

Review

Neurocognitive Functioning after Carotid Revascularization: A Systematic Review

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Key Words

Cognitive outcome · Carotid endarterectomy · Carotid artery stenting · Systematic review · Carotid revascularization · Neuropsychology

Abstract

Background: The objective of this study was to review the recent literature regarding the neurocognitive consequences of carotid endarterectomy (CEA) and carotid stenting (CAS). **Methods and Results:** A PubMed and Web of Science search was conducted using the key words 'carotid' in combination with 'cognitive', 'cognition', 'neurocognition', 'neurocognitive', 'neuropsychology', and 'neuropsychological'. Bibliographies of relevant articles were cross-referenced. We included 37 studies published since 2007 of which 18 examined CEA, 12 CAS, and 7 compared CEA to CAS. There is a wide variability in the reported neurocognitive outcome following CEA and CAS. Nonetheless, none of the included studies unveiled significant differences between CEA and CAS on postoperative neurocognitive functioning. Postoperative changes observed for CEA and CAS separately seem limited to a small percentage (around 10–15%) of patients and can either present as an improvement or impairment. **Key Messages:** The available data seem to suggest that no obvious cognitive differences between CAS and CEA can be observed after intervention. Both improvement and deterioration in cognitive functioning can be observed following CAS or CEA. Methodological differences such as patient heterogeneity, implementation and type of control groups, type of psychometric tests used, statistical analyses, or timing of the assessments play an important role in explaining the sometimes divergent results of the included studies. Large-scale and methodologically solid studies comparing CEA and CAS on neurocognitive outcome remain warranted. Future studies should implement adequate control groups to correct for practice effects in the target groups.

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Introduction

Stroke is the third leading cause of death in most western countries [1]. Carotid stenosis has been identified as a risk factor for stroke, with increasing risk depending on the severity of the stenosis [2]. The prevalence of carotid stenosis increases with age in both men and women [3] and with increasing life expectancy, this problem tends to become more important.

To reduce the risk of stroke, carotid endarterectomy (CEA) is performed and has shown to be effective in reducing stroke in patients with recent carotid territory symptoms [4] as well as in asymptomatic patients [5]. Since CEA reduces stroke risk by half in asymptomatic patients [5], CEA is carried out regularly, although the debate whether asymptomatic patients on appropriate medical treatment should be treated is still ongoing [6].

Carotid artery stenting (CAS) has been suggested to be an alternative for CEA, especially in high-risk patients, reducing cranial nerve injury, wound complications and the possible negative effects of general anesthesia such as myocardial infarction [7]. The use of prophylactic CEA and CAS has been evaluated in many studies, and both methods are safe and effective options for stroke prevention in appropriately selected patients and if treated by proficient surgeons or endovascular therapists [8–10].

Although CREST has suggested that CAS is deemed noninferior to CEA on traditional combined endpoints of stroke, myocardial infarction, and death [8], it is associated with an increased risk of new lesions on diffusion-weighted imaging (DWI) in comparison to CEA [11, 12]. Therefore, other outcome variables like neurocognitive functioning (NCF) should also be studied to evaluate the impact of these lesions in the long term [13]. Any carotid revascularization may lead to cognitive decline caused by procedural emboli, general anesthesia (CEA), or temporary flow interruption [clamping (CEA) or balloon dilatation (CAS)] [13, 14]. Conversely, reopening a stenotic vessel and restoring blood flow to the brain may improve cognitive dysfunction caused by chronic hypoperfusion [13, 14]. To date, it is still unclear whether these complex interactions ultimately result in a net improvement or a deterioration in the cognitive function [15].

Several systematic reviews about NCF after carotid revascularization have been published in 2007 and 2008 [14, 16, 17]. The consensus was that it was unclear whether carotid revascularization results in cognitive decline, improvement, or no change at all. It was stated that further research is necessary to clarify the effects of CEA and CAS.

Several factors may contribute to this inconsistency. First, there is much variability in the demographical and clinical characteristics of patients, such as differences in symptoms (i.e. presence or absence of stroke), baseline cerebral perfusion status, age, sex, education, professional level, side and severity of stenosis, length of time between symptoms and revascularization, and medical, neurological and psychiatric histories [17]. Second, study characteristics also vary widely, in particular the susceptibility of the design to learning and practice effects, type of tests used (and their inherent sensitivity), timing of assessments, and failure to implement a (decent) control group. Other factors, like underpowered studies, and variability of surgical techniques and criteria in detecting postoperative change also flaw these cognitive studies [14, 16].

For this review, we will only include papers published since 2007 for two reasons. First, studies published before 2007 have already been discussed extensively in former reviews while no systematic overview of the recent literature has been reported since 2008. Second, because carotid treatment, including medical equipment (e.g. protection devices for CAS and type of stents used), and drug therapy tend to continuously evolve, it is important to look at the recent papers for a better ecological validity of the findings. Indeed, there seems to be a difference between the results of publications depending on the date of publication [14, 17],

where older studies have a higher chance of finding positive results. As De Rango et al. [14] suggested, this might be the consequence of fewer methodological biases in more recent studies.

We will conclude our review with some methodological remarks about research on the cognitive consequences of carotid revascularization and formulate some guidelines that may be relevant for future research.

Methods

In this systematic review, we focus on the neurocognitive consequences of carotid revascularization. We included all English papers concerning the topic of cognitive effects of carotid revascularization published between 2007 and May 2013. Searches were conducted on PubMed and Web of Science using the key word ‘carotid’ in combination with ‘cognitive’, ‘cognition’, ‘neurocognition’, ‘neurocognitive’, ‘neuropsychology’, and ‘neuropsychological’. References of included papers were cross-checked for other relevant papers. Only papers investigating the effects of carotid revascularization (CEA and CAS) on the cognitive functions were retained; reviews were excluded. Papers were included when neurocognitive testing was carried out preoperatively and at least once postoperatively more than 5 days after carotid treatment. Studies that only examined the cognitive functions on the first postoperative days were excluded because anesthesia and type of postoperative medical care may heavily influence these short-term results. Indeed, by using event-related potentials, Mracek et al. [18] found that general anesthesia had a negative effect on cognition the first postoperative day, but after 6 days no differences in cognitive functions were noted between general and local anesthesia.

To ensure that studies conducted extensive neuropsychological testing, papers that only used cognitive screening instruments, such as the Mini-Mental State Examination (MMSE), were excluded. Furthermore, when in total less than 15 patients adhered to follow-up, we excluded the study to avoid underpowering. Finally, studies that solely investigated the effects of revascularization of carotid occlusions were also excluded, since it may not be possible to extrapolate these results to nonocclusive significant carotid artery stenoses.

Studies were grouped into three categories: CEA alone, CAS alone, and CEA versus CAS. Results in these three categories are reviewed for common findings; a focus is given on papers with solid methodological setups, such as studies using the reliable change indices by calculating z-scores: $(\text{individual test score} - \text{mean score of control group}) / \text{SD of control group}$. When simply comparing pre- and postrevascularization cognitive scores for both patient and control groups separately, results are heavily influenced by characteristics like sample size in both groups. Studies are given a superscript ‘a’ mark when they included a control group and compared the patient group(s) with this control group using statistical methods. A superscript ‘b’ mark was given when they included an adequately sized control group but did not compare the groups with each other directly. Underpowered control groups were defined as sample sizes of less than half of the patient sample size. Studies received a superscript ‘c’ mark when they did not implement a control group, or when they did but did not compare the groups directly, and when the control group contained less than half the amount of subjects in the patient group. All CEA versus CAS studies were reviewed because they have at least two groups, which allows a valid comparison between the two techniques. Of the studies only examining CEA or CAS, only studies that received a superscript ‘a’ or ‘b’ mark were reviewed in the Results section to ensure the focus is given on methodologically sound studies.

Results

Sixty-seven studies were identified, of which 37 were included in this review. The papers excluded were 5 reviews, 5 having a too small sample size in follow-up assessments, 6 only using short screening instruments (MMSE), 1 missing a preoperative assessment, 9 only providing follow-up data for a few days, and 2 focusing on intragroup differences and not reporting results of the whole group. Of the 39 remaining articles, 1 study [19] was also excluded because of a large variation in the timing of the postoperative assessment. Patients were tested between 4 and 41 months after intervention. Since the timing of postoperative testing can also be a confounding factor, results from this study are impossible to interpret and to compare with other studies. Another study [20] was left out of this review because it was a subgroup analysis of another paper already included [21]. So in total, 37 studies were included in this review of which 11, 4, and 22 received the superscript ‘a’, ‘b’, and ‘c’ mark, respectively.

Studies Comparing Neurocognitive Outcome after CEA versus CAS

Five of the 7 studies comparing CEA with CAS found no significant differences in cognitive outcome between procedures [7, 22–25] (table 1). Lal et al. [13] also found no differences in the global cognitive score, but discovered that CEA resulted in a reduction in memory performance compared with CAS, while CAS patients showed reduced psychomotor speed. Wasser et al. [21] also found no significant differences in the global difference score, but the domain verbal learning showed a small improvement for CAS compared with CEA.

Although this review contains 2 studies focusing on symptomatic, 2 on asymptomatic, and 3 on symptomatic as well as asymptomatic patients, and some studies even randomized the patients to CEA and CAS, all these studies concluded that CAS and CEA have a comparable effect on cognition in asymptomatic and symptomatic patients.

When looking at the results for CAS and CEA separately compared to healthy controls and applying the methodological criteria described previously, only 2 of the 7 studies are eligible and both used an extensive neuropsychological test battery (table 1; 2 studies with a superscript ‘a’ mark). Wasser et al. [21] found that both patients after CAS and after CEA deteriorated significantly over time in the domain short-term memory and in visuoconstructive functions compared to controls. Altinbas et al. [22] found for CAS, but not for CEA, a small but significant decrease in the total cognitive sum score.

Studies on Neurocognitive Outcome following CEA

Eleven [26–36] of the 18 studies [26–43] examining the effects of CEA fulfilled our criteria (table 2; 8 studies with a superscript ‘a’ mark and 3 with a superscript ‘b’ mark). The Department of Neurosurgery of the Iwate Medical University published several papers on the cognitive consequences of CEA, all using established tests of intelligence and memory. Studies that examined cognitive deterioration found impairment in 13% of patients after CEA [27, 30], while studies focusing on cognitive amelioration after CEA found improvement in 10% of the cases [28, 29]. One study evaluated both trends and noted improvement in 10% and impairment in another 10% of the patients in one or more cognitive domains. All these studies thus found comparable results.

However, other research groups found no changes over time for the patient group [34], while Baracchini et al. [35] found slight but significant improvements in symptomatic but not in asymptomatic patients. It is important to note though that the latter study showed baseline differences between the symptomatic and asymptomatic groups. Gigante et al. [33] noted a decrease in cognitive score in 6% of CEA patients while Yocum et al. [32] discovered a decrease in 16% of patients.

Table 1. Studies comparing neurocognitive outcome after CEA versus CAS

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CEA versus CAS	Control for effect of previous stroke on NCF	Cognitive domains and tests
Witt et al. [7], 2007 ^c	45 24 CEA vs. 21 CAS without CPD Randomized Sympt.	No	6 and 30 days	No differences between CEA and CAS at 6 or 30 days <i>At 6 days:</i> Decline in 19% of CEA vs. 21% of CAS Improvement in 25% of CEA vs. 14% of CAS in 2 or more tasks <i>At 30 days:</i> Decline in 25% of CEA vs. 24% of CAS Improvement in 29% of CEA vs. 24% of CAS in 2 or more tasks	CAS: 33% stroke CEA: 50% stroke No differences in frequency stroke between groups	Verbal memory: RAVLT Non-verbal memory: CFT-R Attention: Paced Visual Serial Addition Test, TMT (A and B), Modified Stroop Executive function: verbal fluency (phonologic and semantic), RNGT Motor skills: Purdue Pegboard Test, Finger-Tapping Test
Takaiwa et al. [23], 2009 ^c	26 11 CEA vs. 15 CAS with CPD No randomization Asympt. + sympt. (45% CEA, 60% CAS)	No	1 week, 3, 6, and 12 months	No significant differences between CEA and CAS for any of the domains or MMSE Only CEA showed decrease at 1 week <i>At 1 week:</i> CEA: 36% of patients showed decrease for immediate as well as delayed memory, visuospatial construction, language, and total score CAS: 13% showed decrease for visuospatial construction and language / 36% showed improvement for immediate and delayed memory, and total score <i>At 3, 6, and 12 months:</i> Improvement in 54% of CEA vs. 67% of CAS No deterioration	No differences in frequency symptomatic status between groups	MMSE RBANS (immediate memory, visuospatial construction, language, attention, delayed memory, and total score)
Feliziani [24], 2010 ^c	46 22 CEA vs. 24 CAS with CPD No randomization Asympt.	No	3 and 12 months	No significant differences between the groups over time for all studied variables No changes over time for CEA or CAS, except for a slight deterioration in visuospatial construction in the CAS group	NA	MMSE Memory: Babcock Story Recall, RAVLT, semantic fluency Attention and executive functions: TMT (A and B), COWAT Visuospatial construction: Copy Drawing Test
Altinbas et al. [22], 2011 ^a	119 58 CEA vs. 61 CAS (no info about CPD) Randomized Sympt.	75 healthy (historical control)	6 months	No significant differences between CEA and CAS in any of the domains No changes in any of the 6 domains for CAS or CEA A small but significant decrease in cognitive sum score for CAS, but not for CEA	CAS: 42% stroke CEA: 51% stroke No differences in frequency stroke between groups	NRT, MMSE Abstract reasoning: WAIS-III similarities, RAPM Attention: WAIS-III digit span (f), Visual Elevator of the Test of Everyday Attention Executive functioning: BSAT, letter fluency Language: TT, BNT Verbal memory: WAIS-III digit span (b), RAVLT, semantic fluency Visual memory: CFT-R Visual perception: JLO, FRT, CFT-R (copy) Neglect: Star Cancellation Test
Lal et al. [13], 2011 ^c	46 25 CEA vs. 21 CAS with CPD No randomization Asympt.	No	4–6 months	No differences on composite change score for CEA and CAS. Both groups showed improvement on composite change score and each individual test Impairment only observed in CEA for working memory index and CAS for psychomotor speed. No differences between CEA and CAS on other tests	NA	TMT Processing speed index (digit symbol coding and symbol search) of WAIS-III Working memory index (letter-number sequencing and spatial span) of WAIS-III BNT COWAT HVLT

Table 1 (continued)

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CEA versus CAS	Control for effect of previous stroke on NCF	Cognitive domains and tests
Wasser [21], 2011^a	55 31 CEA vs. 24 CAS (CPD in 9 of 24) No randomization Asympt. + sympt. (71% CAS, 39% CEA)	27 healthy Matched (age and education)	3 months	No significant differences between the groups on 5 of the 6 domains. Only verbal learning showed an improvement for CAS whereas CEA showed deterioration Both groups deteriorated significantly over time in the domain of short-term memory, and visuoconstructive functions	CEA: 16% stroke CAS: 30% stroke No differences in frequency stroke between groups	MMSE Attention: TAP (alertness and divided attention) Short-term memory: TAP (working memory), SRT, WMS-R Executive functions: RWFT, WCST, Regard's Five Point Test Verbal learning and memory: SRT, WMS-R, Non-verbal learning and memory: CFT-R (recall), INVLT, Spatial Recall Test Visuoconstructive functions: CFT-R (copy)
Zhou et al. [25], 2012 ^c	51 35 CEA vs. 16 CAS with CPD No randomization Asympt. + sympt. (54% CEA, 50% CAS)	No	1 month	No differences between the groups on test scores No statistical methods were used to evaluate cognitive impairment or improvement	CEA: 20% stroke CAS: 25% stroke No differences in frequency stroke between groups	ART MMSE Memory: RAVLT Attention and executive function: <i>TMT, Digit Span, color-word interference</i> Language: <i>category fluency, BNT</i> , Motor skills: <i>GP</i> <i>(no information about results of tests in italics)</i>

Author names in bold means the study was reviewed in the Results section. NA = Not applicable; CPD = cerebral protection device; WAIS-III = Wechsler Adult Intelligence Scale, third edition; WMS-R = Wechsler Memory Scale Revised; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; HVLTL = Hopkins Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GP = Grooved Pegboard; RWFT = Regensburger Word Fluency Test; NVLT = Non-Verbal Learning Test; SRT = Selective Reminding Test; TAP = Test Battery for Attentional Performance; JLO = Judgement of Line Orientation; RNGT = Random Number Generation Task; FRT = Facial Recognition Task; RAPM = Raven Advanced Progressive Matrices; TT = Token Test; BSAT = Brixton Spatial Anticipation Task; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; WCST = Wisconsin Card Sorting Test; ART = Adult Reading Test.

^a Using statistical methods to compare the patient and control group. ^c No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

In the studies comparing patient groups with control groups separately, Czerny et al. [36] found an improvement over time for the patient group on the Number Connection Test at 1 year but not after 5 years. At 1 month after intervention, Soenne et al. [31] observed NCF impairment in 11% of CEA patients but in 0% of the controls.

We can summarize that in most studies, a decrease in the cognitive score over time is found in 10–15% of patients after CEA. Improvements are also often observed in about 10% of patients.

Studies on Neurocognitive Outcome after CAS

Only 2 [44, 45] of the 12 [44–55] included studies examining the effects of CAS fulfilled our methodological criteria regarding control groups (table 3; 1 study with a superscript 'a' mark and 1 with a superscript 'b' mark). Xu et al. [45] implemented a relevant control group that underwent a carotid angiography to correct for practice effects. They used an extensive neuropsychological battery. Only verbal memory showed better results over time in the CAS group; no deterioration in the other tests was observed. Ishihara et al. [44] did not use a reliable change index to measure differences over time in the CAS group, but they had two different control groups. They found differential effects for right-sided CAS (improvement in performance IQ and delayed memory) and left-sided CAS (improvement in verbal IQ). The first control group undergoing neck clipping through craniotomy had minor but nonsignificant increases in the Wechsler Adult Intelligence Scale (third edition) and the Wechsler

Table 2. Studies on neurocognitive outcome after CEA

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CEA	Control for effect previous stroke on NCF	Cognitive domains and tests
Bossema et al. [34], 2007 ^a	45 CEA (20 ICEA and 25 rCEA) Asympt. + sympt. (ICEA: 45%, rCEA: 76%)	25 healthy (similar education, age, and hand dominance)	3 months	No interactions between time and group. Both groups improved equally No difference between patients and controls on reliable changes after CEA	No stroke included	Dichotic Listening Test Finger Tapping Test Motor Planning Test / Verbal Fluency Test (COWAT + category) Doors Test
Saito et al. [39], 2007 ^c	55 CEA Asympt. + sympt. (62%)	20 patients (neck clipping through craniotomy)	1 month	Impairment: 11% in one or more cognitive domains (only impairments were assessed)	44% stroke No symptoms <1 month No significant differences between groups (impairment/no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Falkensammer et al. [43], 2008 ^c	19 CEA at 7–10 days 16 CEA at 6 months Asympt.	No	7–10 days, 6 months	Overall improvement at 7–10 days and 6 months. 3 patients showed decline (1 with reliable change indices = 6%) Significant improvement in digit symbol, verbal memory. Conversely, there was a significant decline on one test assessing processing speed at 6 months (word reading in SCWT)	NA	Fine motor coordination: GP Expressive language: COWAT, category fluency Verbal memory: RAVLT Mental status screen: MMSE Estimated premorbid verbal IQ: ART Processing speed/attention/executive function: Digit Span and Digit Symbol (WAIS-R), TMT (A and B), SCWT, D-KEF Sorting Test
Hirooka et al. [38], 2008 ^c	158 CEA Asympt. + sympt. (70%)	No	1 month	Impairment: 11% on 1 or more of 5 domains (only impairments were assessed)	51% stroke No control for stroke or symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Chida et al. [27], 2009 ^a	60 CEA Asympt + Sympt (62%)	44 patients (neck clipping through craniotomy; historical control)	1 month	Impairment: 13% in one or more of 5 domains (only impairments were assessed)	43% stroke No significant differences between groups (impairment/no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Soinne et al. [31], 2009 ^b	44 CEA Asympt. + sympt. (48%)	22 healthy Matched (sex, age, education, and social class)	100 days	Equal improvement for CEA and controls At 100 days: Impairment: CEA, 5 patients (11%) vs. controls, 0% On the domain level: attention 48% of CEA vs. 18% of controls had impairment (significant), motor dexterity, 32% of patients vs. 18% of controls (NS)	15% minor stroke No control for stroke on NCF	Language: BNT Verbal memory and learning: RAVLT Immediate verbal memory: WAIS-R Digit Span –F and B Verbal fluency: word and category naming Visual memory: CFT-R – Visual Design Learning Test Immediate visual memory: Corsi Blocks F and B Attention: Letter Cancellation Task, TMT (A) Executive function: Stroop Test, TMT (B) Motor dexterity: Purdue Pegboard
Yocum et al. [32] (2009) ^a	149 CEA Asympt. + sympt. (no percentages are given)	60 patients (lumbar spine surgery)	1 month	<i>At 1 month:</i> moderate to severe cognitive deterioration: 16% (10% severe, 6% moderate)	No information is given about symptoms	Verbal function: BNT Verbal fluency: COWAT Visuospatial construction: CFT-R (copy) Visuospatial memory: CFT-R (recall) Complex conceptual switching: TMT (B) Attention: TMT (A) Verbal learning and memory: HVL T or BSRT

Table 2 (continued)

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CEA	Control for effect previous stroke on NCF	Cognitive domains and tests
Chida et al. [28], 2010 ^a	79 CEA Asympt. + sympt. (59%)	70 healthy	1 month	Improvement: 9% in one or more of 5 domains (only improvements were assessed)	19% stroke No symptoms <2 weeks No significant differences between groups (improvement/no improvement) for symptomatic status or stroke	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Czerny et al. [36], 2010 ^b	25 CEA Asympt. + sympt. (60%)	25 healthy Matched (age and sex)	1 and 5 years	Improvement for patient group at 1 and 5 years on the NCT No changes on MMSE	No stroke included	MMSE NCT
Gigante et al. [33], 2011 ^a	127 CEA Asympt. + sympt. (4%)	71 patients (lumbar laminectomy/similar age and education)	30 days	At 30 days: Moderate to severe deterioration: 6%	No information is given about the type of symptoms in the symptomatic patients	Verbal function: BNT Verbal fluency: COWAT Visuospatial construction: CFT-R (copy) Visuospatial memory: CFT-R (recall) Complex conceptual switching: TMT (B) Attention: TMT (A) Verbal learning and memory: HVLIT or BSRT Manual dexterity: GP
Baracchini et al. [35], 2012 ^b	145 CEA (divided into 2 groups: 70 asympt. and 75 sympt.)	68 patients (laparoscopic cholecystectomy) Matched (age and sex)	3 and 12 months	Symptomatic: cognitive performance (MMSE and MOCA) improved Asymptomatics: no changes (though baseline differences: symptomatics were significantly impaired at baseline, asymptomatics not)	No severe stroke 35% of symptomatic group had minor stroke No control for minor stroke on NCF	MMSE MOCA
Ghogawala et al. [37], 2012 ^c	23 CEA (at 1 month) 20 CEA at 6 months 19 CEA at 12 months Asympt. + sympt. (21%)	No	1, 6, and 12 months	At 1 month: Improvement: 30% Deterioration: 30–40% on TMT (A and B) and HVLIT At 12 months: significant improvement for all tests Improvement: 60%	No stroke included	Attention: TMT (A) Executive functioning: TMT (B) Verbal fluency: COWAT Verbal learning and memory: HVLIT
Nanba et al. [30], 2012 ^a	70 CEA Asympt. + sympt. (71%)	44 patients (neck clipping through craniotomy; historical control)	1 month	Deterioration: 13% in one or more of 5 domains (only impairments were assessed)	31% stroke No symptoms <2 weeks No significant differences between groups (impairment/no impairment) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Yamashita et al. [29], 2012 ^a	140 CEA Asympt. + sympt. (69%)	70 healthy (historical control)	1 month	Improvement in 10% of patients in one or more of 5 domains (only improvements were assessed)	No symptoms <2 weeks No significant differences between groups (improvement/no improvement) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Yosida et al. [40], 2012 ^c	213 CEA Asympt. + sympt. (65%)	40 healthy	1–2 months	Improvement: 13% Deterioration: 12%	No symptoms <2 weeks No control for stroke on NCF	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Inoue et al. [41], 2013 ^c	81 CEA Asympt. + sympt. (54%)	No	6 months	Significant improvement for all scores (VIQ, PIQ, WMS-memory and WMS-attention)	No information about stroke tendency of positive effect of symptomatic status on progress	WAIS-R (verbal IQ + performance IQ) WMS (memory + attention)

Table 2 (continued)

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CEA	Control for effect previous stroke on NCF	Cognitive domains and tests
Saito et al. [26], 2013 ^a	100 CEA Asympt. + sympt. (64%)	40 healthy (historical control)	1 month	Improvement: 10% Impairment: 10% in one or more of the 5 cognitive scores	No symptoms <2 weeks No significant differences between groups (improvement/ deterioration) for symptomatic status	WAIS-R (verbal IQ + performance IQ) WMS CFT-R (copy + recall)
Takaiwa et al. [42], 2013 ^c	15 CEA Asympt.	No	3 months	Improvements in immediate memory, attention, total scale of the RBANS, and 2 subtests of WAIS-R Improvement: 30% Deterioration: 7% in RBANS and WAIS-R subtest scores	NA	RBANS (immediate memory, visuospatial construction, language, attention, delayed memory, and total score) WAIS-R 2 subtests (information and picture completion) ART

Author names in bold means the study was reviewed in the Results section. NA = Not applicable; WAIS-R = Wechsler Adult Intelligence Scale Revised; WMS = Wechsler Memory Scale; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; HVLTL = Hopkins Verbal Learning Test; BSRT = Buschke Selective Reminding Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MOCA = Montreal Cognitive Assessment; GP = Grooved Pegboard; NCT = Number Connection Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; ART = Adult Reading Test; SCWT = Stroop Color and Word Test; D-KEF = Delis-Kaplan Executive Function.

^a Using statistical methods to compare the patient and control group. ^b Calculating differences for the patient and control group over time separately, the control group contains more than half the number of the patient group. ^c No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

Memory Scale scores. The second control group with atherosclerotic disease had no changes over time, but this was a smaller group and thus had lower statistical power. Though there are only 2 studies, methodologically solid enough to draw conclusions, small, but positive results are found over time for CAS patients. The problem of the lack of methodologically solid studies can also be observed in the review of De Rango et al. [14]. Only few studies have been published investigating the cognitive consequences of CAS, and even fewer have recruited a control group.

Additional Findings

Symptomatic Status

Some papers only included asymptomatic patients, some admitted symptomatic patients without major (and minor) stroke, and others included all types of symptomatic patients. Sadly, several studies failed to provide information about the symptomatic status and type of symptoms in their patients. Furthermore, differences in timing between the symptoms and intervention can also influence the results.

As previously stated, symptomatic status does not seem to have an influence on the cognitive differences or similarities found between CAS and CEA. Many studies reported no differences in symptomatic status or stroke between groups improving or deteriorating after CEA [26–30, 39]. In contrast, Baracchini et al. [35] found slight improvements for the symptomatic but not for the asymptomatic group after CEA, though it should be noted that the symptomatic group showed lower baseline scores, which might explain these results. Inoue et al. [41] also reported a (nonsignificant) tendency of a positive effect of symptomatic status on NCF after CEA. For CAS, symptomatic status also does not seem to influence cognitive results [51]. Furthermore, Ortega et al. [54] found an improvement in global cognitive score for patients with, as well as without, previous stroke. We can conclude that symptomatic status does not have a clear impact on the NCF after carotid revascularization.

Table 3. Studies on neurocognitive outcome after CAS

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CAS	Control for effect of previous stroke on NCF	Cognitive domains and tests
Xu et al. [45], 2007 ^a	51 CAS with CPD at 1 week 47 CAS with CPD at 12 weeks Asympt. + sympt. (no percentages are given)	57 patients (carotid angiography)	1 and 12 weeks	CAS patients performed better on the RAVLT at 1 as well as 12 weeks At 1 week but not at 12 weeks, CAS patients showed deterioration in BNT	No stroke <1 month Both groups had similar percentage of stroke	RAVLT CFT-R BNT Digit Span (WAIS) TMT Finger Tapping Test MMSE
Mlekusch et al. [47], 2008 ^c	71 CAS with CPD Asympt. + sympt. (6%)	No	6 months	Significant improvement for TMT (A) Improvement: 45% (at least 2 tests) Deterioration: 8%	No stroke patients included	MMSE Attention: TMT (A and B) Verbal intelligence and fluency: COWAT + semantic
Turk et al. [52], 2008 ^c	17 CAS (no info about CPD) Asympt. + sympt. (76%)	No	3 months	Total RBANS score, immediate memory and attention improved	35% stroke No control for stroke	MMSE RBANS TMT
Tiemann et al. [49], 2009 ^c	22 CAS without CPD Asympt.	No	6 weeks	Improvement: LLT Deterioration: Digit Span Tendency to improvement: phonemic verbal fluency Improvement: 36% Deterioration: 27%	NA	MWT-B, LLT, NCT, Digit Span (F and B), Spatial Span (F and B) Verbal fluency: phonological and semantical Block-Design-Test (WAIS)
Grunwald et al. [48], 2010 ^c	41 CAS without CPD Asympt.	7 patients (endovascular treatment ACA aneurysms)	3 months	CAS: significant increase in cognitive speed but not memory Control group: no significant differences	NA	MMSE Cognitive speed: NCT, Labyrinth Test, Figure-Symbol Test, Color-Word Test Memory: Repeat the Numbers Test, Word List Test, Image Test, Word Pairs Test, Symbol Test, Latent Learning Test
Raabe et al. [51], 2010 ^c	62 CAS with CPD (51 at 3 months, 48 at 6 months, and 51 at 12 months) Asympt. + sympt. (31%)	No	3, 6, and 12 months	<i>At 3 months:</i> 16% improvement, 82% stable, 2% decline <i>At 6 months:</i> 21% improvement, 71% stable, 8% decline <i>At 12 months:</i> 22% improvement, 78% stable, 0% decline	No major stroke 26% minor stroke No effect of symptomatic status on NCF No control for stroke	DRS-2 RAVLT TMT (B) ART MMSE
Murata et al. [53], 2011 ^c	16 CAS with CPD Sympt.	16 healthy	1 month	No differences for total score RBMT. No scores for control group are provided	No info about stroke No control for stroke	RBMT
Chen et al. [46], 2012 ^c	34 CAS with CPD [divided into I (n = 6): ipsilateral ischemia and failed CAS; II (n = 17): ipsilateral ischemia and successful CAS, and III (n = 11): no ischemia and successful CAS] Asympt.	No	3 months	Only group II showed significant improvement in ADAS-cog, MMSE and CTM (A) No changes for CTM (B) and semantic fluency No significant changes for groups I and III	NA	MMSE Alzheimer's Disease Assessment Scale cognitive subscale CTM (A and B) Semantic fluency
Mendiz et al. [55], 2012 ^c	20 CAS with CPD Asympt.	No	3 months	Improvement in set shifting (TMT B), processing speed (digit symbol coding and symbol search), and working memory (digit span backwards), verbal (RAVLT acquisition) and visual memory (CFT-R delayed score) The other tests revealed no differences	NA	MMSE ACE-R BNT Verbal fluency: phonologic and semantic RAVLT CFT-R Digit Span (F and B) TMT (A and B) WCST INECO Frontal Screening, Digit Symbol Coding (WAIS-III) Symbol Search (WAIS-III)

Table 3 (continued)

Reference	Patients in follow-up	Control group	Follow-up period	NCF after CAS	Control for effect of previous stroke on NCF	Cognitive domains and tests
Cheng et al. [50], 2013c	144 CAS (no info about CPD) – all MCI patients Asympt. + sympt. (55%) No randomization	64 MCI patients (carotid stenosis on drug therapy) Asympt. + sympt. (56%)	6 months	CAS group: small but significant improvements in MMSE, MOCA, FOME and digit span. Rapid verbal retrieval showed no significant differences No significant changes for the control group	No stroke <4 weeks Both groups had similar % of stroke	MMSE MOCA FOME Rapid verbal retrieval digit span (WAIS)
Ishihara et al. [44], 2013b	39 (21 rCAS, 18 ICAS) with CPD Asympt. + sympt. (no percentages are given)	2 control groups: (a) 17 patients (neck clipping through craniotomy), (b) 12 patients (atherosclerotic carotid artery disease)	6 months	IQ performance and delayed memory improved after rCAS VIQ improved after ICAS Group A: slight but not significant increases in most WAIS-III and WMS scores Group B: no significant changes in the WAIS-III or WMS scores	No stroke <3 months No control for stroke on NCF	WAIS-III (verbal IQ, performance IQ, and full IQ) WMS-R (general memory, verbal memory, delayed memory, visual memory, attention, and concentration)
Ortega et al. [54], 2013c	33 CAS with flow reversal Asympt. + sympt. (50%)	No	6 months	Global improvement, mainly information processing speed, language, memory and visuospatial function	48% stroke Global score improved for patients with and without previous stroke	Digit Span (WAIS-III), WMS-III Mental Control (attention) BNT Token Test Verbal fluency: COWAT and Semantic Fluency CVLT GP JLO SCWT

Author names in bold means the study was reviewed in the Results section. NA = Not applicable; CPD = Cerebral Protection Device. WAIS-III = Wechsler Adult Intelligence Scale, third edition; WMS = Wechsler Memory Scale; CFT-R = Rey Complex Figure Test; RAVLT = Rey Auditory Verbal Learning Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MOCA = Montreal Cognitive Assessment; GP = Grooved Pegboard; NCT = Number Connection Test; RBMT = Rivermead Behavioral Memory Test; CVLT = California Verbal Learning Test; JLO = Judgement of Line Orientation; FOME = Fuld Object Memory Evaluation; CTM = Color Trail Making Test; ACE-R = Addenbrooke's Cognitive Examination Revised; LLT = List Learning Test; TMT = Trail Making Test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; WCST = Wisconsin Card Sorting Test; ART = Adult Reading Test; SCWT = Stroop Color and Word Test; MWT-B = Mehrfach-Wahl-Wortschatz-Test; ACA = anterior cerebral artery.

^a Using statistical methods to compare the patient and control group. ^b Calculating differences for the patient and control group over time separately, the control group contains more than half the number of the patient group. ^c No control group, or calculating differences for the patient and control group over time separately, with a control group that contains less than half the number of the patient group.

Side of Intervention

For CEA, the side of carotid intervention does not have an influence on cognitive function. By using neuropsychological instruments sensitive to hemispheric specialization, Bossema et al. [34] demonstrated convincingly that changes in cognition occurred irrespective of the side of intervention. Similarly, Baracchini et al. [35] detected no influence of the side of the surgery on any of the test variables. Furthermore, many studies found no difference in the side of intervention between groups improving or groups deteriorating postoperatively [28, 29, 39, 41].

In CAS, results are less consistent. Grunwald et al. [48] and Turk et al. [52] found no correlation between the cognitive results and the side of the intervention. On the other hand, Ishihara et al. [44] and Ortega et al. [54] found differential effects for left and right CAS. Ishihara et al. [44] noted that the performance IQ improved after CAS in patients with severe right-sided carotid artery stenosis while the verbal IQ rose after endovascular treatment of the left carotid artery. Ortega et al. [54] found a significant increase in the global cognitive score, more specifically in language, visuospatial function, and information processing for left CAS, while patients with right CAS only presented a (nonsignificant) trend toward global cognitive improvement.

Age

In large studies and systematic reviews, age has been shown to be a predictor of postoperative cognitive dysfunction after noncardiac surgery [56, 57]. For CAS and CEA, it was also shown that increasing age may raise the risk of cognitive decline [51, 58], though not all studies found a clear effect of age on cognition in CAS [47, 48, 52, 54].

Wasser et al. [20] found that older patients seem to be particularly vulnerable to cognitive decline after CEA, while CAS seems to have better results at follow-up. Feliziani et al. [24], however, did not find these differences between CEA and CAS in elderly patients. In addition, increased neurological complications occur in the elderly after CAS in comparison to CEA, hence a patient-tailored approach is mandatory to reduce stroke and death risk in this high-risk group [8, 59].

Perioperative Embolization

CAS has a higher incidence of perioperative microemboli detected by transcranial Doppler monitoring compared with CEA, despite the use of distal protection devices [60–62]. Crawley et al. [60], however, found no correlation between the amount of emboli of CAS and CEA with neuropsychological measures. Martin et al. [63] concluded in their systematic review that the effect of perioperative embolization on cognition remains undecided. This may be the consequence of the variability in type (gaseous vs. particulate) and size of emboli.

A few particulate emboli can be more damaging than several gaseous emboli. Therefore, differentiation between emboli may be valuable, but even the EmboDop created to differentiate between gaseous and particulate emboli seems up till now unreliable [64, 65].

Transfemoral proximal protection using flow occlusion is increasingly used to protect the brain from cerebral embolization during CAS by blocking or reversing the direction of blood flow in the distal carotid artery [54]. In transcervical stenting with flow reversal it is possible to eliminate the shower of emboli typically seen in CAS with or without distal protection devices [66]. A recent study [62] compared CAS with flow reversal to CAS with a distal protection device and found lower embolization rates for flow reversal, especially during the protection phase of the procedure, though this difference was statistically not significant.

New Brain Lesions after Revascularization

As Schnaudigel et al. [61] showed in their systematic review, CAS is more frequently associated with new DWI lesions compared with CEA (37 vs. 10%). These findings were supported by several recent studies [12, 21, 22, 25]. In a randomized trial, Bonati et al. [11] also found that three times more patients in the CAS group than in the CEA group had new ischemic lesions (DWI) on post-treatment scans. Schnaudigel et al. [61] concluded that the use of cerebral protection devices (33 vs. 45% without) and closed-cell designed stents during CAS (31 vs. 51% with open-cell stents), as well as selective versus routine shunt usage during CEA (6 vs. 16%, respectively) also significantly reduced the incidence of new ipsilateral DWI lesions.

Remarkably, numerous studies have failed to find an association between the incidence, the number, and the volume of new lesions and changes in cognition for CAS as well as CEA [21, 31, 38, 41, 44, 48, 49, 51]. It seems that DWI does not capture all damage that may evoke cognitive deterioration, and some DWI lesions may have little functional value.

Other Findings Related to Postoperative Changes

Using computed tomography perfusion, Cheng et al. [50] found a close relation between the change of perfusion and the change in their cognitive tests. Patients undergoing CAS with baseline impairment of middle cerebral artery blood flow were more likely to experience

improvement in flow after revascularization. Improvement in middle cerebral artery blood flow was associated with greater cognitive improvement in attention and executive functioning [37]. Repair of a presurgical low relative cerebral blood flow in the ipsilateral cerebral hemisphere has been shown to significantly improve postoperative cognitive function in patients undergoing CEA [28, 29].

Postoperative cognitive deterioration on the contrary seems significantly associated with postoperative hyperperfusion regardless of any new lesions on MRI [27, 30, 38]. Similarly, cerebral hyperperfusion after CEA results in postoperative cerebral white matter damage (detected by diffusion tensor imaging), that is related to postoperative cognitive impairment [30]. The provided data show a link between cognition and postoperative perfusion changes for CAS as well as CEA.

Conclusions

In future research, we recommend to include a control group, preferably patients with asymptomatic carotid stenosis not undergoing revascularization. Although several researchers [37, 42] correctly claim that different forms of material reduce practice effects, patients become ‘test wise’. This can also result in significantly increased test scores over time [67]. To avoid alternative explanations, control groups are deemed necessary. Furthermore, future research papers should be clear about the exclusion criteria that are essential to interpret the results, especially about inclusion and exclusion of stroke patients. On the one hand, stroke patients may show better cognitive improvement due to neural reorganization that has nothing to do with revascularization. On the other hand, stroke patients could have fewer benefits of revascularization due to more permanent brain damage that is not alleviated by restored perfusion. When researchers decide to include stroke patients, it is essential to check whether stroke has an influence on the postoperative changes in order to rule out the fact that these changes are the result of stroke instead of the revascularization. Moreover, some researchers use changes in total scores to compare different groups while others employ scores in various domains. The latter is advised because some domains may improve while others may deteriorate, and a global NCF score may not pick up these subtle differences. We recommend to report the percentage of patients in whom NCF improves and in whom NCF deteriorates. Finally, in order to reduce the high dropouts of patients during follow-up, we advise future researchers to test patients at home or to reduce the frequency and duration of the assessments.

In this review, we were not able to be strict on features like the type of control group. Healthy controls might not be an ideal comparison for patients with carotid artery disease, since these two groups are likely to differ on cardiovascular risk factors and general medical condition. Comparing carotid interventions to other interventions is a better alternative but still leaves possibilities for alternative explanations. An ideal comparison is that of patients with significant carotid stenosis undergoing revascularization and similar patients on best drug treatment, though for researchers advocating the usefulness of revascularization in asymptomatic patients, this may be difficult ethically.

In comparison with former reviews, we focused on methodological criteria when interpreting the results, such as the use of a control group, comprehensive psychometric evaluation (not solely short screening instruments), and assessments not only in the early postoperative stage. We can conclude that CEA and CAS have comparable effects on NCF. The inconsistency of the various studies has been explained throughout this review article with NCF deterioration in 10–15% of CEA patients, while an improvement of 10% of patients was also found regularly. Though there are limited methodologically solid studies examining the

effects of CAS on cognitive function, the studies provided show similar results. Nonetheless, there remains a need for larger, controlled prospective studies assessing NCF after carotid revascularization.

Although NCF following intervention for carotid stenosis remains a matter for debate, it is an important outcome measure when comparing different treatments. As stated by Siddiqui and Hopkins [68] and Huang et al. [69], postoperative testing should be performed beyond 3 months to show lasting effects. Especially patients with baseline impaired perfusion could be a vulnerable cohort in which revascularization might enhance NCF.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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