Ethnicity and Other Determinants of Quality of Functional Outcome in Acute Ischemic Stroke
The ENCHANTED Trial

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Background and Purpose—Patient-centered outcomes are important. We aimed to determine predictors of health-related quality of life (HRQoL) and develop utility-weighted modified Rankin Scale (mRS) scores in thrombolyzed acute ischemic stroke patients from both arms of ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study).

Methods—ENCHANTED was an international quasi-factorial clinical trial of different doses of intravenous alteplase and intensities of blood pressure control in acute ischemic stroke patients, with outcomes on the 5-Dimensional European Quality of Life Scale and mRS assessed at 90 days post-randomization. Logistic regression models were used to identify baseline predictors of poor HRQoL (≤mean 5-Dimensional European Quality of Life Scale utility scores). Ordinary least squares regression derived utility-weighted mRS scores.

Results—In 4016 acute ischemic stroke patients with complete 5-Dimensional European Quality of Life Scale and mRS data, independent predictors of poor HRQoL were older age (odds ratio, 1.19 [95% CI, 1.12–1.27], per 10-year increase), non-Asian ethnicity (1.91 [1.61–2.27]), greater stroke severity on the National Institutes of Health Stroke Scale (1.11 [1.09–1.12]), diabetes mellitus (1.41 [1.18–1.69]), premorbid disability (mRS score 1 versus 0; 1.62 [1.33–1.97]), large vessel atheromatous pathogenesis (1.32 [1.12–1.54]), and proxy respondent (2.35 [2.01–2.74]). Sensitivity analyses indicate the ethnicity influence on HRQoL was driven by the high proportion of Chinese (62.9% of Asian) participants with better HRQoL compared with non-Chinese or other Asian groups. Derived utility values across mRS scores 0 to 5 were 0.977, 0.885, 0.748, 0.576, 0.194, and −0.174, respectively. Correlations between mRS and 5-Dimensional European Quality of Life Scale scores were stronger in Asians.

Conclusions—HRQoL is worse after thrombolyzed acute ischemic stroke in the elderly, non-Asians, with greater initial severity, diabetes mellitus, premorbid disability, due to large vessel atheroma, and proxy assessment. The broader significance of better HRQoL in Asians is tempered by Chinese participants dominating analyses. From utility-weighted mRS scores indicating the greatest steps in mRS scores are between 5 and 3, treatments to avoid major disability provide the greatest benefits for patients.

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Key Words: aged ■ humans ■ odds ratio ■ quality of life ■ stroke

As stroke is the leading cause of adult disability and suffering,[1,2] it is important to quantify the health and well-being of survivors who extend beyond functional status according to the modified Rankin Scale (mRS)—the most popular stroke outcome measure used in practice and research. The mRS emphasizes the physical components

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of disability and inadequately captures the overall impact of stroke on one's healthy life or health-related quality of life (HRQoL). A recent approach to address this deficiency is to produce utility-weighted mRS (UW-mRS) scores, which typically combine assessments on the 5-Dimensional European Quality of Life Scale (EQ-5D) and mRS. This allows the steps between mRS scores to move from fixed to variable intervals in an effort to directly reflect patient and societal valuation of disability states in a range from 0 (death) to 1 (perfect health). We aimed to identify the clinical factors that determine poor HRQoL and derive UW-mRS scores among all thrombolyzed patients with acute ischemic stroke (AIS) who participated in the international ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study).

Methods

Data Sharing

Individual participant data used in these analyses can be shared by request from any qualified investigator via the Research Office of the George Institute for Global Health, Australia.

Study Design

ENCHANTED was an international, multicenter, 2×2 quasi-factorial, prospective, randomized open-label, blinded end point trial that assessed the effects of low-dose versus standard-dose intravenous alteplase, and intensive versus guideline-recommended blood pressure (BP) lowering, in thrombolysis-eligible patients with AIS, the details of which are outlined elsewhere.[3–8] In brief, the ENCHANTED trial recruited an overall 4587 patients with AIS, which included 3310 randomly assigned to low-dose (0.6 mg/kg; 15% as bolus, 85% as infusion over 1 hour) or standard-dose (0.9 mg/kg; 10% as bolus, 90% as infusion over 1 hour) intravenous alteplase and 2227 treated with alteplase randomly assigned to intensive BP lowering (target systolic BP, 130–140 mm Hg) or guideline-recommended BP lowering (target systolic BP, <180 mm Hg). The study protocol was approved by the appropriate ethics committee at each participating center, and written informed consent was obtained from each patient or an appropriate surrogate. The study is registered with https://www.clinicaltrials.gov (unique identifier: NCT01422616).

Outcomes

Key patient demographic and clinical characteristics were recorded at the time of enrollment. Their final stroke diagnoses by presumed pathogenesis, including large vessel occlusion/stenosis due to atheroma, were reported by clinician investigators at day 7 (or immediately before discharge, if earlier). Neurological severity was measured using the National Institutes of Health Stroke Scale (NIHSS) at baseline, 24 hours, and day 3 (or earlier on discharge from hospital). Clinical outcomes were assessed by telephone or in person by trained independent researchers at day 90 post-randomization; the primary outcome being functional status on the mRS. The secondary outcome was HRQoL on the 3-level version of EQ-5D,[9] which defines general health status across 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) according to 3 levels of severity (1, no problems; 2, some/moderate problems; and 3, severe problems). Ratings on each subscale of the EQ-5D were synthesized into a single utility score using population-based preference weights obtained for the UK population.[10–12] Utility scores range from −0.594 to 1, with scores of 1 and 0 representing perfect health and death, respectively; negative scores represent health states considered worse than death.[10–12] For these analyses, poor HRQoL was defined as scores of 2 or 3, defining problems reported within each dimension, or an overall health utility score ≤0.7 (rounded mean).

Statistical Analysis

Binary logistic regression was used to define associations between patient characteristics and poor HRQoL. Sensitivity analyses were performed to test associations of patient characteristics and poor HRQoL using different ethnicity analytic approaches, including non-Chinese versus Chinese, non-Asian versus Chinese, non-Asian versus other Asian, and other Asian versus Chinese. Association of NIHSS and EQ-5D utility scores (continuous variable) was assessed by linear regression. Box plots were used to demonstrate relationships of day 90 mRS scores and overall utility scores, while bar charts were used to describe relationships between mRS scores and individual dimensions on the EQ-5D. EQ-5D utility score trends across all mRS levels, between Asian and non-Asian patients, and between Chinese and non-Chinese, were tested using repeated measures ANOVA. Independent sample *t* test was used to assess differences of EQ-5D utility score between different levels of the mRS and at each level of the mRS score according to Asian versus non-Asian and Chinese versus non-Chinese. Associations between mRS and EQ-5D utility scores were assessed using Spearman partial correlation analysis, adjusting for age and baseline NIHSS scores (≥14 versus <14). The proportion of variance in EQ-5D utility scores that was explained by mRS scores was obtained from calculating the multiple correlation coefficient (r^2) in regression models, adjusted for age and NIHSS scores (≥14 versus <14). Correlation coefficients for mRS and EQ-5D utility scores were compared between Asians and non-Asians, and between Chinese and non-Chinese, using *z* test statistic with Fisher r to z transformation.[13] Regression coefficients between Asians and non-Asians, and between Chinese and non-Chinese, were compared with an extensive *t* test.[13] Associations between proxy respondents and mRS were assessed by Spearman partial correlation analysis and by logistic regression where mRS was considered as binary variable (0–1 versus 2–5), adjusted for age, baseline NIHSS (≥14 versus <14), and prestroke mRS (0 versus 1). Associations between proxy respondents and baseline NIHSS (≥14 versus <14) were tested using logistic regression adjusted for age. UW-mRS scores were derived from thrombolyzed participants in both the alteplase-dose and BP-lowering intensity arms of the trial, using ordinary least squares regression with mRS as a discrete ordinal explanatory dummy variable and EQ-5D utility scores as a continuous response variable.[14] Independent sample *t* test was used to assess differences in mean UW-mRS scores between the low-dose and standard-dose alteplase groups and between intensive and guideline-recommended BP-lowering groups. Consistency in the results using UK utility weights was tested with Chinese utility weights.[15,16] Data are presented with odds ratios and 95% CIs, and a significance level was set at $P<0.05$. All analyses were undertaken using SAS enterprise (version 7.1).

Results

Among all 4587 ENCHANTED AIS participants, there were 4016 (mean age, 66.1; 37.6% women; 67.0% Asian [62.9% Chinese]) with available day 90 mRS and EQ-5D utility scores. Differences between included and excluded participants are outlined in Table I in the online-only Data Supplement.

The overall mean EQ-5D utility score of AIS patients was 0.72 (0.37). Variables significantly associated with poor EQ-5D utility score (≤0.7) were older age (odds ratio, 1.19 [95% CI, 1.12–1.27], per 10-year increase), non-Asian ethnicity (1.91 [1.61–2.27]), greater NIHSS score (1.11 [1.09–1.12]), diabetes mellitus (1.41 [1.18–1.69]), premorbid disability (mRS score 1 versus 0; 1.62 [1.33–1.97]), large vessel atheromatous pathogenesis (1.32 [1.12–1.54]), and use of proxy respondent (2.35 [2.01–2.74]; Table). In sensitivity analyses using different ethnicity analytical approaches, there was general consistency for the same variables to be selected when comparing non-Chinese to Chinese, non-Asian to Chinese (except large vessel atheromatous pathogenesis was no longer significant),

Table. Determinants of Poor Health-Related Quality of Life in Thrombolyzed Patients With Acute Ischemic Stroke

	EQ-5D Utility Score*		Univariable		Multivariable	
Variables	>0.7 (2860)	≤0.7 (1156)	OR	*P* Value	OR	*P* Value
Age, y†	64.6 (12.6)	69.6 (12.0)	1.39 (1.31–1.47)	<0.0001	1.19 (1.12–1.27)†	<0.0001
Women	1005/2860 (35.1)	503/1156 (43.5)	1.42 (1.24–1.63)	<0.0001		
Non-Asian	838/2860 (29.3)	483/1156 (41.8)	1.73 (1.50–2.00)	<0.0001	1.91 (1.61–2.27)	<0.0001
Clinical features						
Systolic BP, mm Hg	153.6 (18.5)	154.2 (18.8)	1.00 (1.00–1.01)	0.324		
NIHSS score	6 (4–10)	11 (6–16)	1.12 (1.11–1.14)	<0.0001	1.11 (1.09–1.12)	<0.0001
Medical history						
Hypertension	1799/2857 (63.0)	763/1155 (66.1)	1.15 (0.99–1.32)	0.065		
Stroke	487/2860 (17.0)	220/1156 (19.0)	1.15 (0.96–1.37)	0.905		
Coronary artery disease	347/2857(12.2)	184/1155 (15.9)	1.37 (1.13–1.66)	0.001		
Atrial fibrillation	381/2855 (13.4)	252/1155 (21.8)	1.81 (1.52–2.16)	<0.0001		
Diabetes mellitus	520/2857 (18.2)	277/1155 (24.0)	1.42 (1.20–1.67)	<0.0001	1.41 (1.18–1.69)	0.0002
Hypercholesterolemia	372/2857 (13.0)	234/1155 (20.3)	1.70 (1.42–2.03)	<0.0001		
Prestroke mRS=1	342/2857 (12.0)	277/1153 (24.0)	2.33 (1.95–2.77)	<0.0001	1.62 (1.33–1.97)	<0.0001
Medication at time of admission						
Antihypertensive agents	1207/2857 (42.3)	583/1155 (50.5)	1.39 (1.22–1.60)	<0.0001		
Warfarin anticoagulation	46/2856 (1.6)	30/1153 (2.6)	1.63 (1.03–2.60)	0.039		
Aspirin or other antiplatelet agents	524/2856 (18.4)	312/1153 (27.1)	1.65 (1.41–1.94)	<0.0001		
Glucose-lowering agents	322/2856 (11.3)	180/1153 (15.6)	1.46 (1.20–1.77)	0.0002		
Lipid-lowering agents	451/2855 (15.8)	271/1153 (23.5)	1.64 (1.38–1.94)	<0.0001		
Final diagnosis at time of hospital separation						
Large vessel atheromatous pathogenesis	1125/2853 (39.4)	498/1154 (43.2)	1.17 (1.02–1.34)	0.030	1.32 (1.12–1.54)	0.0008
Small vessel disease	836/2853 (29.3)	189/1154 (16.4)	0.47 (0.40–0.56)	<0.0001		
Cardioemboli	404/2853 (14.2)	252/1154 (21.8)	1.69 (1.42–2.02)	<0.0001		
Others	405/2853 (14.2)	195/1154 (16.9)	1.23 (1.02–1.48)	0.030		
Randomized to low-dose alteplase treatment	998/1994 (50.1)	451/869 (51.9)	0.93 (0.79–1.09)	0.363		
Randomized to intensive BP-lowering treatment	732/1477 (49.6)	234/504 (46.4)	1.13 (0.93–1.39)	0.225		
Proxy respondent	861/2859 (30.1)	641/1156 (55.5)	2.89 (2.51–3.33)	<0.0001	2.35 (2.01–2.74)	<0.0001

Data are n (%), mean (SD), median (IQR), or odds ratio (95% CI). *P* values are based on χ^2, *t* test, Wilcoxon signed-rank test, and simple or multiple logistic regression. BP indicates blood pressure; EQ-5D, 5-Dimensional European Quality of Life Scale; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OR odds ratio.

*Good (above) and poor (below) mean scores on the EQ-5D.

†Per 10-y increase.

and other Asian to Chinese, except ethnicity was no longer significant when non-Asian was compared with other Asian (without Chinese; Tables II through V in the online-only Data Supplement). In particular, the general trend was for non-Asians to have poorer HRQoL compared with Asians (being predominantly Chinese).

EQ-5D utility scores decreased by 0.02 per 1-point increase in NIHSS scores, after adjusting for age, sex, diabetes mellitus, and proxy respondent. Use of a proxy respondent also had a significantly positive, albeit weak, correlation with mRS (r=0.29, *P*<0.0001; odds ratio, 1.16 [95% CI, 1.09–1.22]) after adjustment for age, baseline NIHSS, and prestroke mRS. High baseline NIHSS (≥14) was significantly associated with use of proxy respondents (odds ratio, 2.52 [95% CI, 2.15–2.96]; *P*<0.0001) for day 90 outcome after adjustment for age. Among the baseline variables that were associated with the different dimensions of EQ-5D, the general trend was for most, including age, previous smoke, atrial fibrillation, diabetes mellitus, prestroke disability, and stroke pathogenesis, to be correlated with the physical components—poor function/activity domains, for non-Asian ethnicity, as well as using antiplatelet agents at admission to be correlated with the nonphysical components—poor pain/discomfort and emotion (anxiety/depression) and for baseline NIHSS and proxy assessment to be associated with poor HRQoL in all dimensions (Table VI in the online-only Data Supplement).

Initial symptoms of unilateral weakness affecting the leg/foot and homonymous hemianopia were significantly associated with poor EQ-5D utility score, after adjusting for age, sex, ethnicity, and stroke severity (Table VII in the online-only Data Supplement). However, those associations that remained significant were paresis of the leg/foot in patients with poor (mRS, 2–6) and good (mRS, 0–1) functional outcomes, dysphasia in patients with poor functional outcome, and paresis of the arm/hand in those with good functional outcome (Tables VIII and IX in the online-only Data Supplement). The general trend was for problems with the different EQ-5D dimensions to increase with progressive loss of function according to increasing mRS scores, with the largest step increases in problems to occur between scores 3 and 4 and 4 and 5 (Figure I in the online-only Data Supplement).

Figure 1 shows a strong negative relationship between increasing mRS and EQ-5D utility scores (r=–0.83, P<0.0001), using UK utility weights. The strength of this association was consistent using Chinese and UK utility weights for Chinese and non-Chinese participants, respectively (Figure II in the online-only Data Supplement). Figure 2 shows a stronger correlation between these 2 outcome measures in Asians compared with non-Asians and for significantly fewer problems (ie, higher EQ-5D utility scores) to be recorded in Asians. Similar results were seen when Chinese was compared with non-Chinese ethnicity (Table X in the online-only Data Supplement).

UW-mRS scores across mRS scores 0 to 5 were: 0.977, 0.885, 0.748, 0.576, 0.194, and -0.174, respectively (Table XI in the online-only Data Supplement). The closest mRS levels were 0 and 1, separated by only 0.092, whereas the widest separation of levels was between 3 and 4 (0.382), and 4 and 5 (0.368), respectively (all level differences, P<0.0001). Sensitivity analyses using Chinese utility weights for Chinese participants showed similar results (Table XII in the online-only Data Supplement). Analysis of the separate arms of the ENCHANTED cohort using UW-mRS scores as the primary outcome measure showed no heterogeneity in the effects of low-dose (0.70±0.33) versus standard-dose (0.71±0.33) alteplase (P=0.418) and similarly no difference in the treatment effect of intensive BP lowering (0.74±0.32) versus guideline-recommended (0.72±0.32) BP lowering (P=0.379) in respective arms of the trial.

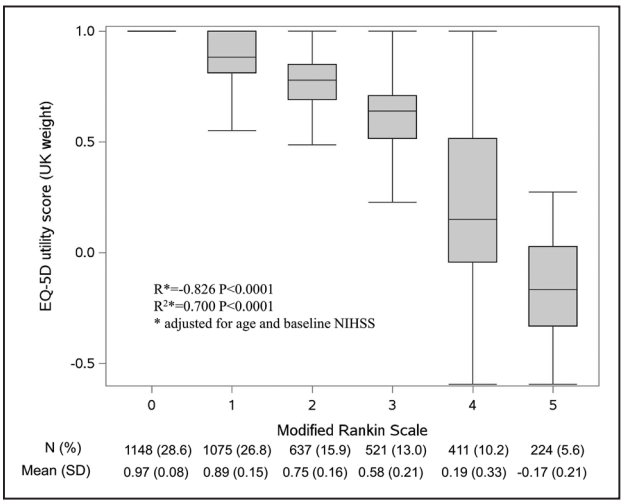

Figure 1. Relation of modified Rankin Scale and 5-Dimensional European Quality of Life Scale (EQ-5D) utility scores. NIHSS indicates National Institutes of Health Stroke Scale; R, Spearman correlation coefficient; and R^2, multiple regression coefficient.

Discussion

These exploratory analyses of the ENCHANTED trial outline the patterns and predictors of HRQoL following thrombolysis treatment for AIS. Specifically, the independent predictors of poor HRQoL were older age, non-Asian ethnicity, more severe neurological impairment, diabetes mellitus, higher prestroke mRS (1 versus 0), large vessel atheromatous pathogenesis, and use of proxy respondents. Sensitivity analyses showed the influence of ethnicity on HRQoL was driven by Chinese participants (62.9% of Asians) who had better HRQoL when compared with either non-Chinese or other Asian groups. Although there was a strong correlation between day 90 mRS and HRQoL utility scores, which was more strongly correlated in Asians than non-Asians, and in Chinese than non-Chinese participants, the combined UW-mRS scores were consistently unequally spaced across all 6 mRS levels.

Our study confirms previous findings of age,[17–19] female sex,[17] diabetes mellitus,[18,20] neurological severity,[18,19] having a negative influence on HRQoL, and for proxy respondents[17,21–23] to provide lower assessment of HRQoL than patients. Moreover, the influence of diabetes mellitus appears to extend beyond physical functioning into memory and thinking.[24] Although proxies are necessary to obtain EQ-5D scores in patients with severe disability, cognitive impairment, or communication difficulty, it is clear that these data require adjusted analyses to account for their more pessimistic view of health states than patients.[17,21–23]

Ethnicity-specific differences in the perception of HRQoL have been noted by others. For example, a large population-based study of national-level US data showed that Asians had higher HRQoL than whites across a range of similar health and disease conditions[25] and was potentially explained by Asians having higher levels of perceived familial support than other groups.[26] Another study of Chinese-American patients also suggests this ethnic group may be distinguished from others in having better HRQoL due to well-preserved social/family ties[27] and strong relationships and support from friends.[28] Thus, Asian ethnic groups appear to have high levels of collectivism, in which individuals have close binds, connections, and obligations to social/family norms and duties,[29] which may attenuate the adverse effects of illness, including stroke.

Compared with other studies, the ENCHANTED cohort produced lower UW-mRS scores despite exhibiting similar trends in steps between mRS scores,[14] which may reflect differences between study populations and methods of deriving UW-mRS scores. Our study included a much larger multiethnic population specifically in thrombolysis-eligible and treated AIS patients[20] than, for example, a UK study of 1283 patients with stroke or transient ischemic attack.[14] Another study by Hong et al[30] found even smaller HRQoL gaps between mRS

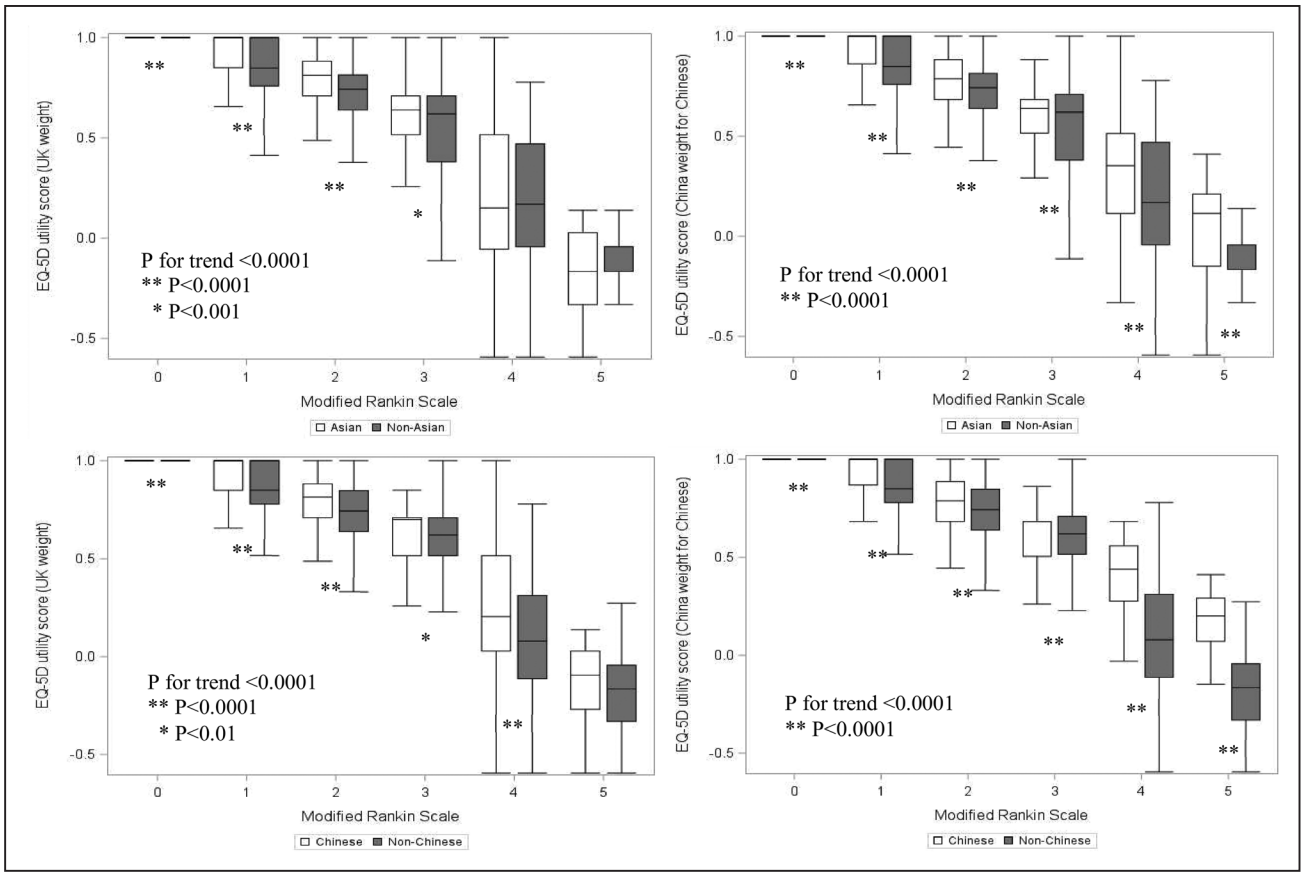

Figure 2. Relation of modified Rankin Scale (mRS) and 5-Dimensional European Quality of Life Scale (EQ-5D) utility score by Asian vs non-Asian, and by Chinese vs non-Chinese, ethnicity of participants. *P* for trend relates to comparison of EQ-5D utility scores across all mRS scores, between Asian and non-Asian patients, and between Chinese and non-Chinese, using repeated measures ANOVA. * and ** indicate significantly different EQ-5D utility scores on each mRS score between Asian and non-Asian, and between Chinese and non-Chinese, patients.

scores 4 and 5, and 3 and 4, than in our study. However, the World Health Organization's person-tradeoff procedure was used whereby stroke clinician–derived disability weights were constrained to scores between 0 and 1 and unable to account for scores worse than death.

Strengths of our analyses include the use of a large data set derived from an international multicenter study where data collection was standardized and near complete according to a rigorous protocol. Moreover, HRQoL measures were obtained from blinded assessors, and sensitivity analyses were undertaken according to Chinese and non-Chinese participants. Yet, as this was a selected clinical trial population with a restricted range of variables, there may be concerns over both the internal and external validity of the results. Moreover, the use of UK reference scores on the EQ-5D may not accurately reflect utility scores of AIS patients in other populations, although our results were confirmed in sensitivity analysis using Chinese utility weights.

In summary, the HRQoL of patients who survived thrombolyzed AIS was influenced by age, neurological severity, ethnicity, diabetes mellitus, preexisting disability, large vessel atheromatous pathogenesis, and the use of proxy outcome assessment. Although caution may be warranted regarding the broader generalizability of the influence of Asian ethnicity due to the high proportion of Chinese participants, there was consistency in analyses indicating Asians had a better HRQoL compared with others. In particular, there was a stronger correlation between mRS and EQ-5D scores in Asians (and Chinese) in the context of better overall HRQoL than non-Asians (and non-Chinese). As UW-mRS values showed the largest steps between mRS scores 5 and 4, and 4 and 3, effective therapies targeting reduction in moderate-severe disability have the greatest potential to improve the health and well-being of those experiencing AIS.

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Disclosures

Dr Anderson reports receiving research grants and lecture fees from Takeda, fees for serving on advisory boards for Amgen and Boehringer Ingelheim; Dr Lindley reports receiving fees for serving on a steering committee from Boehringer Ingelheim and lecture fees from Pfizer and Covidien; Dr Chalmers reports research grants and lecture fees from Servier for the ADVANCE trial (Action in Diabetes and Vascular Disease: Preterax and Diamicron) and post-trial follow-up; Dr Lavados reports grants and personal fees from the George Institute for Global Health, grants and nonfinancial support from Clinica Alemana de Santiago during the conduct of the study, grants from CONICYT (Comisión Nacional de Investigación Científica y Tecnológica), and grants and personal fees from Boehringer Ingelheim outside the submitted work; Dr Arima reports personal fees from Bayer, Daiichi Sankyo, Fukuda Denshi, Merck Sharp and Dohme, Takeda, Teijin, and Kyowa Kirin outside the submitted work. The other authors report no conflicts.

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