Neurologic Symptom Severity after a Recent Noncardioembolic Stroke and Recurrent Vascular Risk

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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 data set of a multicenter trial involving 3680 recent noncardioembolic stroke patients aged 35 years or older 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 versus ≥4) and a continuous variable. *Results:* Among study subjects, 550 (15%) had NIHSS scores of 4 or more (overall scores ranged from 0 to 18, median score was 1 [25th-75th percentile 0-2]). NIHSS was measured at a median of 35 days after the index stroke. After adjusting for multiple covariates, NIHSS of 4 or more was independently linked to a higher risk of recurrent stroke (hazard ratio [HR], 1.37; 95% confidence interval [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. **Key Words:** National Institutes of Health Stroke Scale—ischemic stroke—vascular events—risk.

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 because of reactive depression leading to overall poorer regimen adherence, whereas on the other hand, stroke patients who recover with minimal deficit or no deficit may be more vulnerable to future events because of underlying unstable pathophysiology (ie, ongoing thrombosis-thrombolysis).[6] As far as we are aware, only 1 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)

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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 subanalysis of prospectively collected data obtained during the conduct of the Vitamin Intervention for Stroke Prevention (VISP) trial.[8] The 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 or older, with a recent (onset ≤120 days before randomization) nondisabling (modified Rankin Scale ≤3) noncardioembolic stroke.[8] Demographic, physical, neurologic examination including stroke scales, medication use assessment, and laboratory data were 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 data set 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 1 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/day.[8] The trial was approved by the ethics committee or institutional review board at each national or local site, and all participants provided written informed consent.[8] Because this particular study was a post hoc analysis of the trial's publicly accessible de-identified data set, specific and formal institutional review board review was waived.

Predictor Variable

As part of the VISP trial protocol, at the time of randomization after the qualifying stroke event, neurologic symptom severity was measured using the NIHSS score.[9,10] Neurologic symptom severity after the occurrence of a recent stroke, as represented by these poststroke NIHSS values, was used in this subanalysis 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 less than 4[11] and those with nonminor 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, coronary revascularization, cardiac resuscitation, and fatal CHD, or vascular death as major vascular events. Recurrent stroke was diagnosed only with the 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

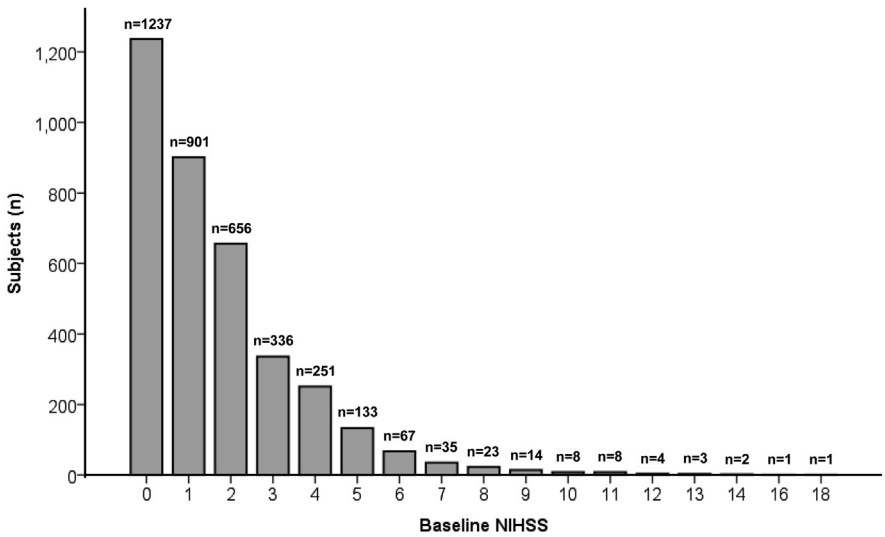

Figure 1. *Distribution of NIHSS scores at baseline randomization among populations after a recent stroke. Baseline NIHSS score was measured at a median of 35 days after the qualifying stroke. Abbreviation: NIHSS, National Institutes of Health Stroke Scale.*