Cognition and Quality of Life in Symptomatic Carotid Occlusion

Marykay A. Pavol, PhD,* Kathryn Sundheim, BA,* Ronald M. Lazar, PhD,* Joanne R. Festa, PhD,† and Randolph S. Marshall, MD*

Purpose: Carotid occlusion may result in stroke, TIA, and cognitive reductions. Whether cognition predicts quality of life (QOL) for patients with carotid occlusion is unknown. Depression is also known to affect QOL. We examined whether cognition and depression predicted QOL in patients with carotid occlusive disease who have not had revascularization.

Methods: Patients with unilateral carotid occlusion and history of TIA or a remote history of minor stroke were included. Patients underwent exam of memory, language, motor, and executive function skills and completed depression and QOL questionnaires (Center for Epidemiological Studies-Depression [CES-D], Stroke Specific QOL [SSQOL]). Deficits from remote stroke were assessed with the NIH Stroke Scale (NIHSS). Z-scores for cognitive tests were averaged (Cog-Z). The SSQOL scores were averaged across subgroup domains. Analyses of patients with all depression levels were followed by subgroup analyses for patients with minimal depression. Correlation findings were used to select the variables in a regression model to predict SSQOL.

Results: Among 37 patients with all depression levels, QOL was predicted by deficits from remote stroke and depression ($F(3, 36) = 21.15$, $P < .0005$; NIHSS Beta = −.392, $P = .001$; CES-D Beta = −.577, $P < .0005$). Among 22 patients with minimal depression, QOL was predicted by cognitive and depression scores, ($F(2,21) = 7.88$, $P = .003$; Cog-Z Beta = .364, $P = .05$; CES-D Beta = −.495, $P = .01$).

Conclusions: In patients with carotid occlusive disease without major stroke and without revascularization, cognitive and depression scores independently predicted QOL. These data demonstrate the clinical relevance of cognitive and mood decline among patients with carotid occlusion.

Key Words: Carotid occlusion—cognition—quality of life—depression

High grade carotid stenosis may cause stroke or transient ischemic attack (TIA).[1,2] Quality of life (QOL) research with these patients has typically focused on outcomes of carotid revascularization and, in particular, on differences between methods of revascularization on QOL.[3,4] QOL for patients with high-grade carotid stenosis who have not undergone revascularization is less-well characterized. One study found patients with TIA or stroke secondary to carotid stenosis, without revascularization, had "slightly" reduced QOL ratings that persisted 1 year after the clinical event.[5]

In addition to effects on QOL, severe carotid stenosis affects cognition, even for patients without recent stroke.[6–8] Comparisons between patients who underwent endarterectomy and those who refused surgery showed improved cognition for the surgical group after

From the *Stroke Division, Department of Neurology, Columbia University College of Physicians and Surgeons, New York, New York; and †Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York.

Received October 31, 2018; revision received April 15, 2019; accepted May 6, 2019.

Portions of this manuscript were presented in poster format at the International Stroke Conference, Houston, Texas, February 22-25, 2017.

Funding: This research was supported by NINDS NS048212. The funding source had no influence on the collection, data analyses/interpretation, or writing of the manuscript.

Address correspondence to Marykay A. Pavol, PhD, Stroke Division, Department of Neurology, Columbia University Medical Center, New York, NY 10032. E-mail address: mp2740@cumc.columbia.edu.

1052-3057/$ - see front matter

https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.05.007

6 months as well as nonsignificant improvements in mood and QOL.[9]

Research on QOL and cognition for patients with severe carotid stenosis has not addressed the possible interaction between these outcomes. Cognition is a recognized influence on QOL ratings for a variety of medical diagnoses.[10–15] Whether cognition influences QOL for patients with carotid occlusion is unknown, with or without revascularization. We sought to address this knowledge gap by examining the influence of cognition on QOL for patients with severe carotid stenosis who have not had revascularization.

We hypothesized that cognition would significantly predict QOL ratings for patients with symptomatic carotid occlusion. Depression is also known to affect QOL ratings[16] so we first examined a group of patients with the full range of scores on a depression screen followed by subanalyses that excluded patients with substantial depression. This approach allowed us to examine QOL with and without the effects of significant depression. Furthermore, acute effects of stroke are known to influence QOL ratings so, to avoid these confounding effects on QOL ratings, we excluded patients with recent stroke.[17,18]

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

All patients provided informed consent. The study was approved by the Columbia University Institutional Review Board.

Participants

Patients were selected from the NIH-sponsored, ancillary study Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON).[7] The study was designed to compare cognitive outcomes for patients in a parent study of symptomatic carotid occlusion treated with medical therapy alone with outcomes for patients treated with medical therapy and surgery (anastomosis of the extracranial superficial temporal artery to the intracranial middle cerebral artery).[19] Patients in the parent study were required to have adequate cognition for informed consent and to have a score greater than or equal to12/20 on the Modified Barthel Index. Additional exclusion criteria for the RECON trial included prior diagnosis of dementia and education under grade 4.[7] Cognitive assessments were performed prior to surgery. The current study included patients with unilateral carotid occlusion and history of TIA attributed to the occlusion and excluded subjects with history of stroke within 4 months prior to enrollment (remote history of minor stroke was allowed). Cognitive test scores confounded by visual impairment were deleted from analyses.

Table 1. *Cognitive tests with presumed cerebral hemisphere sensitivity*

Test	Hemisphere sensitivity
Trail Making Test Part A	Global
Trail Making Test Part B	Global
WAIS-III Digit Span	Global
WAIS-III Digit Symbol	Global
Boston Naming Test	Left
BDAE Repetition of Phrases	Left
Hopkins Verbal Learning Test-Revised	Left
Verbal fluency (FAS)	Left
Rey Complex Figure Test—copy	Right
Rey Complex Figure Test—recall	Right
Line Bisection	Right
Letter Cancellation	Right
Grooved pegboard (“affected” hand)	Left/right
Grooved pegboard (“unaffected” hand)	Global

Measures

Patients underwent examination of memory, language, motor, and executive function skills (Table 1). Patients also completed the Center for Epidemiological Studies-Depression (CES-D)[20] and Stroke Specific QOL (SSQOL)[21] questionnaires. CES-D scores under 16 are interpreted as normal, scores 16-20 suggest mild depression, scores 21-30 suggest moderate depression, and scores greater than 30 suggest severe depression symptoms.[22] The SSQOL is a 49-item self-report QOL measure designed to assess the effect of stroke on the physical, emotional, and social aspects of life. The SSQOL consists of questions in the following subgroup domains with ratings ranging from 1 (most impairment) to 5 (no impairment): energy; family roles; language function; mobility; vision; mood; work; personality; self-care; social roles; thinking; and arm function. SSQOL subgroup domains may be examined separately or, as in the current study, the domain scores may be averaged to produce 1 SSQOL score per patient.[23] The NIH Stroke Scale (NIHSS) was used to assess deficits from remote stroke.[24]

Z-scores for cognitive tests were calculated according to patient age, using published normative samples, and averaged into a composite cognitive z-score (Cog-Z) for each patient, tailored to the side of occlusion. For patients with left carotid occlusion, the z-scores for left-hemisphere-sensitive and globally demanding tests were averaged; for patients with right carotid occlusion, the z-scores for right-hemisphere-sensitive and globally-demanding tests were averaged (please see the first RECON publication for additional details[7]).

Statistical Analyses

Analyses of patients with all depression levels were followed by analyses for a subgroup of patients with

minimal depression (CES-D scores < 21). Correlation analyses were performed to determine univariate relationships between continuous variables (SSQOL, Cog-Z, NIHSS, CES-D). Crosstabs analyses were used to evaluate relationships between categorical variables (sex, education, and remote history of prior stroke) and the SSQOL score. Variables that correlated significantly with the SSQOL were included in a regression model to predict SSQOL scores. All analyses were performed with IBM SPSS Statistics package, version 25.

Results

The initial RECON sample included 40 patients with TIA and without recent stroke. Of this group, 3 patients were missing CES-D data. See Table 2 for demographic characteristics for the 37 subjects. The average Cog-Z score was −1.14 SD (low average range), average CES-D score was 20.30 (mildly-moderately depressed range), average NIHSS was 1.6 (minor stroke range), and the average SSQOL score was 3.85 (needing "a little help"/having "a little trouble"). The correlations between age and SSQOL were nonsignificant. Significant correlations were found between SSQOL scores and Cog-Z, CES-D scores, and NIHSS scores. Crosstabs analyses found no substantial associations between SSQOL, sex, education, and remote history of stroke. In a regression model including Cog-Z, CES-D, and NIHSS, NIHSS and CES-D were significant predictors of SSQOL ($F(3,36) = 21.15$, $P < .000$; NIHSS Beta = −.392, $P = .001$; CES-D Beta = −.577, $P < .000$). This model accounted for 66% of the variance in SSQOL scores ($R^2 = .658$).

In order to study the relationships among the variables in subjects with minimal depression symptoms, subjects with CES-D scores greater than 20 were removed, leaving 22 subjects. See Table 3 for demographic characteristics for the 22 remaining subjects. Among these 22 patients, the average Cog-Z score was −1.03 SD (low average range), average CES-D score was 10.77 (normal range), average NIHSS was .50 (normal range/no stroke symptoms), and the average SSQOL score was 4.37 (needing "a little help"/having "a little trouble"). The correlations between symptoms of remote stroke (NIHSS) and SSQOL were nonsignificant as were the correlations between age and SSQOL. Crosstabs analyses found no significant relationship between SSQOL and sex, education, or remote history of stroke. Significant correlations were found between SSQOL scores and Cog-Z and CES-D scores. In a regression model including Cog-Z and CES-D, both were significant predictors of SSQOL ($F(2,21) = 7.88$, $P = .003$; Cog-Z Beta = .364, $P = .05$; CES-D Beta = −.495, $P = .01$). This model accounted for 45% of the variance in SSQOL scores ($R^2 = .454$). The average z-scores for each of the cognitive tests in the subsample are provided in Table 4 for informal inspection; the sample size prohibited statistical comparisons.

Table 2. *Patient characteristics, all CES-D scores n = 37*

Patient characteristics for sample with all CES-D scores	
Age, years mean/SD (range)	55.22/9.6 (37-76)
Sex, n (%)	
Female	16 (43)
Male	21 (57)
Handedness, n (%)	
Right	33 (89)
Left	4 (11)
Education, n (%)	
High school and below	22 (59)
College and above	15 (41)
Side of carotid stenosis, n (%)	
Right	19 (51)
Left	18 (49)
Remote history of stroke, n (%)	
No	16 (43)
Yes	21 (57)

Table 3. *Patient characteristics, CES-D scores in normal to mildly depressed range n = 22*

Patient characteristics for sample with CES-D scores below 21	
Age, years mean/SD (range)	58.18/10.26 (39-76)
Sex, n (%)	
Female	9 (41)
Male	13 (59)
Handedness, n (%)	
Right	20 (91)
Left	2 (9)
Education, n (%)	
High school and below	13 (59)
College and above	9 (41)
Side of carotid stenosis, n (%)	
Right	8 (36)
Left	14 (64)
Remote history of stroke, n (%)	
No	10 (45)
Yes	12 (55)

Discussion

In patients with symptomatic carotid artery occlusion without revascularization, recent stroke, or substantial depression scores were significant, independent predictors of QOL and associated with a minor reduction in QOL ratings (needing "a little help/having a little trouble" in daily activities). When subjects with significant depression were included in the analyses, the QOL scores were predicted by depression and deficits from remote stroke but not by cognition. A previous study of QOL in patients with carotid occlusion without revascularization also found small reductions in QOL but did not examine the factors *predicting* the QOL ratings.[5]

Our finding is consistent with studies of the influence of cognition on QOL in other patient populations. In a study

Table 4. *Cognitive test average z-scores and percentiles, by side of occlusion, CES-D scores in normal to mildly depressed range*

Cognitive test, Z-score group mean (SD), percentile	Patients with left-sided occlusion, n = 14	Patients with right-sided occlusion, n = 8
Trail Making Test Part A	−.41 (.80), 34 %ile	−1.9 (2.78), 3 %ile
Trail Making Test Part B	−.65 (1.31), 26 %ile	−1.42 (1.58), 8 %ile
WAIS-III* Digit Span	−.38 (.66) 35 %ile	−.29 (.81), 39 %ile
WAIS-III* Digit Symbol	−.71 (1.29), 24 %ile	−.75 (1.72), 23 %ile
Boston Naming Test	−.66 (1.69), 25 %ile	−.13 (.61), 45 %ile
BDAE repetition of phrases	−.92 (1.35), 18 %ile	−.58 (1.38), 28 %ile
HVLT-R†	−.86 (1.09), 19 %ile	−.48 (1.14), 32 %ile
Verbal fluency (FAS)	−.59 (.80), 28 %ile	−.47 (.61), 32 %ile
Rey Complex Figure Test—copy	−3.22 (2.06), <1 %ile	−2.49 (2.0), 1 %ile
Rey Complex Figure Test—recall**,†	−1.45 (1.11), 7 %ile	−1.57 (1.49), 6 %ile
Line bisection	.01 (1.16), 50 %ile	−.59 (2.02), 28 %ile
Letter cancellation	.04 (.88), 52 %ile	−.11 (2.07), 46 %ile
Grooved pegboard (right hand)	−1.20 (1.9), 12 %ile	−2.7 (1.9), <1 %ile
Grooved pegboard (left hand)	−1.7 (1.65), 4 %ile	−3.97 (1.87), <1 %ile

*WAIS-III = Wechsler Adult Intelligence Scale-Third edition.
**Average of recall trials.
†HVLT-R = Hopkins Verbal Learning Test-Revised, average of learning and recall trials.

of patients after stroke, Nys et al reported that cognitive impairment measured in the acute phase predicted patient QOL ratings and depression symptoms several months later.[10] Orbo et al studied survivors of cardiac arrest (excluding those with significant depression symptoms, as in the current study) and found neuropsychological performances 3 months after arrest significantly predicted QOL ratings at that time.[12] Newman et al studied QOL and cognition in a sample of patients assessed 5 years after cardiac surgery and found a relationship between cognition and QOL.[15] In a study of patients with Alzheimer's disease, patient and caregiver assessments of patient QOL were associated with patient cognitive performance.[11] In a study of heart-failure patients living with a left ventricular assistive device, Casida et al reported better scores on a measure of executive function were associated with higher scores in QOL.[13] In a study of patients with Parkinson's disease, QOL was predicted by several variables, including a mental status screen.[14]

Scores on a depression measure also predicted QOL for our patient group, both when the sample included all ranges of depression severity and when the sample was restricted to patients with scores in the normal to mildly-depressed range. The relationship between depression and QOL has been established previously[16] and our finding that depression scores influenced QOL is not surprising, particularly for the group that included all CES-D scores and had a mean depression rating in the mild/moderate range of severity. The above-mentioned study of patients with Parkinson's disease also found depression symptomatology to be an independent predictor of QOL, separate from the influence of cognition.[14] In contrast, Nys et al did not find depression ratings to be a significant predictor of QOL for stroke patients although cognition was a significant predictor of depression symptoms.[10] It is notable that the predictive role of depression remained for the group that excluded high depression scores—the average CES-D score for this subgroup was in the normal range.

Similarly, when cognition was a predictor for QOL, the cognitive scores were not severely low—the average z-score for this group was −1.03, ranking at approximately the 15th percentile (low average range), and all patients were living in the community. This score may represent minor decline but is well within the range of normal cognition. Bakker et al also reported minimal reductions in cognition and QOL for their carotid occlusion patients with TIA[5] and Newman et al found a similar degree of cognitive change in their patients after cardiac surgery.[15] Our subsample that excluded patients with moderate-severe depression provided an opportunity to detect the effects of cognition on QOL, effects that may be obscured by the presence of more substantial depression.

In our sample with all depression scores, the NIHSS was a significant predictor of QOL, in addition to the contribution from the CES-D score. This is consistent with the recognized association between poststroke deficits and QOL.[25,26] The NIHSS was not a predictor in our subsample of patients with no depression/mild depression suggesting that the elimination of patients with higher depression scores removed the influence of NIHSS scores.

There are limitations to this study. Although the exclusion of patients with significant depression in the subsample analyses was useful in removing the confounding effects of depression and isolating the role of cognition, the resulting group was small. Generalizations about our findings are limited to patients without recent stroke and may not apply to patients in the acute-stroke phase. Our sample size precluded analysis of separate QOL domains. Similarly, the use of a composite z-score for cognitive

tests, while useful for including a large number of cognitive variables in a small patient sample, did not allow for formal inspection of the influence of individual tests on QOL ratings. Perhaps most importantly, the clinical relevance of the small changes in cognition, mood, and QOL for these subjects is unknown.

Our study is the first to identify predictive, independent influences of cognition and depression on QOL ratings for patients who have not undergone revascularization for symptomatic carotid occlusion. These findings improve recognition of factors that impact QOL for these patients and suggest a role for even minor declines in mood and cognition. Further study is warranted, particularly given increased focus on nonsurgical management of carotid stenosis.[27]

Acknowledgment

The authors thank RECON coordinator Kevin Slane for his diligent work in gathering data, communicating with patients, and organizing meetings.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Meschia JF, Klaas JP, Bronw RD, et al. Evaluation and management of atherosclerotic carotid stenosis. Mayo Clinic Proc 2017;92:1144-1157.
2. Huang WY, Weng WC, Su FC, et al. Association between stroke severity and 5-year mortality in ischemic stroke patients with high-grade stenosis of the internal carotid artery. J Stroke Cerebrovasc Dis 2018;27:3365-3372.
3. Shan L, Shan J, Saxena A, et al. Quality of life and functional status after carotid revascularization: a systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2015;49:634-645.
4. Cohen DJ, Stolker JM, Wang K, et al. Health-related quality of life after carotid stenting versus carotid endarterectomy; results from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial). J Am Coll Cardiol 2011;58.
5. Bakker FC, Klijn CJM, van der Grond J, et al. Cognition and quality of life in patients with carotid artery occlusion; a follow-up study. Neurology 2004;62:2230-2235.
6. Silvestrini M, Paolino I, Vernieri F, et al. Cerebral hemodynamics and cogniitve performance in patients with asymptomatic carotid stenosis. Neurology 2009;72:1062-1068.
7. Marshall RS, Festa JR, Cheung YK, et al. Cerebral hemodynamics and cognitive impairment. Neurology 2012;78:250-255.
8. Lal BK, Dux MC, Sikdar S, et al. Asymptomatic carotid stenosis is associated with cognitive impaiment. J Vasc Surg 2017;66:1083-1092.
9. Carta MG, Lecca ME, Saba L, et al. Patients with carotid atherosclerosis who underwent or did not undergo carotid endarterectomy: outcome on mood, cognition, and quality of life. BMC Psychiatry 2015;15.
10. Nys GMS, van Zandvoort MJE, van der Worp HB, et al. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. J Neurol Sci 2006;247:149-156.
11. Lacey L, Bobula J, Rudell K, et al. Quality of life and utility measurement in a large clinical trial sample of patients with mild to moderate Alzheimer's disease: determinants and level of changes observed. Value Health 2015;18:638-645.
12. Orbo M, Aslaksen PM, Lardsby K, et al. Relevance of cognition to health-related quality of life in good-outcome survivors of out-of-hospital cardiac arrest. J Rehabil Med 2015;2015:860-866.
13. Casida JM, Yang JJ, Craddock H, et al. Cognitive function: a significant predictor of quality of life in adults with an implantable ventricular assist device. J Heart Lung Transplant 2017;36:S209.
14. van Uem JMT, Cerff B, Kampmeyer M, et al. The association between objectively measured physical activity, depression, cognition, and health-related quality of life in Parkinson's disease. Parkinsonism Relat Disord 2017.
15. Newman MF, Grocott HP, Mathew JP, et al. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke 2001;32:2874-2881.
16. Sivertsen H, Bjorklof GH, Engedal K, et al. Depression and quality of life in older persons: a review. Dement Geriatr Cognit Disord 2015;40:311-339.
17. Sangha RS, Caprio FZ, Askew R, et al. Quality of life in patients with TIA and minor ischemic stroke. Neurology 2015;85:1957-1963.
18. van Mierlo ML, van Heugten CM, Post MWM, et al. Quality of life during the first two years post stroke: the Restore4Stroke Cohort study. Cerebrovasc Dis 2016;41:19-26.
19. Powers WJ, Clarke WR, Grubb RL, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia; the carotid occlusion surgery study randomized trial. J Am Med Assoc 2011;306:1983-1992.
20. Radloff L. The CES-D scale: a new self-report depression scale for research in the general population. Appl Psychol Measur 1977;1:385-401.
21. Williams L, Weinberger M, Harris L, Clark D, Biller J. Development of a stroke-specific quality of life scale. Stroke 1999;30:1362-1369.
22. Barnes GE, Prosen H. Depression in Canadian general practice attenders. Can J Psychiatry 1984;29:2-10.
23. Green TL, King KM. Functional and psychosocial outcomes 1 year after mild stroke. J Stroke Cerebrovasc Dis 2010;19:10-16.
24. Lyden P, Brott T, Tilley B, et al. Improved reliability of the NIH Stroke Scale using video training. Stroke 1994;25:2220-2226.
25. Williams LS, Weinberger M, Harris LE, et al. Measuring quality of life in a way that is meaningful to stroke patients. Neurology 1999;53:1839.
26. Katzan IL, Thompson NR, Uchino K, et al. The most affected health domains after ischemic stroke. Neurology 2018;90:e1364-e1371.
27. Meschia JF, Lal BK, Howard G, et al. Carotid revascularization and medical management for asymptomatic carotid stenosis: Crest-2. Neurology 2018;90. (15 Supplement) S50.006.