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Cognitive Performance in Elderly Patients Undergoing Carotid Endarterectomy or Carotid Artery Stenting: A Twelve-Month Follow-Up Study

F.T. Feliziani[a] M.C. Polidori[d] P. De Rango[b] F. Mangialasche[a, f] R. Monastero[c] S. Ercolani[a] T. Raichi[a] V. Cornacchiola[a] G. Nelles[e] P. Cao[b] P. Mecocci[a]

[a]Institute of Gerontology and Geriatrics, and [b]Division of Vascular Surgery, University of Perugia, Perugia, and [c]Laboratory of Epidemiology and Psychology of Aging and Dementia, Department of Clinical Neuroscience, University of Palermo, Palermo, Italy; [d]Department of Geriatrics, Marienhospital Herne, Ruhr University of Bochum, Bochum, and [e]Department of Neurology, St. Elisabeth-Krankenhaus Köln, Cologne, Germany; [f]Aging Research Center, Karolinska Institutet, Stockholm, Sweden

Key Words
Carotid endarterectomy · Carotid artery stenting · Cognition · Cognitive performance

Abstract
Background: It is still a matter of debate if and to what extent carotid endarterectomy (CEA) and carotid artery stenting (CAS) impair cognitive functioning in the elderly. ***Methods:*** We conducted a nonrandomized clinical trial on subjects with asymptomatic carotid artery stenosis comparing CEA (n = 28; 24 males and 4 females; 72.6 ± 5.8 years old) with CAS (n = 29; 17 males and 12 females; 75.1 ± 5.7 years old). Cognition, mood and functional status were evaluated by a broad spectrum of tests performed on the day prior to carotid reopening as well as 3 and 12 months after. ***Results:*** No significant differences in scores on cognitive tests including the Babcock story recall test and Rey's auditory verbal learning test (memory), category naming test (verbal fluency), trail-making test parts A and B (attention and executive function) and controlled oral word association test (executive functioning) were observed 3 and 12 months after carotid reopening independent of the technique used. Only scores on the copy drawing test (visuospatial and constructional abilities) slightly but significantly ($p < 0.05$) worsened in the CAS group 12 months after the intervention. No significant differences between the CEA and CAS groups were detected regarding mood and functional status after 3 and 12 months. ***Conclusions:*** CEA and CAS seem to be safe procedures in elderly patients in terms of cognitive, mood and functional status in the short and long term. CAS might be preferred for the shorter hospital stay, but further studies with a larger number of old and oldest old subjects with a longer follow-up are needed to better understand the cost-effectiveness of both treatments.

Introduction

Asymptomatic carotid artery stenosis (ACAS) is present in up to 12.5% of subjects older than 70 years [1], and it has been recognized as a risk factor for stroke [2] and cognitive decline [3]. Stroke is the third leading cause of

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Prof. Patrizia Mecocci, MD, PhD, Section of Gerontology and Geriatrics
Department of Clinical and Experimental Medicine, University of Perugia
Ospedale S.M. della Misericordia – S. Andrea delle Fratte
IT–06156 Perugia (Italy)
Tel. +39 075 578 3270, Fax +39 075 573 0259, E-Mail mecocci@unipg.it

death in the USA and Europe [4] and one of the main causes of long-term disability. It has been suggested that one in three North Americans will experience stroke, dementia or both during their life [5] and that after a cerebrovascular event, 64% of subjects will develop dementia [6]. The risk of incident dementia in the elderly increased fourfold after ischemic stroke in cognitively healthy subjects compared to clinically stroke-free controls [7].

A compromised cerebral blood flow plays an important role in the recurrence of ischemic episodes, and ACAS is recognized as a risk factor for vascular cognitive impairment [8]. While the surgical treatment of carotid artery stenosis has been proposed half a century ago to reverse cognitive impairment or prevent its progression [9], the impact of carotid surgery on cognitive functioning has recently gained a great deal of attention. This is due to the occurrence, especially among the elderly, of neurological and cognitive deficits after cardiac and noncardiac surgery [10, 11].

Studies on the effects of carotid reopening on cognition are quite controversial [12]. While the intervention in carotid stenosis might be beneficial by enhancing cerebral perfusion [9], a recent review of population-based studies has suggested that carotid reopening could also lead to cognitive decline through different mechanisms [13]. Carotid reopening can be achieved either by carotid endarterectomy (CEA) or carotid artery stenting (CAS). A decline in cognitive function after carotid reopening could occur from microembolic ischemia during surgical dissection (CEA) or intravascular maneuvering (CAS), or from hypoperfusion during clamping (CEA) or balloon dilation (CAS). It is still unclear whether the carotid revascularization will ultimately result in improving or worsening cognitive functioning. Furthermore, it is unknown whether CEA and CAS have a different effect on cognitive outcomes, especially in the elderly, since the clinical investigations designed to compare the efficacy of these techniques in patients with carotid artery stenosis have mainly focused on classical endpoints such as stroke, myocardial infarction and death [14–16].

The aim of this study was to investigate the short- and long-term impact of CEA and CAS on several cognitive functions in elderly subjects who had previously been cognitively healthy, and were evaluated by a comprehensive neuropsychological battery before intervention and at 3- and 12-month follow-up time points.

Patients and Methods

Patients

Elderly patients aged 65 years and over admitted to the Division of Vascular Surgery at the University Hospital of Perugia from January 2007 to January 2008 with a diagnosis of asymptomatic severe (>70%) internal carotid artery (ICA) stenosis were included in the study after having given their informed consent. The study was approved by the local ethical committee and conforms to the Declaration of Helsinki.

Exclusion criteria were the presence of dementia diagnosed on the basis of DSM-IV [17] criteria and a Mini-Mental State Examination (MMSE) [18] score of <24/30. Other exclusion criteria were the presence of depression diagnosed on the basis of DSM-IV [17] criteria, a history of stroke as well as the inability to provide consent or compliance with the follow-up procedures.

Patients underwent full clinical and neuropsychological evaluation on the day prior to the carotid reopening procedure (T0) and at 3- (T3) and 12-month (T12) follow-up time points by specifically trained geriatricians (F.T.F., F.M., T.R. and V.C.). Demographic, clinical and pharmacological data were also collected. Major vascular risk factors/diseases were recorded as follows: hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg or use of antihypertensive drugs); diabetes (fasting blood glucose ≥126 mg/dl or use of blood-glucose-lowering drugs); hypercholesterolemia (LDL ≥130 mg/dl or use of lipid-lowering drugs); hypertriglyceridemia (≥200 mg/dl or use of specific treatment), and coronary artery disease (previous history of myocardial infarction or ECG signs of ischemic heart disease).

Vascular Diagnostics and Operative Procedures

The diagnosis of severe stenosis of the ICA was ascertained by means of duplex ultrasound performed by independent experienced vascular surgeons, using an ATL HDI 3000 system with a 12.5-MHz linear probe. Measurements of the site, degree and length of stenosis, plaque characteristics and vessel were performed in order to select the adequate size of the balloon and stent in case of CAS intervention. A stenosis of >70% was diagnosed when the peak systolic velocity exceeded 200 cm/s. Duplex velocity criteria had previously been validated against angiography as a gold standard using the European Carotid Surgery Trial criteria [19]. The severity of stenosis in the operated carotid ranged from 70 to 90%. Stenosis of the contralateral carotid is reported in table 1.

CEA or CAS procedures were selected according to plaque morphology and comorbidity. Usually, CAS was preferred in the presence of long plaque, severe coronary or pulmonary disease, previous neck surgery or irradiation. CEA was chosen when a fatty component and/or thrombus within the carotid plaque were probable, in addition to the presence of severe carotid tortuosity or calcification [20]. Both types of interventions were performed by highly experienced vascular surgeons (P.D.R., P.C.).

CAS was performed in a dedicated operating room equipped for endovascular procedures, under local anesthesia and through a femoral approach. Cerebral protection devices and stents of different models were used. CEA was performed under local (15 subjects) or general (7 subjects) anesthesia according to the patients' preferences and vessel anatomy. The patients were continuously monitored during the intervention by transcranial Doppler and by direct neurological assessment while they were awake [20]. No

complications were observed during the intervention and at the follow-up.

Follow-Up Study

The postoperative evaluation consisted of clinical and duplex examinations performed by surgeons before discharge and after 1, 3, 6 and 12 months. A follow-up evaluation of the cognitive status was performed by geriatricians 3 months after the revascularization procedure (short-term follow-up) and 12 months later (long-term follow-up), using the same battery of tests.

Neuropsychological and Functional Assessment

Neuropsychological tests were administered by a trained physician who was blind to the operative procedure in a quiet environment in the hospital. The battery of tests included the MMSE [18] as measure of global cognitive function and tests evaluating the following cognitive domains:

(1) Memory: Babcock story recall (SR) test and Rey's auditory verbal learning test, immediate (Rey-IR) and delayed recall (Rey-DR), to assess episodic memory; verbal fluency with semantic cues (category naming test, CNT) to estimate semantic abilities; in order to minimize the learning effect, 3 alternative lists of words were used for the Rey
(2) Attention and executive functions: trail-making test, part A (TMT-A) and B (TMT-B), to evaluate selective and divided attention, respectively; controlled oral word association test (COWA) to estimate executive functioning
(3) Visuospatial and constructional abilities: copy drawing test (CD).

Details on the administration procedures and scoring as well as the Italian normative data on score adjustment for age and education, and the normality cutoff scores (95% of the lower tolerance limit of the normal population distribution) were used for each test [21, 22].

At the end of the cognitive session, the presence of depressive symptoms was assessed using the 15-item version of the Geriatric Depression Scale (GDS) [23]. Basic activities of daily living (ADL) [24] and instrumental activities of daily living (IADL) [25] were used to examine the functional status.

Statistical Analysis

Data are presented as means ± SD for continuous variables and as proportions for categorical variables. Because of the small number of enrolled subjects and nonnormal distribution of several of the considered variables, a nonparametric statistic was chosen. Comparisons between groups were performed by the Mann-Whitney test for independent samples, and by Fisher's χ^2 test as appropriate, while intragroup comparisons at different points in time were performed by the Wilcoxon signed-rank test.

In order to evaluate cognitive functions, and mood and functional status after surgery, the differences observed in each patient after 3 months (T3 – T0, ΔT3) and 12 months (T12 – T0, ΔT12) with respect to baseline were computed. For neuropsychological tests, Δ was calculated from scores adjusted for age and education according to the Italian normative data. The mean Δ values were compared (i) within each treatment group to assess the variation over time, and (ii) between groups to detect any different effects between CEA or CAS. The data were analyzed using the SPSS statistical software, version 12.0 (SPSS, Chicago, Ill., USA). The level of significance was set at $p < 0.05$ for all analyses.

Table 1. Demographic and clinical characteristics and vascular risk factors in CEA and CAS patients

	CEA (n = 22)	CAS (n = 24)	p
Age, years	71.9 ± 5.7	75.6 ± 5.7	0.19
Range	65 – 82	65 – 88	
Gender – female, n	4 (18%)	11 (46%)	<0.05
Education, years	8.0 ± 5.1	5.7 ± 3.0	0.06
Stenosis of the contralateral carotid, %			
Right	53 ± 23	49 ± 30	0.6
Left	35 ± 29	29 ± 20	0.5
Vascular risk factors, n			
Hypertension	20 (90.0%)	17 (71.0%)	0.1
Diabetes	7 (32.0%)	9 (37.5%)	0.6
Hypercholesterolemia	13 (59.1%)	11 (45.8%)	0.3
Hypertriglyceridemia	5 (27.0%)	6 (25.0%)	0.8
Coronary artery disease	5 (23.0%)	6 (25.0%)	0.8
Atrial fibrillation	1 (4.5%)	2 (4.2%)	0.9
Smoking habit – current smokers	6 (27%)	5 (21%)	0.6

Values are means ± SD, unless specified otherwise.

Results

Fifty-seven patients were enrolled in the study. Of these, 28 (24 males, 4 females; 72.6 ± 5.8 years old) underwent CEA and 29 (17 males, 12 females; 75.1 ± 5.7 years old) underwent CAS. The demographics as well as data on frequency of vascular comorbidity and vascular risk factors of the 2 groups are shown in table 1. No significant differences were observed between the groups, except for gender composition, since women were represented more frequently in the CAS than in the CEA group ($p < 0.05$). The use of antihypertensive, blood-glucose-lowering, lipid-lowering, antiplatelet and anticoagulant drugs was not different between the groups at baseline and at the follow-up evaluations (data not shown).

Among the 28 patients assigned to CEA, 22 completed the study. Six subjects declined to be evaluated at follow-up due to a subsequent diagnosis of cancer (n = 1) and Parkinson's disease (n = 1), while 4 withdrew their consent. Of the 29 patients assigned to CAS, 24 completed the study, 5 withdrew due to a subsequent diagnosis of cancer (n = 2) and abdominal aneurism (n = 1), or withheld their consent (n = 2). In subsequent telephone interviews (at T3 and T12), no vascular event/death was reported for subjects who interrupted the study.

Table 2. Neuropsychological characteristics of CEA and CAS patients at T0, T3 and T12

	CEA (n = 22)			CAS (n = 24)		
	T0	T3	T12	T0	T3	T12
Global cognition						
MMSE	27.8 ± 2.3	27.4 ± 2.4	27.6 ± 3.0	27.2 ± 1.9	26.5 ± 2.8	27.7 ± 2.1
Functional scales						
ADL	5.9 ± 0.4	5.7 ± 0.6	5.7 ± 0.5	5.7 ± 0.5	5.4 ± 0.5	5.6 ± 0.5
IADL	5.6 ± 1.7	5.6 ± 2.0	6.0 ± 1.7	5.9 ± 2.1	6.2 ± 1.4	6.2 ± 2.0
Mood						
GDS	3.0 ± 1.5	2.3 ± 1.9	2.2 ± 1.7	4.4 ± 2.4	2.9 ± 1.9	4.1 ± 3.9
Memory						
Babcock SR	9.1 ± 3.1	10.6 ± 3.0	9.7 ± 4.0	9.0 ± 3.1	8.5 ± 3.6	9.5 ± 2.4
Rey-IR	33.5 ± 7.0	33.9 ± 7.8	35.2 ± 6.7	35.5 ± 8.9	34.7 ± 10.2	34.6 ± 6.1
Rey-DR	8.7 ± 3.8	7.3 ± 2.4	7.8 ± 3.0	7.4 ± 4.0	6.9 ± 2.1	7.7 ± 1.9
CNT	14.3 ± 4.7	16.0 ± 5.6	13.1 ± 4.5	14.3 ± 4.0	15.2 ± 4.7	13.6 ± 4.0
Attention and executive functioning						
TMT-A, s	52.9 ± 24.4	63.2 ± 50[a]	55.6 ± 22.5[b]	74.1 ± 37.7	109.2 ± 74.4	97.2 ± 51.0
TMT-B, s	162.5 ± 108.5	154.9 ± 127.5	134.6 ± 92.3	135.4 ± 78.5	123.7 ± 99.6	118.3 ± 145.2
COWA	22.4 ± 9.1	25.7 ± 11.8	28.0 ± 12.2	22.7 ± 7.8	25.3 ± 7.9	24.0 ± 8.7
Visuospatial and constructional abilities						
CD	12.5 ± 1.7	12.1 ± 1.6	11.5 ± 2.4	12.5 ± 2.0	13.1 ± 1.4	12.0 ± 1.9

Values are presented as means ± SD. [a] $p < 0.05$, [b] $p < 0.01$ versus CAS. MMSE score ranging from 0 (worst) to 30 (best); ADL score ranging from 0 (worst) to 6 (best); IADL score ranging from 0 (worst) to 8 (best).

Cognitive Performance between Groups (CAS and CEA)

The cognitive test scores, functional scale scores and GDS scores at T0, T3 and T12 are reported in table 2. No significant differences were observed at T0, T3 and T12 between CEA or CAS patients, excluding the TMT-A, in which the mean score observed in the CEA group was lower (i.e. better) at T3 and T12 compared to the CAS group. However, patients undergoing CEA showed a non-significantly better performance than patients undergoing CAS in the TMT-A at T0 as well ($p = 0.058$).

Cognitive Changes over Time within Groups (CEA or CAS)

Within each group, the variations over time in mean cognitive test scores (i.e. ΔT3 vs. ΔT12 in the CEA group, ΔT3 vs. ΔT12 in the CAS group) were not significant, with the exception of the visuospatial and constructional abilities (CD), which slightly worsened in the CAS group (ΔT3 vs. ΔT12 on the CD; $p < 0.05$) (table 3). No significant differences were detected in functional abilities and mood status.

Cognitive Changes over Time between Groups (CEA versus CAS)

When assessing the presence of a different effect between the 2 surgical approaches on cognitive performance over time (i.e. ΔT3 CEA vs. ΔT3 CAS, ΔT12 CEA vs. ΔT12 CAS), no significant differences were detected (table 3). Furthermore, no significant differences were detected for functional abilities and mood.

Discussion

Notwithstanding a slight deterioration over time in visuospatial and constructional abilities in the CAS group, the main result of this study is that neither CEA nor CAS appears to significantly affect cognitive functioning in elderly patients three or twelve months after carotid revascularization.

Cognitive impairment has been reported to be one of the earliest and most common manifestations of cerebrovascular disease, and it has been proposed that cognitive

Table 3. Differences with respect to T0 values in neuropsychological and functional scores after 3 and 12 months of follow-up in CEA and CAS groups

	CEA ΔT3	CEA ΔT12	CAS ΔT3	CAS ΔT12
Global cognition				
MMSE	–0.52 ± 2.5	–0.03 ± 2.5	–0.53 ± 3.1	0.13 ± 2.7
Functional scales				
ADL	–0.15 ± 0.60	–0.10 ± 0.47	–0.16 ± 0.51	–0.06 ± 0.5
IADL	–0.15 ± 2.2	0.37 ± 2.0	0.38 ± 2.1	0.06 ± 2.0
Mood				
GDS	–0.6 ± 2.0	–0.8 ± 1.7	–1.0 ± 2.1	–0.2 ± 3.9
Memory				
Babcock SR	1.4 ± 3.9	0.3 ± 5.0	–0.2 ± 4.5	–0.4 ± 3.3
Rey-IR	–1.5 ± 6.3	1.6 ± 6.2	–0.5 ± 12.0	–1.5 ± 9.2
Rey-DR	–1.9 ± 4.8	–0.9 ± 4.6	–0.1 ± 2.6	–0.6 ± 2.4
CNT	1.2 ± 7.1	–1.4 ± 4.5	0.8 ± 5.8	–1.9 ± 3.5
Attention and executive functioning				
TMT-A, s	12.7 ± 57.5	–0.1 ± 28.2	30.7 ± 65.2	21.5 ± 59.1
TMT-B, s	–3.2 ± 98.3	–49.3 ± 88.6	–3.0 ± 122.0	–56.7 ± 72.5
COWA	1.9 ± 10.8	5.0 ± 8.1	0.9 ± 8.5	3.6 ± 8.8
Visuospatial and constructional abilities				
CD	–0.5 ± 1.7	–1.3 ± 2.3	0.8 ± 2.0[a]	–0.7 ± 2.9

Values are presented as means ± SD. [a] $p < 0.05$ versus ΔT12 in CAS group.

testing could be a particularly sensitive outcome measure in primary or secondary prevention studies [6].

If cognitive decline is a clinical manifestation of cerebrovascular disease related to ICA, cognitive assessment will represent a useful tool for exploring the functional outcome of carotid revascularization procedures [26]. This has prompted studies in the field, but few have been performed on the elderly, the population more at risk of cognitive decline and dementia [27], and so far both CEA and CAS have not shown any clear effects on cognitive endpoints.

Although previous reports in this field found an improvement after CEA, more recent studies have consistently demonstrated no change or even cognitive decline [28]. The major points of criticism of the studies on cognitive performance after CEA or CAS include contrasting approaches regarding the assessment timing, typology of cognitive tests, extent of follow-up, number of enrolled patients, lack of a control population, and severity of stenosis [13, 28].

Carotid revascularization is recognizably exposed to show an increased risk of cerebral embolization or silent microembolization with uncertain but potential negative effects on cognition. Therefore, the supposed benefit of a restored cerebral perfusion to cognitive performance [9] is opposed by the potential harm of microembolic lesions occurring during CEA or CAS that could lead to cognitive impairment. However, there is no proof of such a link, and over the past decades, conflicting effects of microembolisms on cognition have been found during carotid vascularization [28].

CAS is a rapidly evolving technique, and technological advances such as the use of embolic protection devices as well as improvements in the experience of operators (specific training and appropriate learning curve) have significantly reduced the rate of adverse events [29]. Thus, in the past few years, CAS has been used increasingly often despite the negative results of some published randomized clinical trials [14–16, 30–32]. Although some recent, large case-series registries have indicated that CAS can be performed at acceptable complication rates, a high incidence of emboli shed to the brain has generated great concern regarding the safety of this technique, especially when considering the established low risk and durability of CEA [30–34]. In fact, higher embolization rates during CAS compared to surgery have been reported using either transcranial Doppler sonography to monitor microembolic events or applying diffusion-weighted imaging (DWI) to detect new embolic brain lesions after the intervention [20, 30, 32, 35].

Recently, the International Carotid Stenting Study showed that the risk of microembolism is threefold increased during CAS compared to CEA for patients with symptomatic carotid stenosis according to DWI MRI

new ischemic lesions (26.3 vs. 14.1% for CAS and CEA patients, respectively; http://www.cavatas.com/). Nevertheless, none of these studies has shown a clear negative effect on cognition after CAS, the clinical relevance of the phenomenon remaining an open issue.

Only few studies analyzed the cognitive effects of carotid percutaneous transluminal angioplasty (PTA) procedures or CAS, three of which being in comparison with CEA. As for CEA, results of the studies conducted on PTA/CAS do not provide us with clear conclusions due to their small patient samples and lack of controls [28].

The three studies directly comparing PTA/CAS [30, 31, 33] with CEA were performed within the randomized controlled Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study, and one [31] has been presented only as an abstract. In 2000, Crawley et al. [30] published the results of a study performed on two matched subgroups of patients randomized in the CAVATAS to undergo CEA or PTA, showing that the latter is not associated with greater neuropsychological impairment than CEA despite the greater incidence of microembolism during PTA. Similar to our results, but with a shorter follow-up period of 6 and 30 days after treatment, Witt et al. [33] showed no significant differences in neuropsychological performances – including verbal and nonverbal memory, concentration, visuospatial abilities, verbal fluency, cognitive flexibility and motor tasks – between patients enrolled in the SPACE study undergoing CEA or CAS.

However, the two large randomized clinical trials CAVATAS and SPACE were carried out on subjects with symptomatic carotid artery stenosis, while in our study, we evaluated a group of subjects with asymptomatic stenosis. Thus, the comparison of those with our results is flawed by the difference in study design and patient selection, particularly because it is possible that subjects with symptomatic carotid artery stenosis may already be cognitively impaired due to a previous stroke or transient ischemic attack.

As revealed by a recent review, neither CEA nor CAS appears to clearly affect cognition [28], and either cognitive impairment or improvement has been reported after either CEA or CAS. In the absence of a control group, it is difficult to disentangle whether the progression of cognitive decline after carotid reopening is due to the progression of the cerebrovascular disease or due to the long-term consequences of the surgical treatment. A study including controls with ACAS is needed to clarify whether carotid reopening can avoid, delay the onset or delay the progression of cognitive decline.

Particular strengths of the present study are the relatively lengthy follow-up period for cognitive evaluation and the use of several neuropsychological tests to evaluate different cognitive domains. We found no substantial differences in cognitive performance including memory, attention, and executive and visuospatial/constructional abilities in patients undergoing either CEA or CAS. Neither CEA nor CAS appears to significantly affect cognitive functioning in elderly patients three or twelve months after carotid revascularization. As atherosclerosis is a progressive disorder, we can speculate that stability of cognitive functions could be considered a positive outcome in subjects who are at a high risk of progression of cerebrovascular lesions. Major limitations of this study are the small sample size, with inherent implications for statistical power, the nonrandomized design and the lack of a control group to compare the cognitive modifications along time, although both treated groups were cognitively normal at baseline and remained so during the follow-up.

Cerebrovascular pathological changes are recognized as important contributors to the onset of cognitive decline and dementia, especially at advanced age [34]. The prevention of cerebrovascular pathological changes may contribute to delay dementia onset and progression, thus CEA and CAS could represent important therapeutic strategies for the prevention of cognitive decline and dementia in the elderly.

Although CAS, as opposed to CEA, is found to be associated with a significantly greater incidence of new DWI lesions both inside and outside the treated artery territory, at this time there is no evidence that this greater amount of ischemic burden may be reflected in a higher percentage worsening of mortality [36] or cognition. Results from ongoing randomized clinical trials analyzing cognition after CAS versus CEA and the use of a battery of tests that probably can detect more subtle alterations in vascular cognitive impairment [37] could clarify which benefit or danger, if any, might be expected from CAS and CEA in the neuropsychological outcome of patients with carotid stenosis.

In conclusion, we did not find significant differences in cognitive, mood and functional measures between CEA and CAS. Due to these negative results and the nonrandomized design of our study, we cannot infer any causal relationship or effects that would allow suggesting CEA or CAS as the treatment of choice for elderly patients with ACAS. Since the safety of CAS compared to

CEA is still under debate [38], further studies with a larger number of old and oldest old subjects and with a longer follow-up, as well as studies using a control group are needed to better understand the cost-effectiveness of both treatments.

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