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Neurological Symptom Severity after a Recent Non-cardioembolic Stroke and Recurrent Vascular Risk

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Abstract

Background—There is a well-established relation of symptom severity with functional status and mortality after an index stroke. However, little is known about the impact of symptom severity of a recent index stroke on risk of recurrent vascular events.

Methods—We reviewed the dataset of a multicenter trial involving 3680 recent non-cardioembolic stroke patients aged ≥ 35 years and followed for 2 years. Independent associations of stroke severity (as measured by National Institutes of Health Stroke Scale [NIHSS] score) with recurrent stroke (primary outcome) and stroke/coronary heart disease (CHD)/vascular death (secondary outcome) were analyzed. NIHSS score was analyzed as a dichotomous (≤ 4 vs. > 4) and a continuous variable.

Results—Among study subjects, 550 (15%) had NIHSS scores ≤ 4 (overall scores ranged from 0 to 18, median score was 1 [25th to 75th percentile 0 to 2]). NIHSS ≤ 4 was measured at a median 35 days after the index stroke. After adjusting for multiple covariates, NIHSS ≤ 4 was independently linked to higher risk of recurrent stroke (HR 1.37, 95% CI: 1.01–1.84) and risk of stroke/CHD/vascular death (HR 1.32, 95% CI: 1.07–1.64). Analysis of NIHSS score as a continuous variable also showed a higher risk of recurrent stroke (HR 1.06, 95% CI: 1.00–1.12) and stroke/CHD/vascular death (HR 1.05, 95% CI: 1.01–1.09) with increasing index stroke symptom severity.

Conclusions—Greater residual symptom severity after a recent stroke is associated with higher risk of recurrent vascular events. Future studies are needed to confirm this relationship and to clarify its underlying mechanisms.

Keywords

National Institutes of Health Stroke Scale; ischemic stroke; vascular events; risk

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Introduction

Symptom severity of an index stroke is a powerful prognosticator of short-term outcomes, especially functional status and mortality.^{1–5} Indeed, it is widely recognized that stroke patients with greater initial symptom severity tend to have more unfavorable prognoses.^{3–5} However, relatively little is known about the possible association of symptom severity and risk of recurrent vascular events after a recent index stroke, particularly over the longer term. On one hand stroke patients with greater baseline symptom severity may be at higher risk for recurrent vascular events due to reactive depression leading to overall poorer regimen adherence; while on the other hand stroke patients that recover with minimal deficit or no deficit may be more vulnerable to future events due to underlying unstable pathophysiology (i.e. ongoing thrombosis-thrombolysis).⁶ As far as we are aware only one published study has explored this issue, showing that higher National Institutes of Health Stroke Scale (NIHSS) score at the time of admission was associated with stroke recurrence at 1 year.⁷ However, the study was small (n=49) and confined to high risk patients with symptomatic middle cerebral artery stenosis.⁷ With this background, we aimed to evaluate the independent relationship of symptom severity of a recent index stroke with risk of recurrent vascular events.

Methods

Database

This is a sub-analysis of prospectively collected data obtained during the conduct of the Vitamin Intervention for Stroke Prevention (VISP) trial.⁸ VISP study was a multicenter, double blind, randomized controlled clinical trial performed at 56 centers across the United States, Canada, and Scotland. The original aim of the study was to determine whether high doses of multivitamin (folic acid, pyridoxine, and cobalamin) given to lower total homocysteine levels would reduce the risk of recurrent stroke and major vascular events in 3680 patients, aged ≥ 35 years, with a recent (onset ≤ 120 days before randomization) non-disabling (modified Rankin Scale ≤ 3) non-cardioembolic stroke.⁸ Demographic, physical, neurological examination including stroke scales, medication use assessment, and laboratory data collected at randomization, with subsequent information obtained at follow-up visits of 1, 6, 12, 18, and 24 months (phone interview at 3, 9, 15, and 21 months). The VISP dataset did not provide information about whether assessments were specifically done during the index hospitalization or not, but given that NIHSS evaluations done during VISP trial randomization were performed at a median time of one month after the qualifying stroke, it is highly likely that the overwhelming majority of NIHSS assessments were done in the ambulatory care setting. Physicians were instructed to provide best available background medical and surgical management to prevent recurrent stroke, which included risk factor control education and, usually, administration of aspirin, 325 mg/d.⁸ The trial was approved by the ethics committee or institutional review board (IRB) at each national or local site, and all participants provided written informed consent.⁸ Since this particular study was a post-hoc analysis of the trial's publicly accessible de-identified dataset, specific and formal IRB review was waived.

Predictor Variable

As part of the VISP trial protocol, at the time of randomization following the qualifying stroke event, neurological symptom severity was measured using the NIHSS score.^{9,10} Neurological symptom severity following the occurrence of a recent stroke, as represented by these post-stroke NIHSS values, was utilized in this sub-analysis as reflective of residual symptoms from the aforementioned index stroke. NIHSS scores in VISP were obtained at a median of 35 days after the VISP qualifying stroke. Subjects were dichotomized into those with minor stroke defined as NIHSS <4,¹¹ and those with non-minor stroke (NIHSS ≥ 4). NIHSS was also assessed as continuous variable. Other baseline measurements included medical history, current medication and vitamin use.

Outcome Variable(s)

Our primary outcome was ischemic stroke. Secondary outcome was a composite of ischemic stroke, coronary heart disease (CHD) including myocardial infarction (MI), coronary revascularization, cardiac resuscitation, and fatal CHD, or vascular death as major vascular events. Recurrent stroke was diagnosed only with evidence of sudden onset of focal neurologic deficit lasting at least 24 hours accompanied by an increased NIHSS score in an area that was previously normal.⁸ When the sudden onset of symptoms lasting at least 24 hours was not accompanied by an increased NIHSS score in an area that was previously normal, then recurrent stroke was diagnosed using cranial CT or MRI evidence of new infarction consistent with the clinical presentation.⁸ Endpoint adjudication was verified by a consensus of the Cerebrovascular Endpoint Review Committee for the primary outcome and the Cardiovascular Endpoint Review Committee for the secondary outcome.⁸

Statistical Analysis

Comparisons across the groups were examined using the χ^2 test for categorical variables and Student *t* test for continuous variables. Subjects with minor stroke were the control group for purposes of comparison. Baseline demographic and clinical covariates were preselected based on previous studies of factors that influence vascular events after ischemic stroke. Backward elimination Cox proportional hazard regression analyses were performed to estimate the risk of outcome events at 2 years in the following ways: (1) after adjusting for baseline covariates (age, sex, body mass index [BMI], high-density lipoprotein cholesterol [HDL-C], ethnicity, hypertension, diabetes, history of prior stroke, history of alcohol use (all $P < 0.10$) and secondary prevention including use of antihypertensive, antithrombotic, and lipid modifiers (model I) ; and (2) after adjusting for model I plus smoking, history of CHD, history of endarterectomy, and history of congestive heart failure that are additionally linked to cardiovascular recurrence or death (model II). Participants not having outcome events were censored at last follow-up examination, or last visit. Participants lost to follow-up during the course of the study were included in the Cox model until the last contact (31 no postrandomization contact). Results are given by hazard ratio (HR) and its 95% confidence interval (CI). All analyses were conducted using IBM SPSS Version 22.0 (IBM Corp., Armonk, NY) and a probability value of < 0.05 was considered statistically significant.

Results

Among 3680 participants, mean age was 66.3 ± 10.8 years, 37.5% were women, and 79.5% were white. Baseline NIHSS median score was 1 (25th to 75th percentile 0 to 2; overall scores ranged from 0 to 18). Baseline NIHSS score was measured at a median of 35 days after the qualifying stroke. Distribution of NIHSS scores are shown in Figure 1. Baseline demographic and clinical characteristics by stroke severity (NIHSS ≥ 4 vs NIHSS <4) are provided in Table 1. Compared to those with minor stroke, subjects with non-minor stroke were more likely to be younger; have lower BMI and serum levels of HDL-C; be non-white; have hypertension, diabetes, or history of prior stroke; and were less likely to have a history of alcohol use.

During 2-years of follow-up, a total of 300 (8.2%) incident stroke and 619 (16.8%) major vascular events were recorded. Results of the unadjusted and adjusted associations between symptom severity and vascular events appear in Table 2. Non-minor stroke was significantly linked to risk of recurrent stroke (HR 1.59; 95% CI, 1.21–2.10) and major vascular events (HR 1.41; 95% CI, 1.16–1.73). Higher NIHSS as a continuous variable was significantly associated with occurrence of stroke (HR 1.11; 95% CI, 1.0531.16) and major vascular events (HR 1.08; 95% CI, 1.0431.11). The adjusted HR (model I) for stroke for non-minor stroke was 1.39 (95% CI, 1.03–1.87) versus minor stroke and this association remained stable (HR 1.37; 95% CI, 1.01–1.84, Figure 2A) after further adjustment for cardiovascular risk factors shown in model II. The adjusted HR for major vascular events was significant in the non-minor stroke versus minor stroke in model I (HR 1.32; 95% CI, 1.07–1.63) and this association also remained similar (HR 1.32; 95% CI, 1.07–1.64, Figure 2B) in model II. Higher NIHSS were also independently linked to risk of recurrent stroke (HR 1.07; 95% CI, 1.01–1.13) and major vascular events (HR 1.05; 95% CI, 1.01–1.09) and these associations remained constant in model II (HR 1.06; 95% CI, 1.00–1.12 and HR 1.05; 95% CI, 1.01–1.09, respectively).

Adjusted HRs of covariates included in the multivariable model appears in Supplementary Table 1. Hypertension, diabetes, and history of prior stroke were significantly associated with both stroke and major vascular events, whereas age, male sex, smoking, history of CHD, history of carotid endarterectomy, and history of heart failure were associated with major vascular events. Lipid modifier use and prior alcohol use were linked to lesser risk of both stroke and major vascular events, while antihypertensive and antithrombotic medications were related to lesser risk of major vascular events.

Discussion

We observed that residual symptom severity from a recent non-cardioembolic stroke was independently associated with a 2-year higher risk of recurrent vascular events including ischemic stroke. This result was similar whether stroke severity was analyzed in a dichotomized or continuous manner.

It is not immediately obvious how residual symptom severity from a recent stroke is related to risk of recurrent vascular events, and the nature of our study precludes us from properly

exploring this relationship. While we did statistically control for major vascular risk factors, we observed that compared to patients with minor stroke, those with a non-minor stroke in this study had a greater prevalence of key risk vascular factors (hypertension, diabetes, and history of a stroke before the VISP-qualifying stroke) possibly reflecting more advanced underlying systemic vascular disease and likely placing them at relatively higher risk for future cardiovascular events. We also cannot exclude the possibility that the higher recurrent vascular risk was related to newly developed stroke mechanism (e.g. atrial fibrillation) or even poor medication adherence in the setting of multiple comorbidities. Yet another potential explanation is that this association might be mediated by a reactive depression linked to the more disabling consequences of more severe strokes. Depression has been related to risk of stroke¹², and its neuroendocrine and immunological/inflammation effects have been postulated to influence vascular risk.^{13,14} Furthermore, depression is associated with adverse health behaviors including smoking, physical inactivity, poor diet, lack of medication adherence, all of which might raise the risk of vascular events.¹⁵ Supporting the notion that the nature of the relationship of stroke symptom severity and recurrent vascular risk may go beyond the pathophysiology of the index stroke, is our finding that stroke symptom severity was also related to the composite vascular endpoint comprising CHD events and death.

It bears reminding that having a stroke is the strongest predictor of having a recurrent event,¹⁶ thus the results of this study should not be viewed as diminishing the substantial risk of recurrent stroke that patients with an index stroke of minor severity carry, particularly when compared with people who have not experienced a stroke in the first place.

This study has limitations. First, it is a retrospective sub-analysis of prospectively collected trial cohort data consisting largely of patients with strokes of mild to moderate severity. Second, timepoint of NIHSS later than 1 month might not be completely reflective of the sole neurological effects of the index stroke, since neurological symptomatology can also be affected by comorbid conditions. Given the initially evolving nature of symptom severity especially earlier on after a new stroke, and the need to optimally identify/treat stroke patients at high risk for recurrent vascular events as soon as possible, the relatively stable VISP NIHSS median assessment timepoint at 1 month might be a pragmatic one. However, since NIHSS measurement was not conducted at a consistent timepoint because of diversity of poststroke time (ranging to 120 days after a stroke), careful interpretation is needed until our findings are proven in future prospective studies. Third, all study subjects experienced non-cardioembolic strokes thereby limiting generalizability to all stroke types. Forth, we could not adjust for functional status before VISP qualifying stroke, initial NIHSS and stroke subtype at the time of VISP stroke because of nonavailability of such data in the VISP database. Finally, since the VISP dataset did not provide this information, we were unable to investigate vascular status using angiographic imaging and correlate it with stroke severity, which could have shed more light on the possible contributions of underlying vascular burden on the association of residual index stroke severity with recurrent events.

In conclusion, we found residual symptom severity of a recent stroke to be associated with risk of recurrent vascular events over a 2-year period. This study suggests that NIHSS assessment in the relatively early post-stroke hospitalization setting (around one month post-

event) might exert as a simple clinical tool for identifying patients at high risk for the vascular event recurrence. Our findings need to be validated through prospective studies with wider ranges of NIHSS score distribution and measurement of potential mediators of this relationship including underlying vascular status and psychosocial factors (e.g. reactive depression after a stroke). While there is no reason to believe that a different finding would be seen among patients with cardioembolic strokes, future studies should also include these patients, especially since they often have index strokes of greater neurological symptom severity,¹⁷ and they are at higher risk for recurrent stroke events.¹⁸

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Distribution of NIHSS scores at baseline randomization among populations after a recent stroke. Baseline NIHSS score was measured at a median of 35 days after the qualifying stroke. NIHSS, National Institutes of Health Stroke Scale.

Figure 2.

Cumulative incidence of stroke (A) and major vascular events (B) at 2 years after non-cardioembolic stroke (NIHSS ≥ 4 vs. NIHSS < 4). HR, hazard ratio; CI, confidence interval.

Table 1

Baseline Demographic and Clinical Characteristics of Study Patients With Minor Stroke and Those With Moderate Stroke

	Qualifying Stroke Severity		<i>P</i>
	Minor (NIHSS <4) (N=3130)	Non-minor (NIHSS ≥4) (N=550)	
Age, years	66.5 ± 10.7	65.1 ± 11.0	0.003
Systolic blood pressure, mmHg	140.7 ± 18.7	141.6 ± 19.0	0.296
Body mass index, kg/m ²	28.4 ± 5.7	27.9 ± 5.6	0.091
Total cholesterol, mg/dL	202.2 ± 47.2	201.0 ± 43.8	0.593
LDL-C, mg/dL	121.6 ± 40.2	124.1 ± 42.3	0.205
Triglycerides, mg/dL	175.3 ± 162.6	173.4 ± 111.5	0.796
HDL-C, mg/dL	45.6 ± 15.3	44.3 ± 16.4	0.074
Creatinine, mg/dL	1.11 ± 0.61	1.11 ± 0.41	0.966
Homocystein, μmol/L	14.1 ± 6.1	14.2 ± 4.6	0.573
Randomization after stroke, days	36.8 ± 34.2	35.1 ± 34.8	0.285
Male	1944 (62.1)	357 (64.9)	0.211
Non-white	574 (18.3)	181 (32.9)	<0.001
Hypertension	2614 (83.5)	484 (88.0)	0.008
Diabetes mellitus	882 (28.2)	219 (39.8)	<0.001
Smoker	525 (16.8)	96 (17.5)	0.696
History			
Prior stroke	675 (21.6)	181 (32.9)	<0.001
Coronary heart disease*	821 (26.2)	141 (25.6)	0.770
Congestive heart failure	163 (5.2)	30 (5.5)	0.822
Carotid endarterectomy	212 (6.8)	35 (6.4)	0.731
Alcohol use	1841 (60.2)	286 (54.7)	0.017
Medication			
High blood pressure	2530 (80.8)	460 (83.6)	0.120
Antithrombotic	2930 (93.4)	513 (93.3)	0.921
Lipid-lowering	1709 (54.6)	300 (54.5)	0.981
High-dose B vitamin	1554 (49.6)	273 (49.6)	0.996

Values provided are number (%) or mean ± SD, as appropriate, otherwise stated. NIHSS, National Institutes of Health Stroke Scale; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

* Defined as history of myocardial infarction, angina, coronary angioplasty/stenting, or coronary artery bypass graft surgery.

Table 2
Estimates of the Hazard Ratio (HR) for the Vascular Outcome Events at 2 Years in Populations after Recent Stroke

Outcome	Minor (NIHSS <4)		Non-minor (NIHSS ≥4)		Unadjusted HR (95% CI)	Model I*		P	Model II†	
	N=3130	N=550	Events, n (%)	HR (95% CI)		HR (95% CI)	P			
Stroke	236 (7.5)	64 (11.6)	64 (11.6)	1.59 (1.21–2.10) [‡]	1.39 (1.03–1.87)	1.37 (1.01–1.84)	0.029	1.37 (1.01–1.84)	0.042	
Stroke/CHD/vascular death	499 (15.9)	120 (21.8)	120 (21.8)	1.41 (1.16–1.73) [‡]	1.32 (1.07–1.63)	1.32 (1.07–1.64)	0.011	1.32 (1.07–1.64)	0.011	

NIHSS as a continuous variable					
	Model I*		P	Model II†	
	Unadjusted HR (95% CI)	HR (95% CI)		HR (95% CI)	P
Stroke	1.11 (1.05–1.16) [‡]	1.07 (1.01–1.13)	0.024	1.06 (1.00–1.12)	0.039
Stroke/CHD/vascular death	1.08 (1.04–1.11) [‡]	1.05 (1.01–1.09)	0.023	1.05 (1.01–1.09)	0.021

NIHSS, National Institutes of Health Stroke Scale; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease.

NIHSS, National Institutes of Health Stroke Scale; HDL-C, high-density lipoprotein cholesterol; CHD, coronary heart disease.

* Adjusted for age, sex, body mass index, HDL-C, ethnicity, hypertension, diabetes, history of prior stroke, history of alcohol use (all $P<0.10$) and secondary prevention including use of antihypertensive, antithrombotic, and lipid modifiers.

† Adjusted for model I plus smoking, history of CHD, history of endarterectomy, and history of congestive heart failure.

[‡] $P<0.01$.