

Factors associated with early neurological improvement after intravenous alteplase alone in acute ischemic stroke

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ABSTRACT

Objective: To determine the rate of early neurological improvement (ENI) and identify factors associated with ENI in patients with acute ischemic stroke (AIS) treated with intravenous alteplase alone.

Methods: A prospective observational study of consecutive patients with AIS who received intravenous alteplase without endovascular thrombectomy at the Stroke Center, Bach Mai Hospital, from November 2024 to August 2025. ENI was defined as a reduction of ≥ 4 points in the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours compared with baseline. Multivariable logistic regression adjusted for baseline stroke severity was used to identify factors independently associated with ENI.

Results: A total of 251 patients were included (mean age 66.6 ± 11.8 years; 64.9% male; median baseline NIHSS 7 [IQR 5–9]). The mean onset-to-needle and door-to-needle times were 172 ± 51 and 44 ± 16 minutes, respectively. ENI occurred in 128 patients (51.0%; 95% CI 44.8–57.1), and its frequency increased steeply with baseline severity (6.2%, 67.2%, and 93.9% for NIHSS < 6 , 6–10, and > 10 , respectively). After adjustment, age ≥ 80 years (aOR 0.14; 95% CI 0.04–0.48; $p = 0.002$) and pre-stroke disability (modified Rankin Scale [mRS] ≥ 2 ; aOR 0.29; 95% CI 0.14–0.63; $p = 0.002$) were independently associated with lower odds of ENI. Diabetes mellitus showed a non-significant trend toward lower odds of ENI (aOR 0.43; 95% CI 0.16–1.15; $p = 0.094$). Treatment within 3 hours was associated with ENI in univariable analysis but not after adjustment for baseline severity (aOR 1.44; 95% CI 0.70–2.96; $p = 0.324$).

Conclusion: About half of the patients treated with intravenous alteplase alone achieved ENI at 24 hours. ENI depended strongly on baseline stroke severity. Very old age and pre-stroke disability were independently associated with a lower likelihood of ENI and should be considered when ENI is used for early prognostication.

Keywords: acute ischemic stroke; alteplase; early neurological improvement; intravenous thrombolysis; NIHSS.

I. INTRODUCTION

Stroke remains one of the leading causes of death and long-term disability worldwide.¹ In Vietnam, ischemic stroke accounts for approximately 77% of newly diagnosed stroke cases.²

Intravenous thrombolysis (IVT) with alteplase is recommended for eligible patients with acute ischemic stroke (AIS) within 4.5 hours of symptom onset.^{3,4} Landmark trials, including NINDS and ECASS III, demonstrated that alteplase given within this window increases the likelihood of a favorable functional outcome at 3 months.^{5,6} Tenecteplase has more recently emerged as an alternative thrombolytic agent,^{7,8} but alteplase remains widely used in clinical practice, including at our center.

After IVT, guidelines recommend close neurological monitoring during the first 24 hours, when both early neurological deterioration and early neurological improvement (ENI) may occur.^{4,9} ENI has been defined in several ways. The most widely used definition is a reduction of ≥ 4 points in the National Institutes of Health Stroke Scale (NIHSS) score at 24 hours, which has been associated with vessel recanalization and favorable functional outcome.¹⁰ Stricter definitions, such as “major neurological improvement” (a reduction of ≥ 8 points or an NIHSS score of 0-1), have also been proposed.¹¹ Across definitions, ENI is consistently associated with a modified Rankin Scale (mRS) score of 0-2 at 3 months,^{12,13} making it a practical early surrogate marker of treatment response.

Data on ENI and its determinants among Vietnamese patients treated with IVT alone remain scarce. Identifying factors associated with ENI may support early prognostication and help interpret early treatment response in routine practice. We therefore aimed to determine the

rate of ENI and to identify factors associated with ENI in patients with AIS treated with intravenous alteplase alone at the Stroke Center, Bach Mai Hospital.

II. PARTICIPANTS AND METHODS

2.1. Study design and setting

This prospective observational study was conducted at the Stroke Center, Bach Mai Hospital, from November 2024 to August 2025. All consecutive patients who met the eligibility criteria during the study period were enrolled. Data were collected prospectively using a standardized case report form at admission and at 24 hours after thrombolysis, supplemented by the medical records.

2.2. Participants

Inclusion criteria: (1) age ≥ 18 years; (2) diagnosis of AIS based on sudden-onset focal neurological deficit with confirmation by computed tomography (CT) or magnetic resonance imaging (MRI), in accordance with the updated AHA/ASA definition;¹⁴ and (3) treatment with intravenous alteplase within 4.5 hours of symptom onset without endovascular thrombectomy.

Exclusion criteria: (1) bridging endovascular thrombectomy; (2) death within 24 hours after thrombolysis, because the 24-hour NIHSS could not be assessed; and (3) refusal to participate.

2.3. Treatment and assessments

All patients were managed according to current guidelines.^{3,4} Alteplase was administered according to the institutional protocol. Vascular imaging was performed in 249 of 251 patients (CT angiography in 164 and MR angiography in 85). Large vessel occlusion (LVO) was defined as occlusion of the internal carotid artery, the M1-M2 segments of the middle cerebral artery, or the basilar artery.

The NIHSS was assessed immediately before the alteplase bolus and at 24 hours after treatment.

2.4. Variables and definitions

Primary outcome: ENI, defined as a reduction of ≥ 4 points in the NIHSS score at 24 hours compared with baseline.¹⁰

Independent variables: age, sex, hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation (known history or newly detected during hospitalization), previous stroke, pre-stroke functional status (mRS), admission glucose, systolic blood pressure, baseline NIHSS, onset-to-treatment time (OTT), door-to-needle time, alteplase dose, LVO, and stroke etiology according to the TOAST classification. Patients with two or more competing etiologies were classified as having an undetermined etiology. Baseline NIHSS was categorized as < 6 , $6-10$, and > 10 . OTT was analyzed both dichotomized at 180 minutes and as a continuous variable (per 30 minutes). Age was dichotomized at 80 years, and pre-stroke disability was defined as a pre-stroke mRS ≥ 2 . Smoking status was not reliably recorded and was therefore not analyzed.

2.5. Statistical analysis

Data were managed in SPSS version 20.0, and statistical analyses were performed in Python 3.13 (NumPy and SciPy libraries). Normality was assessed using the Shapiro-Wilk test. Because most continuous variables were not normally distributed, they were compared using the Mann-Whitney U test and are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Categorical variables are presented as numbers (percentages) and were compared using the chi-square test or Fisher's exact test when expected counts were < 5 . The ENI rate is reported with its 95% confidence interval (CI) calculated using the Wilson method. The 24-

hour NIHSS was not compared between groups because it is used to define the outcome.

Univariable logistic regression was performed for each candidate variable. Variables with $p < 0.20$ in univariable analysis (age ≥ 80 years, diabetes mellitus, pre-stroke mRS ≥ 2 , admission glucose, treatment within 3 hours, and baseline NIHSS category) and LVO, as a clinically relevant variable, were entered into the multivariable model. Dyslipidemia was not entered because of the small number of affected patients ($n = 8$). Results are presented as odds ratios (ORs) with 95% CIs. Multicollinearity was assessed using variance inflation factors (VIF), calibration using the Hosmer-Lemeshow test, and discrimination using the area under the receiver operating characteristic curve (AUC). Analyses were conducted on complete cases. A two-sided $p < 0.05$ was considered statistically significant.

2.6. Ethical considerations

The study was approved by the Ethics Committee of Bach Mai Hospital No 5347/QD-BM. Written informed consent was obtained from all patients or their legally authorized representatives. The study involved no interventions beyond standard clinical care, and patient confidentiality was strictly maintained.

III. RESULTS

3.1. Study population and baseline characteristics

The mean age was 66.6 ± 11.8 years; 29 patients (11.6%) were aged ≥ 80 years, and 163 (64.9%) were male. Pre-stroke disability (mRS ≥ 2) was present in 83 patients (33.1%). The median baseline NIHSS was 7 (IQR 5-9); 81 patients (32.3%) had an NIHSS < 6 , 137 (54.6%) had an NIHSS of $6-10$, and 33 (13.1%) had an NIHSS > 10 . The mean onset-to-needle time was 172 ± 51 minutes, and the mean door-to-needle time

was 44 ± 16 minutes; 240 patients (95.6%) were treated within 60 minutes of arrival, and 138 (55.0%) were treated within 3 hours of symptom onset. The median alteplase dose was 41 (IQR 35-48) mg. LVO was identified in 15 of 249 patients (6.0%) who underwent vascular imaging.

ENI occurred in 128 patients (51.0%; 95% CI 44.8-57.1). The median NIHSS reduction at 24 hours was 6 (IQR 5-8) points in the ENI group and 2 (IQR 1-3) points in the non-ENI group. The ENI rate increased steeply with baseline severity: 5/81 (6.2%) for NIHSS < 6, 92/137 (67.2%) for NIHSS 6-10, and 31/33 (93.9%) for NIHSS > 10. None of the 22 patients with a baseline NIHSS < 4 achieved ENI.

Compared with the non-ENI group, the ENI group had a higher baseline NIHSS, a lower prevalence of diabetes mellitus (12.5% vs. 24.4%; $p = 0.015$), dyslipidemia (0.8% vs. 5.7%; $p = 0.033$), and pre-stroke disability (26.6% vs. 39.8%; $p = 0.025$), a shorter onset-to-treatment time (163 ± 53 vs. 181 ± 48 minutes; $p = 0.005$), a higher proportion of patients treated within 3 hours (64.1% vs. 45.5%; $p = 0.003$), a shorter door-to-needle time, and a higher alteplase dose. Age, sex, hypertension, atrial fibrillation, previous stroke, admission glucose, systolic blood pressure, LVO, and stroke etiology did not differ significantly between the groups (Table 1).

Table 1. Baseline characteristics according to early neurological improvement

Characteristic	ENI (n = 128)	Non-ENI (n = 123)	p
Age, years, mean $\pm$ SD	66 $\pm$ 12	68 $\pm$ 12	0.305
Age $\geq$ 80 years, n (%)	11 (8.6)	18 (14.6)	0.135
Male sex, n (%)	87 (68.0)	76 (61.8)	0.305
Hypertension, n (%)	73 (57.0)	70 (56.9)	0.985
Diabetes mellitus, n (%)	16 (12.5)	30 (24.4)	0.015
Dyslipidemia, n (%)	1 (0.8)	7 (5.7)	0.033
Atrial fibrillation (known or newly detected), n (%)*	14 (11.0)	12 (10.3)	0.846
Previous stroke, n (%)	13 (10.2)	14 (11.4)	0.754
Pre-stroke mRS $\geq$ 2, n (%)	34 (26.6)	49 (39.8)	0.025
Baseline NIHSS, median (IQR)	9 (7-10)	5 (4-6)	< 0.001
Baseline NIHSS category, n (%)			< 0.001
< 6	5 (3.9)	76 (61.8)	
6-10	92 (71.9)	45 (36.6)	
> 10	31 (24.2)	2 (1.6)	
Admission glucose, mmol/L, median (IQR)	6.7 (6.0-7.8)	7.0 (5.9-9.5)	0.204
Systolic blood pressure, mmHg, mean $\pm$ SD	155 $\pm$ 25	156 $\pm$ 23	0.344
Onset-to-treatment time, min, mean $\pm$ SD	163 $\pm$ 53	181 $\pm$ 48	0.005
Treatment within 3 hours, n (%)	82 (64.1)	56 (45.5)	0.003
Door-to-needle time, min, median (IQR)	40 (34-46)	43 (39-51)	0.003

Characteristic	ENI (n = 128)	Non-ENI (n = 123)	p
Alteplase dose, mg, median (IQR)	42 (36-50)	39 (34-45)	0.007
Large vessel occlusion, n (%)†	8 (6.3)	7 (5.7)	0.827
TOAST classification, n (%)‡			0.524
Large-artery atherosclerosis	12 (9.5)	13 (11.1)	
Cardioembolism	15 (11.9)	12 (10.3)	
Small-vessel occlusion	39 (31.0)	41 (35.0)	
Other determined etiology	0 (0.0)	2 (1.7)	
Undetermined etiology	60 (47.6)	49 (41.9)	

ENI, early neurological improvement; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TOAST, Trial of ORG 10172 in Acute Stroke Treatment. *Data available for 244 patients. †Data available for 249 patients. ‡Data available for 243 patients (ENI 126, non-ENI 117); one patient with two competing etiologies was classified as undetermined. Continuous variables were compared using the Mann-Whitney U test; categorical variables using the chi-square test or Fisher’s exact test.

3.2. Univariable analysis

In univariable analysis, diabetes mellitus, pre-stroke mRS ≥ 2 , treatment within 3 hours, a longer onset-to-treatment time, and baseline NIHSS category were significantly associated with ENI. Age ≥ 80 years, dyslipidemia, and admission glucose showed associations with $p < 0.20$ (Table 2).

Table 2. Univariable logistic regression analysis of factors associated with ENI

Variable	OR	95% CI	p
Age ≥ 80 years	0.55	0.25-1.21	0.139
Male sex	1.31	0.78-2.21	0.305
Hypertension	1.00	0.61-1.66	0.985
Diabetes mellitus	0.44	0.23-0.86	0.017
Dyslipidemia	0.13	0.02-1.08	0.059
Atrial fibrillation	1.08	0.48-2.45	0.846
Pre-stroke mRS ≥ 2	0.55	0.32-0.93	0.026
Admission glucose (per 1 mmol/L)	0.92	0.85-1.00	0.055
Systolic blood pressure (per 10 mmHg)	0.97	0.88-1.08	0.590
Treatment within 3 hours	2.13	1.29-3.54	0.003
Onset-to-treatment time (per 30 min)	0.81	0.70-0.94	0.006
Door-to-needle time (per 10 min)	0.92	0.77-1.08	0.305

Variable	OR	95% CI	p
Large vessel occlusion	1.12	0.39-3.20	0.827
Baseline NIHSS < 6 (reference)	1	-	
Baseline NIHSS 6-10	31.1	11.7-82.2	< 0.001
Baseline NIHSS > 10	236	43.4-1280	< 0.001

CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

3.3. Multivariable analysis

The multivariable model included 249 patients (126 with ENI). After adjustment, age ≥ 80 years (aOR 0.14; 95% CI 0.04-0.48; p = 0.002) and pre-stroke mRS ≥ 2 (aOR 0.29; 95% CI 0.14-0.63; p = 0.002) were independently associated with lower odds of ENI. Baseline NIHSS showed the strongest association (6-10 vs. < 6: aOR 44.4; 95% CI 15.4-128; p < 0.001; > 10 vs. < 6: aOR 781; 95% CI 94.4-6459; p < 0.001); the very wide confidence intervals reflect the small number

of patients with ENI in the NIHSS < 6 group and without ENI in the NIHSS > 10 group. Diabetes mellitus showed a non-significant trend toward lower odds of ENI (aOR 0.43; 95% CI 0.16-1.15; p = 0.094). Treatment within 3 hours was no longer associated with ENI (aOR 1.44; 95% CI 0.70-2.96; p = 0.324), and neither were admission glucose nor LVO (Table 3). Patients treated within 3 hours had a higher baseline NIHSS than those treated later (median 7.5 vs. 6.0; p = 0.001). The model showed adequate calibration and good discrimination (Hosmer-Lemeshow χ^2 = 13.04, p = 0.110; AUC = 0.89 (95% CI 0.85-0.93)), with no evidence of multicollinearity (maximum VIF = 1.29).

Table 3. Multivariable logistic regression analysis of factors associated with ENI

Variable	Adjusted OR	95% CI	p
Age ≥ 80 years	0.14	0.04-0.48	0.002
Diabetes mellitus	0.43	0.16-1.15	0.094
Admission glucose (per 1 mmol/L)	0.99	0.87-1.13	0.914
Pre-stroke mRS ≥ 2	0.29	0.14-0.63	0.002
Treatment within 3 hours	1.44	0.70-2.96	0.324
Large vessel occlusion	0.52	0.12-2.28	0.386
Baseline NIHSS 6-10 (vs. < 6)	44.4	15.4-128	< 0.001
Baseline NIHSS > 10 (vs. < 6)	781	94.4-6459	< 0.001

aOR, adjusted odds ratio; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. Complete-case analysis (n = 249; two patients without vascular imaging were excluded).

IV DISCUSSION

In this prospective cohort of patients with AIS treated with intravenous alteplase alone, about half achieved ENI at 24 hours. ENI depended strongly on baseline stroke severity. After

adjustment for severity, very old age and pre-stroke disability were independently associated with lower odds of ENI, whereas diabetes mellitus showed only a trend. The association between earlier treatment and ENI observed in univariable analysis was not independent of baseline severity.

Reported ENI rates vary considerably across studies, depending on the definition used, the distribution of baseline stroke severity, and the proportion of patients with LVO.^{10,12,15} In our cohort, LVO was present in only 6.0% of patients and most strokes were of mild-to-moderate severity, so the ENI rate is not directly comparable with cohorts that include more severe strokes or patients receiving bridging thrombectomy.

Baseline NIHSS showed by far the strongest association with ENI. The ENI rate rose from 6.2% in patients with an NIHSS < 6 to 93.9% in those with an NIHSS > 10, and none of the patients with an NIHSS < 4 could achieve ENI. This pattern is largely explained by the definition of ENI as an absolute reduction of 4 points: patients with mild strokes have little room for improvement (a floor effect), whereas patients with more severe deficits can reach the threshold more easily. Contrary to the expectation that severe strokes respond poorly to IVT alone, patients with an NIHSS > 10 had the highest ENI rate in our cohort, although this group was small ($n = 33$) and few patients had LVO. Comparing patients with an NIHSS of 6-10 with all other patients would therefore combine two groups with opposite ENI rates. These observations indicate that ENI based on an absolute threshold should always be interpreted in relation to baseline severity, and that stricter or relative definitions may be preferable for patients with mild stroke.¹¹

Patients aged ≥ 80 years had markedly lower odds of ENI after adjustment. This association was not significant in univariable analysis because a larger proportion of older patients

had severe strokes (NIHSS > 10: 8 of 29 [27.6%] vs. 25 of 222 [11.3%]), a group with a very high ENI rate. Within each severity category, ENI was less frequent among patients aged ≥ 80 years (for example, 5 of 12 [41.7%] vs. 87 of 125 [69.6%] in the NIHSS 6-10 category). Reduced brain reserve and a higher burden of chronic cerebrovascular disease in very old patients may contribute, but these factors were not measured in our study. The number of patients aged ≥ 80 years was small ($n = 29$), so the effect estimate is imprecise. Importantly, a lower likelihood of early improvement does not imply a lack of benefit from thrombolysis: the individual patient data meta-analysis by Emberson et al. showed that the proportional benefit of alteplase was similar in patients older and younger than 80 years.¹⁶

Pre-stroke disability ($mRS \geq 2$) was present in one-third of our patients and was independently associated with lower odds of ENI. Pre-existing neurological deficits may contribute to the baseline NIHSS score and cannot improve after reperfusion, thereby reducing the observed change in NIHSS. Pre-stroke functional status should therefore be considered when ENI is used to assess early treatment response or quality of care.

Diabetes mellitus was associated with ENI in univariable analysis, but the association was attenuated after adjustment (aOR 0.43; 95% CI 0.16-1.15; $p = 0.094$). Admission glucose was not associated with ENI. Diabetes and admission hyperglycemia have been associated with poorer outcomes after reperfusion therapy,¹⁷ and proposed mechanisms include impaired microvascular reperfusion, excitotoxicity, intracellular acidosis, blood-brain barrier disruption with cerebral edema, and reduced responsiveness to thrombolytic agents.^{17,18} These mechanisms were not assessed in our study, glycated hemoglobin was not measured, and

the confidence intervals were wide. The role of diabetes in ENI therefore requires confirmation in larger studies.

Treatment within 3 hours was associated with ENI in univariable analysis, but this association disappeared after adjustment for baseline severity. Patients treated earlier had more severe strokes (median NIHSS 7.5 vs. 6), probably because more severe symptoms lead to faster presentation, which confounds the crude association. This finding does not contradict the time-dependent benefit of thrombolysis demonstrated in randomized trials,¹⁶ because ENI is a short-term surrogate and our study was not designed to detect modest time effects. In our cohort, the door-to-needle time (44 ± 16 minutes) met the guideline target of < 60 minutes,⁴ whereas the onset-to-needle time remained relatively long (172 ± 51 minutes), indicating that most of the delay occurred before hospital arrival. Reducing prehospital delay therefore remains an important target.

The demographic profile of our cohort (mean age 67 years, male predominance) was similar to that reported in previous ENI studies.^{12,15} Because tenecteplase is increasingly replacing alteplase,^{7,8} further studies are needed to determine whether these findings apply to patients treated with tenecteplase.

This study has several strengths, including its prospective design, consecutive enrollment, and adjustment for baseline stroke severity and pre-stroke functional status. It also has limitations. First, it was conducted at a single center, which may limit generalizability. Second, patients who died within 24 hours were excluded and could not be analyzed, which may have led to an overestimation of the ENI rate. Third, the absolute-threshold definition of ENI is strongly influenced by baseline severity, and sparse cells resulted in wide confidence intervals for

baseline NIHSS and age ≥ 80 years. Fourth, recanalization status and perfusion imaging were not systematically assessed, and LVO was uncommon, precluding subgroup analyses. Fifth, long-term functional outcome and symptomatic intracranial hemorrhage were not assessed, and body weight was not available to express the alteplase dose per kilogram. Finally, smoking status was not reliably recorded, and residual confounding cannot be excluded.

V CONCLUSION

ENI at 24 hours was observed in 51.0% of patients with AIS treated with intravenous alteplase alone. ENI depended strongly on baseline stroke severity. After adjustment for severity, age ≥ 80 years and pre-stroke disability were independently associated with a lower likelihood of ENI, whereas diabetes mellitus showed only a trend and earlier treatment was not independently associated with ENI. These factors should be considered when ENI is used for early prognostication. Multicenter studies with vascular imaging and 3-month functional outcomes are needed to confirm these findings.

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