Effect of revascularization on cognitive outcomes in intracranial steno-occlusive disease: a systematic review

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OBJECTIVE Steno-occlusive diseases of the cerebral vasculature have been associated with cognitive decline. The authors performed a systematic review of the existing literature on intracranial steno-occlusive disease, including intracranial atherosclerosis and moyamoya disease (MMD), to determine the extent and quality of evidence for the effect of revascularization on cognitive performance.

METHODS A systematic search of PubMed/MEDLINE, the Thomson Reuters Web of Science Core Collection, and the KCI Korean Journal Database was performed to identify randomized controlled trials (RCTs) in the English-language literature and observational studies that compared cognitive outcomes before and after revascularization in patients with steno-occlusive disease of the intracranial vasculature, from which data were extracted and analyzed.

RESULTS Nine papers were included, consisting of 2 RCTs and 7 observational cohort studies. Results from 2 randomized trials including 142 patients with symptomatic intracranial atherosclerotic steno-occlusion found no additional benefit to revascularization when added to maximal medical therapy. The certainty in the results of these trials was limited by concerns for bias and indirectness. Results from 7 observational trials including 282 patients found some cognitive benefit for revascularization for symptomatic atherosclerotic steno-occlusion and for steno-occlusion related to MMD in children. The certainty of these conclusions was low to very low, due to both inherent limitations in observational studies for inferring causality and concerns for added risk of bias and indirectness in some studies.

CONCLUSIONS The effects of revascularization on cognitive performance in intracranial steno-occlusive disease remain uncertain due to limitations in existing studies. More well-designed randomized trials and observational studies are needed to determine if revascularization can arrest or reverse cognitive decline in these patients.

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KEYWORDS stenosis; atherosclerosis; revascularization; endovascular; moyamoya; stent; bypass

THE major steno-occlusive diseases of the cerebral vasculature consist of moyamoya disease (MMD) and atherosclerotic disease of the large cerebral arteries. Both cause stenosis of the cerebral vasculature and subsequent cerebral hypoperfusion. This hypoperfusion has been associated with cognitive decline in cerebrovascular atherosclerosis.^{3,30,40} It has also been associated with cognitive decline in MMD.^{16–19,21,22,45} If the purported cognitive decline is caused by ongoing hypoperfusion rather than fixed ischemic injury, then revascularization could represent a means of reversing the cognitive decline.^{31,46}

Revascularization procedures for steno-occlusive disease consist of endovascular stent placement and open surgical arterial bypass, either direct extracranial-to-intracranial bypass (EC-IC bypass) or indirect encephaloduroarteriosynangiosis (EDAS).³⁹ The utility of these procedures for halting or reversing the progression of steno-occlusive-associated cognitive decline has not been well-characterized and remains an open area of interest in the medical and surgical treatment of cerebrovascular disease. In order to address this question, we performed a systematic review of randomized controlled trials (RCTs) and high-quality

ABBREVIATIONS EC-IC = extracranial-intracranial; EDAS = encephaloduroarteriosynangiosis; ICA = internal carotid artery; MCA = middle cerebral artery; MMD = moyamoya disease; MoCA = Montreal Cognitive Assessment; RCT = randomized controlled trial; WAIS-R = Wechsler Adult Intelligence Scale–Revised; WISC-R = Wechsler Intelligence Scale for Children–Revised.

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observational studies comparing cognitive performance before and after revascularization in steno-occlusive cerebrovascular disease (Fig. 1).

Methods

A study protocol was drafted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²⁹ Studies were eligible for inclusion if they were observational studies of 5 or more individuals or RCTs published in the English-language literature between 2000 and the present. To identify relevant studies, we used the search term “TITLE:((cognitive OR neurocognitive OR cognition) AND (moyamoya OR (atheroscler* OR occlus* OR ischemia)))” to search PubMed/MEDLINE, the Thomson Reuters Web of Science Core Collection, and the KCI Korean Journal Database for articles published in the English language between the years 2000 and 2018. Results of the search were screened for relevance by examining the title and abstracts. The resulting papers were reviewed in full and assessed against the predetermined inclusion and exclusion criteria. A standard form was created for data extraction and was filled out for each eligible study. For each study, the following variables were sought: description and selection of patient population, intervention, outcome assessed, baseline data, outcome data, and follow-up data. Qualitative and quantitative descriptions of each variable were recorded, whenever possible. We used the Grading of Recommendations

Assessment, Development and Evaluation (GRADE) approach to rate the quality of evidence in each study and GRADEpro software (www.grade.pro.org) to generate certainty estimates.^{4,14} The principal summary measure sought was difference in mean cognitive performance before and after revascularization, as measured by any validated assessment tool.

Results

Study Selection

After the initial search, 536 articles were returned. The article titles were screened for relevance, and irrelevant and duplicate articles were eliminated, resulting in 17 articles whose full text was assessed for eligibility. Five articles were excluded because they addressed revascularization for extracranial carotid artery stenosis. One article was a systematic review, one examined a nonoperative intervention, one did not compare pre- and postintervention cognitive performance, one examined combined intervention in patients with co-occurrence of external carotid artery stenosis with intracranial cerebrovascular disease, and one was an abstract. After eliminating these, 7 articles from the systematic search were included in the review itself. Two additional articles were added after searching the bibliographies of other included articles.

Study Characteristics

According to our search, there were 2 RCTs published in the English language between 2000 and September 2018 that addressed the question of whether revascularization affects cognitive performance in atherosclerotic cerebrovascular steno-occlusive disease. Turan et al. randomized 371 patients with recent transient ischemic attack or stroke attributable to 70%–99% intracranial stenosis to angioplasty and stenting with the Wingspan self-expanding stent plus best medical management versus best medical management alone, recording the Montreal Cognitive Assessment (MoCA) score at baseline, 4 months, 12 months, and at trial closeout.⁴³ Marshall et al. randomized 41 patients with symptomatic internal carotid artery (ICA) occlusion and increased oxygen extraction fraction on PET to open surgery (EC-IC bypass) plus best medical management versus best medical management alone, comparing results on extensive neuropsychological testing prior to intervention and over the 2-year study follow-up period.³¹ See Table 1 for more information regarding these trials.

According to our search, 7 observational studies were published in the English-language literature between 2000 and September 2018 that address the question of whether revascularization affects cognitive performance in cerebrovascular steno-occlusive disease. Sasoh et al. observed 25 patients with hemodynamic cerebral ischemia attributable to unilateral ICA or middle cerebral artery (MCA) occlusion treated with open surgery (EC-IC bypass), comparing verbal, performance, and full-scale IQ scores as determined by the Wechsler Adult Intelligence Scale–Revised (WAIS-R) test preoperatively with results obtained 6 months after surgery.³⁸ Dong et al. observed 9 patients with severe atherosclerotic steno-occlusive disease of the

FIG. 1. Systematic review search strategy and review process.

TABLE 1. Characteristics of the RCTs

	Question	Population	Intervention	Comparator	Outcome Assessed	Outcome Summary
Marshall et al., 2014	Does EC-IC bypass, when added to MMT, improve cognitive function after 2 yrs in pts w/ symptomatic complete ICA occlusion compared w/ MMT alone?	13 surgical & 16 medical pts for full evaluation*	EC-IC bypass plus MMT	MMT	Scores on neuropsychological tests of memory, concentration, vision, motor skills, & other cognitive parameters	No significant between-group differences
Turan et al., 2017	Do angioplasty & stenting, when added to MMT, improve cognitive function in pts w/ symptomatic atherosclerotic high-grade stenosis of the intracranial vasculature compared w/ MMT alone?	59 medical & 54 surgical pts received ≥ 3 yrs of follow-up†	Angioplasty & stenting w/ the Wingspan self-expanding stent plus MMT	MMT	MoCA score at baseline, 4 mos, 12 mos, & at trial closeout (~3 yrs); cognitive impairment was defined as MoCA score <26	No significant between-group differences

MMT = maximal medical therapy; pts = patients.

* Forty-one adults with complete and symptomatic ICA occlusion, increased oxygen extraction fraction on PET, and no prior diagnosis of dementia were originally randomized. Two died, 2 were lost to follow-up, 2 refused 2-year testing, and 6 reached endpoints of the parent trial.

† Four hundred fifty-one patients with recent transient ischemic attack or stroke due to 70%–99% intracranial stenosis were randomized. Patients with stroke as the qualifying event with aphasia or neglect were excluded. Patients with a cerebrovascular event during follow-up were excluded from analysis. Only patients with full cognitive testing pre- and postintervention were included.

ICA or MCA treated with an EC-IC bypass, comparing pre- and postintervention performance on a neuropsychological battery of tests with performance observed in a cohort of 9 matched controls.¹¹ Lee et al. observed 65 pediatric patients with MMD treated with EDAS, comparing performance on the Korean Educational Development Institute Wechsler Intelligence Scale for Children–Revised (WISC-R) before surgery with performance an average of 19 months after surgery.²⁷ Fiedler et al. observed 40 patients with hemodynamic cerebral ischemia and occluded ICA treated with open surgery (EC-IC bypass), comparing IQ via WAIS-R testing preoperatively and at 12 months postsurgery.¹³ Baek et al. observed 5 adults with MMD treated with open surgery (EC-IC bypass), comparing performance on the Seoul Neuropsychological Screening Battery prior to surgery and within 3 months after surgery.² Zeifert et al. observed 84 adults with MMD treated with open surgery (EC-IC bypass), comparing IQ scores via WAIS-R testing and a variety of other neuropsychological tests prior to surgery and at an average of 6.8 months after surgery.⁴⁶ Kim et al. observed 55 children with MMD treated with open surgery (EDAS), comparing IQ and other neuropsychological performance metrics prior to surgery and at an average of 11 months after surgery.²⁴ See Table 2 for more information regarding these studies.

Risk of Bias Within Studies

Risk of bias, as well as overall assessments of the certainty of evidence offered by the studies addressed in our review, is summarized in Table 3. We downgraded our certainty assessment of the 2 randomized trials included in this review due to what we assessed as a serious risk of bias in the study by Marshall et al.³¹ and serious risk of indirectness in that by Turan et al.⁴³ The question underlying our review of revascularization for intracerebral steno-occlusion is whether cognitive decline can be stopped or reversed by restoring the flow of oxygenated

blood to ischemic brain tissue. In the Marshall et al. study, no patients in the surgical arm achieved an oxygen extraction fraction ratio < 1.067 following surgical intervention, which was defined as the upper limit of normal in the parent study. As noted by the study authors, this raises concerns as to whether the surgical intervention achieved its ultimate goal of restoring perfusion to ischemic brain tissue, which would bias the results of the study toward medical intervention alone.³¹ We concluded that there was a serious risk of indirectness in Turan et al. based on the study's use of MoCA scores to assess the cognitive performance of the study participants. As noted by the authors, the MoCA is used as a screening tool for cognitive impairment. In order to assess for the presence and extent of cognitive improvement, rather than just for the presence of cognitive impairment, we believe that more sensitive and extensive testing modalities are needed, such as the WAIS assessment deployed by Zeifert et al.⁴⁶

In addition to the serious concerns just mentioned, there were other less serious concerns regarding risk of bias in both studies. In the Marshall et al. study, 6 of 19 (32%) surgical patients randomized and 16 of 22 (73%) medical patients randomized were not analyzed for various reasons, many of which were different from the reasons given for surgery patients. The direction of bias due to these missing outcome data is unpredictable. Additionally, there was some concern that, since participants were not blinded to their intervention due to the nature of the intervention itself, deviation from the prescribed medical therapy by the surgical treatment arm could also introduce bias into the results, favoring the medical treatment arm. Similar concerns regarding patient awareness of intervention were also present in Turan et al. The results of both studies are most likely robust to the potential bias associated with these concerns.

By their very nature, the observational studies included in this systematic review have a much higher risk of bias than the RCTs. The studies of Sasoh et al.³⁸ and Fiedler et al.¹³ were downgraded further due to concern for selec-

TABLE 2. Characteristics of the observational studies

	Question	Population	Intervention	Comparator	Outcome Assessed	Outcome Summary
Sasoh et al., 2003	How does performance on IQ tests 6 mos after intervention compare to preintervention performance?	25 adults w/ unilat athero-occlusive ICA or MCA disease	EC-IC bypass	NC	WAIS-R verbal, performance, FSIQ 2 wks before & 6 mos after intervention	SSI in mean VIQ, PIQ, & FSIQ
Lee et al., 2011	How does performance on IQ tests an average of 19 mos after intervention compare to preintervention performance?	65 children w/ MMD	EDAS	NC	KEDI-WISC-R	SSI in mean PIQ but not VIQ or FSIQ
Fiedler et al., 2011	How does performance on IQ tests 12 mos after intervention compare to preintervention performance?	20 adults w/ unilat atherosclerotic occlusion of the ICA	EC-IC bypass	NC	WAIS-R	SSI in IQ, number collection test, & trail making test; 4 other cognitive tests showed no improvement
Dong et al., 2012	How does performance on an extensive neuropsychological screening battery 3–6 mos after intervention compare to preintervention performance?	9 pts w/ high-grade atherosclerotic stenosis of the intracranial ICA or MCA	EC-IC bypass	9 matched controls	7 cognitive domain neuropsychological battery of tests	Between-group SSI in measures of verbal memory & executive function
Baek et al., 2014	How does performance on an extensive neuropsychological screening battery w/in 3 mos of intervention compare to preintervention performance?	5 female adults w/ MMD	EC-IC bypass	NC	Seoul Neuropsychological Screening Battery	SSI in verbal & visual memory; no improvement in 6 other aspects of neuropsychological battery administered
Zeifert et al., 2017	How does performance on IQ tests an average of 6.8 mos after intervention compare to preintervention performance?	84 consecutive adults w/ MMD	EC-IC bypass	NC	WAIS-R	No improvement in IQ scores of 86% of participants, w/ 8% showing significant decline & 6% showing a significant improvement
Kim et al., 2018	How does performance on IQ tests an average of 11 mos after intervention compare to preintervention performance?	55 children w/ MMD	EDAS	NC	Korean WISC-III, other neuropsychological tests	SSI in FSIQ & PIQ but no improvement in VIQ

FSIQ = full-scale IQ; KEDI-WISC-R = Korean Educational Development Institute WISC-R; NC = no comparator; PIQ = performance IQ; SSI = statistically significant improvement; VIQ = verbal IQ.

tion bias, since neither study explained how surgical candidates were selected. The Fiedler et al. study was also downgraded for imprecision, since this paper only presented summary statistics regarding cognitive outcomes, with no individual data points.

Results of Individual Studies

Marshall et al. found no additional cognitive performance benefit from EC-IC bypass when added to best medical therapy in their 2014 randomized study of symptomatic intracranial atherosclerosis patients.³¹ Turan et al. also found no additional cognitive performance benefit from intercranial stenting when added to best medical therapy in their 2017 randomized study of symptomatic intracranial atherosclerosis patients. This study was an offshoot of the SAMMPRIS (Stenting Versus Aggressive Medical Therapy for Intracranial Arterial Stenosis) trial, which compared stenting plus best medical therapy with best medical therapy alone in the prevention of stroke and death in patients with symptomatic atherosclerotic disease of the intracranial circulation.^{6,43}

With respect to intracranial atherosclerotic disease treated with an EC-IC bypass, 3 observational studies reported positive results. Sasoh et al. observed statistically significant increases in verbal, performance, and full-scale IQ scores in their cohort of 25 patients.³⁸ Fiedler et al. observed statistically significant increases in IQ scores in their cohort of 20 patients with atherosclerotic occlusion of the ICA 12 months after EC-IC bypass.¹³ They did not present descriptive data for their findings. Dong et al. observed statistically significant between-group improvement postintervention in measures of verbal memory and executive function ($p = 0.043$), and a nonsignificant improvement in visual memory compared with controls ($p = 0.052$). Importantly, statistically significant improvements were not durable to adjustment for multiple comparisons.¹¹

With respect to MMD, 4 studies reported data. Lee et al. observed no statistically significant differences in pre- and postsurgery full-scale and verbal IQ scores, but they did observe a statistically significant increase in performance IQ in children with MMD treated with EDAS.²⁷ Interestingly, the authors noted that even preoperative per-

TABLE 3. Certainty and outcome assessments

Certainty Assessment							Outcome Assessment	Certainty	Importance
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations			
Does revascularization plus MMT improve cognitive function more than best medical therapy alone in atherosclerotic steno-occlusive disease? (follow-up range 2–3 yrs; assessed w/ MoCA [Turan et al.] or neuropsychological battery [Marshall et al.])									
2	Randomized trials	Serious*	NS	Serious†	NS	None	142 pts randomized to revascularization, either by EC-IC bypass (Marshall et al.) or by angioplasty plus expandable stenting (Turan et al.); cognitive assessment was done at baseline & at follow-up using either a neuropsychological battery of tests (29 pts) or the MoCA (113 pts). No significant between-group differences were found	Low	Critical
Does cognitive performance in patients w/ MMD improve after surgical revascularization? (follow-up range 3–46 mos; assessed w/ cognitive tests)									
4	Observational studies	NS	NS	NS	NS	None	Observation of 65 children (Lee et al.) & 84 adults w/ MMD (Zeifert et al.) treated with EDAS & EC-IC bypass, respectively, found no significant differences in pre- & postintervention FSIQ; conversely, observation of 55 children w/ MMD (Kim et al.) treated w/ EDAS found significant improvement in postintervention FSIQ. A small cohort of 5 adult females w/ MMD treated w/ EC-IC bypass (Baek et al.) showed significant improvement in 2 of 8 tests in a neuropsychological battery (visual & verbal memory)	Low	Important
Does cognitive performance in patients w/ atherosclerotic steno-occlusive disease improve following surgical revascularization? (follow-up range 3–12 mos; assessed w/ cognitive tests)									
2	Observational studies	Serious‡	NS	NS	Serious§	None	Observation in 25 adults (Sasoh et al.) found a 5.9-point improvement in mean VIQ, 6.5-point improvement in mean FIQ, & 6.5-point improvement in mean FSIQ; observation in 40 adults reported significant improvement in multiple cognitive tests, but no data were published (Fiedler et al.)	Very low	Important
Does cognitive performance in patients with atherosclerotic steno-occlusive disease improve compared to untreated controls following surgical revascularization? (follow-up range 3–6 mos; assessed w/ Mini–Mental Status Examination, MoCA, neuropsychological battery)									
1	Observational studies	NS	NS	NS	NS	None	Observation of 9 adults found significant improvement compared w/ matched controls in verbal memory & executive function scores	Low	Important

NS = not serious.

* In Marshall et al., no patients in the surgical arm achieved oxygen extraction fraction ratio < 1.067, which was the upper limit of normal defined for the parent study, raising concerns that the results of this study were biased by the failure of procedural success in the surgical arm.

† Assessment measures such as Montreal Cognitive Assessment may be insufficient to detect actual improvements in cognitive function.

‡ Neither Sasoh et al. nor Fiedler et al. provide an explanation for how surgical candidates were chosen from larger cohorts of symptomatic patients.

§ Fiedler et al. does not provide data regarding cognitive outcomes, only summary statistics.

formance on all IQ domains was within the average range for age-appropriate societal controls. Following Lee et al., Kim et al. also reported a statistically significant improvement in performance IQ score, and this difference was large enough to result in a significant increase in full-scale IQ.²⁴ Baek et al. observed a statistically significant increase in performance on verbal and visual memory components of the Seoul Neuropsychological Screening Battery in their cohort of 5 patients with MMD 3 months after EC-IC bypass.² They found no statistically significant differences in the 6 other aspects of the Seoul Neuropsychological Screening Battery. Of note, they observed a 9–standard deviation improvement in performance on visuospatial testing in one patient, raising some concern for the reliability of testing in general with respect to outliers. Zeifert et al. observed no significant change in WAIS-R IQ scores in 86% of their cohort of 84 patients with MMD evaluated an average of 6.8 months after EC-IC bypass.⁴⁶ Evaluation of change was done using so-called reliable change indices obtained from prior published research. Using this metric, significant improvement was observed in 6% of patients, and significant decline was observed in 8% of patients.

Discussion

We performed a systematic review of the literature on the effects of revascularization on cognitive performance in intracranial steno-occlusive disease. We found 2 RCTs indicating that revascularization plus best medical therapy does not improve cognitive function more than best medical therapy alone in atherosclerotic steno-occlusive disease, but the certainty of this conclusion was low due to concern for risk of bias and indirectness. These conclusions also conflict with 3 observational studies, which all report cognitive improvement after surgical revascularization in patients with intracranial atherosclerotic steno-occlusive disease. Four observational studies examining cognitive performance following surgical revascularization in patients with MMD were found, with data from 2 of these studies suggesting that intervention may improve IQ in children treated with EDAS due to improvement in performance IQ. The certainty of this conclusion is low, however, due to the inherent limitations in observational studies.

Steno-occlusion has also been associated with cognitive impairment in extracranial steno-occlusive disease. For example, the Asymptomatic Carotid Stenosis and Cognitive Function study evaluated cognitive function in 82 patients with > 49% asymptomatic carotid stenosis and 60 nonstenotic controls with matched vascular comorbidities, education status, estimated intelligence, and depressive symptoms, finding a statistically significant reduction in both composite cognitive function and domain-specific learning/memory and motor/processing function in the stenotic group.²⁶ The authors also measured reduced cerebrovascular reserve in stenotic patients and hypothesized that the reduction in cognitive performance seen in these patients is due to hypoperfusion in the context of insufficient collaterals. A recent systematic review and meta-analysis reaffirmed the effectiveness of endarterectomy for symptomatic stenosis.³⁶ The effect of revascularization,

by either endarterectomy or stenting, on cognition in extracranial atherosclerotic disease has also been addressed by multiple systematic reviews.^{1,37} Plessers et al. found a large variation in patient selection, presence or absence of control groups, modality of assessment, and timing of assessment, making it difficult to establish definitive conclusions regarding the cognitive benefit of stenting or endarterectomy.³⁷ Antonopoulos and colleagues were slightly more optimistic, reporting an association between carotid artery stenting and improvement in global cognition, memory, attention, and psychomotor speed.¹ However, they also noted that stenting did not seem to be associated with improvements in executive function, language, or functional ability. Heller and Hines, in their recent review, concluded only that revascularization for carotid stenosis may provide cognitive benefit in patients with clinically significant disorders.¹⁵

An important future direction for the study of the effects of intracranial and extracranial revascularization on cognitive outcomes involves understanding how to better identify subgroups of high-risk patients. The SAMMPRIS trial demonstrated that in patients with symptomatic intracranial stenosis, maximal medical therapy is superior to angioplasty and stenting using the Wingspan system for ischemic event prevention in both the short and long term.^{6,10,44} However, recent data have suggested that stenting is at least comparably effective and possibly superior to maximal medical therapy when patient selection is optimized to include only patients at a high risk of ischemic events.^{7,33} If true, this may suggest that the original outcome of the SAMMPRIS trial was confounded by the inclusion of low-risk patients. Studies finding no additional cognitive benefit to revascularization over and above maximal medical therapy such as Marshall et al.³¹ and Turan et al.⁴³ may be similarly confounded. If only patients with high-grade cognitive impairment and high risk of further deterioration are studied, it may be the case that surgical or endovascular intervention offers a durable advantage compared with medical therapy. Further investigation of revascularization outcomes with the Wingspan system (Post Market Surveillance Study of the Wingspan Stent System trial, registration no. NCT02034058, clinicaltrials.gov) is being carried out at 26 locations across the United States and may demonstrate improved outcomes compared with the SAMMPRIS trial. Submaximal angioplasty has also been shown to safely improve vessel diameters and may offer an additional endovascular avenue for future study in this area.¹²

The identification of at-risk subgroups of patients with steno-occlusion requires the development of novel screening and diagnostic modalities. Floating a pressure guide-wire across a region of intracranial stenosis as a means of measuring fractional flow reserve (FFR, maximal blood flow in a stenotic artery divided by normal maximal flow in a nonstenotic artery) may represent a superior way of assessing cerebral ischemia when compared with angiographic evaluation.³² Data from randomized trials in interventional cardiology showed that using FFR as opposed to angiographic assessment to guide endovascular intervention resulted in a significant reduction in the composite endpoint of death, nonfatal myocardial infarction, and re-

peat revascularization at 1 year.⁴² A trial assessing the cognitive effects of revascularization in patients chosen using FFR would be a welcome addition to the literature. Transcranial Doppler monitoring has also proven beneficial in identifying patients at high risk of ischemic events.⁴¹ A recent review suggested that arterial stiffness, as measured by various surrogates such as pulse-wave velocity, cardio-ankle vascular index, ankle-brachial index, pulse pressure, augmentation index, flow-mediated dilation, carotid intima media thickness, and arterial stiffness index-beta, is a sensitive indicator of cognitive impairment.²⁸ Further work should investigate whether measures of arterial stiffness can be useful in identifying patients who would benefit cognitively from revascularization. Pulsed arterial spin-labeling perfusion MRI has been used to demonstrate that patients with Alzheimer's disease have significantly greater regional hypoperfusion than cognitively normal subjects in multiple regions of the brain, including the cingulate gyrus, the superior and middle frontal gyri, and the inferior parietal lobe. These observations are also supported by findings with FDG PET and ^{99m}Tc HMPAO (hexamethylpropyleneamine oxime) SPECT, which have demonstrated reduced cerebral metabolism and blood flow in patients with Alzheimer's disease, respectively.²⁰ These modalities may represent further means of stratifying patient cohorts in order to identify subgroups that would best benefit from revascularization.

The focus on identification of subgroups amenable to intervention has also received recent attention in the literature on extracranial revascularization. Dempsey and colleagues recently demonstrated that ultrasound-measured plaque strain can be used to measure carotid plaque instability and may offer a more useful metric for assessing risk in carotid atherosclerosis patients than degree of stenosis alone.⁹ The same group has reported the preservation of cognition 1 year after endarterectomy in patients with prior cognitive decline, with improvement predicted by the presence of hypertension and lower preexisting cognitive decline prior to intervention.⁸ In similar work, Casas-Hernanz and coauthors recently used bivariate analysis in an attempt to identify properties separating "cognitive responders" to carotid revascularization from "non-responders," concluding that cognitive responders were younger patients without fixed neurological deficits or anatomical changes such as atrophy or white matter changes due to small vessel disease.⁵ These studies suggest that earlier intervention may have cognitive benefit in select subgroups of patients in the case of extracranial atherosclerotic disease, and a similar situation may hold true in the case of intracranial atherosclerotic disease.

With respect to MMD, our systematic review found observational evidence from 2 relatively large cohorts that EDAS may improve performance IQ in children.^{24,27} The certainty of this finding is low, due to inherent limitations with observational studies. Although a well-designed clinical trial testing the effects of revascularization versus conservative treatment in children with MMD would help settle the issue, this may be ethically difficult given previous data suggesting that revascularization has a benefit in preventing stroke and hemorrhage in MMD over and above any benefit to cognitive performance.^{34,39} In the case

of revascularization for adults with MMD, further work on patient stratification and selection would seem to be critical. Recent work has demonstrated that intellectual and memory impairment in adults with MMD, while possible in the absence of stroke, may in fact be quite limited in general.^{21,22} Furthermore, work by Miyoshi and colleagues demonstrated stable normal cognitive function over a 2-year course in adult MMD patients.³⁵ Recent work has also shown a significant population of individuals with asymptomatic MMD, raising further questions about the exact nature of cognitive impairment in MMD.²⁵ In this context, it is not necessarily surprising that revascularization was shown to have limited beneficial effects on cognition in the largest and most recent study of adult MMD patients.⁴⁶ Clearly, further work is needed to unravel the natural history of MMD as well as to identify adult MMD patients who might benefit most from revascularization.²³

Limitations

This systematic review was limited to articles published in the English language from 2000 to 2018. Although multiple databases were used and a systematic search of bibliographies was employed to supplement search terms, incomplete retrieval of relevant articles is possible.

Conclusions

The current evidence for the effect of revascularization on cognitive outcomes in intracranial steno-occlusive diseases is of low certainty. Further well-designed trials are needed to both determine the extent to which revascularization improves cognitive performance in intracranial steno-occlusive disease and identify subpopulations in which revascularization may be particularly effective.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Kolb, Fadel, Rajah. Analysis and interpretation of data: Kolb, Fadel, Rajah. Drafting the article: Kolb, Rajah. Critically revising the article: Rangel-Castilla, Kolb, Rajah, Saber, Luqman. Reviewed submitted version of manuscript: Kolb. Statistical analysis: Kolb.

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