Statin Therapy: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize current evidence on statin therapy, identifying its multifaceted clinical outcomes, mechanisms, challenges in implementation, and areas for future research. The review utilises 214 studies with 4085869 total participants (naïve ΣN). Statin therapy is a highly effective intervention, fundamentally altering lipid profiles by reducing LDL-C and consistently lowering the risk of major adverse cardiovascular events and mortality. Beyond its primary cardiovascular benefits, evidence suggests statins offer protective effects across a spectrum of non-cardiovascular conditions, including certain cancers, infections, and neurodegenerative diseases. However, challenges persist in achieving optimal LDL-C goals, improving patient adherence, and fully understanding the mechanisms underlying statins' pleiotropic effects. A notable limitation is the heterogeneity in study designs and outcome reporting, which complicates direct quantitative comparisons. Future research should prioritize standardizing outcome metrics and investigating genetic and microbiome factors to personalize statin therapy and maximize its broad health benefits.

Keywords: Statin therapy; Cardiovascular disease; LDL cholesterol; Atherosclerosis; Inflammation; Diabetes mellitus; Plaque regression; Medication adherence; Myocardial infarction; Neurodegenerative diseases

Review Stats

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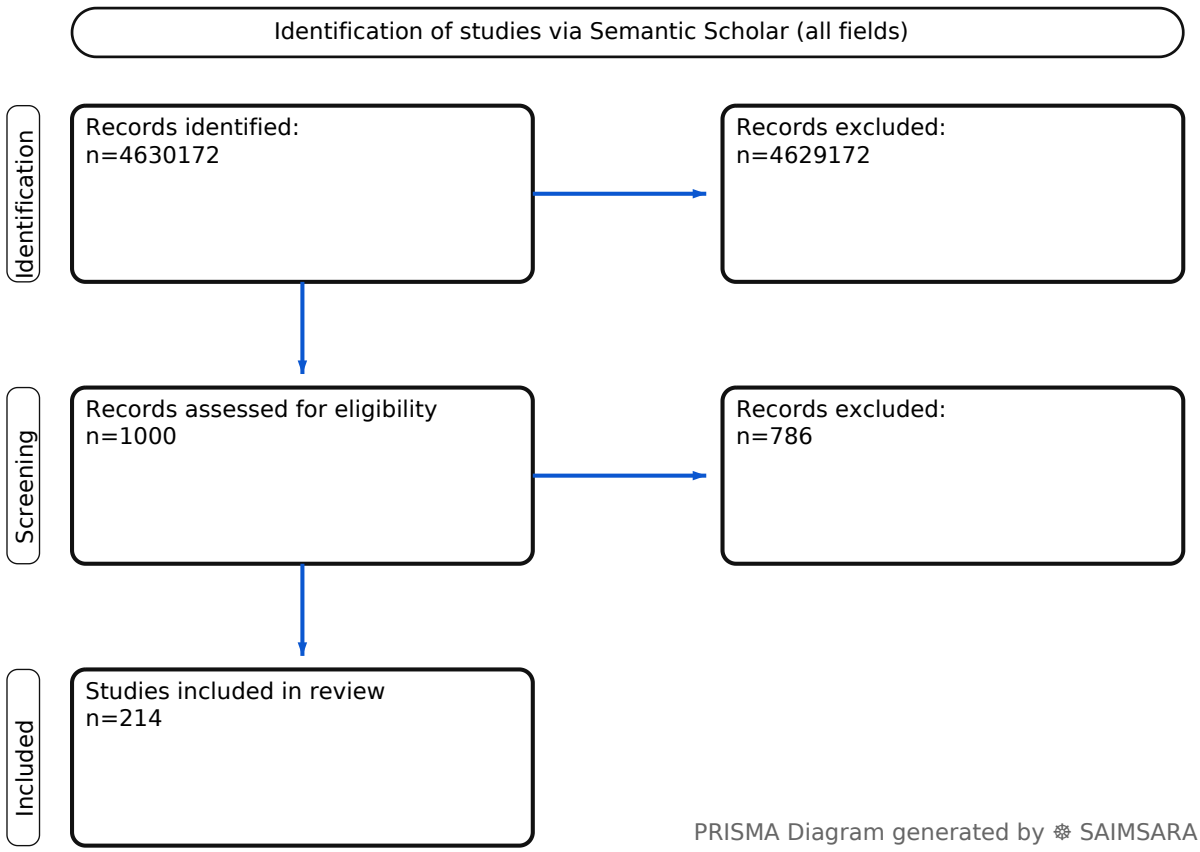
- Included original Abstracts/Papers: 214
- Total study participants (naïve ΣN): 4085869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Records excluded:
n=4629172
Screening
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Included
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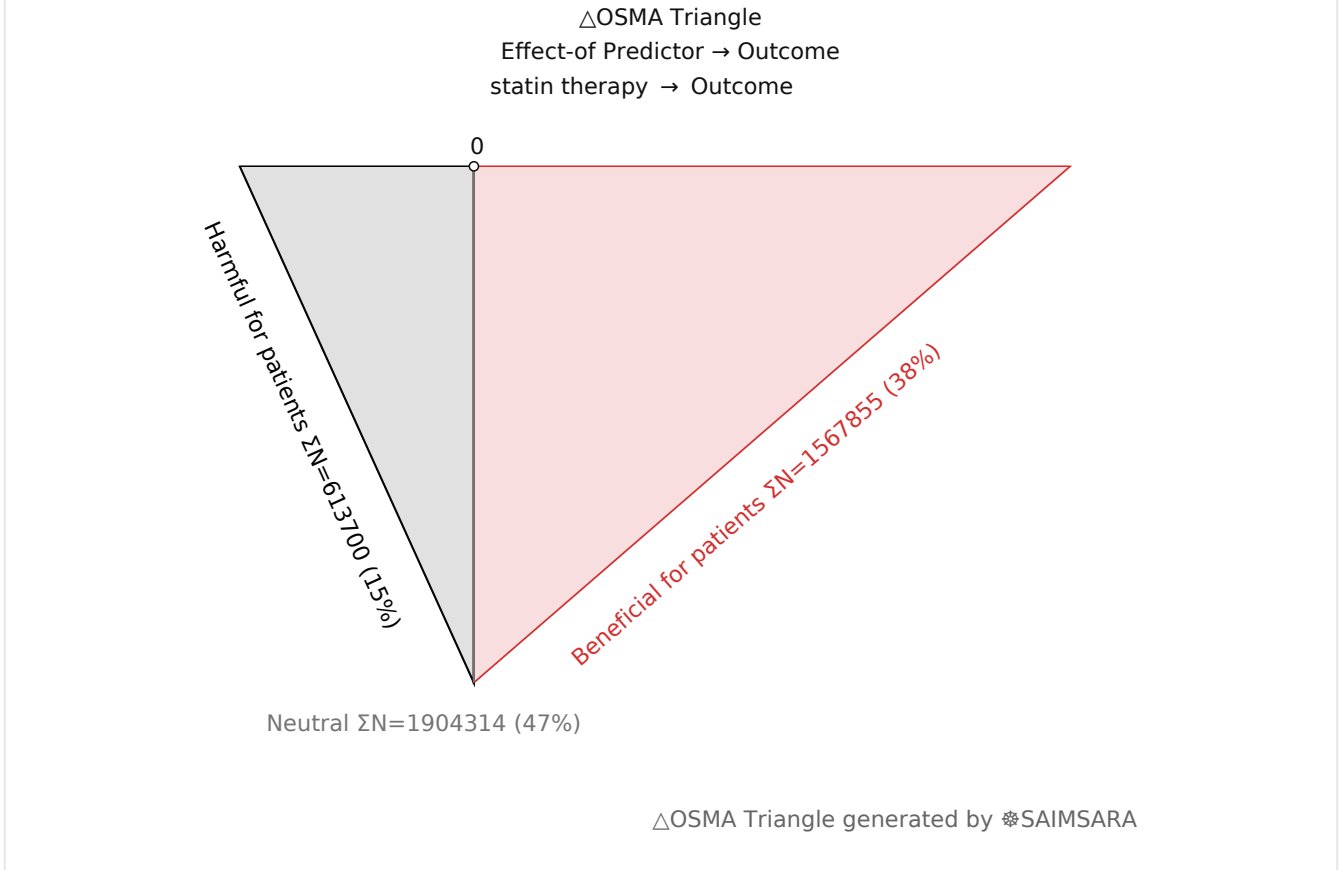
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
statin therapy → Outcome
0
Harmful for patients ΣN=613700 (15%)
Beneficial for patients ΣN=1567855 (38%)
Neutral ΣN=1904314 (47%)
△OSMA Triangle generated by ☸SAIMSARA

Outcome-Sentiment Meta-Analysis (OSMA): *(LLM-only)*

Frame: Effect-of Predictor → Outcome • *Source*: Semantic Scholar

Outcome: Outcome Typical timepoints: 12-mo, 6-mo. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, admission.

Predictor: statin therapy — exposure/predictor. Doses/units seen: 70 mg. Routes seen: oral.

Typical comparator: placebo, placebo over 18 months, placebo or monotherapies when, low- or moderate-intensity….

- **1) Beneficial for patients** — Outcome with statin therapy — [10], [11], [13], [16], [17], [19], [21], [23], [26], [32], [34], [65], [70], [78], [87], [101], [106], [107], [112], [113], [114], [123], [124], [130], [131], [137], [140], [144], [147], [181], [182], [184], [185], [187], [188], [192], [197], [198], [208], [209], [210] — ΣN=1567855
- **2) Harmful for patients** — Outcome with statin therapy — [5], [12], [109], [141], [146], [148], [150] — ΣN=613700
- **3) No clear effect** — Outcome with statin therapy — [1], [2], [3], [4], [6], [7], [8], [9], [14], [15], [18], [20], [22], [24], [25], [27], [28], [29], [30], [31], [33], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [66], [67], [68], [69], [71], [72], [73], [74], [75], [76], [77], [79], [80], [81], [82], [83], [84], [85], [86], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [102], [103], [104], [105], [108], [110], [111], [115], [116], [117], [118], [119], [120], [121], [122], [125], [126], [127], [128], [129], [132], [133], [134], [135], [136], [138], [139], [142], [143], [145], [149], [151], [152], [153], [154], [155], [156], [157], [158], [159], [160], [161], [162], [163], [164], [165], [166], [167], [168], [169], [170], [171], [172], [173], [174], [175], [176], [177], [178], [179], [180], [183], [186], [189], [190], [191], [193], [194], [195], [196], [199], [200], [201], [202], [203], [204], [205], [206], [207], [211], [212], [213], [214] — ΣN=1904314

1) Introduction

Statin therapy represents a cornerstone in the management of cardiovascular diseases (CVD) by primarily targeting dyslipidemia, particularly elevated low-density lipoprotein cholesterol (LDL-C). Beyond their lipid-lowering capabilities, statins exhibit a range of pleiotropic effects, influencing inflammation, plaque stabilization, and potentially impacting various non-cardiovascular conditions. This paper synthesizes a broad spectrum of research on statin therapy, encompassing its efficacy in primary and secondary prevention, its effects on diverse patient populations, associated risks, and

emerging insights into its mechanisms of action.

2) Aim

The aim of this paper is to systematically review and synthesize current evidence on statin therapy, identifying its multifaceted clinical outcomes, mechanisms, challenges in implementation, and areas for future research.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** Qualitatively inferred from study design fields.

4) Results

4.1 Study characteristics:

The included studies comprise a diverse range of designs, with a notable prevalence of randomized controlled trials (RCTs) and cohort studies, alongside mixed-design, cross-sectional, experimental, and case-control investigations. Populations studied are extensive, covering patients with or at high risk of atherosclerotic disease, acute myocardial infarction, familial hypercholesterolemia, diabetes, chronic kidney disease, various infections (e.g., SARS-CoV-2, pneumonia, HIV, tuberculosis), and specific conditions like cancer, cirrhosis, and inflammatory diseases. Follow-up periods varied widely, from short durations of weeks or months to extended periods of up to 20 years, with many studies not specifying a follow-up duration.

4.2 Main numerical result aligned to the query:

Due to heterogeneity in outcome metrics, units, and timepoints across studies, a single central value for the direct effect of statin therapy on lipid reduction or cardiovascular events cannot be precisely computed. However, statin therapy consistently demonstrates significant reductions in low-density lipoprotein cholesterol and a lower risk of major adverse cardiovascular events and mortality across various patient populations. For example, statin treatment for 5 years was associated with a 24% reduction in myocardial infarction and a 35% reduction in heart failure over a 20-year period [23]. In patients with acute myocardial infarction, statin use within 24 hours of hospitalization was associated with a significantly lower in-hospital mortality rate of 4.0% compared to 15.4% in those without statin use [172].

4.3 Topic synthesis:

- **Cardiovascular Event Reduction:** Statin therapy significantly reduces the risk of major adverse cardiovascular events (MACE) and mortality, with high-intensity statins showing a hazard ratio (HR) of 0.51 (95% CI 0.40–0.66) for net adverse clinical and cerebral events (NACCE) in stroke patients [16]. Five years of statin treatment was associated with an 18% reduction in any coronary event and a 24% reduction in myocardial infarction (MI) over 20 years [23]. Statin-based therapy reduced the risk of a first major vascular event by 21% per mmol/L reduction in LDL cholesterol [147].
- **Lipid Modulation (LDL-C, Lp(a), TG, HDL-C):** Statins are effective in lowering LDL-C, with childhood initiation in familial hypercholesterolemia (FH) patients leading to a 32% decrease in mean LDL-C over 20 years [162]. However, statins can significantly increase plasma lipoprotein(a) [Lp(a)] levels by a ratio of geometric means of 1.11 (95% CI, 1.07-1.14) [6]. Many patients, over half (51.2%), do not achieve optimal LDL-C lowering within 2 years, increasing CVD risk by HR 1.17–1.22 [180].
- **Inflammation and Plaque Stabilization:** Statin therapy reduces C-reactive protein (CRP) levels [36, 97] and can lead to rapid reductions in atherosclerotic inflammation [55]. Inflammation, assessed by high-sensitivity CRP, was a stronger predictor for future cardiovascular events and death (HR for MACE 1.31, for cardiovascular mortality 2.68) than LDL-C in patients on contemporary statins [1].
- **Adherence and Persistence:** Adherence to statin therapy remains a challenge, with low persistence reported (e.g., 20.1% after 12 months in Hungary) [67]. Women are less likely than men to be prescribed statins (67.0% vs 78.4%) or receive guideline-recommended intensity (36.7% vs 45.2%) [167]. Low adherence (medication possession ratio < 50%) is associated with a greater risk of dying (HR 1.30) [198].
- **Adverse Effects / Risks (Diabetes, Myopathy, etc.):** Statin use is associated with an increased risk of new-onset diabetes, with intensive-dose statin therapy showing an odds ratio (OR) of 1.12 (95% CI, 1.04-1.22) [31] and an overall pooled HR for incident diabetes of 1.36 (95% CI 1.17 to 1.58) [150]. Myalgia and myopathy are recognized side effects, but vitamin D supplementation can enable successful statin rechallenge in 88% of previously intolerant patients [157].
- **Non-Cardiovascular Benefits (Infections, Cancer, Neurodegenerative, Renal, Hepatic, Ocular, etc.):** Statins offer diverse benefits beyond CVD. They are associated with lower mortality in SARS-CoV-2 infection (HR 0.58) [11], community-acquired pneumonia [21], sepsis [34, 112], and HIV-infected patients (relative hazard 0.33) [192]. Statin exposure is linked to a lower incidence of Alzheimer's disease (relative risk [RR] 0.46) and dementia (RR 0.56) [13]. In cancer, statins are associated with reduced mortality in multiple myeloma (21% decrease) [187] and lung cancer (HR 0.58) [152], and improved response to rectal cancer chemoradiation [64]. Statin therapy also lowers the risk of diabetic retinopathy (HR 0.86) [10] and is negatively associated with non-alcoholic steatohepatitis (NASH) and

significant fibrosis in diabetes and NAFLD [184].

- **Mechanisms of Action (beyond lipid lowering):** Statins modulate the gut microbiota, leading to metabolic alterations [15, 18], increase circulating endothelial progenitor cells [68], and reduce oxidative stress [72]. They can also enhance CD8+ T-cell immune responses against KRAS-mutant tumors [83] and affect gene expression profiles in endothelial cells [193].
- **Guidelines, Dosing, and Implementation:** Gaps persist between guidelines and clinical practice, with high-intensity statin monotherapy often insufficient to achieve LDL-C goals in very high-risk patients [62]. Machine learning risk calculators may improve statin eligibility predictions, recommending statin therapy to fewer individuals while missing fewer events compared to traditional calculators [175]. Discontinuation of statin therapy is associated with worse outcomes, such as increased risk of recurrent stroke (HR 1.42) [210] or cardiovascular events (33% increased risk) [177].

5) Discussion

5.1 Principal finding:

Statin therapy is unequivocally effective in reducing low-density lipoprotein cholesterol and is associated with a lower risk of major adverse cardiovascular events and mortality across a wide range of patient populations [23, 172].

5.2 Clinical implications:

- **Targeted Intensification:** Many patients, especially those at high risk or with existing ASCVD, do not achieve optimal LDL-C goals with statin monotherapy, necessitating consideration of add-on therapies like PCSK9 inhibitors, ezetimibe, or icosapent ethyl [62, 155, 156, 166, 194].
- **Adherence Support:** Strategies to improve statin adherence, such as patient counseling and addressing cost barriers, are crucial to maximize clinical benefits, particularly in women and younger patients who show lower adherence rates [75, 167, 174].
- **Benefit-Risk Assessment:** While statins offer broad benefits, including non-cardiovascular protection, clinicians must weigh the increased risk of new-onset diabetes, especially with intensive dosing, against the substantial cardiovascular and other health advantages [5, 31, 148].
- **Continued Therapy:** Discontinuation of statin therapy, even in specific contexts like advanced illness or post-stroke, is generally associated with worse outcomes and increased mortality, highlighting the importance of long-term adherence [28, 177, 182, 210].

- **Beyond Lipids:** Clinicians should recognize statins' pleiotropic effects, including anti-inflammatory properties and potential benefits in conditions like diabetes-related complications (e.g., retinopathy) and certain cancers, which may influence treatment decisions [10, 55, 151, 187].

5.3 Research implications / key gaps:

- **Genetic Response Heterogeneity:** Further research is needed to understand genetic determinants of statin response and adverse effects, enabling personalized therapy [108, 115, 168, 178].
- **Microbiome-Statin Interaction:** The precise mechanisms by which statins remodel the gut microbiota and its impact on metabolic and therapeutic outcomes require in-depth investigation [15, 18, 84].
- **Non-CV Benefit RCTs:** Rigorous randomized controlled trials are warranted to confirm the observed non-cardiovascular benefits of statins in conditions like specific cancers, infections, and neurodegenerative diseases [13, 39, 83, 152, 187].
- **Optimal Dosing and Goal Attainment:** Studies are needed to determine if empirically prescribed statin doses are superior to titration to specific LDL-C targets, especially given persistent gaps in goal attainment [62, 189].
- **Inflammation-Targeted Therapy:** Further investigation into the role of residual inflammatory risk, even with optimal LDL-C lowering, and the potential for combination therapies targeting inflammation is crucial [1, 14, 59].

5.4 Limitations:

- **Heterogeneity of Study Designs** — Many studies were observational (cohort, retrospective) or mixed-design, limiting causal inference and increasing potential for bias.
- **Inconsistent Outcome Metrics** — Varied reporting of LDL-C reduction, mortality, and event rates prevented direct meta-analysis or calculation of a single central effect size.
- **Adherence and Persistence Challenges** — Observed low adherence rates in real-world settings (e.g., 20.1% after 12 months [67]) may underrepresent the full therapeutic potential of statins.
- **Reporting Bias** — The summary indicates a lack of consistent reporting for certain numerical outcomes, making comprehensive quantitative synthesis challenging.
- **Population Specificity** — Some findings are limited to specific populations (e.g., elderly, cancer, HIV), which may limit the generalizability of these results to broader patient groups.

5.5 Future directions:

- **Standardize Outcome Reporting** — To facilitate robust meta-analyses of statin efficacy across diverse patient cohorts.
- **Investigate Genetic Modifiers** — To enable personalized statin therapy based on individual genetic profiles and predicted response.
- **Elucidate Microbiome Mechanisms** — To understand how statins modulate gut microbiota and its impact on cardiometabolic health.
- **Evaluate Non-Cardiovascular Benefits** — Through targeted randomized controlled trials in specific conditions like cancer or infections.
- **Optimize Adherence Strategies** — To develop and implement effective interventions that improve long-term patient compliance and clinical outcomes.

6) Conclusion

Statin therapy is a highly effective intervention, fundamentally altering lipid profiles by reducing LDL-C and consistently lowering the risk of major adverse cardiovascular events and mortality. Beyond its primary cardiovascular benefits, evidence suggests statins offer protective effects across a spectrum of non-cardiovascular conditions, including certain cancers, infections, and neurodegenerative diseases. However, challenges persist in achieving optimal LDL-C goals, improving patient adherence, and fully understanding the mechanisms underlying statins' pleiotropic effects. A notable limitation is the heterogeneity in study designs and outcome reporting, which complicates direct quantitative comparisons. Future research should prioritize standardizing outcome metrics and investigating genetic and microbiome factors to personalize statin therapy and maximize its broad health benefits.

References

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Figure 1. Publication-year distribution of included originals

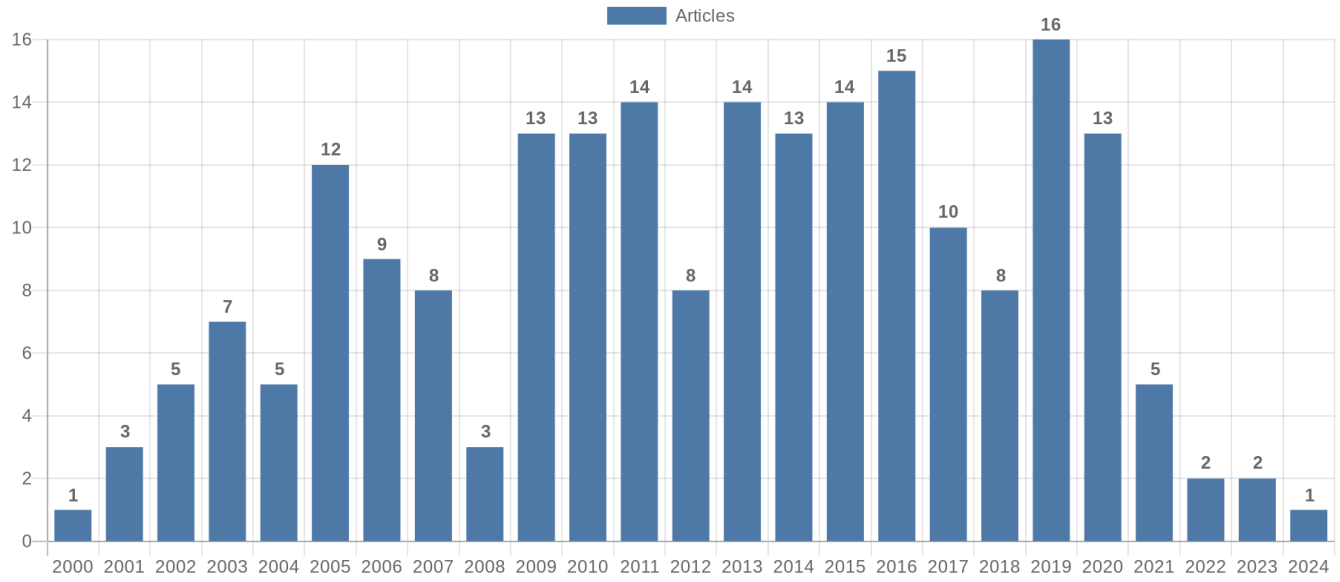

Figure 2. Study-design distribution of included originals

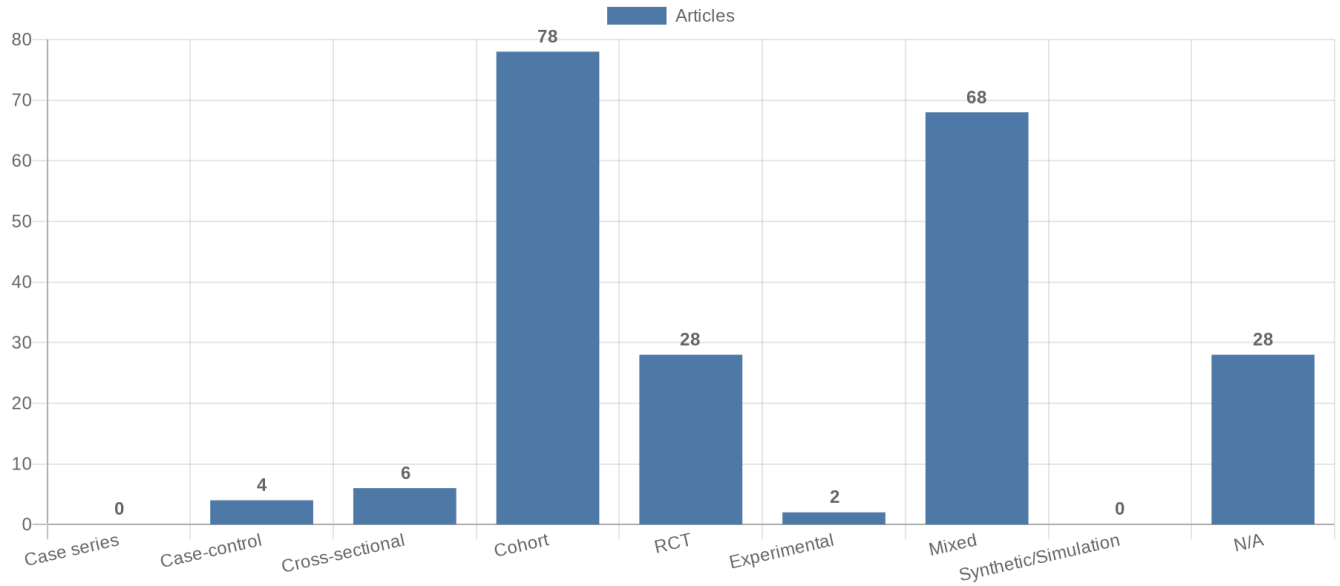

Figure 3. Study-type (directionality) distribution of included originals

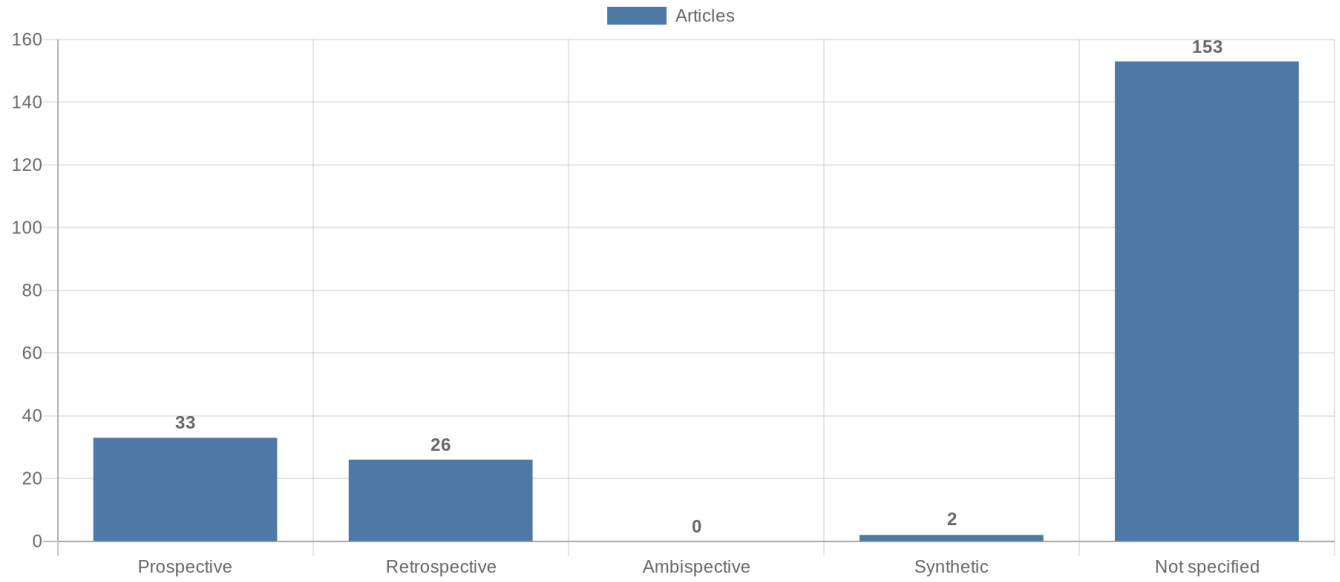

Figure 4. Main extracted research topics

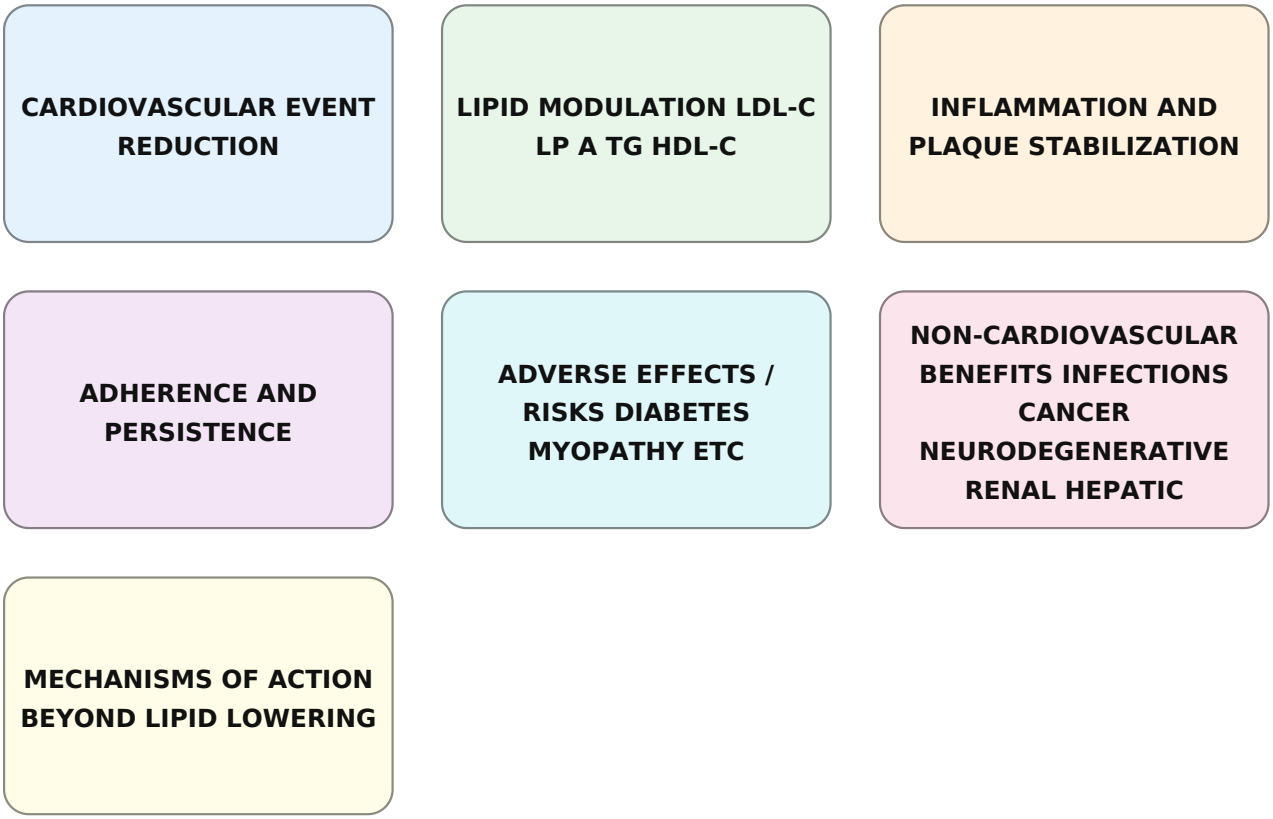

Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)

GENETIC DETERMINANTS OF STATIN RESPONSE AND ADVERSE

MECHANISMS BY WHICH STATINS REMODEL THE GUT

NON-CARDIOVASCULAR BENEFITS OF STATINS

STATIN DOSES

RESIDUAL INFLAMMATORY RISK

STANDARDIZE OUTCOME REPORTING

GENETIC MODIFIERS