Peripheral Artery Disease Drugs: Systematic Review with ☸SAIMSARA.

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Abstract: To systematically review and synthesize the evidence regarding drug therapies for peripheral artery disease, identifying key findings, clinical implications, and research gaps. The review utilises 126 studies with 1471667 total participants (naïve ΣN). Systemic drug therapies for peripheral artery disease (PAD) or its associated cardiovascular risks consistently demonstrated a beneficial effect on various adverse outcomes, with a median hazard ratio for risk reduction of 0.70 (range 0.43 to 0.80). These findings support the widespread use of evidence-based pharmacotherapy in managing PAD across diverse patient populations, including those with comorbidities like diabetes and coronary artery disease. However, the heterogeneity of study designs and outcome measures represents the most significant limitation to synthesizing definitive conclusions. A critical next step is to conduct comparative effectiveness trials to optimize antiplatelet and anticoagulant strategies, particularly addressing clopidogrel resistance and the long-term safety of paclitaxel-coated devices.

Keywords: Peripheral Artery Disease; Pharmacotherapy; Statins; 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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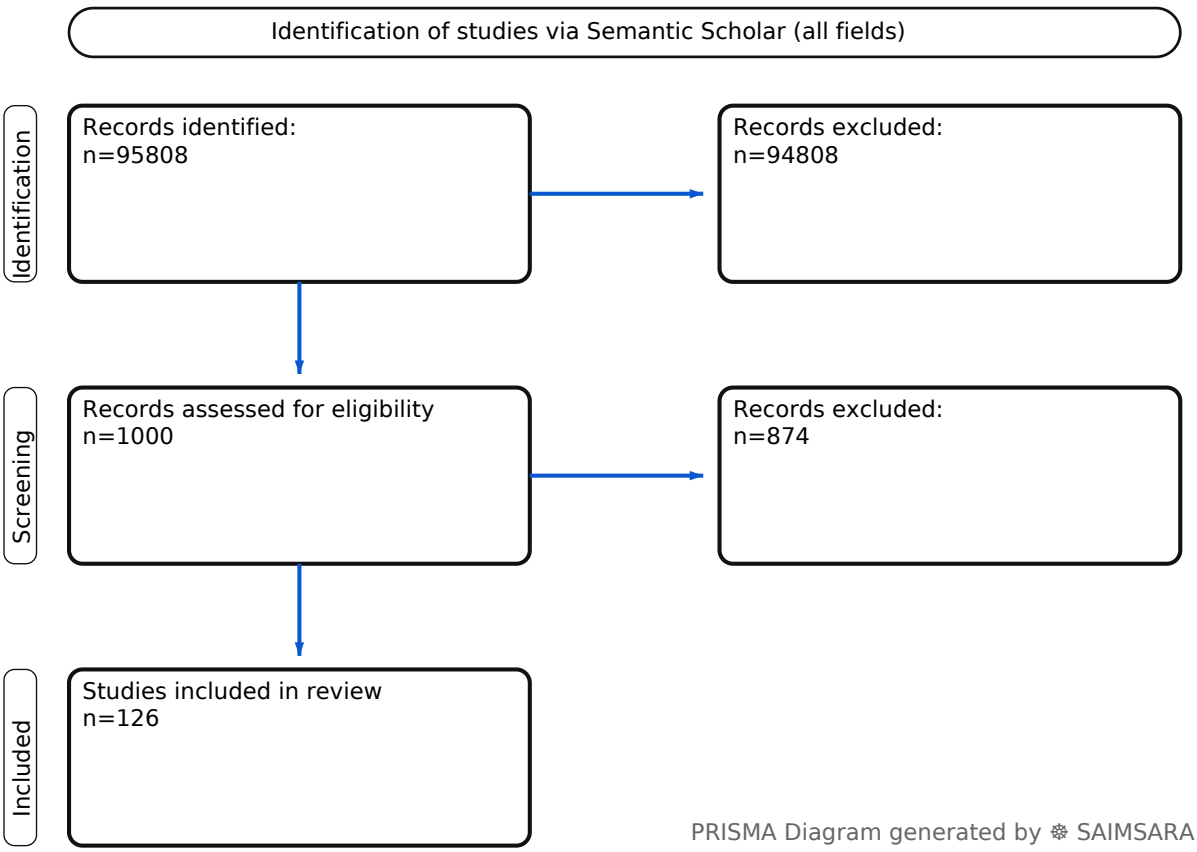
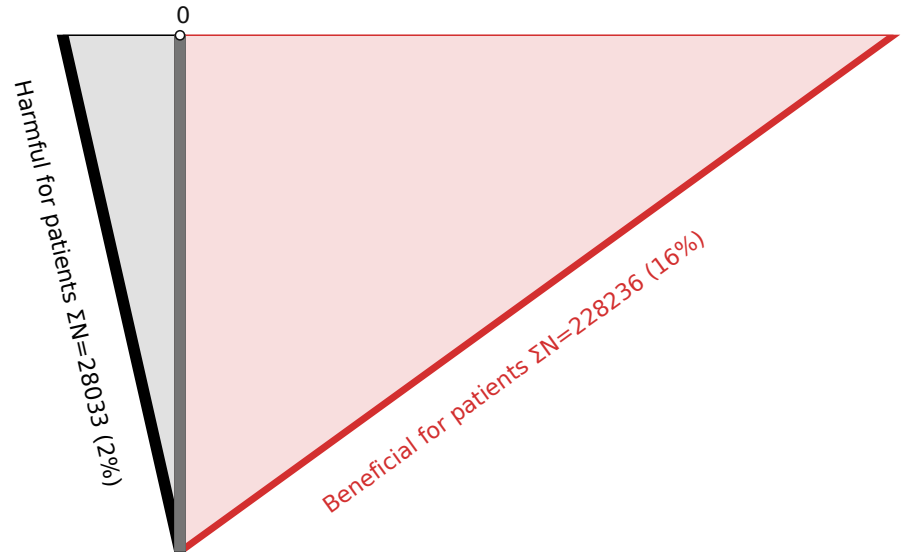
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 126
- Total study participants (naïve ΣN): 1471667



PRISMA Diagram generated by ☸ SAIMSARA

△OSMA Triangle
Effect-of Predictor → Outcome
peripheral artery disease drugs → Outcome



Neutral ΣN=1215398 (83%)

△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: complications, mortality, patency.
Predictor: peripheral artery disease drugs — exposure/predictor. Doses/units seen: 2.5 mg. Routes seen: intravenous, intramuscular, oral. Typical comparator: glp1-ra or other anti-diabetic, atorvastatin, aspirin alone was cost-, bare metal stents….

- **1) Beneficial for patients** — Outcome with peripheral artery disease drugs — [3], [6], [8], [15], [22], [26], [35], [37], [39], [41], [43], [44], [45], [49], [50], [101], [105], [110], [118], [121], [122], [125] — ΣN=228236
- **2) Harmful for patients** — Outcome with peripheral artery disease drugs — [2], [16], [115], [120], [123], [124] — ΣN=28033
- **3) No clear effect** — Outcome with peripheral artery disease drugs — [1], [4], [5], [7], [9], [10], [11], [12], [13], [14], [17], [18], [19], [20], [21], [23], [24], [25], [27], [28], [29], [30], [31], [32], [33], [34], [36], [38], [40], [42], [46], [47], [48], [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], [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], [102], [103], [104], [106], [107], [108], [109], [111], [112], [113], [114], [116], [117], [119], [126] — ΣN=1215398

1) Introduction

Peripheral artery disease (PAD) is a prevalent atherosclerotic condition affecting the arteries supplying the limbs, often leading to significant morbidity and mortality. It is a major cardiovascular risk factor, frequently co-occurring with coronary artery disease (CAD), chronic kidney disease (CKD), and type 2 diabetes mellitus (T2DM) [4, 11, 72]. PAD patients experience increased risks of stroke, myocardial infarction (MI), lower limb amputation (LLA), and major adverse limb events (MALE) [3, 15, 37, 69, 91]. The management of PAD is multifaceted, encompassing lifestyle modifications, revascularization procedures, and pharmacotherapy aimed at reducing cardiovascular risk, improving symptoms, and preventing disease progression [111]. This paper synthesizes current evidence on drug therapies for PAD, examining their efficacy, safety, and emerging applications.

2) Aim

To systematically review and synthesize the evidence regarding drug therapies for peripheral artery

disease, identifying key findings, clinical implications, and research gaps.

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. Cohort studies and mixed designs are susceptible to confounding, selection bias, and information bias. Randomized controlled trials (RCTs) generally offer higher internal validity but may have limitations in generalizability or specific patient populations. Studies with "Not specified" directionality or study type present higher uncertainty regarding methodological rigor. Single-center or small sample size studies may also introduce bias.

4) Results

4.1 Study characteristics

The review included a diverse range of studies, predominantly cohort studies and randomized controlled trials (RCTs), with several mixed design studies and reviews. Populations frequently included patients with type 2 diabetes mellitus (T2DM), coronary artery disease (CAD), or symptomatic peripheral artery disease (PAD), often focusing on femoropopliteal lesions. Follow-up periods varied widely, from short-term (e.g., 1 month for atorvastatin effects [6]) to intermediate (e.g., 12 months for drug-coated balloons [32, 39, 50]) and long-term (e.g., 3 years for vorapaxar [91] or up to 20 years for genetic studies [75]).

4.2 Main numerical result aligned to the query

Systemic drug therapies for peripheral artery disease (PAD) or its associated cardiovascular risks consistently demonstrated a beneficial effect on various adverse outcomes. Across multiple studies, the median hazard ratio (HR) for risk reduction of events such as lower limb amputation (LLA), major adverse limb events (MALE), stroke, or PAD incidence was 0.70, with a range from 0.43 to 0.80 [37, 91, 118, 125]. This indicates that, on average, these drug interventions reduced the risk of adverse events by approximately 30% compared to their respective comparators.

4.3 Topic synthesis

- **Antiplatelet and Anticoagulant Therapies:** Antiplatelet drugs and statins are associated with a lower incidence of stroke in PAD patients [3]. Dual pathway inhibition with low-dose rivaroxaban plus acetylsalicylic acid (aspirin) reduced major adverse cardiovascular events (MACE), major adverse limb events (MALE), and mortality in patients with prior CAD or PAD [15, 22]. Vorapaxar significantly reduced thrombotic cardiovascular events by a Hazard

Ratio (HR) of 0.80 (95% CI 0.73 to 0.89) in patients with prior MI or PAD, but increased moderate or severe bleeding [91]. Non-vitamin K antagonist oral anticoagulants (NOACs) were associated with a lower risk of MALE (adjusted HR [aHR]: 0.72, 95% CI 0.57–0.92) compared to warfarin in diabetic atrial fibrillation patients with PAD [125]. A high proportion (>50%) of diabetic PAD patients in Taiwan showed clopidogrel resistance [33].

- **Lipid-Lowering Agents:** Statins are widely recommended for PAD patients, with atorvastatin improving nitrite levels and decreasing total cholesterol/HDL ratio [6]. High-intensity statin therapy is common in patients with Familial Hypercholesterolemia (FH) and atherosclerotic cardiovascular disease (ASCVD), including PAD [74]. Genetically proxied PCSK9 inhibitors were associated with a reduced risk of PAD (Odds Ratio [OR] = 0.96, 95%CI, 0.94–0.99) [67].
- **Antihypertensive Drugs:** Hypertension is a significant risk factor for PAD [20], and antihypertensive drugs are recommended [13]. Candesartan treatment was associated with a lower aHR for PAD (0.61, 95% CI 0.41–0.91) compared to losartan in hypertensive patients [118]. Amlodipine, however, was associated with a higher rate of peripheral edema (16.6% vs 6.2%, Risk Ratio [RR] 2.9) [71].
- **Anti-Diabetic Medications:** In patients with T2DM, sodium-glucose co-transporter 2 inhibitors (SGLT-2i) were not associated with a higher risk of lower limb amputation (LLA) compared to GLP1-RA or other anti-diabetic drugs (ADDs), and pre-existing PAD was the greatest driver of amputation risk (PAD HR range: 3.6-6.0) [1]. SGLT2i were associated with lower risks of LLA requiring revascularization (HR: 0.73, 95% CI 0.54–0.98), amputation (HR: 0.43, 95% CI 0.30–0.62), and cardiovascular death (HR: 0.67, 95% CI 0.49–0.90) compared to dipeptidyl peptidase-4 inhibitors (DPP4i) in T2DM and PAD patients [37]. Semaglutide treatment in type 1 diabetes mellitus (T1DM) subjects showed a decline in peripheral resistance by 5.1% ($p = 0.046$) [78].
- **Local Drug Delivery for Revascularization:** Drug-coated balloons (DCBs) and drug-eluting stents (DES) demonstrated superior primary patency and reduced target lesion revascularization (TLR) compared to uncoated devices or plain old balloon angioplasty (PTA) in femoropopliteal lesions [32, 39, 50, 84, 88, 94]. For instance, DCBs achieved 12-month primary patency of 82.2% versus 52.4% for PTA ($P<0.001$) [50]. However, some studies associated paclitaxel-coated devices with an increased late mortality risk (38% increased relative mortality risk at 5 years) [81], while others found no significant difference [34, 73, 86].
- **Emerging Therapies and Drug Repositioning:** Neovasculgen is a gene-based drug developed for PAD [12]. Apabetalone, a BET protein inhibitor, restored angiogenic response in diabetic mice with hind limb ischemia [21]. Indole-3-aldehyde, an endogenous tryptophan metabolite, improved neovascularization in a model of diabetic limb ischemia [23]. Uric acid-lowering drugs showed a protective role in reducing the risk of peripheral vascular disease

(OR = 0.60, 95%CI: 0.38, 0.94) [64]. Resveratrol, a polyphenol, increased serum adiponectin and decreased plasminogen activator inhibitor type 1 (PAI-1) in stable CAD patients [8].

- **Medication Adherence and Healthcare Utilization:** Prescription of evidence-based medical therapy prior to hospital discharge increased utilization at 6 months in symptomatic PAD patients [5]. However, studies revealed low compliance with antihypertensive drugs (26.4% low, 67.4% medium) [17] and low utilization rates of secondary prevention therapies like antiplatelet medication in symptomatic PAD patients, who incurred significantly higher medical resource utilization and costs [48, 58]. Patients with PAD expressed a higher willingness to participate in drug infusion studies and trials of investigational drugs [38].

5) Discussion

5.1 Principal finding

Systemic drug therapies for peripheral artery disease (PAD) or its associated cardiovascular risks consistently demonstrated a beneficial effect on various adverse outcomes, with a median hazard ratio for risk reduction of 0.70 (range 0.43 to 0.80) [37, 91, 118, 125]. This indicates a clinically meaningful reduction in the risk of events such as lower limb amputation, major adverse limb events, stroke, or PAD incidence through pharmacological interventions.

5.2 Clinical implications

- **Standard of Care Therapies:** Antiplatelet agents (e.g., aspirin, clopidogrel), statins, and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are cornerstones of PAD management, significantly reducing cardiovascular events and stroke risk [3, 13, 29, 68, 109].
- **Diabetes Management:** Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are particularly beneficial for patients with type 2 diabetes and PAD, demonstrating lower risks of lower limb ischemia, amputation, and cardiovascular death compared to dipeptidyl peptidase-4 inhibitors (DPP4i) [37].
- **Anticoagulation Strategies:** Dual pathway inhibition with low-dose rivaroxaban plus aspirin is effective in reducing major adverse cardiovascular events (MACE) and major adverse limb events (MALE) in CAD/PAD patients [15, 22]. Non-vitamin K antagonist oral anticoagulants (NOACs) may offer a safer alternative to warfarin for MALE reduction in diabetic atrial fibrillation patients with PAD [125].
- **Adherence Importance:** Despite clear benefits, adherence to evidence-based therapies remains suboptimal [17, 48, 58], highlighting the need for improved patient education and support to maximize therapeutic outcomes.

- **Device-Related Drug Safety:** While drug-coated balloons (DCBs) and drug-eluting stents (DES) improve patency and reduce revascularization rates [39, 50, 84], the long-term safety, particularly concerning paclitaxel-coated devices and potential late mortality risk, requires careful consideration [81].

5.3 Research implications / key gaps

- **Paclitaxel Device Safety:** Further long-term, adequately powered randomized controlled trials are needed to definitively assess the all-cause mortality risk associated with paclitaxel-coated devices in femoropopliteal PAD interventions [34, 81, 86, 104].
- **Optimizing Antiplatelet Therapy:** Research should focus on personalized antiplatelet strategies, including the role of genetic testing for clopidogrel resistance and the comparative effectiveness of novel P2Y12 inhibitors like selatogrel [25, 33, 96, 107].
- **Emerging Angiogenic Therapies:** Clinical trials are warranted to evaluate the efficacy and safety of novel pro-angiogenic agents (e.g., apabetalone, indole-3-aldehyde, salidroside) and gene therapies (e.g., Neovasculgen, pl-VEGF165) in promoting neovascularization and limb salvage in critical limb ischemia [12, 21, 23, 43, 55, 56, 98].
- **Advanced Drug Delivery Systems:** Development and clinical evaluation of nanocarriers, novel excipients for drug-coated devices, and localized liquid drug delivery systems (e.g., sirolimus) are needed to improve drug transfer, retention, and reduce systemic side effects in peripheral arteries [20, 24, 26, 80, 82, 100, 103].
- **Impact of Comorbidities on Drug Choice:** Studies should investigate how specific comorbidities (e.g., chronic kidney disease, heart failure, chronic obstructive pulmonary disease) influence the optimal choice and dosing of PAD medications to minimize adverse events and improve outcomes [4, 28, 36, 95, 110].

5.4 Limitations

- **Study Heterogeneity** — The included studies varied widely in design, population, and outcome measures, limiting direct comparisons and meta-analysis.
- **Reporting Inconsistencies** — Some studies lacked detailed statistical reporting or specific drug comparisons, leading to qualitative rather than quantitative synthesis for certain topics.
- **Focus on Specific Lesions** — Many interventional studies concentrated on femoropopliteal lesions, potentially limiting generalizability to other arterial beds in PAD.
- **Observational Study Bias** — A significant number of cohort and mixed-design studies are susceptible to confounding, impacting the certainty of observed associations between drug

use and outcomes.

- **Limited Long-Term Data** — While some studies provided long-term follow-up, comprehensive long-term safety and efficacy data for all drug classes and novel interventions remain limited.

5.5 Future directions

- **Comparative Effectiveness Trials** — Conduct head-to-head trials comparing different drug classes for PAD outcomes.
- **Personalized Medicine Approaches** — Investigate genetic and biomarker-guided therapy selection for PAD patients.
- **Novel Drug Delivery Systems** — Develop and test advanced local drug delivery technologies for revascularization.
- **Longitudinal Safety Studies** — Monitor long-term safety of all PAD drug therapies, especially novel agents.
- **Adherence Intervention Research** — Design and evaluate interventions to improve medication adherence in PAD patients.

6) Conclusion

Systemic drug therapies for peripheral artery disease (PAD) or its associated cardiovascular risks consistently demonstrated a beneficial effect on various adverse outcomes, with a median hazard ratio for risk reduction of 0.70 (range 0.43 to 0.80) [37, 91, 118, 125]. These findings support the widespread use of evidence-based pharmacotherapy in managing PAD across diverse patient populations, including those with comorbidities like diabetes and coronary artery disease. However, the heterogeneity of study designs and outcome measures represents the most significant limitation to synthesizing definitive conclusions. A critical next step is to conduct comparative effectiveness trials to optimize antiplatelet and anticoagulant strategies, particularly addressing clopidogrel resistance and the long-term safety of paclitaxel-coated devices.

References

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Figure 1. Publication-year distribution of included originals

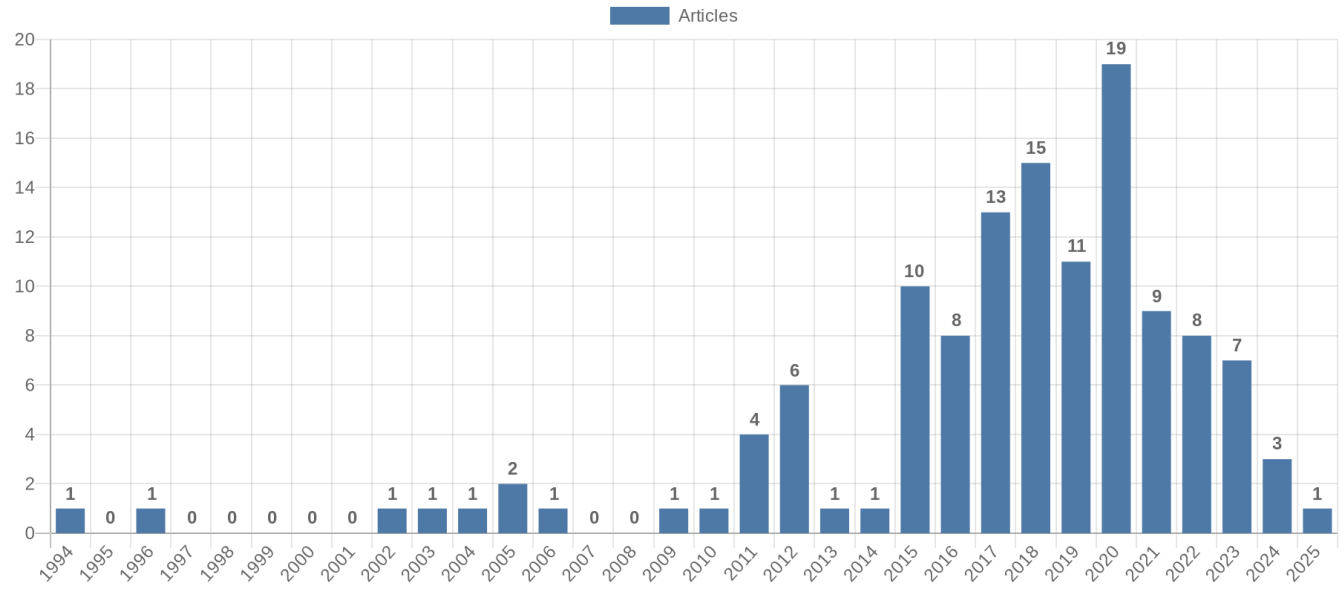

Figure 2. Study-design distribution of included originals

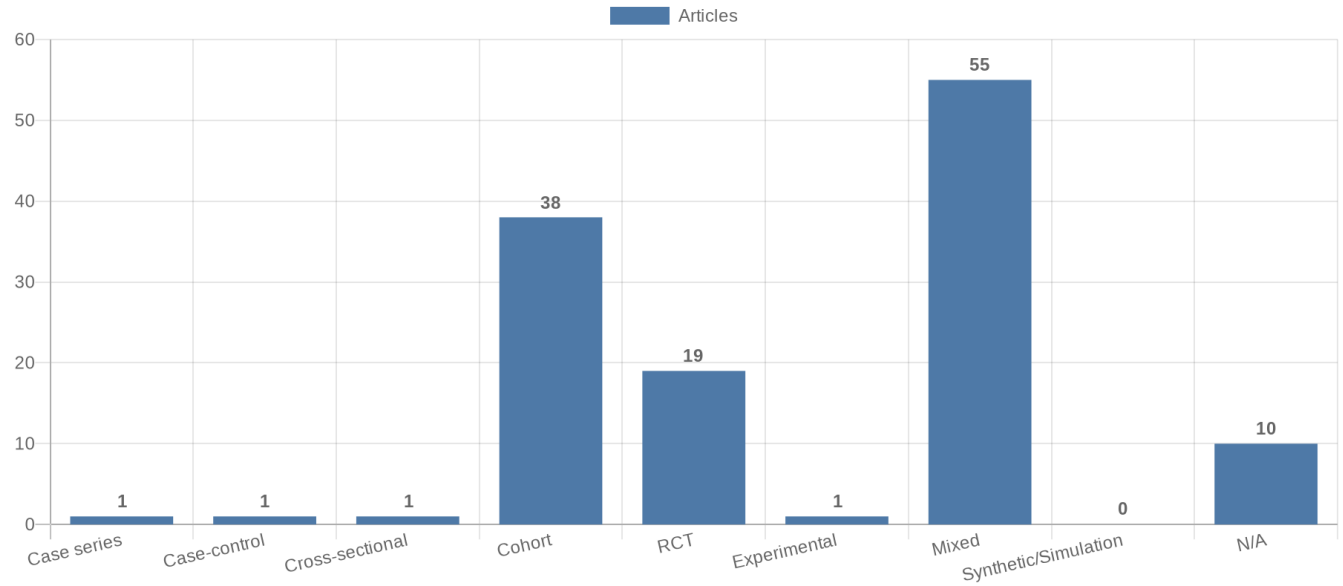

Figure 3. Study-type (directionality) distribution of included originals

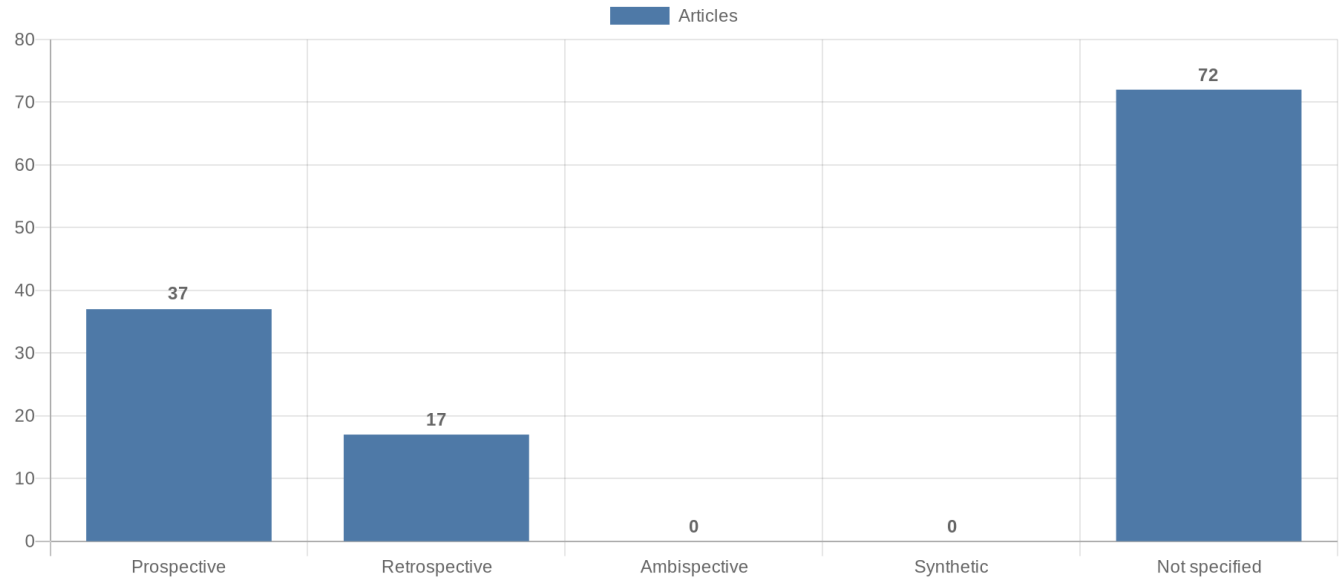

Figure 4. Main extracted research topics

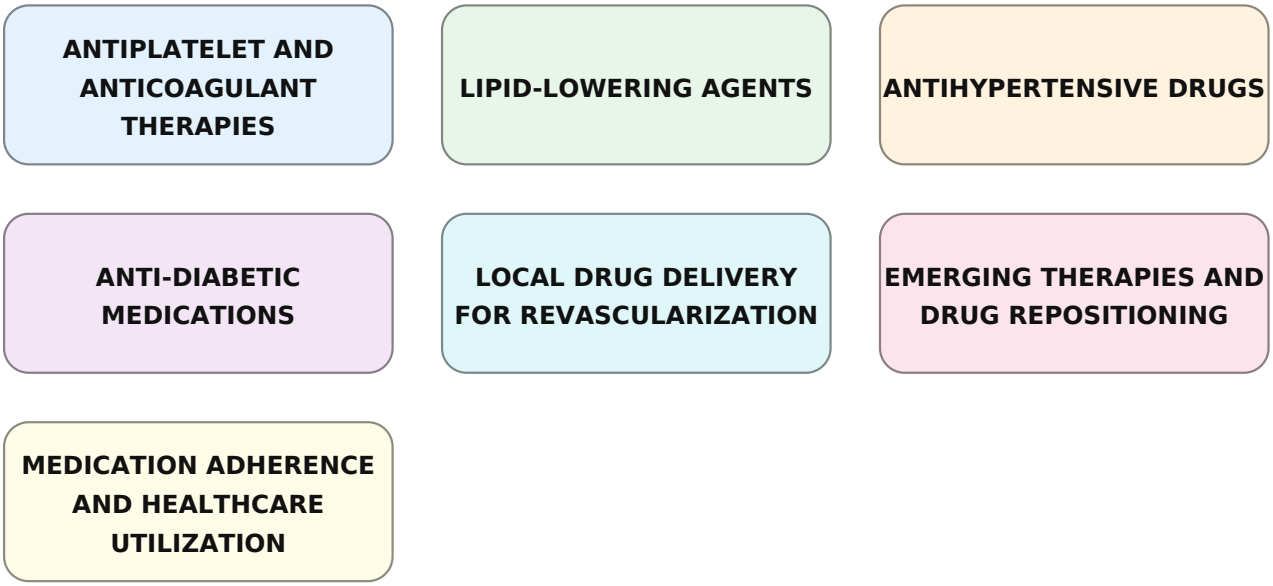

Figure 5. Limitations of current studies (topics)

Figure 6. Future research directions (topics)