ANGIOLOGIA E CIRURGIA VASCULAR
PUBLICAÇÃO OFICIAL SPACV

REVIEW ARTICLE

State of the art on restenosis after carotid artery stenting: incidence, risk factors, mechanisms, diagnosis, and treatment options

Luís D. Fernandes[a,b], **Andreia B. Coelho**[a,b], **João P. Peixoto**[a,b], **Marta M. Machado**[a], **Francisco Basílio**[a], **Patrícia Carvalho**[a], **Diogo Silveira**[a,b], **Alexandra Canedo**[a,b]

[a] Serviço de Angiologia e Cirurgia Vascular, Centro Hospitalar de Vila Nova de Gaia/Espinho. [b] Faculdade de Medicina da Universidade do Porto.

Submitted: May 15, 2023; **Reviewed:** October 15, 2023; **Accepted:** October 20, 2023

ABSTRACT

INTRODUCTION: Carotid revascularization is a well-established technique for preventing stroke in patients with significant symptomatic or asymptomatic carotid artery stenosis. Carotid artery stenting (CAS) has become an alternative to carotid endarterectomy (CEA), especially in high-risk surgical patients. However, restenosis after CAS is a potentially severe complication that can impact the medium and long-term success of the procedure and increase the risk of cerebrovascular events.

METHODS: Relevant articles on restenosis after carotid stenting were searched in the PubMed database. The selected studies were evaluated for quality and relevance, and the information was summarized to provide an overview of the causes, risk factors, diagnosis, and treatment options for restenosis after CAS due to atherosclerotic carotid artery disease.

RESULTS: Restenosis after CAS can occur due to various factors, including thrombosis, intimal hyperplasia, and stent migration. Several risk factors have been identified, such as age, diabetes, hypertension, dyslipidemia, and smoking. Restenosis can be diagnosed with carotid Doppler ultrasound, contrast-enhanced computed tomography, or arteriography. Treatment options include angioplasty with or without rescue stent placement, CEA associated with stent explantation, or medical treatment.

CONCLUSION: Restenosis after carotid stenting is a potentially serious complication. It is especially important to identify the risk factors for restenosis and maintain close follow-up with patients after the procedure. The treatment of restenosis should be individualized. Further studies are needed to define the best strategies for preventing and treating restenosis after carotid stenting.

Keywords: Carotid Stenosis; Carotid stenting; restenosis; physiopathology; diagnostic imaging; surgical outcomes.

INTRODUCTION

Carotid stenosis is a common cause of stroke, and the primary purpose of intervention is to reduce the risk of primary or recurrent cerebrovascular events. Carotid endarterectomy (CEA) is the first-line treatment for carotid stenosis. However, carotid stenting (CAS) has surfaced as a minimally invasive alternative for patients at high surgical risk, although this is a heterogeneous and controversial concept. CAS allows for lumen expansion, cerebral flow improvement, and exclusion of potentially embolic plaque. Although CAS has demonstrated safety and efficacy, restenosis is a possible complication that may lead to recurrent stroke or transient ischemic attacks.[1,2] This article aims to review the

Corresponding Author:
Luís Fernandes | luisdiogoffernandes@gmail.com
Serviço de Angiologia e Cirurgia Vascular do Centro Hospitalar de Vila Nova de Gaia/Espinho, Rua Conceição Fernandes, s/n, 4434-502 Vila Nova de Gaia

Angiol Vasc Surg 2024;20(1):28-31
DOI: https://doi.org/10.48750/ac571

current knowledge on CAS, including incidence, risk factors, mechanisms, diagnosis, and treatment options.

METHODS

Relevant articles on restenosis after carotid stenting were searched in the PubMed database using the keywords "carotid stenosis," "carotid stenting," and "in-stent restenosis." Only original articles published as full text in English were considered, and no time restrictions were applied. After a first screening of title and abstracts, selected studies were evaluated for quality and relevance, and the information was summarized to provide an overview of the causes, risk factors, diagnosis, and treatment options for restenosis after CAS due to atherosclerotic carotid artery disease.

RESULTS

Incidence:

The incidence of restenosis after CAS (in-stent restenosis, or ISR) varies significantly among studies, ranging from 0% to 36%.[3-7] However, most studies report an incidence similar to that of CEA, around 5-10%.[8-14] The most relevant studies reporting follow-up, including the rate of ISR after CAS, are summarized in Table 1. The variability in the reported incidence of restenosis after CAS may be due to patient selection, lesion characteristics, technical evolution of the procedure, and duration of follow-up. However, it may also be due to heterogeneity in the definition of restenosis, which is defined as equal or greater than 70% in CREST, SPACE, and ICSS and equal or greater than 50% in EVA-3S.[15]

Table 1. Rates of restenosis after carotid stenting, as reported in the main randomized trials.

Study	Restenosis rate
CREST	6,0% at two years
EVA-3S	3,3% at three years
SPACE	10,7% at two years
ICSS	10,6% at 5 years
CAVATAS	14% at 1 year
CKD	2.25

Risk factors for carotid stent restenosis:

IRS is a complex and multifactorial process; several risk factors have been identified.[2] These risk factors may be classified as patient-related, lesion-related, intra-procedural, and post-procedural factors.

Patient-related factors: Age is a well-recognized risk factor for ISR, with older patients presenting with a higher risk. Female sex has also been associated with an increase in the risk of restenosis after CAS, possibly due to the smaller vessel diameter. Other patient-related risk factors include smoking, diabetes mellitus, hypertension, dyslipidemia, and chronic renal disease.[7,16] It is generally accepted that these factors contribute to ISR by promoting intimal hyperplasia and inflammation, as discussed later.

Lesion-related factors: The degree and location of the stenosis are important factors that affect the risk of ISR after CAS. Longer lesions with a higher degree of stenosis or located at the carotid bifurcation are more likely to develop restenosis.[2] The presence of heavy lesion calcification has also been associated with a greater risk of restenosis after CAS. Calcification may prevent a complete lesion expansion and, therefore, promote intimal hyperplasia.

Procedure-related factors: The type of stent may affect the risk of restenosis. Stents without drug-elution may be more likely to develop restenosis than those with drug-elution due to the reduction of intimal hyperplasia. However, there are no drug-eluting stents designed explicitly for carotid intervention.[17] Currently, there are different dedicated carotid stents with various stent strut configurations, including open cells (more flexible and suitable for tortuous vessels, but with less plaque coverage) and closed cells (less flexible but with a greater capacity to jail the plaque contents). Hybrid designs are also available, combining the flexibility of open cells and the prevention of plaque prolapse of closed cells. Nevertheless, according to the most recent recommendations of the European Society for Vascular and Endovascular Surgery (ESVS), the choice of stent should be individualized.[7] Other procedural-related factors include the dimensions and location of the stent (including the carotid bifurcation or restricted to the internal carotid artery), the degree of stent expansion, and the degree of post-dilatation.

Post-procedural factors: The management of medical therapy after CAS may also affect the risk of restenosis. While antiplatelet therapy is generally recommended to prevent stent thrombosis, medication adherence may be a concern. Also, despite the overall agreement that dual antiplatelet therapy is recommended after CAS, the preferred regimen and duration still need to be determined. The 2023 ESVS guidelines recommend a minimum of four weeks, after which single platelet therapy should be considered, preferably with clopidogrel (level of evidence Ia).[7] Additionally, smoking and poorly controlled hypertension, diabetes mellitus, and dyslipidemia all contribute to restenosis.[7,11,18,19]

Mechanism:

ISR is a complex process with multiple mechanisms, including neointimal hyperplasia, technical flaws such as stent malposition, and the progression of atherosclerotic disease. Neointimal hyperplasia is the most common mechanism, and the proliferation of smooth muscle cells and extra-cellular matrix deposition causes it. Stent malposition occurs when not adequately implanted, resulting in a space between the stent and the wall with resulting turbulence.[20] This may result in platelet activation, thrombus formation, and consequent worsening of the stenosis in the treated segment. Progression of atherosclerotic disease refers to the development or progression of plaques in the previously treated or adjacent segments, resulting in lumen reduction.[21]

In addition, inflammation and thrombosis are also relevant for developing ISR. Inflammatory cells, such as macrophages or T lymphocytes, may be activated by the stent-induced intimal lesion and by pro-inflammatory cytokines, resulting in the production of growth factors and smooth muscle cell proliferation.[21]

It is important to note that the mechanisms behind ISR are inter-connected and frequently occur simultaneously. As such, finding a primary mechanism is very difficult. Consequently, a global preventive and therapeutic approach to restenosis is necessary. This may involve a combination of mechanical and pharmacological interventions aiming at different mechanisms simultaneously.

Diagnosis:

Early diagnosis of ISR is relevant because it may allow timely intervention to prevent complications. Duplex ultrasonography (DUS) is the preferred noninvasive method for follow-up after CAS, with a relative sensibility of 70-98% and specificity of 83-97%.[22,23] However, this method may have limitations in marked calcification or tortuosity or when the stent is very distal.

Interpretation of flow velocities is more difficult after CAS than after CEA or native arteries, as the stent accelerates flow, even when it is completely expanded and adjusted to the wall.[24] As such, higher peak systolic velocities (PSV) have been proposed, including PSV>220cm/s and a ratio of PSV in the internal carotid artery / PSV in the common carotid artery greater than 2.5 for the diagnosis of <50% restenosis, and a PSV >300cm/s, end-diastolic velocity >90cm/s and a ratio >3.8 to diagnose restenosis greater than 70%.[7,25,26]

Indications for treatment:

Asymptomatic patients: According to Kumar et al., the ipsilateral stroke rate at five years in patients after CAS was 0.8% with restenosis <70% vs 2% without significant restenosis, which was a non-significant difference.[27] Therefore, the indications for intervention due to asymptomatic CAS restenosis are controversial, and there are no randomized trials to guide practice. Although it is generally considered a benign entity, several studies identified that approximately two-thirds of patients treated for ISR were asymptomatic.[7,28] Others suggest that the benefit of reintervention in patients with asymptomatic ISR is low. The rationale for this interpretation is that the risk of (recurrent) stroke in patients with ISR under best medical treatment is low (0.8% at four years) and that 97% of late ipsilateral strokes occurred in patients with no significant restenosis.[27] Among the studies that report reintervention in asymptomatic patients, the majority report thresholds of 70%, and others even higher (80-90%).[29]

Symptomatic patients:

There are no randomized trials on this topic, and practice is based on evidence from retrospective studies, case reports, and expert opinion. The intervention criteria are generally similar to those of primary symptomatic carotid disease. If a patient develops an acute cerebrovascular event and a 50-99% restenosis is present, intervention should be considered in the first two weeks after symptom onset.[7,29] Recent evidence also tells us that symptomatic patients with ipsilateral restenosis <50% should be treated conservatively unless there is symptom recurrence under the best medical therapy.[7] Some, however, propose reintervention despite the degree of stenosis.[29]

Treatment options:

Despite the existence of some clear indications for reintervention, no consensus exists over the optimal management of ISR after CAS. Evidence is scarce and limited by heterogeneity and potential bias. Subsequently, no strong recommendation can be made. Options include optimized medical management with or without endovascular or open carotid reintervention. The best strategy should be individualized according to patient characteristics, including comorbiddities, presentation, and anatomy.

Optimized medical management should always be offered to every patient with carotid stenosis, even before the primary operation. Single antiplatelet therapy with aspirin or clopidogrel is typically continued long-term after CAS to prevent thromboembolic events and reduce cardiovascular risk. Also, moderate to high-intensity statin has been shown to reduce ISR.[30]

Endovascular interventions include simple balloon angioplasty and stent-in-stent implants (bare or covered). However, the efficacy of endovascular interventions for ISR is controversial, with some studies reporting high recurrence rates and others good long-term outcomes.[13]Novel therapeutic options include drug-coated stents or balloons and bioabsorbable vascular devices.[20,31-33] These have shown promising results in preliminary studies, but their efficacy in the long term has yet to be discovered. The mechanism of restenosis should also be considered - in the first three years after stenting, miointimal hyperplasia with smooth muscle cell proliferation is the leading cause of restenosis. Surgical revascularization, such as CEA or carotid bypass, may be considered when endovascular interventions have failed. CEA with stent explant is the most commonly used technique, but it is technically more complex than primary CEA, with morbidity and mortality ranging from 2-5%.[8]

CONCLUSION

In-stent restenosis after carotid stenting is a complex process that may be influenced by several patient, lesion, and procedural factors. A better comprehension of these risk factors is important to identify patients at higher risk of stenosis and optimize their follow-up and management. Future studies are needed to identify novel prevention strategies and improve patient selection and outcomes of reinterventions. This may include novel stent designs and drug-eluting technologies.

Acknowledgments: None

Conflicts of interest: None

Funding: None

REFERENCES

1. Arhuidese IJ, Nejim B, Chavali S, Locham S, Obeid T, et al. Endarterectomy versus stenting in patients with prior ipsilateral carotid artery stenting. J Vasc Surg. 2017;65:1418-28.

2. Wangqin R, Krafft PR, Piper K, Kumar J, Xu K, et al. Management of De Novo Carotid Stenosis and Postintervention Restenosis-Carotid Endarterectomy Versus Carotid Artery Stenting-a Review of Literature. Transl Stroke Res. 2019;10:460-74.

3. Fluri F, Engelter ST, Wasner M, Stierli P, Merlo A, et al. The probability of restenosis, contralateral disease progression, and late neurologic events following carotid endarterectomy: a long-term follow-up study. Cerebrovasc Dis. 2008;26:654-8.

4. Carballo RE, Towne JB, Seabrook GR, Freischlag JA, Cambria RA. An outcome analysis of carotid endarterectomy: the incidence and natural history of recurrent stenosis. J Vasc Surg. 1996;23:749-53

5. Gagne PJ, Riles TS, Jacobowitz GR, Lamparello PJ, Giangola G, et al. Long-term follow-up of patients undergoing reoperation for recurrent carotid artery disease. J Vasc Surg. 1993;18:991-8

6. Norrving B, Nilsson B, Olsson JE. Progression of carotid disease after endarterectomy: a Doppler ultrasound study. Ann Neurol. 1982;12:548-52.

7. Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, et al. Editor's Choice - European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on the Management of Atherosclerotic Carotid and Vertebral Artery Disease. Eur J Vasc Endovasc Surg. 2023;65:7-111.

8. Lal BK, Beach KW, Roubin GS, Lutsep HL, Moore WS, et al. Restenosis after carotid artery stenting and endarterectomy: a secondary analysis of CREST, a randomized controlled trial. Lancet Neurol. 2012;11:755-63.

9. de Borst GJ, Ackerstaff RG, de Vries JP, vd Pavoordt ED, Vos JA, et al. Carotid angioplasty and stenting for postendarterectomy stenosis: long-term follow-up. J Vasc Surg. 2007;45:118-23.

10. Clavel P, Hebert S, Saleme S, Mounayer C, Rouchaud A, et al. Cumulative incidence of restenosis in the endovascular treatment of extracranial carotid artery stenosis: a meta-analysis. J Neurointerv Surg. 2019;11:916-23.

11. Bonati LH, Gregson J, Dobson J, McCabe DJH, Nederkoorn PJ, et al. Restenosis and risk of stroke after stenting or endarterectomy for symptomatic carotid stenosis in the International Carotid Stenting Study (ICSS): secondary analysis of a randomized trial. Lancet Neurol. 2018;17:587-96.

12. Arquizan C, Trinquart L, Touboul PJ, Long A, Feasson S, et al. Restenosis is more frequent after carotid stenting than after endarterectomy: the EVA-3S study. Stroke. 2011;42:1015-20.

13. Brott TG, Hobson RW, 2nd, Howard G, Roubin GS, Clark WM, et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. N Engl J Med. 2010;363:11-23.

14. Bonati LH, Ederle J, McCabe DJ, Dobson J, Featherstone RL, et al. Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. Lancet Neurol. 2009;8:908-17.

15. Sorkin GC, Dumont TM, Eller JL, Mokin M, Hopkins LN, et al. In-stent restenosis after carotid stenting: treatment using an off-label cardiac scoring balloon. J Vasc Interv Neurol. 2014;7:29-34.

16. AbuRahma AF, Santini AG, AbuRahma ZT, Dargy NX, Reading L, et al. Rates of progression of carotid in-stent stenosis and clinical outcomes. J Vasc Surg. 2022;76:1596-602.

17. Tekieli L, Pieniazek P, Musialek P, Kablak-Ziembicka A, Przewlocki T, et al. Zotarolimus-eluting stent for the treatment of recurrent, severe carotid artery in-stent stenosis in the TARGET-CAS population. J Endovasc Ther. 2012;19:316-24.

18. Martelli E, Patacconi D, G DEV, Ippoliti A. Conventional carotid endarterectomy versus stenting: comparison of restenosis rates in arteries with identical predisposing factors. J Cardiovasc Surg (Torino). 2016;57:503-9.

19. Texakalidis P, Tzoumas A, Giannopoulos S, Jonnalagadda AK, Jabbour P, et al. Risk Factors for Restenosis After Carotid Revascularization: A Meta-Analysis of Hazard Ratios. World Neurosurg. 2019;125:414-24.

20. Donas KP, Eisenack M, Torsello G. Balloon angioplasty for in-stent stenosis after carotid artery stenting is associated with an increase in repeat interventions. J Endovasc Ther. 2011;18:720-5.

21. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart. 2014;100:153-9.

22. Liu Z, Pan Y, Zhang Q, Wang X. Predictive Value of Quantitative Duplex Ultrasound Analysis for In-stent Carotid Artery Restenosis. Altern Ther Health Med. 2023;29:52-7.

23. Bitsko LJ, Ryer EJ, Penn EP, Salzler GG, Major M, et al. Defining Duplex Ultrasound Criteria for In-Stent Restenosis of the Carotid Artery Using Computed Tomographic Angiography. Cureus. 2022;14:e26700.

24. de Borst GJ, Meijer R, Lo RH, Vosmeer HW, Ackerstaff RG, et al. Effect of carotid angioplasty and stenting on duplex velocity measurements in a porcine model. J Endovasc Ther. 2008;15:672-9.

25. Stanziale SF, Wholey MH, Boules TN, Selzer F, Makaroun MS. Determining in-stent stenosis of carotid arteries by duplex ultrasound criteria. J Endovasc Ther. 2005;12:346-53.

26. Lal BK, Hobson RW, 2nd, Tofighi B, Kapadia I, Cuadra S, et al. Duplex ultrasound velocity criteria for the stented carotid artery. J Vasc Surg. 2008;47:63-73.

27. Kumar R, Batchelder A, Saratzis A, AbuRahma AF, Ringleb P, et al. Restenosis after Carotid Interventions and Its Relationship with Recurrent Ipsilateral Stroke: A Systematic Review and Meta-analysis. Eur J Vasc Endovasc Surg. 2017;53:766-75.

28. Fokkema M, Vrijenhoek JE, Den Ruijter HM, Groenwold RH, Schermerhorn ML, et al. Stenting versus endarterectomy for restenosis following prior ipsilateral carotid endarterectomy: an individual patient data meta-analysis. Ann Surg. 2015;261:598-604.

29. Bekelis K, Moses Z, Missios S, Desai A, Labropoulos N. Indications for treatment of recurrent carotid stenosis. Br J Surg. 2013;100:440-7.

30. Amarenco P, Labreuche J, Lavallée P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. Stroke. 2004;35:2902-9.

31. Reichmann BL, van Laanen JH, de Vries JP, Hendriks JM, Verhagen HJ, et al. Carotid endarterectomy for treatment of in-stent restenosis after carotid angioplasty and stenting. J Vasc Surg. 2011;54:87-92.

32. Gonzalez A, Drummond M, McCord S, Garrett HE, Jr. Carotid endarterectomy for treatment of in-stent restenosis. J Vasc Surg. 2011;54:1167-9.

33. Heck D. Results of cutting balloon angioplasty for carotid artery in-stent restenosis in six patients: description of the technique, long-term outcomes, and review of the literature. J Neurointerv Surg. 2009;1:48-50.