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REVIEW

50 Shades of 'Groundhog Day'

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Introduction: The 2017 European Society for Vascular Surgery (ESVS) guidelines on carotid and vertebral artery disease concluded that the evidence did not support a role for carotid endarterectomy (CEA) or carotid artery stenting (CAS) in patients with asymptomatic carotid stenosis (ACS) in preventing cognitive impairment or dementia. What new data have emerged since 2017, and have they influenced the 2023 ESVS guidelines?
Report: In a systematic review, 33/35 studies (94%) reported a "significant association" between ACS and cognitive impairment; 20 studies had 1—3 tests with significant cognitive impairment; 10 reported 4—6 tests with cognitive impairment; and three studies reported ≥7 tests with significant cognitive impairment. Baseline data from 1 000 patients with ACS in the second Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST-2) reported that the overall Z score for cognition in patients with ACS was significantly lower than expected, especially for word list recall and word list learning. Another systematic review reported that (in the long term) 69% of patients with ACS undergoing CEA/CAS had no change in cognitive function. However, in another 25%, cognitive scores/domains were mostly unchanged, but 1—2 individual tests were significantly improved. In addition, 1 601 UK and Swedish patients with ACS were randomised in the first Asymptomatic Carotid Surgery Trial (ACST-1) to CEA or best medical therapy (BMT). There was no difference in 10 year rates of dementia (CEA 6.7% *vs.* 6.6% with BMT) or at 20 years (14.3% [CEA] *vs.* 15.5% [BMT]), suggesting that CEA did not prevent dementia *vs.* BMT (hazard ratio 0.98, 95% confidence interval 0.75—1.28; $p = .89$).
Discussion: ACS is associated with significant cognitive impairment, but whether this supports a direct aetiological role, or a marker for something else, remains unknown. There is no evidence that CEA/CAS prevents late dementia. The 2023 ESVS guidelines have not changed its recommendation compared with the 2017 version.
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"I think every day is 'Groundhog Day'

I get to learn from my mistakes and become better every day"

Ashton Kutcher

INTRODUCTION

Over the last 25 years, it has been regularly hypothesised that asymptomatic carotid stenosis (ACS) may be an important aetiological factor in the development of cognitive impairment and or dementia, and that these conditions may be reduced (prevented) by the timely performance of carotid endarterectomy (CEA) or carotid artery stenting (CAS).

Numerous studies have addressed this seemingly simple question, but most have published conflicting findings thereby allowing proponents and opponents to find evidence supporting personal prejudices. This failure to find a consensus was largely because study sample sizes were invariably too small, there was no consensus on choice of cognitive test batteries, rarely any involvement of a neuropsychologist in the design and or assessment of patients, there was no consensus on the optimal timing for post-operative testing (early post-operative outcomes were usually combined with late assessments), there was no correction for "practice effects" associated with repeat cognitive testing, and (most importantly) most studies combined data from symptomatic and asymptomatic patients, which inevitably confounded meaningful interpretation of the data. Consequently, the 2017 European Society for Vascular Surgery (ESVS) guidelines on carotid and vertebral artery disease concluded that there was no evidence supporting a role for CEA/CAS in patients with ACS to prevent cognitive impairment or dementia.[1]

Six years have now elapsed since the publication of the 2017 ESVS guidelines and the controversy endures. What

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new data have emerged, and has it influenced the 2023 ESVS carotid guidelines?[2]

OVERVIEW OF NEW DATA SINCE 2017

Asymptomatic carotid stenosis and cognitive impairment

A 2021 systematic review (commissioned by the Guideline Writing Committee [GWC] of the 2023 ESVS carotid guidelines)[2] identified 35 non-randomised studies that evaluated cognitive function, specifically in patients with ACS.[3] Overall, 33/35 studies (94%) reported a "significant association" between ACS and cognitive impairment. Notwithstanding the considerable variability in the choice of cognitive testing (simpler, thus easier to administer *vs.* complicated and more time consuming), 20 studies reported that 1—3 tests within the overall battery of cognitive tests showed evidence of significant cognitive impairment; 10 reported that 4—6 tests showed cognitive impairment; and three studies reported that ≥7 tests showed evidence of significant cognitive impairment.[3]

Not included in the 2021 systematic review were baseline data from 1 000 patients with ACS in the second Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST-2), which is currently randomising patients with ACS to CEA or CAS plus best medical therapy (BMT) *vs.* BMT alone.[4] The cognitive battery was developed in a general population and includes the tests Word List Learning Sum, Word List Recall, and Word List Fluency for animal names and the letter "F". The overall Z score for patients with ACS was significantly lower than expected, especially for word list recall and word list learning.[4] The unique benefit of the CREST-2 substudy is that it will be able to evaluate prospectively changes in cognition in patients randomised to BMT, as well as evaluating whether CEA or CAS improves cognitive function.

Effect of carotid interventions on cognitive function and dementia

Another 2021 systematic review (also commissioned by the 2023 ESVS carotid guidelines GWC)[2] reported on the early and late effects of CEA or CAS in patients with ACS (Table 1).[5] Twenty-one studies (n = 2 059) included 24 patient cohorts undergoing carotid interventions (11 CEA cohorts; 10 CAS cohorts; three included CEA and CAS) who underwent pre-operative and then early post-operative assessment (≤3 months) of their carotid intervention. By contrast, 16 studies (n = 1 557) included 21 cohorts undergoing carotid interventions in patients with ACS (12 CEA cohorts, seven CAS cohorts; two included CEA and CAS patients) who underwent pre-operative and then late post-operative assessment (≥5 months) after their carotid intervention (13/21 cohorts underwent their last cognitive assessment after one year or more had elapsed).[5]

At late review (Table 1), 69% reported no significant change in cognitive function. However, cognitive scores/domains were mostly unchanged in 25% of patients, but 1—2 individual cognitive tests were significantly improved. Few patients had a significant improvement in late cognitive function *vs.* baseline (one cohort; 1.5% of the study population), while only one cohort (1.8% of the study population) had significant worsening of cognitive impairment at late review.[5] Only one study has reported on whether pre-operative haemodynamic status influenced post-operative cognitive function in three groups of patients with ACS.[6] In this small study, patients with 80%—99% ACS plus normal cerebral vascular reserve (CVR) who underwent CAS had no change in post-operative cognition. Controls with 80%—99% ACS plus impaired CVR who did not undergo CAS also had no change in post-operative cognition. However, patients with 80%—99% ACS and impaired CVR who underwent CAS had significant improvements across all cognitive domains after CAS.[6]

Not included in the 2021 systematic review were long term data from 1 601 UK and Swedish patients with ACS randomised in the first Asymptomatic Carotid Surgery Trial (ACST-1) to CEA or BMT.[7] Using trial data, electronic health records and telephone and postal review, there was no difference in 10 year dementia rates (CEA 6.7% [CEA] *vs.* 6.6% [BMT]) or at 20 years (14.3% [CEA] *vs.* 15.5% [BMT]), suggesting that CEA did not prevent late dementia *vs.*

Table 1. Effect of carotid interventions on cognitive function.

	Early (baseline *vs.* < 3 mo)		Late (baseline *vs.* > 5 mo)	
	Cohorts (n = 24)	Patients (n = 2 059)	Cohorts (n = 21)	Patients (n = 1 554)
All domains/tests significantly improved	2	91 (4.4)	1	24 (1.5)
Most domains unchanged, 1—2 tests significantly improved	7	250 (12.1)	11	386 (24.8)
Mixed findings (some tests improved; similar proportion worse)	3	257 (12.5)	1	19 (1.2)
No change in cognitive function	9	1 086 (52.7)	6	1 073 (69.0)
Most domains unchanged, 1—2 significantly few worse	2	347 (16.8)	1	24 (1.5)
All domains/tests significantly worse	1	28 (1.4)	1	28 (1.8)

Data are provided as n or n (%).

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BMT (hazard ratio 0.98, 95% confidence interval 0.75—1.28; $p = .89$).[7]

DISCUSSION

The 2021 systematic review[3] and the CREST-2 baseline data[4] clearly show that ACS is associated with cognitive impairment. However, the key question is whether ACS has a direct aetiological role or is simply a marker for something else. The 2021 systematic review included a detailed review of the literature supporting a direct aetiological role for ACS, including silent cerebral infarction, silent embolisation, involvement in the pathophysiology of white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI), and a haemodynamic aetiology.[3]

There are two types of silent cerebral infarction (cortical and lacunar). To date, there is very little evidence suggesting that cognitive impairment is associated with silent cortical infarction ipsilateral to a significant ACS. In many studies, the presence of ipsilateral brain infarction was an exclusion criterion. The simple fact is that too few studies have addressed this question, and this is therefore an important area for future research. By contrast, lacunar infarction (known to be an important predictor of developing cognitive impairment over time)[8] is mainly due to small vessel intracranial disease rather than being associated with ACS.[3] Similarly, and contrary to popular opinion, there is no published evidence supporting an aetiological role for silent embolisation as a cause of cognitive decline or dementia in patients with ACS. Most studies report no association.[3] There is also no evidence that ACS is involved in the pathophysiology of WMHs on MRI, which (like lacunar infarction) are more likely to be caused by small vessel intracranial disease.[3] However, the systematic review did find more compelling evidence that where ACS was associated with impaired CVR, a haemodynamic aetiological role in the development of cognitive impairment was more likely.[3]

To date, there is no evidence that performing CEA in patients with ACS prevents dementia.[7] Similarly, the 2021 systematic review observed that the majority of patients with ACS (69%) had no change in late post-operative cognitive function.[5] However, in about 25% of patients with ACS, while there was no significant change in most tests/domains of cognitive function, there were significant improvements in 1—2 individual tests of cognitive function. There was no consensus on which particular types of cognitive function improved post-operatively (executive function, memory, etc.), but these limited improvements may be important for individual patients.

Finally, the first systematic review reported that a haemodynamic aetiology may be an important aetiological factor in a subgroup of patients with ACS.[3] Unfortunately, only one small study has tested whether carotid interventions reverse cognitive impairment in this situation,[6] and this is another important area for future research.

In conclusion, and based on the literature published since 2017, the 2023 ESVS carotid guidelines have not changed the recommendation. Until more compelling data are available, there is no role for CEA or CAS in preventing cognitive impairment or dementia in patients with ACS.[2] However, it should be noted that the presence of impaired CVR in patients with ACS is already an indication for intervention, according to the ESVS, as it is known to be associated with a higher risk of ipsilateral stroke in medically treated patients.[2]

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CONFLICTS OF INTEREST

None.

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