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Quality of life after lacunar stroke: the Secondary Prevention of Small Subcortical Strokes Study

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Abstract

Background—We sought to describe the course and predictors of QOL after lacunar stroke. We hypothesized that there is a decline in QOL after recovery from lacunar stroke.

Methods—SPS3 is a clinical trial in lacunar stroke patients with annual assessments of QOL with the Stroke Specific QOL score (SSQOL). The overall score was used and analyzed as a continuous variable (range 0–5). We fit linear mixed models to assess the trend in QOL over time, assuming linearity of time, and adjusted for demographics, medical risk factors, cognitive factors, and functional status in univariable and multivariable models.

Results—Among 2870 participants, mean age was 63.4 years (SD 10.7), 63% were male, 51% White, 32% Hispanic, 36% had college education, 36% had diabetes, 89% had hypertension, and 10% had prior stroke. Mean post-stroke Barthel index score (BI) was 95.4 (assessed on average 6

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Disclosures

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months after stroke). In the final multivariable model, there was an average increase in QOL of 0.6% per year, and factors associated with decline in QOL over time included age (−0.0003 per year, p<0.0001), any college education (−0.0013 per year, 0.01), prior stroke (−0.004 per year, p<0.0001), and BI (−0.0002 per year, p<0.0001).

Conclusions—In this clinical trial of lacunar stroke patients, there was a slight annual increase in QOL overall, and age, level of education, and prior stroke were associated with changes in QOL over time. Multiple strokes may cause decline in QOL over time in the absence of recurrent events.

Keywords

Lacunar stroke; quality of life; recovery

Introduction

It is well known that stroke causes an acute decrease in quality of life (QOL),[1–3] even among those who have no post-stroke disability.[3, 4] However, the long term course of QOL is not well-described, because prior studies of QOL after stroke have been limited by cross-sectional design,[2, 5] relatively small sample sizes,[5–8] and samples with heterogeneous stroke subtypes.[2, 3, 5, 6, 8–14] Longitudinal studies have been limited by short follow-up,[8, 10, 14–17] few follow-up assessments,[12, 13, 18, 19] and loss to follow-up.[12, 13]

Seeking to clarify the long-term course of QOL after ischemic stroke, the population-based Northern Manhattan Study found a steeper decline among those with lower socioeconomic status (SES) compared to those with higher SES.[20] However, all subtypes of ischemic stroke were included (n=525), out of which only 135 lacunar strokes occurred. These small numbers precluded the ability to model the long-term course of QOL after lacunar stroke, which comprises about 25% of ischemic stroke[21–23] and occurs at younger ages.

The Secondary Prevention of Small Subcortical Strokes Study (SPS3), although a clinical trial, provides a large database for the study of prognosis among patients with MRI-verified lacunar stroke with long-term follow-up. QOL was assessed at multiple follow-up intervals, allowing the use of robust statistical analyses that take into account repeated outcome assessments. Our goal was to describe the course and predictors of QOL after lacunar stroke. We hypothesized that vascular risk factors predicted lower QOL and that there is an ongoing decline in QOL after lacunar stroke.

Methods

The SPS3 study was a randomized, multicenter clinical trial among patients with lacunar stroke, testing different anti-platelet and antihypertensive regimens and with annual assessments of QOL. Details of the study design and results of the anti-platelet arm have been published elsewhere.[24, 25] In brief, subjects were eligible if they had a clinical lacunar stroke syndrome or subcortical transient ischemic attack (TIA) in the 6 months before enrollment with confirmation by magnetic resonance imaging (MRI), no clinical or radiological evidence of cortical involvement, and no surgically amenable ipsilateral carotid

artery disease or major-risk cardioembolic sources. Patients with subcortical TIAs required confirmation by MRI diffusion-weighted imaging (DWI). Exclusion criteria included radiological or clinical evidence of a previous cortical/retinal stroke or TIA, previous intracranial hemorrhage or hemorrhagic infarct, disabling stroke (defined as a score on the modified Rankin scale of ≥4), impaired renal function, high risk of bleeding, or cognitive impairment. Patients were randomized in a 2 × 2 factorial design to one of two interventions: antiplatelet therapy with aspirin 325 mg/day or with aspirin 325 mg/day plus clopidogrel 75 mg/day (double-blind, placebo-controlled), and to one of two target levels of systolic blood pressure control, “higher” (130–149 mmHg) or “lower” (<130 mmHg). The SPS3 study was approved by the Institutional Review Boards of all participating centers, and all patients provided written informed consent.

We included SPS3 participants with a completed baseline assessment as of August 31, 2011. We included up to 5 years of follow-up, and only included participants with at least one follow-up post-stroke.

Baseline assessment

All individuals underwent an interview in which demographic information, behavioral risk factors, and medical history before the qualifying stroke were collected. Race and ethnicity were determined primarily by self-report, modeled after the 2000 US Census. Participants from Spain were categorized as non-Hispanic White.

A history of hypertension was defined by at least one of the following criteria: (1) consistent recording of hypertension in medical records for ≥1 year, (2) medical record or self-reported use of at least one antihypertensive medication and/or adjustment to achieve blood pressure control, and (3) medical record of blood pressure elevation sustained for ≥3 months. A history of diabetes was defined based upon self-reported history of diabetes, chronic elevation of fasting serum glucose >120 mg/dL, or chronic requirement for hypoglycemic medication. Coronary artery disease was defined as a history of definite myocardial infarction, definite/atypical angina, revascularization procedure, or heart failure. Hyperlipidemia was defined as current treatment with a lipid-lowering drug or laboratory data confirming fasting hyperlipidemia. Before entry, patients were screened for cognitive dysfunction with the Folstein Mini Mental Status Examination (MMSE),[26] and only patients with an MMSE score greater than 2 standard deviations below the mean for age and education were entered into the trial. An SPS3-certified examiner administered a blinded, detailed cognitive assessment on every participant. A standardized neurological exam was performed, and the modified Rankin score and the Barthel Index were assessed.

MRI of the brain, electrocardiography, transthoracic or transoesophageal echocardiography, and standard laboratory blood tests were performed on all patients. Imaging of the cervical and intracranial arteries was performed with MR or CT angiography.

Prospective follow-up

All trial participants were seen at least monthly for the first three months after enrollment and then every 3 months. QOL was assessed with the Stroke Specific QOL (SSQOL)[27] at three months, and then at annual follow-ups. The SSQOL measures 12 domains (energy,

family roles, language, mobility, mood, personality, self-care, social roles, thinking, vision, upper extremity function, and work/productivity). The overall score is an unweighted average of Likert scores for each of the 12 domains; this was analyzed as a continuous variable (range 0–5). Primary outcomes were mean SSQOL and change over time. Fifty-nine percent of SSQOL assessments were interviewer-administered, as opposed to self-administered, at 1 year, 49% at 3 years, and 43% at 5 years; the remainder were self-administered.

Depression was assessed at the 3 month follow-up visit with the Patient Health Questionnaire (PHQ)-9,[28] a 9-item scale that assesses the 9 Diagnostic and Statistical Manual of Mental Disorders depression criteria. If least 2 of the 9 symptoms were present more than half of the days, including the anhedonia or depressed mood item, depression was defined as present.[29]

Statistical analysis

For descriptive purposes, means and standard deviations were calculated for continuous variables and proportions for categorical variables.

We fit linear mixed models to determine which factors were associated with QOL, both on average and over time. Our main interest was whether the variables were associated with trends in QOL over time, represented in the models as interactions between each factor and time. Our modeling strategy was first to fit univariable models, then to fit individual models of interactions with time without multivariable adjustment. We then fit a multivariable model that included each of the baseline factors associated with QOL, as well as the significant interactions from the univariate models. The final model excluded non-significant interactions with time and non-significant main effects.

Time was treated as a continuous variable, since it had linear properties in the data. We fit a linear mixed model, and based on the Bayesian Information Criteria (BIC), we used a compound symmetric covariance structure to account for the correlations among a subject's assessments over time. QOL assessments in the first 6 months after stroke were not included in the analysis, since our interest was in the long-term course of QOL. Models were run both with and without censoring of recurrent stroke events occurring during follow-up, and results were similar; the uncensored models are presented here.

Covariates measured at baseline were chosen based upon epidemiological relevance and included demographic variables (age at qualifying stroke, sex, race/ethnicity [White, Hispanic, African-American, and Asian/Pacific Islander], education [any college versus other], marital status), medical risk factors (diabetes, hypertension, tobacco use [current smoker vs. no smoking], regular alcohol use, and coronary artery disease [definite MI, definite/typical angina, definite congestive heart failure, CABG/coronary PTCA/coronary stent]), stroke prior to qualifying event, baseline score on the cognitive assessment screening instrument (CASI), modified Rankin scale score, and Barthel Index score. In the final multivariable model, marital status was excluded, because this question was added to the baseline form later in the study and a significant number of participants had missing values.

To assess whether the effects of the primary exposures of interest were mediated through depression at 3 months, the depression variable was added to the final multivariable model and the effect estimates for the primary exposures of interest were examined for any change. If there was a reduction in the effect estimate, depression was deemed to mediate the relationship between the exposure and QOL.

Because of 3-way interactions with age, in secondary analysis, we fit models stratified by age quartile (<55.5, 55.5–62.6, 62.6–71.5 and >71.5 years of age). To assess whether there was a differential effect of predictors on different domains of QOL, we also performed a domain-specific analysis in which each domain of the SSQOL was analyzed separately as an outcome.

Results

Baseline characteristics of the 2870 participants are summarized in Table 1. Mean post-stroke Barthel index score (BI) was 95.4 (assessed on average 6 months after stroke), reflecting the relatively mild functional impairment expected from lacunar strokes. Of the 2870 patients, 1949 (68%) had at least 3 annual assessments of QOL over the 3.5-year mean follow-up period. The mean QOL score was 4.1 at 3 months and 4.2 at every yearly assessment from years 1–5.

Table 2 shows results from the univariable mixed models testing the association between each factor and QOL. White race, male sex, married status, and living in Spain were associated with higher overall QOL, and vascular risk factors, coronary artery disease, and prior stroke were associated with lower overall QOL. The following variables showed significant interactions with time and are thus associated with change in QOL over time: age ($p < 0.0001$), prior stroke ($p < 0.0001$), lower education ($p = 0.0498$), and baseline Barthel index score ($p < 0.0001$).

In the final multivariable model (Table 3), which incorporated baseline factors associated with QOL and significant interactions from univariable models, the following variables were associated with lower baseline QOL: female sex, diabetes, hypertension, current smoking, coronary artery disease, no alcohol use, lower cognitive status, lower Barthel index score, and residing in North America or Latin America (versus Spain). There was a slight increase in QOL over time on average, of 0.6% per year. Factors associated with a reduced increase in QOL over time included increased age, any college education, prior stroke, and higher Barthel index score. Those without a prior stroke had a higher baseline QOL, and QOL increased over time; for those with a prior stroke, QOL decreased over time. When depression at 3 months was added to the final multivariable model, the effect estimates for diabetes and prior stroke were reduced but remained significant (not shown), suggesting that the effect of diabetes and prior stroke on QOL may be mediated partially but not completely through depression.

In age stratified models (Table 4), there was a significant increase in QOL over time that was most pronounced in the youngest age quartile and progressively less pronounced in higher quartiles. Prior stroke had a significant effect on change in QOL among the three

older quartiles, the Barthel index score had an effect in all quartiles (with borderline significance in the 3rd quartile), and education had an effect only among the youngest quartile.

In domain-specific analyses, older age was a consistent predictor of decrease in QOL over time across all domains; diabetes predicted lower baseline mobility, energy, and work/productivity and decrease over time; prior stroke predicted decrease in QOL over time in all domains except vision, language, thinking, and personality; and higher Barthel index score predicted higher baseline QOL and decrease over time in all domains except vision, language, thinking, and personality.

Discussion

In this clinical trial of lacunar stroke patients, we found high average QOL scores, reflecting relatively mild loss of QOL compared to prior studies among all subtypes of stroke.[6, 18, 20, 30] We found that vascular risk factors were associated with lower average QOL in fully adjusted models, and that depression may partially mediate this association for diabetes and prior stroke in particular. Factors such as hypertension, diabetes, and smoking may cause subclinical or clinical vascular events such as MI or stroke,[31–33] or may cause non-vascular conditions that reduce QOL, such as diabetic neuropathy. In domain-specific analysis, diabetes predicted lower baseline QOL scores in the domains of mobility, energy, and work/productivity, which could reflect mediation through either a vascular or non-vascular pathophysiology.

Contrary to our initial hypothesis, there was a slight overall increase in QOL of 0.6% per year over the 3.5-year mean follow-up period of the study, in contrast to a 1% annual decline seen in prior research.[20] This difference among studies may be due to several factors. The increase in QOL over time in the SPS3 trial was most pronounced in the youngest age quartile and progressively less pronounced in higher quartiles, possibly reflecting the enhanced capacity for recovery among younger stroke survivors.[3, 11] SPS3 comprises lacunar stroke patients with mild post-stroke disability (the average Barthel index score was 95 out of a possible 100). It is possible that the mild severity of the strokes caused little long-term effect on cognition, mood, and functional status. Alternatively, since this was a clinical trial, the enrollment of a select cohort with higher long-term QOL, close follow-up and regular management of risk factors could have resulted in better QOL over time compared to the general population. Prior research in the Northern Manhattan Study among all subtypes of ischemic stroke (n=525) showed a long-term decline in QOL after ischemic stroke that began after 3 years of follow-up,[20] and it is possible that the follow-up period in SPS3 was too short to capture such a decline, or that the younger mean age of the SPS3 cohort (63.4 versus 68.6 years) was responsible for the lack of decline.

Despite this small overall increase in QOL over time, we found that several factors were associated with a downward slope in the trajectory of QOL over time, particularly prior stroke, which had a significant effect on change in QOL among the three older quartiles. The effect of prior stroke was wide-ranging, for in domain-specific analysis, prior stroke predicted a decrease in QOL over time in all domains except vision, language, thinking, and

personality. There are several possible mechanisms by which multiple strokes may cause decline in QOL over time. The accumulation of deficits in gait, continence, and other aspects of ADL may worsen the trajectory of QOL. Stroke recurrence may reflect worse control of risk factors that could result not only in clinical strokes but also subclinical infarcts, which are prevalent,[31] cause cognitive impairment,[32, 33] and would likely negatively impact QOL. Alternatively, ischemic stroke may lead to ongoing non-ischemic damage in surrounding brain regions due to changes in inflammatory profiles[34, 35] that may persist years after stroke.[36] Such changes may promote neurodegeneration or impair recovery mechanisms that would accelerate the loss of QOL.

The results of this study may not be generalizable to other populations, since these trial participants received regular medical care and study medication. However, this study highlights the need to examine patient-centered outcomes such as QOL, for an exclusive focus on event-based outcomes such as mortality or vascular events may underestimate the burden of stroke, especially over the long term. Also, we found that multiple strokes had an independent effect on decline in QOL, suggesting that preventing recurrent stroke may prevent not only discrete vascular events but also improve an individual's QOL over the long term. Further research would clarify the role of antidepressant medication or other non-pharmacological treatments to augment QOL or prevent its decline among older populations. The use of patient-centered outcomes highlights the fact that treating stroke should not be focused solely on preventing events, but also maximizing function and QOL.

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Table 1

Baseline characteristics of study population.

Number of participants, No. (%)	2870 (100)
Demographics:	
Age, mean (SD), y	63.4 (10.7)
Male, No. (%)	1809 (63)
Non-Hispanic white, No. (%)	1459 (51)
African-American, No. (%)	423 (15)
Hispanic, No. (%)	906 (32)
Other race, No. (%)	82 (3)
Any college education, No. (%)	1026 (36)
Marital status, No. (%) married	1456 (65)
Risk factors, No. (%)*	
Regular alcohol use, No. (%)	817 (28)
Current smoking, No. (%)	566 (20)
Hypertension, No. (%)	2568 (89)
Diabetes mellitus, No. (%)	1036 (36)
History of coronary artery disease, No. (%)	202 (7)
Prior stroke, No. (%)	285 (10)
Functional status*	
Cognitive assessment screening instrument (CASI), mean score (SD)	85.2 (12.4)
Modified Rankin score >1, No. (%)	947 (33)
Barthel index score, mean (SD)	95.4 (9.8)
Depression at 3 months, No. (%)	509 (19)
Time since qualifying event, days (SD)	171 (51)

* as defined in text

Table 2

Univariable predictors of quality of life

Variable	Estimate	95% CI	p-value
Age, per 1-year increase	−0.0025	−0.0046, −0.0003	0.026
Male	0.16	0.12, 0.21	<0.0001
Race/Ethnicity			<0.0001
White	0.22	0.15, 0.28	
Hispanic	0.027	−0.041, 0.095	
African American/Other	REF		
Any college	−0.086	−0.13, −0.037	0.0005
Married	0.104	0.049, 0.16	0.0002
Diabetes	−0.21	−0.26, −0.16	<0.0001
Hypertension	−0.16	−0.23, −0.079	<0.0001
Current smoker	−0.033	−0.025, 0.092	0.27
Regular alcohol user	0.17	0.12, 0.22	<0.0001
Coronary artery disease	−0.16	−0.25, −0.066	0.0007
Prior stroke	−0.18	−0.26, −0.10	<0.0001
CASI	0.012	0.011, 0.014	<0.0001
Barthel	0.023	0.021, 0.026	<0.0001
Region			<0.0001
North America	−0.29	−0.36, −0.22	
Latin America	−0.37	−0.45, −0.29	
Spain	REF		

Notes: CI=confidence interval; CASI=cognitive assessment screening instrument score

* adjusted for: age, sex, race-ethnicity, education, marital status, diabetes, hypertension, alcohol use, coronary artery disease, prior stroke, CASI, Barthel index, and region

Table 3

Multivariable model of predictors of quality of life and decline

Variable	Estimate	95% CI	p-value
Predictors of baseline QOL:			
Age, per 1-year increase	0.0052	0.0029, 0.0075	<0.0001
Male	0.089	0.044, 0.13	0.0001
Race/Ethnicity			0.45
White	0.041	−0.023, 0.10	
Hispanic	0.023	−0.067, 0.11	
African American/Other	REF		
Any college	0.023	−0.031, 0.077	0.41
Diabetes	−0.14	−0.19, −0.099	<0.0001
Hypertension	−0.092	−0.16, −0.023	0.0086
Current smoker	−0.14	−0.19, −0.081	<0.0001
Regular alcohol user	0.072	0.023, 0.12	0.0037
Coronary artery disease	−0.14	−0.22, −0.059	0.0008
Prior stroke	−0.031	−0.11, 0.046	0.43
CASI, per point	0.0086	0.0065, 0.011	<0.0001
Barthel	0.023	0.020, 0.025	<0.0001
Region			<0.0001
North America	−0.32	−0.39, −0.24	
Latin America	−0.21	−0.33, −0.099	
Spain	REF		
Predictors of change in QOL over time:			
Change in QOL per year	0.0312	0.026, 0.039	<0.0001
Additional change per year of age	−0.00025	−0.00030, −0.00020	<0.0001
Additional change with any college education	−0.0013	−0.0024, −0.0031	0.011
Additional change with prior stroke	−0.0035	−0.0051, −0.0018	<0.0001
Additional change per point of Barthel score	−0.00016	−0.00022, −0.00010	<0.0001

Notes: QOL=quality of life score; CI=confidence interval; CASI=cognitive assessment screening instrument score

Table 4

Predictors of change in quality of life in age-stratified multivariable models*

	Age Group											
	< 55.5 years			55.5–62.6 years			62.6–71.5 years			>71.5 years		
Variable	**Change in QOL**	**95% CI**	**p-value**	**Change in QOL**	**95% CI**	**p-value**	**Change in QOL**	**95% CI**	**p-value**	**Change in QOL**	**95% CI**	**p-value**
Change in QOL per year	0.028	0.018, 0.044	<0.0001	0.023	0.0095, 0.037	0.0009	0.010	0.00077, 0.019	0.034	0.0091	−0.00056, 0.019	0.065
Additional change with prior stroke	0.0014	−0.0021, 0.0049	0.44	−0.0064	−0.0099, −0.0029	0.0004	−0.0030	−0.0059, −0.0020	0.036	−0.0063	−0.0098, −0.0029	0.0004
Additional change per point of Barthel index score	−0.00028	−0.0042, −0.00014	<0.0001	−0.0002	−0.00034, −0.00006	0.0059	−0.0001	−0.00019, 0	0.053	−0.00013	−0.0023, −0.0003	0.012
Additional change with any college education	−0.0032	−0.0052, −0.0013	0.0014	−0.0016	−0.0037, 0.00056	0.1473	−0.00036	−0.0023, 0.0016	0.72	0.00020	−0.0020, 0.0024	0.85

Notes: CI=confidence interval, QOL=quality of life score

*Models are adjusted for: sex, race, history of coronary artery disease, hypertension, diabetes, current smoker, regular alcohol use, and region