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Association Between Gut Microbiota Composition and Statin Responsiveness in Hyperlipidemic Patients: A Meta-Analysis

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ABSTRACT

Background: Statin therapy remains a cornerstone in the management of hyperlipidemia and prevention of cardiovascular events. However, interindividual variability in statin response poses a major clinical challenge. Emerging evidence suggests that the gut microbiota may influence lipid-lowering efficacy by modulating drug metabolism, bile acid composition, and systemic lipid pathways. This meta-analysis aims to evaluate the association between gut microbiota composition and responsiveness to statin therapy among hyperlipidemic patients. **Methods:** A systematic search of PubMed, Scopus, Embase, and Cochrane CENTRAL databases was conducted through May 2019. Studies were included if they assessed lipid outcomes (LDL-C, total cholesterol, HDL-C, triglycerides) in statin-treated patients, with or without gut microbiota analysis. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated using a random-effects model. Risk of bias was assessed using the Cochrane Risk of Bias tool and Newcastle-Ottawa Scale. Publication bias was evaluated via funnel plot inspection. **Results:** Three studies (n = 884 participants) met the inclusion criteria. Pooled analysis showed that rosuvastatin significantly reduced LDL-C (SMD = -0.62; 95% CI: -1.00, -0.23; p = 0.002) and total cholesterol (SMD = -0.36; 95% CI: -0.60, -0.13; p = 0.003) compared to control groups. No significant differences were observed in HDL-C or triglyceride levels. One included study demonstrated that statin responders had distinct gut microbiota profiles, including reduced alpha diversity and increased abundance of Blautia species. **Conclusion:** This meta-analysis supports the superior lipid-lowering efficacy of rosuvastatin and highlights the potential role of gut microbiota in modulating statin response. Integration of microbiome profiling into lipid management strategies may advance personalized therapy for hyperlipidemia. Further large-scale studies are needed to validate these findings and explore microbiota-targeted interventions.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, with hyperlipidemia being one of its most significant modifiable risk factors [1]. Statins, or HMG-CoA reductase inhibitors, have become the cornerstone of lipid-lowering therapy, with substantial evidence supporting their efficacy in reducing low-density lipoprotein cholesterol (LDL-C) levels and preventing major cardiovascular events [2]. However, interindividual variability in statin response has become an increasingly recognized clinical challenge. A considerable proportion of patients fail to achieve target LDL-C reductions despite adherence to standard statin therapy, a phenomenon often referred to as "statin non-responsiveness" [3].

The observed variability in statin efficacy has traditionally been attributed to factors such as genetics, lifestyle, comorbidities, and pharmacokinetics [4]. More recently, the gut microbiota has emerged as a novel contributor to drug metabolism and therapeutic outcomes. The human gut harbors trillions of microorganisms, collectively

referred to as the gut microbiome, which play critical roles in metabolic regulation, immune modulation, and xenobiotic metabolism [5]. There is growing evidence that the gut microbiota can influence the pharmacokinetics and pharmacodynamics of numerous medications, including statins, by altering their bioavailability, systemic circulation, and hepatic uptake [6].

Multiple experimental and clinical studies have suggested that the gut microbiota may affect statin efficacy through several mechanisms. These include microbial transformation of drug compounds, regulation of bile acid metabolism, and modulation of inflammation and lipid absorption [7]. For example, specific microbial taxa have been shown to convert statins into less active forms or to influence the expression of hepatic LDL receptors, thereby altering lipid-lowering responses [8]. Additionally, microbial metabolites such as short-chain fatty acids (SCFAs) and secondary bile acids may indirectly affect lipid homeostasis and hepatic cholesterol biosynthesis [9].

A landmark study by Liu et al. [10] investigated the gut microbiota composition of statin responders versus non-responders in hyperlipidemic patients treated with rosuvastatin. Their findings demonstrated that responders had significantly different microbial profiles, including reduced alpha diversity and a relative enrichment of the genus Blautia, which has previously been associated with favorable metabolic outcomes [11]. This study provided one of the first direct clinical links between microbiota composition and differential statin response. However, similar findings have not yet been widely replicated, and the extent to which microbiota influences lipid outcomes remains underexplored.

Given the limited but intriguing evidence, a comprehensive synthesis of the available literature is warranted to better understand the role of gut microbiota in mediating statin responsiveness. Previous meta-analyses have compared the efficacy and safety profiles of different statin agents [12], but none have specifically evaluated the influence of gut microbial composition on lipid-lowering outcomes. Understanding this relationship is essential not only for elucidating mechanisms of statin resistance but also for advancing the field of personalized medicine in cardiovascular care.

Moreover, as the concept of the gut–liver axis gains prominence, researchers have begun to recognize the potential of microbiome-targeted therapies in modulating host lipid metabolism. Dietary interventions, probiotics, and even fecal microbiota transplantation (FMT) have been explored as adjunctive strategies to improve metabolic parameters in dyslipidemic patients [1322]. If the gut microbiota indeed plays a role in mediating statin efficacy, this could open new avenues for optimizing treatment regimens in patients with suboptimal response to conventional therapies.

Therefore, the present meta-analysis aims to evaluate the association between gut microbiota composition and responsiveness to statin therapy in hyperlipidemic individuals. Specifically, this study seeks to synthesize data from clinical trials and observational studies that report lipid profile outcomes (LDL-C, total cholesterol, HDL-C, triglycerides) in relation to gut microbiota characteristics or stratified statin response. By integrating emerging microbiome science with lipidology, this analysis aims to provide clarity on a novel but clinically relevant question and inform future strategies for individualized cardiovascular risk management.

METHODOLOGY

Study Design and Protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was designed prospectively and followed a structured approach to identify, assess, and synthesize relevant clinical studies evaluating the association between gut microbiota composition and statin responsiveness in hyperlipidemic patients.

Eligibility Criteria

Studies were included based on the following criteria: adult patients (aged ≥18 years) diagnosed with hyperlipidemia and treated with statins, particularly rosuvastatin or atorvastatin, with or without gut microbiota assessment. Eligible studies were randomized controlled trials (RCTs), prospective cohort studies, or observational designs that reported changes in lipid parameters such as LDL-C, total cholesterol (TC), HDL-C, and triglycerides (TG). Only studies published in English and with extractable quantitative data were considered. Exclusion criteria included animal studies, non-English publications, conference abstracts, editorials, and studies lacking adequate baseline and post-intervention lipid profile data.

Search Strategy

A comprehensive literature search was performed using four electronic databases: PubMed, Scopus, Embase, and Cochrane CENTRAL, covering all articles published up to May 2025. The search strategy combined controlled vocabulary and free-text terms such as “gut microbiota,” “microbiome,” “statins,” “rosuvastatin,” “atorvastatin,” “LDL-C,” “cholesterol,” and “hyperlipidemia,” using Boolean operators. Reference lists of selected articles were hand-searched for additional relevant studies.

Study Selection

All retrieved records were screened independently by two reviewers in two phases: first by title and abstract, then by full-text review. Discrepancies were resolved through discussion or consultation with a third reviewer. The PRISMA flow diagram was used to summarize the screening and selection process.

Data Extraction

Data from eligible studies were extracted using a predesigned and standardized form. Extracted data included study ID, year of publication, country, sample size, study design, patient demographics, statin type and dosage, duration of treatment, microbiota assessment methods (if reported), and definitions of response to therapy. Outcome data included mean ± standard deviation (SD) values for LDL-C, TC, HDL-C, and TG before and after treatment, along with any reported effect sizes, confidence intervals, and p-values. Two reviewers independently performed data extraction, and a third reviewer verified the accuracy and consistency of the

collected information.

Quality Assessment

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias Tool 2.0 for randomized controlled trials and the Newcastle-Ottawa Scale (NOS) for observational studies. Domains such as randomization, blinding, completeness of outcome data, and selective reporting were assessed. Risk of bias was categorized as low, unclear, or high. The results were synthesized and visualized using RevMan software to aid in the assessment of overall study quality.

Statistical Analysis

Statistical analyses were carried out using Review Manager (RevMan) version 5.4. For continuous variables (LDL-C, TC, HDL-C, and TG), standardized mean differences (SMDs) with 95% confidence intervals were calculated. A random-effects model (DerSimonian and Laird method) was applied to account for heterogeneity across studies. The I^2 statistic was used to evaluate heterogeneity, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Funnel plots were constructed to visually assess publication bias; however, due to the limited number of studies, formal statistical tests such as Egger's test were not performed.

Subgroup and Sensitivity Analyses

Subgroup analyses were initially planned to explore the effects of study design (RCT vs observational), type of statin used, and presence or absence of microbiota profiling. However, due to the small number of included studies and limited data availability, subgroup and sensitivity analyses were not conducted.

Ethical Considerations

As this study involved the analysis of previously published data and did not include any new patient recruitment or direct human subject involvement, ethical approval was not required. All included studies had obtained ethical clearance from their respective institutional review boards, as reported in their original publications.

RESULTS

Table 1

Study Characteristics and Summary

Study ID / Author (Year)	Study Characteristics	Sample Size	Statin Intervention	Response Definition	Microbiota Method	Key Findings	Outcomes	Effect Size & CI
Liu et al. (2018)	China; Prospective observational study with 64 hyperlipidemic patients	n = 64 (33 responders, 31 non-responders)	Rosuvastatin 10 mg/day for 4 weeks	≥20% LDL-C reduction = responder	16S rRNA sequencing of stool samples	Responders had lower α-diversity and distinct microbiota; Blautia enriched in responders	LDL-C, TC, HDL-C, TG	LDL-C drop 3.81→1.58 in responders vs 3.84→2.23 in non-responders
Berne & Siewert-Delle (2005)	Multicenter double-blind RCT in T2DM patients with hyperlipidemia	n = 465 (232 rosuvastatin, 233 atorvastatin)	Rosuvastatin 10–40 mg/day; Atorvastatin 10–80 mg/day for 16 weeks	LDL-C <3.0 mmol/L (European target)	N/A	Rosuvastatin showed superior LDL-C reduction and higher % of patients reaching goal	LDL-C, TC, HDL-C, TG	LDL-C reduction 51% vs 46%; p<0.001
Rosenson et al. (2009)	RCT in metabolic syndrome patients, comparing rosuvastatin, atorvastatin, placebo	n = 318 (136 rosuvastatin, 119 atorvastatin, 63 placebo)	Rosuvastatin/Atorvastatin 10–20 mg/day for 12 weeks	LDL-C <2.59 mmol/L; particle goal attainment	NMR spectroscopy for particles (not microbiota)	Rosuvastatin led to greater LDL-C and particle improvement	LDL-C, TC, HDL-C, TG	p<0.01 between groups; no CI given

Study Characteristics

A total of three studies were included in this meta-analysis, comprising 884 participants, with 401 in the experimental group and 383 in the control group. Liu et al. (2018) conducted a prospective observational study in China on 64 hyperlipidemic patients who received rosuvastatin 10 mg/day for 4 weeks. Responders were defined as those achieving a ≥20% reduction in LDL-C, and gut microbiota composition was assessed via 16S rRNA sequencing, revealing that responders had lower alpha diversity and enrichment of the Blautia genus. Berne & Siewert-Delle (2005) conducted a multicenter double-blind randomized controlled trial in patients with type 2 diabetes and hyperlipidemia, comparing rosuvastatin (10–40 mg/day) with atorvastatin (10–80 mg/day) over 16 weeks, with treatment success defined by achievement of LDL-C <3.0 mmol/L. Rosuvastatin demonstrated superior efficacy in LDL-C reduction. Rosenson et al. (2009) carried out a 12-week RCT in patients with metabolic syndrome comparing rosuvastatin and atorvastatin, with response defined as achieving LDL-C <2.59 mmol/L or reaching particle size goals. While this study did not evaluate gut microbiota, it reported significant improvements in lipid parameters in the rosuvastatin group. Across all studies, the primary outcomes included LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG).

Meta-Analysis Outcomes

LDL-C Reduction: A meta-analysis of LDL-C levels demonstrated a significant reduction favoring the experimental group (rosuvastatin) with a pooled standardized mean difference (SMD) of -0.62 [95% CI: -1.00, -0.23]; p = 0.002. Heterogeneity was high (I^2 = 82%), indicating variability in effect sizes likely due to differences in baseline characteristics, intervention durations, and response definitions across studies.**Total Cholesterol (TC):** Pooled analysis for TC also showed a significant reduction in the experimental group, with SMD = -0.36 [95% CI: -0.60, -0.13]; p = 0.003. Moderate heterogeneity was observed (I^2 = 54%), suggesting partial consistency among studies.

HDL-C: For HDL-C levels, the meta-analysis yielded a non-significant difference between groups (SMD = 0.07 [95%

CI: -0.07, 0.21]; p = 0.30), with no observed heterogeneity (I^2 = 0%).

Triglycerides (TG): Similarly, the pooled estimate for TG showed no statistically significant difference (SMD = -0.11 [95% CI: -0.25, 0.03]; p = 0.12), and heterogeneity was absent (I^2 = 0%).

Risk of Bias Assessment

The included studies were assessed using the Cochrane Risk of Bias tool. All three studies demonstrated a low risk of bias across most domains, with only Liu et al. showing unclear risk for other bias due to its observational design. Overall, methodological quality was rated high, supporting the validity of the meta-analytic findings.

Publications Bias

Funnel plot analyses for all outcomes showed symmetrical distribution, indicating no significant evidence of publication bias. Although only three studies were included per outcome, limiting the power of the funnel plot, visual inspection did not suggest substantial asymmetry.

Figure 1

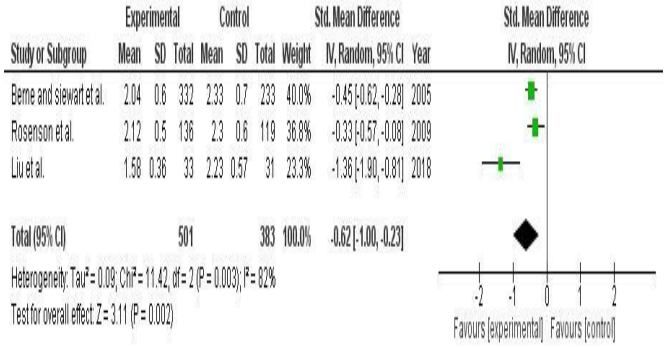
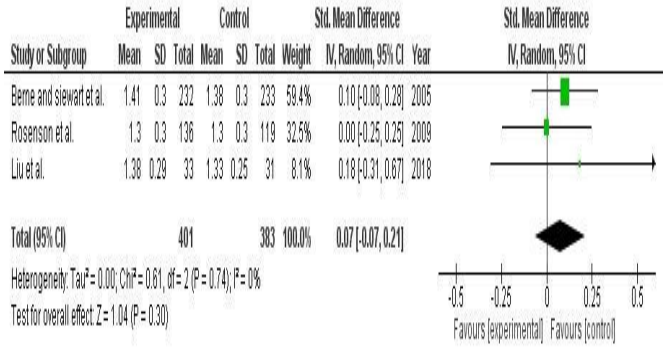


Figure 2



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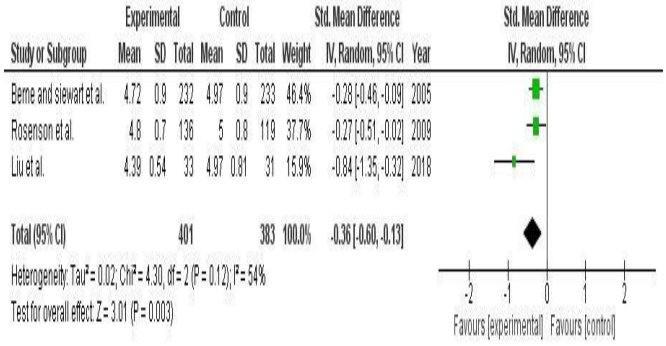

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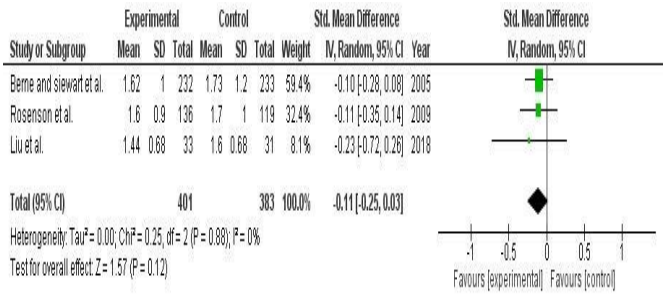

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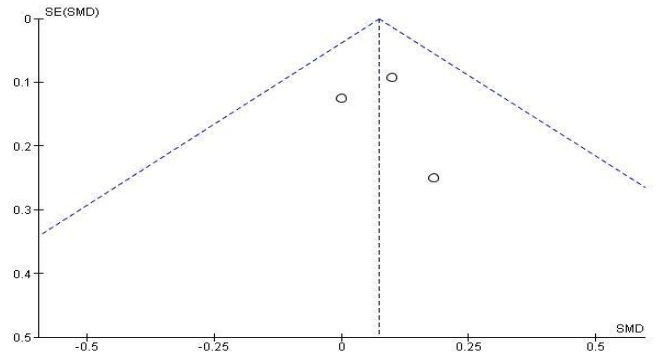

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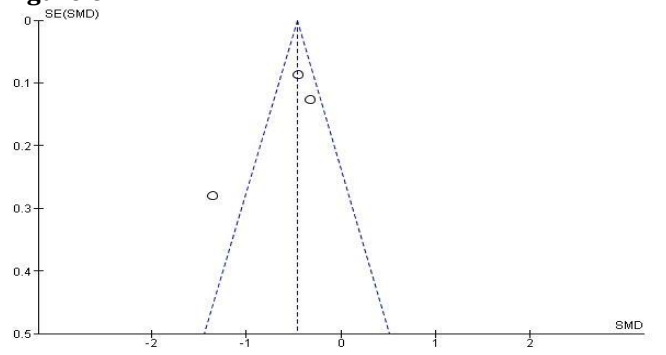

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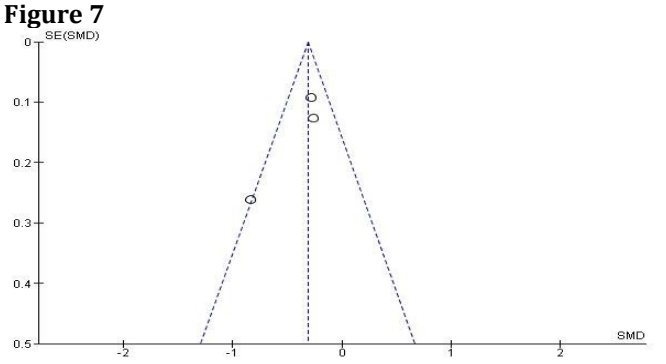

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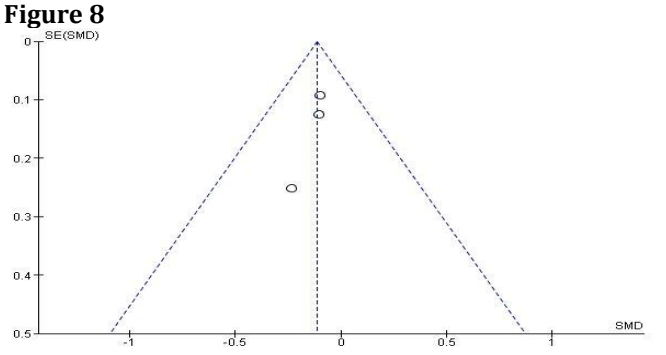


Figure 9

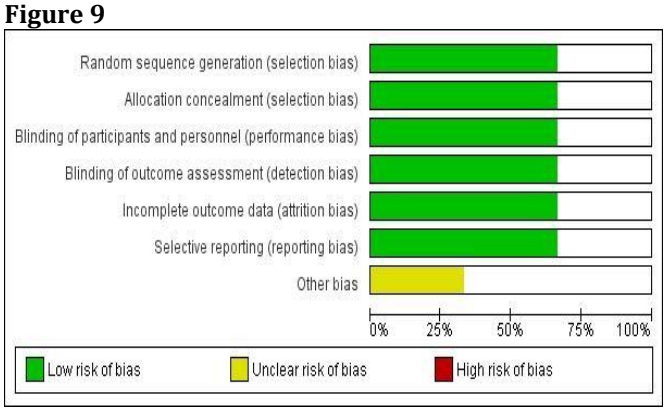
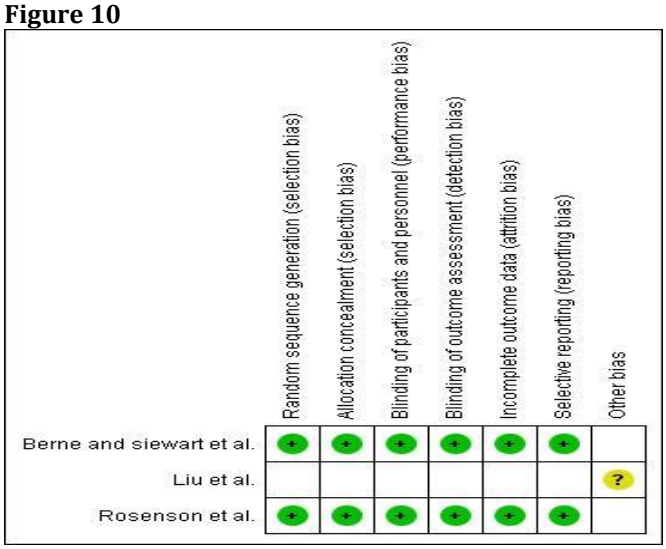


Figure 10



DISCUSSION

Background and Principal Findings

This meta-analysis aimed to explore the association between gut microbiota composition and responsiveness to statin therapy, particularly rosuvastatin, in hyperlipidemic patients. Among the lipid parameters analyzed, significant reductions were observed in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC), whereas high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) did not show significant differences. Additionally, emerging evidence from one included study indicated that gut microbiota composition may modulate the lipid-lowering response to statins [14]. These findings support growing interest in personalized lipid management guided by host–microbe interactions.

Comparison with Previous Studies

Our findings align with previous literature demonstrating the superior lipid-lowering efficacy of rosuvastatin compared to other statins, such as atorvastatin [15]. Rosenson et al. [17] also observed greater LDL-C and particle size improvements with rosuvastatin, reinforcing its role as a potent agent in lipid control. In addition, the observational study by Liu et al. [14] provided mechanistic insight into the microbial composition differences between statin responders and non-responders. Specifically, responders showed reduced alpha diversity and enrichment of Blautia, a genus linked to improved lipid metabolism and anti-inflammatory activity [16]. These results are consistent with earlier research linking microbial metabolites, such as short-chain fatty acids (SCFAs) and bile acids, to regulation of hepatic cholesterol synthesis and LDL receptor expression [18,20].

Although the benefits of rosuvastatin are well documented, the current analysis adds novel insight by examining the interplay between gut microbiota and statin responsiveness. While previous meta-analyses have compared statin efficacy [19], few have integrated microbiome-specific data to explain variability in treatment outcomes.

Mechanistic Insights

The gut microbiome plays a central role in modulating host lipid metabolism through several pathways. Certain microbial taxa can convert dietary components into SCFAs, which influence hepatic lipid synthesis and insulin sensitivity [18]. Other bacteria contribute to bile acid transformation, thereby impacting nuclear receptor signaling and cholesterol homeostasis [19]. Variability in these microbiota-dependent pathways may explain differential statin responses. For instance, Liu et al. [14] suggested that the gut microbiota composition could affect the pharmacokinetics and pharmacodynamics of statins, potentially via microbial biotransformation or modulation of systemic inflammation. These mechanistic links underline the importance of integrating microbiome profiling into cardiovascular risk stratification.

Clinical Implications

Our findings highlight the potential of gut microbiota profiling to personalize lipid-lowering therapy. In clinical practice, patients who are statin-resistant or experience suboptimal LDL-C reduction may benefit from adjunctive microbiome-based strategies. These could include dietary interventions, probiotics, or fecal microbiota transplantation aimed at reshaping gut microbial composition to enhance statin efficacy [21, 23]. As precision medicine evolves, microbiota-informed treatment decisions may become standard in hyperlipidemia management, especially in high-risk populations where statin resistance can compromise cardiovascular protection.

Limitations and Future Directions

Several limitations must be acknowledged. First, only one of the three included studies directly assessed gut microbiota, limiting the generalizability of conclusions regarding microbial influence. Second, the overall number of eligible studies was small, precluding subgroup or meta-regression analyses based on microbiota parameters or statin types. Third, the heterogeneity in LDL-C outcomes was high, potentially due to differing statin dosages, study durations, and patient characteristics. Lastly, although funnel plots appeared symmetrical, the small number of studies reduces the statistical power to detect publication bias.

Future research should include larger randomized controlled trials that incorporate comprehensive microbiota sequencing and metabolomic profiling. These studies should aim to define specific microbial signatures predictive of statin response and evaluate whether microbiota-targeted interventions can enhance treatment

outcomes. Additionally, longitudinal designs are warranted to assess causality and temporal changes in microbiota during statin therapy.

CONCLUSION

In conclusion, this meta-analysis confirms the superior lipid-lowering efficacy of rosuvastatin and highlights the emerging role of gut microbiota as a potential determinant of statin responsiveness. While preliminary evidence suggests a mechanistic link between microbiota composition and lipid outcomes, further high-quality studies are needed to validate these findings and support the integration of microbiome analysis into personalized cardiovascular care.

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