Carotid Disease Medication: Systematic Review with ☸SAIMSARA.

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Abstract: This paper aims to systematically review and synthesize the current evidence regarding medication use in carotid disease, focusing on treatment efficacy, adherence, and outcomes across various patient populations and clinical contexts. The review utilises 250 studies with 404013 total participants (naïve ΣN). Statin therapy is consistently associated with a median 41% (range: 25% to 51.8%) lower risk of adverse outcomes such as major adverse cardiac and cerebrovascular events (MACCE), death post-carotid endarterectomy (CEA), or restenosis. These findings are generally applicable across diverse patient populations with carotid disease, highlighting the critical role of statins in preventing progression and improving outcomes. However, the heterogeneous nature of study designs and outcome metrics represents the most significant limitation to synthesizing a comprehensive understanding of medication efficacy. A concrete next step is to conduct large-scale, prospective, randomized controlled trials with standardized outcome measures to compare the long-term effectiveness of different medication regimens in reducing carotid disease progression and clinical events.

Keywords: Carotid disease; Carotid stenosis; Carotid plaque; Antiplate

Review Stats

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- Plan: Pro (expanded craft tokens; source: Semantic Scholar)
- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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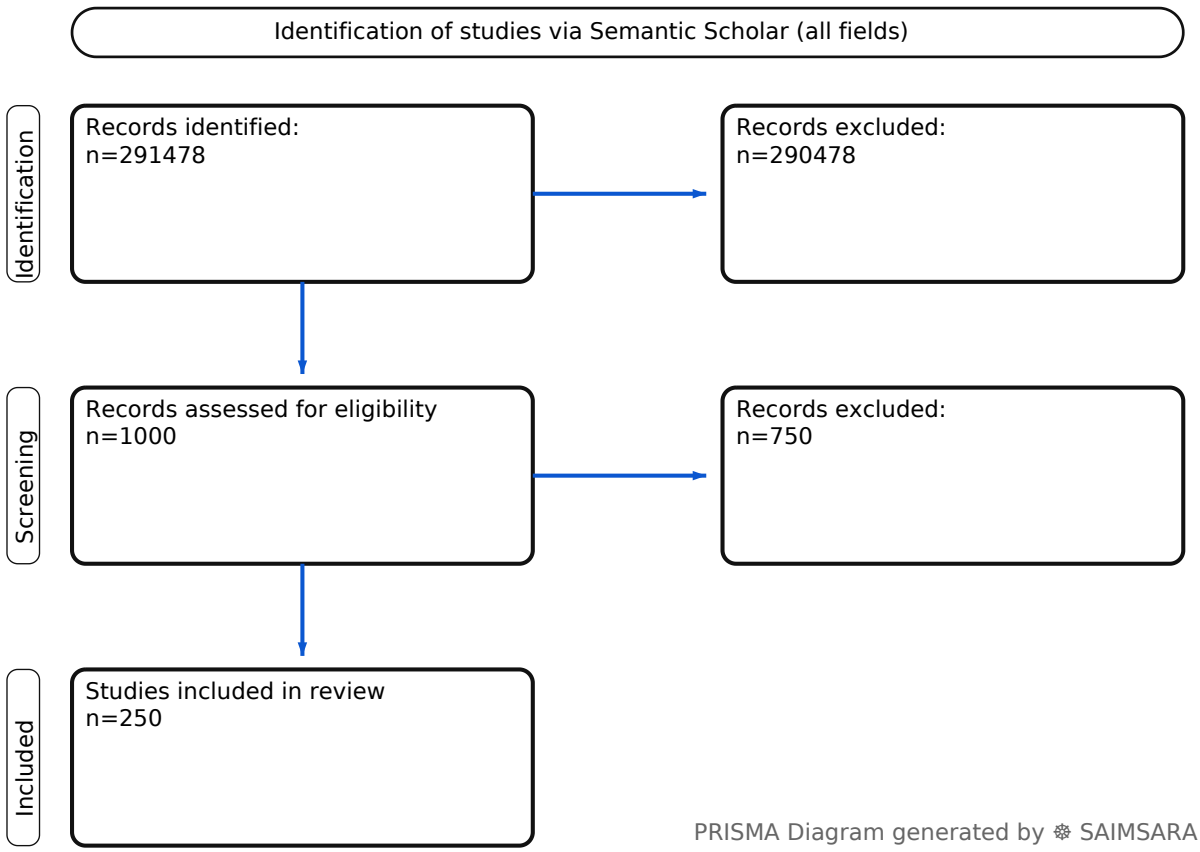
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 250
- Total study participants (naïve ΣN): 404013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Identification
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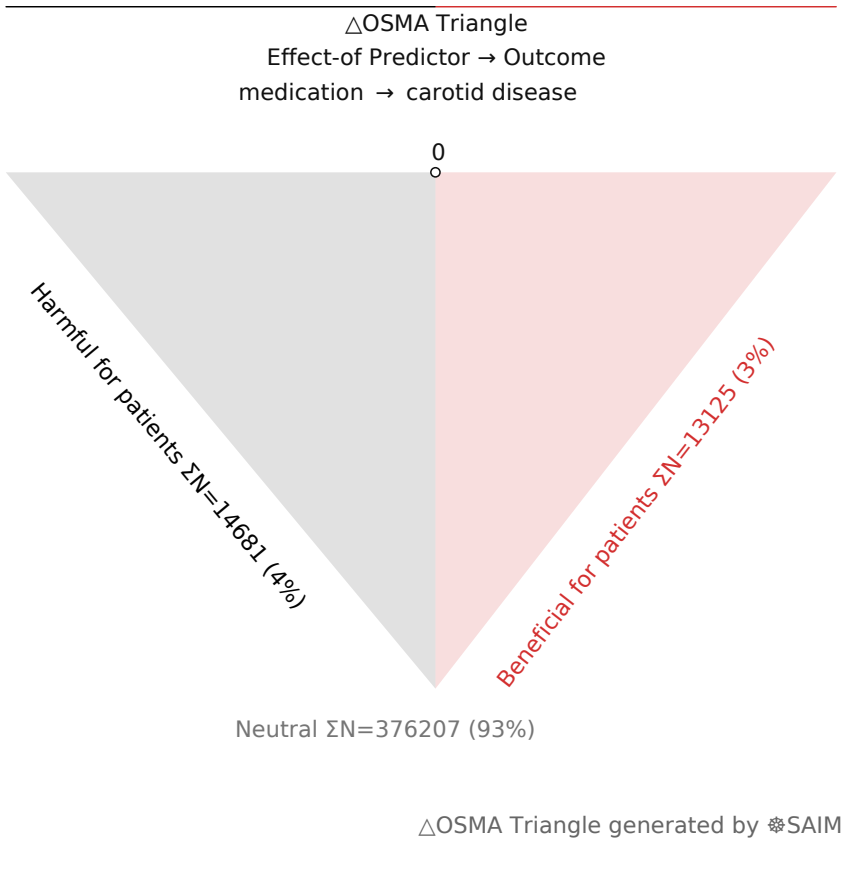
Records excluded:
n=290478
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=750
Included
Studies included in review
n=250
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
medication → carotid disease
0
Harmful for patients ΣN=14681 (4%)
Beneficial for patients ΣN=13125 (3%)
Neutral ΣN=376207 (93%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: carotid disease Typical timepoints: peri/post-op, 1-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, mortality, functional.

Predictor: medication — exposure/predictor. Routes seen: topical, oral, intravenous. Typical comparator: control, healthy controls, those without cognitive, metabolically healthy normal….

- **1) Beneficial for patients** — carotid disease with medication — [6], [12], [13], [17], [18], [20], [23], [44], [48], [56], [58], [72], [73], [105], [108], [113], [114], [117], [124], [131], [133], [137], [141], [145], [147], [178], [181], [186], [192], [200], [203], [212], [213], [225], [238], [245], [249] — ΣN=13125
- **2) Harmful for patients** — carotid disease with medication — [5], [7], [11], [19], [24], [50], [103], [109], [112], [115], [121], [143], [149], [177], [194], [196], [198] — ΣN=14681
- **3) No clear effect** — carotid disease with medication — [1], [2], [3], [4], [8], [9], [10], [14], [15], [16], [21], [22], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [45], [46], [47], [49], [51], [52], [53], [54], [55], [57], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [74], [75], [76], [77], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [101], [102], [104], [106], [107], [110], [111], [116], [118], [119], [120], [122], [123], [125], [126], [127], [128], [129], [130], [132], [134], [135], [136], [138], [139], [140], [142], [144], [146], [148], [150], [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], [179], [180], [182], [183], [184], [185], [187], [188], [189], [190], [191], [193], [195], [197], [199], [201], [202], [204], [205], [206], [207], [208], [209], [210], [211], [214], [215], [216], [217], [218], [219], [220], [221], [222], [223], [224], [226], [227], [228], [229], [230], [231], [232], [233], [234], [235], [236], [237], [239], [240], [241], [242], [243], [244], [246], [247], [248], [250] — ΣN=376207

1) Introduction

Carotid artery disease, a significant contributor to cerebrovascular events, necessitates effective medical management to mitigate progression and prevent adverse outcomes. The landscape of carotid disease medication encompasses a broad spectrum of pharmacological agents, including antiplatelets, lipid-lowering therapies, and antihypertensive drugs, often complemented by lifestyle

modifications. Understanding the efficacy, adherence patterns, and specific considerations for these medications across diverse patient populations is crucial for optimizing clinical practice. This paper synthesizes current research on carotid disease medication, drawing insights from a structured extraction of scientific literature.

2) Aim

This paper aims to systematically review and synthesize the current evidence regarding medication use in carotid disease, focusing on treatment efficacy, adherence, and outcomes across various patient populations and clinical contexts.

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 cohort studies and cross-sectional designs may introduce selection and recall bias, while randomized controlled trials (RCTs) offer higher internal validity. Case reports provide limited generalizability. Many studies mention medication history collection without specific quantitative analysis, introducing reporting bias.

4) Results

4.1 Study characteristics: The review encompassed a diverse range of study designs, including numerous cohort studies (retrospective and prospective), randomized controlled trials (RCTs), cross-sectional studies, and case reports. Populations varied widely, from patients undergoing carotid intervention or with specific comorbidities like type 2 diabetes mellitus (T2DM) and HIV, to healthy community-dwelling individuals. Follow-up periods ranged from short-term (e.g., 24 hours postoperatively [162]) to long-term (e.g., 15.1 years [60], 18.8 years [52]), with many studies not specifying a follow-up duration.

4.2 Main numerical result aligned to the query: Statin therapy is consistently associated with a reduction in adverse cardiovascular events and disease progression in carotid disease patients. Specifically, statin use was linked to a median 41% (range: 25% to 51.8%) lower risk of adverse outcomes such as major adverse cardiac and cerebrovascular events (MACCE) [90], death post-carotid endarterectomy (CEA) [91], or restenosis [87].

4.3 Topic synthesis:

- **Core Pharmacotherapies for Carotid Disease:** Conservative therapy for carotid artery disease primarily involves platelet aggregation inhibitors, antihypertensive, and lipid-lowering medications [8, 203], alongside lifestyle interventions [21].
- **Medication Adherence Challenges and Interventions:** Adherence to anti-platelet and lipid-lowering therapies varies, with reported adherence rates for anti-platelets between 59-62% and lipid-lowering medication at 70% in one RCT [3]. Non-adherence to vascular risk factor medications is significantly higher in patients with cognitive impairment [32, 110]. mHealth apps [6] and physician-patient education [168, 212] can improve adherence.
- **Statins and Carotid Atherosclerosis Regression/Risk Reduction:** Statin use is associated with a 25% lower risk of 1-year major adverse cardiac and cerebrovascular events (HR: 0.76; 95% CI, 0.70–0.83) [90], 51.8% lower risk of death (HR: 0.482; 95% CI: 0.233–0.998) post-CEA [91], and 41% lower risk of restenosis (OR: 0.59) [87]. They can induce regression of carotid plaque height (-0.20±0.34 mm) and reduce LDL-c [141], and decrease the rate of change of carotid lumen area [213].
- **Antihypertensive Medications and Arterial Stiffness/Outcomes:** Antihypertensive medications are crucial for blood pressure control [21]. Their use has been associated with thicker carotid intima-media thickness (cIMT) in adults with congenital heart disease [7] and increased carotid stiffness in metabolic syndrome patients [46]. However, they can also be associated with less cIMT progression in hypertensive subjects [117]. Postoperative use of antihypertensive medication correlated with long-term stroke (P=0.006), restenosis (P=0.01), and mortality (P=0.003) after CEA [79].
- **Antiplatelet Therapy for Prevention and Post-Intervention:** Antiplatelet agents are a cornerstone of intensive medical therapy for symptomatic carotid artery stenosis [21] and are recommended for secondary stroke prevention [225]. Dual antiplatelet therapy (DAPT) is standard after carotid stenting [151] and flow diversion procedures [221]. Aspirin use was associated with lower cognitive performance in one study [5], but did not increase hemorrhage risk during endovascular procedures with bridging thrombolysis [43].
- **Diabetes Medications and Carotid Disease:** Type 2 diabetes mellitus (T2DM) is strongly associated with carotid stenosis [4]. Metformin treatment enhances glyoxalase 1 (GLO1) activity in atherosclerotic lesions [45]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with lower incidences of adverse cardiovascular events (HR 0.88-0.93) and all-cause mortality (HR 0.70) in individuals with non-alcoholic fatty liver disease (NAFLD) and T2DM [137]. Glucose-lowering medication was associated with a more stable plaque phenotype [84].
- **Special Populations and Medication Considerations:** HIV-infected patients are less likely to receive guideline-recommended cardiovascular care, including aspirin (5.1% vs 13.8%) and statin therapy (23.6% vs 35.8%) [197]. Rosuvastatin therapy in people with HIV at moderate cardiovascular risk did not improve cIMT progression but was associated with

adverse events [189]. Elderly patients with atherosclerotic lesions face challenges with polypharmacy and drug therapy problems [51].

- **Emerging and Adjunctive Therapies:** Dual pathway inhibition with rivaroxaban plus aspirin significantly reduced cardiovascular death, myocardial infarction, or stroke in patients with carotid artery disease [73]. Tirofiban improved functional independence in endovascular thrombectomy for intracranial atherosclerosis [83]. Colchicine is being investigated for its potential to reduce vascular inflammation in patients with diabetes and recent vascular events [188].

5) Discussion

5.1 Principal finding: Statin therapy consistently demonstrates a significant protective effect, associated with a median 41% (range: 25% to 51.8%) lower risk of adverse cardiovascular outcomes, death, or restenosis in patients with carotid disease [87, 90, 91].

5.2 Clinical implications:

- **Guideline Adherence:** Clinicians should prioritize and improve adherence to guideline-directed medical therapy, especially statins and antiplatelets, particularly in high-risk populations like those with HIV [197] or after carotid interventions [86, 136].
- **Personalized Blood Pressure Control:** While antihypertensive medications are crucial, their impact on carotid stiffness and long-term outcomes requires careful monitoring, with potential for personalized recommendations using machine learning [169]. Overuse should be avoided, especially in patients susceptible to orthostatic effects [59].
- **Cognitive Impairment Screening:** Patients with cognitive impairment should be screened for medication non-adherence, as this population shows significantly higher rates of non-adherence to vascular risk factor medications [32, 110].
- **Diabetes Management:** Optimal management of diabetes with medications like GLP-1RAs [137] and metformin [45] can positively impact carotid atherosclerosis and overall cardiovascular risk.
- **Post-Intervention Care:** Dual antiplatelet therapy is critical post-carotid stenting [151] and other endovascular procedures, with non-compliance leading to adverse events [211].

5.3 Research implications / key gaps:

- **Standardize Adherence Metrics:** Future studies should use standardized metrics for medication adherence across diverse populations to allow for robust comparisons and meta-

analyses of interventions.

- **Long-term Cognitive Outcomes:** Investigate the long-term impact of antiplatelet therapy on cognitive function, given the observed association with lower cognitive performance in some at-risk patients [5].
- **Optimal Antihypertensive Regimens:** Conduct comparative effectiveness research on different classes and combinations of antihypertensive medications to identify regimens that optimally reduce carotid stiffness and improve long-term outcomes without adverse effects.
- **Colchicine Efficacy:** Further randomized controlled trials are needed to definitively establish the efficacy and safety of colchicine in reducing vascular inflammation and improving outcomes in carotid disease [188].
- **Pharmacist-Led Interventions:** Evaluate the long-term impact and cost-effectiveness of pharmacist-led interventions in reducing drug-related problems and improving adherence in vascular surgery patients [29].

5.4 Limitations:

- **Heterogeneous Study Designs** — The included studies varied significantly in design, from small case reports to large cohort studies and RCTs, limiting direct comparability and meta-analysis.
- **Varied Population Characteristics** — Patient populations differed widely in comorbidities, age, and geographical location, affecting the generalizability of specific findings.
- **Inconsistent Outcome Metrics** — Different studies used diverse endpoints (e.g., IMT, plaque area, stroke, mortality, adherence rates), making it challenging to synthesize a single, unified measure of medication effectiveness.
- **Qualitative Reporting Bias** — Many studies acknowledged collecting medication history but did not provide detailed quantitative results on medication-specific effects, leading to qualitative inferences.
- **Lack of Standardized Follow-up** — The duration of follow-up varied substantially, impacting the ability to draw consistent conclusions about long-term medication effects.

5.5 Future directions:

- **Standardize Adherence Measures**
- **Evaluate Novel Antiplatelets**
- **Longitudinal Statin Effects**
- **AI-Driven Drug Personalization**

- **Integrate Digital Adherence Tools**

6) Conclusion

Statin therapy is consistently associated with a median 41% (range: 25% to 51.8%) lower risk of adverse outcomes such as major adverse cardiac and cerebrovascular events (MACCE), death post-carotid endarterectomy (CEA), or restenosis [87, 90, 91]. These findings are generally applicable across diverse patient populations with carotid disease, highlighting the critical role of statins in preventing progression and improving outcomes. However, the heterogeneous nature of study designs and outcome metrics represents the most significant limitation to synthesizing a comprehensive understanding of medication efficacy. A concrete next step is to conduct large-scale, prospective, randomized controlled trials with standardized outcome measures to compare the long-term effectiveness of different medication regimens in reducing carotid disease progression and clinical events.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

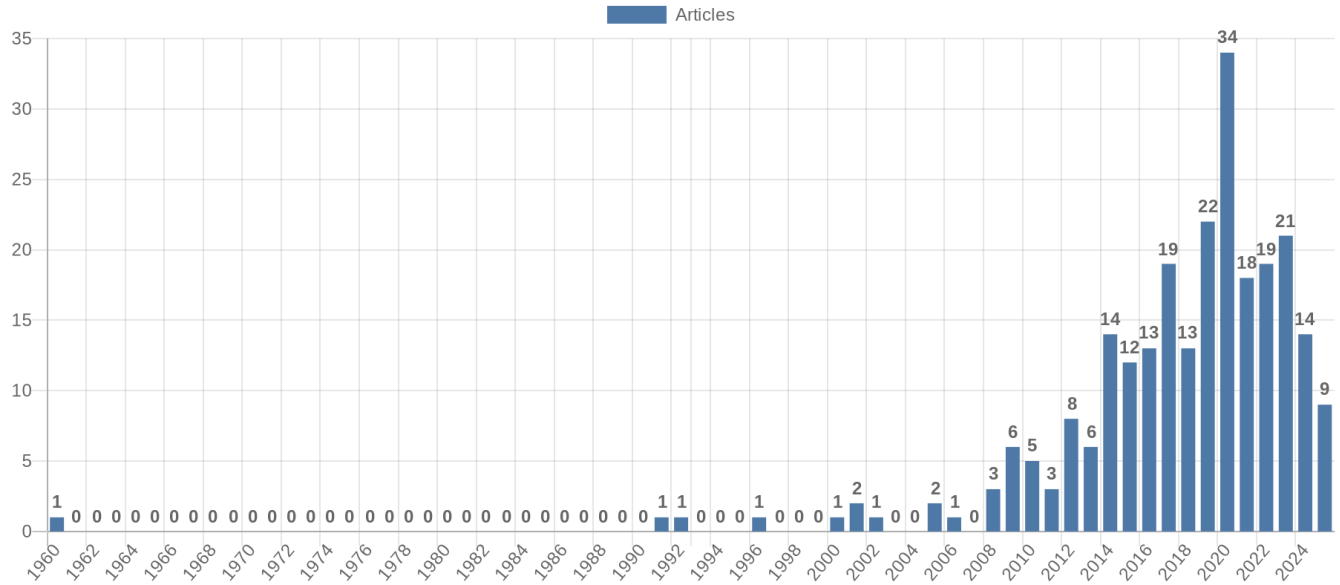


Figure 2. Study-design distribution of included originals

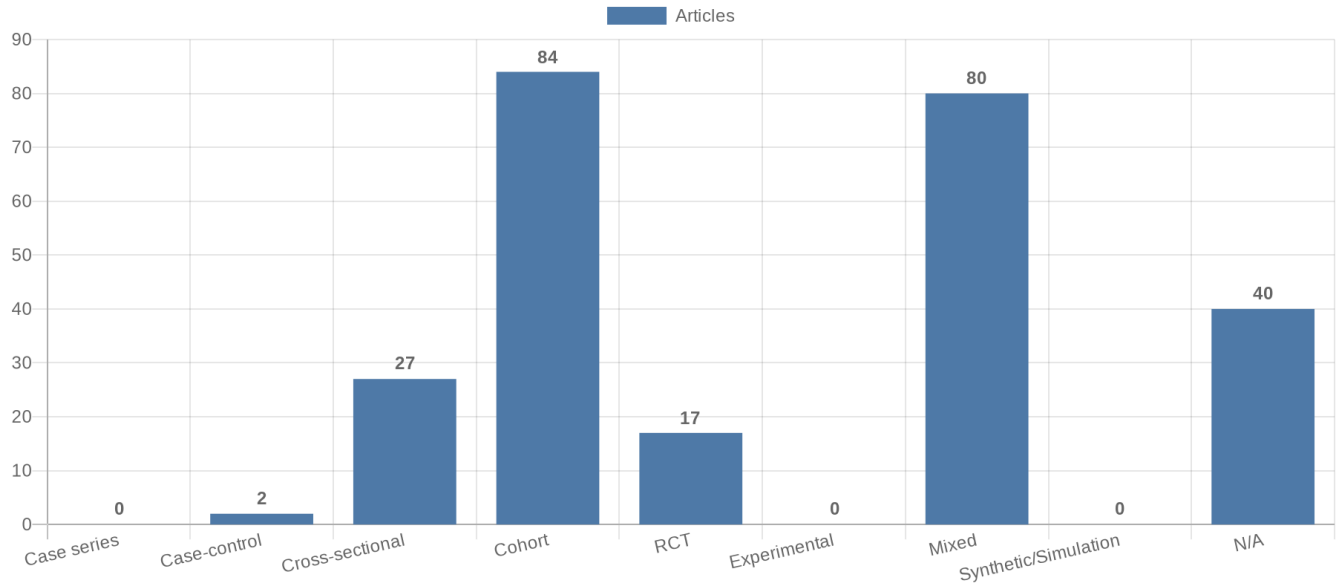


Figure 3. Study-type (directionality) distribution of included originals

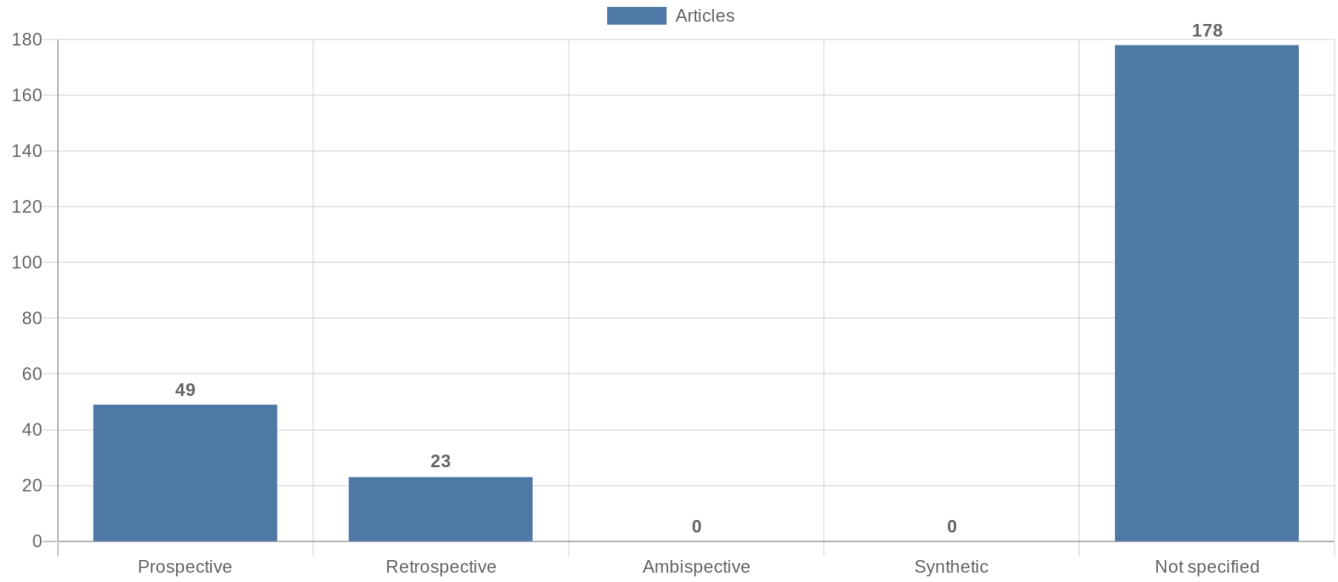


Figure 4. Main extracted research topics

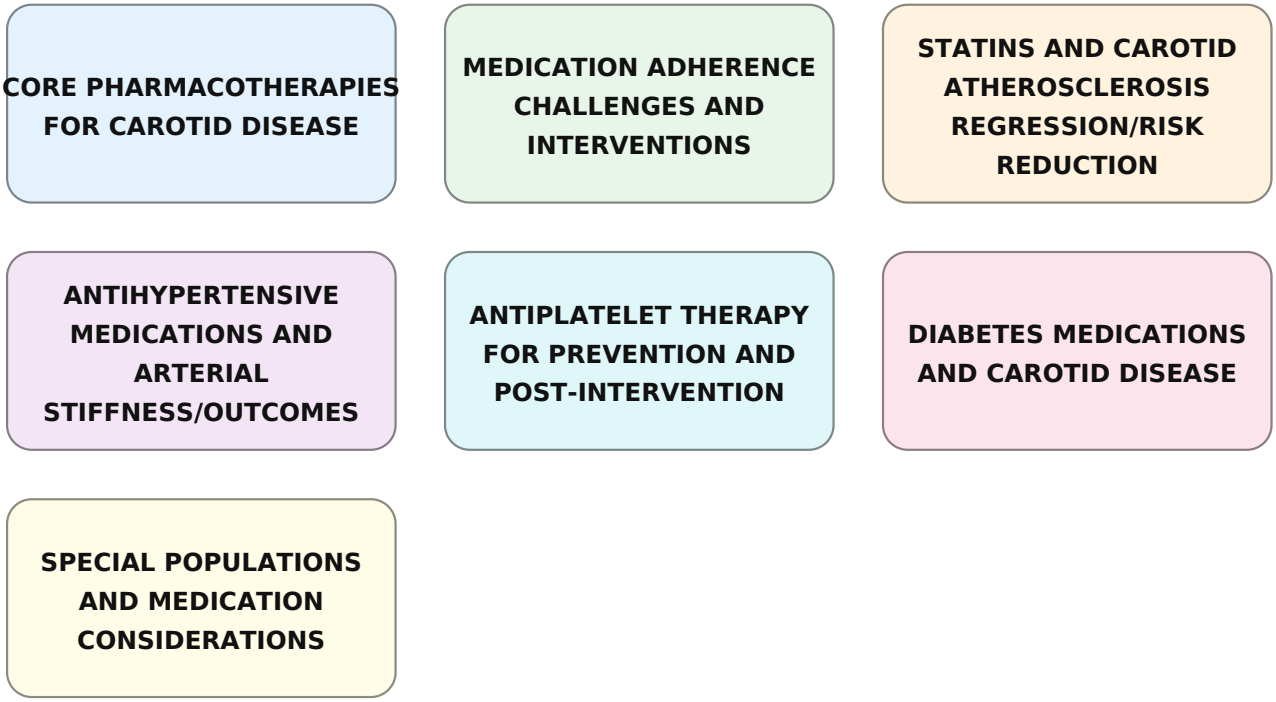


Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)

STANDARDIZE ADHERENCE METRICS

LONG-TERM COGNITIVE OUTCOMES

OPTIMAL ANTIHYPERTENSIVE REGIMENS

COLCHICINE EFFICACY

PHARMACIST-LED INTERVENTIONS

STANDARDIZE ADHERENCE MEASURES

EVALUATE NOVEL ANTIPLATELETS