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Effect of IV Thrombolysis With Alteplase in Patients With Vessel Occlusion in the WAKE-UP Trial

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Abstract

Background and Objectives

Data from randomized trials on the treatment effect of pure thrombolysis in patients with vessel occlusion are lacking. We examined data from a corresponding subsample of patients from the multicenter, randomized, placebo-controlled WAKE-UP trial to determine whether MRI-guided IV thrombolysis with alteplase in unknown-onset ischemic stroke benefits patients presenting with vessel occlusion.

Methods

Patients with an acute ischemic lesion visible on MRI diffusion-weighted imaging but no marked parenchymal hyperintensity on fluid-attenuated inversion recovery images were randomized to treatment with IV alteplase or placebo. The primary end point was a favorable outcome defined by a modified Rankin Scale score of 0–1 at 90 days after stroke. We investigated the interaction between vessel status and treatment effect using an unconditional logistic regression model. Treatment effects (adjusted odds ratio [aOR]) and their 95% CI were compared in patients with and without any vessel occlusion (AVO) and large vessel occlusion (LVO).

Results

185 patients (mean age 64.5 years, 46% female, median NIH Stroke Scale score 9, median time between last seen well and MRI 10.26 hours) received treatment and presented with an occlusion. 98 (20%) had LVO (defined as occlusion of the internal carotid artery, middle cerebral artery trunk, or combination). A favorable outcome was observed in 30 of 94 patients with AVO (31.9%) in the alteplase group and in 18 of 91 (19.8%) in the placebo group (aOR 2.04, 95% CI 1.00–4.18). In the subgroup of patients with LVO, a favorable outcome was observed in 16 of 53 (30.2%) in the alteplase group and in 7 of 44 (15.9%) in

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Glossary

aOR = adjusted OR; **AVO** = any vessel occlusion; **DWI** = diffusion-weighted imaging; **EQ-5D** = EuroQol 5-Dimensions; **FLAIR** = fluid-attenuated inversion recovery; **ICA** = internal carotid artery; **IQR** = interquartile range; **LVO** = large vessel occlusion; **MRA** = MR angiography; **MCA** = middle cerebral artery; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PH-2** = parenchymal hemorrhage type 2; **PV** = patent vessel; **SICH** = symptomatic intracerebral hemorrhage; **SITS-MOST** = Safe Implementation of Thrombolysis in Stroke-Monitoring Study; **TIMI** = Thrombolysis in Myocardial Infarction.

the placebo group (aOR 2.08, 95% CI 0.71–6.10). Treatment with alteplase was associated with higher odds of favorable outcomes with no heterogeneity of treatment effect between patients with AVO and patent vessel ($p = 0.56$), or between patients with and without LVO ($p = 0.69$).

Discussion

Although the WAKE-UP study was not powered to demonstrate treatment efficacy in patient subpopulations, this subgroup analysis points to a benefit of MRI-guided thrombolysis in patients with unknown-onset ischemic stroke, independent of vessel occlusion.

Clinical Trial Registration

Registered at ClinicalTrials.gov with unique identifier NCT01525290 (clinicaltrials.gov/study/NCT01525290). The study was first posted on February 2, 2012; the first patient was enrolled on September 24, 2012.

Classification of Evidence

This study provides Class II evidence that for patients with unknown-onset ischemic stroke with AVO, MRI-guided treatment with IV tissue plasminogen activator improves outcomes.

Introduction

IV alteplase is the standard of care for acute ischemic stroke independent of etiology, localization, or vessel status within 4.5 hours of symptom onset.[1] However, there is an ongoing discussion whether IV thrombolysis (IV tPA) is also sufficiently effective in patients with thrombi leading to occlusion of large intracranial arteries.[2] The multicenter randomized clinical trial (DIRECT-MT)[3] published in 2020 found that endovascular thrombectomy alone was noninferior (regarding functional outcomes) to endovascular thrombectomy preceded by IV alteplase. However, a meta-analysis of 6 randomized trials published in September of 2023 in Lancet was unable to replicate this result.[4] Data from randomized trials on the treatment effect of only thrombolysis (not as bridging IV tPA) in patients with vessel occlusion are still lacking.

When the WAKE-UP trial started in September 2012, there was yet no evidence for the benefit of MT for acute stroke available from randomized controlled trials, and in most of the stroke centers across Europe, endovascular stroke treatment was not the standard of care. Planned endovascular stroke treatment was an exclusion criterion for WAKE-UP; therefore, in this predefined subgroup analysis, we are able to test the hypothesis that MRI-guided IV thrombolysis with alteplase in unknown-onset ischemic stroke would be safe and efficient in patients presenting with vessel occlusion on MR angiography (MRA).

Methods

General Study Information

The WAKE-UP trial[5] was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled clinical trial with an allocation ratio of 1:1, which provided evidence of clinical benefit of MRI-guided treatment with IV alteplase in patients with acute stroke with an unknown time of symptom onset. Patient selection was based on the replacement of a rigid time window with an imaging pattern identifying early acute ischemic lesions on diffusion-weighted imaging (DWI) at a stage where no relevant vasogenic edema exists (reflected by no marked parenchymal hyperintensity on fluid-attenuated inversion recovery [FLAIR] images), the so-called DWI-FLAIR mismatch.[6,7] All investigators received a web-based training to enable harmonized implementation of the DWI-FLAIR mismatch concept.[8] Patients were randomized in WAKE-UP irrespective of infarct location, vessel status, or perfusion measures, and time-of-flight MRA was performed as part of the study protocol.

Primary Research Question

Does treatment with intravenously administered alteplase improve functional outcomes in patients with acute ischemic

stroke of unknown onset and intracranial vessel occlusion? The classification of level of evidence is Class II.

Standard Protocol Approvals, Registrations, and Patient Consents

The study received approval from national competent authorities and ethics committees in all participating countries. WAKE-UP was registered at ClinicalTrials.gov, unique identifier: NCT01525290, and enrolled patients between September 2012 and June 2017. A complete trial methodology was previously published.[5] A detailed trial protocol has been previously published.[9]

Definition of Subgroups

During the course of the trial, 2 experienced neuroradiologists read MRA from all visits, which covered the circle of Willis and were acquired without contrast media. Neuroradiologists were blinded to clinical information, other MR imaging contrasts, and time point of the examination (i.e., baseline or follow-up). MRA results were captured in the study database before database lock and unblinding. For this preplanned subgroup analysis, we dichotomized all patients with MRA of diagnostic quality according to vessel status. The any vessel occlusion (AVO) group included all patients with a Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1 in any intracranial artery at baseline MRA while the patent vessel (PV) group consisted of all patients without an occlusion (TIMI score 2 or 3) at baseline. The large vessel occlusion (LVO) group consisted of a subset of patients with AVO who had an occlusion of the intracranial internal carotid artery (ICA), middle cerebral artery (MCA) trunk, or combination of the 2.

Outcome Measures

We used the same methodology as the one used in the WAKE-UP study.[5]

Favorable clinical outcome was the primary efficacy end point defined as a score of 0 or 1 on the modified Rankin Scale (mRS) 90 days after randomization. Secondary efficacy end points included a shift analysis of the ordinal score on the mRS after 90 days. The primary safety end points were death and a composite outcome of death and dependence (defined as a score of 4–6 on the mRS after 90 days). An additional safety outcome was the incidence of symptomatic intracerebral hemorrhage (SICH) on follow-up imaging according to the definition established in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), that is, local or remote parenchymal hematoma type 2 (PH-2) on the imaging scan obtained 22–36 hours after treatment, plus neurologic deterioration of ≥4 points on the NIH Stroke Scale (NIHSS) between baseline or the lowest value within 24 hours and the value at 24 hours, or hemorrhage leading to death.[10] In addition, the rate of radiologically defined PH-2, that is, clots exceeding 30% of the infarct area and exhibiting mass effect, was evaluated on follow-up MRI 22–36 hours after randomization.

Statistical Analysis

Baseline characteristics were compared between the subgroups AVO and PV. Statistical analyses of treatment effects were performed in the intention-to-treat population with MRA of diagnostic quality available. We used the same methodology as the one used in a previous WAKE-UP substudy.[11] To investigate the interaction between vessel status and treatment effect on the primary end point, an unconditional logistic regression model was used that related the log odds of the primary outcome with the covariate of interest, the treatment group, and their interaction, adjusted for the baseline stratification parameters age and NIHSS score. The Wald chi-squared test was applied to test the interaction. Treatment effect (odds ratio [OR]) and its 95% CI were estimated for each category of vessel occlusion.

In our subpopulation of patients with AVO and LVO, the analysis of primary and secondary end points was performed as in the original trial analysis. In our study, an unconditional logistic regression analysis (estimating the OR and its 95% CI) was applied to test the main efficacy variable and the safety end points. A proportional-odds logistic regression model was fitted to assess the categorical shift in the distribution of mRS scores. All these analyses were adjusted for the stratification parameters of age and NIHSS score. Because all analyses were considered exploratory, all tests were performed with a 2-sided alpha level of 5% without correction for multiple comparisons.

Data Availability

Data not provided in the article due to space limitations may be shared (in an anonymized form) at a reasonable request and for the purpose of replicating procedures and results.

Classification of Evidence

This study provides Class II evidence that for patients with unknown-onset ischemic stroke with AVO, MRI-guided treatment with IV tissue plasminogen activator improves outcomes.

Results

Baseline Characteristics

Of 503 patients randomized in WAKE-UP, 495 had baseline MRA of diagnostic quality (98.4%), including 10 patients with a missing primary end point. AVO on screening MRA was diagnosed during a blinded central reading process in 187 of 503 patients (37.2%), 2 of whom were randomized into the recombinant tissue plasminogen activator (rtPA) group but did not receive treatment. 98 of the 187 patients presented with a LVO; of these, 6 presented with an isolated ICA occlusion, 58 an occlusion of the MCA trunk, and 34 a combined occlusion of the ICA and the MCA. The remaining 87 were divided as follows: 58 had an occlusion of an MCA branch, 18 had an occlusion of the posterior cerebral artery, 9 had occlusions of the vertebral artery (1 with bilateral vertebral artery occlusions), and 2 had an occlusion of the anterior cerebral artery. Patients with AVO had a mean age of 64.5 years, and 46% were female, compared with 65.7 years and 29.5% female in patients with PV. Patients with

Table 1 Group Comparison Between Patients With Any Vessel Occlusion and Those With Patent Vessel in Intention-To-Treat Population

	Any vessel occlusion (N = 187)	Patent vessel (N = 308)	*p* Value
Age, y, mean (SD)	64.5 (11.81)	65.7 (11.24)	0.134
Sex, male, n (%)	101 (54)	217 (70.5)	<0.001
Symptom recognition to start of treatment, h, median (IQR)	3.08 (2.45–3.83)	3.2 (2.58–3.95)	0.473
Arterial hypertension, n (%)	93 (49.7)	170 (55.2)	0.268
Diabetes mellitus, n (%)	25 (13.4)	56 (18.2)	0.302
Atrial fibrillation, n (%)	29 (15.5)	30 (9.7)	0.151
Hypercholesterolemia, n (%)	66 (35.3)	112 (36.4)	0.492
NIHSS score at baseline, median (IQR)	9 (5–15)	5 (3–7)	<0.001
NIHSS score at 7 d after stroke, median (IQR)	6 (2–13)	2 (0–3)	<0.001
Days of hospitalization, median (IQR)	10 (5–22)	5 (3–8)	<0.001
Stroke volume at baseline, mL, median (IQR)	9.1 (2.7–23.3)	1.3 (0.5–2.9)	<0.001
Stroke volume at follow-up, mL, median (IQR)	20.7 (5.2–57.2)	1.5 (0.6–4.0)	<0.001

Abbreviations: IQR = interquartile range; NIHSS = NIH Stroke Scale.
Follow-up was 22–36 hours after treatment.

AVO had more severe strokes with a median NIHSS score of 9 (interquartile range [IQR] 5–15) compared with 5 (IQR 3–7) in patients with PV ($p < 0.0001$). The mean baseline DWI lesion volume was larger in patients with AVO (15 ± 17 mL vs 3 ± 7 mL, $p < 0.001$). Prevalence of risk factors and medical history were largely comparable between groups (Table 1 for details).

No Interaction Between Vessel Status and Treatment Effect on the Primary End Point

Information on the primary end point was available for 243 patients in the alteplase group and 242 patients in the placebo group with diagnostic screening MRA (2 missing primary end points in patients with AVO and 1 in patients with LVO). Among all patients, treatment with alteplase was associated with higher odds of favorable outcomes with no heterogeneity of treatment effect between patients with AVO and patients with PV ($p = 0.56$), or patients with or without LVO ($p = 0.69$) (Figure 1). In patients with AVO, a favorable outcome was observed in 30 of 94 patients (31.9%) in the alteplase group and in 18 of 91 patients (19.8%) in the placebo group (adjusted OR [aOR] 2.04, 95% CI 1.00–4.18) (Figures 1 and 2). In the LVO group, a favorable outcome was observed in 16 of 53 patients (30.2%) with alteplase and in 7 of 44 patients (15.9%) with placebo (aOR 2.08, 95% CI 0.71–6.10) (Figure 2). If the favorable outcome was defined as a mRS score of 0–2, then 23 of 53 patients (43.4%) achieved it in the alteplase group vs 14 of 44 patients (35%) in the placebo arm (aOR 1.4, 95% CI 0.53–3.71).

Secondary Efficacy and Safety Outcomes in Patients With AVO

Of 187 patients with AVO, 91 patients (48.7%) were assigned to placebo and 96 patients (51.3%) to alteplase. Treatment groups were comparable regarding clinical characteristics (Table 2). Results of the efficacy analysis in 185 patients with available end point assessment are presented in Table 3. The distribution of the mRS scores 90 days after stroke showed a significant shift toward better outcomes in patients with AVO treated with alteplase (adjusted common OR, 1.76; 95% CI 1.04–2.98). Analysis of treatment response and global outcome scores also showed trends in favor of treatment with alteplase. Assessment of health-related quality of life using the EuroQol 5-Dimensions (EQ-5D) questionnaire revealed significantly lower values reflecting better quality of life at 90 days in patients treated with alteplase (mean difference in the total score on EQ-5D −0.68; 95% CI −1.33 to −0.05).

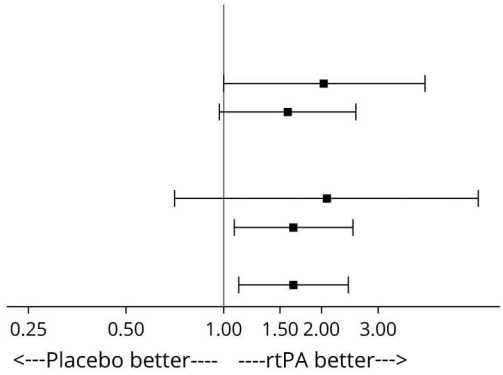
Clinical safety end points did not show significant differences between patients assigned to alteplase and those assigned to placebo. Death or dependence occurred in 22 of 96 patients (23.4%) in the alteplase group and 30 of 91 patients (33%) in the placebo group. There were 5 deaths (5.2%) in the alteplase group and 1 death (1.1%) in the placebo group. SICH occurred in 3 patients (3.1%) in the alteplase group and in no patient in the placebo group. PH-2 occurred in 7 patients (7.3%) in the alteplase group compared with none in the placebo group.

Secondary Efficacy and Safety Outcomes in Patients With LVO

The intention-to-treat cohort included 98 patients presenting with LVO. 54 patients (55.1%) were assigned to alteplase and 44 patients (44.9%) to placebo. The median NIHSS score was 12 vs 13 and the median DWI lesion volume was 9.3 vs 11.6 mL in the alteplase and placebo groups, respectively. 1 patient from the alteplase group was lost to follow-up. Table 4

Figure 1 Forest Plots Depicting the Effect of Alteplase on Favorable Outcomes in Patients With Initial Vessel Occlusion

Subgroup	Alteplase Events/N (%)		Placebo Events/N (%)		OR (95% CI)	*p* Value*
Any vessel occlusion						0.56
Yes	30/94	(31.9)	18/91	(19.8)	2.04 (1.00, 4.18)	
No	99/149	(66.4)	83/151	(55.0)	1.58 (0.97, 2.56)	
Large vessel occlusion						0.69
Yes	16/53	(30.2)	7/44	(15.9)	2.08 (0.71, 6.10)	
No	113/190	(59.5)	94/198	(47.5)	1.65 (1.08, 2.51)	
Overall	129/243	(53.1)	101/242	(41.7)	1.64 (1.11, 2.42)	



**p* Value is the test of interaction between treatment and each subgroup. OR = odds ratio.

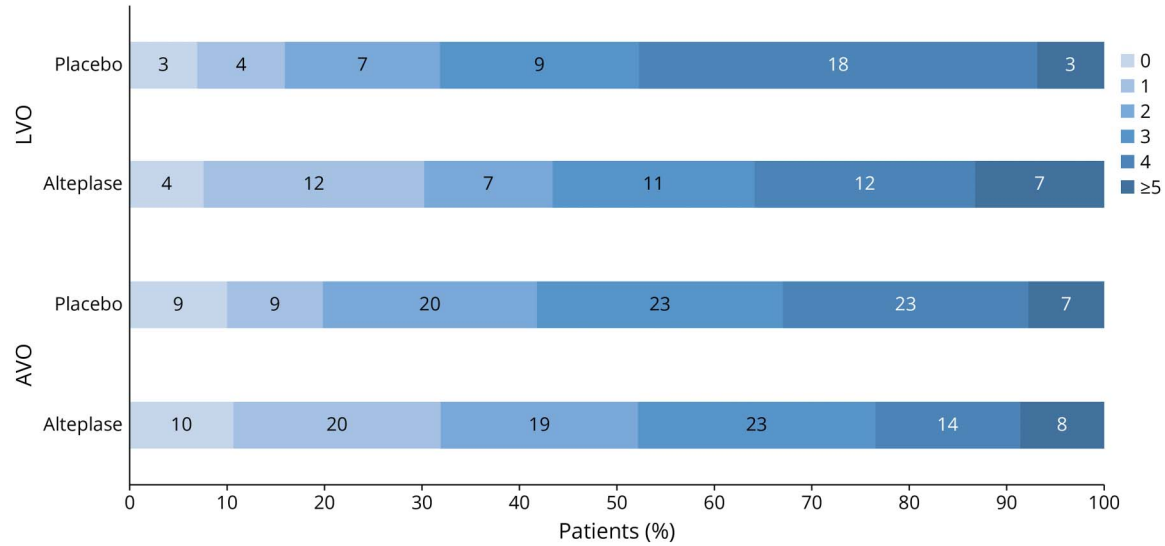
provides the results of the efficacy and safety analyses in 97 patients with available end point assessment. Information on vessel status at follow-up MRA (22–36 hours after randomization) was available for 138 of 187 patients with AVO (73.8%) and 75 of 98 patients with LVO (76.5%). A persistent vessel occlusion was observed in all patients with an isolated ICA occlusion. 15 of 58 patients with MCA occlusion (25.9%) achieved complete recanalization and 22 of 58 (37.9%) partial recanalization while in patients with a combined ICA and MCA occlusion, the rates of complete and partial recanalization were 1/34 (2.9%) and 12/34 (35.3%), respectively. When looking only at patients with an MCA trunk occlusion, some degree of recanalization (complete or partial) was achieved in 19 of 28 patients (67.9%) receiving alteplase, but also in 18 of 30 patients (60%) given placebo.

The distribution of the mRS scores 90 days after stroke showed no difference in outcomes in patients with LVO treated with alteplase compared with placebo (adjusted common OR 1.44, 95% CI 0.70–2.98). Further secondary efficacy end points did not show clear effects of treatment with alteplase. Clinical safety end points also did not show significant differences between patients assigned to alteplase and those assigned to placebo.

Discussion

The WAKE-UP trial demonstrated a clinical benefit of treatment with IV alteplase in patients with an acute ischemic stroke visible on DWI but not yet visible on FLAIR imaging.[5] In this

Figure 2 Distribution of Scores on the Modified Rankin Scale at 90 Days



AVO = any vessel occlusion; LVO = large vessel occlusion.

Table 2 Comparison Between Patients Assigned to Alteplase and Those Assigned to Placebo in the Subgroup of Patients With Any Vessel Occlusion

	Alteplase (N = 96)	Placebo (N = 91)	*p* Value
Age, y, mean (SD)	63.8 (12.5)	65.4 (11.)	0.52
Sex, male, n (%)	53 (55.2)	48 (52.7)	0.77
Symptom recognition to start of treatment, h, median (IQR)	3.14 (2.42–3.67)	3.03 (2.47–3.83)	0.72
Arterial hypertension, n (%)	48 (50.0)	45 (49.5)	1.00
Diabetes mellitus, n (%)	14 (14.6)	11 (12.1)	0.28
Atrial fibrillation, n (%)	16 (16.7)	13 (14.3)	0.71
Hypercholesterolemia, n (%)	36 (37.5)	30 (33.0)	0.50
NIHSS score at baseline, median (IQR)	8 (5–15)	9 (5–14)	0.87
NIHSS score at 7 d after stroke, median (IQR)	5 (1–12)	6 (3–14)	0.27
Days of hospitalization, median (IQR)	9.5 (5–17.5)	12 (5–24)	0.32
Stroke volume at baseline, mL, median (IQR)	8.3 (2.3–23.0)	9.9 (3.2–24.7)	0.65

Abbreviations: IQR = interquartile range; NIHSS = NIH Stroke Scale.

preplanned secondary analysis, we focused on the treatment effect and safety in a subpopulation of patients diagnosed with intracranial vessel occlusion on initial TOF MRA. We found that alteplase seemed effective in both the presence and absence of any visible intracranial vessel occlusion and that vessel occlusion did not modify the treatment effect in our cohort.

A meta-analysis on patients treated 4.5–9 hours after symptom onset or with stroke at awakening included a subgroup of 244 patients with a vessel occlusion in the M1 or M2 segment of the middle cerebral artery. In this study, the OR for favorable outcomes with alteplase was 1.74.[12] The data from our study showed comparable odds for favorable clinical

Table 3 Efficacy and Safety Outcomes for Patients With Any Vessel Occlusion

Outcome variable	Alteplase (n = 94)	Placebo (n = 91)	Effect variable[a]	Adjusted value (95% CI)	*p* Value
Favorable outcome (mRS scores 0–1), n (%)[b]	30 (31.9)	18 (19.8)	Odds ratio	2.11 (1.02, 4.37)	0.04
mRS score, median (IQR)[c]	2 (0–3)	3 (0–4)	Common odds ratio	1.76 (1.04, 2.98)	0.04
Responder analysis: treatment response at 90 d, n (%)	20 (21.3)	12 (13.2)	Odds ratio	1.93 (0.87, 4.30)	0.11
Global outcome score at 90 d			Odds ratio	1.69 (1.00, 2.87)	0.05
EQ-5D sum at 90 d, median (IQR)	3 (1–4.5)	4 (1–6)	Mean difference	−0.69 (−1.33, −0.05)	0.03
Infarct volume at 22–36 h, median (IQR)	20.1 (5.7–47.6)	21.9 (5.0–62.2)	Mean difference (log)	−0.04 (−0.50, 0.41)	0.84
Mortality at 90 d	5 (5.2)	1 (1.1)		NA	0.21[d]
Death or dependence (mRS scores 4–6) at 90 d	22 (23.4)	30 (33.0)	Common odds ratio	0.57 (0.28, 1.15)	0.12
SICH as defined in SITS-MOST[e]	3 (3.13)	0 (0)		NA	
PH-2[f]	7 (7.3)	0 (0)		NA	

Abbreviations: EQ-5D = EuroQol 5-Dimensions; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PH-2 = parenchymal hemorrhage type 2; SICH = symptomatic intracerebral hemorrhage; SITS-MOST = Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
[a] All odds ratios were adjusted for the stratification factors (age and symptom severity).
[b] mRS score was missing in 3 patients (2 of the alteplase and 1 of the placebo group).
[c] Categorical shift in the distribution of mRS scores between the 2 treatment groups.
[d] Fisher exact test.
[e] The definition of symptomatic intracranial hemorrhage according to the SITS-MOST was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22–36 hours after treatment, plus neurologic deterioration ≥4 points on the NIHSS between baseline or the lowest value within 24 hours and the value at 24 hours, or hemorrhage leading to death.
[f] PH-2 was defined as an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area.

Table 4 Efficacy and Safety Outcomes for Patients With Large Vessel Occlusion

Outcome variable	Alteplase (n = 54)	Placebo (n = 44)	Effect variable[a]	Adjusted value (95% CI)	*p* Value
Favorable outcome (mRS scores 0–1), n (%)[b]	16 (30.2)	7 (15.9)	Odds ratio	2.10 (0.73, 6.07)	0.17
mRS score, median (IQR)[c]	3 (1–4)	3 (2–4)	Common odds ratio	1.44 (0.70, 2.98)	0.33
Responder analysis: treatment response at 90 d, n (%)	11 (20.8)	5 (11.4)	Odds ratio	1.97 (0.61, 6.37)	0.26
Global outcome score at 90 d			Odds ratio	1.27 (0.57, 2.81)	0.56
EQ-5D sum at 90 d, median (IQR)	4 (1–5)	5 (2–6)	Mean difference	−0.51 (−1.42, 0.40)	0.27
Infarct volume at 22–36 h, median (IQR)	21.8 (12.5–81.0)	48.5 (15.7–64.8)	Mean difference (log)	−0.12 (−0.67, 0.42)	0.66
Mortality at 90 d	5 (9.3)	0 (0)		NA	0.06[d]
Death or dependence (mRS scores 4–6) at 90 d	19 (35.8)	21 (47.7)	Common odds ratio	0.67 (0.27, 1.65)	0.38
SICH as defined in SITS-MOST[e]	2 (3.7)	0 (0)		NA	
PH-2[f]	5 (9.3)	0 (0)		NA	

Abbreviations: EQ-5D = EuroQol 5-Dimensions; IQR = interquartile range; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PH-2 = parenchymal hemorrhage type 2; SICH = symptomatic intracerebral hemorrhage; SITS-MOST = Safe Implementation of Thrombolysis in Stroke-Monitoring Study.
[a] All odds ratios were adjusted for the stratification factors (age and symptom severity).
[b] mRS score was missing in 3 patients (2 of the alteplase and 1 of the placebo group).
[c] Categorical shift in the distribution of mRS scores between the 2 treatment groups.
[d] Fisher exact test.
[e] The definition of symptomatic intracranial hemorrhage according to the SITS-MOST was local or remote parenchymal hematoma type 2 on the imaging scan obtained 22–36 hours after treatment, plus neurologic deterioration ≥4 points on the NIHSS between baseline or the lowest value within 24 hours and the value at 24 hours, or hemorrhage leading to death.
[f] PH-2 was defined as an intracerebral hemorrhage that involved more than 30% of the infarcted area with a substantial space-occupying effect or that was remote from the original infarcted area.

outcome; however, this was not significantly different when comparing placebo with alteplase in the LVO subgroup. This could be a result of the limited sample size, but it may also be due to the limited efficacy of IV rtPA to quickly and efficiently dissolve clots large enough to block a major intracranial artery.[13] It has been shown that, in the setting of LVO, tenecteplase is associated with a higher incidence of reperfusion than alteplase[14]; however, there is still lacking evidence regarding its use in wake-up stroke.[15] Bhatia et al.[13] showed an early recanalization rate of 32% in patients with an MCA trunk occlusion and 4% with an ICA occlusion treated only with rtPA. Although we saw considerable rates of at least partial recanalization after alteplase in our patients with an MCA occlusion (68%) and even in those with a combined ICA and MCA occlusion (30.8%), we assessed follow-up vessel status late (2–3 days after therapy) and, therefore, cannot offer information as to how much of alteplase's effect was due to early unblocking of vessels. This time frame is one where spontaneous recanalization is also present,[16] as highlighted in our data where 52% of all placebo-receiving patients also showed some degree of recanalization at follow-up MRA.

Previous trials investigating alteplase against placebo in ischemic stroke did not systematically assess vessel status at screening.[17] Because intracranial LVO is strongly linked to greater clinical stroke severity, data from more severely affected patients in clinical trials that did not use imaging selection offer insight into the magnitude of treatment effect. A meta-analysis showed efficacy of alteplase with increased odds for beneficial clinical outcomes between 1.22 and 1.5 for groups of patients with NIHSS scores 5–10, 11–15, and even 16–21, as based on results including 2,533, 1,488, and 1,333 patients, respectively.[18] In contrast to these CT-based trials that are potentially diluted by patients with TIA and stroke mimics, WAKE-UP was focused on patients with proven DWI lesion. The median stroke severity in WAKE-UP patients with AVO was NIHSS score 9, and in this subgroup, alteplase doubled the likelihood for a favorable outcome with an absolute difference of 12.1%.

The favorable outcome observed in WAKE-UP patients with AVO, together with the subanalysis results in WAKE-UP patients presenting with a lacunar infarct,[19] indicates a thrombolysis benefit, which does not depend on a specific lesion pattern or vessel status.

Although there was a trend toward smaller final infarct volumes after alteplase in the LVO population, when observed for the entire AVO cohort, we did not find any appreciable difference in this parameter between the placebo and the alteplase arm. Infarct growth is possible even in circumstances of macrovascular recanalization[20,21] because it is determined by several additional factors such as the collateral status before recanalization, the timing and extent of the recanalization, successful reperfusion on the microvascular level,[20] and the severity of reperfusion injury. Therefore, any combination of these aspects may be responsible for explaining why we did not see a positive effect of alteplase compared with placebo on

lesion growth. This need not have a direct bearing on the functional outcome because this association has been shown to be imperfect and often of limited value for prediction of individual patient outcomes.[22]

In our study, we observed higher rates of SICH and parenchymal hemorrhage in the alteplase group than in the placebo group. Although this rate of SICH in our cohort of patients with AVO and LVO (3% and 4%, respectively) is higher than desirable and needs further evaluation in clinical practice, it did not exceed the values from previous randomized controlled trials.[23] The SICH rate was comparable with what was found in a recently published meta-analysis of 754 patients with wake-up stroke [24] and did not outweigh the positive effect of alteplase on the functional outcome.

A limitation of the study is that it was not powered to demonstrate treatment efficacy in patient subgroups. Exclusion of patients receiving endovascular treatment, especially after December 2014 when evidence for safe and effective endovascular recanalization was presented,[25] may have created a bias for our cohort. In addition, it is possible that some patients with a high-grade stenosis were misclassified as having an occlusion because of the flow-sensitive properties of time-of-flight angiography.

Recent work has hinted as the possibility of replacing MRI with computer tomography, because of the comparable predictive power of CT-based lesion water imaging to identify patients within the time window of thrombolysis.[26] In contrast to this method, however, the WAKE-UP trial required neither the administration of iodinated contrast agents (for CT perfusion) nor a perfusion software license and image segmentation. Avoiding additional imaging exclusion criteria (save for the DWI/FLAIR mismatch) in WAKE-UP led to an inclusion of a broad spectrum of patients with ischemic stroke. Replacing the time window by an imaging surrogate of tissue integrity was safe and efficient in patients presenting with intracranial vessel occlusion and stroke of unknown onset. Owing to its proved inferior efficacy, the use of IV tPA in isolation cannot be advocated ahead of endovascular treatment in these patients. However, our study lends additional support to the concept that, in those individuals and hospital settings where endovascular therapy is either contraindicated or not available, alteplase alone can offer sufficient safety and tangible benefit for the patient.

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Jochen B. Fiebach, MD	Center for Stroke Research Berlin, Charité-Universitätsmedizin Berlin	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Florent Boutitie, PhD	Service de Biostatistique, Hospices Civils de Lyon	Analysis or interpretation of data
Bastian Cheng, MD	Department of Neurology, University Medical Center Hamburg-Eppendorf	Major role in the acquisition of data
Tae-Hee Cho, MD	Department of Stroke Medicine, Université Claude Bernard Lyon 1, Hospices Civils de Lyon	Major role in the acquisition of data
Martin Ebinger, MD	Neurologie der Rehaklinik Medical Park Humboldtmühle	Major role in the acquisition of data

Appendix 1 *(continued)*

Name	Location	Contribution
Matthias Endres, MD	Klinik und Hochschulambulanz für Neurologie, Charité-Universitätsmedizin Berlin; Center for Stroke Research Berlin; German Center for Neurodegenerative Diseases (DZNE), partner site Berlin; German Centre for Cardiovascular Research (DZHK), partner site Berlin; German Center for Mental Health (DZPG), partner site Berlin	Major role in the acquisition of data; study concept or design
Christian Enzinger, MD, PhD	Department of Neurology, Medical University of Graz	Major role in the acquisition of data
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Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 2 Coinvestigators

Coinvestigators are listed at Neurology.org.

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