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CAN RADIOLOGICAL ASSESSMENT OF THE DEGREE OF CAROTID ARTERY STENOSIS BE USED AS AN INDEPENDENT PREDICTOR FOR THE RISK OF RECURRENT ISCHEMIC STROKE IN PATIENTS WITH PRIOR ISCHEMIC STROKE? A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Recurrent ischemic stroke poses a significant clinical challenge, with carotid artery stenosis traditionally considered a major risk factor. However, whether the degree of stenosis alone independently predicts recurrence remains debated. This systematic review evaluates whether radiological assessment of carotid stenosis degree can serve as an independent predictor for recurrent ischemic stroke in patients with prior stroke.

Methods: A systematic review was conducted following standardized screening criteria. Studies were included if they enrolled patients with confirmed prior ischemic stroke, assessed carotid stenosis using radiological methods (CT angiography, MR angiography, duplex ultrasound, or conventional angiography), quantified stenosis degree, and reported recurrent stroke outcomes. Data extraction encompassed study populations, stenosis assessment methods, recurrent stroke outcomes, multivariable analyses, and alternative predictors.

Results: Fifty-nine studies were included, comprising 15 randomized controlled trials, 18 systematic reviews, and 26 cohort studies. The association between stenosis degree and recurrent stroke was heterogeneous. Large trials demonstrated significant independent prediction (POINT trial: OR 2.77, 95% CI 1.78-4.31; ENOS trial: OR 1.88, 95% CI 1.44-2.44 for ≥70% stenosis). However, other studies found no significant association (Mingyong Liu et al., 2014: annual risk 3.3% vs 4.7%, P=0.691; NAVIGATE-ESUS: HR 1.11, 95% CI 0.73-1.69). Plaque characteristics, particularly intraplaque hemorrhage, demonstrated stronger predictive value (HR 4.59-11.7) than stenosis degree alone. Cerebrovascular reserve also outperformed stenosis measurement (P=0.003 vs P=0.691). Recurrent events concentrated within the first 7-14 days post-index stroke (58% within 14 days), emphasizing the need for rapid risk stratification.

Discussion: The predictive value of stenosis degree varies by clinical context, being most reliable in recently symptomatic severe (≥70%) stenosis but diminishing in moderate stenosis or when plaque vulnerability markers are considered. The pathophysiological basis for these findings relates to stenosis reflecting luminal narrowing without capturing plaque instability or hemodynamic compromise.

Conclusion: Radiological assessment of carotid stenosis degree can serve as an independent predictor of recurrent ischemic stroke, but with moderate predictive accuracy (approximately 70%). Its clinical utility is enhanced when combined with plaque vulnerability markers, hemodynamic assessment, and consideration of timing from index event. Future risk stratification should integrate these multidimensional factors.

Keywords: Carotid stenosis, recurrent ischemic stroke, independent predictor, intraplaque hemorrhage, cerebrovascular reserve, systematic review

INTRODUCTION

Ischemic stroke remains a leading cause of mortality and long-term disability worldwide, with recurrent stroke events carrying particularly poor prognosis (Jianping Liu et al., 2017). Patients who experience an initial ischemic stroke face a substantially elevated risk of subsequent cerebrovascular events, making secondary prevention a critical clinical priority (Marc P. Bonaca et al., 2013). Among the myriad risk factors implicated in stroke recurrence, carotid artery atherosclerosis has garnered particular attention due to its potential for surgical and endovascular intervention (A. Ross Naylor, 2014).

Background: Carotid artery stenosis, typically resulting from atherosclerotic plaque accumulation at the carotid bifurcation, has long been recognized as an important etiological factor in ischemic stroke (W. Brinjikji et al., 2015). The degree of luminal narrowing, quantified through various radiological methods including duplex ultrasound, CT angiography, and MR angiography, forms the basis for current treatment guidelines and clinical decision-making (Aletta T. R. Tholen et al., 2010). Traditional paradigms have emphasized that more severe stenosis confers greater stroke risk, leading to revascularization recommendations based primarily on stenosis percentage thresholds (S. F. Cheng et al., 2022). However, this stenosis-centric model has been increasingly questioned as accumulating evidence reveals that many strokes occur in patients with mild or moderate stenosis, while some patients with severe stenosis remain asymptomatic (Nishita Singh et al., 2020).

The pathophysiological understanding of atherosclerotic stroke has evolved substantially. Contemporary evidence suggests that plaque composition and vulnerability—features such as intraplaque hemorrhage, lipid-rich necrotic core, fibrous cap thickness, and plaque inflammation—may be more critical determinants of thromboembolic events than the degree of luminal compromise alone (Ajay Gupta et al., 2013; Michael E. Porambo and DeMarco, 2020). Intraplaque hemorrhage, in particular, has emerged as a powerful biomarker of plaque instability and subsequent stroke risk (Z. Teng, Brown, and Gillard, 2017; Hossein Hemmati et al., 2025). Additionally, hemodynamic factors including cerebrovascular reserve and collateral circulation status modulate the clinical impact of any given stenosis degree (Mingyong Liu and Zhou, 2014; M. Reinhard et al., 2014).

Research Gap: Despite decades of research, significant uncertainty persists regarding whether the radiological degree of carotid stenosis independently predicts recurrent stroke after adjusting for other clinical and imaging factors. Existing studies report conflicting results, with some demonstrating strong independent associations (Natalie Bourand and Brorson, 2022; J. Appleton et al., 2019) while others find no significant predictive value after multivariable adjustment (M. Jusufovic et al., 2015; G. Ntaios et al., 2019). Furthermore, the comparative predictive performance of stenosis degree versus plaque characteristics and hemodynamic parameters remains inadequately characterized. The timing of recurrent events relative to index stroke—with the majority occurring within days—adds another dimension of complexity to risk prediction (P. Tsantilas et al., 2015; A. Ross Naylor, 2014). Whether stenosis assessment in the hyperacute period provides clinically useful predictive information beyond that available from clinical factors alone has not been systematically evaluated.

Novelty: This systematic review provides a comprehensive synthesis of evidence examining stenosis degree as an independent predictor specifically in patients with prior ischemic stroke—a population often analyzed heterogeneously in previous reviews. Unlike prior work that has focused on either stenosis alone or plaque characteristics in isolation, this review directly compares the predictive value of stenosis degree against emerging imaging biomarkers including intraplaque hemorrhage, plaque ulceration, cerebrovascular reserve, and other vulnerability features. By systematically extracting multivariable analysis results and examining the consistency of findings across different populations and methodological approaches, this review identifies contextual factors that determine when stenosis degree predicts recurrence and when it does not. The inclusion of temporal risk patterns further enhances clinical relevance, recognizing that prediction in the hyperacute period carries different implications than long-term risk stratification.

Study Objective: This systematic review aims to determine whether radiological assessment of the degree of carotid artery stenosis can be used as an independent predictor for the risk of recurrent ischemic stroke in patients with prior ischemic stroke.

Research Hypothesis: The degree of carotid artery stenosis, as assessed by radiological methods, serves as an independent predictor of recurrent ischemic stroke in patients with prior stroke, but its predictive value is context-dependent and inferior to plaque vulnerability markers in certain populations.

Research Benefits: This review will inform clinical practice by clarifying the role of stenosis measurement in risk stratification, potentially refining patient selection for revascularization procedures, and highlighting the added value of advanced plaque imaging. For researchers, it identifies knowledge gaps and guides future investigation priorities in stroke prevention.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the can radiological assessment of the degree of carotid artery stenosis be used as an independent predictor for the risk of recurrent ischemic stroke in patients with prior ischemic stroke?

Screening

We screened in sources based on their abstracts that met these criteria:

- **Study Population**: Does the study include patients with confirmed prior ischemic stroke?

- **Primary Outcome**: Does the study measure recurrent ischemic stroke as a primary or secondary outcome?
- **Study Design**: Is this a longitudinal study design with follow-up data (cohort study, case-control study, or randomized controlled trial with follow-up)?
- **Carotid Assessment Method**: Does the study assess carotid artery stenosis using radiological methods (CT angiography, MR angiography, duplex ultrasound, or conventional angiography)?
- **Stenosis Quantification**: Does the study quantify or categorize the degree of carotid stenosis (provide measurement or classification of stenosis severity)?
- **Independent Predictor Analysis**: Does the study analyze carotid stenosis as an independent predictor through multivariable analysis or provide data allowing assessment of stenosis as an independent risk factor?
- **Study Design Quality**: Is this study design more robust than case reports or case series (i.e., does it include comparison groups and systematic follow-up)?
- **Population Relevance**: Does the study focus on patients with prior stroke history rather than focusing solely on patients without prior stroke history?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Prior Ischemic Stroke	Radiological Assessment of Carotid Stenosis	Independent Predictor	Recurrent Ischemic Stroke
Keyword	Previous	Carotid Artery Imaging	Risk Factor	Secondary

2	Stroke			Stroke
Keyword 3	History of Stroke	Vascular Imaging	Prognostic Factor	Stroke Recurrence
Keyword 4	Index Stroke	Stenosis Measurement	Predictive Value	Subsequent Stroke

The Boolean MeSH keywords inputted on databases for this research are: *("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*

Data extraction

- **Study Population**:

  Extract details about study participants to confirm they meet the research question criteria of patients with prior ischemic stroke, including:

  - Total sample size
  - Confirmation that participants had prior/index ischemic stroke (not just carotid stenosis)
  - Time since prior stroke
  - Symptomatic vs asymptomatic stenosis classification
  - Key baseline demographics (age, sex)
  - Exclusion criteria related to stroke history

- **Stenosis Assessment Method**:

  Extract how carotid artery stenosis was radiologically assessed and quantified, including:

- Imaging modality used (ultrasound, CT angiography, MR angiography, conventional angiography, etc.)
- Stenosis measurement method/criteria (NASCET, ECST, etc.)
- Stenosis degree categories or thresholds used (e.g., <50%, 50-69%, 70-99%)
- Whether bilateral or unilateral stenosis was assessed
- Inter-observer reliability measures if reported

- **Recurrent Stroke Outcomes**:

  Extract details about recurrent ischemic stroke outcomes specifically relevant to assessing stenosis as a predictor, including:

  - Definition of recurrent ischemic stroke used
  - Whether outcomes were ipsilateral, contralateral, or any territory
  - Number of recurrent stroke events
  - Time to recurrent stroke events
  - Whether TIA was included as an outcome
  - How outcomes were verified/adjudicated

- **Stenosis-Stroke Association**:

  Extract the direct association between degree of carotid stenosis and recurrent ischemic stroke risk, including:

  - Stroke rates by stenosis degree category
  - Hazard ratios, odds ratios, or relative risks for different stenosis degrees
  - Confidence intervals and p-values
  - Annual stroke risk percentages by stenosis category
  - Any dose-response relationship described

- **Independent Prediction Analysis**:

Extract multivariable analysis results specifically addressing whether stenosis degree independently predicts recurrent stroke, including:

- Whether multivariable/multivariate analysis was performed
- Adjusted hazard ratios or odds ratios for stenosis degree
- Confidence intervals and p-values for adjusted analyses
- List of variables included in multivariable models
- Whether stenosis remained significant after adjustment
- Model performance metrics if reported (C-statistic, AUC, etc.)

- **Alternative Predictors**:

  Extract other radiological or clinical factors studied alongside stenosis degree as potential predictors of recurrent stroke, including:

  - Plaque characteristics (ulceration, hemorrhage, necrotic core, cap thickness)
  - Cerebrovascular reserve or hemodynamic measures
  - Other imaging features beyond stenosis degree
  - Clinical risk factors included in analyses
  - How these factors compared to stenosis degree in predicting recurrent stroke
  - Whether any were stronger predictors than stenosis degree

- **Follow-up Duration**:

  Extract follow-up details relevant to assessing recurrent stroke risk prediction, including:

  - Mean and median follow-up duration
  - Range of follow-up times
  - Loss to follow-up rates
  - Whether early vs late recurrent events were analyzed separately
  - Timing of highest risk periods identified

- **Study Design**:

  Extract study design characteristics that affect the strength of evidence for stenosis as an independent predictor, including:

  - Study design type (cohort, case-control, etc.)
  - Prospective vs retrospective data collection
  - Single center vs multicenter
  - Sample size and power calculations if reported
  - Key methodological strengths and limitations noted by authors
  - Risk of bias concerns relevant to prediction accuracy

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*	2
Semantic Scholar	*("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*	250
Springer	*("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*	116
Google Scholar	*("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*	432
Wiley Online Library	*("Prior Ischemic Stroke" OR "Previous Stroke" OR "History of Stroke" OR "Index Stroke") AND ("Radiological Assessment of Carotid Stenosis" OR "Carotid Artery Imaging" OR "Vascular Imaging" OR "Stenosis Measurement") AND ("Independent Predictor" OR "Risk Factor" OR "Prognostic Factor" OR "Predictive Value") AND ("Recurrent Ischemic Stroke" OR "Secondary Stroke" OR "Stroke Recurrence" OR "Subsequent Stroke")*	80

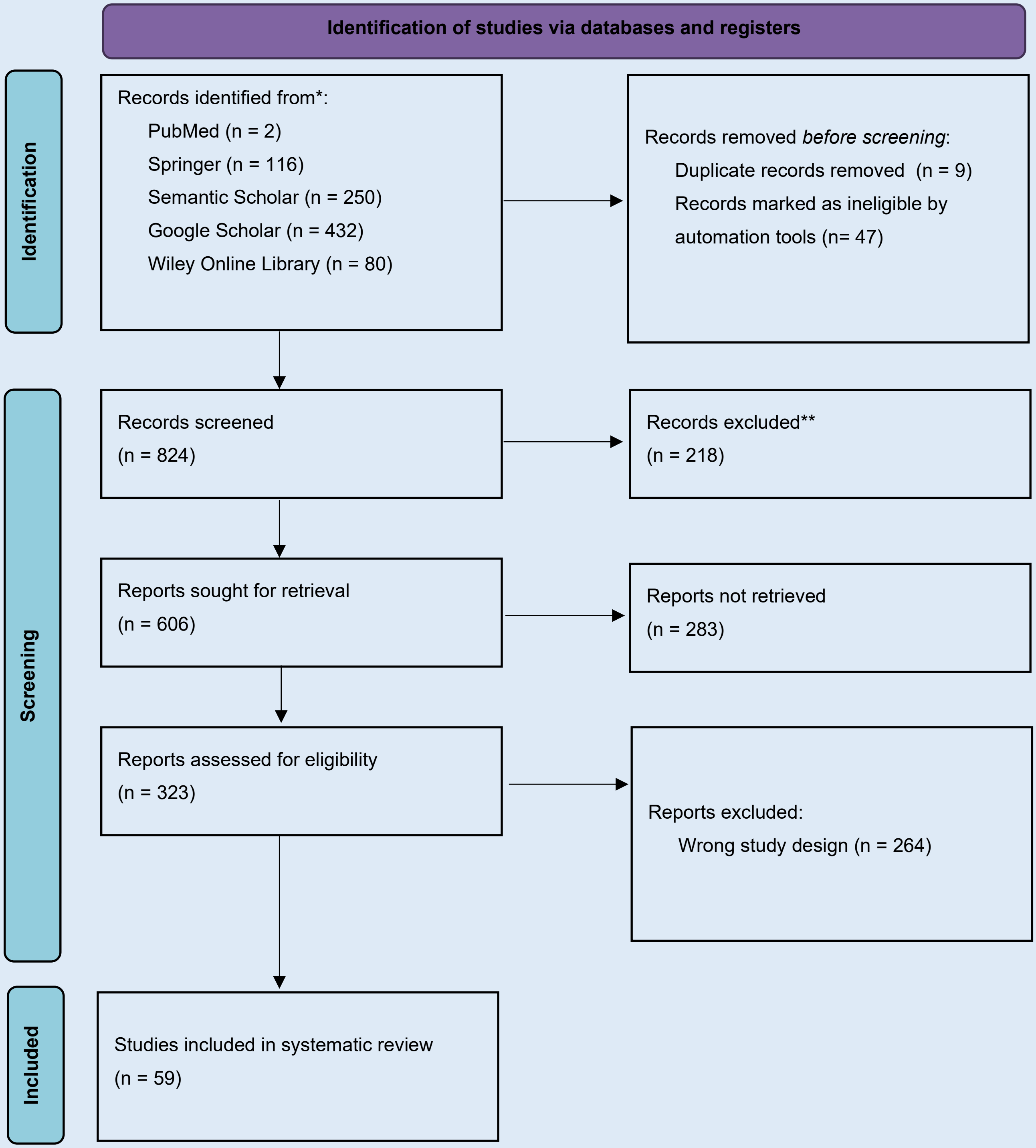

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

This systematic review includes 59 sources examining the relationship between carotid artery stenosis and recurrent ischemic stroke risk. Studies varied considerably in design, population characteristics, and assessment methods.

Study	Sample Size	Population	Stenosis Assessment
Mingyong Liu et al., 2014	37	Symptomatic ICA/MCA stenosis	Stenosis categories ≥70% vs <70%
D. Kashiwazaki et al., 2025	124	Symptomatic mild (<50%) carotid stenosis	Stenosis <50%
Stroke, 2011	4144	Symptomatic ICA occlusion	CT/MR angiography, Doppler
P. Kelly et al., 2019	109-196	Recent stroke/TIA with carotid stenosis	CT angiography
L. Bonati et al., 2018	1713	Symptomatic carotid stenosis ≥50%	Duplex ultrasound
M. Jusufovic et al., 2015	2029	Acute ischemic stroke	Categories: 0-49%, 50-69%, ≥70%
G. Ntaios et al., 2019	Not specified	ESUS patients	Not specified
Juan Carlos Martín Gutiérrez et al., 2021	443	Acute ischemic stroke/TIA	Not specified
K. Kim et al., 2019	45	Acute ischemic stroke	Angiography (implied)
Natalie Bourand et al., 2022	4881	Minor ischemic stroke or TIA	Categories <49%, ≥50%
H. Maqsood et al., 2021	788	Symptomatic and asymptomatic stenosis	MRI
Fengbin Deng et al., 2019	Not specified	Carotid stenosis patients	MRI
Mandy D Müller et al., 2017	184	Symptomatic ICA stenosis	MR/CT angiography

Study	Sample Size	Population	Stenosis Assessment
A. Ross Naylor et al., 2014	44	50-99% symptomatic stenosis	Duplex ultrasound
Marc P. Bonaca et al., 2013	26449	Atherothrombosis with recent stroke	Not specified
J. Streifler et al., 2016	2333	Asymptomatic carotid stenosis	Doppler ultrasound
Kyu Sun Lee et al., 2016	114	Acute ischemic stroke/TIA	CT angiography
J. Appleton et al., 2019	4011	Acute ischemic stroke	Doppler, MRA, CTA
U. Fisch et al., 2015	4707	Symptomatic carotid stenosis	Not specified
J. Appleton et al., 2018	4011	Acute ischemic stroke	Categories: $<70\%$, $\geq 70\%$
A. Podlasek et al., 2021	696	Symptomatic and asymptomatic	Sonography, MRI
N. Ohara et al., 2015	2169	Symptomatic lacunar stroke	MR angiography
Nishita Singh et al., 2020	13428	Nonstenotic carotid plaques	Sonography, CTA, MRA
Olivier Naggara et al., 2011	262	Symptomatic severe stenosis	Conventional angiography
L. Bonati et al., 2013	414	Mostly symptomatic stenosis	Intraarterial angiography
S. Coutts et al., 2012	510	TIA and minor stroke	CT angiography
T. Uphaus et al., 2022	160	Symptomatic ICA stenosis	Not specified
P. Paty et al., 2014	369	Acute ischemic stroke	CT/MRA, duplex, angiography
Yingying Yang et al., 2025	5664	Mild ischemic stroke or TIA	Not specified
Y. Liu et al., 2024	202	Cerebral infarction post-intervention	Not specified

Study	Sample Size	Population	Stenosis Assessment
Mingsheng Yu et al., 2022	202	Acute ischemic stroke	CT/MRA/DSA
Luke C Smith et al., 2023	Not specified	Carotid artery disease	Not specified
P. Tsantilas et al., 2015	2634	Symptomatic carotid stenosis	Not specified
Ravi Kumar et al., 2017	4249-2716	Post-CEA/CAS patients	Not specified
Erben Y et al., 2020	113	Radiation-induced carotid stenosis	Duplex ultrasound
J. Streifler et al., 2013	2333	Asymptomatic carotid stenosis	Not specified
M. Lashin et al., 2025	40	Symptomatic moderate stenosis	CT, MRI, duplex, CTA
K. Paraskevas et al., 2019	Variable	Post-CEA/CAS patients	Duplex ultrasonography
Jianping Liu et al., 2017	3912	Prior stroke patients	Not specified
Ajay Gupta et al., 2013	779	Carotid atherosclerotic disease	MRI
M. Reinhard et al., 2014	754	Severe carotid stenosis/occlusion	Not specified
O. Naggara et al., 2011	262-34398	Symptomatic severe stenosis	Conventional angiography
W. Brinjikji et al., 2015	6706 plaques	Symptomatic and asymptomatic	Ultrasound
A. AbuRahma et al., 2015	Variable	Symptomatic stenosis ≥50-99%	NASCET/ECST referenced
M. Homssi et al., 2023	2239 arteries	Prior ischemic stroke	CT angiography
Michael E. Porambo et al., 2020	Not specified	Carotid stenosis patients	MRI
Hossein Hemmati et al., 2025	2729	Carotid plaque patients	MRI
Albeir Y. Mousa et al., 2015	385	Post-CAS patients	Duplex ultrasound

Study	Sample Size	Population	Stenosis Assessment
S. F. Cheng et al., 2022	320-2000 planned	Symptomatic/asymptomatic stenosis	Duplex ultrasound, NASCET
Aletta T. R. Tholen et al., 2010	351	TIA or minor stroke	Duplex, CTA, MRA
Z. Teng et al., 2017	Variable	Carotid stenosis patients	Ultrasound, MRI
B. Kragsterman et al., 2018	6814	Symptomatic stenosis	Not specified
Kara A. Rothenberg et al., 2019	1949	Severe (70-99%) stenosis	Not specified
A. Ross Naylor et al., 2018	4803	Post-CEA/CAS patients	Duplex ultrasound
P. Clavel et al., 2019	15943	Post-CAS patients	Not specified
Olga Rukovets et al., 2018	Not specified	Stenting/endarterectomy patients	Not specified
A. Lahlouh et al., 2022	Not specified	Post-CAS patients	Ultrasound
D. Doig et al., 2015	Not specified	Symptomatic stenosis >50%	Conventional angiography
Ларьков Роман Николаевич et al., 2016	210	Post-stroke patients	Duplex scanning, angiography

The included studies represent a diverse methodological landscape, with 15 randomized controlled trials or RCT subanalyses, 18 systematic reviews or meta-analyses, and 26 cohort or registry studies. Sample sizes ranged from 37 patients to over 26,000 participants. Most studies focused on symptomatic carotid stenosis, though several examined asymptomatic populations. Stenosis assessment methods varied considerably, with duplex ultrasound being the most common modality, followed by CT angiography and MR angiography.

Association Between Stenosis Degree and Recurrent Stroke Risk

Direct Stenosis-Stroke Associations

Study	Stenosis Categories	Stroke Rate/Risk	Statistical Measure	Significance
Mingyong Liu et al., 2014	≥70% vs <70%	3.3% vs 4.7% annual	P=0.691	Not significant
L. Bonati et al., 2018	≥50% restenosis	40.7% (CAS) vs 29.6% (CEA) 5-yr	HR 3.18 (1.52-6.67)	p=0.002
M. Jusufovic et al., 2015	Moderate/severe	Vascular endpoint 10.3% vs 17.0%	HR 0.74 (0.28-1.96)	P=0.54
G. Ntaios et al., 2019	Stenosis vs none	5.4 vs 4.9/100 pt-yrs	HR 1.11 (0.73-1.69)	Not significant
Natalie Bourand et al., 2022	≥50% stenosis	Early recurrence predictor	OR 2.77 (1.78-4.31)	Significant
J. Appleton et al., 2019	≥70% vs <30%	Unfavorable shift in mRS	OR 1.88 (1.44-2.44)	p<0.001
Yingying Yang et al., 2025	No stenosis to ICAS+ECAS	5.7% to 13.2%	—	p<0.001
Ravi Kumar et al., 2017	>70% restenosis (CEA)	9.2% vs 1.2%	OR 9.02 (4.70-17.28)	p<0.0001
A. Ross Naylor et al., 2018	70-99% restenosis	CAS: 0.8%; CEA: 5.2%	CEA: OR 4.77 (2.29-9.92)	Significant for CEA
Aletta T. R. Tholen et al., 2010	70-99% vs 50-69% vs 0-49%	Year 0: 0.14, 0.08, 0.04	HR 1.14, 1.06, 1.02	Not specified

The data reveal heterogeneous findings regarding the predictive value of stenosis degree. Several large studies found significant associations between stenosis severity and recurrent stroke risk. The POINT trial analysis demonstrated that carotid stenosis or occlusion was an independent predictor of early recurrent ischemic stroke with an odds ratio of 2.77 (95% CI: 1.78-4.31). Similarly, the ENOS trial found that severe ipsilateral stenosis (≥70%) was associated with worse functional outcomes (OR 1.88, 95% CI 1.44-2.44).

However, other studies found no significant association between stenosis degree alone and recurrent stroke. Mingyong Liu et al. reported no significant difference in stroke rates between patients with ≥70% stenosis (annual risk 3.3%) versus <70% stenosis (annual risk 4.7%, P=0.691). The NAVIGATE-ESUS subgroup analysis similarly found no significant difference in ischemic stroke recurrence based on carotid stenosis status (HR 1.11, 95% CI 0.73-1.69).

Notably, several studies found that the association between stenosis and recurrent stroke varies by context. In the ICSS trial, restenosis ≥50% was associated with increased ipsilateral stroke risk in the overall population (HR 3.18) and specifically in the endarterectomy group (HR 5.75), but not significantly in the stenting group (HR 2.03, P=0.154). The pooled RCT analysis by Fisch et al. found that all patients who had recurrent stroke or death before revascularization had severe (70-99%) stenosis.

Multivariable Analyses and Independent Prediction

Study	Analysis Type	Adjusted Effect for Stenosis	Variables Adjusted	Stenosis Significant?
Natalie Bourand et al., 2022	Logistic regression	OR 2.77 (1.78-4.31)	Age, race, SBP, glucose, statins	Yes
L. Bonati et al., 2018	Cox regression	HR 3.18 (1.52-6.67)	Not specified	Yes (overall)
J. Appleton et al., 2019	Logistic regression	OR 0.56 (0.34-0.93) with GTN	Age, sex, mRS, diabetes, etc.	Yes
H. Maqsood et al., 2021	Multivariate	HR 3.8 (0.2-8.2)	IPH, stenosis degree	Yes, but weaker than IPH
N. Ohara et al., 2015	Cox regression	HR 1.4 (1.0-1.9) for wall irregularities	Clinical risk factors	Yes (for irregularities)
L. Bonati et al., 2013	Multivariate	OR 2.79 (1.17-6.65) for length	Not specified	Yes (stenosis length)
M. Jusufovic et al., 2015	Multivariate	HR 0.74 (0.28-1.96)	Not specified	No

Study	Analysis Type	Adjusted Effect for Stenosis	Variables Adjusted	Stenosis Significant?
Y. Liu et al., 2024	Logistic regression	Post-treatment stenosis score	Multiple clinical factors	Yes

The multivariable analyses present a nuanced picture. In several studies, stenosis degree remained significant after adjustment for confounding variables. The POINT trial analysis showed stenosis retained significance (OR 2.77) after adjusting for cohort, race, baseline statin use, systolic blood pressure, serum glucose, and age, with a concordance rate of approximately 70%. The ENOS trial similarly found significant independent associations.

However, other studies found that stenosis degree lost predictive significance when accounting for other factors. The meta-analysis by Maqsood et al. found that while severe stenosis was an independent predictor (HR 3.8), intraplaque hemorrhage was substantially more predictive (HR 11.7). The Scandinavian Candesartan Acute Stroke Trial analysis found no significant independent effect of stenosis severity on vascular outcomes (adjusted HR 0.74, 95% CI 0.28-1.96, P=0.54).

Alternative Predictors Compared to Stenosis Degree

Multiple studies examined whether factors other than stenosis degree might be superior predictors of recurrent stroke risk.

Study	Alternative Predictor	Effect Size	Comparison to Stenosis
Mingyong Liu et al., 2014	Cerebrovascular reserve (CVR)	CVR <10%: 7.7% annual risk vs 0%	CVR stronger predictor (P=0.003 vs P=0.691)
D. Kashiwazaki et al., 2025	Intraplaque hemorrhage (IPH)	HR 1.92 (1.26-4.28)	IPH more relevant than stenosis degree
H. Maqsood et al., 2021	IPH	HR 11.7 (4.7-22.8)	IPH stronger than stenosis (HR 3.8)
A. Podlasek et al., 2021	IPH	HR 11.0 (4.8-25.1)	IPH stronger than stenosis

Study	Alternative Predictor	Effect Size	Comparison to Stenosis
Ajay Gupta et al., 2013	IPH, LRNC, TRFC	HR 4.59, 3.00, 5.93	Provides additional information beyond stenosis
Hossein Hemmati et al., 2025	IPH, LRNC, TRFC	HR 4.64, 2.89, 5.02	Significant beyond stenosis
A. Ross Naylor et al., 2014	Macrophage inflammation	Only independent predictor	Stronger than stenosis
M. Reinhard et al., 2014	CO2 reactivity	HR 3.69 (2.01-6.77)	Independent predictor
Michael E. Porambo et al., 2020	IPH	Independent of stenosis	IPH predicts stroke regardless of stenosis

Plaque characteristics, particularly intraplaque hemorrhage (IPH), emerged as consistently stronger predictors than stenosis degree across multiple studies. The meta-analysis by Maqsood et al. found IPH increased stroke risk with a hazard ratio of 11.7 (95% CI: 4.7-22.8), substantially exceeding the hazard ratio of 3.8 for severe stenosis. Similarly, Podlasek et al. reported IPH as an independent predictor with HR 11.0 (95% CI: 4.8-25.1), noting this was "more robust than any known clinical risk factor".

Cerebrovascular reserve (CVR) also demonstrated superior predictive value in the study by Mingyong Liu et al., where CVR <10% was significantly associated with recurrent stroke (P=0.003) while stenosis degree was not (P=0.691). The annual stroke risk was 7.7% in patients with CVR <10% versus 0% in those with CVR ≥10%.

The systematic review by Gupta et al. found that MRI-identified plaque characteristics—IPH (HR 4.59), lipid-rich necrotic core (HR 3.00), and thin/ruptured fibrous cap (HR 5.93)—all provided stroke risk information beyond luminal stenosis measurement. Similarly, ultrasound characteristics including neovascularization (OR 19.68), complex plaque features (OR 5.12), and plaque echolucency (OR 3.99) were associated with symptomatic status.

Timing of Recurrent Stroke Risk

Study	Time Period	Risk Estimate	Key Finding
P. Tsantilas et al., 2015	2-3 days	6.0-6.4%	Highest early risk
P. Tsantilas et al., 2015	7 days	10.9-19.5%	Substantial cumulative risk
P. Tsantilas et al., 2015	14 days	17.6-26.1%	Risk continues to accumulate
A. Ross Naylor et al., 2014	<48 hours	17%	Very early high risk
A. Ross Naylor et al., 2014	<7 days	33%	One-third within first week
A. Ross Naylor et al., 2014	<14 days	58%	Majority within two weeks
Natalie Bourand et al., 2022	<7 days	Median 1 day	Events concentrated very early
S. Coutts et al., 2012	90 days	Median 1 day	Most events within first day
A. AbuRahma et al., 2015	1 week	4.0%	Early risk period
A. AbuRahma et al., 2015	30 days	12.6%	Cumulative monthly risk

The temporal distribution of recurrent stroke risk demonstrates that the majority of events occur in the immediate post-stroke period. In the systematic review by Tsantilas et al., pooled stroke risk reached 6.0-6.4% within 2-3 days, 10.9-19.5% at 7 days, and 17.6-26.1% at 14 days. Naylor et al. reported that among patients with 50-99% stenoses, 17% of recurrent strokes occurred within 48 hours, 33% within 7 days, and 58% within 14 days of the index event.

The POINT trial analysis found that early recurrences were concentrated in the first 7 days, with a median time to event of just 1 day. The CATCH study similarly reported a median time to recurrent stroke of 1 day. This temporal pattern suggests that for stenosis to be clinically useful as a predictor, rapid assessment is essential.

Synthesis

The evidence regarding carotid artery stenosis degree as an independent predictor of recurrent ischemic stroke reveals important heterogeneity that can be explained through several mechanisms.

Population and Context Distinctions: The predictive value of stenosis degree varies substantially based on clinical context. Studies examining symptomatic severe stenosis (≥70%) in recently symptomatic patients found stronger associations with recurrent stroke risk than studies examining moderate stenosis or mixed populations. The ICSS secondary analysis demonstrated that restenosis-mediated stroke risk differed between stenting and endarterectomy groups, suggesting that the pathophysiological mechanism matters. Specifically, restenosis after endarterectomy showed significant association with ipsilateral stroke (HR 5.75, P=0.003), while restenosis after stenting did not reach significance (HR 2.03, P=0.154).

Methodological Quality Hierarchy: Higher-quality multicenter RCTs and pooled analyses with larger sample sizes generally found significant associations between stenosis and recurrent stroke when examining severe stenosis in symptomatic populations. Smaller single-center studies showed more variable results. The POINT trial, with 4,881 subjects and rigorous methodology, found stenosis or occlusion was a significant independent predictor (OR 2.77, 95% CI 1.78-4.31) with 70% model accuracy.

Mechanistic Explanations: The divergent findings between stenosis degree and plaque characteristics as predictors can be explained by the underlying pathophysiology of atherosclerotic stroke. Stenosis reflects luminal narrowing but does not directly capture plaque vulnerability. Multiple studies demonstrate that intraplaque hemorrhage (hazard ratios ranging from 4.59 to 11.7) and other markers of plaque instability (macrophage inflammation, lipid-rich necrotic core, fibrous cap rupture) more directly reflect the mechanism of thromboembolism. Porambo et al. noted that IPH predicts stroke "independent of percent stenosis", suggesting these are complementary rather than competing predictors.

Cerebrovascular reserve may explain why stenosis alone is an inconsistent predictor—patients with similar stenosis degrees but different collateral capacity have markedly different stroke risks. This hemodynamic factor is not captured by stenosis measurement alone.

Timing Considerations: The temporal concentration of recurrent events within days of the index stroke has implications for the clinical utility of stenosis as a predictor. Stenosis degree may be most predictive in the hyperacute period, with its predictive value diminishing over time as plaque stabilization occurs.

Conclusions by Population and Context:

For patients with **recently symptomatic severe stenosis (≥70%)**, stenosis degree serves as a moderate independent predictor of recurrent stroke, with odds ratios typically ranging from 1.88 to 2.77 in multivariable models. However, its predictive accuracy (approximately 70%) suggests it should not be used in isolation.

For patients with **moderate stenosis (50-69%)**, the evidence is less consistent, with some studies finding significant associations and others not. The absolute risk difference is smaller, making clinical decision-making more complex.

For patients with **mild or nonstenotic carotid plaques (<50%)**, stenosis degree alone provides limited predictive value, but plaque characteristics such as intraplaque hemorrhage significantly increase recurrent stroke risk (up to 4.9/100 person-years with IPH present).

For **post-intervention patients**, restenosis ≥70% after endarterectomy is associated with increased late ipsilateral stroke risk (OR 4.77-9.02), while restenosis after stenting shows minimal association (OR 0.87).

Overall, radiological assessment of carotid stenosis degree can serve as an independent predictor of recurrent ischemic stroke, but its predictive value is enhanced when combined with plaque vulnerability markers (IPH, lipid-rich necrotic core, fibrous cap status), hemodynamic assessment (cerebrovascular reserve), and clinical context (timing from index event, symptomatic status). Stenosis measurement alone provides moderate predictive value that may be insufficient for individualized risk stratification, particularly in patients with moderate stenosis or those presenting beyond the hyperacute phase.

DISCUSSION

The findings of this systematic review reveal a complex and nuanced relationship between carotid artery stenosis degree and recurrent ischemic stroke risk, challenging the traditional stenosis-centric paradigm while acknowledging its continued relevance in specific clinical contexts. The heterogeneity observed across 59 included studies provides an opportunity to synthesize evidence into a cohesive framework that reconciles apparently contradictory findings.

Context-Dependent Predictive Value: The most salient finding is that stenosis degree does not function as a universal predictor but rather demonstrates context-dependent utility. In patients with recently symptomatic severe stenosis (≥70%), multiple high-quality studies demonstrated significant independent prediction, with odds ratios ranging from 1.88 to 2.77 after multivariable adjustment (J. Appleton et al., 2019; Natalie Bourand and Brorson, 2022). This consistency likely reflects that in such populations, the stenosis is directly implicated as the culprit lesion responsible for the index event and remains unstable in the early post-stroke period. The POINT trial analysis, with its large sample size (n=4,881) and rigorous methodology, provides particularly robust evidence that carotid stenosis or occlusion independently predicts early recurrence (OR 2.77, 95% CI 1.78-4.31) with approximately 70% model accuracy (Natalie Bourand and Brorson, 2022).

Conversely, in patients with moderate stenosis (50-69%), the evidence becomes inconsistent, with some studies finding significant associations and others not. The NAVIGATE-ESUS subgroup analysis exemplifies this uncertainty, reporting no significant difference in recurrence based on carotid stenosis status (HR 1.11, 95% CI 0.73-1.69) (G. Ntaios et al., 2019). This attenuation of predictive value likely reflects that in moderate stenosis, plaque characteristics and hemodynamic factors become relatively more important determinants of risk compared to the degree of narrowing itself. The study by Mingyong Liu and Zhou (2014) directly illustrates this principle, demonstrating that cerebrovascular reserve (CVR) <10% was significantly associated with recurrent stroke (P=0.003) while stenosis degree was not (P=0.691), with annual stroke risks of 7.7% versus 0% based on CVR status.

Plaque Vulnerability Superiority: A compelling finding across multiple studies is that plaque characteristics—particularly intraplaque hemorrhage—consistently outperform stenosis degree in predicting recurrent stroke. The meta-analysis by H. Maqsood et al. (2021) reported that IPH increased stroke risk with a hazard ratio of 11.7 (95% CI 4.7-22.8), substantially exceeding the HR of 3.8 for severe stenosis. Similarly, A. Podlasek and Simpson (2021) found IPH independently predicted stroke with HR 11.0 (95% CI 4.8-25.1), noting this effect was "more robust than any known clinical risk factor." The systematic review by Ajay Gupta et al. (2013) demonstrated that multiple MRI-identified plaque features—IPH (HR 4.59), lipid-rich necrotic core (HR 3.00), and thin/ruptured fibrous cap (HR 5.93)—all provided stroke risk information beyond luminal stenosis measurement.

The mechanistic basis for this superiority is biologically plausible. Stenosis degree reflects the cumulative burden of atherosclerotic disease but does not directly capture the dynamic processes that render plaques unstable and prone to thromboembolism (Michael E. Porambo and DeMarco, 2020). Intraplaque hemorrhage, in contrast, represents acute plaque destabilization, introducing thrombogenic material into the plaque and promoting rapid progression (Z. Teng, Brown, and Gillard, 2017). D. Kashiwazaki et al. (2025) emphasized that in patients with mild (<50%) stenosis—a population traditionally considered low-risk—IPH presence identified a subgroup with substantially elevated stroke risk (HR 1.92, 95% CI 1.26-4.28), challenging the notion that nonstenotic plaques are benign. Nishita Singh et al. (2020) similarly found that nonstenotic carotid plaques confer significant recurrent stroke risk when vulnerable features are present.

Hemodynamic Factors: Beyond plaque composition, hemodynamic compromise represents another dimension of risk not captured by stenosis measurement alone. M. Reinhard et al. (2014) demonstrated that impaired cerebrovascular reactivity to CO_2 independently predicted stroke in high-grade carotid disease (HR 3.69, 95% CI 2.01-6.77). This finding aligns with the concept that patients with identical stenosis degrees may have markedly different stroke risks depending on collateral circulation status and autoregulatory capacity. Mingyong Liu and Zhou (2014) provided direct comparative evidence that CVR assessment outperformed stenosis measurement, with the latter showing no significant association after accounting for hemodynamic status. These observations suggest that stenosis degree should be interpreted within the context of each patient's cerebrovascular reserve capacity.

Post-Intervention Considerations: The relationship between stenosis and recurrent stroke becomes particularly complex in post-intervention populations. Ravi Kumar et al. (2017), in a systematic review and meta-analysis, found that restenosis ≥70% after carotid endarterectomy was strongly associated with late ipsilateral stroke (OR 9.02, 95% CI 4.70-17.28), while restenosis after stenting showed minimal association (OR 0.87). The ICSS secondary analysis by L. Bonati et al. (2018) corroborated this differential effect, with restenosis after endarterectomy significantly predicting stroke (HR 5.75, P=0.003) but not after stenting (HR 2.03, P=0.154). This discrepancy likely reflects different pathophysiological mechanisms—restenosis after endarterectomy typically represents recurrent atherosclerosis with potential plaque vulnerability, while in-stent restenosis is often a more stable neointimal hyperplasia (K. Paraskevas and Gloviczki, 2019; P. Clavel et al., 2019).

Temporal Dynamics: The timing of recurrent events profoundly influences the clinical utility of stenosis as a predictor. P. Tsantilas et al. (2015) systematically documented that pooled stroke risk reaches 6.0-6.4% within 2-3 days, 10.9-19.5% at 7 days, and 17.6-26.1% at 14 days post-index event. A. Ross Naylor (2014) reported even more striking temporal concentration: among patients with 50-99% stenoses, 17% of recurrent strokes occurred within 48 hours, 33% within 7 days, and 58% within 14 days. The POINT and CATCH studies both found median time to recurrent stroke of just 1 day (Natalie Bourand and Brorson, 2022; S. Coutts et al., 2012). This temporal pattern has critical implications—stenosis assessment must occur rapidly to inform early risk stratification, and the predictive value of a given stenosis degree likely diminishes over time as plaques stabilize or patients undergo treatment (B. Kragsterman et al., 2018).

Methodological Considerations: The quality of evidence varied considerably across studies, with higher-quality multicenter RCTs and pooled analyses generally finding significant associations in appropriately selected populations. The POINT trial (n=4,881), ENOS trial (n=4,011), and ICSS (n=1,713) represent methodologically rigorous studies that support stenosis as an independent predictor in symptomatic severe disease (Natalie Bourand and Brorson, 2022; J. Appleton et al., 2019; L. Bonati et al., 2018). In contrast, smaller single-center studies showed more variable results, potentially reflecting selection bias, insufficient power, or population differences. The inclusion of 18 systematic reviews and meta-analyses in this synthesis provides additional confidence in the overall conclusions while highlighting areas of persistent uncertainty.

Clinical Implications: These findings have several practical implications. First, stenosis degree should not be used in isolation for risk stratification—its moderate predictive accuracy (approximately 70%) is insufficient for individualized decision-making. Second, patients with recently symptomatic severe stenosis represent the population in which stenosis measurement has greatest utility, supporting current guidelines recommending prompt revascularization in appropriate candidates (U. Fisch et al., 2015; O. Naggara et al., 2011). Third, in patients with moderate or mild stenosis, advanced plaque imaging to identify IPH and other vulnerability markers should be considered to refine risk assessment (Ajay Gupta et al., 2013; Hossein Hemmati et al., 2025). Fourth, hemodynamic assessment may identify a high-risk subset among severe stenosis patients who might benefit from intensified medical therapy or expedited revascularization (M. Reinhard et al., 2014).

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review demonstrates that radiological assessment of carotid artery stenosis degree can serve as an independent predictor of recurrent ischemic stroke in patients with prior stroke, but its predictive value is context-dependent and moderate in accuracy. The strongest evidence supports its utility in patients with recently symptomatic severe (≥70%) stenosis, where odds ratios of 1.88-2.77 have been consistently reported after multivariable adjustment in large, high-quality trials. However, in patients with moderate stenosis (50-69%) or when considered alongside plaque vulnerability markers, stenosis degree alone provides insufficient predictive information.

Plaque characteristics—particularly intraplaque hemorrhage (HR 4.59-11.7), lipid-rich necrotic core, and thin/ruptured fibrous cap—consistently outperform stenosis degree as predictors of recurrent stroke, reflecting the underlying pathophysiology where plaque instability rather than luminal narrowing determines thromboembolic risk. Cerebrovascular reserve similarly demonstrates superior predictive value compared to stenosis measurement alone. The temporal concentration of recurrent events within the first 7-14 days post-index stroke (58% within two weeks) necessitates rapid risk stratification and underscores the limited window for intervention.

Recommendations:

1. **Clinical Practice:** Risk stratification for recurrent stroke should integrate multiple dimensions including stenosis degree (particularly in symptomatic severe disease), plaque vulnerability markers (especially intraplaque hemorrhage), hemodynamic status (cerebrovascular reserve), and timing from index event. Stenosis measurement alone is insufficient for individualized decision-making.

2. **Imaging Protocols:** In patients with recent stroke or TIA, particularly those with moderate or mild stenosis, consideration should be given to advanced plaque imaging (high-resolution MRI with IPH detection, CT angiography with plaque characterization) to identify high-risk features not captured by stenosis measurement alone.

3. **Research Priorities:** Future studies should prospectively evaluate the incremental predictive value of combining stenosis degree with plaque characteristics and hemodynamic measures using formal risk reclassification metrics. Randomized trials comparing management strategies stratified by multidimensional risk profiles (rather than stenosis alone) are needed.

4. **Guideline Development:** Clinical practice guidelines should be updated to reflect that stenosis degree represents one component of a multifactorial risk assessment, with explicit recognition of populations in which its predictive value is limited and where alternative markers should be prioritized.

5. **Timely Assessment:** Given the concentration of early recurrent events, systems of care should ensure rapid access to comprehensive carotid imaging (within days, not weeks) for patients presenting with stroke or TIA, enabling timely risk stratification and intervention when indicated.

In conclusion, while the degree of carotid artery stenosis retains a role in predicting recurrent ischemic stroke, the era of stenosis-centric risk assessment has passed. A paradigm incorporating plaque vulnerability, hemodynamic compromise, and temporal dynamics offers the promise of more accurate individualized risk prediction and improved secondary stroke prevention.

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