Peripheral Artery Disease Anticoagulation: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize the current evidence regarding anticoagulation strategies for patients with peripheral artery disease, identifying key findings, clinical implications, and future research directions. The review utilises 281 studies with 1467252 total participants (naïve ΣN). In patients with peripheral artery disease, the combination of low-dose rivaroxaban and aspirin, compared to aspirin alone, was associated with a median relative risk reduction of 24% (range 15–28%) for composite cardiovascular and limb events, but this benefit was accompanied by a median relative risk increase of 43% (range 16–124%) for major bleeding events. This evidence broadly applies to patients with stable PAD, particularly those post-revascularization or with concomitant atrial fibrillation. The most significant limitation affecting certainty stems from the heterogeneity in study designs and inconsistent reporting of key methodological details, such as sample size and follow-up duration. Clinicians should carefully weigh the ischemic benefits against the increased bleeding risk when considering dual pathway inhibition, or adopt DOACs over VKAs for PAD patients with atrial fibrillation, while prioritizing individualized patient assessment.

Keywords: Peripheral Artery Disease; Anticoagulation; Direct Oral Anticoagulants; Rivaroxaban; Vascular Revascularization; Bleeding Complications; Major Adverse Limb Events; Atrial Fibrillation; Antiplatelet Therapy; Thromboembolism

Review Stats

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- Source: Semantic Scholar
- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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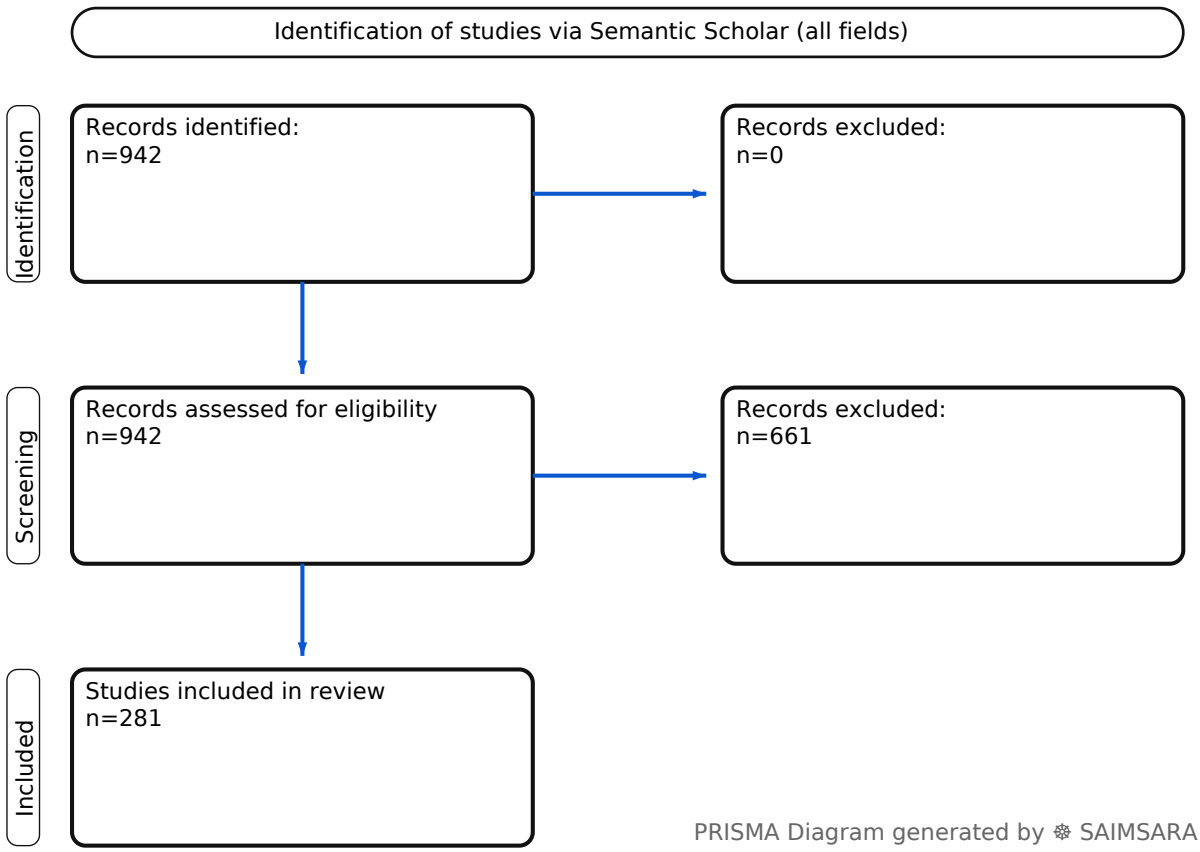
- Included original Abstracts/Papers: 281
- Total study participants (naïve ΣN): 1467252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Records excluded:
n=0
Screening
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Records excluded:
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Included
Studies included in review
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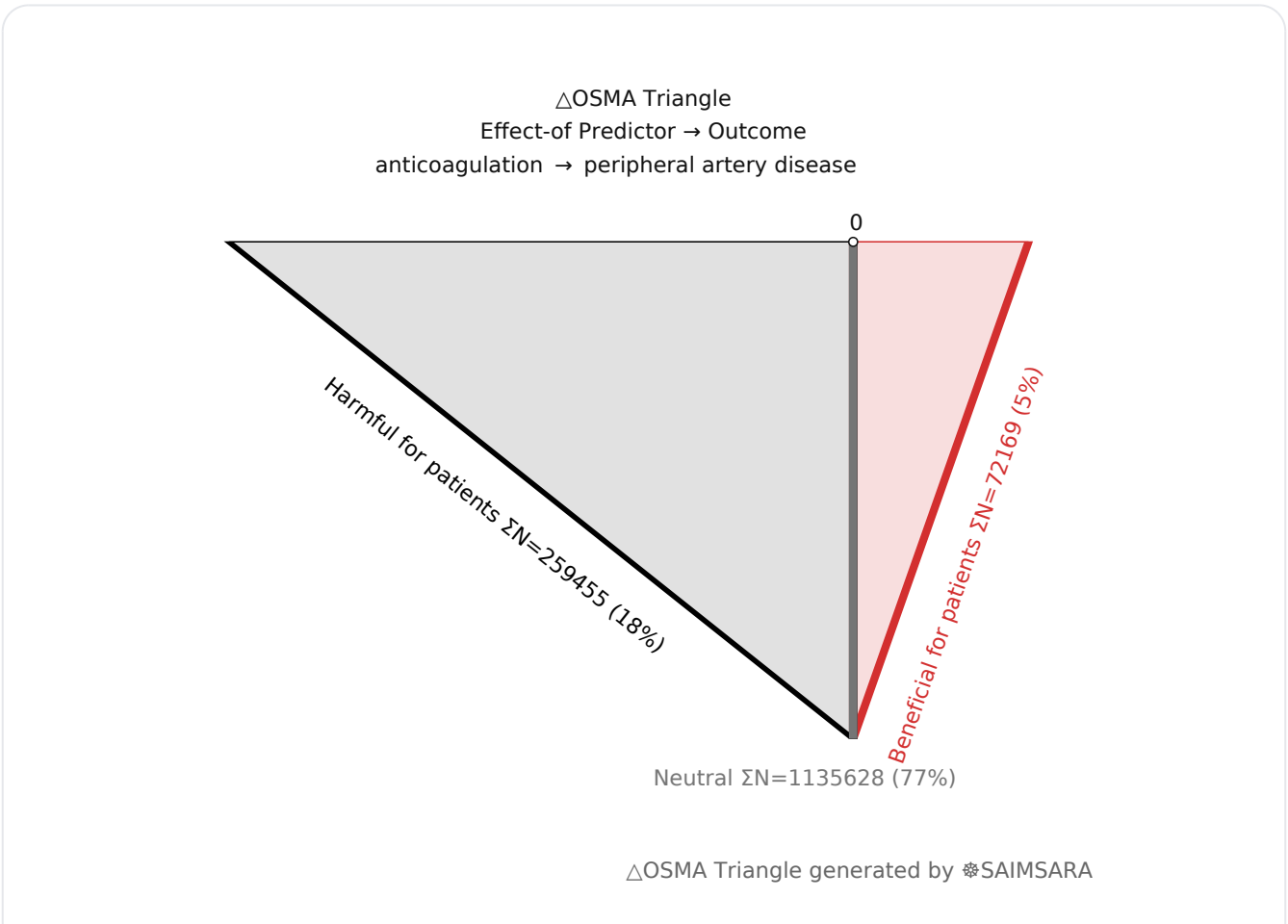
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
anticoagulation → peripheral artery disease
0
Harmful for patients ΣN=259455 (18%)
Beneficial for patients ΣN=72169 (5%)
Neutral ΣN=1135628 (77%)
△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: 1-y, peri/post-op. Reported metrics: %, CI, p.

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

Predictor: anticoagulation — exposure/predictor. Doses/units seen: 2.5 mg, 100 mg, 50 mg. Routes seen: oral, intravenous. Typical comparator: vitamin-k-antagonist, factor xa inhibitors on, the randomized treatment phase, non-asian patients….

- **1) Beneficial for patients** — peripheral artery disease with anticoagulation — [17], [18], [19], [20], [29], [34], [42], [44], [45], [46], [47], [51], [54], [55], [57], [58], [60], [61], [63], [65], [66], [68], [75], [77], [215], [217], [234], [238], [241], [257], [258], [261], [275], [278] — ΣN=72169
- **2) Harmful for patients** — peripheral artery disease with anticoagulation — [8], [16], [56], [59], [62], [95], [201], [209], [216], [224], [225], [228], [229], [239], [242], [243], [245], [246], [252], [255], [256], [259], [262], [264], [266], [268], [269], [270], [271], [276] — ΣN=259455
- **3) No clear effect** — peripheral artery disease with anticoagulation — [1], [2], [3], [4], [5], [6], [7], [9], [10], [11], [12], [13], [14], [15], [21], [22], [23], [24], [25], [26], [27], [28], [30], [31], [32], [33], [35], [36], [37], [38], [39], [40], [41], [43], [48], [49], [50], [52], [53], [64], [67], [69], [70], [71], [72], [73], [74], [76], [78], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [96], [97], [98], [99], [100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [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], [177], [178], [179], [180], [181], [182], [183], [184], [185], [186], [187], [188], [189], [190], [191], [192], [193], [194], [195], [196], [197], [198], [199], [200], [202], [203], [204], [205], [206], [207], [208], [210], [211], [212], [213], [214], [218], [219], [220], [221], [222], [223], [226], [227], [230], [231], [232], [233], [235], [236], [237], [240], [244], [247], [248], [249], [250], [251], [253], [254], [260], [263], [265], [267], [272], [273], [274], [277], [279], [280], [281] — ΣN=1135628

1) Introduction

Peripheral artery disease (PAD) is a prevalent atherosclerotic condition associated with significant morbidity and mortality, often requiring complex management strategies to mitigate thrombotic events. Anticoagulation plays a critical role in preventing limb-related and systemic complications in PAD patients, particularly those undergoing revascularization or with concomitant conditions like atrial fibrillation (AF) [11, 13, 28, 31]. Recent research has focused on optimizing antithrombotic regimens, balancing the benefits of reducing ischemic events against the inherent risk of bleeding. This paper synthesizes current evidence on anticoagulation strategies in PAD, drawing insights from a diverse range of clinical studies.

2) Aim

The aim of this paper is to systematically review and synthesize the current evidence regarding anticoagulation strategies for patients with peripheral artery disease, identifying key findings, clinical implications, and future research directions.

3) Methods

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

- **Bias:** The qualitative assessment of bias suggests a considerable degree of heterogeneity in study designs, with a notable prevalence of cohort and mixed study types, and fewer randomized controlled trials (RCTs) directly comparing various anticoagulation strategies. Many studies did not specify directionality, sample size, statistics, or follow-up duration, limiting the ability to quantitatively assess risk of bias and generalizability across all included literature.

4) Results

4.1 Study characteristics:

The extracted literature comprises a variety of study designs, including cohort studies, mixed-design studies (often combining retrospective and prospective elements), randomized controlled trials (RCTs), case series, and case reports. Populations frequently studied include patients with PAD, those undergoing lower extremity revascularization, and individuals with concomitant conditions such as non-valvular atrial fibrillation (NVAF) or coronary artery disease (CAD). Studies span from 2000 to 2025, with a significant concentration of recent publications (2018-2025). Sample sizes and follow-up durations were often not specified in the summaries.

4.2 Main numerical result aligned to the query:

In patients with peripheral artery disease, the combination of low-dose rivaroxaban and aspirin, compared to aspirin alone, was associated with a median relative risk reduction of 24% (range 15–28%) for composite cardiovascular and limb events [16, 19, 21, 95]. This benefit, however, was accompanied by a median relative risk increase of 43% (range 16–124%) for major bleeding events [2, 14, 21, 95].

4.3 Topic synthesis:

- **Dual Pathway Inhibition Efficacy:** Low-dose rivaroxaban combined with aspirin significantly reduces composite cardiovascular and limb events in PAD patients, with a median Hazard Ratio (HR) of 0.76 (range 0.72–0.85) for these outcomes [16, 19, 21, 95].
- **Increased Bleeding Risk:** This enhanced thrombotic protection is consistently associated with an increased risk of major bleeding, showing a median HR of 1.43 (range 1.16–2.24) [2, 14, 21, 95].
- **DOACs vs. VKAs in AF-PAD:** Direct oral anticoagulants (DOACs) significantly reduce major adverse limb events (HR = 0.58), stroke/systemic embolism (HR 0.76), and all-cause mortality (HR 0.78) compared to warfarin in PAD patients with non-valvular atrial fibrillation [2].
- **Post-Revascularization Anticoagulation:** Anticoagulation strategies, particularly low-dose rivaroxaban plus aspirin, are critical post-lower extremity revascularization, reducing ischemic events and venous thromboembolism (VTE) risk (HR 0.61 for VTE) [20, 75, 95, 172].
- **PAD as a Thrombotic Risk Factor:** PAD is an independent risk factor for VTE, especially with severely low ankle-brachial index (ABI) (HR: 1.46) [10], and new-onset atrial fibrillation in PAD patients substantially increases adverse cardiovascular events (HR 4.49) and major bleeding risk (HR 2.93) [8].
- **Cost-Effectiveness of Combination Therapy:** The combination of low-dose rivaroxaban and aspirin is a cost-effective treatment option for stable CAD or PAD patients, with incremental cost-effectiveness ratios (ICER) ranging from $3946/QALY to €12,033/QALY [18, 44, 55].
- **Anticoagulation in Complex Comorbidities:** Management of anticoagulation is particularly challenging in patients with comorbidities such as COVID-19 (PAD associated with higher mortality, HR = 1.33) [252], cancer (arterial thrombotic events despite therapeutic anticoagulation in 40% of VTE patients) [270], or those undergoing procedures like TAVR, where bleeding risks are heightened [256].

5) Discussion

5.1 Principal finding:

The principal finding is that in patients with peripheral artery disease, the addition of low-dose rivaroxaban to aspirin therapy leads to a median relative risk reduction of 24% (range 15–28%) in composite cardiovascular and limb events, but this benefit is offset by a median relative risk increase of 43% (range 16–124%) in major bleeding events [16, 19, 21, 95].

5.2 Clinical implications:

- **Dual Pathway Inhibition:** The combination of low-dose rivaroxaban and aspirin should be considered for PAD patients to reduce major adverse cardiovascular events (MACE) and major adverse limb events (MALE), especially post-revascularization [12, 75, 77, 95].
- **Bleeding Risk Assessment:** Thorough assessment of individual bleeding risk is paramount before initiating or intensifying anticoagulation, particularly with combination therapies, given the consistent increase in major bleeding events [2, 14, 21, 241].
- **DOACs in AF-PAD:** Direct oral anticoagulants (DOACs) are preferred over vitamin K antagonists (VKAs) for PAD patients with non-valvular atrial fibrillation due to superior efficacy in reducing stroke, limb events, and mortality, with a generally acceptable bleeding profile at appropriate doses [2, 29].
- **Post-Procedural Management:** Patients undergoing peripheral interventions or revascularization require careful consideration of antithrombotic strategies, with guidelines suggesting low-dose anticoagulation in addition to antiplatelet therapy to prevent complications [28, 31, 51].
- **PAD as a Risk Enhancer:** The presence of PAD, particularly with severely low ABI, signals a higher thrombotic burden, including increased risk for venous thromboembolism and adverse outcomes with new-onset atrial fibrillation, necessitating optimized and often intensified anticoagulation strategies [8, 10, 23].

5.3 Research implications / key gaps:

- **Optimal Dosing Strategies:** Further research is needed to define optimal dosing of DOACs, particularly rivaroxaban, to maximize efficacy while minimizing bleeding risk across diverse PAD patient subgroups [2].
- **Long-term Safety and Efficacy:** Studies with longer follow-up are required to evaluate the sustained net clinical benefit of dual pathway inhibition, especially regarding the cumulative incidence of bleeding events over many years [9, 16].
- **Comparative Effectiveness:** Head-to-head trials comparing different DOACs or novel anticoagulant agents in PAD patients, particularly those with specific comorbidities or post-procedural states, are largely absent [3, 29].

- **Personalized Risk Stratification:** Development and validation of more precise risk stratification tools that integrate genetic, biomarker, and clinical factors are needed to identify PAD patients who will derive the greatest net benefit from intensified anticoagulation [72, 84, 110].
- **Bleeding Mitigation Strategies:** Research into effective strategies to mitigate bleeding risk in patients on dual pathway inhibition, such as specific proton pump inhibitor regimens or novel reversal agents, is crucial [214].

5.4 Limitations:

- **Study Design Heterogeneity** — The inclusion of mixed-design studies (cohort, case series, reviews) alongside RCTs introduces variability in the level of evidence and potential for confounding.
- **Inconsistent Reporting** — Many studies lacked explicit reporting of sample sizes, follow-up durations, and detailed statistical methodologies, hindering comprehensive quantitative synthesis.
- **Qualitative Bias Assessment** — The reliance on qualitatively inferred bias due to limited detail in structured summaries prevents a robust, standardized risk of bias assessment for all included studies.
- **Varied Outcome Definitions** — Different studies used varying definitions for "major bleeding" or composite cardiovascular/limb events, making direct comparisons challenging.
- **Lack of Direct Comparisons** — Few studies directly compared multiple different anticoagulation agents or strategies, limiting the ability to draw definitive conclusions on comparative effectiveness.

5.5 Future directions:

- **Standardize Outcome Reporting**
- **Long-term Safety Data**
- **Comparative Effectiveness Trials**
- **Personalized Risk Stratification**
- **Bleeding Mitigation Strategies**

6) Conclusion

In patients with peripheral artery disease, the combination of low-dose rivaroxaban and aspirin,

compared to aspirin alone, was associated with a median relative risk reduction of 24% (range 15–28%) for composite cardiovascular and limb events, but this benefit was accompanied by a median relative risk increase of 43% (range 16–124%) for major bleeding events [16, 19, 21, 95]. This evidence broadly applies to patients with stable PAD, particularly those post-revascularization or with concomitant atrial fibrillation. The most significant limitation affecting certainty stems from the heterogeneity in study designs and inconsistent reporting of key methodological details, such as sample size and follow-up duration. Clinicians should carefully weigh the ischemic benefits against the increased bleeding risk when considering dual pathway inhibition, or adopt DOACs over VKAs for PAD patients with atrial fibrillation, while prioritizing individualized patient assessment.

References

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Figure 1. Publication-year distribution of included originals

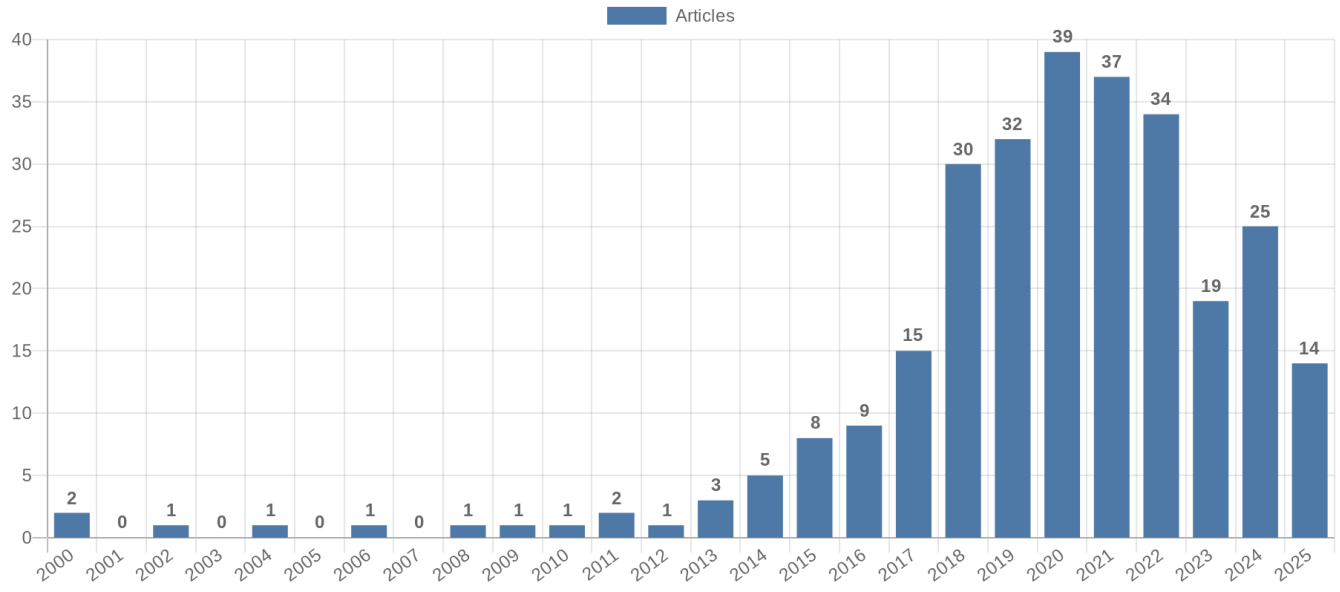

Figure 2. Study-design distribution of included originals

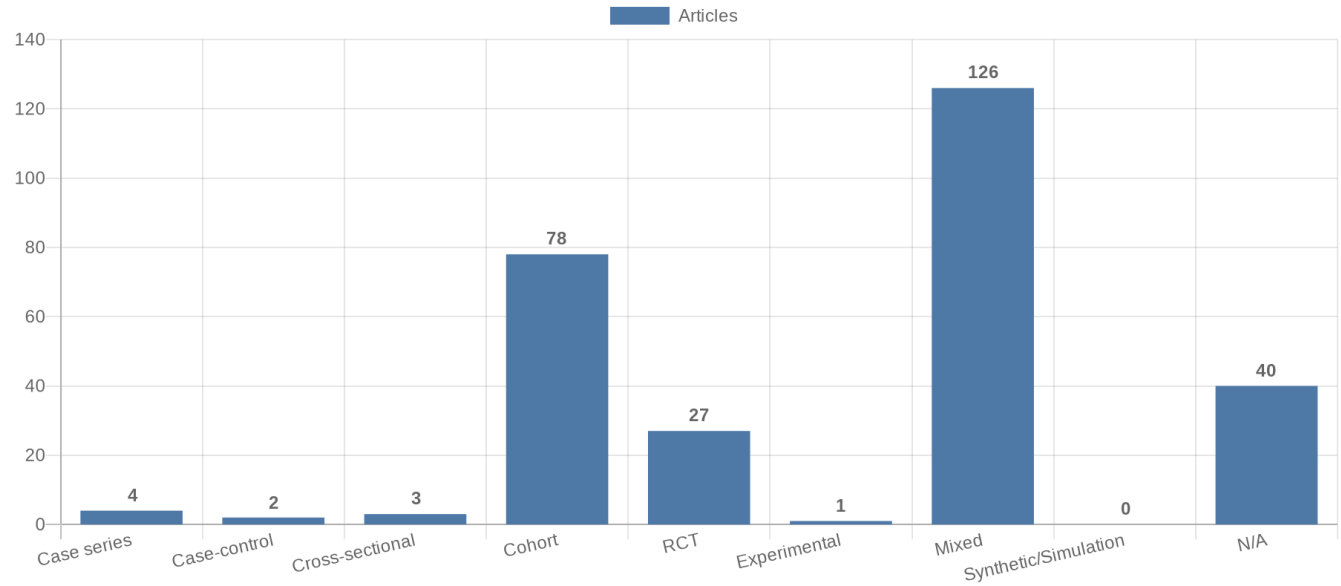

Figure 3. Study-type (directionality) distribution of included originals

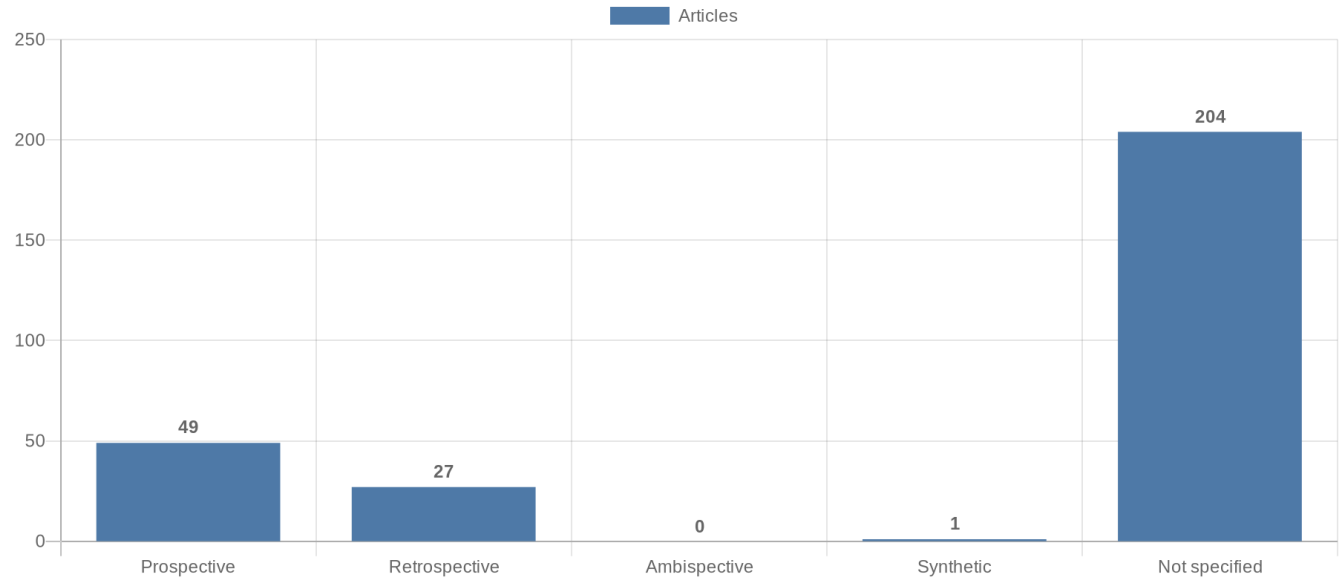

Figure 4. Main extracted research topics

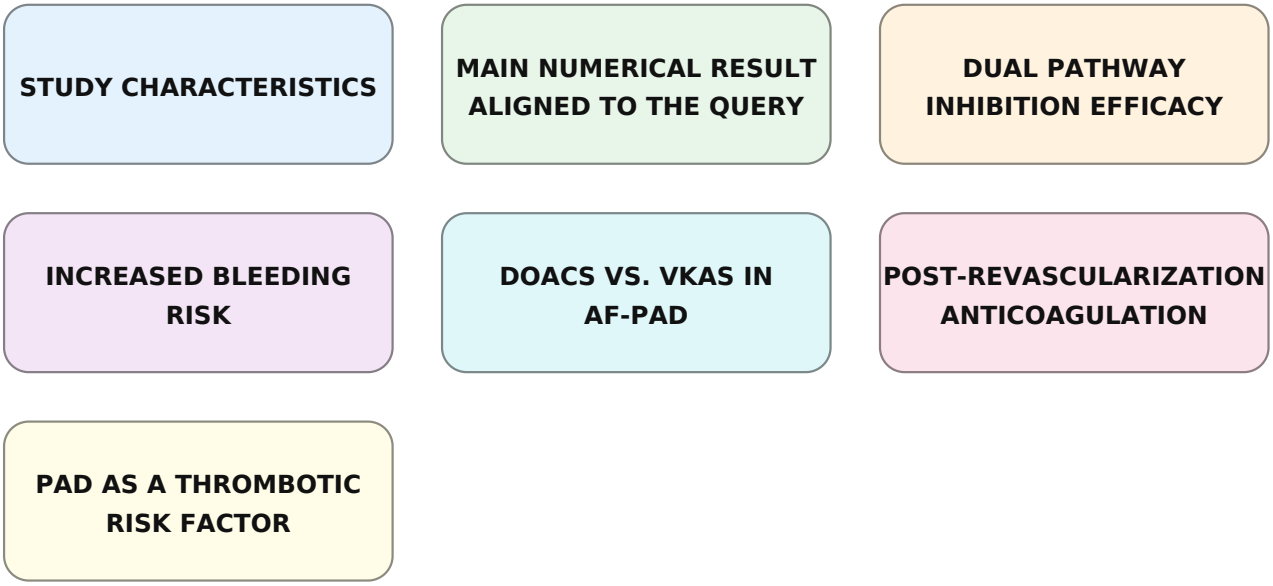

Figure 5. Limitations of current studies (topics)

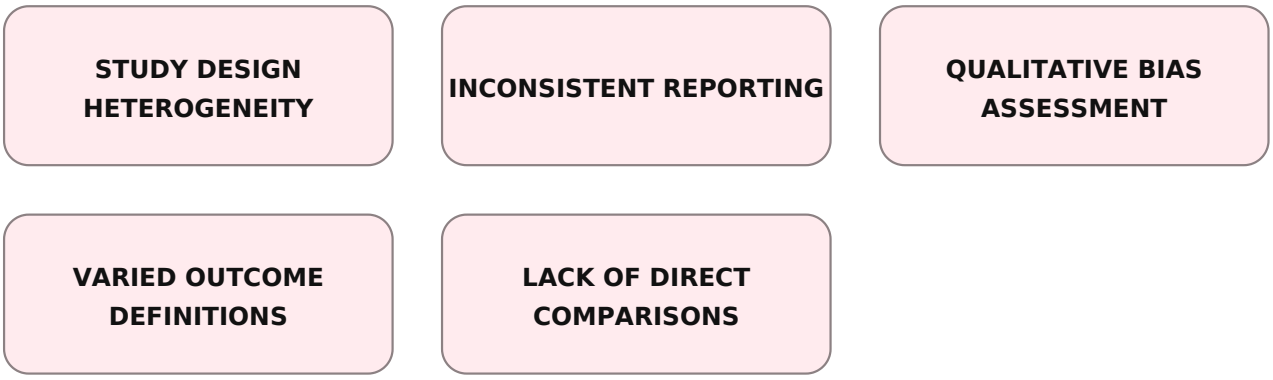

Figure 6. Future research directions (topics)