Discontinuation of statin therapy – an updated review

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Purpose of review
This narrative review aims to provide an updated synthesis of the recent epidemiology, clinical determinants, and consequences of statin discontinuation.

Recent findings
Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, with elevated low-density lipoprotein cholesterol (LDL-C) representing a key modifiable risk factor. Statins are first-line lipid-lowering agents that reduce major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality. Despite their efficacy, statin discontinuation and suboptimal adherence remain common. Discontinuation rates within the first-year range widely (0.8–70.5%), with higher rates observed in primary prevention populations. Factors associated with discontinuation include male sex, non-White ethnicity, smoking, and lack of insurance, whereas secondary prevention is consistently associated with better persistence. Interestingly, polypharmacy demonstrated conflicting associations across studies. Overall, approximately 40% of patients fail to achieve optimal adherence. Discontinuation is consistently associated with increased cardiovascular events, hospitalizations, and all-cause mortality.

Summary
Statin discontinuation and poor adherence remain major barriers to effective cardiovascular risk reduction. Addressing patient-, clinician-, and system-level determinants is essential to improve long-term adherence and clinical outcomes.

Keywords
adherence, cardiovascular disease, statin discontinuation, statin therapy

INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide [1]. Elevated low-density lipoprotein cholesterol (LDL-C) levels are a major modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), and lipid-lowering therapy represents a cornerstone of both primary and secondary prevention strategies [2▪]. Statins are first-line agents for LDL-C lowering and have been consistently demonstrated to reduce major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality across a wide range of patient populations [3]. Despite their well-established efficacy, statin non-adherence and discontinuation remain common in clinical practice, with a substantial proportion of patients interrupting therapy temporarily or permanently [4▪▪]. In 2009, Daskalopoulou highlighted early evidence suggesting that statin discontinuation may be associated with adverse cardiovascular outcomes and should be avoided when possible [3]. Since that time, dyslipidemia management guidelines have evolved substantially, while additional observational and interventional data have emerged, particularly in the context of polypharmacy, adverse effects, and deprescribing in older adults. The objective of this narrative review is to provide an updated synthesis of the biological mechanisms, clinical determinants, implications, and consequences of statin discontinuation.

BIOLOGICAL MECHANISMS OF STATIN THERAPY AND DISCONTINUATION

Statins primarily inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

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KEY POINTS

- Statin discontinuation is common (0.8–70.5% within the first year), and approximately 40% of patients fail to achieve optimal adherence.
- Discontinuation and poor adherence are associated with increased cardiovascular events, including MI and stroke, and higher mortality, with a graded increase in risk as adherence declines.
- Discontinuation is driven by perceived muscle symptoms, nocebo effects, and external influences such as misinformation and mistrust.
- Many patients can tolerate statins upon rechallenge, with up to 67% successfully resuming therapy and only about one-third demonstrating true intolerance.

[5]. This inhibition upregulates hepatic LDL receptors, increasing clearance of circulating LDL-C, thereby substantially reducing plasma LDL-C levels. Beyond lipid lowering, statins exert pleiotropic effects, including anti-inflammatory, antioxidant, endothelial-protective, and anti-thrombotic actions [6–8], which collectively reduce the risk of myocardial infarction (MI), ischemic stroke, and cardiovascular death, even in old and very old populations treated for primary prevention [9,10]. Consequently, statin discontinuation leads to loss of both lipid-lowering and pleiotropic effects, triggering physiological changes that increase cardiovascular risk. The benefits of statin therapy and the consequences of its discontinuation are summarized in Fig. 1.

After cessation, restoration of hepatic cholesterol synthesis and downregulation of LDL receptors result in rising LDL-C levels, promoting vascular lipid deposition and accelerating atherosclerosis in coronary, carotid, cerebral, and peripheral arteries [11,12]. Plaques with large lipid cores and thin fibrous caps are particularly prone to rupture [13,14]. Statins reduce plaque lipid content [15], decrease macrophage infiltration [16], and promote the formation of a thicker, more stable fibrous cap [17,18]; discontinuation reverses these effects, resulting in more lipid-rich, inflammatory plaques with weakened caps that increase susceptibility to rupture and trigger acute thrombosis, leading to MI and ischemic stroke [11].

Statins also exert significant anti-inflammatory effects by reducing circulating inflammatory markers such as C-reactive protein and modulating vascular immune activity [19,20▪]. Discontinuation reactivates inflammatory pathways, increasing cytokine production and promoting plaque progression and

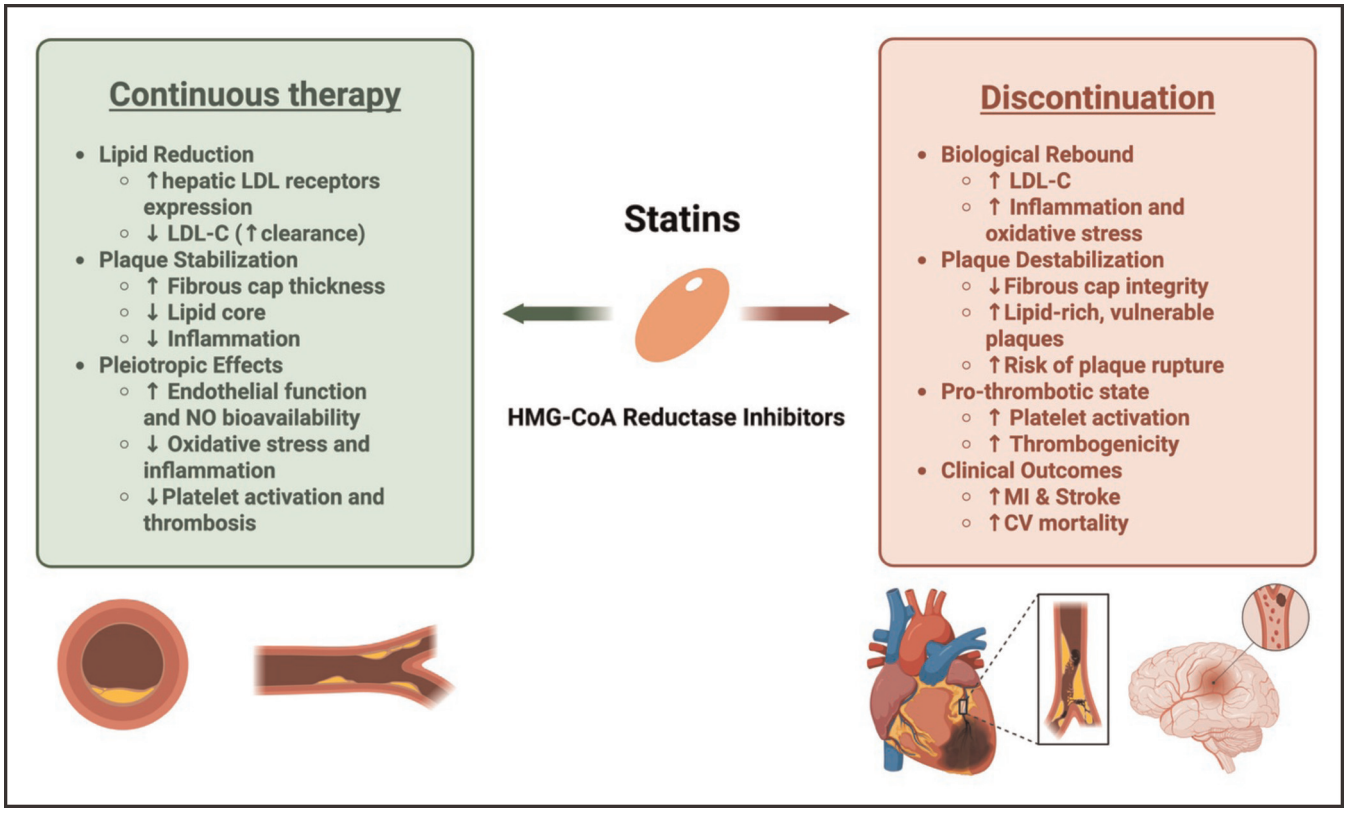

FIGURE 1. Beneficial effects of statin therapy and consequences of discontinuation. LDL-C, low-density lipoprotein cholesterol; NO, nitric oxide; MI, myocardial infarction; CV, cardiovascular.

instability [21]. Additionally, endothelial function is also affected; statins enhance nitric oxide bioavailability and vasodilatory, anti-adhesive properties [22], whereas withdrawal leads to endothelial dysfunction, reduced vasodilation, and increased vascular tone [23], with a more pro-inflammatory, pro-adhesive endothelial state that impairs blood flow and increases cardiovascular risk.

In parallel, statins exert anti-thrombotic properties by reducing platelet activation, limiting thrombin generation, and improving fibrinolytic balance [24,25]. Discontinuation shifts this equilibrium toward increased platelet reactivity and thrombogenicity, particularly in unstable plaques, where rupture-induced thrombosis can rapidly occlude an artery [26]. In high-risk settings, abrupt statin withdrawal may precipitate an acute rebound phenomenon characterized by rapid endothelial dysfunction, increased oxidative stress and inflammation [21]. These abrupt changes may explain early cardiovascular events after discontinuation, even before substantial lipid changes occur. Additionally, chronic cessation further removes the cumulative protective effects of statins on atherosclerosis progression, allowing plaque growth to resume and increasing long-term cardiovascular risk.

EPIDEMIOLOGY

Statin discontinuation and suboptimal adherence remain highly prevalent worldwide, with substantial variability across study designs, populations, and definitions of discontinuation. In a 2024 systematic review including 52 studies and over 4.2 million individuals, Ageeb *et al.* reported first-year statin discontinuation rates ranging from 0.8% to 70.5%, with higher discontinuation rates observed in primary prevention populations [4▪▪]. Factors associated with increased discontinuation included male sex, non-White ethnicity, smoking status, and lack of insurance coverage, whereas secondary prevention indications and interestingly, polypharmacy, were associated with greater treatment persistence. Among studies reporting outcomes, discontinuation was associated with increased cardiac-related admissions within 6 and 12 months and higher all-cause mortality. Similar findings have been observed in large real-world cohorts. In a retrospective Spanish cohort of over 400 000 individuals, Martín-Fernández *et al.* demonstrated significantly higher adherence and persistence among prior statin users compared with first-time users, particularly in secondary prevention settings [27▪▪].

Beyond discontinuation alone, adherence remains suboptimal even among patients who continue therapy. A 2025 systematic review and meta-analysis by Basios *et al.*, including 76 studies and nearly 6 million participants, estimated that the prevalence of good adherence (defined as >80%) to statin monotherapy was 62.4%, with higher adherence in secondary prevention compared with primary prevention (64.4% vs. 57.5%) [28▪▪]. Lower adherence was associated with female sex, depression, active smoking, Black race, and heart failure, whereas older age, prior MI, hypertension, polypharmacy, and multimorbidity were associated with improved adherence. Despite these findings, the association between polypharmacy and statin adherence remains inconsistent across studies, with some reporting improved adherence [27▪▪,28▪▪], and others suggesting that increased regimen complexity and polypharmacy may contribute to discontinuation [29▪▪,30]. Overall, approximately 40% of patients fail to achieve optimal adherence, highlighting statin discontinuation and non-persistence as ongoing and clinically significant barriers to effective cardiovascular risk reduction in contemporary practice.

DETERMINANTS OF STATIN DISCONTINUATION

Discontinuation of statin therapy is multifactorial. Muscle-related symptoms are the most frequently reported reason for stopping treatment [31,32], typically as myalgia, weakness, or proximal muscle cramps. These symptoms frequently occur without creatine kinase elevation and may reflect underlying musculoskeletal disease rather than drug toxicity. Contemporary definitions of statin intolerance emphasize that symptoms alone do not establish causality and that intolerance exists as a spectrum, from partial to complete inability to tolerate therapy [33].

Perceived intolerance is strongly influenced by expectations about adverse effects. Blinded studies in patients who previously discontinued statins show similar symptom burden during placebo and statin exposure, suggesting a substantial nocebo contribution. In the Self-Assessment Method for Statin Side-effects or Nocebo (SAMSON) N-of-1 trial, approximately 90% of symptom burden was reproduced by placebo tablets [34], while the Statin Web-based Investigation of Side Effects (StatinWISE) randomized N-of-1 trial found no meaningful difference in muscle symptoms between statin and placebo groups [35]. Collectively, these findings help explain higher intolerance rates reported in observational studies compared with blinded randomized trials.

Patient-driven factors also contribute to discontinuation. Patients may stop therapy due to concerns about long-term medication use, polypharmacy, perceived lack of benefit, or fear of adverse effects, sometimes without consulting their physician [29▪▪]. In the Provider Assessment of Lipid Management (PALM) Registry, over half of statin-eligible patients cited

side-effect concerns as the primary reason for refusal or discontinuation [36]. Because statins may be used to treat an asymptomatic condition, patients who feel well may question the need for continued therapy, particularly if lipid levels improve or cardiovascular risk is not fully understood. Additionally, external influences, including media coverage and online information, can further shape perceptions of statin safety, with negative reporting associated with increased discontinuation, likely by amplifying concerns about side effects and undermining trust in therapy [37,38]. Exposure to conflicting or inaccurate information, particularly through non-scientific sources, may reinforce fears and contribute to nonadherence even among patients at high cardiovascular risk.

Despite these factors, many patients can tolerate statins upon rechallenge. In a retrospective cohort of patients with prior statin intolerance, approximately 67% resumed statin therapy after a median of 17 months. Patients were managed with either same-statin rechallenge, an alternative statin switch, or non-statin therapy. Those who resumed statins achieved greater LDL-C reductions compared with those maintained on non-statin therapy (-38.8 $\pm$ 3.4% for same-statin rechallenge, vs. –36.4 $\pm$ 2.9% for statin switch, vs. –17.3 $\pm$ 4.5% for non-statin therapy; $P = 0.0007$) [39]. Evidence from a recent systematic review supports this, with intolerance reported in 36% of patients receiving statins vs. 26% receiving placebo, with no significant differences in symptom score [40]. Notably, only about one-third of participants were unable to tolerate statins on rechallenge, while approximately 16% reported intolerance in the non-statin group, suggesting perhaps the nonspecific nature of reported symptoms. These findings indicate that permanent discontinuation after an initial adverse experience may be premature and that structured rechallenge strategies can help differentiate true pharmacologic intolerance from coincidental or expectation-related symptoms.

CONSEQUENCES OF STATIN DISCONTINUATION AND NONADHERENCE

Evidence across populations links statin discontinuation with adverse outcomes. In patients with acute MI, withdrawal was associated with increased mortality. In a population-based cohort of individuals (n = 9939) who survived at least 90 days following their first MI, Daskalopoulou *et al.* reported increased 1-year all-cause mortality [hazard ratio (HR) 1.88, 95% confidence interval (CI) 1.13–3.07] compared with individuals who were not treated with statins, suggesting potential harm from abrupt withdrawal [41]. Similarly, Kim *et al.* evaluated 3807 Korean patients who survived one year after acute MI, of whom 603 (15.8%) discontinued statin therapy [42]. Statin withdrawal was associated with significantly higher long-term mortality compared with continued statin use, largely driven by increased cardiac death (HR 4.65, 95% CI 3.14–6.87). Similar associations have also been observed beyond coronary disease. In a prospective Brazilian cohort study, Vitturi and Gagliardi followed 479 patients admitted with acute ischemic stroke between 2014 and 2018 for 24 months, stratifying patients based on statin adherence and withdrawal [43]. Statin withdrawal occurred in 54 patients (15.7%) and was associated with significantly worse functional outcomes and a markedly increased risk of stroke recurrence, with discontinuation conferring an adjusted odds ratio of 4.70 (95% CI 2.47–8.94) for recurrent stroke [43]. Importantly, evidence from large secondary prevention cohorts indicates that even partial non-adherence carries measurable risk. In a large retrospective cohort study of 347 104 adults with established ASCVD treated within the U.S. Veterans Affairs Health System (2013–2014), Rodriguez *et al.* assessed statin adherence using the medication possession ratio (MPR) and followed patients for a mean of 2.9 ($\pm$0.8) years. Compared with patients with very high adherence (MPR $\geq$ 90%), lower adherence was associated with a graded increase in all-cause mortality, with the lowest adherence group (MPR $<$ 50%) demonstrating a significantly higher risk of death (adjusted HR 1.36, 95%, CI 1.34–1.38). These findings support a dose–response relationship between statin non-adherence and mortality in stable secondary prevention populations [44,45▪].

More recent evidence further supports this association. In a 2024 systematic review (n = 1 708 684), Peixoto *et al.* demonstrated that discontinuation was associated with a higher risk of all-cause mortality (HR 1.92, 95% CI 1.52–2.44), cardiovascular mortality (HR 1.63, 95% CI 1.27–2.10), and MACE (HR 1.31, 95% CI 1.23–1.39) [46▪▪]. Similarly, a 2024 systematic review by Ageeb *et al.* including 52 studies and over 4.2 million patients reported that statin discontinuation was common and associated with an increased risk of adverse cardiovascular outcomes. Among studies reporting clinical outcomes, discontinuation was linked to higher all-cause mortality within the first year, with HRs ranging from 1.36 (95% CI 1.08–1.70) to 3.45 (95% CI 2.81–4.24) across individual studies [4▪▪].

Global data further highlight the persistence of this issue. In the multinational Prospective Urban Rural Epidemiology (PURE) cohort, Joseph et al. conducted a large prospective analysis evaluating trends in secondary prevention medication use across 17 countries grouped by income level. Over a median

12 years of follow-up, use of one or more secondary prevention medication class, including statins, remained low globally and decreased from 41.3% at baseline to 31.3% by the final visit. In lower-middle income countries, use declined to 13.4%, highlighting persistent gaps in evidence-based therapy after coronary artery disease or stroke [47▪]. Even within high-income health systems, long-term persistence remains poor. Koenig *et al.* performed a retrospective real-world cohort study using German prescription data including 865,732 new statin users, followed for up to 39 months. Persistence declined steeply, with 71% of statin users discontinuing therapy by 300 days, and only 20.6% remaining persistent at 36 months. Although adherence among persistent users remained relatively high (mean proportion of days covered 0.84), these findings demonstrate that long-term discontinuation is extremely common, even in a high-income health system [48].

Importantly, adherence appears to modify clinical outcomes in a graded fashion. Jones et al. conducted a systematic review and meta-analysis including 39 observational studies evaluating objective adherence/persistence to lipid-lowering therapy in patients with established ASCVD. Using an adherence threshold of 80% or greater, good adherence was associated with significantly reduced risk of death (HR 0.56, 95% CI 0.34–0.92), major adverse cardiovascular events (HR 0.77, 95% CI 0.68–0.86), and MI (HR 0.86, 95% CI 0.79–0.95), with a non-significant reduction in cardiovascular death (HR 0.44, 95% CI 0.12–1.60) and ischemic stroke (HR 0.83, 95% CI 0.58–1.18). These results provide strong contemporary evidence that poor adherence or discontinuation of lipid-lowering therapy is associated with worse cardiovascular outcomes in secondary prevention populations [49▪▪]. These findings are supported by additional large meta-analytic evidence. Basios *et al.* included 66 studies comprising 3 345 718 individuals and evaluated the relationship between statin adherence and ASCVD outcomes [50]. Good statin adherence compared with poor adherence was associated with significantly reduced risk of all-cause mortality [relative risk (RR) 0.65, 95% CI 0.56–0.76], cardiovascular events (RR 0.76, 95%, CI 0.72–0.80), MI (RR 0.70, 95% CI 0.62–0.80), and stroke (RR 0.68, 95% CI 0.46–1.00). Importantly, statin discontinuation was associated with a markedly increased mortality risk (RR 1.90, 95% CI 1.33–2.71), reinforcing that withdrawal of statin therapy is not a benign clinical decision [50]. Collectively, these findings indicate that statin discontinuation and suboptimal adherence remain prevalent worldwide and are consistently associated with significant clinical harm across both primary and secondary prevention populations.

CONCLUSION

Statin discontinuation represents a crucial and underrecognized barrier in cardiovascular prevention. Key drivers include perceived statin-associated muscle symptoms, the nocebo effect, and the influence of misinformation from non-scientific sources. As a result, suboptimal adherence or complete withdrawal from statin therapy is consistently associated with worse clinical outcomes, including increased cardiovascular morbidity and mortality. Emerging data highlighting the role of the nocebo effect and the success of structured rechallenge strategies suggest that a substantial proportion of individuals labeled as statin intolerant may ultimately tolerate and benefit from therapy. These findings underscore the importance of a proactive, patient-centered approach that focuses on patient education, shared decision-making, and individualized treatment strategies. Future research should prioritize the development and implementation of pragmatic interventions to improve long-term adherence and integrate adherence as a central component of cardiovascular risk management, particularly in high-risk populations such as those with established cardiovascular disease, recent acute events, or advanced age.

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Conflicts of interest

There are no conflicts of interest.

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