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

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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. 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. 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. 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$_{\text{BC boot}}$ 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.\(^\text{16}\)

**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. 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} 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\textsubscript{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\textsubscript{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\textsubscript{BC boot} 0.10-0.29, P<0.001), whereas the NDE was not significant (standardized NDE=0.03, 95% CI\textsubscript{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\textsubscript{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\textsubscript{BC boot} 0.07-0.24, P=0.001), while 60% was via the direct path (standardized NDE=0.21, 95% CI\textsubscript{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. 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. 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. 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. 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. PROMs have been used to assess QoL after stroke in patients treated in an outpatient clinic, and to evaluate outcome of acute stroke patients in clinical practice. 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, identifying patient characteristics associated with persistent impairments, or the predictive value of PROMs for new hospital admissions.

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\textsuperscript{28} and REVASCAT\textsuperscript{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.\textsuperscript{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.\textsuperscript{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


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

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

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.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Alteplase Group</th>
<th>Placebo Group</th>
<th>Adjusted Mean Difference (95% CI&lt;sub&gt;boot&lt;/sub&gt;) ‡</th>
<th>Standardized Adjusted Mean Difference (95% CI&lt;sub&gt;boot&lt;/sub&gt;) ‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean EQ-5D Index at 90 days (SD)</td>
<td>0.75 (0.30)</td>
<td>0.67 (0.36)</td>
<td>0.07 (0.02-0.12)</td>
<td>0.22 (0.06-0.37)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean EQ VAS at 90 days (SD) ¶§</td>
<td>72.6 (19.7)</td>
<td>64.9 (23.8)</td>
<td>7.6 (3.9-11.8)</td>
<td>0.34 (1.17-0.51)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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).

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