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Impact of baseline features and risk factor control on cognitive function in the SAMMPRIS trial

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Abstract

Background: Cerebrovascular disease is an important cause of cognitive impairment. The aim of this study is to report the relationship between cognitive function and risk factors at baseline and during follow-up in the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial.

Methods: Subjects in the SAMMPRIS trial were included in this study. In order to have an assessment of cognitive function independent of stroke, patients with a stroke as a qualifying event whose deficits included aphasia or neglect were excluded from these analyses as were those with a cerebrovascular event during follow up. The Montreal Cognitive Assessment (MoCA) score was used to assess cognitive impairment at baseline, 4 months, 12 months and closeout. Cognitive impairment was defined as MoCA < 26. A multivariate analysis was performed to determine what risk factors were independent predictors of cognitive function at baseline, 12 months and closeout. Among patients randomized to aggressive medical management (AMM) only, the percentage of patients with cognitive impairment was compared between patients in vs out of target for each risk factor at 12 months and closeout.

Results: Of the 451 patients in SAMMPRIS, 371 patients met the inclusion criteria. MoCA < 26 was present in 55% at baseline. Older age and physical inactivity were associated with cognitive impairment at baseline. Older age, non-white race, lower baseline body mass index (BMI), and baseline cognitive impairment were associated with cognitive impairment at 12 months. In the AMM group, at 12 months, physical inactivity during follow-up was the strongest risk factor associated with cognitive impairment.

Conclusion: Cognitive impairment is common in patients with severe symptomatic intracranial atherosclerosis. Physical inactivity at baseline and during follow up is a strong predictor of cognitive impairment.

Keywords

Intracranial atherosclerosis; cognitive impairment; ischemic stroke

Introduction:

Cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia, preceded only by Alzheimer disease(1). It has been estimated that around 10% of patients with first-time stroke develop new dementia, and at least one third of patients will have dementia after recurrent strokes(2). Vascular risk factor control has emerged as an important modifiable factor in the development of cognitive dysfunction in later life(3). However, the relationship between risk factor control and the development of cognitive impairment in patients with prior stroke or TIA is not well explored. In particular, patients with stroke or TIA due to stenotic cerebral arteries may be at high risk of cognitive impairment due to hypothesized decreased brain perfusion. Analyses from the SAMMPRIS trial, which employed aggressive medical management of vascular risk factors in patients with stroke or TIA due to severe intracranial atherosclerosis (ICAS), showed no benefit of revascularization over aggressive medical management (AMM)(4). Therefore, we sought to further study the association between cognitive dysfunction and risk factor control at both baseline and during follow-up in the SAMMPRIS trial.

Methods:

The rationale, design, participant characteristics and primary outcome results of the SAMMPRIS trial have been previously reported(5-7). In brief, patients with recent transient ischemic attack (TIA) or stroke attributed to 70-99% intracranial stenosis were randomized to percutaneous angioplasty and stenting (PTAS) plus AMM or AMM alone. In order to minimize the impact of focal neurological deficits from stroke, such as aphasia or neglect, on cognitive outcome, patients presenting with stroke in SAMMPRIS who had a National Institutes of Health Stroke Scale (NIHSS) score at enrollment indicating aphasia (items 1c or 9) or neglect (item 11) were excluded from these analyses. Additionally, patients with any ischemic stroke, cerebral infarct with temporary signs (CITS), or intracerebral hemorrhage (ICH) during follow-up were excluded from these cognitive analyses.

The Montreal Cognitive Assessment (MoCA) was the primary measure used to assess cognitive function in the SAMMPRIS trial because of its sensitivity for detecting cognitive impairment in stroke patients(8). Cognition was assessed at baseline; 4 months, 12 months, and closeout (mean follow-up was 3.05 years in the AMM group, 3.12 years in the PTAS group). Cognitive impairment was primarily defined as a MoCA score < 26, the standard value that has 90% sensitivity for detecting mild cognitive impairment(9). Secondary analyses also examined cognitive impairment using a MoCA < 23 to define cognitive impairment, and mean MoCA scores. We also examined a MoCA sub-score of 11 points

that focused on frontal and subcortical function (MoCA FS), which used the Trails B, clock drawing, attention (3 tasks), and fluency portions of the MoCA.

Statistical Analyses:

The prevalence of cognitive impairment at baseline, 12 months, and closeout was determined in patients randomized to both arms of the study (PTAS and AMM) using standard descriptive statistics.

To determine risk factors that were independent predictors of cognitive function at baseline, 12 months, and closeout, we performed a multivariable analysis of baseline demographic, medical history, laboratory and neuroimaging characteristics in a step-wise logistic regression, using the variables listed in Table 2. The models also included the baseline MoCA score so that the analyses are adjusted for baseline cognitive function. The outcomes assessed included cognitive impairment defined as MoCA < 26, cognitive impairment defined as MoCA < 23, the mean MoCA-FS sub score, and mean MoCA score.

To determine the relationship between risk factor control during follow-up and cognitive impairment, we analyzed patients randomized to the AMM only group and compared the percentage of patients with cognitive impairment that were in vs. out of target for the primary risk factor targets (SBP and LDL) and physical activity, since exercise was associated with fewer vascular events during follow-up(7, 10, 11). For each patient in the AMM group, values from baseline until the time of the MoCA scores (e.g. 12 months or closeout) were averaged for each risk factor and dichotomized as in-target or out-of-target. The percentage of patients with cognitive impairment was compared between patients in vs. out of target for each risk factor at 12 months and closeout using a Chi-square test. MoCA scores of < 26 and < 23 were used to define cognitive impairment for these analyses. All reported P values are two sided and have not been adjusted for multiple testing.

Results:

Among the 451 patients, 371 patients met the inclusion criteria for analysis (in both AMM and PTAS groups) for the prevalence of cognitive impairment analysis.

Prevalence of Cognitive Impairment

As shown in Table 1, the overall prevalence of cognitive impairment using the standard primary definition of MoCA < 26 at baseline was 203/371 (55%). At 12 months and closeout, the prevalence of cognitive impairment was 103/253 (41%) and 82/199 (41%), respectively. To account for possible overestimation of cognitive impairment using the higher cutoff, the prevalence of MoCA score < 23 was also determined. The overall prevalence using this cutoff at baseline, 12 months, and closeout was 103/371 (28%), 48/253 (19%), and 34/199 (17%). The mean MoCA score increased from 24.4 at baseline to 25.6 at closeout.

Baseline Predictors of Cognitive Impairment

The results of the multivariate analyses to determine the baseline factors associated with cognitive impairment at baseline, 12 months, and closeout, using the primary definition (MoCA < 26) and other measures of cognitive impairment are shown in Table 2. Only older age (OR 1.05 [95% CI: 1.03-1.07]) and physical inactivity (OR 1.77 [95% CI: 1.11-2.82]) were associated with more cognitive impairment at baseline. Baseline cognitive impairment was not related to other vascular risk factors, severity of stenosis, prior stroke, or white matter lesions on CT or MRI. Older age at baseline (OR 1.06 [95% CI: 1.01-1.10]) and baseline cognitive impairment (OR 18.96 [95% CI: 7.16 - 0.18]) were positively associated with more cognitive impairment at 12 months, but white race (OR 0.20 [95% CI: 0.08-0.54]) and higher body mass index (BMI) at baseline (OR 0.92 [95% CI: 0.86-0.99]) were negatively associated with cognitive impairment. Elevated baseline lipoprotein (a) at baseline (OR 1.01 [95% CI: 1.00-1.02]) and baseline MoCA < 26 (OR 16.33 [95% CI: 6.03-4.19]) were associated with more cognitive impairment at closeout, but higher BMI at baseline (OR 0.92 [95% CI: 0.85-0.99]) was protective.

When a MoCA < 23 was used as the definition of cognitive impairment, at 12 months, angina at baseline (OR 12.83 [95% CI: 2.34-0.33]) and baseline MoCA < 23 (OR 22.8 [95% CI: 7.11-3.44]) were associated with more cognitive impairment, while white race (OR 0.26 [95% CI: 0.09-0.72]) was protective. Similarly, older age at baseline (OR 1.14 [95% CI: 1.05-1.23]), and baseline MoCA < 23 (OR 15.49 [95% CI: 3.91-1.39]) were associated with more cognitive impairment at close out and white race (OR 0.04 [95% CI 0.01-0.18]) was protective.

When using the frontal/subcortical MoCA sub-score (MoCA FS) to assess deficits that are more commonly observed with vascular cognitive impairment, baseline physical inactivity (-0.67 , $p=0.0104$) was associated with more cognitive impairment at 12 months. Older age at baseline (-0.03 , $p=0.0156$) and baseline physical inactivity (-0.75 , $p=0.0125$) were associated with cognitive impairment at close out. High baseline MOCA FS was negatively associated with cognitive impairment at both time points.

Risk Factor Control During Follow-up

The relationship between risk factor control during follow-up among patients in the AMM only group and cognitive impairment is shown in Table 3. At 12 months ($n=84$), physical inactivity during follow-up was the strongest risk factor that was associated with cognitive impairment (54.4% of patients out-of-target for physical activity had cognitive impairment vs 23.7% in-target, $p=0.0044$). At closeout ($n=62$), patients who were out-of-target for LDL were less likely to be cognitively impaired compared those that were in target (13.8% vs 57.6%, $p=0.0004$). The association between LDL and cognitive impairment persisted when using the lower cutoff of MoCA < 23 to define cognitive impairment (6.9% of those out of LDL target with cognitive impairment vs 27.3% of those in target ($p=0.0361$)).

Discussion:

In the SAMMPRIS trial, greater than half of the patients in both AMM and PTAS groups were found to have cognitive impairment at the time of enrollment. The prevalence of cognitive impairment at the time of stroke has varied in the literature depending on the study design and the definition and methods used to assess cognitive impairment(12). In a meta-analysis, the pooled prevalence of pre-stroke dementia recorded at the time of admission for all patients with stroke was 14.4% in hospital-based studies(12). The higher prevalence of cognitive impairment in our study could be partially explained by the fact that most studies used MMSE whereas we used MoCA to assess cognitive impairment. MoCA has been shown in previous studies to be a more sensitive test at screening for cognitive impairment(8).

Older age and baseline physical inactivity were the only predictors of low MoCA at baseline and older age was predictive of a lower MoCA score at 12 months. This result is consistent with previous studies in which advanced age has consistently been shown to be a predictor of cognitive impairment (13, 14). White race was also a predictor of less cognitive impairment in SAMMPRIS, consistent with other studies showing that white patients had a lower rate of cognitive impairment than non-white patients (15, 16). The reasons for racial differences in cognition are unclear, but some have postulated that non-white ethnic groups may be at a higher risk for vascular disease in general, leading to greater burden of ischemic disease, and consequently poorer cognitive outcomes(16). We also found that higher BMI at baseline was related to a higher MoCA score, consistent with previous studies that suggested a lower BMI may be an early indication of cognitive decline(17).

To account for possible over-estimation of cognitive impairment using MoCA score < 26, we lowered the cutoff for cognitive impairment to < 23 to determine baseline predictors of cognitive dysfunction. Many of the baseline predictors were similar, but a new finding using the lower cutoff was that having a history of angina increased the likelihood of having cognitive impairment. A coronary heart disease secondary prevention study testing a fibric acid derivative also found that patients with angina were more likely to have cognitive impairment, regardless of age, gender, or education; however, once adjusted for vascular risk factors, the association diminished(18). In addition, to further evaluate specific deficits seen in vascular cognitive impairment (i.e. subcortical cognitive impairment), we looked at a subscale of frontal executive function within the MoCA (MoCA FS). Older age and physical inactivity at baseline were associated with a lower MoCA FS score during follow-up as well.

Despite the known cognitive benefits of a multi-modal risk factor intervention(3), when analyzing the impact of control of individual risk factors (SBP, LDL, physical activity) during follow-up on cognition in SAMMPRIS, we found that only physical inactivity and LDL in-target were associated with cognitive impairment. Physical activity has been associated with lower risk of cognitive decline in several studies(19, 20) and therefore exercise is a well-established recommendation(15). The observed association between exercise and cognitive function may have multiple mechanisms. Given that we found a benefit of physical activity on cognitive function when excluding patients who had recurrent vascular events during follow-up, our results suggest that the benefit of physical

activity on cognition may be independent of its stroke prevention effect. One possible mechanism is that physical activity may be associated with less small vessel disease, as fewer white matter disease lesions and brain atrophy are observed in those who exercise(21). However, we did not find a significant association between white matter lesions and cognitive impairment at baseline in this population. Alternatively, animal model studies have shown that exercise induces expression of genes associated with plasticity and promotes brain vascularization(22), which may lead to preserving cognitive function. In contrast, the association between good LDL control and cognitive impairment during follow-up in SAMMPRIS is more difficult to explain. While a few studies have suggested that lipid lowering medication use may be linked to memory loss(23, 24), an alternative explanation is that cholesterol levels decrease with age, chronic disease, poor nutrition and inflammation, so perhaps the association between low LDL and cognitive impairment during follow-up is confounded by baseline older age or lower weight, which were associated with cognitive impairment in this study, or even related to another unmeasured factor. Another possibility for the paradoxical association between low LDL and cognitive impairment is that the result may be affected by index-event bias (25) because this analysis was focused on a different outcome (cognitive impairment) than the cohort was selected for in SAMMPRIS (stroke or TIA due to severe ICAS). In other words, because risk factors for ICAS and cognitive impairment overlap, the selection of patients with symptomatic ICAS impacted the distribution of risk factors and therefore may have affected the association of LDL with the outcome cognitive impairment. This is supported by the higher percentage of patients with LDL out of target at 12 months in the cognitive impairment analysis subgroup (56%) compared to the overall study population (5) (< 40% out of target).

While observational studies have shown that hypertension is the vascular risk factor with the highest correlation with dementia(15), better blood pressure control during follow-up in SAMMPRIS was not associated with improved cognitive function. This finding has been reported in other clinical trials evaluating the impact of blood pressure treatment on cognition (1, 26, 27). Recently, a prespecified analysis of the Small Subcortical Strokes (SPS3) trial, which compared intensive blood pressure to usual blood pressure management, found no reduction in cognitive impairment with intensive blood pressure control(28), which is consistent with our findings. It is also possible that the length of follow-up in SAMMPRIS was not long enough to identify a relationship between better blood pressure control and improved cognitive function. Results of the Systolic Blood Pressure Intervention-Memory and cognition In Decreased hypertension (SPRINT-MIND) study, which is a pre-specified component of the SPRINT trial that examined the impact of lower systolic blood pressure on cognitive function in patients without prior stroke(29), are expected to be published soon.

Our study has some limitations. First, after excluding patients with baseline aphasia or neglect and those with recurrent ischemic stroke, CITS, or ICH during the follow-up period, as well as those with missing MoCA data, there was small number available to determine the association of risk factor control and cognitive function during follow-up, increasing the chance of Type 2 error. Also, the remaining patients without recurrent events in follow-up may differ from the overall cohort in that patients with recurrent events were more likely to have poorer risk factor control based on prior analyses(10). However, it was important to exclude those patients so that we could determine the impact of treatment on

cognition independent of the impact of a recurrent cerebrovascular event. Second, multiple comparisons were performed increasing the probability of Type 1 error. Additionally, given that preventing or slowing the rate of cognitive decline might require prolonged control of risk factors over several years but we only assessed patients at 12 months and close out, it is difficult to draw conclusions about the long-term relationship between risk factor control and cognitive function from these analyses. Finally, one could argue that the cognitive improvement seen in patients during the study may be due to a possible learning effect of the MoCA. In a previous MoCA validation study, the test-retest performance showed that there was no significant learning effect at one month but it is recommended that alternative but equivalent MoCA versions be used if testing frequently(9). In contrast, prior studies have evaluated change in MoCA scores over time and showed that there is practice effect when the test was repeated 12 months later (30-33). Given that we did not change the version of MoCA used in the trial due to practical issues of a clinical trial, a practice effect may explain part of the cognitive improvement observed.

Conclusion:

Among patients with severe symptomatic intracranial atherosclerosis, physical inactivity is the strongest risk factor associated with cognitive impairment, further emphasizing the importance of exercise in stroke patients.

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Table 1:

Overall prevalence of cognitive impairment*

	MoCA <26	MoCA <23	Mean MoCA score (sd)
Baseline (n=371)	203 (55%)	103 (28%)	24.4 (4.1)
12 months (n=253)	103 (41%)	48 (19%)	25.5 (3.8)
Closeout (n=199)	82 (41%)	34 (17%)	25.6 (3.7)

* patients with a stroke as the qualifying event whose deficits included aphasia or neglect were excluded from these analyses as were those with a cerebrovascular event during follow up

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Table 2:

Multivariable Baseline Predictors[‡] of MoCA among the overall SAMMPRIS cohort at baseline, 12 months, and closeout.

MoCA Score	Time Point	Baseline Variables	P-value	OR [95% CI]		
Impairment = Moca <26	Baseline*	Older age	<0.0001	1.047 [1.026,1.067]		
		Physical inactivity	0.0166	1.77 [1.109,2.824]		
	12 months	Older age	0.0149	1.053 [1.010, 1.097]		
		White race	0.0014	0.201 [0.075, 0.538]		
		Higher BMI	0.0234	0.922 [0.860, 0.989]		
		Baseline MoCA <26	<0.0001	18.956[7.161,50.182]		
	Closeout	Higher BMI	0.0171	0.917 [0.854, 0.985]		
		Elevated Lp(a)	0.0290	1.011 [1.001, 1.020]		
		Baseline MoCA <26	<0.0001	16.325 [6.03, 44.188]		
Impairment = Moca <23	12 months	White race	0.0094	0.257 [0.092, 0.717]		
		Angina	0.0033	12.828[2.340,70.331]		
		Baseline MoCA <23	<0.0001	22.852 [7.111,73.438]		
	Closeout	Older age	0.0014	1.135 [1.050, 1.227]		
		White race	<0.0001	0.035 [0.007, 0.182]		
		Baseline MoCA <23	<0.0001	15.487[3.907,61.387]		
				Linear Regression Slope [95% CI]		
Frontal/Subcortical MoCA sub-score (MoCA FS)	12 months	Physical inactivity	0.0104	-0.666[-1.173,-0.159]		
		Baseline high MoCA FS [‡]	<0.0001	0.621 [0.512, 0.720]		
	Closeout	Older age	0.0156	-0.03 [-0.054, -0.006]		
		Physical inactivity	0.0125	-0.750[-1.336,-0.164]		
		Baseline high MoCA FS	<0.0001	0.590 [0.472, 0.708]		
Raw MoCA score	12 months	Older age	0.0305	-0.041[-0.077,-0.004]		
		White race	0.0002	1.722 [0.828, 2.619]		
		History of lipid disorder	0.0234	1.558 [0.215, 2.921]		
		Angina	0.0127	-1.856[-3.275,-0.397]		
			Baseline MoCA >26	<0.0001	0.540 [0.438, 0.642]	
	Closeout	Older age	0.0002	-0.081[-0.123,-0.040]		
		Elevated Lp(a)	0.0232	-0.011 [-0.02, -0.001]		
		White race	0.0062	1.594 [0.462, 2.728]		
				Baseline MoCA >26	<0.0001	0.495 [0.339, 0.580]

* **Baseline Univariate predictors in the model:** age, race (white vs. other), male gender, history of hypertension, mean SBP (mmHg), drop in BP with standing (mmHg), BP medication use before enrollment, history of lipid disorder, lipid levels, LDL (mg/dL), HDL (mg/dL), total cholesterol (mg/dL), Lp(a) (mg/dL), statin use before enrollment, any lipid lowering drug use before enrollment, history of diabetes or baseline A1c > 6.5%, smoking status, BMI (kg/m²), moderate physical activity, stroke as qualifying event, prior stroke (not qualifying event), antithrombotic medication use before enrollment, symptoms related to hypoperfusion, % stenosis, symptomatic vessel in anterior circulation, more than one intracranial stenosis, old infarcts on CT or MRI, presence of white matter lesions on CT or MRI, and extent of white matter lesions by Fazeka score.

[‡]**Baseline Multivariable predictors for 12 months and closeout in the model:** age, elevated Lp(a), race (white vs. other), history of lipid disorder, angina, physical inactivity at baseline, CHF, stroke within 30 days of enrollment (not qualifying event), history of extracranial angioplasty or stenting, small vessel disease, and baseline MoCA score.

[‡]FS = frontal subcortical MoCA score

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Table 3:

Relationship between risk factor control during follow-up and cognitive impairment in the AMM only group at 12 months and closeout.

	Cognitive Impairment defined as MoCA < 26			Cognitive Impairment defined as MoCA < 23		
	Impaired n (%)	Not impaired n (%)	p-value	Impaired n (%)	Not impaired n (%)	p-value
12 months						
Physical Activity*						
In target (n=38)	9 (23.7%)	29 (76.3%)	0.0044	5 (13.2%)	33 (86.8%)	0.1421
Out of target (n=46)	25 (54.4%)	21 (45.6%)		12 (26.1%)	34 (73.9%)	
Systolic blood pressure**						
In target (n=45)	16 (35.6%)	29 (64.4%)	0.3237	9 (20.0%)	36 (80.0%)	0.9535
Out of target (n=39)	18 (46.2%)	21 (53.8%)		8 (20.5%)	31 (79.5%)	
Low density lipoprotein[†]						
In target (n=37)	18 (48.6%)	19 (51.4%)	0.1758	9 (24.3%)	28 (75.7%)	0.4082
Out of target (n=47)	16 (34.0%)	31 (66.0%)		8 (17.0%)	39 (83.0%)	
Closeout						
Physical activity*						
In target (n=36)	11 (30.6%)	25 (69.4%)	0.2096	4 (11.1%)	32 (88.9%)	0.1078
Out of target (n=26)	12 (46.2%)	14 (53.8%)		7 (26.9%)	19 (73.1%)	
Systolic blood pressure**						
In target (n=38)	12 (31.6%)	26 (68.4%)	0.2577	7 (18.4%)	31 (81.6%)	0.8602
Out of target (n=24)	11 (45.8%)	13 (54.2%)		4 (16.7%)	20 (83.3%)	
Low density lipoprotein[†]						
In target (n=33)	19 (57.6%)	14 (42.4%)	0.0004	9 (27.3%)	24 (72.7%)	0.0361
Out of target (n=29)	4 (13.8%)	25 (86.2%)		2 (6.9%)	27 (93.1%)	

* Physical activity target defined by a mean PACE score of < 4 (with 3 = trying to do vigorous exercise and moderate exercise but not exercising regularly, 2 = no vigorous or moderate exercise but thinking of starting within 6 months, and 1 = no vigorous or moderate exercise and no intention to start in next 6 months. Examples of moderate exercise are brisk walking, gardening, slow cycling that lasts at least 10 minutes. Examples of vigorous exercise are jogging, running, fast cycling that lasts at least 20 minutes.)

** SBP target: mean SBP < 140 mm Hg (< 130 if diabetic)

[†] LDL target: mean LDL < 70 mg/dL