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*Article*

# The Statin Floor Effect: A Mechanistic Framework for Residual Cardiovascular Risk

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**Abstract**

**Background and Aims:** Despite substantial statin-induced low-density lipoprotein cholesterol (LDL-C) lowering, residual cardiovascular risk remains a major clinical challenge. A mechanistic synthesis of preclinical and clinical evidence was undertaken to explain why inflammation and risk persist despite optimal lipid control. **Methods:** Literature from preclinical models, clinical trial data, mechanistic modeling, and biomarker trajectories was reviewed and integrated to construct a unified framework linking lipid lowering with persistent immunometabolic activity. **Results:** Long-term, high-dose statin exposure has been associated with paradoxical effects in arterial macrophages, including activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, impaired resolution pathways, and promotion of elevated blood glucose and insulin resistance, including via reduction of circulating glucagon-like peptide-1 (GLP-1) in a microbiota-dependent manner. These local effects may coexist with systemic anti-inflammatory benefits, creating a lower bound beyond which arterial inflammation does not regress. Adaptive immune feedback, Lipoprotein(a)-driven amplification, and vascular remodeling further contribute to inter-individual variability. Temporal biomarker evolution defines three mechanistic phases that may assist in stratifying patient response and guiding therapy design. **Conclusions:** Residual cardiovascular risk can be reframed as an unintended but potentially modifiable immunometabolic plateau. By integrating established lipid-lowering outcomes with emerging insights into inflammation and metabolism, this framework provides a testable model to support biomarker-driven precision strategies and the earlier adoption of complementary therapies, thereby improving outcomes.

**Keywords:** statin paradox; NLRP3 inflammasome; protein prenylation; lipoprotein(a); IL-1β; insulin resistance; residual risk; cardiovascular disease

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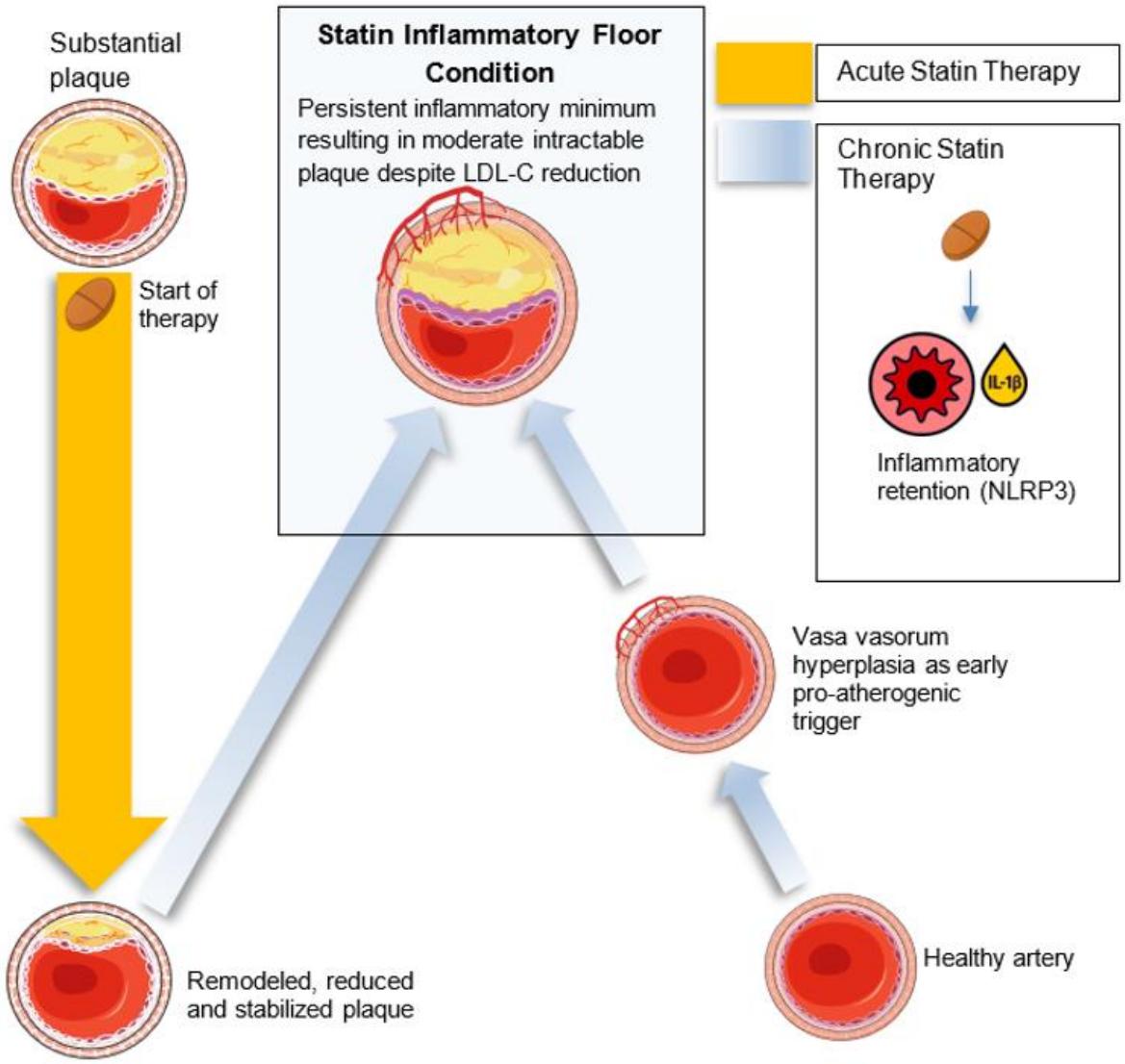


**Figure 1.** Graphical Abstract – The Statin Floor Effect. Conceptual overview of the Statin Floor Effect. Long-term high-intensity statin therapy lowers LDL-C but establishes a localized arterial inflammatory floor through NLRP3 activation, adaptive immune modulation, and metabolic disruption. Vasa vasorum hyperplasia and diffuse intimal hyperplasia are depicted as early pro-atherogenic triggers that create a permissive substrate for lipid retention and inflammation. Together, these elements integrate molecular mechanisms, biomarker trajectories, and clinical observations to explain the plateau in cardiovascular risk reduction and highlight avenues for therapeutic innovation.

## 1. Introduction

Despite substantial [LDL-C][1] lowering [1], statin-treated cohorts still exhibit ~75% baseline relative risk that plateaus, in absolute terms, at ≈5–10% by year five [2–4]. Anti-inflammatory trials (CANTOS, LoDoCo2 [5,6]) confirm that arterial inflammation drives residual events beyond lipid control, yet despite comparable [LDL-C], anti-C-Reactive Protein (CRP) therapy responses vary, underpinning the effect that chronic high-dose statins induce a persistent inflammatory minimum.

The Statin Floor Effect (SFE) is presented as a conceptual framework that integrates the temporal dynamics and pleiotropic complexity of statin therapy. Statin effects are not uniformly beneficial, and chronic, high-dose statin therapy can establish a persistent inflammatory minimum in arterial macrophages that limits further cardiovascular event risk reduction, despite continued systemic

[1] Square-bracket notation (e.g., [LDL-C]) denotes molar concentration throughout

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benefits. In constructing this model, the post-statin residual inflammatory floor has been explicitly distinguished from the mechanisms driving plaque initiation [7]. Multiple studies demonstrate that foam cells originate from monocyte-derived macrophages, and via Kruppel-like Factor 4-dependent phenotypic modulation and transdifferentiation of vascular smooth muscle cells [8,9]. Accordingly, the residual inflammatory floor encompasses contributions from both monocyte- and smooth muscle cell-derived foam cells within the atherosclerotic plaque.

In murine macrophages, statins trigger NLRP3 inflammasome activation [10], and intriguingly, context-dependent paradoxes between toll-like receptor (TLR) signaling and inflammasome engagement have been reported [11]. Mechanistic studies show that chronic statin exposure impairs protein prenylation and small GTPase function, offering a unified upstream pathway linking NLRP3 activation with insulin resistance [12]. In addition, recent translational work has demonstrated that statin exposure can aggravate insulin resistance through a gut microbiota–bile acid-GLP-1 axis, with reductions in circulating GLP-1 providing an additional route by which high-dose therapy reinforces a persistent inflammatory floor [13]. Direct confirmation of these interconnected processes in human atheroma, however, remains outstanding.

There is recent evidence also to suggest that an inflammatory floor may be preceded by structural vascular priming. Adventitial vasa vasorum hyperplasia and diffuse intimal hyperplasia, proposed as initiating events in atherosclerosis, may create a permissive microenvironment for lipid retention and immune activation, particularly in high-risk individuals. These early non-inflammatory structural changes may well interact with the mechanisms described in this framework and support the need for temporally stratified preventive approaches. In parallel, residual risk may also be sustained or amplified by LDL-independent pathways, including elevated [Lp(a)], [small dense LDL], and inflammatory cytokine axes such as interleukins (IL) IL-17/IL-23. These factors may converge on macrophage activation and inflammasome priming, reinforcing the localized inflammatory floor and contributing to inter-individual heterogeneity in treatment response. These elements collectively form a unified model for residual cardiovascular risk in the statin era, mechanistically grounded and clinically actionable. By locking arterial macrophages into a low-grade inflammatory floor, subtly deranging insulin signaling, and possibly influencing angiogenesis, chronic high-dose statins may limit full resolution of old lesions.

Although the framework centers on unintended immunometabolic adaptation, it also aligns with established observations that plaque burden alters local hemodynamics. Regions of disturbed flow, characterized by low turbulence or oscillatory shear stress, are known to promote endothelial dysfunction, leukocyte adhesion, and pro-inflammatory signaling [14]. These shear-sensitive pathways can be activated even in the absence of lipid level elevation and may synergize with residual inflammatory cues to sustain arterial lesion progression. Importantly, such flow disturbances persist or worsen in the presence of pre-existing plaques, creating a feed-forward loop that enhances plaque vulnerability and propagation [15].

Low shear stress has also been directly implicated in NLRP3 inflammasome activation in vascular endothelial cells, providing a mechanistic link between mechanical stress and innate immune priming [16]. These structural and mechanical factors may therefore act as physical amplifiers of the inflammatory floor, particularly in advanced atheroma, where statin effects on plaque architecture may reach their limits.

Although statins are not classified as antihypertensive agents, they may modestly influence blood pressure and vascular tone through pleiotropic effects [17]. Acute administration increases endothelial nitric oxide (NO) bioavailability and inhibits Ras homolog family member A/Rho-associated coiled-coil containing protein kinase (RhoA/ROCK) signaling, promoting vasodilation and transient reductions in peripheral resistance [18]. With chronic therapy, additional benefits emerge, including improved arterial compliance, reduced oxidative stress, and modulation of sympathetic tone and the renin–angiotensin–aldosterone system [19]. Meta-analyses of randomized controlled trials report small but statistically significant reductions in systolic (1–5 mmHg) and diastolic (0.5–3 mmHg) blood pressure with long-term statin use [17]. While insufficient to replace conventional

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antihypertensive therapy, these effects may contribute additively to vascular stabilization, particularly during early atheroma remodeling, when statin-mediated lipid lowering and inflammation resolution are most responsive. Moreover, computational modeling supports the interplay between hemodynamics and vascular biology. Recent mechano-chemo-biological models and multiscale simulations demonstrate that adventitial remodeling and vasa vasorum proliferation, hallmarks of the "outside-in" theory, can reinforce lesion development independent of luminal lipid burden [20,21]. These structural changes may serve as chronic reinforcers of localized inflammation, especially when coupled with sub-resolution plaque instability and altered flow dynamics. Paradoxically, chronic high-dose statin therapy has been shown to induce vascular endothelial growth factor and matrix metalloproteinase (MMP) expression in vessel wall cells, thereby potentiating adventitial vasa vasorum proliferation. These findings suggest that mechanical, structural, and immunometabolic pathways converge to establish and maintain the inflammatory floor observed in statin-treated patients.

Within this framework, mechanistic contributors are organized into *primary pathways*, centered on dose-dependent NLRP3 inflammasome activation in arterial macrophages, and *secondary pathways* that amplify or sustain the inflammatory floor. These include impaired protein prenylation, insulin resistance, adaptive immune modulation, and emerging factors such as red-blood-cell–derived extracellular vesicles, as well as *parallel pathways* involving oxidized lipoproteins, Lp(a), and IL-17/IL-23 signaling. This structure provides a scaffold for the mechanistic framework that follows.

## 2. Methods/Approach

*Literature Search*

This work was undertaken as a mechanistic narrative review, integrating preclinical studies, clinical trial findings, biomarker trajectories, and computational modeling relevant to statin pharmacology and residual cardiovascular risk. An integrative PubMed, Google Scholar, and Web of Science search (2000–September 2025) was conducted for terms covering statin pharmacology, residual cardiovascular risk, NLRP3 inflammasome priming, foam cell biology, protein prenylation, LDL-C, ApoB, lipoprotein(a)/oxidized phospholipids (OxPL), and adaptive immunity. Peer-reviewed mechanistic studies, meta-analyses, and key reviews were prioritized, with additional references obtained by backward citation tracking to develop thematic clusters and identify testable predictions. The aim was to construct a unifying conceptual framework, the Statin Floor Effect, linking established lipid-lowering outcomes with emerging immunometabolic and vascular mechanisms. The focus was the development of a mechanistic framework; consequently, the work was not designed as a systematic review; PRISMA methodology and formal risk-of-bias assessment were therefore not applied.

*Conceptual Framework Development*

The model was built by first gathering and synthesizing key themes from the literature on long-term statin use. As the narrative was refined, mechanistic findings were organized into five core pathways:

- Inflammasome activation (NLRP3, IL-1β, IL-18)
- Disruption of protein prenylation (Ras-related C3 Botulinum Toxin Substrate [Rac1], geranylgeranylation)
- Insulin resistance acting as an inflammation amplifier
- Shifts in thymus-derived lymphocyte (T-cell) balance (T Helper 17 cell subtype [Th17] versus regulatory T-cells [Tregs])
- Immune priming driven by Lp(a) and oxidized phospholipids

These pathways were then aligned with clinical observations, such as the plateauing of major adverse cardiovascular events (MACE) reduction and persistent CRP elevation despite low [LDL-C], to generate clear, testable predictions. This process defined a unified framework for explaining residual cardiovascular risk in patients receiving statin therapy.

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## 3. Mechanistic Framework

The mechanistic framework of the Statin Floor Effect is organized around a *primary* pathway, dose-dependent NLRP3 inflammasome activation in arterial macrophages, and a set of *secondary pathways* that amplify or sustain this inflammatory floor, including impaired protein prenylation, insulin resistance, and adaptive immune modulation. In addition, *parallel pathways* such as Lp(a)–oxidized phospholipids and IL-17/IL-23 signaling act as independent but convergent reinforcers. Against this backdrop, three paradoxes highlight the clinical and biological challenges that shape residual cardiovascular risk.

*Clinical Problem and Paradoxes*

The Residual Risk Paradox

- Inflammation drives residual risk (CANTOS, LoDoCo2) [5,6]
- Statins reduce MACE by ~25% per mmol/L [LDL-C] lowering but leave ~75% of events even with [LDL-C] <1.4 mmol/L [3,4] a gap better predicted by Apolipoprotein (Apo)B [22,23]
- Early epidemiological work, in particular the Framingham Study and its stress-defense analyses, established the baseline event rates and risk factors still used to benchmark modern therapies [24]
- A large meta-analysis confirms persistent risk and treatment heterogeneity [3] and statin-treated patients with low [LDL-C] still face higher event rates than untreated peers with similar concentrations [25]

The Statin Pleiotropy Paradox

Statins exhibit systemic anti-inflammatory effects [25,26] but demonstrate diminishing MACE benefit at higher doses [3,26], increase diabetes risk [27] and appear to produce dose-dependent Fourier Transform Infrared spectroscopy markers of oxidative stress consistent with NLRP3 priming [28]; interindividual response variability underscores mechanistic heterogeneity [29].

The Temporal Paradox

Event rates plateau at ≈5–10% by year five [2,30,31]; CRP reductions may not predict long-term resolution [32,33]; in type 2 diabetes cohorts, statin therapy duration, more than dose or [LDL-C] achieved, best predicts risk reduction [34]; and secondary prevention patients still exhibit residual events after years of treatment [25].

*The Enhanced Mechanistic Model*

Core Framework Statement

> *The statin floor effect emerges when chronic, high-intensity statin therapy creates a net pro-inflammatory state in arterial macrophages despite systemic anti-inflammatory benefits, establishing a localized inflammatory minimum that limits further cardiovascular risk reduction.*

Temporal Stratification Model

Three overlapping phases of statin-induced mechanistic shifts are conceptualized (Figure 2), each building on the last:

- *Phase 1 (0–6 months):* rapid [LDL-C] lowering with predominant anti-inflammatory benefit

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- *Phase 2 (6–24 months):* competing beneficial and detrimental effects as mevalonate pathway disruption accumulates
- *Phase 3 (>24 months):* a persistent inflammatory floor limits further MACE reduction despite maintained [LDL-C] suppression

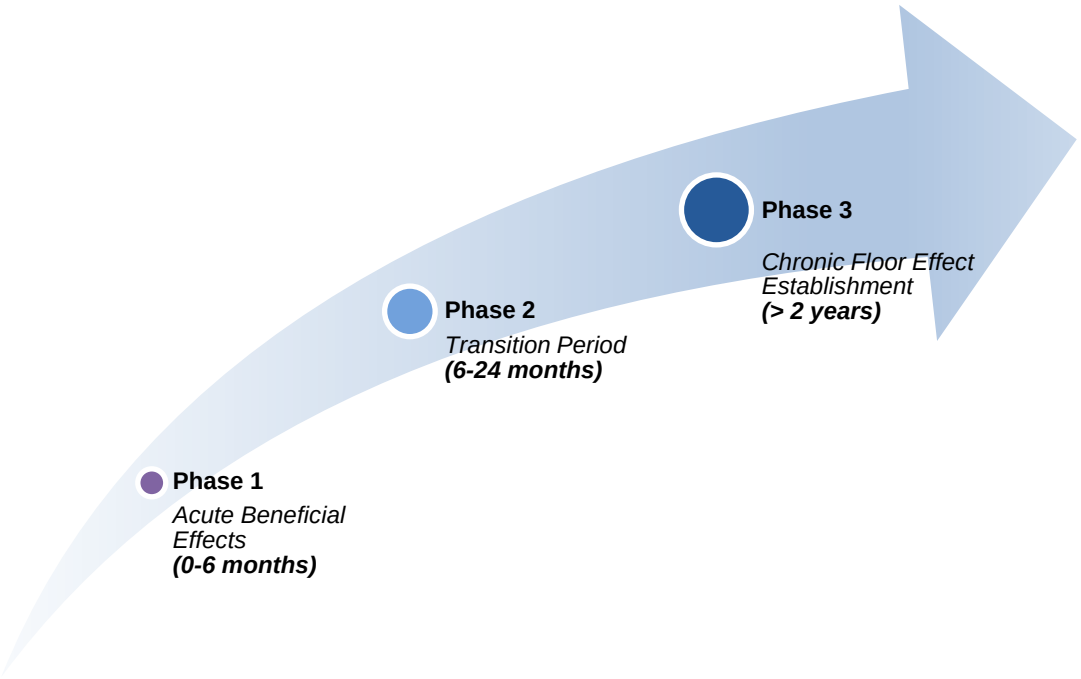


**Figure 2.** Mechanistic details of each temporal phase of the SFE. *Phase 1:* Statin-mediated 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition increases endothelial NO and inhibits RhoA/ROCK, stabilizing plaque and suppressing nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)–driven cytokines[17,19,35]. Rapid [LDL-C] reduction drives foam cell apoptosis and efferocytosis [36–38]. *Phase 2:* Depletion of mevalonate-derived isoprenoids (GGPP, farnesyl pyrophosphate) impairs prenylation of small GTPases, resulting in NLRP3 inflammasome–dependent caspase-1 activation and IL-1β secretion—effects that are reversible with geranylgeraniol supplementation in both macrophages and adipocytes[10,39]. Concurrent mitochondrial stress fosters insulin resistance (↑ HOMA-IR) [10,27], dampening resolution pathways. *Phase 3:* Adaptive immune feedback (Th17 expansion, IL-17/IL-23 signaling) [40–44] and Lp(a)-derived OxPLs [45–47], potentially driven up by statins, reinforce NLRP3 activation. Adventitial vasa vasorum hyperplasia primes new LDL retention [48], cementing a self-sustaining inflammatory minimum that caps further MACE reduction.

*Primary Pathway: Dose-Dependent NLRP3 Activation*

- NLRP3 inflammasome activation in arterial macrophages arises from convergent lipid-sensing pathways, Rac1 dysregulation, impaired protein prenylation, and oxidized lipids, forming the core of the inflammatory floor effect [49,50]
- Statins inhibit the mevalonate pathway, reducing geranylgeranylation and impairing Rac1 regulation to augment NLRP3 activity[2] [49,50], with mathematical and spectroscopic modeling confirming dose-dependent stress signatures consistent with inflammasome priming [28]. Moreover, statins modestly elevate Lp(a) levels [51], whose oxidized phospholipid cargo directly triggers NLRP3 activation, thereby offering a unified upstream pathway linking NLRP3

[2] This mechanism is supported by murine and cell culture studies, full validated in human arterial macrophages is yet to occur

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activation with insulin resistance and reinforcing the inflammatory floor despite optimal LDL-C levels[3] [45,46].

- Statin-mediated menaquinone-4 (MK-4) depletion may impair inflammasome regulation via reduced SXR activation (vide infra: Section 4 - **Therapeutic Potential** subsection).
- Macrophages retain IL-1β and IL-18 secretion despite expressing alternatively activated (pro-resolution) macrophage (M2) markers [52,53], driving LDLR-mediated lipid uptake [52], foam cell persistence [50,54] and cytokine-reinforced plaque instability [55]
- Statins also inhibit GTPase prenylation, suppressing Th17 differentiation [56,57] and expanding Tregs [58,59], though these adaptive immune effects vary among individuals [60] and sustain a pro-inflammatory milieu[4]. In contrast, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (FOURIER) and bempedoic acid (CLEAR Outcomes) show continuously diverging event-reduction curves at 2–3 years without the early plateau seen in statin trials [31,61].

Additional translational evidence strengthens this link between statins, mitochondrial dysfunction, and inflammasome priming. In a controlled study of overweight adults, 56 days of high-dose atorvastatin reduced insulin sensitivity in most participants and selectively inhibited mitochondrial complex IV activity at clinically relevant tissue concentrations. Mitochondrial calcium retention capacity was also diminished, a change that predisposes to permeability transition and ROS-driven NLRP3 activation. These findings provide direct human support for the notion that chronic statin therapy establishes a pro-inflammatory floor not only through prenylation-dependent Rac1 dysregulation but also by converging on mitochondrial stress pathways [62].

Recent evidence further reinforces the role of the NLRP3 inflammasome as a persistent driver of residual cardiovascular risk. Mo et al. [63] reviewed accumulating preclinical and clinical data showing that NLRP3 activation in macrophages, smooth muscle cells, endothelial cells, and cardiomyocytes contributes to lesion progression, fibrosis, and maladaptive remodeling even when lipid levels are reduced. Importantly, elevated IL-1β and IL-18 remain associated with adverse cardiovascular outcomes despite [LDL-C] lowering, consistent with the inflammatory plateau described in the SFE framework. The review also highlights that NLRP3 activation depends on multiple signals, including oxidative stress, mitochondrial dysfunction, and ionic flux, that are not addressed by statin therapy. This mechanistic independence from cholesterol burden provides a clear rationale for adjunctive therapeutic strategies, such as direct NLRP3 inhibition, which have shown benefit in preclinical models and are entering translational development.

These findings indicate that while statins provide a rapid early reduction in risk, their long-term benefit plateaus in a way not observed with newer agents or lifestyle interventions. This pattern is summarized in Table 1 and illustrated in the hypothetical trajectories of Figure 3, which emphasize the differing temporal dynamics across therapeutic classes.

**Table 1. Temporal MACE Reduction Profiles by Therapy Class.**

| Therapy Class | Trial(s) | Time for Initial Risk Reduction | Temporal Pattern | Plateau Observed | Notes |
|---|---|---|---|---|---|
| **Statins (moderate–high dose)** | CTT meta-analysis [2,3,26] | Within 3–6 months | Rapid early ↓, then plateau | Yes | Clear early benefit, but ~75% of events still occur despite [LDL-C] <1.4 mmol/L |

[3] In vitro models support OxPL–NLRP3 activation, the in vivo contribution of Lp(a) to this pathway is yet to be quantified

[4] The role of adaptive immune–macrophage crosstalk in this context has not yet been fully mapped, however, emerging data suggest that insulin resistance may modulate T-cell polarization and indirectly reinforce pro-inflammatory macrophage phenotypes.

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| Therapy Class | Trial(s) | Time for Initial Risk Reduction | Temporal Pattern | Plateau Observed | Notes |
|---|---|---|---|---|---|
| **PCSK9 inhibitors** | FOURIER, ODYSSEY OUTCOMES [31,64] | 12–24 months | Progressive over time | No | In FOURIER and ODDYSEY, event curves continue diverging through their 2-3 year follow-up, but longer-term trajectories remain to be determined |
| **Ezetimibe** | IMPROVE-IT [65] | ~24 months | Delayed, modest effect | Mild | Additive to statins; risk reduction ~6% over 6 years |
| **Bempedoic acid** | CLEAR Outcomes [61] | ≥24 months | Linear, steady | No | Benefit emerges gradually, consistent with an early plateau in statin curves, and raises the question of a statin-linked inflammatory floor |
| **Lifestyle interventions** | PREDIMED, PURE, observational cohorts [66–68] | 2–5 years | Slow, cumulative | Not applicable | Heterogeneous effects: within 2–5 year studies, no clear plateau is observed, but longer-term data are limited |

Statins demonstrate an early, steep reduction in major adverse cardiovascular events (MACE) that plateaus within 3–6 months, leaving ~75% of residual risk despite optimal [LDL-C] suppression. In contrast, non-statin agents and lifestyle interventions display more gradual or sustained trajectories without the early plateau, highlighting mechanistic differences that may relate to inflammasome activation, mitochondrial dysfunction, and other statin-linked adaptive processes.

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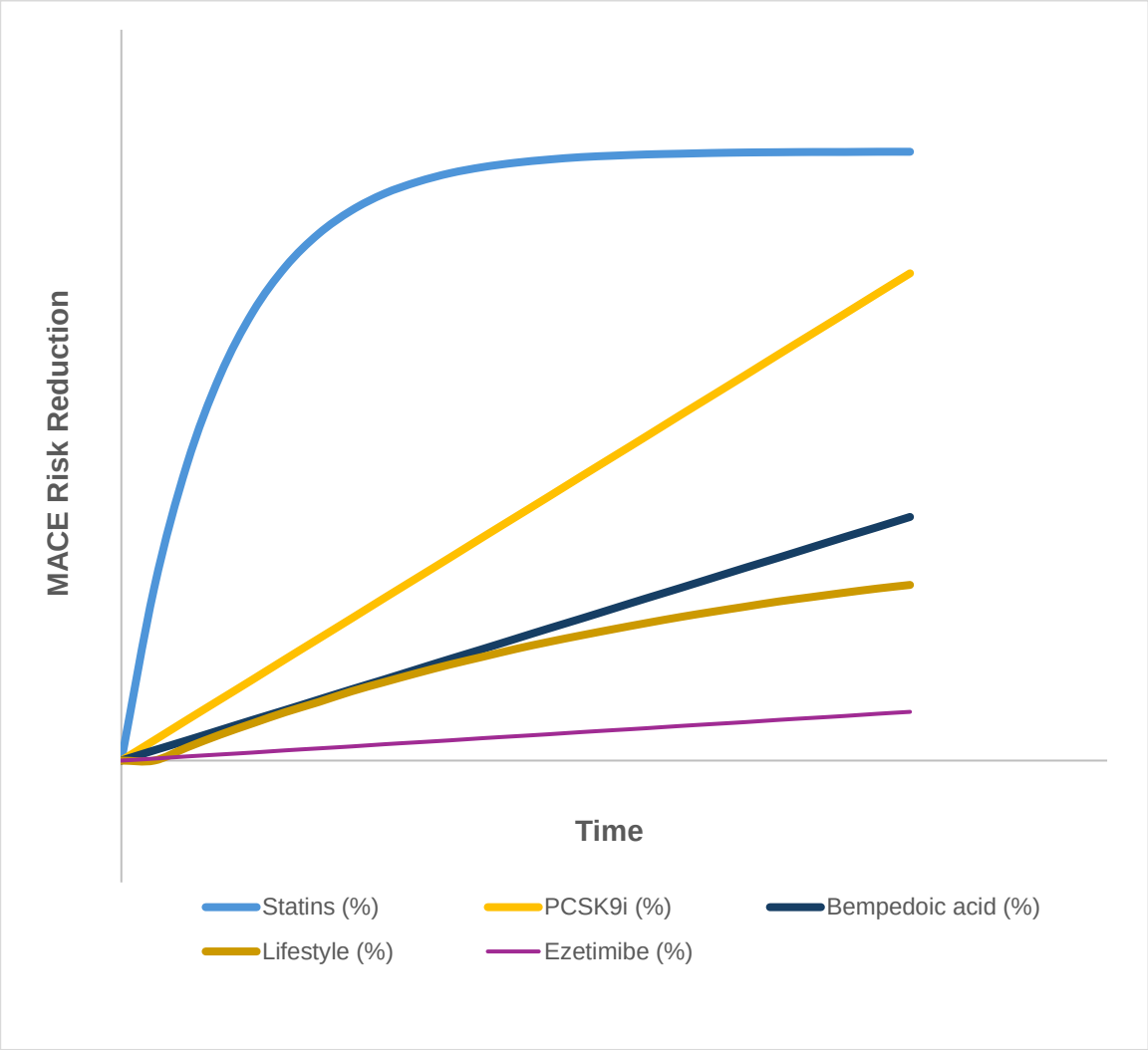


**Figure 3.** Hypothetical MACE Reduction Risk Trajectories. Illustrative risk reduction curves are shown over time for statins, PCSK9 inhibitors, bempedoic acid, ezetimibe, and lifestyle interventions. Statins demonstrate an early, steep reduction in major adverse cardiovascular events (MACE) that plateaus over time, whereas non-statin therapies and lifestyle measures exhibit more gradual, additive, or linear trajectories. The figure highlights the relative differences in temporal dynamics between lipid-lowering and adjunctive approaches.

Secondary Pathways

- Statin-induced NLRP3 activation → systemic IL-1β elevation
- IL-1β → worsens insulin sensitivity [69]
- Insulin resistance → further chronic inflammation [70]
- 10–15% increased diabetes risk with statin use[5] [27]
- Human and translational studies show statins can aggravate insulin resistance by reducing circulating GLP-1 via a Clostridium–Ursodeoxycholic acid (UDCA)–bile-acid axis; UDCA supplementation restores GLP-1 and improves glycemia [13]
- Red blood cell (RBC)-derived extracellular vesicles in diabetes: Glycated or fragile RBCs release vesicles enriched in arginase-1, which are taken up by endothelial cells to suppress nitric oxide bioavailability and increase reactive oxygen species, driving endothelial dysfunction and inflammation [71]. In the statin context, where diabetes risk is elevated, such RBC-EV–mediated

[5] Meta-analytic evidence links statin therapy to new-onset diabetes, with heightened risk in patients with pre-existing metabolic dysfunction—supporting a systemic feedback loop

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insults may synergize with impaired metabolic resilience to sustain a permissive vascular milieu for lipid retention and inflammasome activation.

- Insulin resistance enhances NLRP3 priming in macrophages[6] [72]
- Metabolic dysfunction amplifies pro-inflammatory cytokine production [73]
- A self-reinforcing cycle maintains the inflammatory floor [73]

Tissue-Specific Context Dependency

- *Hepatocytes:* Retain beneficial responses and systemic anti-inflammatory effects [72]
- *Arterial Macrophages:* Susceptible to prenylation disruption, driving persistent inflammasome activation [49]
- *Systemic Immune Cells:* Mixed responses influenced by genetic predisposition [74]

Parallel Amplification Pathways

Having outlined the core mechanistic pathways, including NLRP3 inflammasome activation, protein prenylation disruption, adaptive immune-macrophage crosstalk, and Lp(a) amplification, the following section examines the histological mapping and clinical correlates that substantiate each facet of the SFE (see Figure 4).

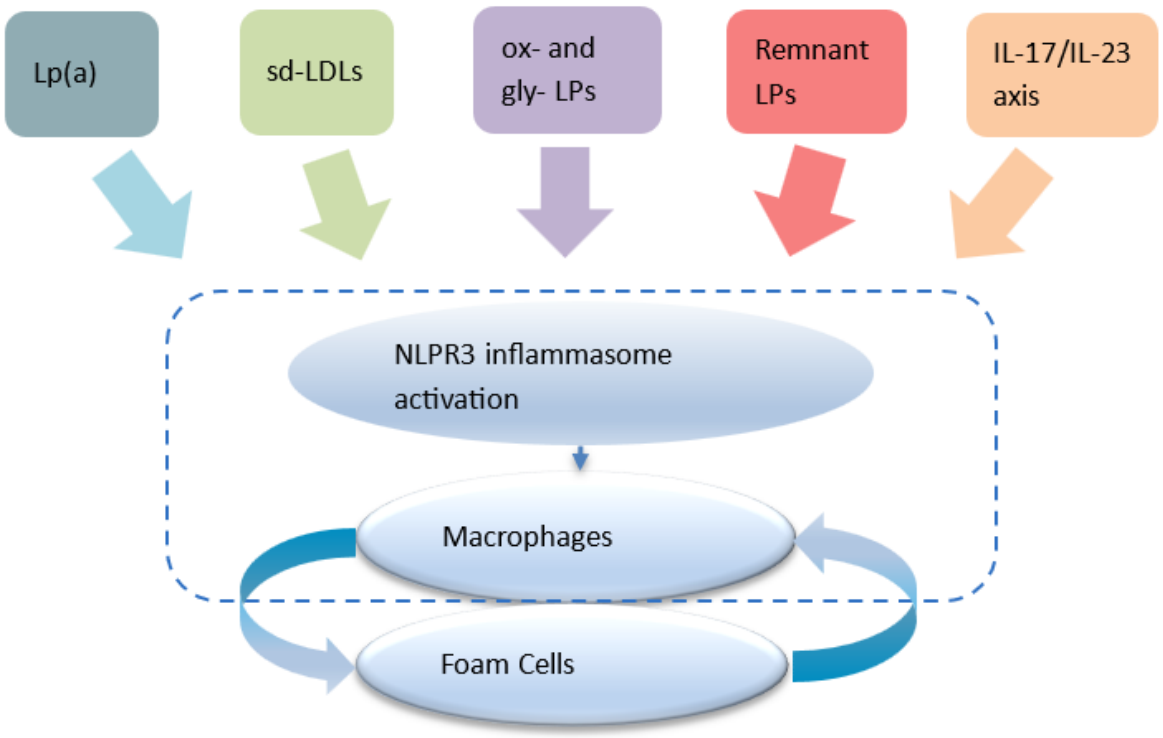


**Figure 4.** Parallel amplification pathways converging on the inflammatory floor. Schematic illustrating distinct axes, lipoprotein(a), including oxidized phospholipids (Lp(a)–OxPL), oxidized and glycated lipoproteins (ox-LPs and gly-LPs), small dense low-density lipoprotein (sd-LDL), remnant lipoproteins (remnant LPs), and IL-17/IL-23 signaling, converging on activation NLRP3 inflammasome in arterial macrophages, thereby promoting foam cell persistence. *Lp(a):* Carries OxPLs that serve as damage-associated molecular patterns, directly triggering NLRP3 and IL-1β release in macrophages [45,46,51]; Apo(a) kringle repeat modulates OxPL burden [75,76]. *sd-LDL:* Prone to oxidative modification and increased endothelial retention; engages lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1) and cluster of differentiation 36 (CD36), generating reactive oxygen species and activating NF-κB [77–79]. *Remnant LPs:* Cholesterol-rich remnants penetrate the intima, activate

[6] While IL-1β–induced insulin resistance is supported by human and animal data, the bidirectional loop involving macrophages remains under active investigation

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TLR2/4 on macrophages, and impair cholesterol efflux via ATP-binding cassette sub-family A member 1 (ABCA1) downregulation [80,81]. *IL-17/IL-23 axis:* Vascular Th17 cells secrete IL-17A/IL-22, upregulating MMPs and downregulating IL-10 in macrophages, thereby sustaining foam cell survival [41–44].

Supporting Evidence

Molecular Mechanisms

- Histological mapping of human plaques confirms the persistence of macrophage-driven inflammation in morphologically stable lesions, reinforcing the concept of a durable, non-resolving inflammatory floor even in the absence of systemic flare markers [82].
- Statins increase IL-1β in macrophages in a dose-sensitive, NLRP3-dependent manner [11,27]
- Disruption of Rac1 and protein prenylation alters macrophage phenotype [49]
- M2 macrophages retain pro-inflammatory characteristics under chronic statin exposure [83]
- Foam cells are maintained due to impaired mobility and IL-1β-mediated LDL uptake [54]
- Geranylgeraniol supplementation mitigates statin-induced inflammasome activation [84]

*Clinical Correlates*

- Dose-dependent diabetes risk with statin therapy; mechanistic human evidence indicates statin-associated GLP-1 reduction contributes to this phenotype [13]
- Residual risk concentrated in secondary prevention populations [24,85]
- Colchicine reduces CV events by ~34% in statin-treated patients [6]
- Early vs late statin initiation shows different inflammatory profiles [32]
- Although statin therapy often reduces [CRP] to within the clinically acceptable range as measured by hs-CRP assays [86], concentrations may still exceed thresholds associated with arterial inflammation and cardiovascular risk. In other words, [CRP] falls, but not necessarily far enough to extinguish the inflammatory floor that sustains residual events. Meta-analytic evidence confirms that, even with optimal [LDL-C] reduction, many patients continue to experience cardiovascular events, often in association with persistent, albeit subclinical, elevations in inflammatory markers [23,32].
- Arterial vs Systemic Inflammation Decoupling: reflects systemic IL-6 levels, while NLRP3 activation is local and may be insulin resistance-amplified [26]. Positron Emission Tomography (PET) imaging shows arterial vs systemic dissociation [86].
- PCSK9 inhibitors show diminishing returns in heavily statin-treated populations [87]

*Biomarker Evolution Patterns*

- Initial [CRP] reduction followed by plateau or slight increase, while IL-18 levels remain elevated and predictive of cardiovascular death in both stable and unstable angina [33]
- Persistent elevation of IL-18 in high-dose statin users [88]
- Divergence between systemic and arterial inflammatory markers [86]
- Elevated IL-1β and IL-18 remain predictive of adverse cardiovascular outcomes despite LDL-C lowering, consistent with persistent inflammasome activity [63]

The persistence of inflammatory signaling despite intensive [LDL-C] lowering indicates that the Statin Floor Effect represents a plausible molecular and cellular state, discernible through biomarker trajectories. This framework provides a rationale for therapeutic strategies that extend beyond statin intensification to address the immunometabolic mechanisms sustaining the floor.

## 4. Therapeutic Implications

The mechanistic framework suggests that residual cardiovascular risk persists because of a localized, statin-induced inflammatory floor. This recognition redirects therapeutic emphasis away from further intensification of statin monotherapy toward targeted combination approaches. The

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following predictions and implementation strategies are derived directly from the framework and highlight opportunities for earlier, more individualized interventions.

*Refined Biomarker Strategy and Monitoring*

Dynamic Biomarker Panel

A refined biomarker strategy is central to detecting and monitoring the inflammatory floor phenotype. Table 2 outlines a proposed dynamic panel that integrates inflammatory mediators, metabolic indices, and lipid-related markers to provide longitudinal resolution of residual risk.

**Table 2. Inflammatory and Metabolic Biomarkers Relevant to the Statin Floor Effect.**

| Biomarker | Mechanistic Role | Interpretive Value | Preferred Monitoring |
|---|---|---|---|
| **ApoB** | Structural protein for all atherogenic lipoproteins | Direct measure of total atherogenic particle burden | Immunoassay; preferable to LDL-C in residual risk evaluation |
| **IL-1β** | Primary NLRP3 inflammasome effector cytokine | Direct marker of inflammasome activation and macrophage priming | Plasma assay (ELISA or multiplex) |
| **IL-18** | Co-product of NLRP3 activation | Correlation with plaque activity; elevated in persistent risk | Plasma assay; potential for plaque-specific imaging correlation |
| **IL-18/IL-10 Ratio** | Balance between inflammation and resolution | Indicator of inflammatory floor and impaired resolution capacity | Calculated from serum cytokine panel |
| **TNF-α** | Promotes foam cell persistence, metabolic dysfunction | Marker of chronic plaque inflammation and macrophage dysfunction | Serum or plasma; longitudinal tracking preferred |
| **CRP** | Downstream IL-6–driven acute-phase reactant | Systemic surrogate for residual inflammatory risk | Standard clinical immunoassay |
| **Adiponectin** | Anti-inflammatory adipokine is suppressed in insulin resistance | Negative correlation of NLRP3 activation | ELISA or multiplex adipokine panel |
| **HOMA-IR** | Composite index of insulin resistance | Proxy for systemic metabolic reinforcement of NLRP3 | Derived from fasting insulin and glucose |
| **GLP-1** | Incretin reduced by statins via microbiota–bile acid axis | Lower levels flag insulin-resistance amplification under statins; candidate for UDCA rescue | Fasting plasma GLP-1 (stabilized tubes); paired with HOMA-IR |

Abbreviations not previously mentioned: ELISA, enzyme-linked immunosorbent assay; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance. NB: Elevated IL-17 levels may serve as a biomarker for heightened Th17 activity in atherosclerotic patients [40,89].

Functional Assays

- Ex vivo macrophage polarisation capacity
- LDL uptake studies

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- Inflammasome activation assays

Precision Monitoring Strategy

- *Genetic screening:* 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), NLRP3, IL-1β, Rac1 variants
- *Baseline phenotyping:* Metabolic and inflammatory profile assessment
- *Longitudinal tracking:* Biomarker evolution over therapy duration
- *Imaging correlation:* Arterial inflammation persists despite systemic reduction[7] [90]; advanced PET tracers such as $^{18}$F-NaF (detecting microcalcification) and $^{68}$Ga-DOTATATE or $^{68}$Ga-PentixaFor (targeting activated macrophages or C-X-C chemokine receptor type 4 (CXCR4) expression) provide tissue-specific insight into persistent plaque activity, helping distinguish inflammatory floor regions from systemic responses [86,91]

The mechanistic framework outlined above generates a set of predictions that can be evaluated in clinical cohorts and experimental systems. These predictions span the clinical, mechanistic, and interventional domains, linking biomarker trajectories with cellular behavior and therapeutic outcomes. By formalizing them, the framework provides a pathway from conceptual synthesis to empirical validation.

*Testable Predictions*

Clinical Predictions

- On maximal-dose statin therapy, IL-1β/IL-18 will fall initially in step with [LDL-C], but after 12–24 months will plateau or rebound, so that at long-term steady-state (≥2 years) patients have higher IL-1β/IL-18 despite [LDL-C] remaining low
- Carriers of HMGCR or NLRP3 variants show greater susceptibility to the inflammatory floor effect
- Arterial inflammation persists on PET imaging despite systemic normalization
- Statin-induced diabetics show higher arterial inflammatory markers independent of glycemic control

Mechanistic Predictions

- Statin-treated macrophages express M2 markers but retain IL-1β secretion[8]
- Geranylgeraniol supplementation suppresses IL-1β without altering [LDL-C]
- Early vs late statin exposure yields distinct epigenetic and inflammatory profiles
- Anti-inflammatory agents benefit genetically susceptible patients more than average

Intervention Predictions

- Early combination therapy prevents inflammatory floor effect establishment
- Metformin co-therapy lowers localized IL-1β levels and diabetes risk
- Biomarker-guided statin dosing improves risk/benefit balance
- Genetic profiling enables earlier combination treatment
- Adjunct UDCA will restore GLP-1 and attenuate elevated blood glucose and insulin-resistance amplification in patients on high-intensity statins [13]

[7] [CRP] reflects measured concentrations via hs-CRP assay, and there is a distinction between clinical targets and immunologic sufficiency

[8] Bentzon et al. have extensively characterized macrophage dynamics in plaque progression and regression models, forming a foundational framework for interpreting phenotypic transitions in atherosclerosis.

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*Clinical Implementation Strategy*

Translating these mechanistic insights into practice requires a structured approach to patient stratification and therapy sequencing. Figure 5 summarizes a proposed clinical implementation framework that links risk tiers to biomarker-guided monitoring and combination treatment strategies.

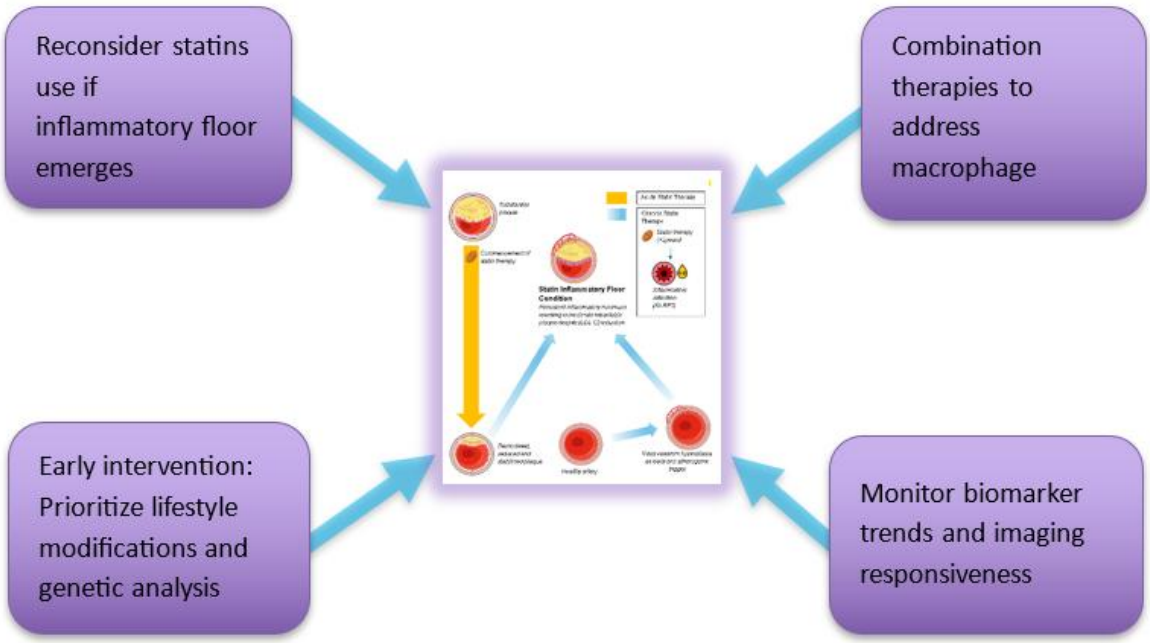


**Figure 5.** Proposed Clinical Implementation Strategies. Framework linking early lifestyle modification, genetic risk assessment, and biomarker-guided monitoring to individualized treatment decisions. The figure emphasizes reconsideration of high-intensity statin therapy if an inflammatory floor phenotype emerges, the use of imaging and biomarker trends to guide precision intervention, and the role of combination therapies targeting macrophage dysfunction.

*Risk Stratification Approach*

- *Aggressive systolic blood pressure control:* (120-90 mmHg) and polyphenol-rich diets may blunt mechanical and immunometabolic triggers, reducing NLRP3 activation, improving insulin sensitivity, and lowering endothelial shear stress, to support plaque resolution [92–94]
- *Low Risk:* Statin monotherapy, routine monitoring
- *Moderate Risk:* Enhanced biomarker tracking, conditional combination therapy
- *High Risk:* Immediate combination therapy and intensive monitoring

*Precision Medicine Integration*

- One off determination of [LP(a)]
- Genetic testing to identify susceptible variants
- Metabolic and inflammatory baseline profiling
- Individualized ApoB, LDL-C, and inflammatory targets
- Dynamic treatment adjustments
- Therapeutic approaches that enhance Treg function or suppress Th17 responses could be beneficial, as suggested by recent insights into T-cell roles in atherosclerosis [95,96]

*Therapeutic Sequencing*

1. Pre-Phase (Structural Priming and Vascular Neogenesis)
   In the SFE framework, adventitial vasa vasorum hyperplasia and diffuse intimal hyperplasia

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prime arteries for lipid retention and inflammation, Yang et al. showed in rabbits that adventitial vasa vasorum proliferation precedes intima–media thickening and predicts plaque development [97]. Following this, diffuse intimal hyperplasia (DIH), as described by Subbotin, may further predispose to lipid retention by increasing oxygen diffusion distance and creating localized hypoxia. This facilitates smooth muscle cell phenotypic modulation and extracellular matrix accumulation [98]. Together, adventitial vasa vasorum and DIH can create a permissive terrain upon which lipids accumulate and immune processes initiate. Identifying and interrupting these early, pre-lipid stages may offer an opportunity for pre-emptive vascular therapy in at-risk individuals.

2. Phase 1 (0–6 months): Statin therapy initiation
3. Phase 2 (6–24 months): Monitor for inflammatory floor effect
4. Phase 3 (>2 years): Maintain combination therapy for at-risk individuals

*Research Priorities and Study Design*

Building on the predictions derived from the framework, specific research priorities can be defined to test, refine, and extend the model. These include longitudinal human studies, targeted intervention trials, mechanistic validation in preclinical systems, and integrative modeling approaches. Together, these strategies provide a roadmap for translating the SFE concept into evidence-based clinical practice.

Longitudinal Mechanistic Studies

- 5-year biomarker tracking studies
- Stratified cohorts by genetic risk
- Human arterial tissue sampling
- PET imaging to correlate markers with inflammation

Intervention Trials

- Early statin + anti-inflammatory randomized controlled trials
- Biomarker-guided versus standard care dosing
- Metformin combination trials
- Personalized therapy based on genomic risk

Mechanistic Validation

- Murine models to examine NLRP3–foam cell trajectory
- Ex vivo validation of macrophage phenotypes
- Prospective validation of biomarker panels

Modeling Research

A multiscale hybrid model, combining statin pharmacokinetics, adherence, and plaque biomechanics, predicts plateaued regression and persistent plaque despite ongoing therapy, implying unmodeled resistance factors and, even without NLRP3 detail, supporting a residual inflammatory floor [99]. Several pharmacologic and systems-biology models demonstrate nonlinear, plateauing statin responses aligned with the framework; notably, Mylonas et al.'s fractional-calculus dose-response model identified thresholds where lipid-lowering plateaus and cellular toxicity/oxidative stress emerge, consistent with in vitro inflammasome priming [28]. Separately, Lei et al. modeled the growth of necrotic cores in atherosclerotic plaques under statin influence, showing that while progression slows, it rarely reverses completely, reinforcing the concept of partial resolution limitations central to the SFE construct [100]. While these models do not simulate NLRP3 activation or T-cell polarization explicitly, their combined outcomes support a multidimensional framework in which statin efficacy is modulated by nonlinear biology, treatment timing, and tissue-specific effects.

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*Clinical Implications and Future Directions*

The framework also carries immediate clinical relevance and longer-term implications for cardiovascular medicine. By guiding risk stratification, informing therapeutic combinations, and shaping precision medicine approaches, it has the potential to reshape both patient care and research priorities. Future directions extend beyond statin therapy alone, toward broader immunometabolic strategies and innovative therapeutic development.

Immediate Clinical Applications

- Biomarker screening for residual inflammatory risk
- Early combination therapy consideration
- Avoid unnecessary statin up-titration in the inflammatory floor effect phenotype
- Better risk communication strategies

Long-Term Paradigm Shifts

- Broaden to immunometabolic cardiology
- Genetically informed prevention models
- Simultaneous targeting of lipid, metabolic, and immune pathways
- Integrated biomarker and imaging-based care models
- While NLRP3 remains the most extensively characterized inflammasome in atherosclerosis, other complexes such as absent in melanoma 2 and NOD-like receptor family CARD domain containing 4 may also contribute to vascular inflammation [53]. Recognizing the pivotal role of adaptive immunity in atherosclerosis, future paradigms may shift towards immunomodulatory therapies [50,101]. Their integration into the SFE framework awaits further mechanistic clarity.

Therapeutic Innovation Opportunities

- NLRP3-specific anti-inflammatory therapies
- Fixed-dose statin + anti-inflammatory combinations
- Genetic testing panels for cardiovascular risk
- Point-of-care inflammatory biomarker devices
- *Adventitial vasa vasorum modulation:* Early detection and targeting of proliferation, via ultrasound or contrast-enhanced imaging, may offer a window to prevent downstream plaque formation before intimal thickening or immune infiltration
- *Structural-stage targeting:* Therapeutic modulation of DIH and matrix remodeling, especially in metabolically susceptible individuals, may delay or prevent the creation of lipid-retentive terrain. This approach expands risk-reduction efforts upstream of lipid-lowering or anti-inflammatory therapies.
- *Targeted modulation of Lp(a)-associated risk* - is now achievable through gene-silencing therapies such as pelacarsen (antisense oligonucleotide), olpasiran and zerlasiran (small interfering RNAs, siRNAs), which have been shown to reduce [Lp(a)] by up to 90% in clinical trials. These agents provide precision strategies for genetically mediated [Lp(a)] elevation.
- Statins can variably raise [Lp(a)] in some individuals, though this effect is not universal and may not always be clinically significant
- Novel agents like muvalaplin (an oral inhibitor of Apo(a)-ApoB binding) offer non-injectable alternatives
- While colchicine does not reduce [Lp(a)], it may blunt downstream inflammation triggered by Lp(a)-bound OxPLs, offering potential therapeutic synergy in high-risk inflammatory phenotypes

*Why This Framework Matters*

Clinical Relevance

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- Explains paradoxes in residual cardiovascular risk
- Enables identification of patients needing intensified therapy
- Enhances clinical efficiency via better risk stratification
- Supports enhanced cardiovascular disease risk reduction

Scientific Impact

- Postulates a unifying mechanistic model
- Encourages precision research designs
- Enhances biomarker development
- Sets the stage for future immunometabolic therapies

**Therapeutic Potential**

- *RNA-silencing approaches:* Recent preclinical studies demonstrate that hepatocyte-targeted siRNA and GalNAc-conjugated oligonucleotides against Farnesyl-diphosphate Farnesyltransferase 1 (FDFT1) achieve >70% knockdown of squalene synthase mRNA, reduce plasma [LDL-C] by 30–40%, and attenuate atherosclerotic lesion development in animal models. Early human Phase I data with GalNAc–FDFT1 siRNA suggest durable [LDL-C] lowering with quarterly subcutaneous dosing and a favorable safety profile [102,103].
- *Combination with Statins:* Preclinical co-administration of low-dose statin plus FDFT1 siRNA yielded additive [LDL-C] lowering (~60-70% total) and greater atherosclerotic plaque regression than either alone, supporting a dual-mechanism strategy to overcome the inflammation floor of statin monotherapy
- *Targeting the rescue of the impaired synthesis of MK-4:* a form of vitamin $K_2$ that modulates inflammatory resolution and mitochondrial homeostasis - although direct clinical evidence is lacking, murine studies show that statins can suppress MK-4 formation in extrahepatic tissues. MK-4 deficiency impairs activation of matrix Gla protein (MGP), promoting microcalcification, and may enhance NLRP3 inflammasome activity by removing antioxidant and anti-NF-κB restraints [104]. Observational human data further link low circulating [MK-4] with greater coronary calcification, suggesting a plausible translational mechanism [105]. Thus, MK-4 depletion may represent a second direct molecular axis, alongside geranylgeranyl gyrophosphate / Rac1 disruption, through which statins promote a persistent inflammatory floor within atherosclerotic lesions. This again illustrates the paradoxical effect of statins in that they also enhance plaque stabilization through calcification.
- *FDFT1 silencing:* limits squalene-derived isoprenoids, reducing macrophage endoplasmic reticulum stress and NLRP3 activation, offering a novel strategy to target the inflammatory floor
- *IL-10:* may drive post-MI plaque regression and myocardial remodeling by enhancing M2 polarization, suppressing MMP-9, and boosting mitochondrial function, but its efficacy falls off above ~1 μg/mL, highlighting the need for controlled delivery [106]
- *Eicosapentaenoic acid (EPA)-driven plaque reduction:* a meta-analysis of 23 intravascular ultrasound trials showed each 1% decrease in percent atheroma volume was linked to a 19% lowering of MACE [107], and in statin-treated coronary artery disease patients, a higher ratio of EPA-derived mediators (18-hydroxyeicosapentaenoic acid + resolvin E1) to leukotriene $B_4$ strongly predicted actual plaque regression [108]
- *New gene-editing approaches:* such as VERVE-102, which offers durable, possibly lifelong PCSK9 silencing in humans, may further decouple [LDL-C] lowering from the immunometabolic disruptions observed with statins and thus represent an ideal platform for combination therapy targeting inflammatory floor mechanisms [109]
- *Unique protein dysregulations:* opportunities lie in their discovery by the application of proteomics mass spectrometry, paving the way to new therapies and mechanistic insights. Early spatially resolved proteomic studies of human plaques [110] (preprint) suggest that arterial PCSK9 secretion, ECM remodeling, and region-specific inflammatory pathways may be

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particularly tractable targets, underscoring the value of local proteomic mapping for future therapy development.

These therapeutic strategies and research priorities emphasize the SFE as a clinically relevant and experimentally tested construct, setting the stage for the conclusion of its greater significance.

## 5. Conclusions

The *Statin Floor Effect* framework integrates clinical and molecular observations to account for the early reduction in cardiovascular events with high-dose statin therapy and the subsequent plateau in benefit. Beyond [LDL-C] lowering, prolonged statin exposure may plausibly establish a localized arterial inflammatory state, driven by NLRP3 inflammasome activation, adaptive immune modulation, and depletion of metabolic cofactors, that constrains further risk reduction. Framed in this way, the construct offers both a coherent explanation for long-standing therapeutic paradoxes and a foundation for precision strategies aimed at overcoming residual cardiovascular risk.

Some aspects remain to be substantiated in larger human studies, but their inclusion highlights valuable avenues for mechanistic investigation and the identification of novel therapeutic targets. Clarifying the relative contribution of each mechanism will be essential to refining the model and informing intervention design.

While non-statin interventions often demonstrate extended, near-linear benefit within 2–5 year studies, their long-term trajectories may also converge toward asymptotic limits beyond typical follow-up durations. From a clinical perspective, the framework suggests that optimal risk reduction is likely to require combining lipid-lowering with interventions that ameliorate residual inflammation and metabolic dysregulation. Prospective studies incorporating serial biomarker assessments and carefully timed adjunct therapies will be essential to test the Statin Floor Effect and to determine whether addressing the "inflammatory floor" can extend and complement the benefits of statin treatment.

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**Conflict of Interest:** None declared.

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