Symptomatic Carotid Stenosis: Systematic Review with ☸SAIMSARA.

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Abstract: To systematically review the evidence on symptomatic carotid stenosis, synthesizing key findings regarding its diagnosis, risk factors, treatment efficacy, and plaque characteristics, and to identify critical gaps for future research. The review utilises 229 studies with 84507 total participants (naïve ΣN). The perioperative stroke or death rate for carotid endarterectomy (CEA) in symptomatic carotid stenosis patients ranged from 1.7% to 8.1%, with a median of 4.0%, while for carotid artery stenting (CAS) or transfemoral carotid artery stenting (TFCAS), it ranged from 2.0% to 8.5%, with a median of 5.1%. This review highlights the ongoing debate and evolving landscape of interventions for symptomatic carotid stenosis, emphasizing the importance of individualized patient assessment. The heterogeneity in study designs and outcome definitions across the literature is the single limitation that most affects certainty in drawing definitive conclusions. Clinicians should consider plaque characteristics and the timing of intervention in addition to stenosis degree when selecting revascularization strategies, with newer techniques like TCAR showing promise.

Keywords: Symptomatic Carotid Stenosis; Carotid Endarterectomy; Car

Review Stats

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- Scope: All fields
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
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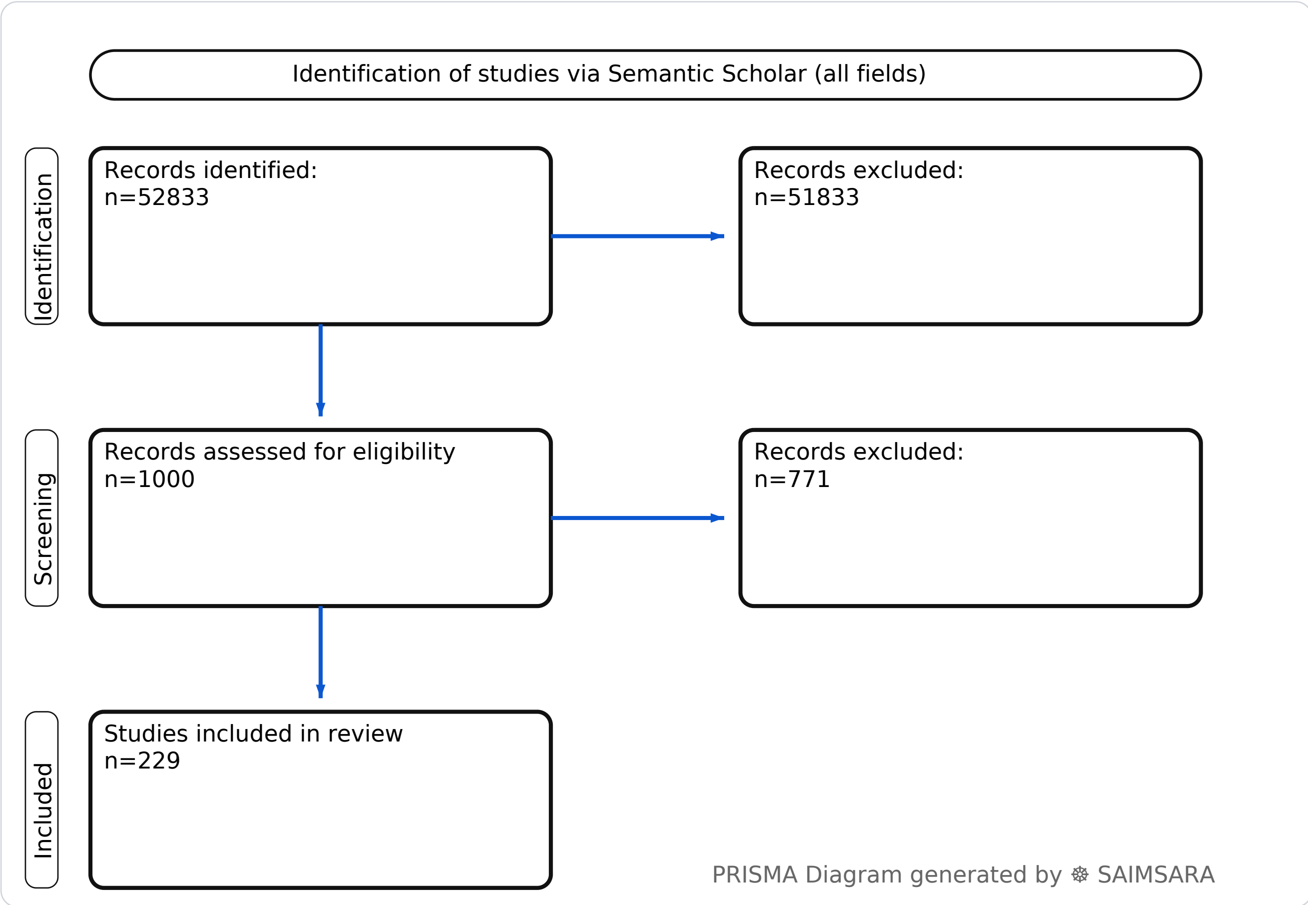
- Downloaded Abstracts/Papers: 1000
- Included original Abstracts/Papers: 229
- Total study participants (naïve ΣN): 84507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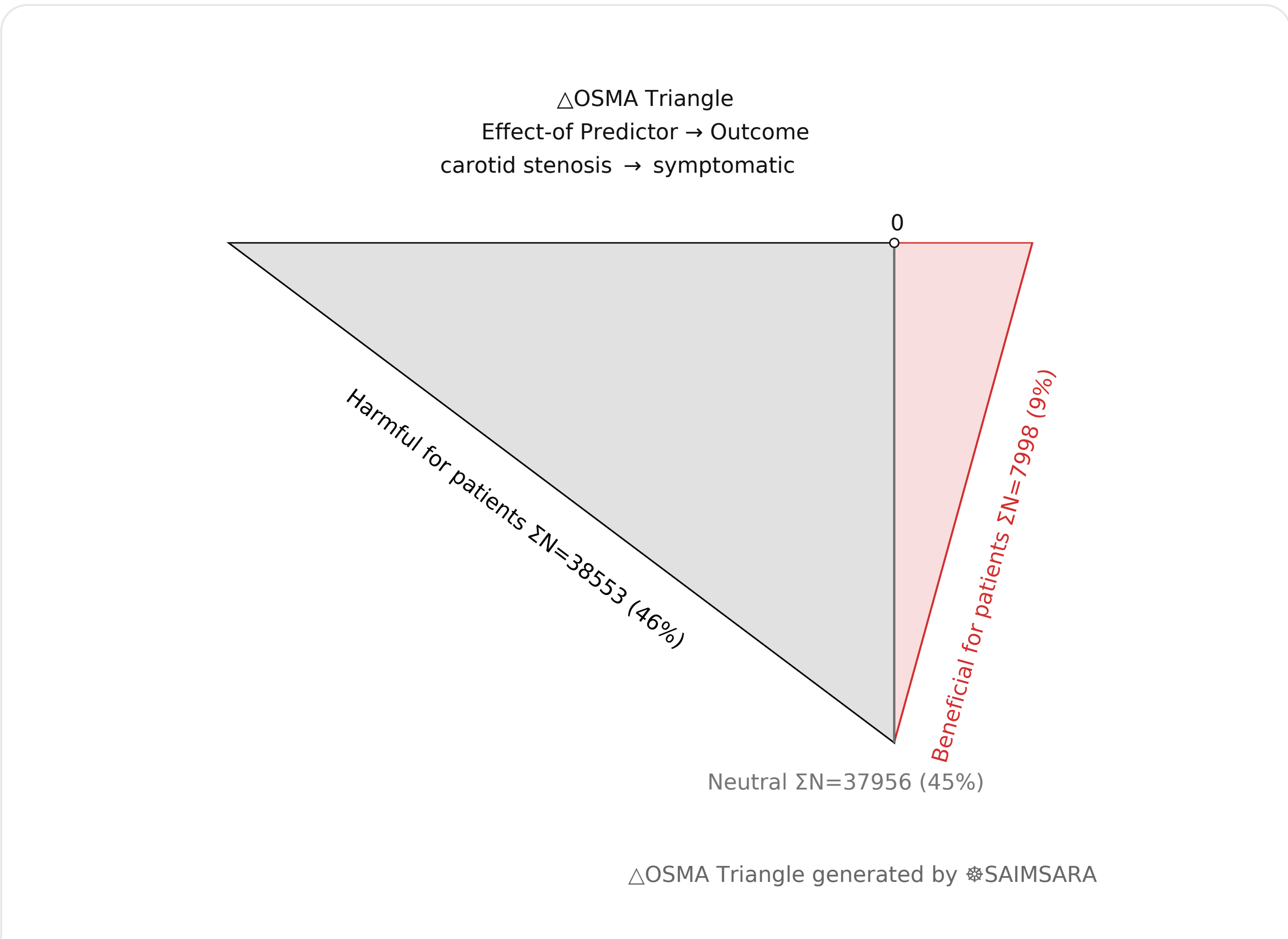
Records excluded:
n=51833
Screening
Records assessed for eligibility
n=1000
Records excluded:
n=771
Included
Studies included in review
n=229
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
carotid stenosis → symptomatic
0
Harmful for patients ΣN=38553 (46%)
Beneficial for patients ΣN=7998 (9%)
Neutral ΣN=37956 (45%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: symptomatic Typical timepoints: peri/post-op, 7-day. Reported metrics: %, CI, p.

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

Predictor: carotid stenosis — exposure/predictor. Routes seen: intravenous. Typical comparator: endarterectomy for the, carotid endarterectomy, optimized medical therapy, cea across all timing cohorts….

- **1) Beneficial for patients** — symptomatic with carotid stenosis — [9], [31], [36], [37], [41], [42], [46], [75], [85] — ΣN=7998
- **2) Harmful for patients** — symptomatic with carotid stenosis — [4], [7], [12], [13], [16], [22], [27], [29], [67], [76], [78], [89], [90], [97], [100], [206], [224], [225], [226], [228], [229] — ΣN=38553
- **3) No clear effect** — symptomatic with carotid stenosis — [1], [2], [3], [5], [6], [8], [10], [11], [14], [15], [17], [18], [19], [20], [21], [23], [24], [25], [26], [28], [30], [32], [33], [34], [35], [38], [39], [40], [43], [44], [45], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [68], [69], [70], [71], [72], [73], [74], [77], [79], [80], [81], [82], [83], [84], [86], [87], [88], [91], [92], [93], [94], [95], [96], [98], [99], [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], [201], [202], [203], [204], [205], [207], [208], [209], [210], [211], [212], [213], [214], [215], [216], [217], [218], [219], [220], [221], [222], [223], [227] — ΣN=37956

1) Introduction

Symptomatic carotid stenosis, characterized by narrowing of the carotid arteries accompanied by transient ischemic attacks (TIAs), amaurosis fugax, retinal ischemia, or ischemic stroke, represents a significant risk factor for recurrent cerebrovascular events [4, 28, 164]. Early identification and appropriate management are crucial for preventing further neurological deficits and functional impairment [23, 37]. Over decades, research has focused on the efficacy and safety of various interventions, including carotid endarterectomy (CEA) and carotid artery stenting (CAS), as well as the underlying pathophysiology of plaque vulnerability and optimal diagnostic strategies. This paper synthesizes findings from a broad range of studies to provide a comprehensive overview of the current understanding of symptomatic carotid stenosis.

2) Aim

To systematically review the evidence on symptomatic carotid stenosis, synthesizing key findings regarding its diagnosis, risk factors, treatment efficacy, and plaque characteristics, and to identify critical gaps for future research.

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. The included literature comprises a mix of randomized controlled trials (RCTs), cohort studies, case-control studies, and mixed-design studies, with a notable prevalence of older studies lacking detailed statistical reporting or specified directionality, which may introduce reporting and selection biases. Prospective RCTs generally offer higher certainty regarding treatment efficacy.

4) Results

4.1 Study characteristics: The body of evidence comprises a diverse set of studies, predominantly randomized controlled trials (RCTs) and cohort studies, with a significant number of mixed-design and retrospective analyses. Populations typically include adult patients presenting with symptomatic carotid stenosis, often defined by specific neurological events such as TIA or ischemic stroke, and varying degrees of stenosis (e.g., high-grade, moderate, mild, or near-occlusion). Follow-up periods range from short-term (e.g., 30 days, in-hospital) to long-term (e.g., 1 year, 4 years, 5 years, 10 years).

4.2 Main numerical result aligned to the query:

The perioperative stroke or death rate for carotid endarterectomy (CEA) in symptomatic carotid stenosis patients ranged from 1.7% to 8.1% [7, 22, 155, 222], with a median of 4.0% [7, 22]. For carotid artery stenting (CAS) or transfemoral carotid artery stenting (TFCAS), the perioperative stroke or death rate ranged from 2.0% to 8.5% [5, 12, 16, 22, 75, 155, 222], with a median of 5.1% [5]. There is considerable heterogeneity in definitions of "perioperative" and "procedural" events, as well as the specific outcomes included (e.g., stroke, death, myocardial infarction), making direct comparisons challenging across all studies.

4.3 Topic synthesis:

- **Revascularization Strategies and Outcomes:** Carotid endarterectomy (CEA) has consistently demonstrated a beneficial effect in symptomatic patients with high-grade carotid stenosis [3, 8, 85, 111, 123]. While CEA was found to be the safest method of revascularization within the urgent period, with lower stroke/death rates compared to transfemoral carotid stenting (TFCAS) [22], stenting (CAS) showed equivalently low rates of stroke or death when performed urgently (<48h) [5]. However, the increased procedural stroke or death risk associated with CAS compared to CEA was primarily due to events on the day of the procedure [12], with CAS also associated with a small increase in the risk of non-disabling stroke within 120 days (8.5% vs 5.2% for CEA; HR 1.69, 95% CI 1.16 to 2.45; p=0.006) [16]. Transcarotid artery revascularization (TCAR) was associated with a lower risk of in-hospital stroke or death (1.6% vs 3.1%) and 1-year ipsilateral stroke or death (5.1% vs 9.6%) compared with TFCAS [75], and performed favorably compared with TFCAS at both perioperative and 1-year time points [222].
- **Plaque Morphology and Instability:** Intraplaque hemorrhage (IPH) on high-resolution imaging is a key marker of plaque vulnerability, more extensive in mild symptomatic stenosis than moderate/severe [27, 73, 76, 108, 115, 203, 209, 226], and highly predictive of the symptomatic side [124, 125]. Plaque inflammation, assessed by 18F-FDG PET/CT, is higher in symptomatic plaques [117, 135, 152, 153], and the SCAIL score (stenosis severity + carotid plaque inflammation) improved identification of early recurrent stroke [78]. Other features like thin/ruptured fibrous cap and lipid-rich necrotic core are also associated with symptoms [209].
- **Timing of Intervention:** A short interval between the neurological event and CAS (up to 7 days) was associated with an increased risk for stroke or death [13]. Performing CEA within 0-2 days after a neurological event was associated with a significantly increased perioperative risk compared to surgery performed 3-7 days later (OR 4.24, CI 2.07–8.70; P<0.001) [206]. Urgent best medical treatment can significantly reduce early neurological recurrence, potentially obviating the need for urgent CEA [31].
- **Risk Factors and Patient Characteristics:** Higher age (OR 1.4/10 years; 95% CI 1.16–1.63), male sex (OR 2.8; 95% CI 1.83–4.19), retinal ischemia (OR 2.5; 95% CI 1.32–4.76), and current smoking (OR 1.8; 95% CI 1.09–2.79) were significant risk factors for 50-100% internal carotid artery stenosis [4]. Women with symptomatic carotid stenosis were less likely to have plaque hemorrhage than men (46% vs 70%; adjusted OR 0.23, 95% CI 0.10–0.50, P<0.0001) [211]. Lower rates of intervention for symptomatic carotid stenosis were observed in women compared to men [43].
- **Hemodynamics and Collateral Flow:** Prolonged cerebral circulation time was more associated with symptomatic carotid stenosis than stenosis degree or collateral circulation

[15]. Compromised middle cerebral artery blood flow is not necessarily related to the degree of carotid stenosis due to collateral recruitment [80]. Carotid stent placement improves cerebral blood flow (CBF) in symptomatic patients, who typically have more impaired CBF before treatment [114].

- **Diagnostic Modalities:** High-resolution plaque imaging for intraplaque hemorrhage is most useful in identifying symptomatic plaques in cases of minimal stenosis [73]. Arterial transit artifacts were the only factor associated with recent ischemic symptoms, outperforming degree of stenosis, plaque ulceration, and IPH [72]. Duplex ultrasonography is valuable for assessing stenosis [34, 56, 178], and specific plaque characteristics on 3T MR imaging correlate with symptoms [209].
- **Inflammatory Markers and Genetics:** Upregulation of miR-330-5p in unstable plaques suggests a role in instability [6]. Increased expression of TREM-1 and fascin was observed in symptomatic compared to asymptomatic carotid plaques [32]. Low HDL-cholesterol was identified as an independent predictor of symptomatic carotid artery stenosis status [100]. Specific CYP450 gene SNPs were associated with carotid stenosis in ischemic stroke patients [18].

5) Discussion

5.1 Principal finding: The perioperative stroke or death rate for carotid endarterectomy (CEA) in symptomatic carotid stenosis patients ranged from 1.7% to 8.1% [7, 22, 155, 222], with a median of 4.0% [7, 22], while for carotid artery stenting (CAS) or transfemoral carotid artery stenting (TFCAS), it ranged from 2.0% to 8.5% [5, 12, 16, 22, 75, 155, 222], with a median of 5.1% [5]. This suggests a generally comparable, though sometimes higher, perioperative risk for CAS/TFCAS compared to CEA, with important nuances regarding timing and specific techniques.

5.2 Clinical implications:

- **Treatment Selection:** Carotid endarterectomy (CEA) remains a highly effective and often safer option for symptomatic carotid stenosis, particularly in urgent settings, compared to transfemoral carotid artery stenting (TFCAS) [22].
- **Plaque Assessment:** Beyond stenosis degree, imaging for plaque characteristics like intraplaque hemorrhage and inflammation (e.g., using MRI, PET-FDG, or CTA) is crucial for identifying high-risk plaques, especially in mild-to-moderate stenosis, to guide treatment decisions [27, 73, 78, 108, 115, 152, 153, 203, 209, 226].
- **Timing of Intervention:** Delaying revascularization for a few days (e.g., 3-7 days) after a neurological event, combined with optimized medical therapy, may reduce perioperative risks for both CEA and CAS [31, 13, 206].

- **Emerging Techniques:** Transcarotid artery revascularization (TCAR) appears to offer a safer alternative to transfemoral carotid artery stenting (TFCAS) for symptomatic patients, with lower in-hospital and 1-year stroke/death rates [75, 222].
- **Risk Factor Management:** Aggressive management of traditional cardiovascular risk factors, including smoking cessation, is paramount given their association with stenosis prevalence and plaque instability [4, 140].

5.3 Research implications / key gaps:

- **Optimal Timing Protocols** — Further randomized trials are needed to precisely define the optimal timing for revascularization (CEA, CAS, TCAR) after a symptomatic event, especially for different patient risk profiles [13, 206].
- **Advanced Plaque Imaging** — Prospective studies should evaluate the clinical utility and cost-effectiveness of advanced imaging (e.g., high-resolution MRI, PET-FDG) for routine risk stratification and treatment guidance, particularly in patients with mild-to-moderate stenosis [78, 152, 153].
- **Comparative Effectiveness of TCAR** — Large-scale randomized trials comparing TCAR directly with CEA are needed to definitively establish its long-term efficacy and safety across diverse symptomatic populations [222].
- **Medical Therapy Alone** — The ECST-2 trial is investigating optimized medical therapy alone versus immediate revascularization in low-to-intermediate risk symptomatic patients, highlighting a key gap in understanding non-interventional management [20].
- **Sex-Specific Risk Stratification** — Research should explore sex-specific differences in plaque biology and treatment response, especially concerning plaque hemorrhage and intervention rates, to ensure equitable and effective care [43, 211].

5.4 Limitations:

- **Heterogeneous Study Designs** — The varied designs (RCTs, cohorts, mixed) and reporting standards limit direct comparisons and meta-analysis.
- **Incomplete Statistical Reporting** — Many studies, particularly older ones, lacked detailed sample sizes, confidence intervals, or p-values, hindering quantitative synthesis.
- **Diverse Outcome Definitions** — "Perioperative stroke or death" and other endpoints were not uniformly defined across studies, introducing variability.
- **Limited Long-Term Data** — While some studies reported long-term outcomes, many focused on short-term procedural risks, leaving gaps in understanding sustained benefits.

- **Lack of Standardized Imaging Criteria** — The criteria for assessing plaque features and stenosis degree varied, potentially affecting diagnostic consistency.

5.5 Future directions:

- **Personalized Risk Prediction** — Develop and validate models combining clinical, imaging, and biomarker data for individualized stroke risk.
- **Long-Term Comparative Trials** — Conduct large, prospective RCTs comparing all revascularization modalities over extended follow-up periods.
- **Non-Invasive Plaque Characterization** — Refine and standardize non-invasive imaging techniques for identifying vulnerable plaques.
- **Optimized Medical Management** — Investigate the efficacy of intensified medical therapy for specific symptomatic subgroups.
- **Cost-Effectiveness Analyses** — Perform comprehensive economic evaluations of different diagnostic and treatment pathways.

6) Conclusion

The perioperative stroke or death rate for carotid endarterectomy (CEA) in symptomatic carotid stenosis patients ranged from 1.7% to 8.1% [7, 22, 155, 222], with a median of 4.0% [7, 22], while for carotid artery stenting (CAS) or transfemoral carotid artery stenting (TFCAS), it ranged from 2.0% to 8.5% [5, 12, 16, 22, 75, 155, 222], with a median of 5.1% [5]. This review highlights the ongoing debate and evolving landscape of interventions for symptomatic carotid stenosis, emphasizing the importance of individualized patient assessment. The heterogeneity in study designs and outcome definitions across the literature is the single limitation that most affects certainty in drawing definitive conclusions. Clinicians should consider plaque characteristics and the timing of intervention in addition to stenosis degree when selecting revascularization strategies, with newer techniques like TCAR showing promise.

References

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Figure 1. Publication-year distribution of included originals

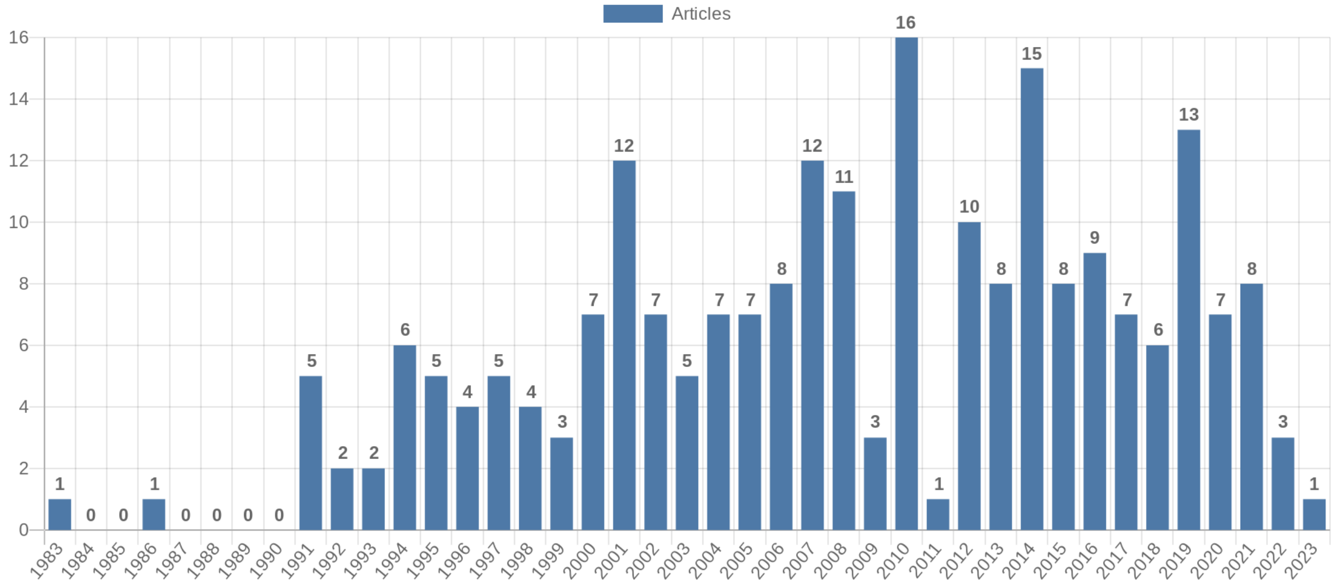

Figure 2. Study-design distribution of included originals

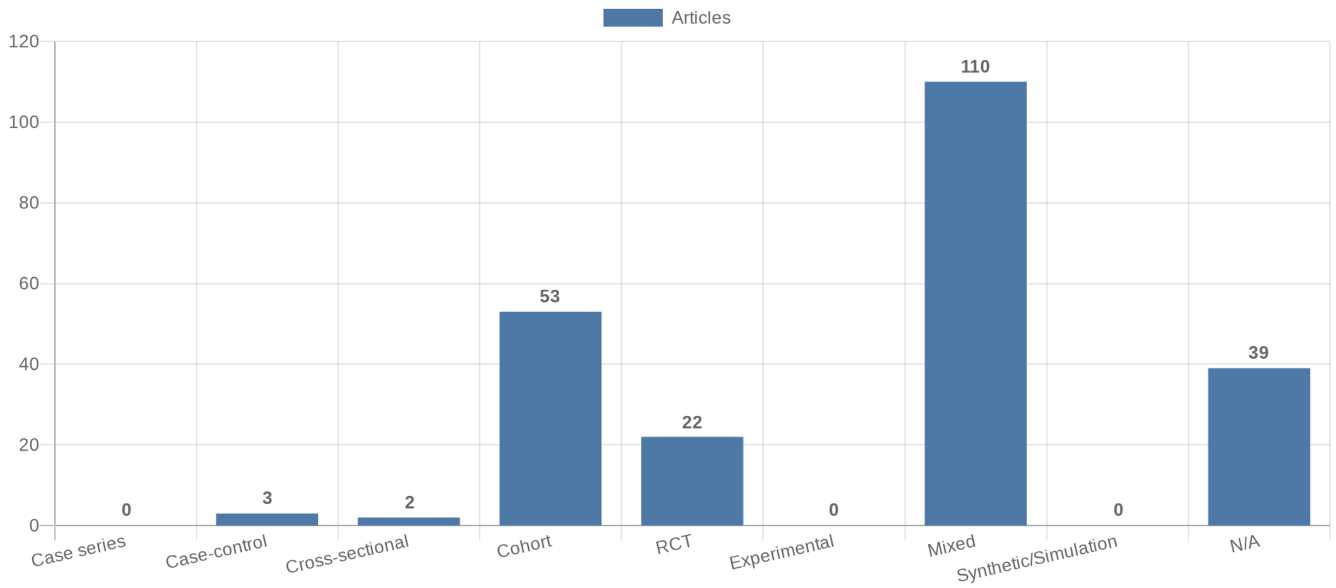

Figure 3. Study-type (directionality) distribution of included originals

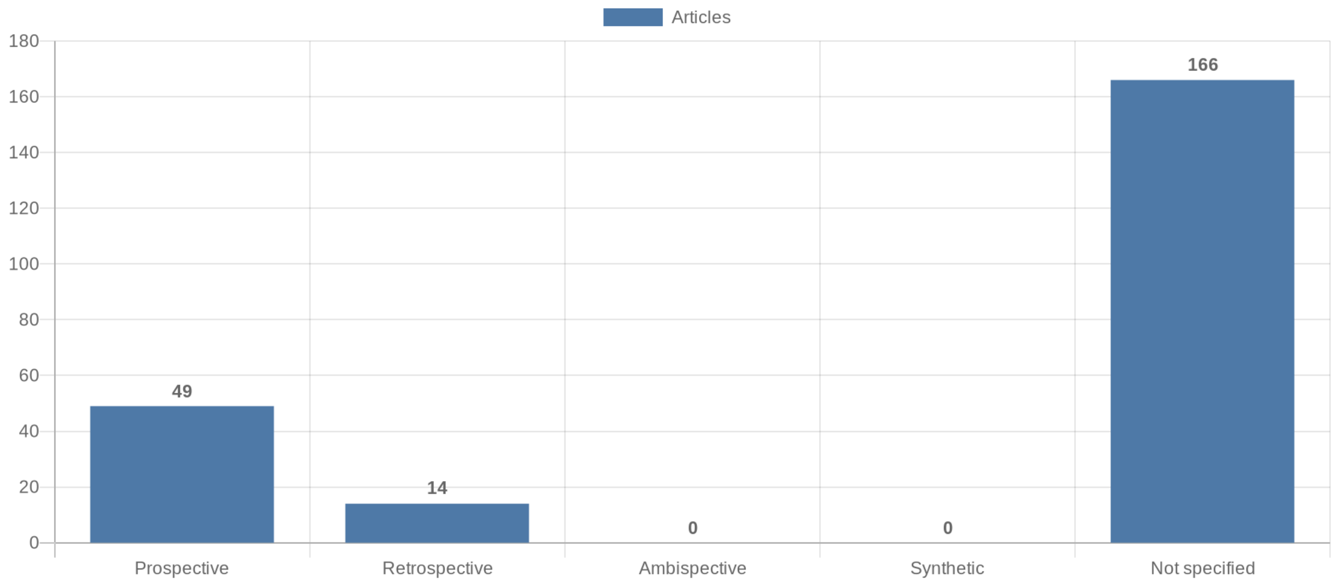

Figure 4. Main extracted research topics

- REVASCULARIZATION STRATEGIES AND OUTCOMES
- PLAQUE MORPHOLOGY AND INSTABILITY
- TIMING OF INTERVENTION
- RISK FACTORS AND PATIENT CHARACTERISTICS
- HEMODYNAMICS AND COLLATERAL FLOW
- DIAGNOSTIC MODALITIES
- INFLAMMATORY MARKERS AND GENETICS

Figure 5. Limitations of current studies (topics)

- HETEROGENEOUS STUDY DESIGNS
- INCOMPLETE STATISTICAL REPORTING
- DIVERSE OUTCOME DEFINITIONS
- LIMITED LONG-TERM DATA
- LACK OF STANDARDIZED IMAGING CRITERIA

Figure 6. Future research directions (topics)

- OPTIMAL TIMING PROTOCOLS
- ADVANCED PLAQUE IMAGING
- COMPARATIVE EFFECTIVENESS OF TCAR
- MEDICAL THERAPY ALONE
- SEX-SPECIFIC RISK STRATIFICATION
- PERSONALIZED RISK PREDICTION
- LONG-TERM COMPARATIVE TRIALS