Peripheral Artery Disease Medication: Systematic Review with ☸SAIMSARA.

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Abstract: To systematically review and synthesize current evidence on peripheral artery disease medication, focusing on efficacy, adherence, and associated outcomes, to identify key clinical and research implications. The review utilises 216 studies with 1803676 total participants (naïve ΣN). Cardioprotective medications, including statins, beta-blockers, aspirin, and ACE inhibitors, are significantly associated with reduced long-term mortality in patients with peripheral arterial disease, with a median Hazard Ratio of 0.70 (range: 0.46–0.80). These findings are generally applicable to diverse PAD populations, including those with comorbidities like diabetes and those undergoing revascularization. However, the heterogeneity of outcomes reported across studies and the prevalence of retrospective designs are significant limitations affecting the certainty of specific quantitative conclusions. A concrete next step for clinicians is to consistently reinforce guideline-directed medical therapy, addressing patient adherence and managing comorbidities as integral components of PAD care.

Keywords: Peripheral Artery Disease; Pharmacotherapy; Antiplatelet Agents; Anticoagulants; Statins; Guideline-Directed Medical Therapy; Atherosclerosis; Cardiovascular Outcomes; Treatment Adherence; Restenosis

Review Stats

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- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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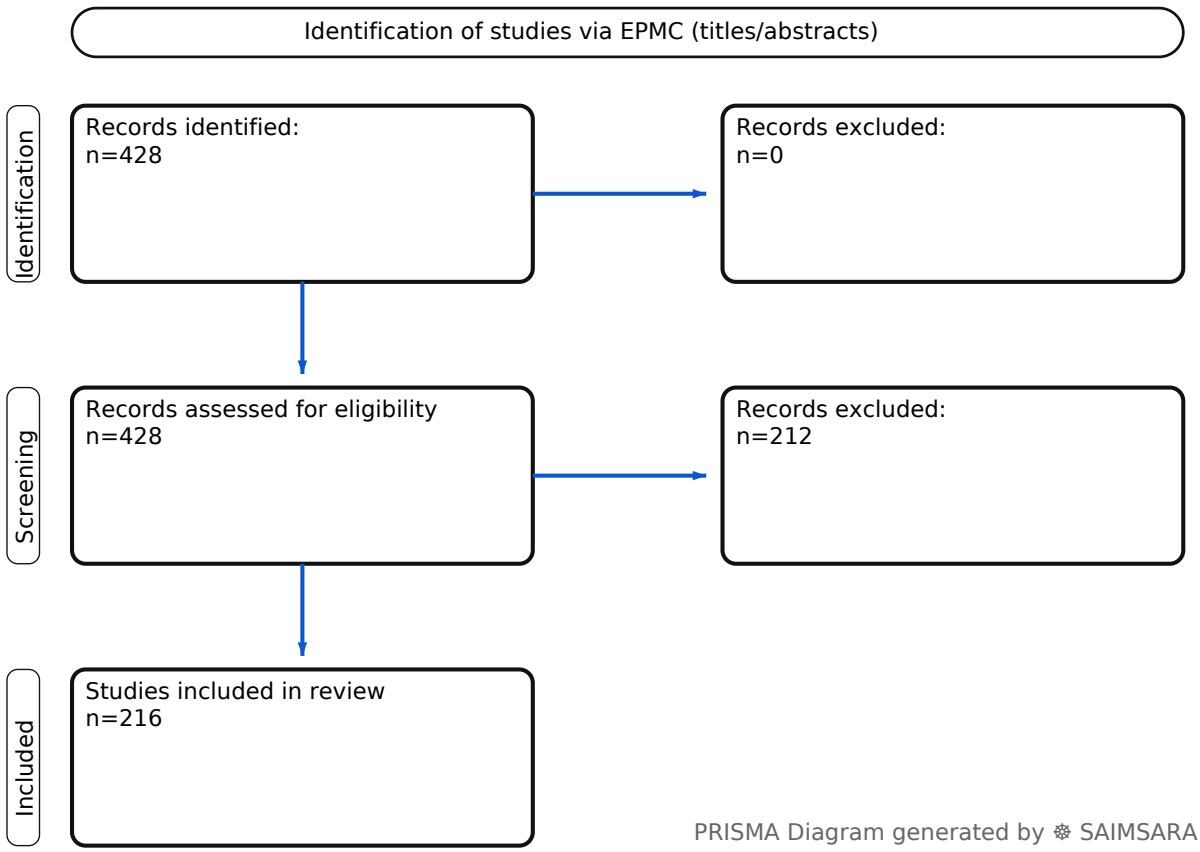
- Downloaded Abstracts/Papers: 428
- Included original Abstracts/Papers: 216
- Total study participants (naïve ΣN): 1803676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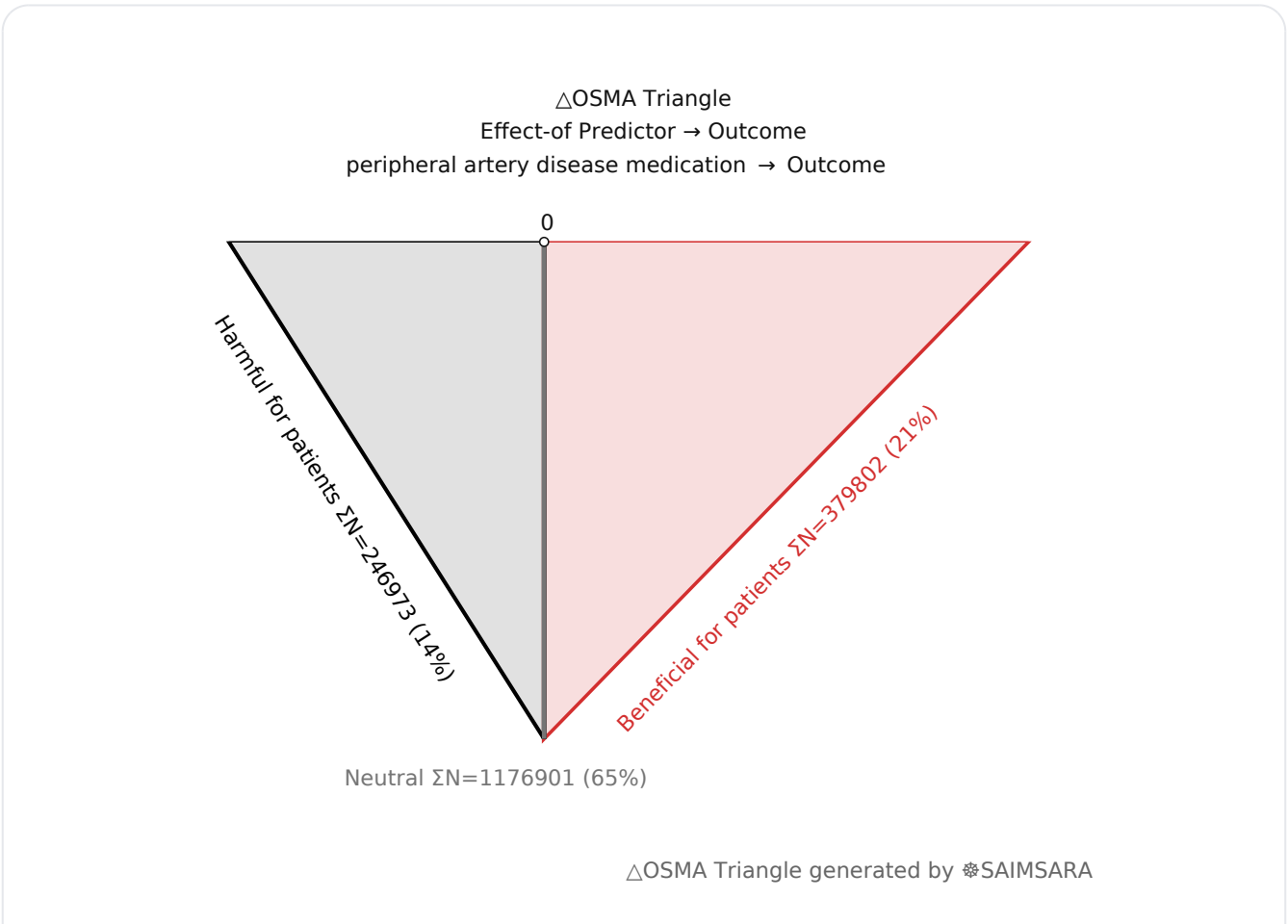
Identification
Records identified:
n=428
Records excluded:
n=0
Screening
Records assessed for eligibility
n=428
Records excluded:
n=212
Included
Studies included in review
n=216
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease medication → Outcome
0
Harmful for patients ΣN=246973 (14%)
Beneficial for patients ΣN=379802 (21%)
Neutral ΣN=1176901 (65%)
△OSMA Triangle generated by ☸SAIMSARA

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

Frame: Effect-of Predictor → Outcome • *Source*: Europe PMC

Outcome: Outcome Typical timepoints: 1-y, 2-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, survival.

Predictor: peripheral artery disease medication — exposure/predictor. Doses/units seen: 2.5 mg, 50 mg. Routes seen: oral. Typical comparator: dual antiplatelet therapy, patients with other, permanent metallic stents, hormone therapy….

- **1) Beneficial for patients** — Outcome with peripheral artery disease medication — [1], [2], [8], [18], [19], [22], [25], [30], [32], [34], [42], [43], [45], [77], [85], [88], [96], [98], [104], [107], [110], [114], [115], [118], [129], [132], [133], [134], [137], [138], [140], [143], [145], [146], [149], [150], [161], [165], [166], [175] — ΣN=379802
- **2) Harmful for patients** — Outcome with peripheral artery disease medication — [9], [11], [13], [20], [38], [44], [46], [47], [50], [76], [82], [87], [91], [92], [93], [95], [97], [108], [111], [112], [119], [120], [122], [125], [127], [128], [135], [139], [142], [144], [147], [148], [152], [153], [154], [155], [157], [162], [163], [164], [168], [169], [170], [171], [173], [174] — ΣN=246973
- **3) No clear effect** — Outcome with peripheral artery disease medication — [3], [4], [5], [6], [7], [10], [12], [14], [15], [16], [17], [21], [23], [24], [26], [27], [28], [29], [31], [33], [35], [36], [37], [39], [40], [41], [48], [49], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [78], [79], [80], [81], [83], [84], [86], [89], [90], [94], [99], [100], [101], [102], [103], [105], [106], [109], [113], [116], [117], [121], [123], [124], [126], [130], [131], [136], [141], [151], [156], [158], [159], [160], [167], [172], [176], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [197], [198], [199], [200], [201], [202], [203], [204], [205], [206], [207], [208], [209], [210], [211], [212], [213], [214], [215], [216] — ΣN=1176901

1) Introduction

Peripheral artery disease (PAD) represents a significant global health burden, characterized by atherosclerotic narrowing of non-coronary arteries, predominantly affecting the lower extremities. It is strongly associated with other cardiovascular diseases (CVD) such as coronary artery disease (CAD) and stroke, contributing to increased morbidity and mortality [119, 157, 186, 187]. Effective medication management is crucial for improving patient outcomes, reducing adverse events, and

enhancing quality of life. Despite established guidelines, challenges persist in optimal prescribing, patient adherence, and the integration of novel therapeutic strategies. This paper synthesizes recent findings on the efficacy, safety, and adherence patterns of various medications used in PAD management, highlighting current gaps and future research directions.

2) Aim

To systematically review and synthesize current evidence on peripheral artery disease medication, focusing on efficacy, adherence, and associated outcomes, to identify key clinical and research implications.

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. Retrospective and mixed-design studies, as well as those with unspecified directionality or N/A study design, introduce potential for selection and reporting bias. Small sample sizes and short follow-up periods in some studies further limit generalizability and long-term insights.

4) Results

4.1 Study characteristics

The included studies encompassed a range of designs, primarily mixed-design (combining retrospective and prospective elements), cohort studies, and randomized controlled trials (RCTs). Populations frequently included patients with symptomatic PAD, those undergoing revascularization procedures (e.g., DCB angioplasty, lower extremity revascularization, infrainguinal bypass), and individuals with comorbidities such as diabetes, coronary artery disease, or abdominal aortic aneurysm. Follow-up periods varied widely, from short-term (e.g., 6 weeks, 3 months) to longer-term (e.g., 1 year, 2 years, 10 years, or lifetime projections).

4.2 Main numerical result aligned to the query

Cardioprotective medications are associated with a reduction in long-term mortality in patients with peripheral arterial disease. Specifically, statins, beta-blockers, aspirin, and ACE inhibitors were associated with reduced long-term mortality, with a median Hazard Ratio (HR) of 0.70 (range: 0.46–0.80) [177].

4.3 Topic synthesis

- **Antiplatelet and Anticoagulant Therapies:** Rivaroxaban plus aspirin reduced primary efficacy outcomes (HR 0.77, P = 0.006) but increased TIMI major bleeding events (HR 2.6, P = 0.04) compared to dual antiplatelet therapy (DAPT) [3, 4]. DAPT is projected to dominate single antiplatelet therapy (SAPT) post-revascularization, potentially reducing healthcare costs and increasing quality of life [22]. Clopidogrel monotherapy is supported for symptomatic PAD [85], and was found cost-effective for secondary prevention of atherothrombotic events (ICER €4038 for LY, €5518 for QALY) [193]. Aspirin low response is common and increases after vascular procedures [84, 121].
- **Lipid-Lowering Medications:** Statin therapy significantly lowered longer-term restenosis risks after DCB treatment (HR 0.78 for one medication, HR 0.66 for two medications) [2] and reduced mortality in symptomatic PAD patients [63, 177]. Despite increased use over time, underuse persists [5, 55, 170], and attainment of LDL-C targets remains unsatisfactory in many PAD patients [56, 130, 182, 184]. Peripheral artery disease was associated with lower odds of primary nonadherence to SGLT2 inhibitors and GLP-1 agonists (aOR 0.73) [58].
- **Diabetes Management Medications:** Semaglutide significantly improved walking function in symptomatic PAD patients with type 2 diabetes [18]. Metformin improved hind limb blood supply in a mouse model [27] and was associated with enhanced glyoxalase 1 activity in atherosclerotic lesions in diabetic patients [109]. Medication-controlled diabetes was a protective factor against surgical site infection (OR 0.75) following infrainguinal bypass [19].
- **Antihypertensive Agents:** Renin-angiotensin-system (RAS) inhibitors are effective in reducing cardiovascular risk in PAD patients, and beta-blockers are not contraindicated [77]. Better adherence to antihypertensive agents is related to a risk reduction of end-stage renal disease (HR 0.67) [149]. However, anti-hypertensive medication did not significantly affect leg ischemia measures in patients with intermittent claudication [143].
- **Adherence and Under-prescription:** Non-adherence to evidence-based secondary prevention therapies (antiplatelet agents, statins, antihypertensive agents) is associated with a significant increase in long-term adverse events (HR 1.18–1.19) [168]. A significant proportion of patients with chronic limb-threatening ischemia (CLTI) did not meet optimal medical therapy (OMT) recommendations (only 25% met all four criteria) [52], and PAD patients globally are often undertreated [100, 105, 124, 138, 156, 179, 186, 205, 208]. Patients with peripheral vascular disease showed higher rates of non-adherence to treatment during the COVID-19 pandemic (OR 1.55) [68].
- **Novel Therapies and Adjunctive Treatments:** Cilostazol is the only FDA-approved medication for PAD-related ischemic symptoms [96] and significantly reduces in-stent restenosis after SFA stent placement (HR 5.4, P = 0.042) [175]. Targeting an olfactory receptor (OR2L13) with a non-odorant compound suppressed platelet aggregation and arterial thrombosis, suggesting a novel antithrombotic strategy [34]. Colchicine is being

evaluated for its impact on cardiovascular events, including PAD [24].

- **Impact of Comorbidities and Risk Factors:** Diabetes is highly prevalent in PAD patients, associated with coronary artery disease, tissue loss, and polypharmacy (POR 2.43, 3.39, 10.8 respectively) [11]. Smoking is significantly associated with altered coagulation profiles [13], and smoking cessation is linked to lower all-cause mortality and improved amputation-free survival [140]. Depression is underdiagnosed and undertreated in PAD patients and associated with increased mortality [91].

5) Discussion

5.1 Principal finding

The principal finding is that cardioprotective medications, including statins, beta-blockers, aspirin, and ACE inhibitors, are significantly associated with reduced long-term mortality in patients with peripheral arterial disease, with a median Hazard Ratio of 0.70 (range: 0.46–0.80) [177]. This underscores the critical role of comprehensive medical therapy in improving survival outcomes for this vulnerable population.

5.2 Clinical implications

- **Prioritize Guideline-Directed Medical Therapy (GDMT):** Despite clear benefits, GDMT for PAD, including antiplatelet agents, statins, and antihypertensives, is consistently underutilized and poorly adhered to [5, 52, 105, 168, 179, 208]. Clinicians should actively review and reinforce these therapies.
- **Address Bleeding Risks with Combination Therapies:** While rivaroxaban plus aspirin improves efficacy outcomes, it significantly increases bleeding risks [3, 4]. Careful patient selection and monitoring for bleeding events are crucial, especially after revascularization procedures [9].
- **Personalize Diabetes Management:** Semaglutide shows promise in improving walking function in diabetic PAD patients [18], and medication-controlled diabetes protects against surgical site infections [19]. Tailoring diabetes medications can yield direct PAD benefits.
- **Enhance Adherence Strategies:** Patient perception of medication necessity is low [90], and non-adherence is common, particularly in specific populations or during events like pandemics [68, 151]. Multicomponent interventions need to incorporate behavioral science approaches to improve adherence [12].
- **Consider Novel and Adjunctive Therapies:** Cilostazol remains a key symptomatic treatment [96, 175], and emerging therapies targeting pathways like olfactory receptors [34] or using existing drugs like colchicine [24] may offer future options.

5.3 Research implications / key gaps

- **Optimal Combination Therapy Trials:** Future RCTs are needed to determine the optimal combination of antiplatelet and anticoagulant therapies that balance efficacy with bleeding risk in diverse PAD patient subgroups, especially post-revascularization [75].
- **Behavioral Interventions for Adherence:** Prospective studies should evaluate multi-component interventions incorporating behavioral science to improve long-term adherence to guideline-recommended PAD therapies across different socioeconomic and ethnic groups [12, 61].
- **Long-term Outcomes of Novel Agents:** RCTs with extended follow-up are required to assess the long-term efficacy and safety of novel therapeutic targets, such as olfactory receptor modulators [34], and to further investigate the cardiovascular benefits of drugs like colchicine in PAD [24].
- **Impact of Comorbidity Management on PAD:** Research should explore integrated care models that systematically address comorbidities like depression [16, 91] and smoking cessation [140] within PAD management, evaluating their impact on PAD progression and medication adherence.
- **Biomarker-Guided Antithrombotic Therapy:** Prospective studies are needed to validate the use of thromboelastography with platelet function analysis [25, 29] to guide personalized antithrombotic treatments after revascularization, aiming to improve limb salvage and prevent adverse events.

5.4 Limitations

- **Heterogeneity of Outcomes** — The studies report a wide variety of outcomes (e.g., mortality, restenosis, walking distance, adherence rates), making direct quantitative comparison and meta-analysis challenging.
- **Study Design Variability** — A substantial number of studies were retrospective or mixed-design, which inherently carry a higher risk of bias and limit the ability to establish causality compared to prospective RCTs.
- **Inconsistent Follow-up Periods** — Follow-up durations varied significantly, from short-term to several years, which impacts the comparability of long-term efficacy and safety assessments.
- **Under-reporting of Adherence** — Many studies highlight suboptimal medication adherence, but comprehensive data on the specific reasons for non-adherence and the effectiveness of interventions are often lacking.
- **Population Specificity** — Some findings are specific to certain populations (e.g., Chinese patients [7], American Indians [28], Hispanic/Latino individuals [61]), limiting direct

generalizability to broader PAD populations.

5.5 Future directions

- **Standardize Outcome Reporting** — Future studies should adopt core outcome sets for PAD medication trials to facilitate comparability and meta-analysis.
- **Prospective Adherence Trials** — Conduct large-scale prospective randomized trials evaluating tailored behavioral interventions to improve long-term medication adherence in PAD.
- **Real-World Effectiveness Studies** — Investigate the real-world effectiveness and safety of novel PAD medications and combination therapies using large registry data and pragmatic trials.
- **Biomarker-Driven Treatment Algorithms** — Develop and test algorithms that integrate biomarkers (e.g., GDF15 [14, 21], platelet reactivity [50]) to personalize medication selection and dosing in PAD patients.
- **Integrated Care Pathway Development** — Design and evaluate integrated care pathways that address both PAD and its common comorbidities, including mental health, to optimize overall patient management.

6) Conclusion

Cardioprotective medications, including statins, beta-blockers, aspirin, and ACE inhibitors, are significantly associated with reduced long-term mortality in patients with peripheral arterial disease, with a median Hazard Ratio of 0.70 (range: 0.46–0.80) [177]. These findings are generally applicable to diverse PAD populations, including those with comorbidities like diabetes and those undergoing revascularization. However, the heterogeneity of outcomes reported across studies and the prevalence of retrospective designs are significant limitations affecting the certainty of specific quantitative conclusions. A concrete next step for clinicians is to consistently reinforce guideline-directed medical therapy, addressing patient adherence and managing comorbidities as integral components of PAD care.

References

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Figure 1. Publication-year distribution of included originals

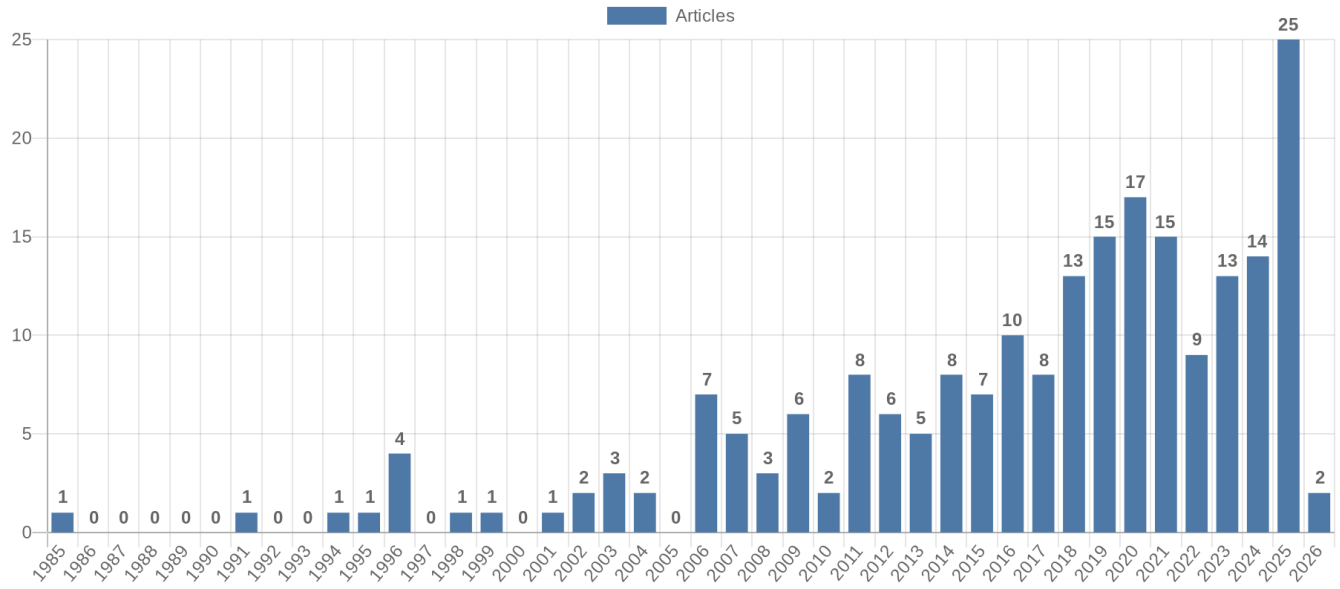

Figure 2. Study-design distribution of included originals

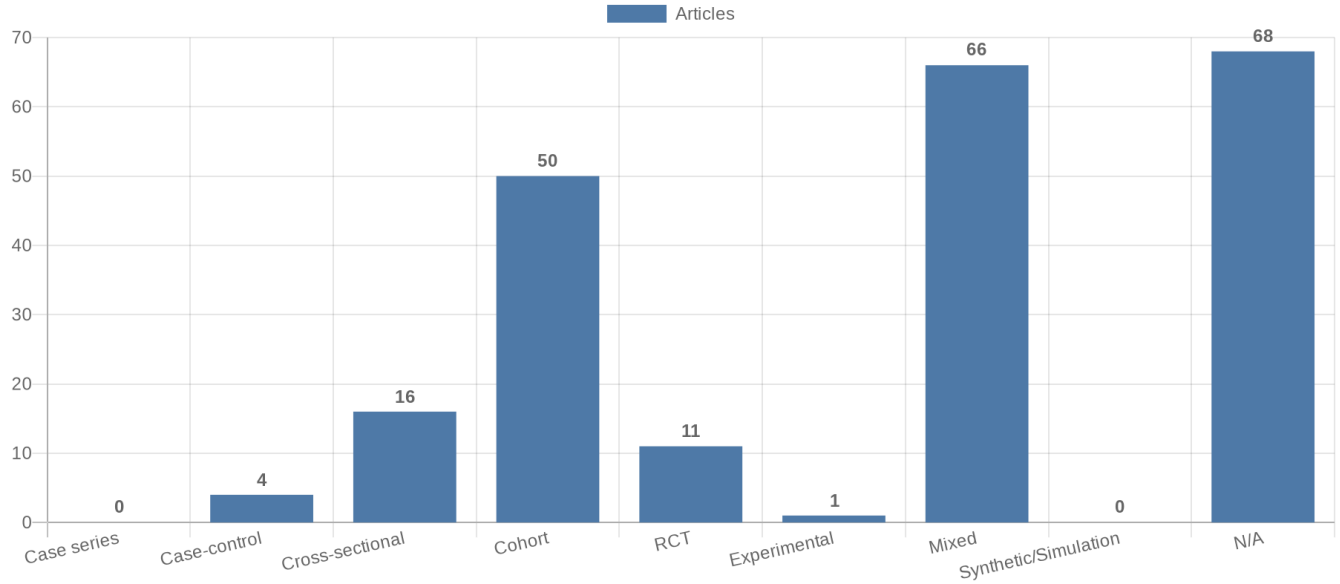

Figure 3. Study-type (directionality) distribution of included originals

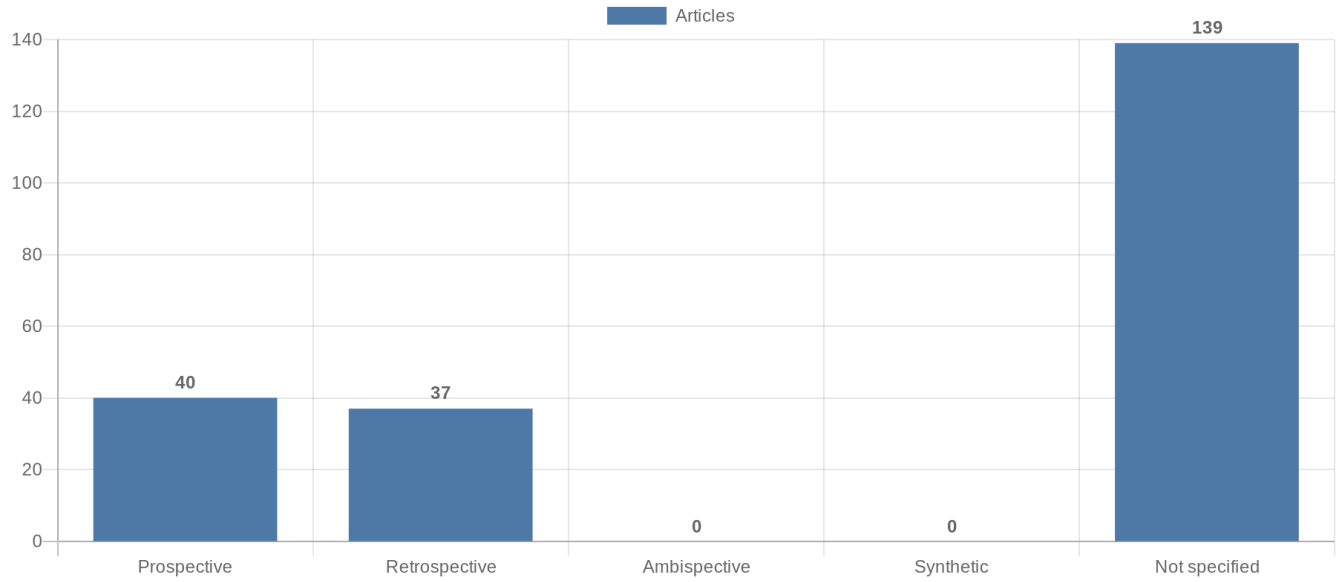

Figure 4. Main extracted research topics

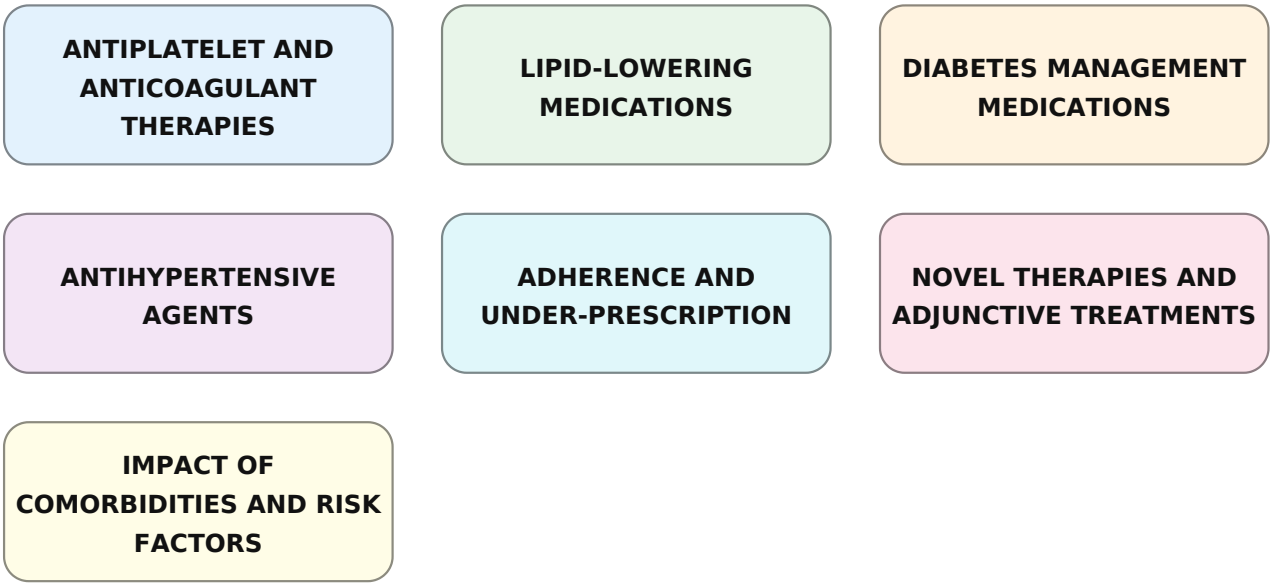

Figure 5. Limitations of current studies (topics)

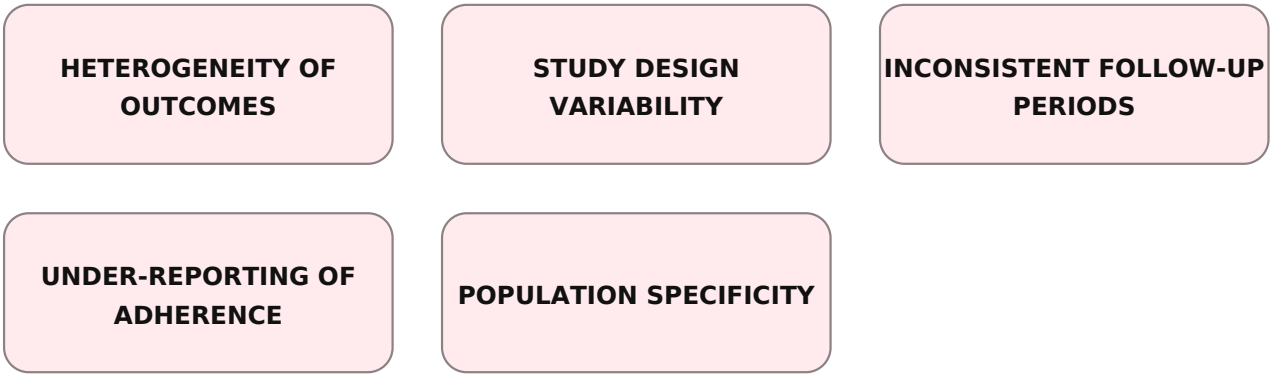

Figure 6. Future research directions (topics)