Published Ahead of Print on October 27, 2022 as 10.1212/WNL.0000000000201375

Neurology®
The most widely read and highly cited peer-reviewed neurology journal
The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000201375

Patient-Reported Quality of Life After Intravenous Alteplase for Stroke in the WAKE-UP Trial

Author(s):
Märit Jensen, MD[1]; Susanne Sehner, PhD[2]; Bastian Cheng, MD[1]; Eckhard Schlemm, MD, PhD[1]; Fanny Quandt, MD[1]; Ewgenia Barow, MD[1]; Karl Wegscheider, PhD[2]; Florent Boutitie, PhD[3]; Martin Ebinger, MD, PhD[4,5]; Matthias Endres[4,6,7,8,9]; Jochen Fiebach, MD[4]; Vincent Thijs, PhD[10,11]; Robin Lemmens, MD[12,13,14]; Keith Muir, MD[15]; Norbert Nighoghossian, MD[16]; Salvador Pedraza, MD[17]; Claus Z Simonsen, MD, PhD[18]; Götz Thomalla, MD[1]; Christian Gerloff, MD[1]

Corresponding Author:
Märit Jensen, m.jensen@uke.de

Affiliation Information for All Authors: 1. Klinik und Poliklinik für Neurologie, Kopf- und Neurozentrum, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany; 2. Institut für Medizinische Biometrie und Epidemiologie, Zentrum für Experimentelle Medizin, Universitätsklinikum Hamburg- Eppendorf, Hamburg, Germany; 3. Hospices Civils de Lyon, Service de Biostatistique, F-69003 Lyon, France; Université Lyon 1, F-69100 Villeurbanne, France; CNRS, UMR 5558, Laboratoire de Biométrie et Biologie Evolutive, Equipe Biostatistique-Santé, F-69100 Villeurbanne, France; 4. Centrum für Schlaganfallforschung Berlin (CSB), Charité - Universitätsmedizin Berlin, Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany; 5. Neurologie, Medical Park Berlin Humboldtmühle, An der Mühle 2-9, 13507 Berlin, Germany 6. Klinik und Hochschulambulanz für Neurologie, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany; 7. German Center for Neurodegenerative Disease (DZNE), partner site Berlin; 8. German Center for Cardiovascular Research (DZHK), partner site Berlin; 9. Excellence Cluster NeuroCure, Berlin, Germany; 10. Florey Institute of Neuroscience and Mental Health, University of Melbourne, 245 Burgundy Street, Heidelberg, VIC 3084, Victoria, Australia; 11. Austin Health, Department of Neurology, 145 Studley Road, Heidelberg, VIC 3084, Australia; 12. Department of Neurology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium; 13. KU Leuven University of Leuven, Department of Neurosciences, Experimental Neurology, Oude Markt 13, bus 5005, 3000 Leuven, Belgium 14. VIB, Center for Brain & Disease Research, Laboratory of Neurobiology, Campus Gasthuisberg, Herestraat 49, bus 602, 3000 Leuven, Belgium; 15. Institute of Neuroscience & Psychology, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK; 16. Department of Stroke Medicine, Université Claude Bernard Lyon 1, CREATIS CNRS UMR 5220-INSERM U1206, INSA-Lyon; Hospices Civils de Lyon, Lyon, France; 17. Department of Radiology, Institut de Diagnostic per la Image (IDI), Hospital Dr Josep Trueta, Institut dInvestigació Biomèdica de Girona (IDIBGI), Parc Hospitalari Martí i Julià de Salt - Edifici M2, 17190 Salt, Girona, Spain; 18. Department of Neurology, Aarhus University Hospital, 8200 Aarhus N, Denmark

Equal Author Contribution:

Contributions:
Märit Jensen: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Susanne Sehner: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Bastian Cheng: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Eckhard Schlemm: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Fanny Quandt: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Ewgenia Barow: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Karl Wegscheider: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Florent Boutitie: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Martin Ebinger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Matthias Endres: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Jochen Fiebach: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Vincent Thijs: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Robin Lemmens: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Keith Muir: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Norbert Nighoghossian: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Salvador Pedraza: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Claus Z Simonsen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Götz Thomalla: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Christian Gerloff: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
3

Table Count:
2

Search Terms:
[2] All Cerebrovascular disease/Stroke, [20] Clinical trials Randomized controlled (CONSORT agreement), [113] Quality of life, [120] MRI

Acknowledgment:

Study Funding:
WAKE-UP received funding from the European Union Seventh Framework Program [FP7/2007-2013] under grant agreement n°278276 (WAKE-UP). The European Union Seventh Framework Program [FP7/2007-2013] had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosures:
M. Endres reports grants from Bayer, DFG under Germany´s Excellence Strategy – EXC-2049 – 390688087, Collaborative Research Center ReTune TRR 295- 424778381, BMBF, DZNE, DZHK, EU, Corona Foundation, and Fondation Leducq, and institutional fees from Abbot, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Sanofi, Novartis, Pfizer, all outside the submitted work. J. Fiebach reports personal fees from Abbvie, AC Immune, Artemida, Bioclinica/Clairo, Biogen, BMS, Brainomic, Daiichi-Sankyo, Eisai, F.Hoffmann-La Roche AG, Eli Lilly, Guerbet, Ionis Pharmaceuticals, IQVIA, Janssen, Julius Clinical, Jung Diagnostics, Lysogene, Premier Research and Tau Rx, outside the submitted work. C. Gerloff reports personal fees from Abbott, Amgen, Bayer Vital, Bristol-Myers-Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Sanofi Aventis and Prediction Biosciences outside the submitted work. R. Lemmens reports institutional fees from Genentech and Boehringer Ingelheim outside the submitted work. K. Muir reports supply with tenecteplase within the ATTEST-2 trial from Boehringer Ingelheim, and personal fees from Abbvie, Biogen, and Boehringer Ingelheim outside the submitted work. C.Z. Simonsen reports grants from Novo Nordisk Foundation and Health Research Foundation of Central Denmark Region outside the submitted work. V. Thijs reports grants from the Medical Research Future Fund and the Stroke Foundation of Australia, and personal fees from Abbott, Allergan, Amgen, Bayer, Boehringer Ingelheim, BristolMyersSquibbb/Pfizer, and Medtronic outside the submitted work. G. Thomalla reports personal fees from Acandis, Alexion, Amarin, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, Portola, and Stryker outside the submitted work. The other authors report no competing interests.

Preprint DOI:

Received Date:
2022-03-09

Accepted Date:
2022-08-23

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was José Merino, MD, MPhil, FAAN.

ABSTRACT

Background and Objectives: Intravenous alteplase improves functional outcome after acute ischemic stroke. However, little is known about the effects on self-reported health-related quality of life (HRQoL).

Methods: WAKE-UP was a multicenter, randomized, placebo-controlled trial of MRI-guided intravenous alteplase in stroke with unknown onset time. HRQoL was assessed using the EQ-5D questionnaire at 90 days, comprising the EQ-5D index and the EQ visual analogue scale (VAS). Functional outcome was assessed by the modified Rankin Scale (mRS). We calculated the effect of treatment on EQ-5D index and EQ VAS using multiple linear

regression models. Mediation analysis was performed on stroke survivors to explore the extent to which the effect of alteplase on HRQoL was mediated by functional outcome.

Results: Among 490 stroke survivors, the EQ-5D index was available for 452 (92.2%), of whom 226 (50%) were assigned to treatment with alteplase and 226 (50%) to placebo. At 90 days, mean EQ-5D index was higher, reflecting a better health state, in patients randomized to treatment with alteplase than with placebo (0.75 vs. 0.67) with an adjusted mean difference of 0.07 (95% CI 0.02-0.12, P=0.005). Also mean EQ VAS was higher with alteplase than with placebo (72.6 vs. 64.9), with an adjusted mean difference of 7.6 (95% CI 3.9-11.8, P<0.001). 85% of the total treatment effect of alteplase on the EQ-5D index was mediated via the mRS score, while there was no significant direct effect. In contrast, the treatment effect on the EQ VAS was mainly via the direct pathway (60%), whereas 40% was mediated by the mRS.

Discussion: Assessment of patient-reported outcome measures reveals a potential benefit of intravenous alteplase for HRQoL beyond improvement of functional outcome.

Clinical Trial Registration: ClinicalTrials.gov number, NCT01525290; EudraCT number, 2011- 005906-32.

INTRODUCTION

Stroke is a major cause of disability and loss of disability-adjusted life years (DALYs) worldwide with an increasing societal burden despite improvements in prevention and treatment.[1, 2] At the individual level, stroke can affect multiple health domains with significant impairment in functional status, well-being, and quality of life (QoL).[3, 4] Trials of acute stroke treatment have largely focused on the assessment of functional outcome to define efficacy of treatment, most frequently using the modified Rankin Scale (mRS). The mRS relies on the assessment by a trained investigator and is based on evaluation of objective impairment of function, e.g., independency in daily activities and mobility, while more subjective symptoms

such as pain, depression, but also social interaction and cognitive deficits, which are known to play an important role for patients' QoL, are not explicitly covered. Recent studies have shown that depressive symptoms and impaired health-related QoL (HRQoL) are observed in a substantial proportion of stroke patients and go beyond the impairments measured by the mRS.[5]

In recent years, there has been a movement towards patient-centered value-based health care[6], which has also influenced the assessment of stroke outcome. A consensus among stroke survivors, caregivers, and health professionals, has identified a patient-centered approach to stroke research as a priority area.[7] Likewise, patient-reported outcome measures (PROMs) are a recommendation and target of the 2030 action plan for Europe by the European Stroke Organization (ESO).[8]

Simple and standardized tools for assessment of self-reported HRQoL have been validated and used in stroke research, e.g., the EuroQol five-dimensional questionnaire (EQ-5D), being a short, standardized instrument for measuring generic health status and HRQoL.[9, 10]

Thrombolysis using intravenous alteplase is standard of care in acute ischemic stroke treatment and has a strong effect on functional independence after stroke.[11] Only limited data are available on the effect of intravenous alteplase on self-reported HRQoL beyond functional disability after stroke. The aim of our study was to analyze the effect of intravenous alteplase on HRQoL after stroke, and to determine whether this effect extends beyond improvement in functional outcome. To this end, we used data from the randomized controlled WAKE-UP trial of MRI-guided intravenous alteplase in unknown onset stroke, which involved the systematic evaluation of self-reported HRQoL at 90 days after stroke together with the assessment of functional outcome.

METHODS

Study design

In this post-hoc analysis, we reviewed clinical data and outcome measures of all patients randomized in the WAKE-UP trial. WAKE-UP was a multicenter, randomized, double-blind, placebo-controlled clinical trial to study the efficacy and safety of intravenous thrombolysis with alteplase in patients with an acute stroke of unknown onset time, guided by MRI. Inclusion criteria comprised the mismatch between an acute ischemic lesion visible on diffusion-weighted imaging (DWI) but with no corresponding marked parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) as a surrogate marker of lesion age, indicating that the stroke onset most likely occurred within 4.5 hours.[12]

For this analysis, we included patients with available data on HRQoL and functional outcome.

Outcome measures

Outcome was assessed at 90 days after stroke. HRQoL was measured using the EQ-5D-3L instrument in stroke survivors.[9, 10] It consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises 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. A unique health state is defined by combining one level from each of the five dimensions. Based on patients' responses, a unique EQ-5D index can be calculated based on valuations for all health states which have been generated for different populations.[13] Here, we used the valuation set based on a representative population from the UK. The resulting EQ-5D index ranges from -0.594 to 1 (where 1 represents perfect health, 0 represents a state equivalent to death, and negative values represent states deemed worse than death). The EQ VAS records the patient's self-rated health on a visual analogue scale from 0 to 100, where the endpoints are labelled 'Worst imaginable health state' (=0) and 'Best imaginable health state' (=100).

Functional outcome was assessed by the mRS. Information on EQ-5D was collected from the patients themselves. If necessary, e.g., due to severe paresis, support by proxies or staff in completing the questionnaire was allowed. Proxies were not asked to respond on behalf of the patient.

Statistical analysis

Baseline data are reported as absolute and relative frequencies, mean ± standard deviation (SD), or median with interquartile range (IQR), depending on distributional properties of the data. Subgroups are compared according to the descriptive statistics above using Fishers exact test, t-test or Wilcoxon rank-sum test.

Statistical analysis of the treatment effect of alteplase on QoL was performed in the intention-to-treat population for all stroke survivors with available information for the composite endpoint EQ-5D index and EQ VAS. The effect of treatment on either EQ-5D index or EQ VAS was estimated using multiple linear regression models adjusted for the randomization stratification factors age (≤60 vs >60) and National Institutes of Health Stroke Scale (NIHSS; ≤10 vs >10) at baseline, as in the analysis of the primary endpoint of the WAKE-UP trial. For both models the adjusted mean differences and standardized adjusted mean differences with bias-corrected bootstrap (1000 replication) 95% confidence intervals ($CI_{BC\ boot}$)[14] were calculated.

Furthermore, for both outcome variables a causal mediation analysis using parametric regression models was performed to decompose the total effect (TE) into a natural direct effect (NDE) and natural indirect effect via a mediator (NIE). The exposure in the mediation analysis was treatment with alteplase, and the mediator functional outcome assessed by the mRS score at 90 days. Four assumptions are required to obtain valid estimates of the NDE and NIE. Given the measured covariates C[15]:

(1) there are no unmeasured exposure-outcome confounders;

(2) there are no unmeasured mediator-outcome confounders;

(3) there are no unmeasured exposure-mediator confounders;

(4) there is no effect of exposure that confounds the mediator-outcome relationship.

In a randomized controlled trial the assumptions (1) to (3) are satisfied by random allocation of the treatment variable. To satisfy the assumption (4) the exposure-mediator interaction was included in the mediation analyses. If no relevant interaction between the effects of the exposure and the mediator on the outcome was observed, this interaction term was rejected. The randomization strata covariates age and NIHSS were included as linear (continuous) factors for better control of potential confounding. In addition to these factors, sex was included as covariate in all mediation analyses.

The estimated effects of the mediation analyses were visualized with bias-corrected bootstrap (1000 replications) 95% $CI_{BC\ boot}$ as well as the proportion mediated (=NIE/TE). Furthermore, the coefficients of the parametric regression models with corresponding 95% CI were reported.

To enable comparability of the mediated effects all analyses were additionally conducted for the standardized outcome variables.

All analyses represent available case analyses and were performed using Stata software (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC) and the package rwrmed.[16]

Standard protocol approvals, registrations, and patient consents

For each study site, the competent authorities and the corresponding ethics committee approved the trial. Written informed consent was obtained from patients or their legal representatives according to national and local regulations. There was an exception from explicit informed consent in emergency circumstances in some countries. The WAKE-UP

study was pre-registered (ClinicalTrials.gov number, NCT01525290; EudraCT number, 2011-005906-32).

Data availability statement

The full trial protocol and the statistical analysis plan of WAKE-UP have already been published along with the main trial publication.[12] Individual patients' data, after de-identification, will be shared with the Virtual International Stroke Trials Archive (VISTA) and be accessible for researchers who provide a methodologically sound proposal according to the VISTA rules (http://www.virtualtrialsarchives.org/vista/).

RESULTS

Patient characteristics

Of 503 patients enrolled, 13 (2.6%) died within the observation period. Among the surviving 490 patients, the EQ-5D descriptive system and index were available for 452 (92.2%). Of these, 226 (50%) were assigned to treatment with alteplase and 226 (50%) to placebo. A flowchart is shown in Figure 1. Mean age was 64.9 (SD 11.5), 160 (35.4%) were female, and median NIHSS score was 5 (IQR 4-9). There were no significant differences in clinical characteristics between patients with and without available EQ-5D data (Table 1). The EQ VAS was available in 438 of the 452 (96.9%) patients.

Effect of intravenous alteplase on EQ-5D index and EQ VAS

Mean EQ-5D index at 90 days after stroke was higher in patients randomized to treatment with alteplase as compared to placebo (0.75 vs. 0.67) with an adjusted mean difference of 0.07 (95% $CI_{BC\ boot}$ 0.02-0.12, P=0.005, Table 2). The distribution of individual EQ-5D

subscore levels revealed a consistent pattern of numerically lower rates of “some problems” and “extreme problems” in the alteplase group for all five subscores (Figure 2A to E). Mean EQ VAS was also higher with alteplase than with placebo (72.6 vs. 64.9) with an adjusted mean difference of 7.6 (95% $CI_{BC\ boot}$ 3.9-11.8, P<0.001).

Mediation analysis

The results of the mediation analysis are shown in Figure 3. Treatment with alteplase had a significant total effect on the EQ-5D index (standardized TE=0.22, 95% $CI_{BC\ boot}$ 0.07-0.38, P=0.006). The effect was mediated by the mRS score at 90 days as shown by a significant NIE (standardized NIE=0.19, 95% $CI_{BC\ boot}$ 0.10-0.29, P<0.001), whereas the NDE was not significant (standardized NDE=0.03, 95% $CI_{BC\ boot}$ -0.11-0.16, P=0.6). In this model, 85% of the treatment effect of alteplase on the EQ-5D index was mediated by the mRS score at 90 days (Figure 3C). In a sensitivity analysis restricted to patients with an available EQ VAS, the proportion of the treatment effect of alteplase on the EQ-5D index mediated by the mRS score was 83%. In a further sensitivity analysis, all deceased patients were assigned an EQ-5D index of zero. In this analysis, the standardized NIE was 0.12 (0.02-0.21), and the proportion of the treatment effect of alteplase on the EQ-5D index mediated by the mRS score was 78%.

Results for the EQ VAS were different. The total effect of treatment with alteplase on the EQ VAS was significant (standardized TE=0.35, 95% $CI_{BC\ boot}$ 0.17-0.52, P<0.001). However, only 40% of the treatment effect of alteplase was mediated by the mRS score at 90 days (standardized NIE=0.14, 95% $CI_{BC\ boot}$ 0.07-0.24, P=0.001), while 60% was via the direct path (standardized NDE=0.21, 95% $CI_{BC\ boot}$ 0.04-0.37, P=0.012). In all mediation analyses, no relevant exposure-mediator interaction was observed.

DISCUSSION

In this post-hoc analysis of the WAKE-UP trial, treatment with intravenous alteplase was associated with better self-reported HRQoL measured by the EQ-5D at 90 days after stroke as compared to placebo. The beneficial effect of alteplase was observed both for the EQ-5D index and the EQ VAS indicating a benefit across a wide range of domains of HRQoL. The effect of alteplase on the EQ VAS was largely independent of the effect on functional outcome, thus indicating a beneficial effect of intravenous alteplase on HRQoL beyond the known association of alteplase with better functional outcome of stroke as captured by the mRS.

Intravenous thrombolysis has been standard of care for acute ischemic stroke for more than two decades, and several trials have demonstrated that alteplase improves functional outcome of stroke[12, 17-20]. In contrast, reports on the effect of alteplase on HRQoL in randomized controlled trials are largely lacking. IST-3 was the only trial documenting that intravenous alteplase leads to improvement in HRQoL. At 18 months, treatment with alteplase was associated with a higher EQ index, but no significant difference in the EQ VAS score.[21] In line with the results from IST-3, the first main finding of our study was a higher EQ-5D index in patients treated with alteplase. In WAKE-UP, alteplase also exerted a beneficial effect on EQ VAS, which provides a subjective assessment of the current health state on a visual analogue scale. The different patterns for EQ-5D index and EQ VAS in both studies underline that these two metrics reflect different and complementary aspects of QoL.

The second main finding of our study was the fact that the beneficial effect of alteplase on self-reported QoL assessed by the EQ VAS was only partly mediated by the effect on functional outcome but to a larger extent independent of the association of alteplase and mRS at 90 days. This finding is novel and of clinical importance for two reasons. First, it proves that intravenous alteplase in the rigorous setting of a randomized controlled trial has beneficial effects on a wide range of outcomes including more subjective measures of self-

reported HRQoL not captured in the well-documented effect on functional outcome assessed by the mRS. Second, it demonstrates that the use of patient-reported outcome measures (PROMSs) has a clear additional value to the established assessment using outcome rating scales in stroke by capturing a treatment effect independent from the effect on functional outcome. These results further corroborate the notion that EQ-5D index and EQ VAS cover different aspects of QoL, as previously reported in a mediation analysis involving EQ-5D data in a different context.[22] In our analysis, in contrast to EQ VAS, the largest part of the effect of alteplase on the EQ-5D index was mediated by the mRS score at 90 days. This is plausible given the fact that three of the five dimensions that inform the EQ-5D index refer to activities (mobility, self-care, usual activities) that also determine the assessment of functional outcome by the mRS. This finding is also consistent with the fact that the mRS, although not considered a typical PROM, relies on information provided by patients or caregivers to assess functional outcome.

From a more general perspective, these results add to the expansion of healthcare towards a value-based framework with strong emphasis on the use of PROMs to estimate the value of individual treatments.[23] This patient-centered approach provides opportunities for performance improvement at an individual patient level in clinical practice, but also for comparing treatment approaches or benchmarking across healthcare providers.[24] PROMs have been used to assess QoL after stroke in patients treated in an outpatient clinic[3], and to evaluate outcome of acute stroke patients in clinical practice.[25] These assessments have confirmed the additional value of PROMs for stroke outcome evaluation, e.g., by revealing high rates of impairment in mental domains not captured by classical outcome scales,[25] identifying patient characteristics associated with persistent impairments,[26] or the predictive value of PROMs for new hospital admissions.[27]

Our results confirm that PROMs capture significant and clinically relevant effects of acute reperfusion treatment. Similar observations have been made for stroke thrombectomy, which

improved HRQoL assessed by the EQ-5D across all dimensions in the randomized ESCAPE[28] and REVASCAT[29] trials. The dispatch of mobile stroke units, compared with conventional ambulances, was also associated with improved HRQoL assessed by the EQ-5D total score and the EQ VAS.[30] The association of the EQ-5D index with functional outcome assessed by the mRS, as reflected by the mediation effect of mRS on EQ-5D index in our analysis, is consistent with previous observations.[31]

This is a post-hoc analysis of secondary outcomes from a randomized controlled trial, hence findings must be interpreted with caution. Results may also be biased by missing data, although the rate of missing EQ-5D index values for patients with known survival status at 90 days was only 7% (32 of 490). As the study population mainly suffered from mild to moderate strokes as reflected by a median NIHSS of 5, it remains to be determined whether our results can be generalized to patients with more severe strokes. Our finding, that large parts of the effect of treatment on QoL are mediated by functional outcome may be linked to applying the EQ-5D for assessment of QoL. Although the EQ-5D has clear advantages for the use in a clinical trial, as it is short, available in many languages and well established, it is also quite basic and does not cover as many domains of QoL as other more refined instruments which might yield different insights. In general, PROMs have the limitation that they rely on patients being able and willing to provide information. Severely disabled stroke patients and patients with significant impairment of speech or cognition, i.e., patients who are not capable of completing questionnaires of responding to questions themselves, are left out of the analysis. This may limit the informative value of PROMs in populations of more severely affected stroke patients. On the other hand, PROMs may be of special value in stroke survivors with only mild to moderate disability, in whom other complaints beyond functional disability may play a greater role regarding the subjective impairment of QoL.

To summarize, this analysis of the randomized controlled WAKE-UP trial demonstrates that intravenous alteplase has a beneficial effect on self-reported HRQoL measured by the EQ-5D.

The effect of intravenous alteplase on subjective unstructured assessment of the current health state by the EQ VAS goes beyond the improvement of functional outcome. These findings indicate the added value of PROMs for assessment of stroke treatment.

REFERENCES

1. *GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:439-458.*

2. *Feigin VL, Norrving B, Mensah GA. Global Burden of Stroke. Circ Res 2017;120:439-448.*

3. *Katzan IL, Thompson NR, Uchino K, Lapin B. The most affected health domains after ischemic stroke. Neurology 2018;90:e1364-e1371.*

4. *Rimmele DL, Lebherz L, Frese M, et al. Outcome evaluation by patient reported outcome measures in stroke clinical practice (EPOS) protocol for a prospective observation and implementation study. Neurol Res Pract 2019;1:28.*

5. *Konigsberg A, Sehner S, Arlt S, et al. Effect of intravenous alteplase on post-stroke depression in the WAKE UP trial. Eur J Neurol 2021;28:2017-2025.*

6. *Porter ME. What is value in health care? N Engl J Med 2010;363:2477-2481.*

7. *Salinas J, Sprinkhuizen SM, Ackerson T, et al. An International Standard Set of Patient-Centered Outcome Measures After Stroke. Stroke 2016;47:180-186.*

8. *Norrving B, Barrick J, Davalos A, et al. Action Plan for Stroke in Europe 2018-2030. Eur Stroke J 2018;3:309-336.*

9. *EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208.*

10. *Rabin R, Gudex C, Selai C, Herdman M. From translation to version management: a history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. Value Health 2014;17:70-76.*

11. *Lees KR, Emberson J, Blackwell L, et al. Effects of Alteplase for Acute Stroke on the Distribution of Functional Outcomes: A Pooled Analysis of 9 Trials. Stroke 2016;47:2373-2379.*

12. *Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. N Engl J Med 2018;379:611-622.*

13. *Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;35:1095-1108.*

14. *Mackinnon DP, Lockwood CM, Williams J. Confidence Limits for the Indirect Effect: Distribution of the Product and Resampling Methods. Multivariate Behav Res 2004;39:99.*

15. *VanderWeele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Statistics and Its Interface 2009;2:457-468.*

16. *Linden A, Huber C, Wodtke GT. A regression-with-residuals method for analyzing causal mediation: The rwrmed package. The Stata Journal 2021;21:559-574.*

17. *National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587.*

18. *Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-1329.*

19. *Ma H, Campbell BCV, Parsons MW, et al. Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke. N Engl J Med 2019;380:1795-1803.*

20. *Thomalla G, Boutitie F, Ma H, et al. Intravenous alteplase for stroke with unknown time of onset guided by advanced imaging: systematic review and meta-analysis of individual patient data. Lancet 2020;396:1574-1584.*

21. *IST-3 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;12:768-776.*

22. *Gottschalk S, Konig HH, Schwenk M, et al. Mediating factors on the association between fear of falling and health-related quality of life in community-dwelling German older people: a cross-sectional study. BMC Geriatr 2020;20:401.*

23. *Willke RJ, Burke LB, Erickson P. Measuring treatment impact: a review of patient-reported outcomes and other efficacy endpoints in approved product labels. Control Clin Trials 2004;25:535-552.*

24. *Porter ME, Teisberg EO. Redefining competition in health care. Harv Bus Rev 2004;82:64-76, 136.*

25. *Rimmele DL, Lebherz L, Frese M, et al. Health-related quality of life 90 days after stroke assessed by the International Consortium for Health Outcome Measurement standard set. Eur J Neurol 2020;27:2508-2516.*

26. *Rimmele DL, Schrage T, Lebherz L, et al. Profiles of patients' self-reported health after acute stroke. Neurol Res Pract 2021;3:43.*

27. *Katzan IL, Thompson N, Schuster A, Wisco D, Lapin B. Patient-Reported Outcomes Predict Future Emergency Department Visits and Hospital Admissions in Patients With Stroke. J Am Heart Assoc 2021;10:e018794.*

28. *Joundi RA, Rebchuk AD, Field TS, et al. Health-Related Quality of Life Among Patients With Acute Ischemic Stroke and Large Vessel Occlusion in the ESCAPE Trial. Stroke 2021;52:1636-1642.*

29. *Davalos A, Cobo E, Molina CA, et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (REVASCAT): 1-year follow-up of a randomised open-label trial. Lancet Neurol 2017;16:369-376.*

30. *Ebinger M, Siegerink B, Kunz A, et al. Association Between Dispatch of Mobile Stroke Units and Functional Outcomes Among Patients With Acute Ischemic Stroke in Berlin. JAMA 2021;325:454-466.*

31. *Katzan IL, Thompson NR, Lapin B, Uchino K. Added Value of Patient-Reported Outcome Measures in Stroke Clinical Practice. J Am Heart Assoc 2017;6.*

FIGURE LEGENDS

Figure 1. Study flow chart.

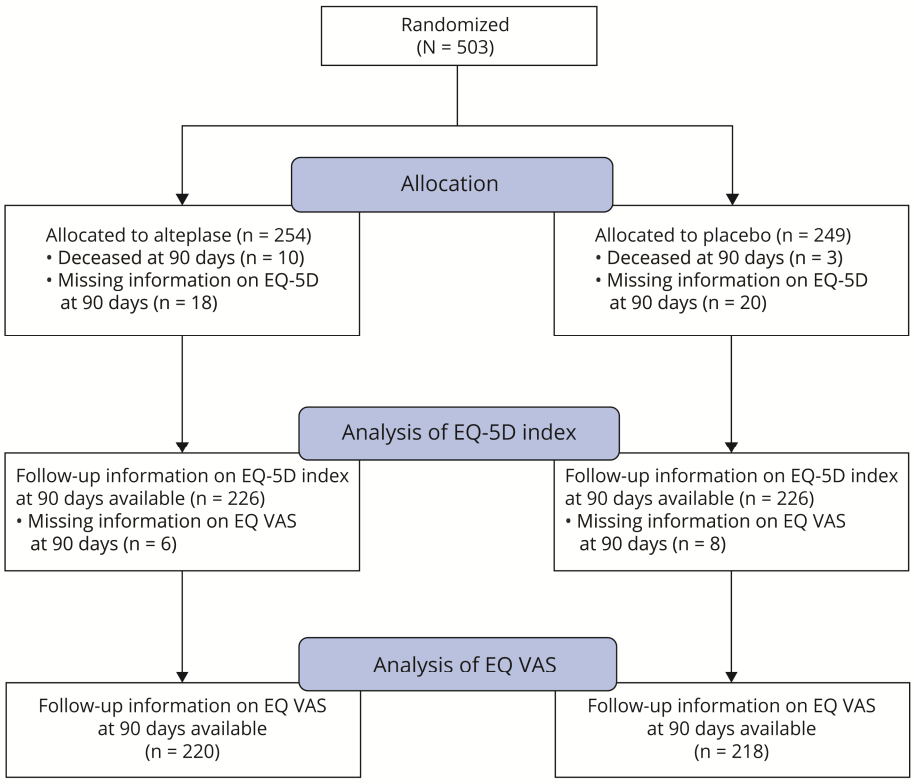


Figure 2. Distribution of EQ-5D descriptive system subscore levels. In the alteplase group numerically lower rates of “some problems” and “extreme problems” were reported.

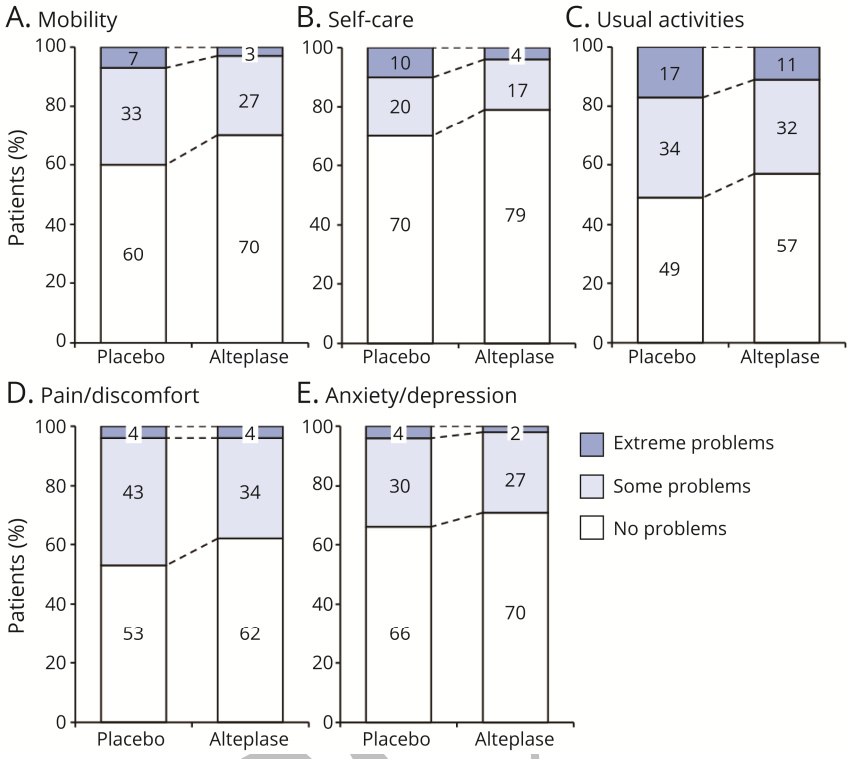
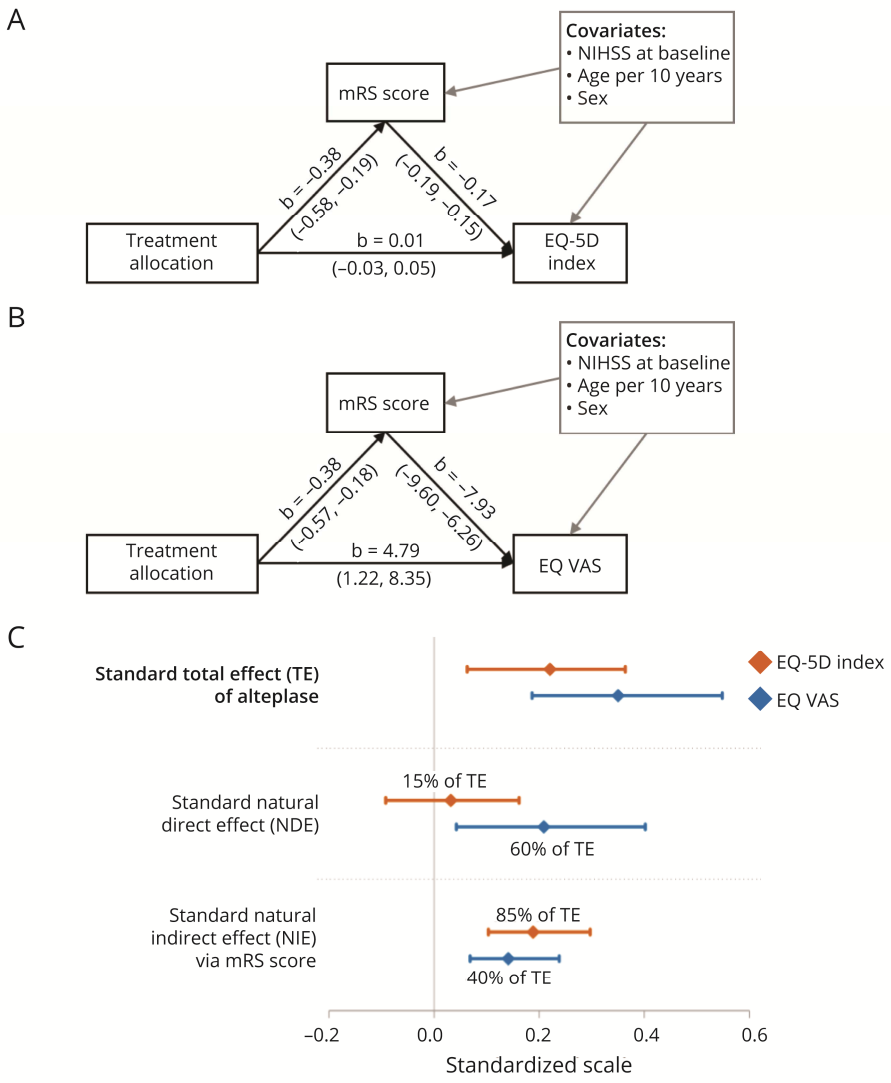


Figure 3. Mediation analysis of the effect of thrombolysis with alteplase on EQ-5D outcome measures through functional outcome. Schematic representation of mediation analyses of the exposure alteplase directly and via the mediator mRS score at 90 days on the original scales of A) EQ-5D index and B) EQ VAS; numbers above the arrows indicate regression coefficients with 95% CI; C) mediated proportion, direct and indirect effects with bias-corrected bootstrap 95% CI of mediation analyses on the standardized scales of EQ-5D index and EQ VAS.



TABLES

Table 1. Demographic and clinical characteristics of patients at baseline.

Variable	Patients with EQ-5D n=452	Patients without EQ-5D n=38	P Value	Dead patients n=13
Age, mean (SD), years	64.9 (11.5)	65.6 (12.3)	0.73	74.4 (6.4)
Female, n (%)	160/452 (35.4)	13/38 (34.2)	1.0	5/13 (38.5)
Medical history or risk factors, n/N (%)				
Arterial hypertension	237/449 (52.8)	22/38 (57.9)	0.61	7/13 (53.8)
Diabetes mellitus	72/447 (16.1)	9/37 (24.3)	0.25	1/13 (38.5)
Hypercholesterolemia	163/432 (37.7)	9/37 (24.3)	0.11	6/12 (50.0)
Atrial fibrillation	52/444 (11.7)	3/38 (7.9)	0.60	4/13 (30.8)
History of ischemic stroke	62/452 (13.7)	4/37 (10.8)	0.80	2/13 (15.4)
National Institute of Health Stroke Scale score, median (IQR)	5.0 (4.0-9.0)	6.0 (4.0-10.0)	0.46	10.0 (7.0-15.0)
Diffusion-weighted imaging lesion volume at baseline, median (IQR), mL	2.2 (0.7-8.2)	2.6 (1.0-9.6)	0.67	7.0 (2.9-17.7)
Time from symptom recognition to treatment initiation, median (IQR), min	185 (150-230)	200 (152-240)	0.53	217 (168-248)
Treatment with Alteplase, n (%)	226/452 (50)	18/38 (47.4%)	0.87	10/13 (76.9%)

EQ-5D denotes EuroQol–5 Dimension instrument for measuring quality of life, SD standard deviation, IQR interquartile range.

Table 2. Treatment effect of alteplase on quality of life.

Outcome	Alteplase Group	Placebo Group	Adjusted Mean Difference (95% $CI_{BC\ boot}$) ‡	Standardized Adjusted Mean Difference (95% $CI_{BC\ boot}$) ‡	P Value
Mean EQ-5D Index at 90 days (SD) *	0.75 (0.30) (n=226)	0.67 (0.36) (n=226)	0.07 (0.02-0.12)	0.22 (0.06-0.37)	0.005
Mean EQ VAS at 90 days (SD) ¶§	72.6 (19.7) (n=220)	64.9 (23.8) (n=218)	7.6 (3.9-11.8)	0.34 (0.17-0.51)	<0.001

EQ-5D denotes EuroQol–5 Dimension instrument for measuring quality of life, SD standard deviation, CI confidence interval, VAS visual analogue scale.

* Scores on the EQ-5D index range from -0.594 to 1 with higher values indicating a better quality of life.

¶ Scores on the EQ VAS range from 0 (indicating the worst imaginable health state) to 100 (indicating the best imaginable health state).

§ Data on EQ-5D VAS at 90 days were missing for 6 patients in the alteplase and 8 in the placebo group.

‡ Mean differences were adjusted for the randomization stratification factors (i.e., age groups and National Institute of Health Stroke Scale score groups).

Patient-Reported Quality of Life After Intravenous Alteplase for Stroke in the WAKE-UP Trial

Märit Jensen, Susanne Sehner, Bastian Cheng, et al.

Neurology published online October 27, 2022
DOI 10.1212/WNL.0000000000201375