcomes.

2.4 Metabolic Dysfunction and Insulin Resistance

Metabolic disorders, including obesity, insulin resistance, and type 2 diabetes, are strongly associated with residual cardiovascular risk (16). These conditions are characterized by a cluster of abnormalities, including elevated triglycerides, low HDL cholesterol, and increased levels of small dense LDL particles (16).

In addition to lipid abnormalities, insulin resistance promotes systemic inflammation, endothelial dysfunction, and oxidative stress, all of which contribute to atherosclerosis (16). The coexistence of metabolic and inflammatory pathways creates a pro-atherogenic environment that persists despite LDL lowering.

3. Clinical Evidence Supporting Residual Risk

The concept of residual cardiovascular risk is supported by a substantial body of clinical evidence from randomized controlled trials and observational studies (2,4).

The PROVE-IT TIMI 22 trial demonstrated that intensive statin therapy reduced cardiovascular events compared with moderate therapy; however, a significant proportion of patients continued to experience recurrent events (17). Similarly, the IMPROVE-IT trial showed that adding ezetimibe to statin therapy provided additional benefit, yet residual risk remained substantial (18).

Observational studies have further highlighted that patients with controlled LDL-C but elevated hs-CRP or triglycerides remain at increased risk of cardiovascular events (3, 4). These findings underscore the importance of addressing non-LDL pathways in cardiovascular prevention.

4. Therapeutic Strategies to Address Residual Cardiovascular Risk

Recognition of residual cardiovascular risk has shifted clinical focus from an exclusively LDL-centric approach to a broader strategy targeting multiple pathogenic pathways (3–5). Several therapeutic approaches have emerged to address these mechanisms, with varying degrees of clinical success.

4.1 Intensification of Lipid-Lowering Therapy

Although residual risk extends beyond LDL cholesterol, further LDL reduction remains beneficial, particularly in high-risk populations. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, such as evolocumab and alirocumab, provide substantial additional reductions in LDL-C when added to statin therapy (6).

The FOURIER trial demonstrated that evolocumab significantly reduced cardiovascular events in patients with established atherosclerotic cardiovascular disease who were already receiving statins (6). Similarly, the ODYSSEY OUTCOMES trial showed that alirocumab reduced major adverse cardiovascular events in patients following acute coronary syndrome (19).

Despite these benefits, residual risk persists even with very low LDL-C levels, reinforcing the need to address non-LDL pathways (4).

4.2 Targeting Inflammation

Inflammation represents one of the most compelling therapeutic targets for reducing residual cardiovascular risk. The success of the CANTOS trial established proof-of-concept that selective inhibition of interleukin-1β can reduce cardiovascular events independently of lipid lowering (11).

However, the clinical applicability of canakinumab is limited by high cost and increased risk of infection (11). Alternative approaches targeting inflammation are currently being explored, including colchicine, which has shown promise in trials such as COLCOT and LoDoCo2 (20). These studies demonstrated that low-dose colchicine significantly reduced cardiovascular events, likely through inhibition of inflammatory pathways.

The contrasting outcomes of different anti-inflammatory trials highlight the importance of pathway-specific targeting rather than broad immunosuppression (11, 20).

4.3 Triglyceride-Lowering Strategies

Elevated triglycerides represent an important modifiable contributor to residual risk. The REDUCE-IT trial provided strong evidence that icosapent ethyl, a highly purified eicosapentaenoic acid derivative, significantly reduced cardiovascular events in high-risk patients with elevated triglyceride levels (13).

Notably, the magnitude of risk reduction observed in REDUCE-IT exceeded what would be expected from triglyceride lowering alone, suggesting additional mechanisms such as anti-inflammatory and plaque-stabilizing effects (13). However, other trials using mixed omega-3 formulations have not consistently demonstrated similar benefits, highlighting the importance of formulation and dosing.

4.4 Lipoprotein(a)-Targeted Therapies

Lipoprotein(a) has long been recognized as a contributor to cardiovascular risk, but effective therapies have historically been lacking (14, 15). Recent advances in RNA-based therapeutics have led to the development of agents capable of significantly lowering Lp(a) levels.

Pelacarsen, an antisense oligonucleotide targeting apolipoprotein (a), has demonstrated reductions of up to 80% in circulating Lp (a) levels in phase 2 trials (15). Ongoing outcome trials, such as Lp (a) HORIZON, are expected to determine whether these reductions translate into clinical benefit.

If successful, these therapies could represent a major breakthrough in addressing genetically mediated residual risk.

4.5 Addressing Metabolic Dysfunction

Metabolic abnormalities, particularly insulin resistance and obesity, contribute significantly to residual cardiovascular risk and require targeted intervention (16). Lifestyle modification remains the cornerstone of management, including dietary changes, physical activity, and weight reduction.

Pharmacological therapies, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, have demonstrated cardiovascular benefits beyond glycemic control (21). These agents improve metabolic parameters, reduce inflammation, and may directly influence atherosclerotic processes.

A summary of key contributors and therapeutic strategies is presented in Table 1.

Table 1: Contributors to Residual Cardiovascular Risk and Targeted Therapies

Contributor	Mechanism	Therapeutic Approach
Inflammation	Cytokine activation	Canakinumab, colchicine
Triglycerides	Remnant lipoproteins	Icosapent ethyl
Lipoprotein(a)	Genetic, prothrombotic	Antisense therapies
Metabolic dysfunction	Insulin resistance	GLP-1 agonists, SGLT2 inhibitors

5. Precision Medicine and Risk Stratification

The heterogeneity of residual cardiovascular risk underscores the need for a personalized approach to treatment (22). Precision medicine aims to identify the dominant drivers of risk in individual patients and tailor therapy accordingly.

Biomarkers such as hs-CRP, triglycerides, and Lp (a) levels can help stratify patients and guide therapeutic decisions (10,12,14). For example, patients with elevated inflammatory markers may benefit from anti-inflammatory therapies, while those with elevated triglycerides or Lp (a) may require targeted lipid-modifying treatments.

Advances in genomics and multi-omics technologies are expected to further refine risk prediction and enable more individualized approaches to cardiovascular prevention (22).

6. Future Directions

Future research in residual cardiovascular risk is likely to focus on multi-pathway interventions and combination therapies targeting multiple mechanisms simultaneously (4). Integration of artificial intelligence and machine learning into clinical practice may enhance risk prediction and identify novel therapeutic targets.

Additionally, ongoing clinical trials evaluating Lp (a)-lowering therapies and novel anti-inflammatory agents are expected to provide further insights into the management of residual risk (15, 20).

7. Limitations

Despite advances in understanding and management, several challenges remain. Many therapies targeting residual risk are costly and may not be accessible in all healthcare settings (4). Furthermore, variability in patient response and lack of standardized treatment algorithms complicate clinical decision-making.

The complexity of residual risk also makes it difficult to isolate the relative contribution of individual pathways, emphasizing the need for integrated approaches to treatment.

8. Conclusion

Residual cardiovascular risk remains a major challenge in contemporary cardiovascular medicine despite the widespread use of statins and effective LDL-C lowering (3, 4). The persistence of cardiovascular events reflects the multifactorial nature of atherosclerosis, involving inflammation, triglyceride-rich lipoproteins, lipoprotein(a), and metabolic dysfunction.

Emerging therapies targeting these pathways, along with advances in precision medicine, offer promising opportunities to further reduce cardiovascular risk. A comprehensive, individualized approach that addresses multiple mechanisms simultaneously is likely to be essential for improving long-term outcomes.

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