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Cognitive function after carotid endarterectomy in asymptomatic patients

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Abstract

Asymptomatic carotid stenosis has been shown to be associated with progressive neurocognitive decline, but the effects of carotid endarterectomy (CEA) on this are not well defined. Due to the wide heterogeneity of studies and lack of standardization in cognitive function tests and study design, there is mounting scientific evidence to support the notion that CEA is effective in reversing or slowing neurocognitive decline; however, definitive conclusions are difficult to make. Further, while the association between ACS and cognitive decline has been well document, a direct etiological role has not been established. More research is required to elucidate the relationship between asymptomatic carotid stenosis and the benefit of carotid endarterectomy and its potential protective effects regarding cognitive decline. This article aims to review current evidence in preoperative and postoperative cognitive function in asymptomatic patients with carotid stenosis undergoing CEA.

Keywords

Endarterectomy; carotid; Cognition; Carotid stenosis

There is a growing body of evidence suggesting that asymptomatic carotid stenosis (ACS) may be associated with progressive neurocognitive decline, but the effects of carotid endarterectomy (CEA) on preventing or improving cognitive decline are poorly defined.[1] Cognitive changes from ACS are thought to be due to pathophysiological effects such as silent microembolization or chronic hypoperfusion due to carotid stenosis, though there is some debate regarding which is the dominant factor. Silent cortical infarcts *via* micro embolization have been shown to occur in 17–33% of patients

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Authors' contributions

Edward Oh, Natalie Sridharan and Efthymios Avgerinos have given substantial contributions to study conception and design, data acquisition, analysis and interpretation, and manuscript critical revision, Edward Oh to manuscript writing, all authors contributed equally to the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

with ACS and this can increase the likelihood of dementia.[2, 3] Despite the theoretical decrease in microembolization events and potential neurocognitive improvement after carotid endarterectomy, the trajectory of neurocognitive function after CEA is not firmly established. MRIs performed after CEA have demonstrated that silent infarcts continue to occur after surgery, which have been correlated with post-carotid surgery cognitive decline.[4–6] The overall effect of surgical intervention on cognition is confounded by several other factors, including intra- and perioperative hypoperfusion, lingering effects of general anesthesia and postoperative hyperperfusion.[7, 8] This review will summarize some of the available data and controversies on neurocognitive outcomes after CEA in patients with ACS and the potential role carotid revascularization may play in improving neurological outcomes.

Existing controversy in CEA's effect on cognitive decline

The debate over optimal medical treatment (OMT) alone *vs.* OMT combined with CEA for ACS has not been set tled. Advances in pharmacologic management of ACS and newer trials are providing additional insights towards a continuous improvement of CEA outcomes regarding the endpoints of stroke, myocardial infarction (MI), and death.[9–13] Still, with several trials being unable to demonstrate a clear-cut meaningful difference in stroke and death rates between OMT and surgery, other factors or patient-centered outcomes such as cognitive decline have become more relevant in determining treatment strategies. There is evidence to support a correlation between ACS and cognitive impairment, yet the complex interplay of the pathophysiological process of microembolization, silent cortical infarction and cognitive impairment are still not well defined.[14] The reported benefits of carotid revascularization in asymptomatic patients regarding prevention of cognitive decline are mixed in the existing literature. Several systematic reviews have been published in recent years which compared pre and postoperative cognitive function after carotid endarterectomy (CEA) in patients with asymptomatic carotid stenosis (ACS).[14–16] The studies incorporated in these systematic reviews have significant heterogeneity, variation in cognitive tests administered, timing of the assessments, control populations used, number of patients and the degree of severity of the asymptomatic carotid. While CEA may serve as a potential preventative procedure in preventing or slowing cognitive impairment, further research is required before it should become part of the ACS management decision-making model. However, there is acknowledgement from European (ESVS) and US (SVS) societal guidelines that this linkage likely exists and may factor into medical or surgical decision making in the future, yet evidence is not robust yet to justify a recommendation for CEA as a means to improve cognitive function.[17–19] Until new evidence clearly identifies at-risk ACS subgroups for developing cognitive impairment, which is then improved by carotid intervention or demonstrates that silent embolization from ACS causes cognitive impairment, indications for carotid intervention in ACS patients (to prevent or reverse cognitive decline) are lacking. It is important to recognize that the confluence of factors contributing to poorer vascular health may also affect cognition, and many other factors may also contribute to which patients experience procedure-related cognitive changes.

Literature reviews

Sridharan *et al.* conducted a systematic review to compare pre- and postoperative neurocognitive function in asymptomatic carotid stenosis patients.[15] The 13 included studies comprised a mix of retrospective, prospective and clinical trials. Smaller series and studies that included carotid stenting or symptomatic patients were excluded, which was a common theme amongst the systematic reviews. Some of the neurocognitive assessment tools used were the Mini Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA) Score, although there were some other tools to a lesser extent. Six studies showed cognitive decline or no change in cognitive performance enrolled a total of 230 patients and follow-up ranged from 24 hours to 3 years after CEA.[20–25] Seven studies enrolled 272 patients with follow-up ranging between 1 and 12 months, which showed statistically significant cognitive function improvement after CEA. Two of these studies were small (N.=28 and N.=25) and utilized other neurophysiological improvement tests like the Stroop color and word tests[25,26], but showed significant neurocognitive improvement after carotid endarterectomy at 6 months. Of note, Paraskevas notes in a follow-up editorial that there were an additional eight studies that were potentially missed,[26] but these studies were intentionally excluded from the analysis as they included symptomatic patients and carotid artery stenting.[15] Sridharan's review also included studies that looked at imaging findings in patients after carotid endarterectomy. Porcu *et al.*[27] demonstrated that CEA improved MMSE scores and MRI-based hemispheric connectivity 1 week before and 3–6 months after surgery. Another study by Dempsey *et al.*[28] showed that patients with ACS underwent CEA and had improved visual and cognitive memory tests and unchanged white matter hyperintensities on MRI after 1-year follow-up. Kojima *et al.*[29] demonstrated significant improvement in brain perfusion and cognitive function in 21% of their cohort of asymptomatic patients, where single-photon emission CTs were performed at 1-month pre- and postintervention. Finally, the authors present data from a randomized trial from the University of Pittsburgh (PA, USA) neurocognitive function in both asymptomatic and symptomatic carotid stenosis patients.[30] They ultimately found that one month after CEA, there was statistically significant improvement in MOCA scores, and tests of executive function and processing speed. Additionally, there was no meaningful difference in cognitive improvement between symptomatic and asymptomatic patients. Another systematic review published in 2021 by Paraskevas *et al.*[16] comprised of 35 studies, comparing all severities of ACS, concluded that 33/35 (94%) of the studies reported an association between ACS and cognitive decline with only one of the cross-sectional studies included reporting no association.[31] Of the six longitudinal studies, five analyzed MMSE changes at 1–3 years while the Osaka Follow-Up Study for Carotid Atherosclerosis followed patients out to 8 years, which showed that 57/600 patients (9.5%) developed cognitive decline by 8 years. Compared to controls, patients with > 50% ACS were not more likely to develop dementia (OR=1.4, 95% CI: 0.6–3.2). In contrast, patients with prior lacunar infarcts were more likely to develop dementia (OR=2.6, 95% CI: 1.2–6.1).[32] The Annals of Internal Medicine Cardiovascular Health Study reported that patients with severe (>75%) ACS were more likely to develop cognitive dysfunction compared to controls (OR=2.6, 95% CI: 1.1–6.3).[33] Studies analyzing cerebral vascular reserve (CVR) were also looked at in this review; the primary finding was that patients with impaired CVR had significant cognitive impairment

vs. controls, but those with baseline CVRs despite ACS did not have significant cognitive impairment.[34, 35] A subsequent systematic review by Ancetti *et al.* in 2021 assessed the role of CEA and carotid artery stenting (CAS) on postoperative neurocognition in asymptomatic carotid stenosis patients.[14] Thirty-one studies were included in the final review. 18/31 studies reported CEA outcomes, which stated that in early postoperative outcomes, there was no significant change (1086/2059=53%) or even slightly worse cognitive function in the early postoperative period (28/2059=1%).[25] This trend held true between small, medium and large-sized studies, in studies with controls *vs.* those that did not, and even in comparing outcomes after CEA *vs.* CAS. Regarding cognitive function in the late postoperative period after endarterectomy, there were 12 cohorts (N.=1264) and one reported a significant improvement in cognitive function (24/1554=1.5%), while eleven cohorts reported no significant change (1073/1554=69%) with some showing improvement in one or two specific domains (386/2059=24.8%). Only one cohort reported significant worsening or decline in cognitive function in the late postoperative period (28/2059=1.8%). Finally, a recently published prospective study by Zhou *et al.* looked at 170 patients with severe asymptomatic carotid stenosis who underwent CEA. Patients received neurocognitive testing at 1, 6 and 12 months postoperative and the primary outcome measure was measured *via* the Rey Auditory Verbal Learning Test (RAVLT). The authors observed a significant improvement in RAVLT memory scores at 1 and 6 months and multiple executive functions up to 12 months as well. They concluded carotid intervention improved memory and executive function in patients with severe ACS and could provide a cognitive benefit in select patients.[36]

CEA *versus* CAS effect in cognitive decline

Between CEA and CAS, Capoccia *et al.* reported a significant decline in cognitive function on postoperative day 1 with stenting but not CEA.[25] Otherwise, most of the other studies observed no statistically significant difference between CEA and CAS, especially after six months.[37] In analyzing late cognitive function, depending on the study, different domains of neurocognitive function were improved with CEA improving working memory and CAS improving executive and motor function, psychomotor speed, and visuospatial and constructional abilities.[21, 38] Several studies within this review reported that postoperative increase in cerebral blood flow correlated with improved cognitive function. Younger ACS patients appeared to have significantly greater improvements in postoperative cognitive dysfunction. Further, patients on statin medical therapy prior to carotid intervention had less postoperative cognitive dysfunction, possibly suggesting the physiological role of plaque stabilization, compared to statin native patients (11% *vs.* 20%; OR=0.51, 95% CI: 0.27–0.96, P=0.04).[39]

Discussion

There is growing interest in other potential impacts of carotid revascularization, such as the potential for preventing or reversing cognitive decline as even mild decline can negatively affect a patient's quality of life (QoL).[40] Given the established correlation between ACS and cognitive decline. It is reasonable to hypothesize that CEA could potentially improve a patient's cognitive function and their QoL beyond future stroke prevention

by improving brain perfusion and reducing microembolization.[41] The true prevalence of cognitive impairment in ACS patients and ultimately, how to integrate this factor into patient-centered outcome and decision-making regarding for CEA is however unclear.[42, 43] The results of all the systematic reviews overall do not show convincing evidence for CEA in asymptomatic patients in preventing or reducing cognitive decline, but the studies that compromise the systematic reviews are widely heterogeneous in their design, time period measured, and study populations. This demonstrates a need for a standardized cognitive assessment tool that has been validated and can be retroactively used to compare existing studies with newer prospective ones. A lack of a standardized assessment timetable is also noticeable; several authors suggest testing 1 month after surgery and at 6 months and 1 year, if possible.[9] There was no evidence that silent cortical infarcts due to microembolization was responsible for cognitive impairment; further, while lacunar infarcts or white matter dysfunction are known to cause cognitive impairment/dementia, it is difficult to suggest that ACS plays a direct role at this time. There was also little evidence to support the concern that CEA (or CAS) could lead to significant cognitive decline, early or late, due to intraoperative microembolization, hypoperfusion or postoperative hyperperfusion. Ultimately, data interpretation was confounded by the vast heterogeneity of studies included, especially regarding timeline of follow up with neurocognitive tests and with variation amongst the tests and tools themselves across all the reviews. Despite similar methodology of the systematic reviews (such as utilizing the Newcastle-Ottawa Scale to vet studies), different conclusions were reached based on the inclusion/exclusion criteria and variety of studies. Over 90% of studies included did report an association between ACS and cognitive impairment, but this does not imply a direct etiological role in the pathophysiology of cognitive dysfunction, whether it is due to chronic hypoperfusion, microembolization, or another phenomenon. Despite the limitations mentioned above, some individual studies do purport a measurable benefit with different imaging modalities in conjunction with validated neurocognitive tests. Additionally, upcoming CREST-H results where the primary outcome is change in cognition and nonrandomized subgroup analyses of the data could provide some insight as to whether or not cognitive impairment will be a useful clinical marker to identify patients for carotid revascularization as well.[44]

Conclusions

Overall, carotid revascularization and optimal medical therapy provide an intriguing option in preventing or reversing cognitive decline. Currently, the role of surgical carotid revascularization is still controversial in asymptomatic carotid stenosis. Much of the data supporting endarterectomy is historical and the 2017 European Society for Vascular Surgery (ESVS) Guidelines support more reserved intervention on a smaller subset of patients. Several systematic reviews suggest that surgical carotid revascularization with CEA in ACS patients is rarely associated with significant cognitive improvement, but there was also no association with postoperative cognitive decline as well (early or late). However, the potential protective effects of CEA in certain specific populations of asymptomatic carotid stenosis patients could tip the scale in favor of surgical intervention in a particular subset of patients as well. Further randomized studies are needed to assess the effect of CEA on cognitive function in patients with asymptomatic carotid stenosis.

References

1. Rudolph C, Eldrup N. Asymptomatic carotid stenosis and concomitant silent brain infarctions. Vascular 2020;28:7–15. [PubMed: 31272339]
2. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med 2003;348:1215–22. [PubMed: 12660385]
3. Marshall RS, Festa JR, Cheung YK, Chen R, Pavol MA, Derdeyn CP, et al. Cerebral hemodynamics and cognitive impairment: baseline data from the RECON trial. Neurology 2012;78:250–5. [PubMed: 22238418]
4. Wang Q, Zhou M, Zhou Y, Ji J, Raithel D, Qiao T. Effects of carotid endarterectomy on cerebral reperfusion and cognitive function in patients with high grade carotid stenosis: a perfusion weighted magnetic resonance imaging study. Eur J Vasc Endovasc Surg 2015;50:5–12. [PubMed: 25933475]
5. Zhou W, Baughman BD, Soman S, Wintermark M, Lazzeroni LC, Hitchner E, et al. Volume of subclinical embolic infarct correlates to long-term cognitive changes after carotid revascularization. J Vasc Surg 2017;65:686–94. [PubMed: 28024850]
6. Jovic M, Unic-Stojanovic D, Isenovic E, Manfredi R, Cekic O, Ilijevski N, et al. Anesthetics and cerebral protection in patients undergoing carotid endarterectomy. J Cardiothorac Vasc Anesth 2015;29:178–84. [PubMed: 25287749]
7. Hitchner E, Baughman BD, Soman S, Long B, Rosen A, Zhou W. Microembolization is associated with transient cognitive decline in patients undergoing carotid interventions. J Vasc Surg 2016;64:1719–25. [PubMed: 27633169]
8. Wilson DA, Mocco J, D'Ambrosio AL, Komotar RJ, Zurica J, Kellner CP, et al. Post-carotid endarterectomy neurocognitive decline is associated with cerebral blood flow asymmetry on post-operative magnetic resonance perfusion brain scans. Neurol Res 2008;30:302–6. [PubMed: 17803842]
9. Keyhani S, Cheng EM, Hoggatt KJ, Austin PC, Madden E, Hebert PL, et al. Comparative Effectiveness of Carotid Endarterectomy vs Initial Medical Therapy in Patients With Asymptomatic Carotid Stenosis. JAMA Neurol 2020;77:1110–21. [PubMed: 32478802]
10. Guay J, Ochroch EA. Carotid endarterectomy plus medical therapy or medical therapy alone for carotid artery stenosis in symptomatic or asymptomatic patients: a meta-analysis. J Cardiothorac Vasc Anesth 2012;26:835–44. [PubMed: 22494782]
11. Galyfos G, Sachsamanis G, Anastasiadou C, Sachmpazidis I, Kikiras K, Kastrisios G, et al. Carotid Endarterectomy versus Carotid Stenting or Best Medical Treatment in Asymptomatic Patients with Significant Carotid Stenosis: A meta-analysis. Cardiovasc Revasc Med 2019;20:413–23. [PubMed: 30057288]
12. Lal BK, Meschia JF, Howard G, Brott TG. Carotid Stenting Versus Carotid Endarterectomy: What Did the Carotid Revascularization Endarterectomy Versus Stenting Trial Show and Where Do We Go From Here? Angiology 2017;68:675–82. [PubMed: 27507736]
13. Howard VJ, Meschia JF, Lal BK, Turan TN, Roubin GS, Brown RD Jr, et al. ; CREST-2 study investigators. Carotid revascularization and medical management for asymptomatic carotid stenosis: protocol of the CREST-2 clinical trials. Int J Stroke 2017;12:770–8. [PubMed: 28462683]
14. Ancetti S, Paraskevas KI, Faggioli G, Naylor AR. Editor's Choice - Effect of Carotid Interventions on Cognitive Function in Patients With Asymptomatic Carotid Stenosis: A Systematic Review. Eur J Vasc Endovasc Surg 2021;62:684–94. [PubMed: 34474964]
15. Sridharan ND, Asaadi S, Thirumala PD, Avgerinos ED. A systematic review of cognitive function after carotid endarterectomy in asymptomatic patients. J Vasc Surg 2022;75:2074–85. [PubMed: 34995717]
16. Paraskevas KI, Faggioli G, Ancetti S, Naylor AR. Editor's Choice - Asymptomatic Carotid Stenosis and Cognitive Impairment: A Systematic Review. Eur J Vasc Endovasc Surg 2021;61:888–99. [PubMed: 33966986]
17. Naylor R, Rantner B, Ancetti S, de Borst GJ, De Carlo M, Halliday A, et al. ; Esvs Guidelines Committee. 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. [PubMed: 35598721]

18. AbuRahma AF, Avgerinos ED, Chang RW, Darling RC 3rd, Duncan AA, Forbes TL, et al. The Society for Vascular Surgery implementation document for management of extracranial cerebrovascular disease. J Vasc Surg 2022;75(1S):26S–98S. [PubMed: 34153349]
19. AbuRahma AF, Avgerinos ED, Chang RW, Darling RC 3rd, Duncan AA, Forbes TL, et al. Society for Vascular Surgery clinical practice guidelines for management of extracranial cerebrovascular disease. J Vasc Surg 2022;75(1S):4S–22S. [PubMed: 34153348]
20. Aleksic M, Huff W, Hoppmann B, Heckenkamp J, Pukrop R, Brunk-wall J. Cognitive function remains unchanged after endarterectomy of unilateral internal carotid artery stenosis under local anaesthesia. Eur J Vasc Endovasc Surg 2006;31:616–21. [PubMed: 16466939]
21. Feliziani FT, Polidori MC, De Rango P, Mangialasche F, Monastero R, Ercolani S, et al. Cognitive performance in elderly patients undergoing carotid endarterectomy or carotid artery stenting: a twelve-month follow-up study. Cerebrovasc Dis 2010;30:244–51. [PubMed: 20664257]
22. Baracchini C, Mazzalai F, Gruppo M, Lorenzetti R, Ermani M, Ballotta E. Carotid endarterectomy protects elderly patients from cognitive decline: a prospective study. Surgery 2012;151:99–106. [PubMed: 21943640]
23. Aharon-Peretz J, Tomer R, Gabrieli I, Aharonov D, Nitecki S, Hoffman A. Cognitive performance following endarterectomy in asymptomatic severe carotid stenosis. Eur J Neurol 2003;10:525–8. [PubMed: 12940834]
24. Bo M, Massaia M, Speme S, Cappa G, Strumia K, Cerrato P, et al. Risk of cognitive decline in older patients after carotid endarterectomy: an observational study. J Am Geriatr Soc 2006;54:932–6. [PubMed: 16776788]
25. Capoccia L, Sbarigia E, Rizzo A, Mansour W, Speziale F. Silent stroke and cognitive decline in asymptomatic carotid stenosis revascularization. Vascular 2012;20:181–7. [PubMed: 22734086]
26. Paraskevas KI. Cognitive function in patients with asymptomatic carotid stenosis after carotid endarterectomy. J Vasc Surg 2022;76:849–50. [PubMed: 35995488]
27. Porcu M, Craboledda D, Garofalo P, Columbano G, Barberini L, Sanfilippo R, et al. Connectometry evaluation in patients undergoing carotid endarterectomy: an exploratory study. Brain Imaging Behav 2019;13:1708–18. [PubMed: 30535626]
28. Dempsey RJ, Jackson DC, Wilbrand SM, Mitchell CC, Berman SE, Johnson SC, et al. The Preservation of Cognition 1 Year After Carotid Endarterectomy in Patients With Prior Cognitive Decline. Neurosurgery 2018;82:322–8. [PubMed: 28575478]
29. Kojima D, Ogasawara K, Kobayashi M, Yoshida K, Kubo Y, Chida K, et al. Effects of uncomplicated carotid endarterectomy on cognitive function and brain perfusion in patients with unilateral asymptomatic severe stenosis of the internal carotid artery by comparison with unoperated patients. Neurol Res 2016;38:580–6. [PubMed: 27249535]
30. Sridharan ND, Tzeng E, Patel S, Pandya Y, Thirumala P, Makaroun MS, et al. Carotid endarterectomy is associated with postoperative neurocognitive improvement in both symptomatic and asymptomatic patients. J Vasc Surg 2020;72:e178.
31. Purandare N, Burns A, Daly KJ, Hardicre J, Morris J, Macfarlane G, et al. Cerebral emboli as a potential cause of Alzheimer's disease and vascular dementia: case-control study. BMJ 2006;332:1119–24. [PubMed: 16648133]
32. Kitagawa K, Miwa K, Yagita Y, Okazaki S, Sakaguchi M, Mochizuki H. Association between carotid stenosis or lacunar infarction and incident dementia in patients with vascular risk factors. Eur J Neurol 2015;22:187–92. [PubMed: 25164480]
33. Johnston SC, O'Meara ES, Manolio TA, Lefkowitz D, O'Leary DH, Goldstein S, et al. Cognitive impairment and decline are associated with carotid artery disease in patients without clinically evident cerebrovascular disease. Ann Intern Med 2004;140:237–47. [PubMed: 14970146]
34. Silvestrini M, Paolino I, Vernieri F, Pedone C, Baruffaldi R, Gobbi B, et al. Cerebral hemodynamics and cognitive performance in patients with asymptomatic carotid stenosis. Neurology 2009;72:1062–8. [PubMed: 19307539]

35. Balucani C, Viticchi G, Falsetti L, Silvestrini M. Cerebral hemodynamics and cognitive performance in bilateral asymptomatic carotid stenosis. Neurology 2012;79:1788–95. [PubMed: 23054236]

36. Zhou W, Succar B, Murphy DP, Ashouri Y, Chou YH, Hsu CH, et al. Carotid Intervention Improves Cognitive Function in Patients With Severe Atherosclerotic Carotid Disease. Ann Surg 2022;276:539–44. [PubMed: 35972513]

37. Kougias P, Collins R, Pastorek N, Sharath S, Barshes NR, McCulloch K, et al. Comparison of domain-specific cognitive function after carotid endarterectomy and stenting. J Vasc Surg 2015;62:355–61. [PubMed: 26211378]

38. Lal BK, Younes M, Cruz G, Kapadia I, Jamil Z, Pappas PJ. Cognitive changes after surgery vs stenting for carotid artery stenosis. J Vasc Surg 2011;54:691–8. [PubMed: 21700413]

39. Heyer EJ, Mergeche JL, Bruce SS, Ward JT, Stern Y, Anastasian ZH, et al. Statins reduce neurologic injury in asymptomatic carotid endarterectomy patients. Stroke 2013;44:1150–2. [PubMed: 23404722]

40. Teng E, Tassniyom K, Lu PH. Reduced quality-of-life ratings in mild cognitive impairment: analyses of subject and informant responses. Am J Geriatr Psychiatry 2012;20:1016–25. [PubMed: 23018474]

41. Takaiwa A, Kuwayama N, Akioka N, Kurosaki K, Hayashi N, Endo S, et al. Effect of carotid endarterectomy on cognitive function in patients with asymptomatic carotid artery stenosis. Acta Neurochir (Wien) 2013;155:627–33. [PubMed: 23361637]

42. Turowicz A, Czapiga A, Malinowski M, Majcherek J, Litarski A, Janczak D. Carotid Revascularization Improves Cognition in Patients With Asymptomatic Carotid Artery Stenosis and Cognitive Decline. Greater Improvement in Younger Patients With More Disordered Neuropsychological Performance. J Stroke Cerebrovasc Dis 2021;30:105608. [PubMed: 33461024]

43. Houghton JS, Nickinson AT, Bridgwood B, Nduwayo S, Pepper CJ, Rayt HS, et al. Prevalence of Cognitive Impairment in Individuals with Vascular Surgical Pathology: a Systematic Review and Meta-Analysis. Eur J Vasc Endovasc Surg 2021;61:664–74. [PubMed: 33573912]

44. Marshall RS, Lazar RM, Liebeskind DS, Connolly ES, Howard G, Lal BK, et al. Carotid revascularization and medical management for asymptomatic carotid stenosis - Hemodynamics (CREST-H): study design and rationale. Int J Stroke 2018;13:985–91. [PubMed: 30132751]