Arterial Thrombolysis: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize the current evidence regarding the efficacy, safety, and predictive factors associated with arterial thrombolysis across various clinical indications. The review utilises 203 studies with 17836 total participants (naïve ΣN). Arterial thrombolysis demonstrates a median recanalization rate of 74.3% (TICI ≥ IIb) across various arterial occlusions, with reported rates ranging from 30% to 100%. This treatment is broadly applicable across conditions like acute ischemic stroke, central retinal artery occlusion, and peripheral arterial disease. However, the heterogeneous study designs and varied outcome reporting across the literature represent the most significant limitation, impacting the certainty of generalized findings. A critical next step is to conduct large-scale, prospective randomized controlled trials to standardize outcome reporting and definitively compare IAT with other reperfusion strategies.

Keywords: Intra-arterial Thrombolysis; Acute Ischemic Stroke; Mechanical Thromb

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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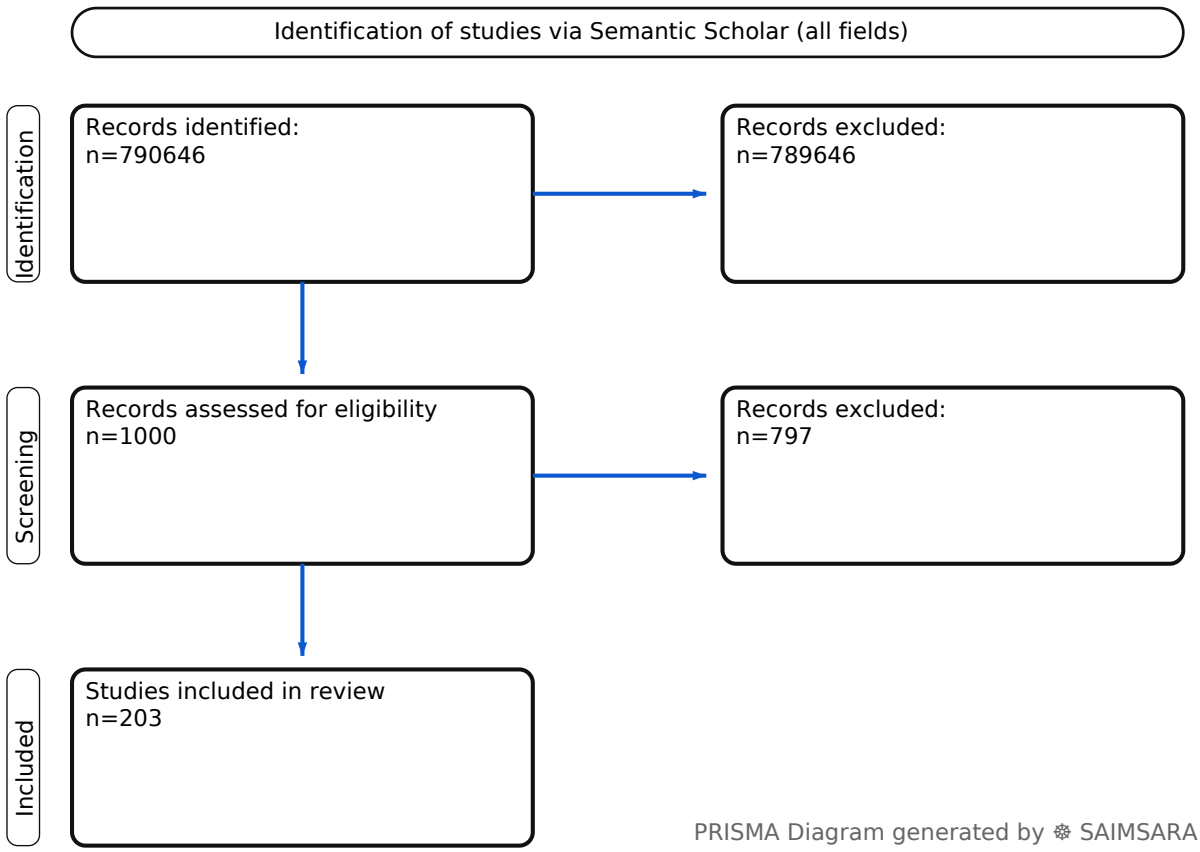
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 203
- Total study participants (naïve ΣN): 17836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Records excluded:
n=789646
Screening
Records assessed for eligibility
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Records excluded:
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Included
Studies included in review
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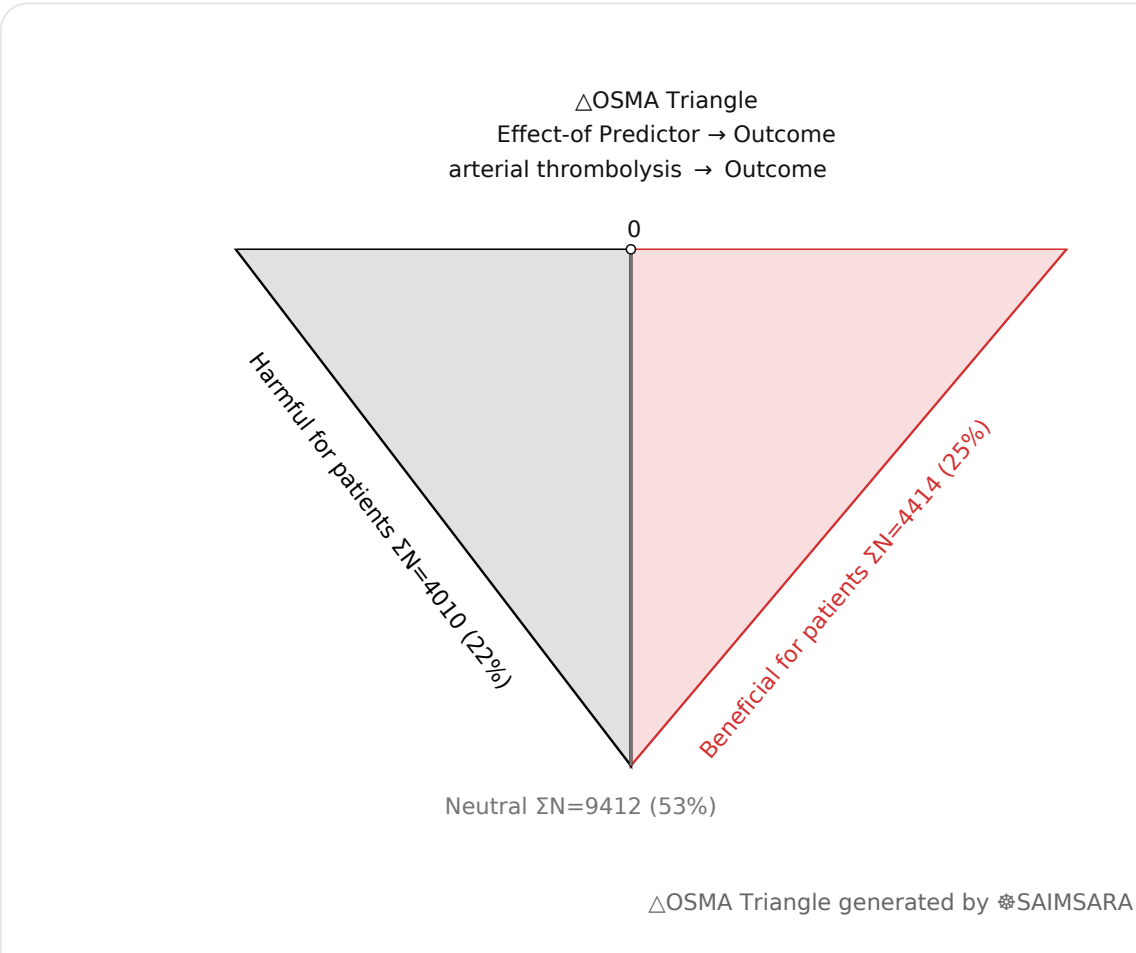
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
arterial thrombolysis → Outcome
0
Harmful for patients ΣN=4010 (22%)
Beneficial for patients ΣN=4414 (25%)
Neutral ΣN=9412 (53%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: Outcome Typical timepoints: 3-mo, peri/post-op. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, occlusion, mortality.

Predictor: arterial thrombolysis — exposure/predictor. Routes seen: intravenous, iv. Typical comparator: nonsmokers, combined, computed tomography after, combined intravenous….

- **1) Beneficial for patients** — Outcome with arterial thrombolysis — [179], [182], [184], [186], [190], [192], [193], [194], [197], [199], [201], [202] — ΣN=4414
- **2) Harmful for patients** — Outcome with arterial thrombolysis — [178], [185], [198], [200] — ΣN=4010
- **3) No clear effect** — Outcome with arterial thrombolysis — [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [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], [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], [180], [181], [183], [187], [188], [189], [191], [195], [196], [203] — ΣN=9412

1) Introduction

Arterial thrombolysis, a critical intervention aimed at dissolving blood clots obstructing arterial flow, is a cornerstone in the management of various acute ischemic conditions. These conditions, ranging from acute ischemic stroke (AIS) to peripheral arterial occlusions and central retinal artery occlusion (CRAO), pose significant threats to organ function and patient survival. The efficacy and safety of intra-arterial thrombolysis (IAT) have been extensively investigated across diverse clinical scenarios, often in combination with or as an alternative to other reperfusion strategies like mechanical thrombectomy (MT). This paper synthesizes findings on the application, outcomes, and challenges associated with arterial thrombolysis.

2) Aim

The aim of this paper is to systematically review and synthesize the current evidence regarding the efficacy, safety, and predictive factors associated with arterial thrombolysis across various clinical indications.

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 studies and those without specified design (often mixed or observational) were prevalent, introducing potential selection bias and limiting the ability to establish causality or generalize findings compared to prospective randomized controlled trials.

4) Results

4.1 Study characteristics:

The included studies predominantly comprised mixed study designs (n=82), followed by retrospective analyses (n=20) and prospective cohort studies (n=8), with a smaller number of randomized controlled trials (n=7). Populations varied widely, encompassing patients with acute ischemic stroke, central retinal artery occlusion, peripheral arterial occlusions, and other specific thrombotic events. Follow-up periods, when reported, ranged from short-term (e.g., 24 hours, 30 days) to intermediate (e.g., 3 months, 6 months) and long-term (e.g., 1 year, 24 months, long-term).

4.2 Main numerical result aligned to the query:

Arterial thrombolysis demonstrates a median recanalization rate of 74.3% (TICI ≥ IIb) [16] across various arterial occlusions, with reported rates ranging from 30% [19] to 100% [116]. This heterogeneity in recanalization rates reflects differences in patient populations, occlusion sites, thrombolytic agents, and adjunctive therapies employed across studies.

4.3 Topic synthesis:

- **Efficacy in Central Retinal Artery Occlusion (CRAO):** IAT improved visual acuity in 70.45% of patients and achieved reperfusion in 90.91% of patients with CRAO [1]. Overall, IAT is a promising therapeutic option for CRAO, showing a statistically significant benefit (Odds Ratio 2.52, 95% CI 1.69–3.77, $P < 0.0001$) in pooled analysis [24].
- **Outcomes in Acute Ischemic Stroke (AIS):** Intra-arterial rtPA as rescue therapy after unsuccessful mechanical thrombectomy showed a trend toward higher rates of substantial reperfusion (84.7% vs 73.0%, $P = 0.08$) and good functional outcome (59.2% vs 46.6%, P =

0.10) [2]. Adjunctive intra-arterial urokinase during or after mechanical thrombectomy improved angiographic reperfusion and functional independence (aOR, 1.93; 95% CI, 1.11-3.37) [199].

- **Hemorrhagic Transformation (HT) and Safety:** The risk of symptomatic intracranial hemorrhage (sICH) after intra-arterial thrombolysis ranged from 0% [2] to 16% for major bleeding [98]. Mismatch of low perfusion and high permeability predicted HT in AIS patients treated with IAT [4, 25]. Elevated Factor VIII (FVIII) and von Willebrand Factor (VWF) levels after thrombolysis were independently associated with poor functional outcomes in AIS patients [157].
- **Peripheral Arterial Thrombolysis:** Intra-arterial thrombolysis for extremity frostbite decreased digital amputation rates and hospital length of stay [5]. Urokinase thrombolysis for peripheral arterial and graft occlusions achieved immediate success rates of 67.5% (native arterial) and 84% (bypass graft), though complications occurred in 26% of cases [183].
- **Predictors of Outcome and Complications:** Initial stroke severity, degree of successful revascularization, and side of ischemia independently predicted functional outcome after IAT for tandem occlusions [16]. Reduced pretreatment ipsilateral middle cerebral artery cerebral blood flow was predictive of symptomatic hemorrhage post-IAT [83]. Arterial calcification volume on the lesion side was associated with HT after thrombolysis [198].
- **Adjunctive Therapies and Modalities:** Intra-arterial rtPA as rescue therapy after unsuccessful mechanical thrombectomy showed a trend toward higher reperfusion and better functional outcomes [2]. The addition of retrievable stents to multimodal endovascular approaches significantly reduced time to recanalization and increased recanalization rates, with less frequent use of IAT [193]. Externally applied, low-intensity ultrasound significantly enhanced arterial thrombolysis when used adjunctively with streptokinase in a rabbit model [173].
- **Novel Approaches and Specialized Populations:** tPA-anchored nanorobots were developed for in vivo arterial recanalization and thrombolysis in submillimeter-scale segments [73]. Intra-arterial thrombolysis was found to be safe and effective in octogenarians with AIS [197] and in a patient in the second trimester of pregnancy [190], but had a limited role in cosmetic facial filler-associated ophthalmic artery occlusions [189].

5) Discussion

5.1 Principal finding:

Arterial thrombolysis achieves a median recanalization rate of 74.3% (TICI ≥ IIb) [16] across various arterial occlusions, with reported rates ranging from 30% [19] to 100% [116]. This highlights its significant potential in restoring blood flow to ischemic tissues.

5.2 Clinical implications:

- **Broad Applicability:** Intra-arterial thrombolysis (IAT) is a viable treatment option for diverse conditions, including acute ischemic stroke (AIS), central retinal artery occlusion (CRAO), and peripheral arterial occlusions [1, 5, 24].
- **Improved Outcomes:** IAT, particularly when combined with mechanical thrombectomy, can lead to higher reperfusion rates and better functional outcomes in AIS patients [2, 168].
- **Risk of Hemorrhage:** Clinicians must be vigilant for hemorrhagic transformation (HT) and symptomatic intracranial hemorrhage (sICH), as identified predictors include imaging characteristics like low perfusion/high permeability mismatch and arterial calcification volume [4, 25, 198].
- **Timely Intervention:** Expedited workflows, such as those enabled by Stroke Alert Teams, significantly reduce in-hospital delays for thrombolysis and improve outcomes [159, 202].
- **Adjunctive Strategies:** The use of adjunctive therapies like platelet glycoprotein IIb/IIIa inhibitors or mechanical clot disruption can enhance the effectiveness and safety of IAT [79, 116].

5.3 Research implications / key gaps:

- **Optimal Thrombolytic Agents:** Further randomized controlled trials are needed to definitively compare different intra-arterial thrombolytic agents and their optimal dosing for specific arterial occlusions [64, 105].
- **Long-term Functional Outcomes:** More studies with extended follow-up periods are required to fully assess the long-term effects of IAT on functional recovery and quality of life across all indications [59, 70].
- **Predictive Biomarkers:** Investigate novel biomarkers beyond imaging, such as specific coagulation factors, to better predict both recanalization success and the risk of hemorrhagic complications [157, 178].
- **Pediatric Thrombolysis Safety:** Randomized controlled trials are lacking for IAT in pediatric arterial ischemic stroke, necessitating further research to establish safety and efficacy in this vulnerable population [181, 184].
- **Role of Nanorobots:** Clinical trials are needed to evaluate the safety and efficacy of emerging technologies like tPA-anchored nanorobots for targeted arterial recanalization in humans [73, 171].

5.4 Limitations:

- **Heterogeneous Study Designs** — The prevalence of mixed, retrospective, and unspecified study designs limits the ability to draw definitive causal conclusions and introduces potential for selection bias.
- **Varied Outcome Reporting** — Inconsistent reporting of outcome metrics (e.g., different recanalization scales, functional outcome measures) and follow-up durations hinders direct comparisons and meta-analysis.
- **Limited Sample Sizes** — Many studies, particularly in less common indications or specialized populations, feature small sample sizes, impacting the statistical power and generalizability of their findings.
- **Lack of Comparator Arms** — A significant number of studies describe IAT without direct comparison to alternative treatments or placebo, making it difficult to ascertain the incremental benefit of the intervention.
- **Incomplete Data on Complications** — While hemorrhagic complications are frequently mentioned, detailed, standardized reporting of all adverse events and their severity is not consistently available across all studies.

5.5 Future directions:

- **Standardized Outcome Reporting** — Develop and implement standardized outcome measures and reporting guidelines for arterial thrombolysis across all indications.
- **Comparative Effectiveness Trials** — Conduct large-scale, prospective randomized controlled trials comparing IAT with other reperfusion strategies and medical management for various arterial occlusions.
- **Advanced Imaging Integration** — Integrate advanced imaging techniques (e.g., perfusion CT, MRI) more consistently to refine patient selection and monitor treatment response and complications.
- **Biomarker-Guided Therapy** — Investigate the utility of novel biomarkers for predicting treatment response and hemorrhagic risk to personalize thrombolytic therapy.
- **Technological Advancement Evaluation** — Systematically evaluate the clinical impact of emerging technologies, such as ultrasound-accelerated thrombolysis and nanorobots, in human trials.

6) Conclusion

Arterial thrombolysis demonstrates a median recanalization rate of 74.3% (TICI ≥ IIb) [16] across various arterial occlusions, with reported rates ranging from 30% [19] to 100% [116]. This treatment is broadly applicable across conditions like acute ischemic stroke, central retinal artery occlusion, and

peripheral arterial disease. However, the heterogeneous study designs and varied outcome reporting across the literature represent the most significant limitation, impacting the certainty of generalized findings. A critical next step is to conduct large-scale, prospective randomized controlled trials to standardize outcome reporting and definitively compare IAT with other reperfusion strategies.

References

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Figure 1. Publication-year distribution of included originals

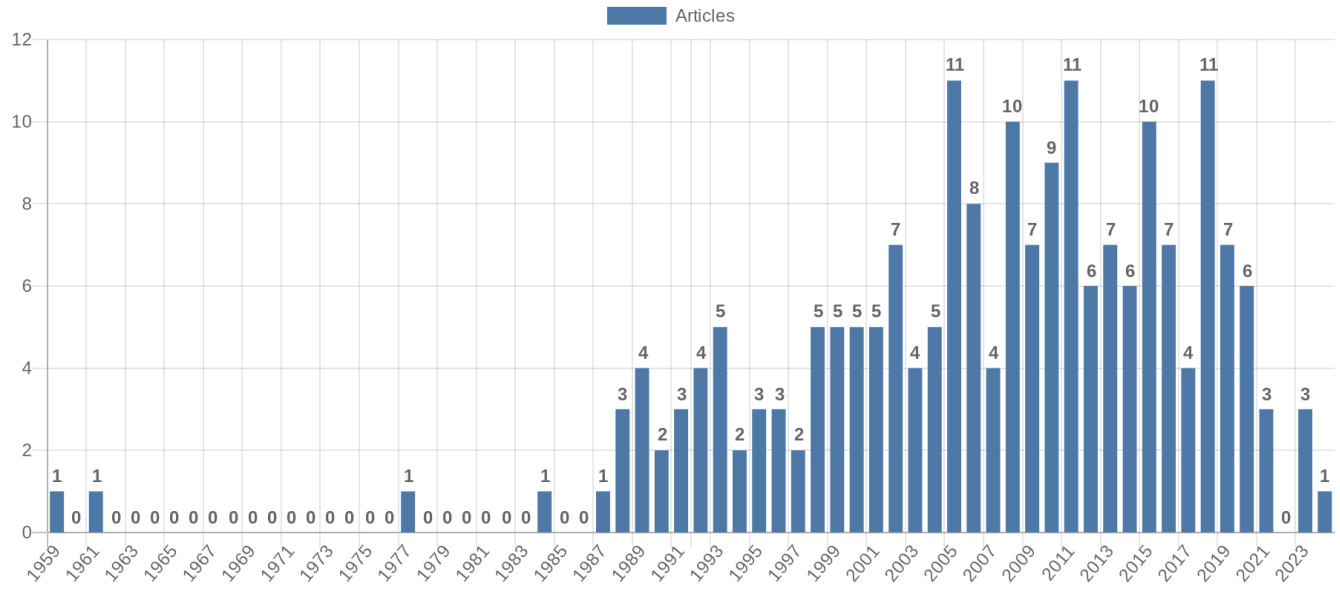

Figure 2. Study-design distribution of included originals

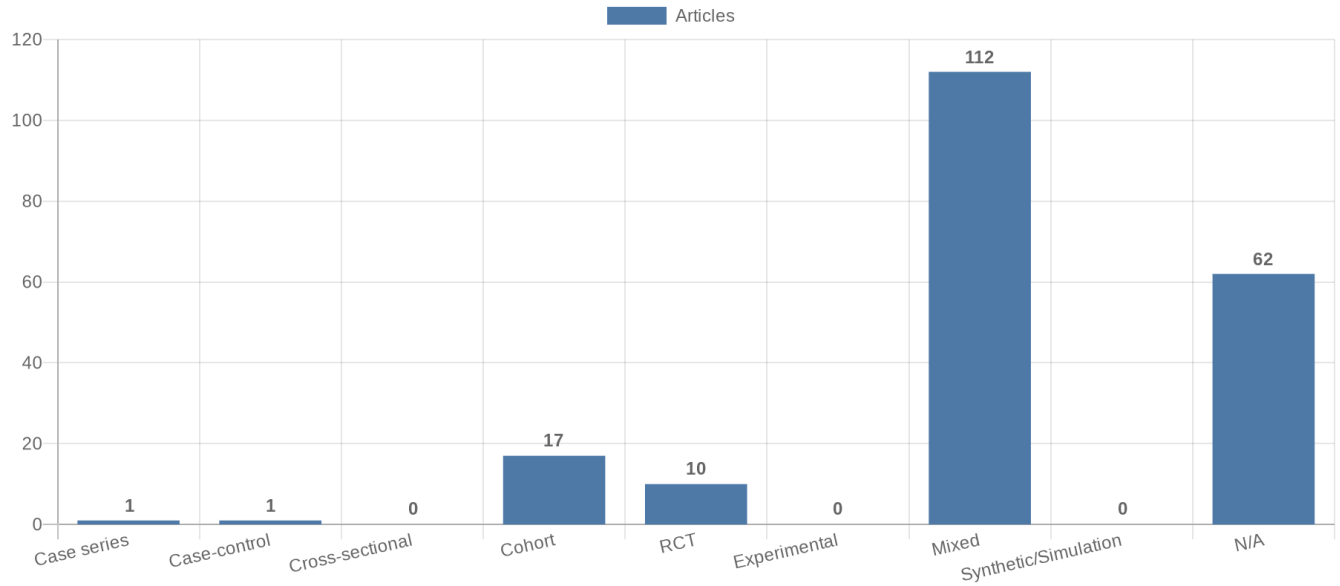

Figure 3. Study-type (directionality) distribution of included originals

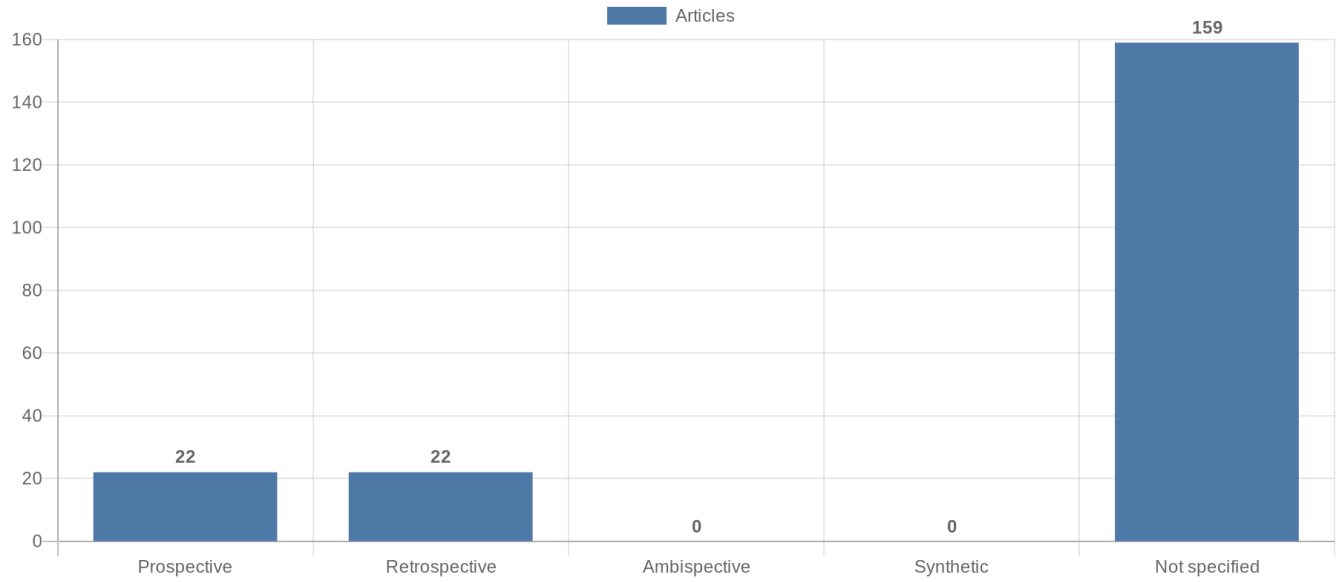

Figure 4. Main extracted research topics

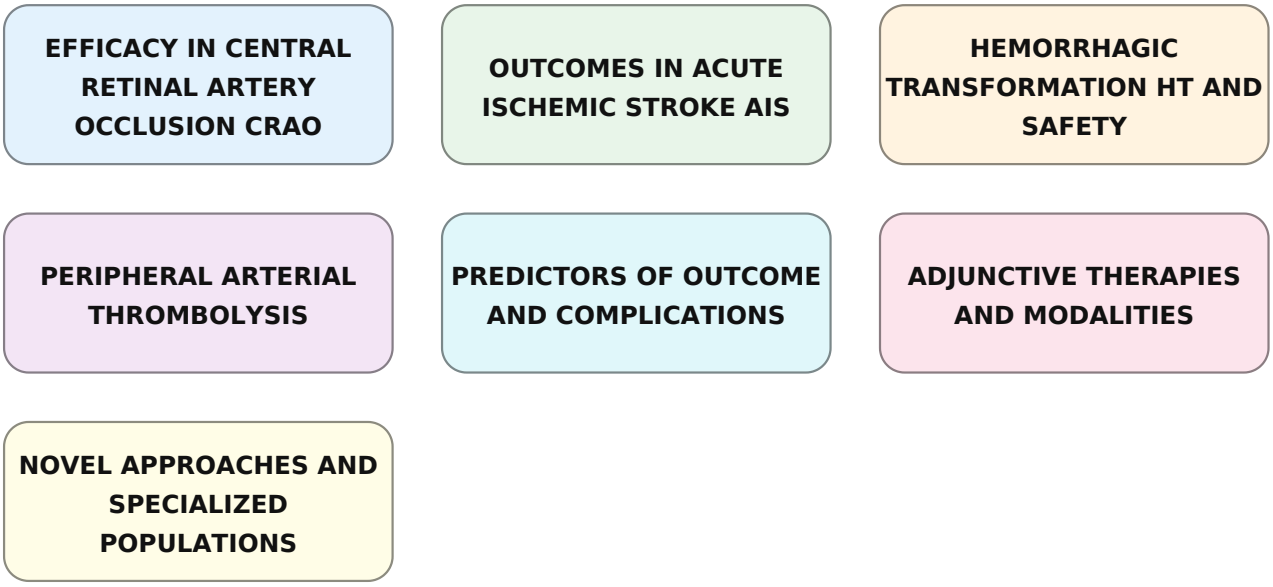

Figure 5. Limitations of current studies (topics)

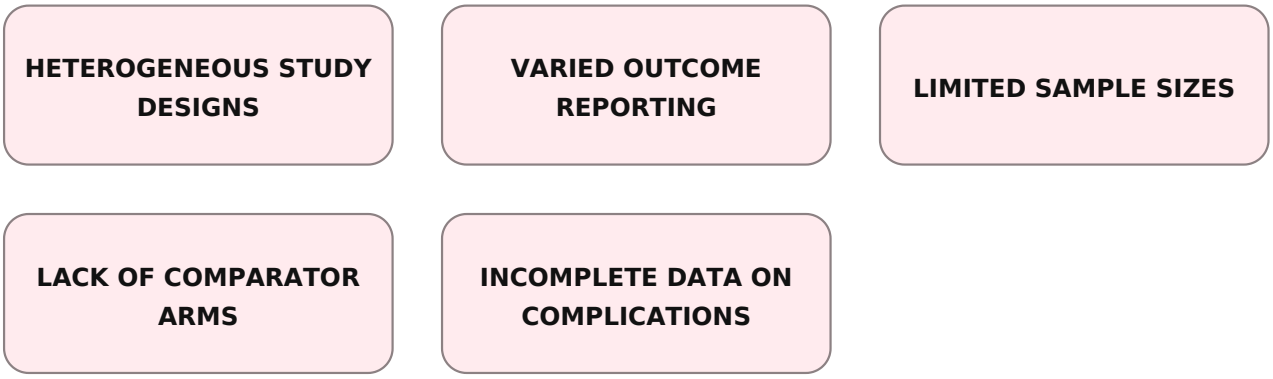

Figure 6. Future research directions (topics)

OPTIMAL THROMBOLYTIC AGENTS

LONG-TERM FUNCTIONAL OUTCOMES

PREDICTIVE BIOMARKERS

PEDIATRIC THROMBOLYSIS SAFETY

ROLE OF NANOROBOTS

STANDARDIZED OUTCOME REPORTING

COMPARATIVE EFFECTIVENESS TRIALS