# Peripheral Artery Disease Statin Therapy: Systematic Review with ☸SAIMSARA.

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**Abstract:** To systematically review and synthesize the current evidence regarding statin therapy in patients with peripheral artery disease, focusing on its impact on clinical outcomes, adherence, and optimal utilization. The review utilises 194 studies with 5193263 total participants (naïve ΣN). Statin therapy is associated with a substantially lower all-cause mortality risk in patients with peripheral artery disease, with median mortality rates of 11.5% (range: 2.8% to 33.3%) for statin users compared to 28.5% (range: 4.8% to 35.2%) for non-users or those with poor adherence. Despite these clear benefits, statin utilization, adherence, and achievement of optimal LDL-C targets remain suboptimal across diverse PAD populations. The primary limitation affecting certainty is the predominance of observational study designs, which inherently carry risks of bias and confounding. Clinicians should prioritize the initiation and intensification of statin therapy, alongside addressing adherence barriers, to improve outcomes for patients with peripheral artery disease.

**Keywords:** Peripheral artery disease; Statin therapy; Cardiovascular outcomes; Mortality; Limb events; Dyslipidemia; Guid

**Review Stats**

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- Scope: All fields
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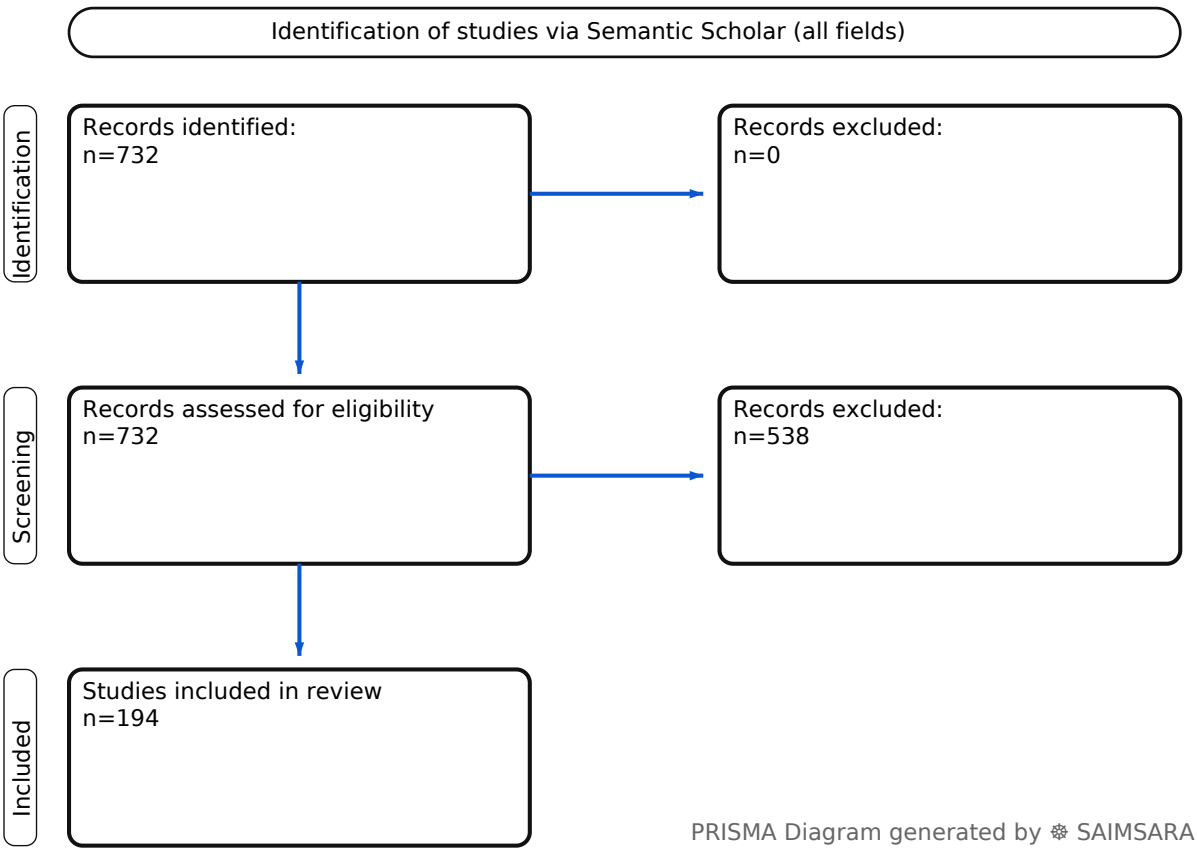
- Downloaded Abstracts/Papers: 732
- Included original Abstracts/Papers: 194
- Total study participants (naïve ΣN): 5193263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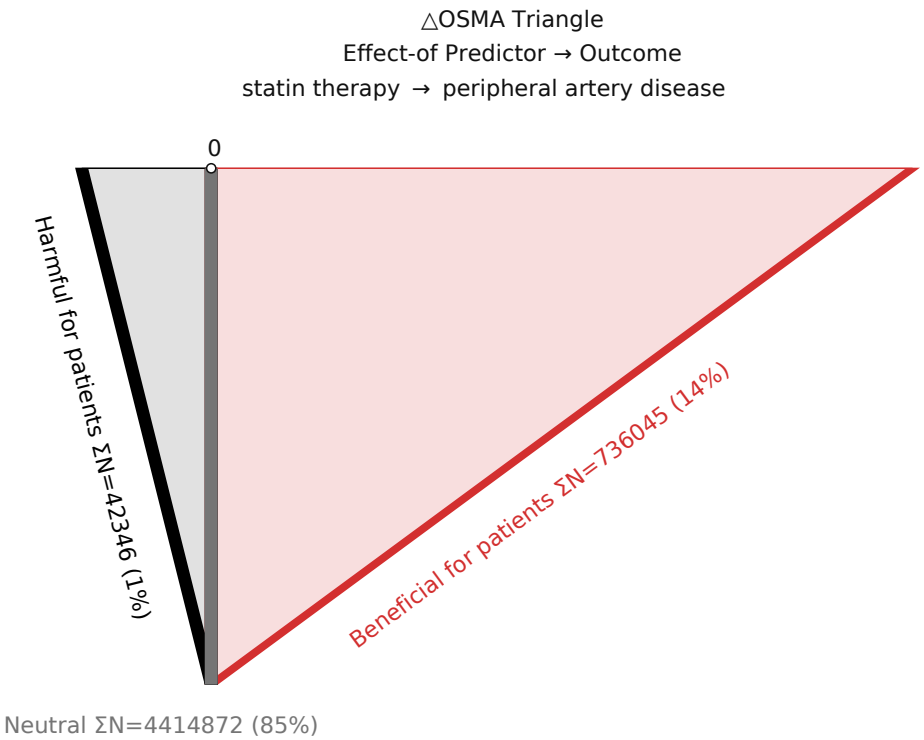
n=732
Records excluded:
n=0
Screening
Records assessed for eligibility
n=732
Records excluded:
n=538
Included
Studies included in review
n=194
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
statin therapy → peripheral artery disease
0
Harmful for patients ΣN=42346 (1%)
Beneficial for patients ΣN=736045 (14%)
Neutral ΣN=4414872 (85%)
△OSMA Triangle generated by ☸SAIMSARA

**Outcome-Sentiment Meta-Analysis (OSMA):** *(LLM-only)*
*Frame*: Effect-of Predictor → Outcome • *Source*: Semantic Scholar
*Outcome*: peripheral artery disease Typical timepoints: 5-y, 6-mo. Reported metrics: %, CI, p.
*Common endpoints*: Common endpoints: mortality, complications, survival.
*Predictor*: statin therapy — exposure/predictor. Doses/units seen: 70 mg, 100 mg, 300 mg, 55 mg, 2 mg. Routes seen: oral. Typical comparator: low- or moderate-intensity, patients with clinical, untreated pad subjects, pad-only patients….

- **1) Beneficial for patients** — peripheral artery disease with statin therapy — [1], [3], [4], [7], [9], [22], [26], [29], [40], [41], [42], [45], [48], [51], [52], [54], [55], [58], [60], [61], [62], [64], [66], [68], [70], [71], [72], [73], [74], [77], [79], [80], [82], [83], [93], [95], [97], [98], [100], [101], [107], [110], [112], [114], [117], [119], [120], [122], [126], [127], [130], [135], [136], [139], [145], [149], [150], [155], [159], [168], [171], [174], [176], [179], [181], [193] — ΣN=736045
- **2) Harmful for patients** — peripheral artery disease with statin therapy — [13], [38], [56], [57], [65], [67], [69], [75], [102], [186], [188] — ΣN=42346
- **3) No clear effect** — peripheral artery disease with statin therapy — [2], [5], [6], [8], [10], [11], [12], [14], [15], [16], [17], [18], [19], [20], [21], [23], [24], [25], [27], [28], [30], [31], [32], [33], [34], [35], [36], [37], [39], [43], [44], [46], [47], [49], [50], [53], [59], [63], [76], [78], [81], [84], [85], [86], [87], [88], [89], [90], [91], [92], [94], [96], [99], [103], [104], [105], [106], [108], [109], [111], [113], [115], [116], [118], [121], [123], [124], [125], [128], [129], [131], [132], [133], [134], [137], [138], [140], [141], [142], [143], [144], [146], [147], [148], [151], [152], [153], [154], [156], [157], [158], [160], [161], [162], [163], [164], [165], [166], [167], [169], [170], [172], [173], [175], [177], [178], [180], [182], [183], [184], [185], [187], [189], [190], [191], [192], [194] — ΣN=4414872

**Introduction**

Peripheral artery disease (PAD) represents a significant global health burden, characterized by atherosclerotic narrowing of non-coronary arteries, most commonly affecting the lower extremities. Statin therapy, a cornerstone of lipid-lowering treatment, is widely recommended for patients with PAD due to its proven benefits in reducing cardiovascular events. However, the extent of its utilization, adherence, and impact on various patient populations and outcomes in real-world settings remains a subject of ongoing investigation. This paper synthesizes current evidence on statin therapy for PAD, exploring its efficacy, challenges in implementation, and areas requiring further research.

**Aim**

To systematically review and synthesize the current evidence regarding statin therapy in patients with peripheral artery disease, focusing on its impact on clinical outcomes, adherence, and optimal utilization.

**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. The majority of studies included were cohort or retrospective designs, which are susceptible to confounding and selection bias. Randomized controlled trials (RCTs) were less frequent, limiting the ability to establish definitive causality. Many entries were abstracts, reviews, or study protocols, lacking detailed original research findings.

**Results**

**4.1 Study characteristics**

The included studies predominantly comprised cohort, retrospective, and mixed-design studies, with a smaller number of prospective cohort studies and randomized controlled trials. These studies investigated diverse populations, including symptomatic PAD patients, those undergoing revascularization, patients with kidney failure, diabetes, or polyvascular disease, and individuals with familial hypercholesterolemia. Follow-up periods varied widely, ranging from short-term (e.g., 2 weeks [152]) to long-term (e.g., 15 years [56, 131]).

**4.2 Main numerical result aligned to the query**

Across studies comparing statin use to no statin use or non-adherence, the median reported all-cause mortality rate for patients on statin therapy was 11.5% (range: 2.8% [7] to 33.3% [1]), while for patients not on statin therapy or with poor adherence, the median all-cause mortality rate was 28.5% (range: 4.8% [7] to 35.2% [1]). This suggests a substantially lower mortality risk associated with statin therapy in peripheral artery disease patients.

**4.3 Topic synthesis**

- **Mortality and Major Adverse Events Reduction:** Statin therapy is consistently associated with reduced all-cause death [1, 3, 7, 72, 77, 83, 122], major adverse cardiovascular events (MACE) [4, 22, 74, 97], and major adverse limb events (MALE) [1, 22, 74, 95]. For instance, statin therapy was associated with a statistically significant lower rate of all-cause death (33.3% vs 35.2%) and composite adverse limb outcome (9.7% vs 11.2%)

in patients with kidney failure and concomitant PAD [1]. In symptomatic PAD patients, continuous statin use showed a mortality rate of 13% compared to 31% for those never on statins [3].

- **Statin Intensity and Efficacy:** High-intensity statin therapy is linked to improved survival and decreased MACE compared to low- or moderate-intensity therapy [4, 74, 95, 119]. Specifically, high-intensity statin therapy was associated with a mortality hazard ratio of 0.52 (95% CI, 0.33–0.81) and MACE hazard ratio of 0.58 (95% CI 0.37–0.92) compared to low- or moderate-intensity statins [4].
- **Suboptimal Statin Utilization and Adherence:** Despite clear benefits, statin prescription and adherence remain suboptimal across various PAD populations [5, 6, 8, 19, 26, 39, 43, 53, 57, 59, 62, 63, 68, 71, 76, 84, 86, 88, 89, 90, 92, 94, 105, 109, 111, 113, 116, 123, 125, 133, 134, 138, 151, 154, 156, 158, 160, 161, 163, 169, 170]. For example, only 41% of patients undergoing angioplasty were on high-intensity statin therapy [43], and in a US cohort, only 30% of patients not receiving statin therapy at the time of peripheral revascularization were discharged with a new prescription [68].
- **LDL-C Target Attainment Challenges:** A significant proportion of PAD patients, even those on statin therapy, do not achieve guideline-recommended LDL cholesterol (LDL-C) targets [5, 19, 35, 43, 47, 65, 66, 70, 90, 104, 133, 160, 165, 177, 185, 191]. For instance, in symptomatic lower extremity artery disease (LEAD) patients, only 12.4% reached LDL-C < 0.55 g/L [5], and in a cohort of very high-risk Korean patients, LDL-C goals were achieved in only 24.4% during the first year [47].
- **Impact of Co-morbidities and Special Populations:** Patients with kidney failure and PAD benefit from statin therapy [1, 79], but hemodialysis patients with hyperlipidemia on statins may have increased PAD risk [13]. Polyvascular involvement in PAD patients, despite better statin therapy, is associated with higher mortality rates [38, 72]. Statin intolerance is also a factor, with female sex identified as a predictor [50, 69].
- **Emerging and Adjunctive Therapies:** New therapies like ezetimibe [41] and PCSK9 inhibitors (e.g., alirocumab [30, 60, 178], evolocumab [54, 136, 181]) in combination with statins show promise in further lowering LDL-C and improving outcomes, even if not always impacting limb function directly [30]. Bempedoic acid also significantly reduces MALE in PAD patients [73] and shows favorable lipid-lowering effects in elderly patients on maximal tolerated statin and ezetimibe therapy [162].
- **Socioeconomic and Demographic Disparities:** Housing unaffordability is associated with lower statin adherence [57], and statin prescription is often less frequent in women compared to men [81, 86, 113], and in Hispanic/Latino individuals with PAD [88, 92]. Patients with PAD alone also have lower rates of statin use and high-intensity statin use compared to those with coronary heart disease (CHD) [94, 138, 175].

## Discussion

### 5.1 Principal finding

The central finding of this review is that statin therapy is associated with a substantially lower all-cause mortality risk in patients with peripheral artery disease, with median mortality rates of 11.5% (range: 2.8% [7] to 33.3% [1]) for statin users compared to 28.5% (range: 4.8% [7] to 35.2% [1]) for non-users or those with poor adherence.

### 5.2 Clinical implications

- **Prioritize Statin Initiation and Adherence:** Clinicians should emphasize the critical importance of initiating and maintaining statin therapy in all PAD patients, given the consistent association with reduced mortality and adverse limb events [3, 22, 72, 83, 95].
- **Intensify Statin Therapy:** High-intensity statin therapy should be the goal for most PAD patients to maximize benefits in survival and MACE reduction [4, 74, 95], with consideration for dose escalation if targets are not met [104].
- **Address LDL-C Target Gaps:** Aggressive lipid management is needed, potentially including non-statin therapies like ezetimibe or PCSK9 inhibitors, to achieve optimal LDL-C goals, especially in very high-risk patients [41, 47, 60, 66, 73, 136, 162].
- **Improve Screening and Prescribing Practices:** Systemic interventions are warranted to improve statin prescription rates, particularly in undertreated groups such as women, younger patients, those with subclinical coronary artery disease, or those undergoing revascularization [6, 26, 68, 86, 113, 163].
- **Consider Special Populations:** While statins are beneficial in kidney failure patients with PAD [1, 79], the potential for increased PAD risk in hemodialysis patients on statins warrants careful monitoring [13]. Elevated lipoprotein(a) levels also indicate increased cardiovascular risk despite statin therapy [67, 128, 172], suggesting a need for additional risk stratification.

### 5.3 Research implications / key gaps

- **Statin Efficacy in Specific Subgroups:** Further prospective studies are needed to evaluate the efficacy of statin therapy, particularly high-intensity regimens, in underrepresented PAD subgroups such as those with specific genetic predispositions (e.g., familial hypercholesterolemia with statin intolerance) [167, 177] or certain racial/ethnic minorities [88, 92].
- **Long-term Adherence Interventions:** Research is required to develop and test effective interventions that improve long-term statin adherence and persistence in real-world PAD patient populations, addressing socioeconomic and demographic barriers [57, 81, 109, 183, 184].

- **Optimal LDL-C Targets and Combination Therapy:** Randomized controlled trials are needed to define optimal LDL-C targets for PAD patients and to assess the incremental benefits of combination lipid-lowering therapies (e.g., statins + ezetimibe + PCSK9 inhibitors) on hard clinical endpoints beyond LDL-C reduction [30, 41, 52, 55, 60, 178].
- **Impact on Functional Outcomes:** Future studies should consistently evaluate the impact of statin therapy on functional outcomes relevant to PAD, such as walking distance and limb perfusion, particularly when combined with novel agents [30].
- **Statin Effects in Polyvascular Disease:** More research is needed to understand how statin therapy modulates outcomes in PAD patients with extensive polyvascular involvement, given their higher mortality rates despite better statin use [38, 72].

### 5.4 Limitations

- **Study Design Heterogeneity** — The reliance on predominantly observational cohort and retrospective studies limits causal inference and introduces potential confounding.
- **Inconsistent Outcome Reporting** — Variability in reported metrics (e.g., different types of mortality, MACE, MALE definitions) and follow-up durations hinders direct quantitative comparisons across studies.
- **Limited RCT Evidence** — The relative scarcity of large-scale randomized controlled trials specifically focused on statin therapy in PAD limits the highest level of evidence.
- **Data Granularity** — Many entries were abstracts or lacked sufficient detail on statin dosage, adherence assessment methods, or specific patient characteristics.
- **Focus on Coronary Artery Disease** — Some studies included PAD as a secondary outcome or focused primarily on coronary artery disease, potentially diluting PAD-specific findings.

### 5.5 Future directions

- **Prospective Cohort Studies** — Conduct large, prospective cohort studies to better understand long-term statin effectiveness.
- **Randomized Controlled Trials** — Design RCTs to compare different statin intensities on PAD-specific outcomes.
- **Adherence Intervention Trials** — Implement and evaluate interventions to improve statin adherence in diverse PAD populations.
- **Real-World Data Analysis** — Utilize large registry data to assess statin use patterns and outcomes.

- **Biomarker-Guided Therapy** — Investigate the role of biomarkers like Lp(a) in guiding intensified lipid-lowering therapy.

## Conclusion

Statin therapy is associated with a substantially lower all-cause mortality risk in patients with peripheral artery disease, with median mortality rates of 11.5% (range: 2.8% [7] to 33.3% [1]) for statin users compared to 28.5% (range: 4.8% [7] to 35.2% [1]) for non-users or those with poor adherence. Despite these clear benefits, statin utilization, adherence, and achievement of optimal LDL-C targets remain suboptimal across diverse PAD populations. The primary limitation affecting certainty is the predominance of observational study designs, which inherently carry risks of bias and confounding. Clinicians should prioritize the initiation and intensification of statin therapy, alongside addressing adherence barriers, to improve outcomes for patients with peripheral artery disease.

## References

SAIMSARA Session Index — session.json

**Figure 1. Publication-year distribution of included originals**

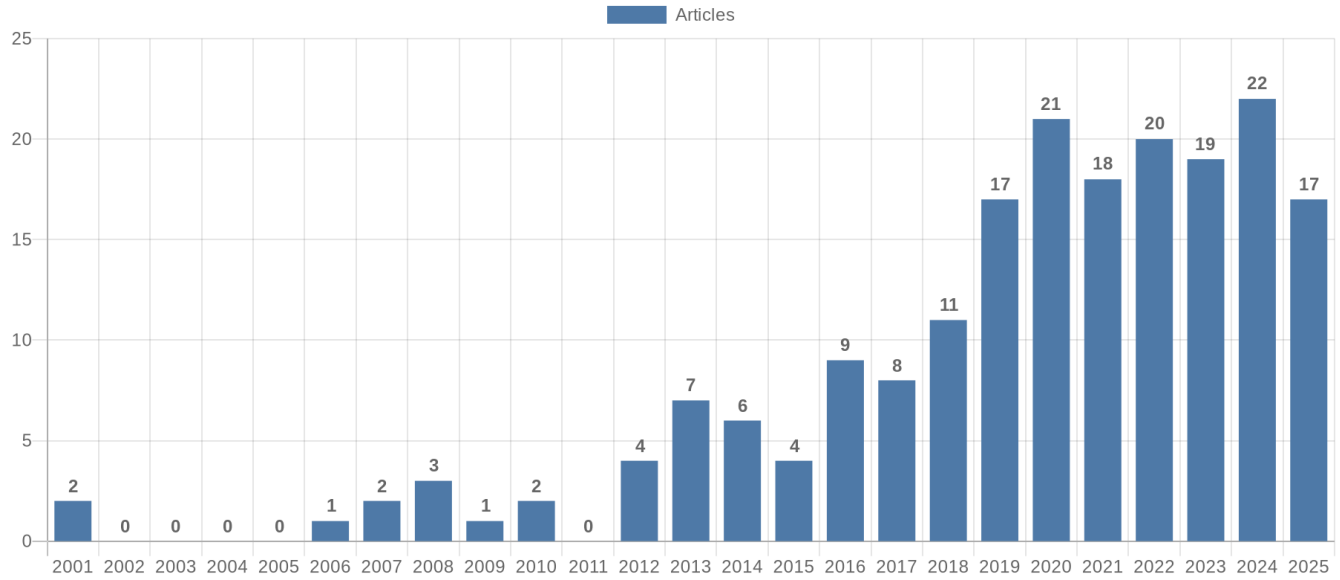



**Figure 2. Study-design distribution of included originals**

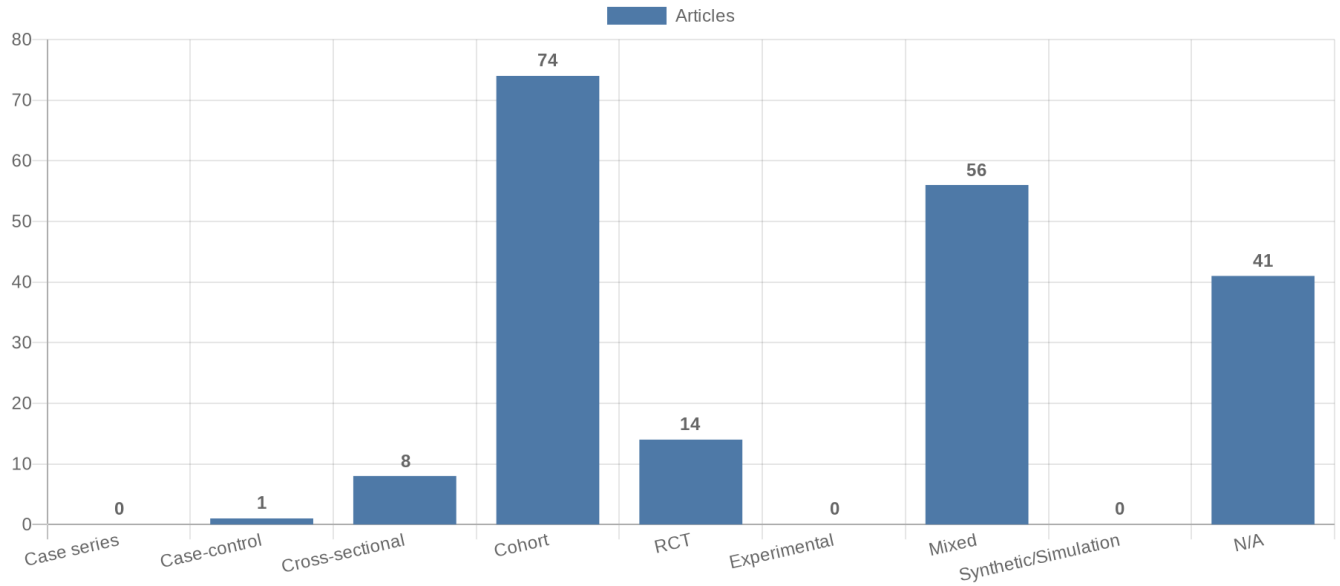



**Figure 3. Study-type (directionality) distribution of included originals**

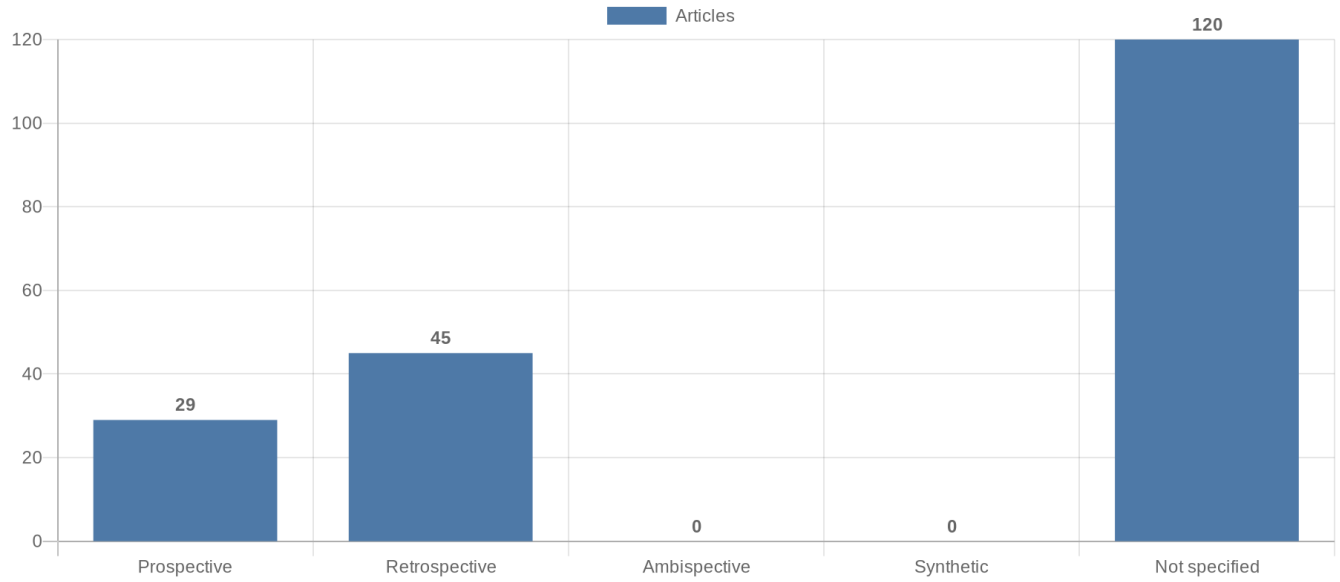



**Figure 4. Main extracted research topics**

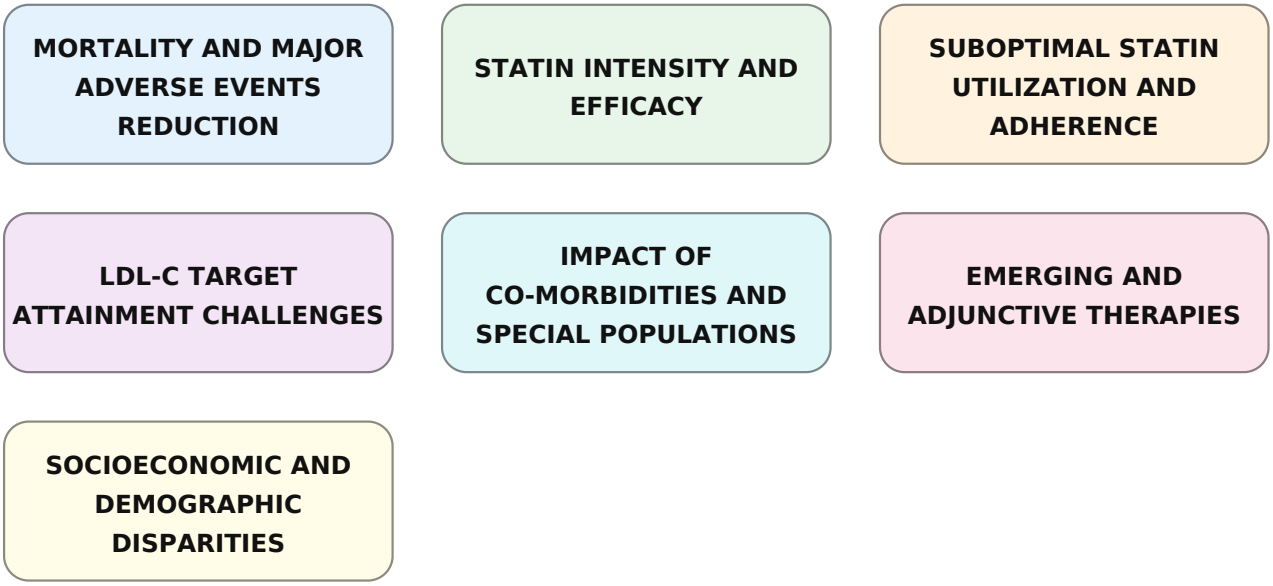



**Figure 5. Limitations of current studies (topics)**

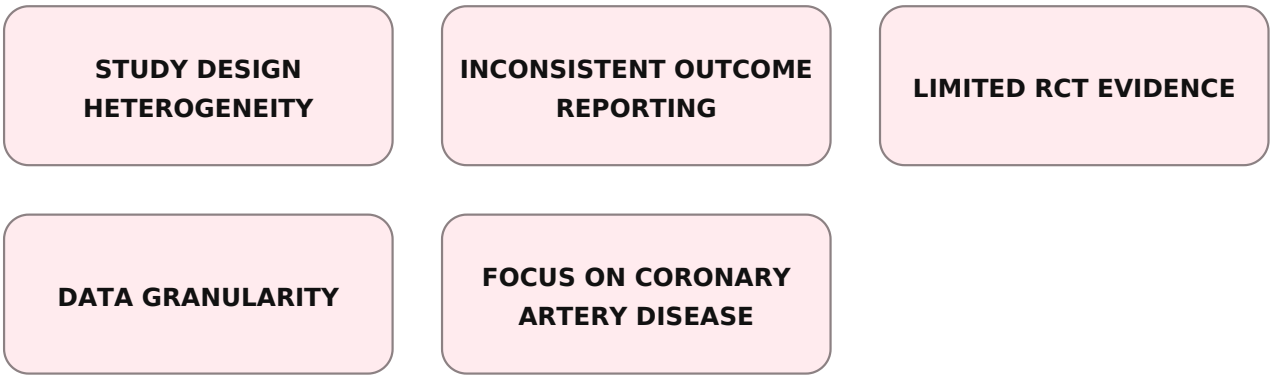



**Figure 6. Future research directions (topics)**