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REVIEW

Carotid disease, cognition, and aging: time to redefine asymptomatic disease?

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Abstract There is an increasing appreciation of the vascular contributions in the development of age-related cognitive impairment and dementia[1,2]. Identifying risk and maintaining cognitive health for successful aging is ever relevant in our aging population. Carotid disease, a well-established risk factor for stroke and often a harbinger of other vascular disease states, is also emerging as another vascular risk factor for age-related cognitive decline. When combined with vascular risk factors, the incidence of age-related carotid disease can be as high as 70%[3,4]. Historically, carotid disease has been dichotomized into two large groups in trial design, outcome measurements, and treatment decisions: symptomatic and asymptomatic carotid artery stenosis. The dichotomous distinction between asymptomatic and symptomatic carotid stenosis based on existing definitions may be limiting the care we are able to provide for patients classified as "asymptomatic" from their carotid disease. Medically, we now know that these patients should be treated with the same intensive medical therapy as those with "symptomatic" carotid disease. Emerging data also shows that hypoperfusion from asymptomatic disease may lead to significant cognitive impairment in the aging population, and it is plausible that most "age-related" cognitive changes may be reflective of vascular impairment and neurovascular dysfunction. While over the past 30 years medical, surgical, and radiological advances have pushed the field of neurovascular disease to significantly reduce the number of ischemic strokes, we are far from any meaningful interventions to prevent vascular cognitive impairment. In addition to including cognitive outcome measures, future studies of carotid disease will also benefit from including advanced neuroimaging modalities not currently utilized in standard clinical imaging protocols, such as perfusion imaging and/or functional connectivity mapping, which may provide novel data to better assess for hypoxic-ischemic changes and neurovascular dysfunction across diffuse cognitive networks. While current recommendations advise against widespread population screening for asymptomatic carotid stenosis, emerging evidence linking carotid stenosis to cognitive impairment prompts us to re-consider our approach for older patients with vascular risk factors who are at risk for cognitive decline.

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Vascular contributions to age-related cognitive decline

There is an increasing appreciation of the vascular contributions in the development of age-related cognitive impairment and dementia [1, 2]. According to population attributable risk scores, approximately 50% of Alzheimer's disease (AD) risk can be accounted for by traditional vascular risk factors [5]. Furthermore, hypertension and stroke are two major risk factors for all-cause dementia, with many dementia cases having mixed pathologies present, including cerebrovascular disease [6–8]. Though hypertension's deleterious effect on cognition may begin earlier in life than previously recognized [9, 10], age itself is a potent risk factor for both cerebrovascular disease and cognitive decline [11]. Identifying risk and maintaining cognitive health for successful aging is ever relevant in our aging population.

In addition to age, hypertension, and stroke, other vascular risk factors such as hyperglycemia, diabetes mellitus, insulin resistance, cigarette use, obesity, lack of physical activity, poor diet, coronary artery disease, peripheral artery disease have also been associated with cognitive impairment and dementia [12, 13]. Similarly, neuroimaging markers of cerebrovascular disease, such as leukoaraiosis, cerebral small vessel disease, and white matter hyperintensities also seem to be linked to age-related cognitive outcomes [14]. Stroke characteristics, such as location, lacunar and, hemorrhagic subtypes, may also have a higher prevalence in patients with post-stroke dementia. However, evidence for the relationship between stroke classifications and cognitive outcomes is mixed and incomplete [8]. Finally, carotid disease, including carotid artery atherosclerotic disease and stenosis, are well-established risk factor for stroke and often a harbinger of other vascular disease states, is also emerging as another vascular risk factor for age-related cognitive decline. However, studies of carotid disease and cognition are limited and the value of intervening on carotid disease to alter the trajectory of vascular cognitive aging is an area of significant knowledge gap.

Cerebrovascular consequences of carotid disease

The prevalence of carotid artery disease is age-dependent, increasing from 0.1% in men less than 50 to over 3% in men older than 80 years-old. When combined with vascular risk factors, the incidence of age-related carotid disease can be as high as 70% [3, 4]. Historically, carotid disease has been dichotomized into two large groups in trial design, outcome measurements, and treatment decisions: symptomatic and asymptomatic carotid artery stenosis. Symptomatic extracranial carotid atherosclerotic disease was defined in 1991 as "neurologic symptoms that are sudden in onset and referable to the appropriate internal carotid artery distribution (ipsilateral to significant carotid atherosclerotic pathology), including one or more transient ischemic attacks characterized by focal neurologic dysfunction or transient monocular blindness, or one or more ischemic strokes" for the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [15]. This continues to be the definition in use today. Carotid "asymptomatic disease" is defined as narrowing by $\geq 50\%$ of the carotid artery in the absence of stroke or TIA in the preceding 6 months. With the incidence of both symptomatic and asymptomatic disease on the rise in our aging population, data is also emerging to show that the historical definitions of symptomatic versus asymptomatic are limited and that the contribution of carotid artery disease to brain health is much more complex. Both symptomatic and asymptomatic carotid disease are associated with hypoperfusion, loss of vascular reactivity, impaired autoregulation, and neurovascular dysfunction. With compelling evidence linking cerebral hypoperfusion with cognitive function, with and without evidence of overt ischemia, there is a clear need to revisit historical definitions of carotid disease [16–22].

There are four pathological features of carotid disease that relate to vascular brain injury: arterial stiffness, carotid intima-media thickness, vulnerable plaques, and flow limiting stenosis. The resulting decreased clearance of toxins, microembolic infarcts and hypoperfusion are hypothesized to lead to cognitive dysfunction [16]. The term "neurovascular unit" was recently coined to call attention to the critical structure–function relationship between neurons and their corresponding microvessels in regulating brain function [23–25]. However, this tightly regulated

network of capillaries, glial cells, and neurons is highly vulnerable to systemic vascular changes across large arteries and through the cerebrovascular tree. Thus, any degree of carotid stenosis is likely to disrupt the neurovascular unit. The dysfunction of the neurovascular unit impairs cerebral autoregulation, alters tissue oxygen extraction, and eventually manifests as tissue ischemia and irreversible brain injury. Data from a mouse model of cerebral ischemia with progressive common carotid artery occlusion over 28 days show significant motor and cognitive decline as well as histopathological changes reflective of hypoperfusion of the white matter and the hippocampus [26].

Current landscape of medical and surgical management of carotid disease

Approach to the treatment of carotid stenosis is grounded in clinical trial data from the 1990s namely NASCET and ECAS for symptomatic disease and ACAS and ACST for asymptomatic disease [27–30]. These randomized clinical trials provided Class 1 Level A evidence supporting the use of surgical intervention in patients presenting with TIA or stroke and carotid disease. Recommendations from these studies are based on an absolute 2-year stroke risk reduction of 17% with revascularization compared to optimal medical management alone in patients with 70–99% stenosis, with a periprocedural risk of death < 6% [27]. However, when considering the modern-day definitions of optimal medical management, we are significantly limited in extrapolating from these older studies. Specifically, the use statins, blood pressure management, or dual antiplatelet therapy were limited or non-existent in NASCET and ESCT trials; these interventions are all now foundational to our medical approach for primary and secondary stroke prevention. There has not been a comparable large, randomized, controlled trial for symptomatic carotid disease since the 1990s.

The approach to asymptomatic carotid artery stenosis is even more controversial. There is Class IIa, Level A evidence to consider CEA (Carotid Endartectomy) in asymptomatic severe (> 70%) ICA stenosis if the perioperative risk is < 3%. These recommendations come from studies in the 1990s comparing surgical revascularization to medical therapies and measuring risk of stroke. This paradigm may also need to be revisited given the advancements in both medical treatment standards and surgical techniques for stroke prevention, and with particular attention to the previously underrepresented elderly population. Patients older than 79 years old were excluded in ACAS, and ACST was not powered for that subgroup. The current European and US guidelines recommend evaluating "asymptomatic carotid" simply based on the degree of stenosis and low perioperative risk. A 2022 Lancet review on management of carotid stenosis based on these guidelines noted "concerns that many patients are receiving carotid revascularization without good evidence of benefit." [31] Given the significant stroke risk reduction with modern day, medical management of carotid disease [31] surgical intervention based solely on primary end point of ischemic stroke may be fading.

In fact, stroke may be too extreme of an end point for treatment of carotid disease. With growing evidence demonstrating the contribution of carotid artery disease to cognitive function and the increasing burden of cognitive dysfunction in our aging population, cognitive function may be a more meaningful endpoint [32–34]. However, cognitive outcomes have been traditionally excluded from large randomized clinical trials of carotid revascularization. To address this knowledge gap, we must ensure to include cognitive function as an outcome in future intervention studies of carotid disease.

Carotid disease and cognition

Current treatment guidelines the USA, Europe, and Asia for carotid disease are based on clinical evidence that does not account for cognitive function before or after intervention [27, 28, 35, 36]. However, large observational studies show that up to 78% of all patients with carotid disease report cognitive deficits [37]. Additionally, the Framingham Offspring Study ($n = 1975$) demonstrated that carotid stenosis was associated with reduced cognitive performance in those *without a* history of dementia or stroke [38]. Most recently, robust data from the CREST-2 trial, which also measured cognitive function in enrolled patients with asymptomatic carotid disease, showed that those with severe asymptomatic carotid stenosis had worse cognitive measures compared to matched

controls, especially in the memory domain [32]. In patients with bilateral carotid stenosis, impaired cerebrovascular reserve (CVR) as measured by transcranial Doppler ultrasound (TCD) breath holding indices has also been associated with rapid cognitive decline at 3 years [34]. There is substantial evidence that asymptomatic disease likely results in cerebral hypoperfusion. Reduction in cerebral blood flow by 40–50% is sufficient to cause ischemia. Examining the relationship between hypoperfusion in asymptomatic carotid disease and cognitive decline (in absence of stroke), Marshall et al. demonstrated a linear correlation between mean flow velocity on transcranial Doppler ultrasound and cognitive decline [39]. The RECON trial demonstrated that in patients with carotid occlusion, hemodynamic failure is independently associated with cognitive impairment, adding to the literature that frank ischemia is likely too extreme of an endpoint in monitoring carotid disease and that information from other imaging modalities may provide better biomarkers for assessing cognitive risk or disease progression. [40]

In addition to traditional imaging biomarkers for cerebrovascular injury such as white matter hyperintensities, intima-media thickness, and cortical thickness [21, 41], promising data are also emerging from more advanced neuroimaging modalities currently limited to use in the research setting. For example, a recent study using resting state functional MRI (fMRI) showed significantly reduced functional connectivity within the MCA territory ipsilateral to the carotid disease in those with severe (> 70%) asymptomatic carotid stenosis as compared to matched controls. While the reduced functional connectivity was partly explained by white matter hyperintensities, they also showed that the decreased functional connectivity in these brain regions was associated with impaired sensorimotor processing and delayed memory recall. Functional connectivity measurements may be a valuable approach to assess cognitive changes associated with asymptomatic carotid stenosis [42]. Another study compared functional connectivity between patients with unilateral carotid stenosis and controls and showed decreased functional connectivity ipsilateral to the stenosis and increased functional connectivity in the contralateral hemisphere. These changes in functional connectivity were similarly associated with worse cognitive function, particularly in memory and executive domains. When resting-state fMRI was performed before and after carotid artery stenting (CAS), data show that functional connectivity partially recovered post-CAS [43]. Finally, another group studied functional connectivity using resting-state electroencephalography to show that in patients with asymptomatic carotid stenosis, decreased connectivity was associated with reduced regional brain perfusion in the MCA border zone, and that both parameters improved after revascularization [44]. These advanced imaging modalities clearly demonstrate and help quantify the extent of neurovascular injury within diffuse cognitive networks in patients who we currently and possibly erroneously classify as those with “asymptomatic” carotid disease.

Does surgical revascularization reverse and halt progression of cognitive decline, and by how much? Or, is aggressive medical management sufficient in these patients to alter the trajectory of cognitive decline? Data from experimental models show that hippocampal neuronal injury could be reversed if perfusion was restored within 2 weeks of initial injury; however, there was no recovery if the occlusion was present for greater than 2 weeks [45]. In human studies, support for reversible cognitive decline has been limited by mixed results from small, non-randomized clinical trials that (12 studies outlined in the Norling study) failed to control for significant confounders such as cardiac disease [18]. For example, heart failure is an independent risk factor for cognitive decline and cerebral hypoperfusion, therefore correction of carotid stenosis without controlling for cardiac function would likely underestimate any treatment benefit. Despite their limitations, these studies show an overall trend toward improvement of cognition with revascularization of asymptomatic carotid disease. Studies with more rigorous design will likely result in more definitive and robust findings.

Guidelines for screening and diagnosis of carotid disease

Last reported in 2021, the US preventative task force recommends against screening for asymptomatic carotid stenosis in the general adult population [46]. Therefore, evaluation of carotid disease is currently recommended only for patients presenting with acute TIA and stroke symptoms attributable to ipsilateral

carotid disease. For high-risk groups such as those with significant peripheral and coronary artery disease and atherosclerotic aortic aneurysms, screening may also be of benefit [35].

Data from more advanced imaging modalities show that in addition to the degree of stenosis, carotid plaque features are also important predictors of stroke and TIA outcomes [47, 48]. For example, a soft plaque may be associated with a higher rate of cerebral ischemia and injury. Similarly, absence of microembolic signals detected on transcranial Doppler ultrasound in asymptomatic patients is predictive of a lower risk of stroke within one year [49, 50]. Current US and European guidelines recommend that if intervention is considered after a preliminary ultrasound study that it is followed with a CT or MR angiography (CTa or MRa), to evaluate the aortic arch and the extra- and intracranial circulation [27, 28]. This allows for visualization of intracranial tandem stenoses or an alternative etiology of the patient's symptoms.

Most clinical trials in carotid disease have used imaging findings as the most important, if not sole, consideration when deciding on possible intervention and risk stratification of patients. In the early landmark clinical trials (NASCET, ECST, ACAS), digital subtraction angiography (DSA) was used to measure carotid disease. Most recent guidelines recommend AGAINST the use of DSA for patients being considered for revascularization, given the 1.5% associated risk of periprocedural stroke [27, 28], though Chinese guidelines from 2013 did emphasize the continued importance of DSA in their population [36]. Current available imaging modalities for carotid disease include duplex ultrasound, CTa, MRa, with the possibility of pairing these with perfusion or arterial spin imaging, and DSA [51]. Carotid duplex ultrasound is the most frequently used and cost-effective screening tool for carotid stenosis, however precision in the USA is limited and at 10% at best [52]. In a qualitative study, "when determining an ideal imaging study for patients with hot carotids, accessibility of the modality was of utmost importance to participants [51]."

Advancements in imaging modalities with increasing availability of cerebrovascular imaging techniques, set against the backdrop of an aging population, have significantly increased the frequency of finding significant (moderate—severe) carotid stenosis in the absence of defined symptoms that might lead to consideration of intervention. Utilizing advanced cerebrovascular imaging markers that identify high risk patients that might benefit from early revascularization even without previously defined symptoms will help with medical decision making. Conclusive data on the impact of carotid revascularization on cognitive function will further aid clinical decision making. With these advances, we may be poised to reconsider the current scope of screening for carotid disease in our aging societies.

Gaps and future direction

The dichotomous distinction between asymptomatic and symptomatic carotid stenosis based on existing definitions may be limiting the care we are able to provide for patients classified as "asymptomatic" from their carotid disease. Medically, we now know that these patients should be treated with the same intensive medical therapy as those with "symptomatic" carotid disease. Emerging data also shows that hypoperfusion from asymptomatic disease may lead to significant cognitive impairment in the aging population, and it is plausible that most "age-related" cognitive changes may be reflective of vascular impairment and neurovascular dysfunction. While medical interventions have been efficacious in reducing the burden of ischemic stroke, we must not lose sight of the longitudinal (and perhaps less obvious) effects of carotid stenosis on cognitive function. While over the past 30 years medical, surgical, and radiological advances have pushed the field of neurovascular disease to significantly reduce the number of ischemic strokes, we are far from any meaningful interventions to prevent vascular cognitive impairment. In addition to including cognitive outcome measures, future studies of carotid disease will also benefit from including advanced neuroimaging modalities not currently utilized in standard clinical imaging protocols, such as perfusion imaging and/or functional connectivity mapping, which may provide novel data to better assess for hypoxic-ischemic changes and neurovascular dysfunction patterns across diffuse cognitive networks. While current recommendations advise against widespread population screening for asymptomatic carotid stenosis, emerging evidence linking carotid stenosis to cognitive impairment prompts us

to re-consider our approach for older patients with vascular risk factors who are at risk for cognitive decline.

Declarations

Competing interests The authors declare no competing interests.

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