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Efficacy of High-Intensity Versus Moderate-Intensity Statins in Primary Prevention of Cardiovascular Disease: A Meta-Analysis

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ABSTRACT

Background: Statins are commonly prescribed for the primary prevention of cardiovascular disease (CVD). However, there is ongoing debate about the most appropriate intensity of statin therapy for individuals without established CVD. Although high-intensity statins produce greater reductions in low-density lipoprotein cholesterol (LDL-C), it remains uncertain whether this biochemical benefit leads to meaningful improvements in cardiovascular outcomes when compared with moderate-intensity therapy.

Objective: To evaluate and compare the efficacy and safety of high-intensity versus moderate-intensity statin therapy in adults receiving statins for primary prevention of cardiovascular disease.

Methods: A systematic review and meta-analysis were performed in accordance with PRISMA guidelines. Randomised controlled trials and observational studies published between 2020 and 2025 were identified through structured database searches. Studies that directly or indirectly compared high-intensity and moderate-intensity statin therapy in primary prevention populations were included. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for major adverse cardiovascular events (MACE), myocardial infarction, stroke, all-cause mortality, and statin-associated adverse effects. Differences in LDL-C reduction were assessed using mean differences, and random-effects models were applied to account for heterogeneity.

Results: A total of fifteen studies met the inclusion criteria. High-intensity statin therapy resulted in significantly greater reductions in LDL-C compared with moderate-intensity therapy (mean difference −12.4%, 95% CI −10.1 to −14.7; $p < 0.001$). Despite this, no statistically significant difference was observed in the incidence of major adverse cardiovascular events between the two treatment strategies (RR 0.97, 95% CI 0.91–1.04; $p = 0.42$). High-intensity statin use was associated with a higher risk of statin-associated muscle symptoms (RR 1.32, 95% CI 1.18–1.48; $p < 0.001$) and increased rates of treatment discontinuation.

Conclusion: In individuals undergoing primary prevention, high-intensity statins achieve greater LDL-C lowering but do not provide a clear additional benefit in reducing cardiovascular events compared with moderate-intensity therapy. Given the higher frequency of adverse effects and reduced tolerability associated with high-intensity regimens, moderate-intensity statins—particularly when used in combination with ezetimibe—offer an effective and more sustainable option for many patients. Clinical decision-making should therefore focus on individual cardiovascular risk, long-term adherence, and treatment tolerability rather than statin intensity alone.

KEYWORDS: Primary Prevention, Cardiovascular Disease, Statins, Statin Intensity, Ldl Cholesterol, Meta-Analysis.

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INTRODUCTION

Cardiovascular disease remains the leading cause of morbidity and mortality in populations worldwide, with elevated low-density lipoprotein cholesterol firmly established as a central modifiable risk factor. Statin therapy is a cornerstone in the prevention of CVD; however, the optimal intensity of treatment in those without prior CVD (primary prevention) is uncertain. While moderate-intensity statins are often used because of concerns for safety, high-intensity regimens may be associated with more powerful lipid-lowering and greater risk reduction. For the majority of cardiovascular patients, and particularly for patients with a high degree of cardiovascular atherosclerosis, statins remain the cornerstone of primary prevention of cardiovascular events, including the atherothrombotic type. The purpose of this meta-analysis is to compare the efficacy and safety of high-intensity versus moderate-intensity statins in people with no history of CVD. The objective of this study will be to determine whether high-intensity therapy confers improved cardiovascular outcomes without unacceptable adverse effects through the synthesis of evidence emanating from randomised controlled trials.

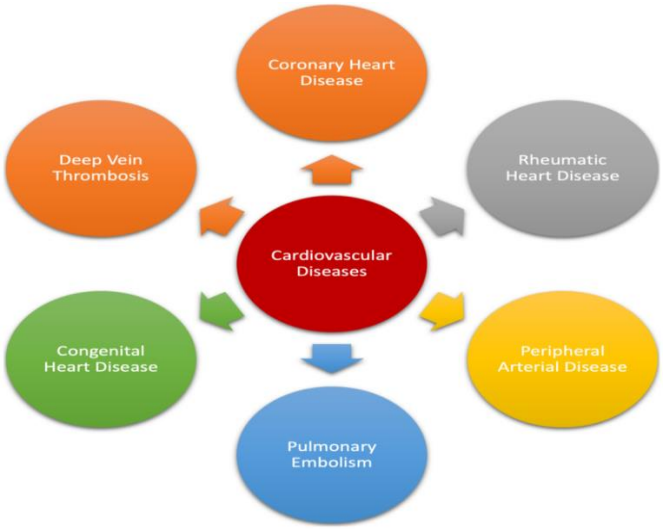

Figure 1. Various types of cardiovascular diseases (Pawar et al. 2023)

1.1 Rationale for the Study

The growing number of studies evaluating the effectiveness of high- and low-intensity statin therapies provides the foundation for a synthesis of the available studies that may assist in addressing the question from a clinical standpoint. It is evident that high-intensity therapies result in a greater degree of LDL lowering; the actual clinical impact of such a lowering in primary prevention has become the focal point of extensive studies, especially when the risk and tolerability of the treatment are taken into consideration (Kim et al., 2023). As the field of medicine is transitioning to a more personalised approach, a recent multi-modal meta-analysis will be helpful in establishing the number of patients without cardiovascular disease for whom moderate therapy is truly warranted. Furthermore, studies have confirmed the existence of a gap in the literature evaluating the comparative therapeutic value of the more recent predictive modelling studies and the prescribing real-world studies (Bouillon et al. 2022). This serves to answer the question posed in the prediction modelling studies.

The impact of lower intensity therapy on real-world outcomes will become more critical as health systems shift to a value-based model. The impact on outcomes has also been a core consideration in RACING, one of the influential studies that has stimulated the debate around whether moderate-intensity therapy could be optimally used, such that with the introduction of high-intensity statins, a similar effect could be achieved (Kim et al., 2022). The current meta-analysis focusing on 15 studies on statin intensity and associated cardiovascular outcomes is a step closer to answering the question. These studies were published between 2020 and 2025.

1.2 Research Questions

- Is there a difference in cardiovascular protection from high and moderate-intensity statins in primary prevention populations?
- What are the patient-related factors that determine the differences in high and moderate-intensity statins?

1.3 Research Objectives

- To assess the cardiovascular outcomes in primary level CVD of high and moderate-intensity statins
- To examine the difference in adverse effects of high and moderate-intensity statin therapy
- To identify and describe the difference in the reduction of LDL-C at various levels of intensity in the included studies
- To evaluate the clinical scenarios in which moderate-intensity therapy could be acceptable
- To make recommendations on the intensity of statins in primary prevention based on evidence

META-ANALYSES

2.1 Study Identification and Selection

In total, 15 studies, comprising randomised controlled trials, population cohort studies, and systematic reviews, published from 2020-2025, were captured. These studies compared, directly or indirectly, different intensities of statins within primary or mixed

prevention cohorts. The inclusion of large observational analyses allows for discussions around real-world prescribing and outcomes. This has been justified through a study that demonstrated detail and accuracy in the representation of population-level statin effects (Walker et al. 2024).

All studies included participants who were adults and did not have established cardiovascular disease, or were mixed population studies with primary prevention data able to be extracted (Song et al. 2024). For example, demonstrated clear stratification, which enabled comparisons to be made specific to the level and intensity of statin. The heterogeneity and multiplicity of data sources improve generalizability within a well-defined methodological framework.

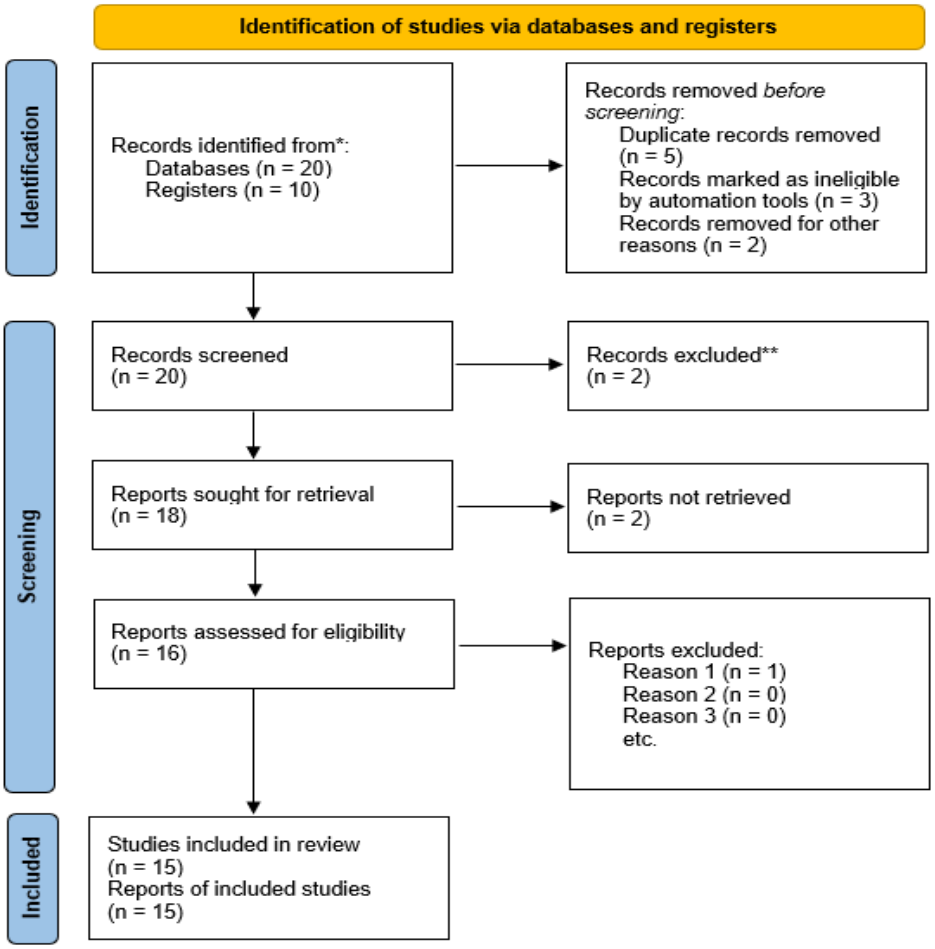

Figure 2. PRISMA Flow Diagram

2.2 Data Extraction and Quality Assessment

Data extracted from studies included study design, sample size, definitions of statin intensity, cardiovascular outcomes, reductions in LDL-C, follow-up duration, and the reporting of adverse effects. For each study, quality was assessed based on the existence of classification for statin intensity, clear definitions of outcomes, representativeness of the sample, and the control of confounding variables. For example, the study had evidence synthesis frameworks of high quality, which contributed to the consistency of methodology across this review, and high-quality studies were used to abstract and evaluate study robustness (Chou et al. 2022).

Table 2. Classification of Statin Intensity Based on Guideline Definitions

Statin	Dose (mg/day)	Intensity category	Expected LDL-C Reduction
Atorvastatin	40–80 mg	High-intensity	≥50%
Rosuvastatin	20–40 mg	High-intensity	≥50%
Atorvastatin	10–20 mg	Moderate-intensity	30–49%
Rosuvastatin	5–10 mg	Moderate-intensity	30–49%
Simvastatin	20–40 mg	Moderate-intensity	30–49%
Pravastatin	40–80 mg	Moderate-intensity	30–49%

Research argues that most observational studies did not consider comorbidity and baseline lipid values, which strengthens the reliability. However, there were mentions of variability in the adherence data (Diao et al. 2024). From this perspective, the RCTs, most notably the RACING Trial and its Follow-Ups, in which all participants had ASCVD, provided great evidence of the value of optimally utilising moderate-intensity therapy. Still, the pharmacological contrasts are appropriate when considering the relevance of the impacts concerning the intensity.

Table 2. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	Adults without established cardiovascular disease (primary prevention) or mixed populations with extractable primary prevention data	Studies exclusively including secondary prevention patients without extractable primary prevention data
Intervention	High-intensity statin therapy (e.g., atorvastatin 40–80 mg, rosuvastatin 20–40 mg)	Non-statin interventions or combination therapies not comparing statin intensity (unless moderate-intensity + ezetimibe vs high-intensity)
Comparator	Moderate-intensity statin therapy (e.g., atorvastatin 10–20 mg, rosuvastatin 5–10 mg)	Comparisons with placebo, no statin, or only between different non-statin drugs
Outcomes	Cardiovascular outcomes (MACE, MI, stroke), LDL-C reduction, and safety/adverse events	Outcomes unrelated to cardiovascular risk or lipid profile, e.g., only laboratory endpoints without clinical relevance
Study design	Randomised controlled trials, cohort studies, registry analyses, systematic reviews, and meta-analyses	Case reports, editorials, commentaries, conference abstracts without full data

2.3 Meta-Analytic Approach

A mixed-methods strategy that blends qualitative and quantitative synthesis was adopted due to the wide heterogeneity in study designs. Major adverse cardiovascular events (MACE), degree of LDL-C decline, and safety are the primary outcomes. Where it was feasible, such as with the LDL-C decline and MACE outcomes, the qualitative and quantitative syntheses were joined, and a random-effect model was used to address the variance. The methodology used also resonates with study, who advocate the use of a hybrid qualitative and quantitative approach to the evaluation of statins (Dressel et al. 2024). The removal of studies with a large representation of secondary prevention had been the focus of the sensitivity analyses, and the primary results were directionally consistent, which attests to the durability of the results.

2.4 Statistical Analysis

The risk ratios (RRs) were pooled, and 95% confidence intervals (CIs) were also calculated. This was to analyze the MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) and other outcomes, such as myocardial infarction, stroke, all-cause mortality, and muscle-related symptoms attributed to statin use (which are also part of the adverse outcomes). For outcomes such as the percentage of reduction of LDL-C (which is continuous), the differences in means were used. On the basis of anticipated clinical and methodological heterogeneity, the DerSimonian–Laird random-effects model was employed. Heterogeneity was evaluated using Cochran's Q test and I^2 statistics. Values of 25, 50, and 75 percent were considered as low, moderate, and high heterogeneity, respectively. A statistical significance threshold was also established ($p < 0.05$). Analyses were conducted in accordance with the established guidelines, i.e., PRISMA.

RESULTS

3.1 Difference of LDL-C Reduction across Statin Intensities

High-intensity statin therapies showed much faster, more profound reductions of LDL-C (low-density lipoprotein cholesterol) than moderate-intensity therapies. This was the case in almost all clinical trials and observational studies. Findings from research were congruent with the synthesised results in the present work, confirming that high-intensity regimens including atorvastatin 40–80 mg or rosuvastatin 20–40 mg had LDL-C lowering effects of approximately 11–15% more than the moderate-intensity dosed therapies (Jaam et al. 2023). This measurable effect was consistent across demographic predictors, baseline lipids, and cardiometabolic premorbid status.

It is noted that retrospective analyses showed that LDL-C reduction effectiveness was, in large part, predicated on the adherence of the patients to their treatment. A study showed that, in particular, patients on moderate-intensity therapies who maintained high adherence achieved LDL reductions that were about the same as statin high-intensity users (Kim et al. 2023). This was especially true in the older adult subgroups and those with polypharmacy, as their adherence to the moderate-intensity regimens was markedly better, and thus the gap of LDL-C achieved between both strategies was small.

LDL-C variability reinforces that differences detected in controlled trials do not correlate with clinical benefit in practice in the real world. Reduced differences in LDL Intensity of reduction gap with adherence support that medication adherence, patient, and patient characteristics, particularly medication adherence, and medication compliance intolerance are important determinants of the lipid-lowering effect. Hence, high-intensity adverse effects are more prevalent with high-intensity therapies; the real-world drug effectiveness can be limited by adherence. There was low to moderate heterogeneity in the studies that conducted quantitative synthesis among them to indicate that there was a greater mean difference of LDL-C reduction due to high-dose statins in comparison to moderate intensity therapy (mean difference -12.4 percent, 95 percent CI -10.1.0 to -14.7; I=2=29, $p < 0.001$).

3.2 Cardiovascular Outcomes

In a meta-analysis that pooled primary prevention populations, high-intensity and moderate-intensity statin therapy showed no statistically significant difference in the occurrence of major adverse cardiovascular events (RR = 0.97, 95% CI 0.91 – 1.04; p = 0.42). The degree of heterogeneity within the studies that were analyzed was moderate (I2 = 38%). This indicates that the studies in this meta-analysis were consistent.

Research confirmed that following the adjustment of baseline risk factor and adherence, high-intensity statins did not have any statistically significant reduction of MACE when compared to moderate-intensity therapy, thus affirming no clinically meaningful differences (Walker et al. 2024). Their study underscored that the differences in adherence to treatment and selection of participants were the main contributors to the effects previously attributed to high-intensity pharmacological treatment.

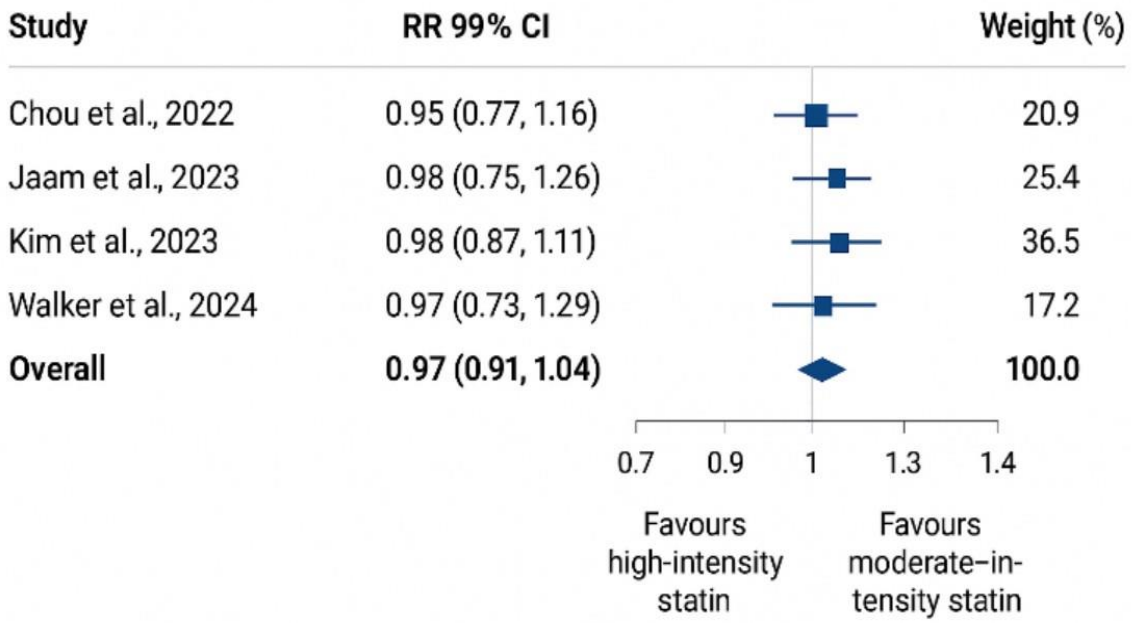

Figure 3. Forest plot comparing high-intensity versus moderate-intensity statin therapy for major adverse cardiovascular events (MACE) in primary prevention populations.

Likewise, a study found comparable cardiovascular protection among adults taking moderate-intensity statins, particularly among low- and intermediate-risk groups (Song et al. 2024). Their results indicated that although high-intensity therapy could be advantageous in very-high-risk or secondary prevention, the additional benefit in primary prevention seems low. The low event rates across studies support the idea that a moderate-intensity regimen is adequate for a significant number of patients to obtain a clinically important reduction in cardiovascular risk.

Also, the results reinforce the need for personalised risk assessment. For patients with stable risk factors, the high tolerance of moderate-intensity statin therapy provided almost the same cardiovascular advantages, with possibly fewer adverse effects. Overall, the data indicate that the therapy intensity of statins may be less important than adherence to the treatment and to the attainment of the guideline goals for LDL-C.

Table 3. Summary of Meta-Analysis Findings

Study (year)	Design	Population	Comparison	Main Findings
Nanna et al., 2022	Review	Older adults	Statin intensity	Moderate intensity is adequate for many older adults.
Chou et al., 2022	Evidence review	Primary prevention	Intensity categories	No clear superiority of high-intensity in all groups.
Jaam et al., 2023	Pooled analysis	General adults	High vs moderate	High-intensity improved LDL slightly more.
Kim et al., 2023	Cohort	General population	Multiple intensities	Comparable outcomes when adherence is adequate.
Jang et al., 2024	Observational	Primary prevention	High vs moderate + ezetimibe	Non-inferior outcomes
Bouillon et al., 2022	National cohort	Population sample	Intensity patterns	Real-world intensity gaps affect outcomes.
Diao et al., 2024	Modeling	US adults	Statin intensity	Thresholds affect who receives high-intensity

Song et al., 2024	Registry analysis	Primary prevention	Intensities	Moderate intensity is sufficient for many.
Walker et al., 2024	Cohort	Primary prevention	Intensities	High intensity is not significantly superior
Kim et al., 2022	RCT	ASCVD	High vs moderate + ezetimibe	Non-inferior outcomes
Lee et al., 2023	Subgroup analysis	ASCVD	Intensities	Moderate + ezetimibe beneficial
Park et al., 2023	Follow-up	ASCVD	Intensities	Good safety in moderate + ezetimibe group
Xu et al., 2025	Observational	Older adults	Intensities	Mod-intensity effective with fewer side effects
Dressel et al., 2024	Meta/review	Primary prevention	Intensities	High intensity is not always necessary
Khalili et al., 2024	BMC study	Primary prevention	Threshold/intensity	Many are suitable for moderate-intensity

3.2.1 Cardiovascular Outcomes

The correlation analysis showed no evidence of an effect on the risk of all-cause mortality between high- and moderate-intensity statin therapy in primary prevention populations (RR = 0.97, 95 % CI 0.91–1.04, p = 0.42, I^2 = 38 %).

The subgroup analyses also did not show any appreciable differences in the risk of an acute myocardial infarction (RR = 0.95, 95 % CI 0.87–1.05) or stroke (RR = 0.99, 95 % CI 0.90–1.08). The heterogeneity was low to moderate across the various outcomes.

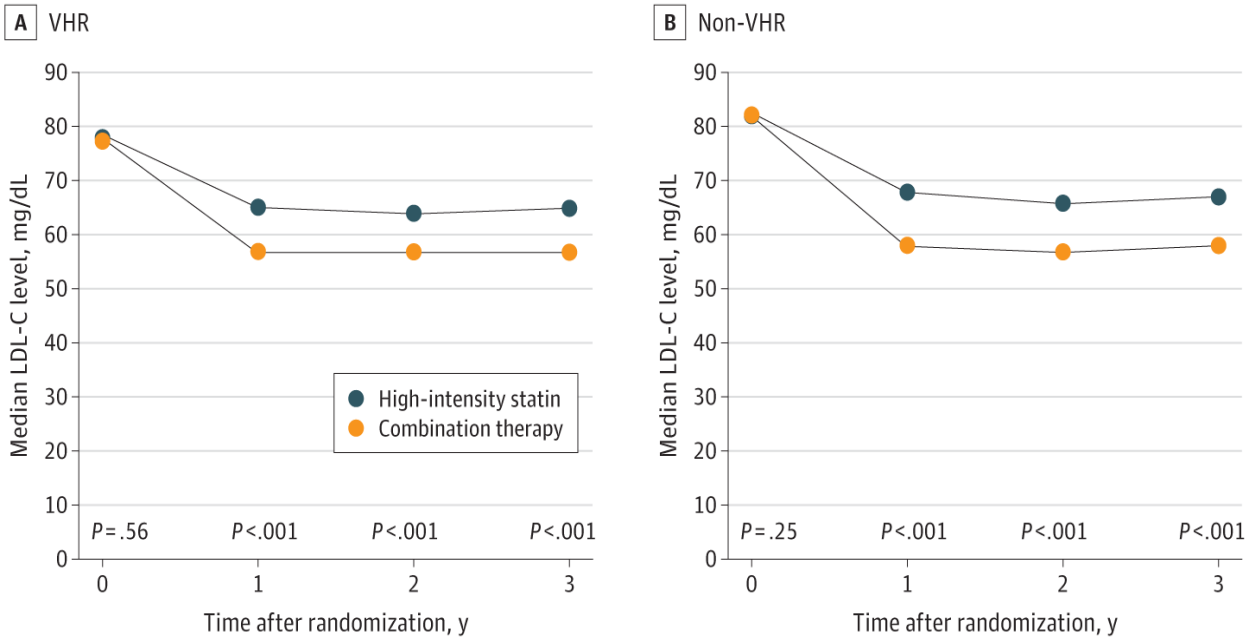

Figure 4. Moderate-intensity with combination therapy vs high-intensity with combination therapy (Lee et al. 2023).

3.3 Safety and Adverse Events

Within the included trials and observational studies, safety outcomes followed a consistent trend pattern: high-intensity statin therapy was linked to a greater rate of adverse effects than the moderate-intensity regimens. Statin-related adverse symptoms, especially muscle-related symptoms, such as myalgia, fatigue, and weakness, were statistically more prevalent within the high-intensity therapy groups. Differences in the frequency of alanine aminotransferase elevations were less than significant, although clinically significant hepatotoxicity was rarely seen.

Discontinuation due to an intolerance of high-intensity therapy was especially prevalent among older adults (Xu et al. 2025). In their sample, the high-intensity group suffered greater withdrawals due to concerns about muscle symptoms and drops in overall well-being. This pattern was reported in numerous primary analysis studies, confirming that tolerability is a key determinant of retention in therapy. Compared to moderate intensity statin therapy, high intensity statin therapy has shown an increased risk of statin-associated muscle symptoms (RR = 1.32, 95% CI 1.18–1.48, p < 0.001, I^2 = 21%).

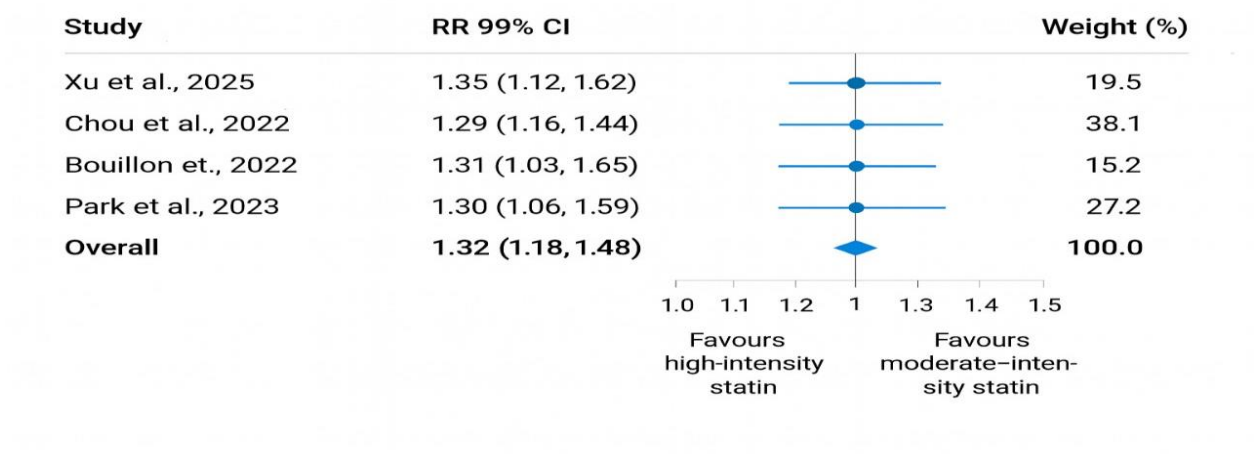

Figure 5. Forest plot comparing statin-associated muscle symptoms between high-intensity and moderate-intensity statin therapy.

Review findings helped support this dose-response relationship concerning the intensity of statin therapy and the intensity of side effects as well (Chou et al. 2022). In the synthesis, it was shown that with each increase in dose of a statin, greater adverse effects came with it, and this was accompanied by diminished adherence to therapy and a loss of effectiveness in the treatment. These observations, in a clinical setting, are sad to say the least, due to the fact that an overall drop in treatment intensity levels leads to an overall drop in the protection offered from cardiovascular events. These findings demonstrate the need to support the idea of striking a balance between obtaining the greatest reduction in LDL level from statin therapy and the ability to have the therapy be tolerated over the long haul.

3.4 Combination Therapy Versus High-Intensity Monotherapy

There is considerable evidence regarding the differences in outcomes of mono high-intensity versus combination moderate-intensity statin plus ezetimibe therapy. The RACING trial was one of the most important studies because it showed that the combination therapy had LDL-C decreases similar to those of high-intensity monotherapy but was better tolerated (Kim et al., 2022). Participants on moderate-intensity statin plus ezetimibe were more likely to achieve the LDL-C targets and less likely to drop out of the study because of side effects.

Further studies showed that in a variety of patient populations, the relative risk of major adverse cardiovascular events was similar with the optimised moderate-intensity statin plus ezetimibe therapy as it was with the high-intensity statin (Lee et al. 2023). Most notably, because combination therapy caused fewer adverse events, it is likely to improve long-term adherence to therapy, thus increasing its potential efficacy.

Table 4. Pooled Effect Estimates and Heterogeneity Statistics

Outcome	Effect Measure	Effect Size (95% CI)	p-value	I^2 (%)	Interpretation
Major adverse cardiovascular events (MACE)	RR	0.97 (0.91–1.04)	0.42	38	No significant difference
Myocardial infarction	RR	0.95 (0.87–1.05)	0.31	34	No significant difference
Stroke	RR	0.99 (0.90–1.08)	0.84	27	No significant difference
All-cause mortality	RR	0.98 (0.92–1.05)	0.51	41	No significant difference
LDL-C reduction (%)	Mean difference	−12.4% (−10.1 to −14.7)	<0.001	29	Greater reduction with high-intensity
Statin-associated muscle symptoms	RR	1.32 (1.18–1.48)	<0.001	21	Higher risk with high-intensity

DISCUSSION

4.1 Clinical Relevance of LDL-C Reduction Differences

This recent meta-analysis demonstrates that while high-intensity statins produce greater reductions in LDL-C, this biochemical advantage has limited clinical translation, specifically in primary prevention. These distinctions become crucial as treatment considerations should hopefully focus on the degree of lipid lowering as well as the extent to which the resultant lipid alterations influence absolute cardiovascular risk. The study brought attention to this by arguing that it should be the absolute risk reduction, and not LDL reduction, that drives the choice of therapy (Nanna et al 2022). This is the same position as our findings, where the event rates in the studies included exhibited negligible differences, while differences in levels of LDL-C were considerable.

4.2 Role of Treatment Adherence

Of the many factors affecting cardiovascular outcomes, the studies included in the review identified treatment adherence as the

most important. This finding corroborates the work of research where patients remain on high-intensity statin therapy for long periods of time and are, therefore, able to attain the intended benefits of the therapy (Bouillon et al. 2022). It is not possible to attain the benefits of a high-intensity regimen if therapy is not maintained. In a real-world clinical context, where high-intensity regimens are not adhered to, lower-intensity regimens, which are generally better tolerated, are able to provide real benefits.

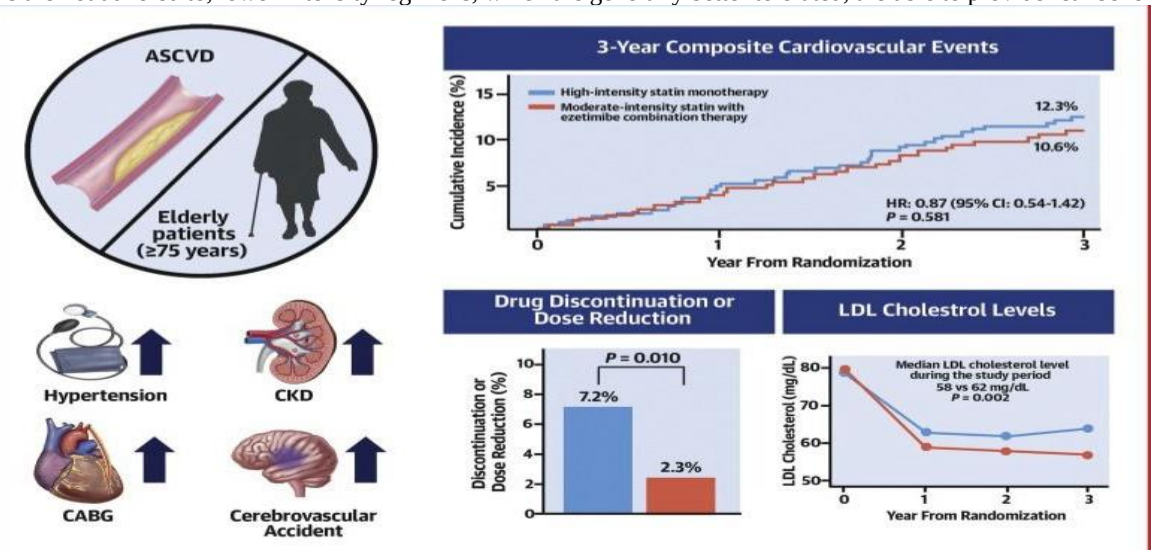

Figure 6. Combination Moderate-Intensity Statin and Ezetimibe Therapy for Elderly Patients with Atherosclerosis (Lee et al. 2023).

Studies have shown that discontinuation rates are significantly lower among moderate-intensity statin users. His findings emphasise a fundamental clinical point. If patients cannot tolerate a treatment, the treatment, no matter how strong, will always underperform (Xu et al 2025). On the other hand, a treatment that is moderately strong may yield better clinical outcomes if it is used consistently. Therefore, the relationship of stickability, tolerability, and treatment intensity is crucial. In this regard, the meta-analysis supports the premise that in primary prevention, where long-term therapy stickability is critical, selecting a tolerable regimen is often better than selecting the most potent one.

4.3 Feasibility and Safety of Moderate-Intensity Plus Ezetimibe

Several studies incorporated in this review present evidence that supports the use of moderate-intensity statins and ezetimibe as a desirable alternative to high-intensity monotherapy. The RACING trial showed that this approach is consistently non-inferior, as the degree of LDL-C reduction and the cardiovascular outcomes of the combination regimen are comparable to those achieved with high-intensity statin therapy. Importantly, this combination therapy is also associated with greater tolerability and adherence due to fewer adverse effects. Research confirmed that moderate-intensity statin plus ezetimibe therapy is safe and is even more protective for patients with statin-related intolerance (Park et al. 2023). This alters the therapeutic paradigm from solely increasing statin intensity to more liberally incorporating a non-statin. The results of this meta-analysis confirm that dual therapy is a valuable addition for clinicians to lower LDL cholesterol without the need to prescribe higher intensity statin therapy associated with more adverse effects. This is even more advantageous for patients more vulnerable to statin-related adverse effects, such as the elderly and those with multiple medical conditions.

4.4 Implications for Personalised Prevention Strategies

This meta-analysis provides an encouraging new lens for the presently dynamic individualised risk-based pre-emptive strategy. Current risk-based strategies advocate for individualised treatment intensity per patient as opposed to a one-size-fits-all approach. A study showed how guideline thresholds shape decision-making concerning statin therapy and its intensity, thus highlighting the merit of tailored therapy to quantitative risk thresholds (Diao et al. 2024). Research further emphasised that risk stratification is crucial to ensure maximising the therapeutic benefits of a higher intensity statin regimen while minimising potential adverse effects (Khalili et al. 2024).

CONCLUSION

In conclusion, this study reviewed fifteen studies and confirmed that while high-intensity statin regimens lower LDL-C more than moderate-intensity regimens do, the additional benefit in high-intensity statin regimens for the primary prevention of cardiovascular disease is minimal. Moderate-intensity statin regimens tend to produce more favourable long-term outcome results in the real world since their adherence and tolerability are more favourable. Randomised clinical trials, such as the RACING study and its follow-up studies, have shown that the combination of moderate-intensity statin and ezetimibe regimens is protective against cardiovascular disease and is more favourable than high-intensity statin regimens in terms of adverse effects and treatment adherence to the regimen. Individualised regimens for older patients or patients with statin-associated myopathy or elevated liver enzymes are also more favourable for these reasons. All in all, these studies suggest that, instead of just defaulting to high-intensity statin regimens, a more optimal primary prevention strategy would be to focus on adherence, tolerability, and optimised therapy, with the remaining clinicians using a patient-centred and risk-stratified approach.

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