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ORIGINAL ARTICLE

Recurrent Stroke was Associated with Poor Quality of Life in Patients with Transient Ischemic Attack or Minor Stroke: Finding from the CHANCE Trial

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CHANCE investigators are given in the Appendix S1.

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SUMMARY

Aims: To examine the health-related quality of life (HRQOL) in patients with transient ischemic attack (TIA) or minor stroke and assess the impact of recurrent stroke on HRQOL. **Methods:** Health-related quality of life data on patients participated in the Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial were analyzed. The available 90-day EuroQoL data (EQ-5D) were used to calculate EQ-5D index score. Poor HRQOL was defined as an EQ-5D index score $\leq$0.5. The characteristics of HRQOL and factors predicting poor HRQOL in these patients were then explored. **Results:** Among the total 5170 patients enrolled, 90-day HRQOL data were obtained from 5104 patients for analysis. The mean EQ-5D index score at day 90 was 0.88 ± 0.21 for all patients, but only 0.42 ± 0.35 for those with recurrent strokes. Poor 90-day HRQOL was found in 294 (5.8%) patients. Patients with poor HRQOL had more strokes during follow-up than patients with good HRQOL (94.9 vs. 4.7%, $P < 0.001$). Age, history of hypertension and diabetes, and NIHSS at baseline were independent risk factors for predicting poor HRQOL. Stroke recurrence, NIHSS at baseline, age, and minor stroke on admission became independent risk factors once stroke recurrence was added into the model. **Conclusions:** Stroke recurrence was associated with poor HRQOL in patients with TIA or minor strokes. Interventions focusing on controlling risk factors and prevention of worsening of neurological function may prevent poor HRQOL in these patients.

Introduction

Health-related quality of life (HRQOL) offers a comprehensive measurement of the impact of a disease and recovery process from the perspective of the patient. It is now a commonly used outcome measurement tool in stroke trials [1–4]. Previous studies have described the long-term HRQOL of stroke survivors and identified age [1,5,6], gender [5], baseline severity [1,4–7], diabetes [7], hypertension [1,8], disability [4,9], aphasia [10], depression [4,9,11], cognitive impairment [8], and low socioeconomic status [5] as independent risk factors predicting poor long-term HRQOL after stroke. However, these studies were conducted in patients with either ischemic stroke [10,11], intracerebral hemorrhage [1], subarachnoid hemorrhage [6] or all strokes combined together [4,5,8,9,12]. Patients with transient ischemic attack (TIA) or minor ischemic stroke were reported to have short-term poor prognosis [13–15]. Patients with nondisabling cerebrovascular events (TIA or minor stroke) may also have poor HRQOL at 90 days after the index event because of high rates of stroke recurrence [4,12]. To our knowledge, few studies have assessed HRQOL in these patients after TIA or minor stroke.

Using data from the recently completed Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial [16], we aimed to describe the 90-day HRQOL and examined the potential influence of stroke recurrence on HRQOL in these patients with TIA or minor stroke.

Materials and Methods

Study Design and Subjects

The CHANCE trial (ClinicalTrials.gov number: NCT00979589) was a randomized, double-blind, placebo-controlled trial conducted

at 114 centers in China between October 2009 and July 2012 [16]. Details on the rationale, design, and major results have been described in previous articles [16,17]. Briefly, 5170 patients within 24 h of onset of minor stroke or high-risk TIA were randomized to combination therapy with clopidogrel and aspirin or placebo plus aspirin. The primary outcome was stroke (ischemic or hemorrhagic) during 90 days of follow-up. The CHANCE protocol was approved by the ethics committee at each study center. All participants or their legal proxies provided written informed consent.

Patients enrolled in the CHANCE trial met the following inclusion criteria: age ≥ 40, diagnosis of an acute minor ischemic stroke (National Institute of Health Stroke Scale [NIHSS] ≤ 3) or high-risk TIA ($ABCD^2 \geq 4$), and ability to start the study drug within 24 h after symptom onset. Patients with pre-existing disabling conditions defined as modified Rankin Scale (mRS) >2 were excluded. For this study, 5104 patients were included after excluding patients who died (20) and were without 90-day EQ-5D data (46).

Data Collection and Risk Factors Definition

Baseline demographics, vascular risk factors, premorbid mRS, medications, and clinical measures were collected. Vascular risk factors included history of stroke or TIA, myocardial infarction, congestive heart failure, atrial fibrillation or flutter, hypertension, diabetes mellitus, dyslipidemia, current or previous smoking, and alcohol consumption. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, history of hypertension or antihypertensive drug use [18]. Dyslipidemia was defined as serum triglyceride ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, history of dyslipidemia, or lipid-lowering drug use. Diabetes was defined as fasting glucose concentration ≥7.0 mmol/L, nonfasting glucose concentration ≥11.1 mmol/L with classic symptoms of hyperglycemia or hyperglycemic crisis, history of diabetes or glucose-lowering drugs use [18,19]. Heavy alcohol consumption was defined as consumption of ≥2 standard alcoholic beverages per day.

At day 90 after the onset of TIA or minor stroke, mRS and NIHSS scores were collected by trained and certified investigators through face-to-face interview. Poor functional outcome was defined as mRS 3-5 (dependence) [20].

Quality of Life

Health-related quality of life was assessed using the EuroQoL questionnaire [21] at day 90 follow-up visit. EuroQoL consists of two parts: EQ-5D and EQ visual analogue scale (EQ-VAS). EQ-5D comprises of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. The EQ-VAS is carried out by patient as an assessment of self-well-being in the vertical and visual analogue scales. A value of 100 on this scale indicates a perfect score for health but a score of 0 means death. A single utility score can be calculated using the population-based preference weights for each dimension of EQ-5D [22–24]. We used the Chinese preference weights developed by Liu et al. [24]. The EuroQoL scale was also completed by investigators through face-to-face interview. All investigators were trained and certified based on a shared standardized interview protocol. For those patients with dysarthria or disability caused by severe stroke, EuroQoL was completed by a proxy. Patient and proxy respondent agreement was assessed using intraclass correlation coefficient (ICC). The ICC of EQ-5D index was 0.72 (95% confidence intervals 0.60–0.81).

Statistical Analysis

Categorical variables were presented as percentages and continuous variables as mean with standard deviation (SD) or median with interquartile (IQR). The associations between EuroQoL (EQ-5D index score and EQ-VAS) and clinical outcome (mRS and NIHSS) were assessed using partial correlations, adjusting for age

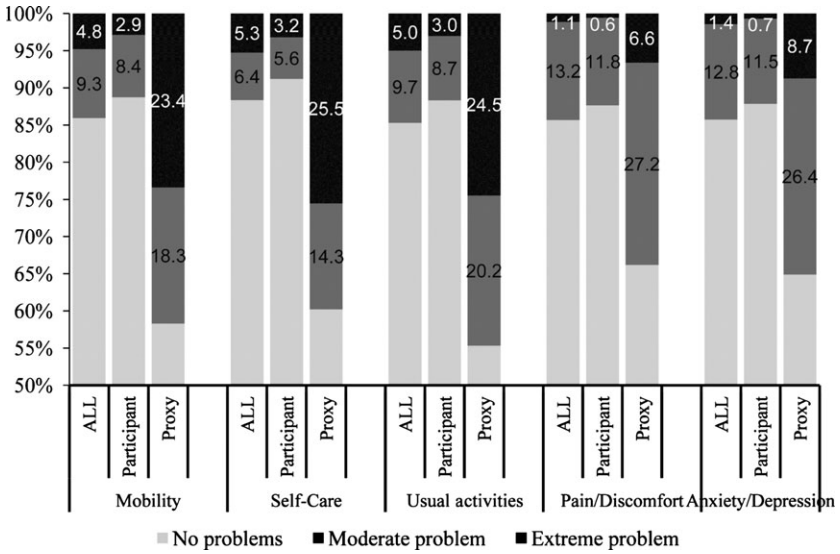

Figure 1 EQ-5D domains for patients at day 90 after a transient ischemic attack or minor stroke.

Table 1 Quality of life compared to stroke recurrence and modified Rankin scale at day 90 after a transient ischemic attack or minor stroke

		EQ-5D index score		EQ visual analog scale	
	N	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)
All	5104	0.88 ± 0.21	0.96 (0.89, 0.96)	84 ± 15	89 (80, 95)
Without stroke recurrence	4598	0.93 ± 0.09	0.96 (0.96, 0.96)	87 ± 11	90 (80, 95)
With stroke recurrence	506	0.42 ± 0.35	0.35 (0.11, 0.71)	58 ± 24	60 (40, 76)
90-day mRS[a]					
0	3120	0.95 ± 0.05	0.96 (0.96, 0.96)	89 ± 10	90 (85, 95)
1	1454	0.89 ± 0.11	0.96 (0.87, 0.96)	83 ± 12	85 (80, 90)
2	196	0.67 ± 0.19	0.68 (0.54, 0.83)	71 ± 16	72 (62, 80)
3	92	0.44 ± 0.24	0.51 (0.29, 0.60)	59 ± 19	60 (50, 72)
4	213	0.16 ± 0.19	0.11 (0.09, 0.23)	44 ± 18	45 (30, 57)
5	28	0.10 ± 0.18	0.11 (−0.02, 0.21)	36 ± 22	30 (20, 50)

EQ-5D, European quality of life scale; mRS, modified Rankin scale; SD, standard deviation; IQR, interquartile range. [a]1 missing value for 90-day mRS.

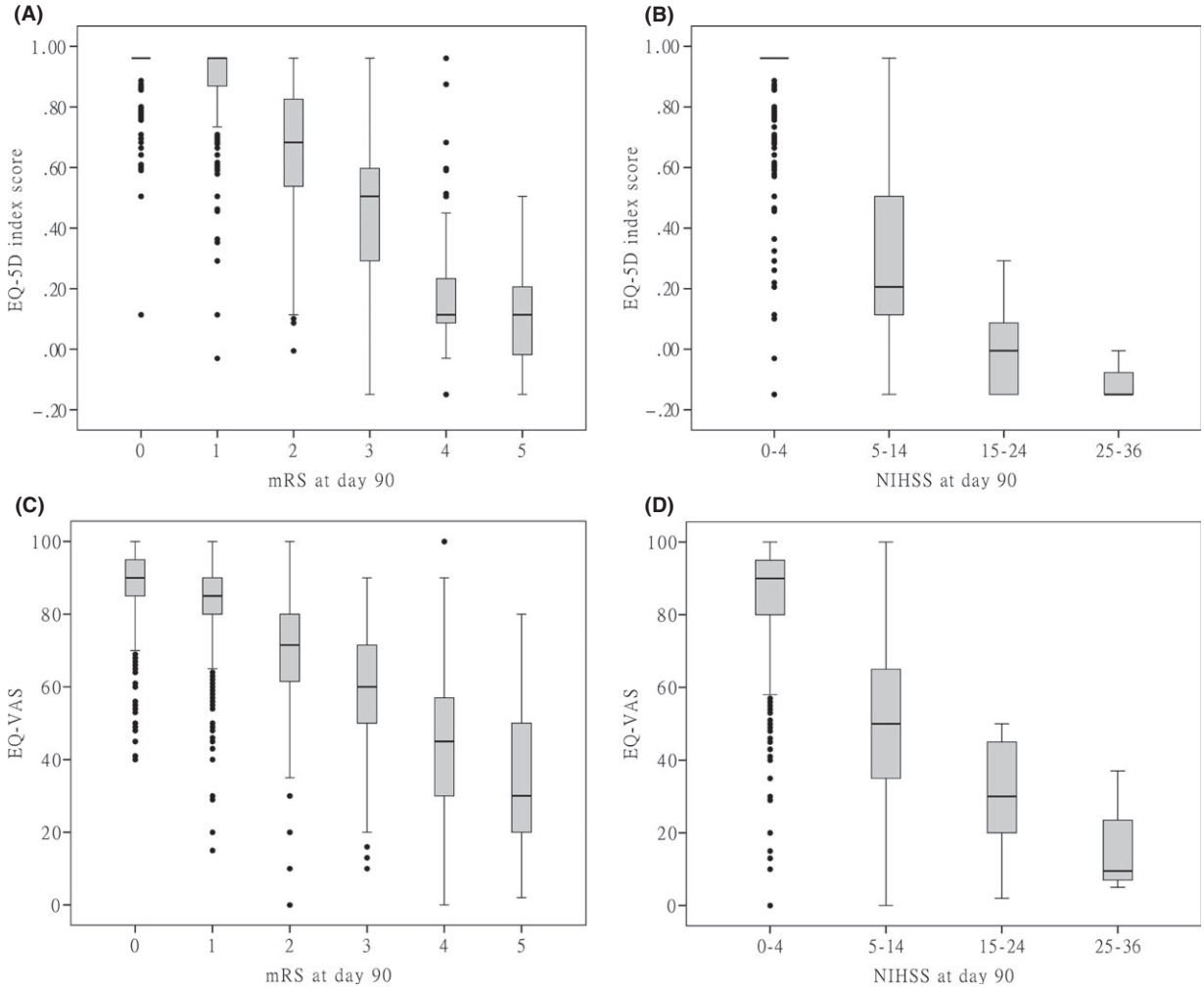

Figure 2 Box plot of EQ-5D index score and EQ-VAS by mRS and NIHSS levels at day 90 after a transient ischemic attack or minor stroke. EQ-5D, European quality of life scale; VAS, visual analog scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health stroke scale. (**A**): EQ-5D index score by mRS levels at day 90. (**B**): EQ-5D index score by NIHSS levels at day 90. (**C**): EQ-VAS by mRS levels at day 90. (**D**): EQ-VAS by NIHSS levels at day 90.

and sex. Spearman's rank correlation coefficients were used to take into account the ordinal and nonparametric nature of the scales.

Poor HRQOL was defined as an EQ-5D index score of ≤0.5, and good HRQOL was defined as an EQ-5D index score of >0.5 [1]. Univariable and multivariable analyses were performed to identify predictors of poor HRQOL at day 90 after the onset of a TIA or minor stroke. Differences on baseline variables between the poor and good HRQOL groups were compared using chi-square (χ^2) test for categorical variables and t-test or Mann–Whitney *U*-tests for continuous variables. All baseline variables with a *P*-value of ≤0.1 were included in a stepwise multivariable logistic regression. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated using the good HRQOL group as the reference. EQ-VAS was used as sensitivity analyses, with a definition of EQ-VAS score of ≤40 as poor HRQOL [25]. Dual antiplatelet treatment was forced to be included in all models. We set up models with or without the predictor of stroke recurrence during follow-up, respectively.

The α level of significance was $P < 0.05$ two-sided. All analyses were performed with SAS software version 9.3 (SAS Institute Inc, Cary, NC, USA).

Results

Patients

Among the 5170 patients with confirmed diagnosis of TIA or minor stroke in the CHANCE study, 90-day EQ-5D scores from 5104 patients were obtained for analysis. Twenty patients died during the study period. HRQOL data were missing in 46 patients of whom 36 were lost to follow-up. Among the 5104 patients, 4034 (79.0%) completed the assessment independently; 600 (11.8%) were with assistance and 470 (9.2%) completed by a proxy because of dysarthria or disability caused by severe stroke.

Quality of Life

In 5104 survivors after a TIA or minor stroke, 244 (4.8%), 268 (5.3%), and 255 (5.0%) patients reported extreme problems in mobility, self-care, and usual activities at day 90, respectively. In contrast, only 58 (1.1%) patients reported pain/discomfort, and 73 (1.4%) reported anxiety/depression. Proxy respondents reported significantly worse problems in all domains of EQ-5D than patients who were self-respondents (Figure 1, $P < 0.001$).

Table 2 Baseline demographics, risk factors, and clinical measures by HRQOL category

	All (N = 5104)	Poor HRQOL[a] (N = 294)	Good HRQOL (N = 4810)	*P*
Age (year), mean (SD)	62.6 ± 10.7	65.2 ± 11.0	62.4 ± 10.7	<0.001
Female sex, n (%)	1728 (33.9)	117 (39.8)	1611 (33.5)	0.03
Han ethnic, n (%)	5034 (98.6)	290 (98.6)	4744 (98.6)	1.00
Body mass index, mean (SD)	24.7 ± 3.0	24.8 ± 3.1	24.7 ± 3.0	0.18
Vascular risk factors, n (%)				
Ischemic stroke	1018 (20.0)	56 (19.0)	962 (20.0)	0.69
TIA	172 (3.4)	10 (3.4)	162 (3.4)	0.98
Myocardial infarction	92 (1.8)	6 (2.0)	86 (1.8)	0.75
Congestive heart failure	77 (1.5)	7 (2.4)	70 (1.5)	0.31
Known atrial fibrillation or flutter	173 (3.4)	10 (3.4)	163 (3.4)	0.99
Hypertension	3358 (65.8)	219 (74.5)	3139 (65.3)	0.001
Diabetes mellitus	1083 (21.2)	82 (27.9)	1001 (20.8)	0.004
Dyslipidemia	560 (11.0)	34 (11.6)	526 (10.9)	0.74
Current or previous smoking	2191 (42.9)	106 (36.1)	2085 (43.3)	0.01
Alcohol consumption	1582 (31.0)	85 (28.9)	1497 (31.1)	0.43
Index event, n (%)				
Minor stroke	3677 (72.0)	249 (84.7)	3428 (71.3)	<0.001
TIA	1427 (28.0)	45 (15.3)	1382 (28.7)	
Premorbid mRS, n (%)				
0	4212 (82.5)	249 (84.7)	3963 (82.4)	0.30
1	757 (14.8)	39 (13.3)	718 (14.9)	
2	135 (2.6)	6 (2.0)	129 (2.7)	
NIHSS at baseline, median (IQR)	2 (0–2)	2 (1–3)	1 (0–2)	<0.001
In-hospital treatment, n (%)				
Antihypertensive	1450 (28.4)	17 (5.8)	1433 (29.8)	<0.001
Hypoglycemic	520 (10.2)	6 (2.0)	514 (10.7)	<0.001
Lipid-lowering	1824 (35.7)	22 (7.5)	1802 (37.5)	<0.001
Dual antiplatelet	2550 (50.0)	129 (43.9)	2421 (50.3)	0.03

HRQOL, Health-related quality of life; SD, standard deviation; IQR, interquartile range; mRS, modified Rankin score; NIHSS, National Institutes of Health stroke scale; TIA, transient ischemic attack. [a]Poor HRQOL defined as EQ-5D index score of 0.5 or less using the Chinese preference weights. Comparison by chi-square test for categorical and *t*-test or Mann–Whitney *U*-test for continuous variables.

Table 3 Independent risk factors for poor quality of life at day 90 after a transient ischemic attack or minor stroke

	EQ-5D index[a]		EQ-VAS[b]	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Model 1				
Age, per 10 years	1.26 (1.12–1.41)	<0.001	1.19 (1.02–1.38)	0.03
History of hypertension	1.74 (1.32–2.31)	<0.001	1.60 (1.10–2.33)	0.01
History of diabetes	1.65 (1.24–2.20)	<0.001	1.93 (1.33–2.78)	<0.001
NIHSS at baseline	1.65 (1.48–1.86)	<0.001	1.58 (1.36–1.84)	<0.001
Antihypertensive treatment	0.20 (0.12–0.33)	<0.001	0.31 (0.17–0.57)	<0.001
Hypoglycemic treatment	0.27 (0.11–0.63)	0.002	0.37 (0.14–0.96)	0.04
Lipid-lowering treatment	0.19 (0.12–0.29)	<0.001	0.19 (0.11–0.35)	<0.001
Dual antiplatelet treatment	0.78 (0.61–1.004)	0.054	0.84 (0.60–1.16)	0.28
c-statistic	0.81		0.79	
Model 2				
Stroke recurrence	402.11 (232.96–694.07)	<0.001	109.72 (63.55–189.45)	<0.001
NIHSS at baseline	1.40 (1.16–1.70)	<0.001	1.38 (1.17–1.64)	<0.001
Age, per 10 years	1.26 (1.07–1.49)	0.006	–	–
Index event is minor stroke	1.98 (1.20–3.29)	0.008	–	–
History of diabetes	–	–	1.62 (1.08–2.44)	0.02
Dual antiplatelet treatment	1.16 (0.81–1.65)	0.42	1.11 (0.76–1.61)	0.60
c-statistic	0.97		0.94	

EQ-5D, European quality of life scale; VAS, visual analog scale; OR, odds ratio; CI, confidence intervals. [a]Poor HRQOL was defined as an EQ-5D index score of 0.5 or less using the Chinese preference weights. [b]Poor HRQOL was defined as an EQ-VAS score of 40 or less.

The overall mean EQ-5D index score was 0.88 ± 0.21, and overall mean EQ-VAS was 84 ± 15 at the day 90 visit. The mean EQ-5D index score of patients with recurrent stroke during follow-up was much lower than those without stroke recurrence (0.42 ± 0.35 vs. 0.93 ± 0.09, $P < 0.001$) (Table 1). Both EQ-5D index score and EQ-VAS were correlated with the 90-day mRS scores (EQ-5D index score: Spearman $r = -0.62$, $P < 0.001$; EQ-VAS: Spearman $r = -0.47$, $P < 0.001$) and NIHSS (EQ-5D index score: Spearman $r = -0.55$, $P < 0.001$; EQ-VAS: Spearman $r = -0.44$, $P < 0.001$) (Figure 2). The mean EQ-5D index score was 0.95 ± 0.05 for patients with a mRS of 0, but decreased to 0.10 ± 0.18 for patients with a mRS of 5 at day 90 (Table 1).

Poor Quality of Life

Of 5104 patients, 294 (5.8%) had an EQ-5D index score of ≤0.5 (poor HRQOL). Among patients with recurrent strokes, 279 (55.1%) had poor HRQOL. Only 15 (0.3%) had poor HRQOL in those without recurrent strokes.

The baseline demographic and medical characteristics by HRQOL category are shown in Table 2. Older age, history of hypertension and diabetes, and NIHSS at baseline were independent risk factors predicting poor HRQOL at day 90 after a TIA or minor stroke. In-hospital treatments of risk factors (antihypertensive, hypoglycemic, and lipid-lowering treatment) prevented poor HRQOL at day 90 (Table 3). The results were similar in sensitivity analyses using EQ-VAS as the measure of HRQOL.

More patients with poor HRQOL had recurrent stroke during follow-up than patients with good HRQOL (94.9% vs. 4.7%, $P < 0.001$). Older age, high body mass index, NIHSS at baseline, history of hypertension and diabetes, and failure to initiate in-hospital treatments of risk factors (antihypertensive, hypoglycemic, lipid-lowering, and dual antiplatelet treatment) were independent risk factors of stroke recurrence within 90 days after a TIA or minor stroke (Tables S1 and S2). Stroke recurrence, NIHSS at baseline, older age, and minor stroke as index event were independent risk factors of poor HRQOL if stroke recurrence during follow-up was added into the analytic model predicting HRQOL (Table 3, model 2). The models explained a large amount of the variation in the utility score (*c*-statistic 0.97; 0.94).

Discussion

Based on the results of the CHANCE trial, TIA or minor ischemic stroke survivors had a mean utility score of 0.88 (mean EQ-VAS, 84) at day 90 after symptom onset, and 5.8% of these patients had a poor HRQOL (i.e., EQ-5D index score of 0.5 or less). The 90-day HRQOL in patients after a TIA or minor stroke was better than those with ischemic stroke [4], intracerebral hemorrhage [1,4,26], or subarachnoid hemorrhage [6]. However, recurrence of stroke after TIA or minor stroke may be associated with poor HRQOL.

As expected, age, history of hypertension and diabetes, and NIHSS at baseline were independent predictors of poor HRQOL at day 90 for patients with a TIA or minor stroke, which was similar to the findings in the literature [1,4–11]. Previous studies have reported that older age [1,5,6], female sex [5], baseline severity [1,4–7], diabetes [7], hypertension [1,8], disability [4,9], aphasia [10], depression [4,9,11], cognitive impairment [8], and low socioeconomic status [5] were independent predictors of poor long-term HRQOL after stroke. Our data indicated that poor HRQOL after a TIA or minor stroke was largely attributable to recurrence of stroke within 90 days after the onset of the index events as 94.9% of those with poor HRQOL had another stroke. Hypertension and diabetes lost predictive power for poor HRQOL

after recurrence of stroke was added into the model. These risk factors may influence HRQOL through affecting the recurrence of stroke [12].

About 9.2% of patients had severe strokes at day 90; therefore, their HRQOL questionnaires were completed by proxies. EuroQol that completed by proxy was validated in our study, with an acceptable agreement (ICC = 0.72) similar to previous studies [27,28]. However, another previous study showed that HRQOL could be reported differently by proxy from patients. The explanation was that patient could be depressed and proxy was overburdened by the need to provide care [29]. Proxy respondents reported more problems of self-care and mobility but less problems of pain or discomfort [4,27]. In our study, proxy respondents reported significantly worse problems in all domains of EQ-5D than self-respondents. The explanation was that in our study, proxies were only used when patients had disability or inability to complete the assessment independently.

Our study shows that HRQOL after stroke/TIA highly correlated with the neurological and functional outcome measures (NIHSS, mRS). Modified Rankin Scale and Barthel Index emphasize on the functional outcome but are not generated by patient's self-perceptions [7]. There is an overall correlation between disability and HRQOL, and these measurements translated into HRQOL utility values in patients with stroke/TIA [1,2,30]. It appeared that mRS correlated well with stroke survivors' perceptions and captured more information on HRQOL than either NIHSS or Barthel Index [2]. Given the frequent use of mRS as an outcome measurement tool in managing patients with stroke/TIA [20,31], it could be used as proxy for HRQOL when it is unavailable. In fact, many cost-effectiveness analyses on stroke management employ quality-adjusted life years (QALYs) as the outcome measurement tool, with utility weights predicted by mRS [32,33]. The HRQOL scores generated by mRS category in our study may be used as utility weights in future cost-effectiveness analyses for stroke/TIA care in China [33].

A major strength of our study was the prospective assessment of HRQOL in a large TIA or minor stroke population with rather thorough follow-ups. We selected easily identifiable risk factors at baseline and in the acute phase of treatment to illustrate the potential for clinicians to affect the HRQOL of patients in the acute phase after the onset of a TIA or minor stroke in clinical practice. Our data showed that controlling risk factors (hypertension, diabetes, and dyslipidemia) and preventing neurological worsening can improve the HRQOL in these patients.

Our study has several limitations. First, our findings may not be externally generalizable to non-Chinese population. This analysis was based on data from the CHANCE trial, which was performed in Chinese patients. HRQOL may be affected by patient's ethnicity and culture. Second, the data came from a randomized, controlled trial that selected patients only with high-risk TIA ($ABCD^2 \geq 4$, able to start drug within 24 h after onset, and mRS < 3). Our finding is limited to this population of patients. Third, our study used the available data from the CHANCE trial and only estimated HRQOL at 3 months after the onset of a TIA or minor stroke. Previous population-based studies showed that HRQOL declined annually up to 5 years after stroke [12,34]. The results of our study require more verification. Finally, other significant factors that may impact HRQOL of patients, such as socioeconomic status [5], possible cognitive impairment [8], or depression [1,4,29,35], were not assessed in this trial.

In summary, recurrent stroke was associated with poor HRQOL in patients with high-risk TIA or minor strokes. Aggressive risk factor control and prevention of recurrence of stroke or neurological worsening may be potential strategies to improve HRQOL in patients after TIA or minor stroke.

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Conflict of Interest

Dr. Johnston is the principal investigator of the POINT trial, a NIH-sponsored trial with clopidogrel and placebo donated by Sanofi.

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Supporting Information

The following supplementary material is available for this article:

Table S1. Baseline Demographics and Risk Factors of Stroke Recurrence at 90 days.

Table S2. Independent Predictors of Stroke Recurrence at 90 days after a Transient Ischemic Attack or Minor Stroke.

Appendix S1. The CHANCE investigators.