FULL TITLE: Associations with health-related quality of life after intracerebral haemorrhage: pooled analysis of INTERACT studies

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COVER TITLE: Quality of life after ICH

TABLES: 3

FIGURES: 0

ONLINE-ONLY Supplementary material: 6 tables and 1 figure

KEY WORDS: stroke, outcome research, health policy, quality of life, health services

WORD COUNT: 2686 (excluding title page, abstract, references, figures and tables)

ABSTRACT

Background and purpose: Limited data exist on health-related quality of life (HRQoL) after intracerebral haemorrhage (ICH). We aimed to determine baseline factors associated with HRQoL among participants of the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trials (INTERACT 1 and 2).

Methods: The INTERACT studies were randomised controlled trials of early intensive blood pressure (BP) lowering in patients with ICH (<6h) and elevated systolic BP (150-220 mm Hg). HRQoL was determined using the European Quality of Life Scale (EQ-5D) at 90 days, completed by patients or proxy-responders. Binary logistic regression analyses were performed to identify factors associated with poor overall HRQoL.

Results: 2756 patients were included. Demographic, clinical and radiological factors associated with lower EQ-5D utility score were: age, randomisation outside of China, antithrombotic use, high baseline National Institutes of Health Stroke Scale (NIHSS) score, larger ICH, presence of intraventricular extension, and use of proxy-responders. High (≥14) NIHSS score, larger ICH and proxy-responders were associated with low scores in all five dimensions of the EQ-5D. NIHSS score had a strong association with poor HRQoL ($p<0.001$). Female gender and antithrombotic use were associated with decreased scores in dimensions of pain/discomfort and usual activity, respectively.

Conclusions: Poor HRQoL was associated with age, comorbidities, proxy source of assessment, clinical severity, and ICH characteristics. The strongest association was with initial clinical severity defined by high NIHSS score.

Trial registration numbers: URL, http://www.clinicaltrials.gov. Unique identifier, NCT00226096 and NCT00716079.

INTRODUCTION

As most stroke survivors have some degree of disability, assessment of their quality of life is important for healthcare providers, policy maker and researchers. Health-related quality of life (HRQoL) measures key physical and emotional aspects of disease on a person's quality of life. Although several studies of mixed ischaemic stroke and intracerebral haemorrhage (ICH) patient groups are consistent in reporting age and physical disability as predictors of poor HRQoL,[1,2] few have focused specifically on ICH, the least treatable and the most disabling type of stroke. Analysis from the Factor Seven for Acute Haemorrhagic Stroke Treatment (FAST) trial showed that low overall HRQoL, as measured by the European Quality of Life Scale (EQ-5D)[3] utility score, was associated with age, clinical factors (stroke severity, systolic blood pressure [BP], and neurological deterioration), and imaging features (larger and deep ICH).[4] Yet, the number of participants was still relatively small (n=621) and individual HRQoL dimensions within EQ-5D were not reported. We aimed to determine the clinical and imaging factors associated with overall HRQoL and its constituents in the pooled dataset of participants of the pilot and main phases of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT 1 and 2).[5,6]

METHODS

Participants

The INTERACT studies[5,6] were multicentre, randomised, controlled clinical trials that included 3233 participants from 22 countries during 2005-2013. We pooled the pilot and main phase INTERACT studies to increase the sample size and the precision of the estimates. Patients with imaging-confirmed ICH were randomly assigned to receive either early intensive BP lowering treatment (<140 mm Hg systolic goal) or contemporaneous guideline-recommended standard BP lowering (<180 mm Hg systolic goal) within 6 hours of onset.

The study protocol was approved by appropriate ethics committees at each site and registered with ClinicalTrials.gov (NCT00226096 and NCT00716079). Written informed consent was obtained from patients or their legal surrogates when they were unable to do so.

Procedures

Demographics and clinical characteristics were recorded at patient enrolment, with stroke severity measured on the Glasgow coma scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS). CT scans were performed according to standardised techniques at baseline and centrally analysed for the volume and location of ICH, and the presence of intraventricular extension of ICH (IVH).

Outcomes

The outcome for this analysis was HRQoL, as assessed directly by a patient or by a proxy-responder, using the EQ-5D[3] questionnaire at 90 days. This descriptive system defines the state of general health across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels (no problems, some/moderate problems, and severe problems). The EQ-5D utility score integrates the ratings of the 5 dimensions into a single score, calculated using population-based preference weights for each subscale. In the present analysis, we used the weights obtained from the United Kingdom population. Utility scores express HRQoL quantitatively as a fraction of perfect health, with a score of 1 representing perfect health, a score of 0 representing death, and negative scores (minimum score -0.109) representing health states considered worse than death. The average utility score in disease-free populations range between 0.8 and 0.9.[7-9] When patients were not able to answer the questionnaire themselves, proxy-responders, such as their caregiver or doctor, were asked to rate the patient's HRQoL. The EQ-5D has previously been validated for use in proxy-responders..[10-11] The protocol did not stipulate the process of proxy-responder selection; the decision was opportunistic and arose during a telephone or face-to-face interview between the responsible neurologically competent person (blinded to treatment arm) and the patient or caregiver at the scheduled time of follow-up.

Statistical Analysis

We evaluated baseline characteristics of the patients by utility score groups [≤0.7 (median utility score) and >0.7] summarised by means and standard deviations (SD), median and interquartile range (IQR) for continuous variables and numbers (%) for categorical variables. The baseline differences in patient characteristics between utility score groups were also assessed by the χ^2 test and the Wilcoxon test. Similarly, patient characteristics between the included (alive at 90 days and with complete EQ-5D data) and excluded (dead at 90 days or incomplete EQ-5D data) study participants were compared.

The associations of baseline characteristics and EQ-5D utility score at 90 days were evaluated in a binary regression model which included clinically important variables, as described elsewhere[12-13] and/or variables found significant in the crude analysis (age, sex, country of enrolment, medical history, antithrombotic use, onset to randomisation time, systolic BP, NIHSS score (≥14 vs. <14), CT findings, intensive BP lowering treatment, and proxy-responders). All the analysis included 'study' as a covariate to account for the differential effect between the pilot and main phases of INTERACT study. Each dimension of EQ-5D was treated as categorical variable with two levels (answer of 2 or 3 meaning some/moderate or severe problems in the corresponding dimension vs. answer 1 meaning no problem in the corresponding dimension). The associations of low HRQoL in each dimension of EQ-5D were also assessed in binary logistic regression models (answer of 2 or 3 vs. 1) including the same covariates as the overall utility score model.

To test the robustness of results, we first conducted stratified analyses for associations of utility score as a binary outcome variable in patients who completed the EQ-5D questionnaire themselves and proxy-responders. Secondly, we applied Chinese norms to the Chinese study population[14,15] and UK preference weights to the other participants and repeated the logistic regression analysis. Thirdly, we forced all baseline variables into our analysis model. Finally, we conducted linear regression analysis with overall utility score as a continuous outcome, to estimate changes in the utility score associated with variations in the independent covariates. A standard level of significance ($P<0.05$) was used and the data are reported with odds ratios (OR) and 95% confidence intervals (CI). All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of 3233 patients in the INTERACT pooled cohort, 2756 with information on HRQoL at 90 days were included in the present analyses (Figure 1 in the online-only supplementary material). The distribution of EQ-5D utility scores was left skewed (Figure 2 in the online-only supplementary material) with 1251 patients having a utility score equal or lower than the median (≤0.7), and 1505 with a utility score higher than the median (>0.7). The variables associated with lower utility scores were age, female gender, randomisation outside of China, previous acute coronary syndrome, being on an antithrombotic, having a high baseline systolic BP, receiving non-intensive BP lowering (as per INTERACT protocol), clinical severity (lower GCS and higher NIHSS), larger, and deep ICH, intraventricular extension of the ICH, completion of the questionnaire by a proxy-responder and being an INTERACT2 patient. (**Table1**).

Table 1. Patient characteristics

	EQ-5D utility score		
	≤0.7 (n=1251)	**>0.7 (n=1505)**	***P***
Demographics			
Age, years	65±13	61±12	<0.001
Female	516 (41)	529 (35)	0.001
Randomised in China	848 (68)	1195 (79)	<0.001
Medical history			
ICH	110 (9)	112 (7)	0.192
Ischaemic stroke	130 (10)	146 (10)	0.543
Acute coronary syndrome	43 (3)	27 (2)	0.006
Hypertension	894 (72)	1102 (73)	0.283
Diabetes mellitus	140 (11)	135 (9)	0.052
Medication history			
Antihypertensives	554 (44)	652 (43)	0.599
Antithrombotics	168 (13)	107 (7)	<0.001
Clinical features			
Onset to randomisation time, h:mm	3:39 (2:44-4:36)	3:47 (2:54-4:50)	0.441
Systolic BP, mmHg	180±17	178±17	0.001
Diastolic BP, mmHg	101±14	102±14	0.150
NIHSS score	13 (9-17)	7 (4-11)	<0.001
GCS score	14 (12-15)	15 (14-15)	<0.001
CT findings			
Baseline ICH volume, mL	12.4 (7.1-22.0)	8.1 (4.0-14.2)	<0.001
Deep ICH location	997 (87)	1128 (82)	<0.001

Presence of IVH	374 (33)	274 (20)	<0.001
Intensive BP lowering	590 (47)	777 (52)	0.020
Proxy responders	629 (50)	417 (28)	<0.001
INTERACT2 study	1121 (90)	1290 (86)	0.002

Data are n (%), mean (SD), or median (interquartile range). EQ-5D indicates European Quality of Life Scale; ICH, intracerebral haemorrhage; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; CT, computed tomography; IVH, intraventricular extension of ICH and INTERACT2, the main phase of the Intensive Blood Pressure Reduction in Acute Intracerebral Haemorrhage Trial. Median EQ-5D utility score =0.7

After excluding 477 patients either due to death within 90 days (n=382) or because of missing HRQoL data (n=95), there remained 2756 patients who were included in these analyses (Figure 1 in the online-only supplementary material). Supplementary Table 1 in the online-only supplementary material outlines the clinical characteristics of the included and excluded patients.

The EQ-5D questionnaire was completed either by face-to-face or telephone interview directly with patients (n=1710, 1294 randomised in China and 416 outside of China) or by proxy-responders (n=1046, 749 randomised in China and 297 outside of China).

Table 2 shows the multivariable binary logistic regression analysis for associations between decreased utility score (≤0.7) at 90 days. Variables significantly associated with decreased EQ-5D utility score were older age, randomisation outside of China, antithrombotic use, shorter onset to randomisation time, higher baseline NIHSS score (≥14), larger and deep ICH, presence of IVH and proxy-responders.

Table 2. Multivariable binary logistic regression analysis for associations with decreased EQ-5D utility score* at 90 days

	OR	**95% CI**	***P***
Demographics			
Age, per 10 years	1.26	1.17-1.36	<0.001
Female	1.16	0.97-1.40	0.109
Randomised in China	0.74	0.60-0.93	0.008
Medical history			
Acute coronary syndrome	1.36	0.76-2.41	0.301
Hypertension	0.93	0.76-1.13	0.461
Diabetes mellitus	1.17	0.87-1.57	0.313
Medication history			
Antithrombotics	1.62	1.18-2.24	0.003
Clinical features			
Onset to randomisation time, per hour	0.90	0.84-0.97	0.007
Systolic BP, per 5 mm Hg	1.03	1.00-1.05	0.067
NIHSS score (≥14 vs <14)	3.14	2.53-3.88	<0.001
CT findings			
Baseline ICH volume, per 10 mL	1.41	1.30-1.54	<0.001
Deep ICH location	1.56	1.21-2.02	0.001
Presence of IVH	1.64	1.34-2.00	<0.001
Others			
Intensive BP lowering	0.89	0.75-1.06	0.186
Proxy-responders	1.94	1.61-2.34	<0.001
INTERACT2 study	1.05	0.79-1.40	0.749

EQ-5D indicates European Quality of Life Scale; OR, odds ratio; CI, confidence interval; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ICH, intracerebral haemorrhage; IVH, intraventricular extension of ICH and

INTERACT2, the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial.

* EQ-5D utility score categorization: group 1 (≤0.7, reference), n=1251; group 2 (>0.7), n=1505.

The binary logistic regression model explained a very large proportion of the variation in utility score (C statistics=0.77). Supplementary analysis of direct responses from patients only (without proxy-responders) (n=1710) showed similar results. In the sub-group of proxy-responders only (n=1046), age, antithrombotics, high NIHSS, large baseline ICH volume and IVH remained significant but country of randomisation, onset to treatment time and deep location became non-significant. (Table 2 and 3 in the online-only supplementary material). Supplementary analysis with Chinese utility weights for the Chinese participants and UK weights for others showed similar results with the exception of 'randomisation in China', which was no longer associated with increased quality of life (Table 4 in the online-only supplementary material). Chinese weights applied to the Chinese population produced less variation in the utility score with higher minimum scores than when UK norms were used (-0.149 to 1 vs. -0.594 to 1, respectively). Supplementary analysis forcing all baseline variables into the model with linear regression showed broadly similar results (Table 5-6 in the online-only supplementary material).

Table 3 shows the multivariable binary logistic regression analysis of HRQoL by EQ-5D dimensions. The associations with mobility problems (1762 scoring 2 or 3 [some/moderate or severe problems] vs. 994 scoring 1 [no problem]), were age, past history of an acute coronary syndrome and hypertension, onset to randomisation time, NIHSS score, volume and deep location of ICH, IVH, and proxy-responders. Factors associated with problems in self-care (1320 scoring 2 or 3 vs. 1436 scoring 1) were age, country of randomisation, diabetes mellitus, onset to randomisation time, NIHSS score, volume and deep location of ICH, IVH, and proxy-responders. Usual activity (1694 scoring 2 or 3 vs. 1062 scoring 1) was independently associated with age, country of randomisation, antithrombotic use, onset to randomisation time, NIHSS score, volume and deep location of ICH, IVH, and proxy-responders. Pain/discomfort (1154 scoring 2 or 3 vs. 1602 scoring 1) were associated with gender, history of an acute coronary syndrome, NIHSS score, ICH volume, and proxy-responders. Finally, anxiety/depression (982 scoring 2 or 3 vs. 1774 scoring 1) was associated with age, NIHSS score, volume of ICH, and proxy-responders.

Table 3. Multivariable binary logistic regression analyses for associations with poor HRQoL by dimension (some/moderate or severe problems vs. no problem)

	Mobility		Self-care		Usual activity		Pain/discomfort		Anxiety/depr	
	Affected n (%)		Affected n (%)		Affected n (%)		Affected n (%)		Affected n (%	
	1762 (64)		1320 (48)		1694 (61)		1154 (42)		982 (36)	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% C**
Demographics										
Age, per 10 years	1.33	1.23-1.44‡	1.35	1.25-1.47‡	1.29	1.19-1.40‡	1.05	0.98-1.13	1.13	1.05-1.2
Female	0.98	0.81-1.17	1.07	0.88-1.29	1.08	0.89-1.30	1.23	1.04-1.46*	1.04	0.87-1.2
Randomised in China	0.89	0.71-1.12	0.68	0.54-0.85‡	0.52	0.41-0.66‡	1.21	0.98-1.48	0.83	0.67-1.0
Medical history										
Acute coronary syndrome	0.55	0.31-0.98*	0.95	0.53-1.71	0.81	0.43-1.50	1.85	1.10-3.13*	0.93	0.54-1.5
Hypertension	0.80	0.65-0.98*	0.88	0.72-1.08	0.90	0.73-1.11	1.06	0.88-1.28	1.08	0.89-1.3
Diabetes mellitus	1.33	0.97-1.81	1.49	1.10-2.02†	1.27	0.92-1.74	0.79	0.60-1.05	1.03	0.78-1.3
Medication history										
Antithrombotics	1.32	0.94-1.86	1.22	0.88-1.70	1.83	1.26-2.65†	1.28	0.95-1.72	1.29	0.95-1.7
Clinical features										
Onset to randomisation time, per hour	0.87	0.81-0.94‡	0.90	0.84-0.97†	0.89	0.82-0.96†	0.98	0.92-1.05	0.96	0.89-1.0
Systolic BP, per 5 mm Hg	1.03	1.00-1.05	1.03	1.00-1.05	1.02	1.00-1.05	1.00	0.97-1.02	1.02	0.99-1.0
NIHSS score (≥14 vs <14)	2.58	2.02-3.29‡	3.31	2.65-4.13‡	3.30	2.56-4.26‡	1.94	1.59-2.36‡	1.97	1.61-2.4
CT findings										
Baseline ICH volume, per 10mL	1.37	1.24-1.51‡	1.53	1.39-1.68‡	1.53	1.38-1.70‡	1.14	1.07-1.23‡	1.16	1.08-1.2

Deep ICH location	1.30	1.02-1.66*	1.79	1.38-2.33‡	1.48	1.15-1.90†	1.23	0.97-1.54	1.26	0.99-1.6
Presence of IVH	1.82	1.46-2.26‡	1.53	1.24-1.88‡	1.55	1.24-1.93‡	0.97	0.81-1.18	1.12	0.92-1.3
Others										
Intensive BP lowering	0.94	0.79-1.12	0.90	0.75-1.07	0.85	0.71-1.02	0.89	0.75-1.05	0.91	0.77-1.0
Proxy-responders	1.96	1.61-2.39‡	2.46	2.03-2.98‡	2.53	2.06-3.10‡	1.37	1.15-1.63‡	1.43	1.19-1.7
INTERACT2 study	1.23	0.94-1.62	0.94	0.70-1.25	1.20	0.91-1.59	1.05	0.81-1.37	0.90	0.68-1.1

HRQoL indicates health-related quality of life; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; ICH, intracerebral haemorrhage; IVH, intraventricular extension of ICH and INTERACT2, the main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial.

*$P<0.05$; †$P<0.01$; ‡ $P<0.001$.

DISCUSSION

In this study involving a large multi-ethnic group of ICH patients, poor HRQoL at 90 days was associated with older age, randomisation outside of China, antithrombotic use, greater severity (higher baseline NIHSS score, larger ICH, and presence of IVH) and proxy assessment. In particular, a highly significant association was found between stroke severity and poor HRQoL, across all five dimensions of the EQ-5D. The relation of other variables across specific dimensions varied, with ICH volume and having a proxy-responder being associated with at least some problems across all dimensions, whilst being female but not age was associated with poor scores for pain/discomfort. Antithrombotic use, diabetes mellitus, and coronary disease were associated with low scores in usual activity, self-care and mobility, and pain/discomfort, respectively; hypertension was associated with reduced mobility; and Chinese patients reported better scores in usual activity and self-care.

As in the FAST trial,[4] our study showed that ICH imaging features of large ICH with associated IVH was related to poor HRQoL. In studies of HRQoL after aneurysmal subarachnoid haemorrhage, IVH predicted worse HRQoL on the Aachen Life Quality Inventory (ALQI), and particularly for the psychosocial dimension which is a summary score of free-time activities, family relations, social contact, communication, and cognition.[16] Since the EQ-5D rating cover social interactions within the usual activities dimension (family and leisure activities), our results show a similar relationship in which IVH was found to impact on mobility, self-care, and daily activities dimensions. This is likely due to the direct influence of IVH, producing a high risk of reduced consciousness, disability and death[17-19] in relation to a given volume of IVH.

In the present analysis, prior antithrombotic use (which may be regarded as a marker of cardiovascular disease risk) was associated with poor overall utility score and usual activity. Co-morbidities of diabetes mellitus, hypertension and coronary artery disease, were each associated with poor utility score within these domains, which is consistent with prior studies. Co-morbidities may negatively affect physical function, memory and thinking, but also social participation, as measured by the Stroke Impact Scale (SIS).[12,20-21] Our study results corroborate prior findings and suggest that the added burden of pre-existing comorbidities affects not only functional outcome but also HRQoL among ICH patients.[22]

In our analysis, female gender was not associated with poor overall HRQoL, except with respect to pain/discomfort. Conversely, several prior studies have indicated this variable is a common predictor of poor HQoL after stroke.[1,2] In these studies, though, low education and different work and household living among females compared to males, were postulated as possible reasons. Intriguingly, a recent American multicentre, longitudinal registry study has shown a similar tendency for a higher proportion of women than men to report problems in the EQ-5D dimension of pain/discomfort after ischemic stroke or transient ischemic attack.[23] Although we speculated that post-stroke headache, spasticity, or joint contracture, could be possible underlying reasons, data pertaining to these variables were not available in our study.

Proxy-responder assessment was associated with decreased EQ-5D utility score and poor HRQoL across all five individual dimensions. The involvement of proxy-responders may be a reflection of post-stroke cognitive and communication disabilities preventing patients from answering the questionnaire themselves. Proxy-responders provide their assessment of patients' HRQoL, which is in itself inherently subjective, and can be related to various factors such as patient and caregiver education levels, family relationships, and caregiver psychological distress and burden.[24] It is also recognized that proxy-responders have a tendency to report more problems and have a more pessimistic appreciation of patients' HRQoL than patients themselves, which introduces bias related to stroke severity.[1,25-27]

Interestingly, in China, although participants self-reported a better quality of life than patients randomized outside of China, proxy-responders responded in the same way as non-Chinese proxy-responders. Patients randomised in China reported better scores in the self-care and usual activity dimensions and this was not be explained by younger age, milder clinical severity or smaller ICH in the models. Chinese patients may have been more likely to receive informal caregiving and have higher perceived levels of family support, which may have led to a more positive life outlook as compared to participants in others countries[28], where the elderly and infirm are often cared for by health agency services or institutions. In addition, Chinese patients may be more engaged spiritually, which may also affect psychosocial aspects of the patient's life.[29] Finally, the associations between randomisation in China and increased total utility score that are present when adjusted UK norms are used but which disappear when Chinese norms are applied to patients randomised in China, suggests that Chinese patients have a more optimistic view of their quality of life than residents of the United Kingdom. How much ethnic differences in HRQoL outcomes can be attributed to psychosocial characteristics[30] as well as stroke management and rehabilitation practices in China requires further study.

Strengths of our analyses include the access to a large dataset derived from an international multicentre study with a rigorous protocol and collection of outcome data by assessors blinded to the study groups. The robustness of our findings was validated through a range of sensitivity analyses involving ordinal logistic regression model, binary logistic regression model forcing all the baseline characteristics, stratification by patients versus proxy-responders and by applying Chinese norms to patients randomised in China. However, we recognise that there are limitations, in particular of selection bias as the findings were based upon a clinical trial population where cases of large volume ICH were under-represented, and patients with a very high likelihood of early death and planned surgical evacuation of ICH were excluded. This and the proportion of surviving patients without complete assessment of quality of life at 90 days probably lead as to underestimating the total reduction in quality of life associated with ICH. The influence of socioeconomic factors could not be assessed in the INTERACT studies and about 40% of responses were given by proxies, who are known to give a more pessimistic view of HRQoL. Finally, use of the UK weighted HRQoL equation for all patients in this study may not accurately reflect the true utility score in certain non-UK participants. Nevertheless, this reference has been used in prior investigations and we have confirmed our findings through sensitivity analyses using Chinese HRQoL norms for patients enrolled in China.[14,15,31,32]

In summary, significant associations were shown between clinical severity and poor HRQoL at 90 days in a large population of patients with acute ICH. Poor HRQoL was also associated with older age, co-morbidities, ICH imaging characteristics (large and deep ICH and the presence of IVH) and proxy assessment.

ACKNOWLEDGEMENTS

Drs Delcourt, Zheng, Anderson and Sato contributed to the concept and rationale for the study. Drs Zheng and Sato contributed to statistical analyses. Drs Delcourt, Zheng, and Sato were responsible for the first draft of the manuscript. Drs Delcourt, Zheng, Chen, Anderson and Sato contributed to the interpretation of the results. All authors participated in the drafting and took responsibility for the content and integrity of this article.

SOURCES OF FUNDING

The National Health and Medical Research Council of Australia provided funding for this research.

DISCLOSURES

Dr Anderson receives speaker fees from Takeda China and Advisory Committee reimbursement from Medtronic and Astra Zeneca. The other authors report no conflicts of interest.

REFERENCES

1. Hackett ML, Duncan JR, Anderson CS, et al. Health-related quality of life among long-term survivors of stroke : Results from the Auckland Stroke Study, 1991-1992. *Stroke* 2000;31:440-7.
2. Sturm JW, Donnan GA, Dewey HM, et al. Quality of life after stroke: The North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2004;35:2340-5.
3. EuroQol G. Euroqol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
4. Christensen MC, Mayer S, Ferran JM. Quality of life after intracerebral hemorrhage: Results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial. *Stroke* 2009;40:1677-82.
5. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 2013;368:2355-65.
6. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol* 2008;7:391-9.
7. Hoi le V, Chuc NT, Lindholm L. Health-related quality of life, and its determinants, among older people in rural Vietnam. *BMC Public Health* 2010;10:549.
8. Burstrom K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Qual Life Res* 2001;10:621-35.
9. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26:410-20.
10. Dorman PJ, Waddell F, Slattery J, et al. Are proxy assessments of health status after stroke with the EuroQol questionnaire feasible, accurate, and unbiased? *Stroke* 1997;28:1883–7.

11. Pickard AS, Johnson JA, Feeny DH, et al. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke* 2004;35:607–12.

12. Nichols-Larsen DS, Clark PC, Zeringue A, et al. Factors influencing stroke survivors' quality of life during subacute recovery. *Stroke* 2005;36:1480-4

13. Luengo-Fernandez R, Gray AM, Bull L, et al. Quality of life after TIA and stroke: Ten-year results of the oxford vascular study. *Neurology* 2013;81:1588-95

14. Liu GG, Wu H, Li M, et al. Chinese trade-off values for EQ-5D health states. *Value in Health* 2014; 17:597-604.

15. Zhang Y, Zhou Z, Gao J, et al. Health-related quality of life and its influencing factors for patients with hypertension: evidence from the urban and rural areas of Shaanxi province, China. *BMC Health Serv Res* 2016;16:277.

16. Hutter BO, Kreitschmann-Andermahr I, Gilsbach JM. Health-related quality of life after aneurysmal subarachnoid hemorrhage: impacts of bleeding severity, computerized tomography findings, surgery, vasospasm, and neurological grade. *J Neurosurg*. 2001;94 :241-51.

17. Bhattathiri PS, Gregson B, Prasad KS, et al. Intraventricular hemorrhage and hydrocephalus after spontaneous intracerebral hemorrhage: results from the STICH trial. *Acta Neurochir Suppl* 2006;96:65-8.

18. Steiner T, Diringer MN, Schneider D, et al. Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage: risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. *Neurosurgery*. 2006;59:767-773.

19. Chan E, Anderson CS, Wang X, et al. Significance of intraventricular hemorrhage in acute intracerebral hemorrhage: Intensive blood pressure reduction in acute cerebral hemorrhage trial results. *Stroke* 2015;46:653-8.

20. Suenkeler IH, Nowak M, Misselwitz B, et al. Timecourse of health-related quality of life as determined 3, 6 and 12 months after stroke. Relationship to neurological deficit, disability and depression. *J Neurol* 2002;249:1160-7.

21. Mackenzie AE, Chang AM. Predictors of quality of life following stroke. *Disabil Rehabil* 2002;24:259-65.

22. Bar B, Hemphill JC, 3rd. Charlson comorbidity index adjustment in intracerebral hemorrhage. *Stroke* 2011;42:2944-6.

23. Bushnell CD, Reeves MJ, Zhao X, et al. Sex differences in quality of life after ischemic stroke. *Neurology* 2014;82:922-31.

24. Williams LS, Bakas T, Brizendine E, et al. How valid are family proxy assessments of stroke patients' health-related quality of life? *Stroke* 2006;37:2081-5.

25. Duncan PW, Lai SM, Tyler D, et al. Evaluation of proxy responses to the Stroke Impact Scale. *Stroke* 2002;33:2593-9.

26. Hilari K, Owen S, Farrelly SJ. Proxy and self-report agreement on the Stroke and Aphasia Quality of Life Scale-39. *J Neurol Neurosurg Psychiatry* 2007;78:1072-5.

27. Pickard AS, Johnson JA, Feeny DH, et al. Agreement between patient and proxy assessments of health-related quality of life after stroke using the EQ-5D and Health Utilities Index. *Stroke* 2004;35:607-12.

28. Tsouna-Hadjis E, Vemmos KN, Zakopoulos N et al. First-stroke recovery process: the role of family social support. *Arch Phys Med Rehabil* 2000;81:881-7.

29. Reeves SL, Brown DL, Baek J, et al. Ethnic differences in Poststroke Quality of Life in the Brain Attack Surveillance in Corpus Christi (BASIC) project. *Stroke* 2015;46:2896-901.

30. Fu AZ, Kattan MW. Racial and ethnic differences in preference-based health status measure. *Curr Med Res Opin* 2006; 22:2439-48.

31. Sprigg N, Selby J, Fox L, et al. Very low quality of life after acute stroke: Data from the Efficacy of Nitric Oxide in Stroke trial. *Stroke* 2013;44:3458-62.

32. IST3 collaborative group. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. *Lancet Neurol* 2013;12:768-76.