Stroke

ORIGINAL CONTRIBUTION

Baseline Cognitive Impairment in Patients With Asymptomatic Carotid Stenosis in the CREST-2 Trial

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BACKGROUND AND PURPOSE: Studies of carotid artery disease have suggested that high-grade stenosis can affect cognition, even without stroke. The presence and degree of cognitive impairment in such patients have not been reported and compared with a demographically matched population-based cohort.

METHODS: We studied cognition in 1000 consecutive CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) patients, a treatment trial for asymptomatic carotid disease. Cognitive assessment was after randomization but before assigned treatment. The cognitive battery was developed in the general population REGARDS Study (Reasons for Geographic and Racial Differences in Stroke), involving Word List Learning Sum, Word List Recall, and Word List fluency for animal names and the letter F. The carotid stenosis patients were >45 years old with ≥70% asymptomatic carotid stenosis and no history of prevalent stroke. The distribution of cognitive performance for the patients was standardized, accounting for age, race, and education using performance from REGARDS, and after further adjustment for hypertension, diabetes, dyslipidemia, and smoking. Using the Wald Test, we tabulated the proportion of Z scores less than the anticipated deviate for the population-based cohort for representative percentiles.

RESULTS: There were 786 baseline assessments. Mean age was 70 years, 58% men, and 52% right-sided stenosis. The overall Z score for patients was significantly below expected for higher percentiles ($P<0.0001$ for 50th, 75th, and 95th percentiles) and marginally below expected for the 25th percentile ($P=0.015$). Lower performance was attributed largely to Word List Recall ($P<0.0001$ for all percentiles) and for Word List Learning (50th, 75th, and 95th percentiles below expected, $P\leq0.01$). The scores for left versus right carotid disease were similar.

CONCLUSIONS: Baseline cognition of patients with severe carotid stenosis showed below normal cognition compared to the population-based cohort, controlling for demographic and cardiovascular risk factors. This cohort represents the largest group to date to demonstrate that poorer cognition, especially memory, in this disease.

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GRAPHIC ABSTRACT: An online graphic abstract is available for this article.

Key Words: carotid stenosis ■ cognition ■ memory ■ population ■ risk factors

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Nonstandard Abbreviations and Acronyms

CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CREST-2	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial
REGARDS	Reasons for Geographic and Racial Differences in Stroke Study
SND	standard normal distribution

Carotid artery stenosis, a major risk factor for ischemic stroke, accounts for 8% of stroke events.[1] Although cognitive decline can occur with stroke,[2] carotid disease with high-grade stenosis can affect cognition[3–5] but has never been tested in a large-scale randomized controlled trial. We wanted to determine whether participants have diminished cognition with asymptomatic carotid disease before study treatment. The CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) addressed this question.

CREST-2 has 2 trials of primary stroke prevention in patients with high-grade asymptomatic carotid stenosis comparing: (1) treatment differences between intensive medical management alone compared to carotid endarterectomy plus intensive medical management and (2) treatment differences between intensive medical management alone compared to carotid stenting.[6] Randomization began December 2014 and is ongoing, with a goal of 1240 patients in each trial.

A secondary outcome in CREST-2 is the impact of treatment on the change in cognitive function, with evaluations at baseline and yearly thereafter. We employ a centrally-administered telephone battery, with tests derived from the REGARDS study (Reasons for Geographic and Racial Differences in Stroke),[7–9] a population sample of 30 239 community-dwelling black and white participants aged 45+ years living in the 48 contiguous US states randomly chosen from a commercially available list. They were recruited through a combination of mail and telephone contact between 2003 and 2007. The primary exclusion criteria were having actively-treated cancer, residence in (or on a waiting list for) a nursing home, and non-English preferred language. The estimated participation rate was 34% and annual retention is 97.4%, comparable to other longitudinal cohort studies. The cohort has been accepted as generally representative of the US black and white population (see https://www.uab.edu/soph/regardsstudy/ for details). The REGARDS cognitive test battery, administered by telephone, has been shown to yield normally distributed scores and is sensitive to cognitive change[8,9] and cerebrovascular risk factors.[10] We hypothesized that CREST-2 patients would have significantly lower scores on baseline cognitive testing than participants in the REGARDS cohort with adjustment for (1) age, education, and race and (2) further adjustment for cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and smoking) associated with the development of carotid atherosclerosis[11] and cognitive impairment.[9] Because of the well-accepted association between prevalent stroke and cognitive performance, we excluded CREST-2 participants with reported stroke at baseline. The analysis of baseline cognitive function was prespecified, although the N was not determined until CREST-2 had begun. Nevertheless, we chose the milestone of 1000 patients a priori, not by a formal power/sample size analysis but rather with confidence that this sample size would achieve the aims of this article.

METHODS

Data Availability

The data for this article come from CREST-2 and REGARDS. To abide by obligations with National Institutes of Health/National Institute of Neurological Disorders and Stroke and their respective institutional review boards (IRBs), these studies facilitate data sharing through data use agreements. Requests for access to baseline CREST-2 data may be sent to meschia.james@mayo.edu and data related to REGARDS to regardsadmin@uab.edu.

Participants

We studied the first 1000 consecutive patients in CREST-2. The list of inclusion-exclusion criteria and definitions of cardiovascular risk factors is published elsewhere.[6] In general, eligibility includes men and women ≥35 years old who have ≥70% asymptomatic stenosis involving the carotid bifurcation with or without involvement of the contralateral internal carotid artery. A patient is considered asymptomatic in the absence of ipsilateral symptoms within 180 days before randomization with a modified Rankin Scale score ≤1. Exclusions include history of severe dementia by self-/family-report or the presence of neurological symptoms that could be confused for stroke or transient ischemic attack. Patients underwent baseline cognitive assessment either before revascularization or no later than 44 days after randomization if assigned to intensive medical management alone. For inclusion in these analyses, allowing comparison to the REGARDS participants, the CREST-2 patients had to be free of prevalent stroke at baseline, Black or White, and age of ≥45 years older.

Cognitive Measures

The CREST-2 neurocognitive battery is administered via telephone by certified interviewers at the Survey Research Unit at the University of Alabama at Birmingham, blinded to trial (carotid endarterectomy or carotid stenting) and treatment assignment. The battery includes measures (See Table 1) administered in identical fashion (same order) as REGARDS study and comprised of CERAD (Consortium to Establish a Registry for Alzheimer's Disease) Memory Registration[12] (Word List Learning Sum), for 10 words over 3 trials), Word Fluency for animal names and for the single letter, F (Controlled Oral

Table 1. The REGARDS/CREST-2 Measures in Common

Test	Cognitive domain	Outcome
CERAD Word List Learning (WLL-Sum)	Learning	Sum of 3 learning trials (0–30)
CERAD World List Recall (WLL-Delay)	Memory	Number correct (0–10)
Animal naming CERAD; NINDS-CSN	Executive Function	Number correct in 60 s
Letter fluency (F) (NINDS-CSN)		Number correct in 60 s

CERAD indicates Consortium to Establish a Registry for Alzheimer's Disease; CREST-2, Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial; NINDS-CSN, National Institute of Neurological Disorders and Stroke - Canadian Stroke Network; REGARDS, Reasons for Geographic and Racial Differences in Stroke; WLL-Delay, Word List Learning–Delay Recall; and WLL-Sum, Word List Learning Sum.

Word Association),[13] CERAD Recall[12] (Word List Recall after a 10-min delay, or Word List Learning–Delay Recall [WLL-Delay], for the 10 words), and a brief screen for depression.[14] This battery follows the harmonization guidelines for the assessment of vascular cognitive impairment.[15,16] Additional measures were added to the CREST-2 battery in December 2017 to accommodate the mechanistic goals of the CREST-H ancillary study (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis - Hemodynamics),[17] but not included here because few participants had undergone the extended battery at the time of this analysis.

Statistical Methods

The statistical analysis approach used the population-based REGARDS study as norms for performance on the CREST-2 cognitive tasks after adjustment for (1) demographic factors (age strata, race, and education) and (2) after further adjustment for major cardiovascular risk factors associated with cognitive performance (hypertension, diabetes, dyslipidemia, and smoking). Because of the number of factors considered in the development of these norms, stratification would require an unwieldy large number of strata (for the joint consideration of demographic and risk factors: 5×2×4×2×2×2×2=640 strata). As such, the expected performance (ie, the normative standard) for each potential combination of the demographic factors, and demographic plus risk factors, was calculated from regression models. Specifically, for the first analysis adjusting for age, race, and education, a cell-means model was used in REGARDS to estimate the stratified mean for the 40 cells (5 age strata, by 2 race strata, by 4 education strata), with the residual mean square error used as the SD, to be used to calculate the deviation score in the CREST population. For the second analysis incorporating further adjustment for risk factors: (1) the mean score for the same 40 cells was estimated in REGARDS using a reference cell approach, with the reference cell being those with no risk factors and (2) the main effect impact of the 4 risk factors was estimated in the same model. The deviation score for the CREST patients was then calculated by adjusting their age-race-education mean by subtracting off the main effect for each of their prevalent risk factors. Because the distribution of each of the individual cognitive tests is normally distributed, the distribution of the performances of the CREST-2 patients would be a standard normal distribution (SND or a normal curve with a mean of 0.0 and SD of 1.0) if their performances were the same as the general population.

As a result, the extent to which the standardized *Z* scores from the CREST-2 population matches (or fails to match) the SND provides an assessment of the similarity of their performance compared to the general population, adjusted for demographic factors, or demographic factors plus risk factors. Specifically, the deviates of the SND provide the expected proportion of the population at or below that level of cognitive functioning. For example, under the null hypothesis that the CREST-2 population has the same cognitive performance as the general population, 5% of the CREST-2 population should have a *Z* score <—1.64 (the fifth percentile of the SND), 25% <—0.67 (the 25th percentile of the SND), 50% <0.0 (the 50th percentile of the SND), 75% <0.67 (75th percentile of the SND), and 95% <1.64 (95th percentile of the SND). If the distribution of the CREST-2 participants does not reflect the SND, then there is evidence that the cognitive performance of these patients is different from the general population. For example, if for one of the cognitive assessments the 25th percentile of the *Z* scores for the CREST-2 patients is —1.00 (rather than the expected —0.67), this represents a lower than expected performance. Furthermore, if 40% of CREST-2 patients have a *Z* score value below —0.67 (rather than the expected 25%), then this represents too many CREST-2 patients with lower than expected performance. Whether this proportion is significantly below the expected 25% was assessed with a binomial test. We also assessed if there were differences in the distribution if *Z* scores between those with right versus left target lesions using quantile regression. We also compared *Z* score distribution of cognitive scores for each of the four tests between those with left versus right carotid occlusive disease.

Standard Protocol Approvals, Registrations, and Participant Consents

The CREST-2 protocol was approved by a Central IRB at the University of Cincinnati, and all participants provided written informed consent before randomization. For REGARDS, the protocol was approved by the University of Alabama at Birmingham IRB, and consent was obtained initially by telephone and later in writing during the in-person evaluation. The study methods were approved by the institutional review boards of participating institutions not governed by the Central IRB.

RESULTS

Of the first 1000 CREST patients, we removed 113 patients with a previous stroke, and 4 patients with missing data on the presence of a previous stroke. Also removed were 24 patients with missing data for education, 1 missing hypertension, 3 missing diabetes, and 5 missing dyslipidemia. Finally, 62 participants were neither Black nor White and were deleted, resulting in a final analytic sample of 786 patients.

Table 2 shows that there was a high prevalence of cardiovascular risk factors (hypertension, elevated lipids, smoking, and diabetes). Slightly more than half (52%) of the patients had the target carotid vessel on the right, and all began their assigned treatments after baseline cognitive assessment. About half the patients were enrolled in

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Table 2. Descriptive Statistics of the White and Black Patients Included in the First 1000 CREST-2 Randomizations

	All	White participants	Black participants
N	786	722	64
Age, mean (SD)	69.6 (7.6)	69.6 (7.6)	69.5 (7.0)
Education n (%)			
<High school	99 (13)	83 (11)	Education n (%)
High school graduate	225 (29)	211 (29)	14 (19)
Some college	303 (39)	279 (39)	27 (37)
College graduate	159 (20)	149 (21)	14 (19)
Male, n (%)	458 (58)	430 (60)	28 (44)
Hypertension, n (%)	673 (86)	615 (85)	58 (91)
Diabetes, n (%)	279 (35)	250 (35)	29 (45)
Dyslipidemia, n (%)	727 (92)	668 (93)	59 (92)
Right target artery, n (%)	408 (52)	373 (52)	35 (55)

CREST-2 indicates Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial.

each of the carotid endarterectomy and carotid stenting trials, respectively. Because only 7% of the total cohort was Black, we were underpowered to perform demographic and cognitive comparisons across racial groups.

Figure 1 and Table 3 summarize our findings for all 786 patients after adjustment for demographic factors (age strata, race, and education). The left-most box-and-whisker plot in Figure 1 shows the expected distribution of *Z* scores under the null hypothesis (with the dashed lines provided for comparison); corresponding percentile ranks are depicted to the right. The 5 box-and-whisker plots on the right of Figure 1 correspond to observed distribution for the overall cognitive score and each of the 4 cognitive tests, with higher *Z* scores representing higher levels of cognitive function. The upper percentiles of distribution of the overall cognitive score were significantly lower than expected from the general population (*P* values of 0.015 for the 25th percentile, and <0.0001 for other percentiles). Among the 4 tests, the greatest cognitive differences were detected for WLL-Delay for which the observed percentiles were significantly lower than the REGARDS cohort for all percentiles considered (*P*<0.0001). The Word List Learning Sum scores were also below expected at the 50th percentile (*P*=0.0012), the 75th percentile (*P*<0.0001), and 95th percentile (*P*<0.0001). Likewise, the observed CREST-2 distribution for the letter F was below expected at the 50th percentile (*P*=0.010) and 75th percentile (*P*=0.00001) and the 95th percentile (*P*<0.0001). Conversely, the fifth percentile of animal naming was above expected (*P*=0.0017), as was the fifth percentile for letter F (*P*=0.015). Hence, the

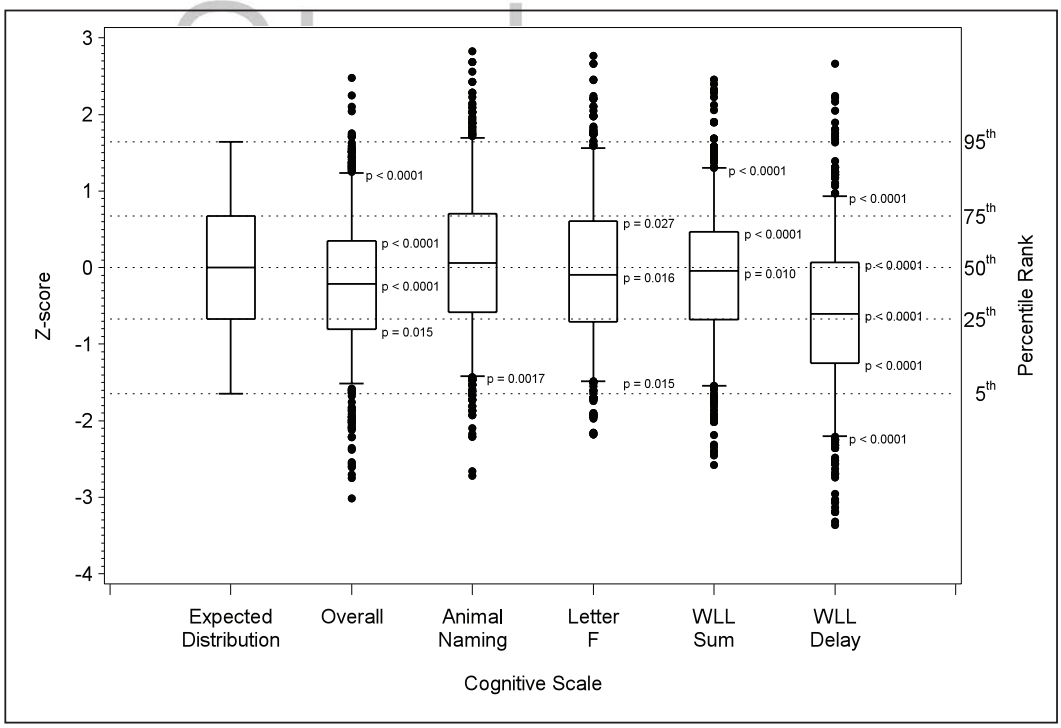

Figure 1. Box-and-whisker plots showing the distribution of cognitive performance in the CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) value where scores are standardized using the general population values from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) population.
The box-and-whisker plot is drawn with the box showing the 25th and 75th percentiles, the line within the box the 50th percentile, the whiskers the fifth and 95% percentiles, and observations below the fifth percentile or above the 95th percentile. WLL-Delay indicates Word List Learning–Delay Recall; and WLL-Sum, Word List Learning Sum.

Table 3. Percent of Observations With a Standardized Value Below The Threshold Values From a Standard Normal Distribution Associated With the Specific Percentiles (5th=−1.64, 25th=−0.67, 50th=0.00, 75th=0.67, 95th=1.64), and *P* Value for Difference From the Expected Proportion

Percentile	Overall		Animal Naming		Letter F		WLL-Sum		WLL-Delay	
	Age-race-education adjusted	+Risk factors	Age-race-education adjusted	+Risk factors	Age-race-education adjusted	+Risk factors	Age-race-education adjusted	+Risk factors	Age-race-education adjusted	+Risk factors
5%	4.1	3.9	2.6	2.2	3.1	2.8	3.8	3.1	15.3	13.4
	0.26	0.15	0.0017	0.0003	0.015	0.0058	0.13	0.0012	<0.0001	<0.0001
25%	28.8	24.1	22.6	20.7	25.8	21.9	27.0	22.5	49.0	41.5
	0.015	0.58	0.12	0.0053	0.60	0.049	0.20	0.11	<0.0001	<0.0001
50%	59.7	55/2	48.0	45.7	54.3	50.8	54.6	50.3	74.4	72.0
	<0.0001	0.0045	0.26	0.017	0.016	0.64	0.010	0.89	<0.0001	<0.0001
75%	85.2	83.1	72.7	71.4	78.5	74.7	82.4	78.4	90.1	89.7
	<0.0001	<0.0001	0.13	0.020	0.027	0.85	<0.0001	0.029	<0.0001	<0.0001
95%	99.0	98.2	94.4	94.3	95.5	94.8	98.1	97.3	98.6	98.5
	<0.0001	<0.0001	0.43	0.34	0.54	0.84	<0.0001	0.0027	<0.0001	<0.0001

WLL-Delay indicates Word List Learning–Delay Recall; and WLL-Sum, Word List Learning Sum.

distribution of cognitive performance of the CREST-2 was substantially below that of a general population, with the differences being larger for the higher percentiles and with the differences being primarily attributable to WLL-Delay (and to a lesser extent Word List Learning Sum and letter F).

Table 3 provides a similar assessment of the impact of further adjustment for cardiovascular risk factors associated with cognitive performance (hypertension, diabetes, dyslipidemia, and smoking), showing a small downward shift of the distribution for CREST-2 patients but with the same general pattern of significant differences. A corresponding box-and-whisker plot showing the percentiles for each scale is also provided as Figure I in the Data Supplement. The striking lower than expected performance for WLL-Delay persisted at all percentiles (P<0.0001) as did the lower than expected performance for the upper percentiles of both Word List Learning Sum ($P_{95\ percentile}$=0.0027, $P_{75\ percentile}$=0.029) and the overall scores ($P_{95\ percentile}$ and $P_{75\ percentile}$<0.0001, $P_{50\ percentile}$=0.0045). For animal fluency, the proportion of patients above the expected levels remained significant at the 25th (P=0.0003), and the nonsignificantly higher proportions in the age-race-education adjusted models became significantly higher at the 25th (P=0.0053), 50th (P=0.017), and 75th (P=0.020) percentiles. For letter fluency, the proportion of patients above expected also became significant at the 25th percentile (P=0.049). For letter F, however, the lower than expected scores at the 50th and 75th percentiles were attenuated by the adjustment for risk factors and became nonsignificant.

Figure 2 shows the similar Z score distribution of cognitive scores for the overall measure and the four tests in our test battery between those with left versus right carotid occlusive disease. Of the 25 percentiles displayed in the figure (5 cognitive assessments times 5 percentiles), none differed significantly between those with a left versus right target lesion (P>0.05).

DISCUSSION

Of the first 1000 CREST-2 patients, baseline cognitive examination from the 786 stroke-free, evaluable Black and White patients with severe, unilateral, asymptomatic carotid stenosis showed a downward shift for those performing at higher levels of cognitive functioning, compared with the REGARDS normative participants, controlling for demographic factors (age, education, and race) and with further adjustment for cardiovascular risk factors associated with cognitive outcomes. Performance of CREST-2 patients for WLL-Delay was lower than expected across the entire distribution of cognitive performance. Conversely, there appears to be a smaller upward shift in performance for those performing lower on cognitive function for other cognitive domains. The CREST-2 cohort represents the largest group of patients to date to demonstrate that poorer cognition was associated with carotid occlusive disease, an effect only modestly attenuated by further adjustment for cardiovascular risk factors associated with cognitive impairment.

There is increasing evidence that asymptomatic stenosis is associated with alterations in cognitive function.[18,19] Among 1975 stroke-free participants in the Framingham Offspring Study assessed with carotid ultrasound, magnetic resonance imaging, and neuropsychological tests, carotid stenosis was associated with reduced cognitive performance and indices of cerebral ischemia on imaging.[20] Individuals with advanced carotid disease, however, have a higher prevalence of cardiovascular factors conveying risk for both atherosclerosis[11] and cognitive impairment,[9] including diabetes,[21] hypertension,[22] and likely white matter disease and silent brain infarction.[23]

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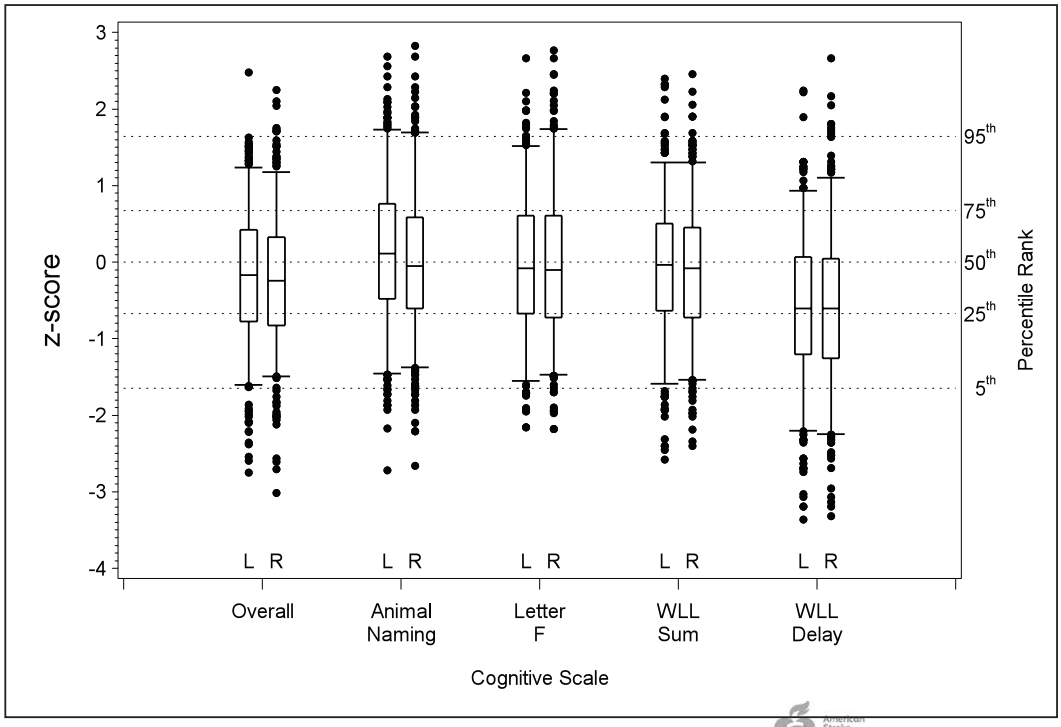

Figure 2. Box-and-whisker plots showing the distribution of cognitive performance in the CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) value where scores are standardized using the general population values from the REGARDS (Reasons for Geographic and Racial Differences in Stroke) population shown by the hemisphere of the target artery.

The box-and-whisker plot is drawn with the box showing the 25th and 75th percentiles, the line within the box the 50th percentile, the whiskers the fifth and 95% percentiles, and observations below the fifth percentile or above the 95th percentile. Of the 25 percentiles shown (5 cognitive domains times 5 percentiles), only the fifth percentile of Word List Learning Sum (WLL-Sum) differed significantly by hemisphere ($P<0.05$). L indicates left; R, right; and WLL-Delay, Word List Learning–Delay Recall.

We showed, however, that accounting for the higher risk factor prevalence in those with advanced carotid stenosis was associated with only a modest attenuation of the lower cognitive performance.

We found that CREST-2 patients with lower cognitive performance (ie, the above-expected performance at lower percentiles) were slightly above expected levels (particularly for fluency measures). This higher-than-expected performance could be attributed to the explicit or implicit exclusion of patients from CREST-2 where potential dementia was concerning, an exclusion that would specifically affect the lower end of the distribution of cognitive performance. The impact of cardiovascular risk factors on cognitive performance was estimated in the REGARDS population using linear regression, an approach that models the average (mean) difference for a risk factor being prevalent. Second, this average impact of a risk factor was then assumed to have an equal impact across the entire distribution of cognitive performance in CREST-2. In CREST-2, magnitude of the higher-than-expected performance for those with lower cognitive performance increased with adjustment for the cardiovascular risk factors. This larger difference may be a product of risk factors having a smaller impact on cognitive performance (ie, a floor effect) at the lower end of the distribution cognitive performance. This would result in an underestimate of performance for those with lower cognitive performance in REGARDS, making the performance of lower-performing CREST-2 patients appear better.

There is increasing evidence that chronic cerebral hypoperfusion is associated with cognitive decline in severe carotid stenosis. Unilateral high-grade disease resulting in impaired vasomotor reactivity was found to be associated with cognitive impairment specific to the ipsilateral hemisphere.[3] Baseline cognitive scores in the RECON study (Randomized Evaluation of Carotid Occlusion and Neurocognition) were compared between patients with carotid occlusion with and without hemodynamic failure by positron emission tomography oxygen extraction fraction (with failure defined as increased oxygen extraction fraction), with otherwise no other differences in demographic, clinical or radiological factors between groups. Among individuals with no stroke as a qualifying event, those who were positron emission tomography–positive (increased oxygen extraction fraction) had significantly lower average Z scores than those who were positron emission tomography–negative, controlling for age, education, and side of occlusion.[4]

Because all of our tests were administered via telephone requiring verbal responses, it might have been expected that scores would have been lower among individuals with left-sided stenosis.[24,25] We did not, however, find differences in cognitive scores among those with left versus right disease, with learning and memory carrying the burden of impairment. That memory might have been affected by perfusion failure was not surprising, with known susceptibility of amygdala and hippocampal structures to ischemia.[26] Bilateral effects of severe unilateral carotid stenosis were recently addressed by Marshall et al,[27] who investigated the association of regional cortical blood flow and regional cortical thickness in asymptomatic patients. Using pseudocontinuous arterial spin labeling magnetic resonance imaging, this study found significantly greater thinning of motor cortex in the anterior circulation on the side of stenosis where blood flow was significantly lower than on the nonoccluded side. Interestingly, there was also some thinning on the nonoccluded side in the anterior circulation, whereas there was no thinning in the visual cortex in the posterior circulation. It was hypothesized that there might have been a synergistic effect of underlying small vessel cerebrovascular disease in the anterior circulation on the nonoccluded side, resulting in susceptibility to hemodynamic effects of both small and large vessels to blood flow. Adding to evidence of a bilateral effect is the finding that cognitive function associated with the presumably unaffected side in RECON was −0.76 SDs below the normative mean.[4] Conversely, the absence of an effect on word list generation for animal names and the letter F from a critical stenosis in either hemisphere in the current study, more typically seen in executive dysfunction of vascular origin, suggests that not all cognitive domains are comparably affected by carotid disease. Because we controlled for education, the intactness of word list generation indicates that our memory findings were not related to lower than expected verbal intelligence in our study cohort.[28]

Although an exclusion criterion for CREST-2 participation was a prior diagnosis of dementia, the cognitive performance of the CREST-2 patients was substantially reduced. To put the cognitive findings into perspective, a patient who scored at the 50th percentile among CREST-2 participants on WLL-Delay scored at the 25th percentile of those in the normative REGARDS cohort. Similarly, a patient scoring at 25th percentile among those in CREST-2, ranked at the 8th percentile compared to those in REGARDS. One point regarding clinical relevance is that that a score ≤15th percentile (or −1.03 SD below the normative mean) correlates with a change in the quality of life in the setting of symptomatic carotid occlusion.[29] Moreover, severe carotid stenosis has been associated with increased rates of cognitive deterioration during a 3-year follow-up in 210 patients with asymptomatic disease.[30] Importantly, that cohort was functioning no differently than normal controls with comparable risk factors at baseline. That the CREST-2 participants are already functioning worse than the normal population may place them at even greater risk for progression to mild cognitive impairment, or worse, a question that will be answered in CREST-2 since patients will be followed for four years.

Limitations of this study include a limited cognitive battery because of administration over the telephone, made necessary by the large number of participating centers, although there is good validity between our telephone and in-person administration.[31] We could not, for example, examine visual-spatial skills and a broader range of executive skills. Another limitation is that only those who were English speaking were tested, so generalization to non-English speaking groups cannot be made. Third, CREST-2 permits a variety of diagnostic modalities as part of its enrollment criteria. As a result, we are not able to correlate our cognitive findings with specific hemodynamic measurements. Moreover, with ≥70% stenosis being the structural criterion, participants were included with only mild hypoperfusion and as well as those with more severe stenoses having substantial impacts on perfusion. Thus, our patient cohort represented the overall population of individuals under consideration for treatment of their disease. Nevertheless, the finding that memory was the most affected cognitive domain is not typical in vascular cognitive impairment in the absence of frank stroke and hemorrhage and suggests a possible perfusion-related mechanism.[32] Indeed, the absence of impact on word list generation as a marker of processing speed makes small vessel disease a less likely explanation.[33] On a related matter, we were unable to adjust for contralateral disease because we could not match cases to REGARDS, which has not collected those data. The hemodynamic threshold for cognitive impairment from carotid disease is not yet known. Fourth, we controlled for the most common confounders but acknowledge that other unmeasured factors could modify the relationship between this disease and cognition. There are, however, several advantages of centralized assessment. First, we are able to present a standardized administration to patients at >100 clinical sites. Second, the REGARDS study provides a large, well-characterized, population-based cohort, enabling us to control for age, education, race, and sex and, additionally, with risk factor assessment allowing for adjustment in the CREST-2 patients. Third, the battery follows the harmonization guidelines for the assessment of vascular cognitive impairment,[15] and there is established sensitivity to vascular risk factors in predicting incident cognitive impairment and to change in cognitive status among those with greater risk factor exposure.[9] Nevertheless, a more comprehensive battery may have detected a broader range of cognitive deficits typical of profiles commonly seen in vascular cognitive impairment.[33]

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CONCLUSIONS

We have shown that there are below normal cognitive test scores in patients with severe, asymptomatic carotid stenosis about to undergo randomized treatment in a very large clinical trial when compared with a demographically matched population-based cohort. The precise mechanisms for cognitive change are not yet known. Cerebral hypoperfusion is one plausible mechanism since memory was the most impacted function, in contrast to measures of executive function more commonly found in vascular cognitive impairment. Because patients in CREST-2 are followed for several years with annual cognitive assessments, we will uniquely be able to characterize functional trajectories over time.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Online Figure I

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