

# Lipid-Lowering Pretreatment and Outcome Following Intravenous Thrombolysis for Acute Ischaemic Stroke: A Post Hoc Analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study Trial

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## Keywords

Lipid-lowering therapy · Statins · Stroke · Intracranial haemorrhage · Risk factors · OR · Acute stroke outcome

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## Abstract

**Background:** Debate exists as to whether statin pretreatment confers an increased risk of 90-day mortality and symptomatic intracranial haemorrhage (sICH) in acute ischaemic stroke (AIS) patients treated with intravenous thrombolysis. We assessed the effects of undifferentiated lipid-lowering pretreatment on outcomes and interaction with low-dose versus standard-dose alteplase in a post hoc subgroup analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study. **Methods:** In all, 3,284 thrombolysis-eligible AIS patients (mean age 66.6 years; 38% women), with information on lipid-lowering pretreatment, were randomly assigned to low-dose (0.6 mg/kg) or standard-dose (0.9 mg/kg) intravenous alteplase within 4.5 h of symptom onset. Of the total number of patients, 615 (19%) received statin or other lipid-lowering pretreatment. The primary clinical outcome was combined endpoint of death or disability (modified Rankin Scale scores 2–6) at 90 days. **Results:** Compared with patients with no lipid-lowering pretreatment, those with lipid-lowering pretreatment were significantly older, more likely to be non-Asian and more likely to have a medical history including vascular co-morbidity. After propensity analysis assessment and adjustment for important baseline variables at the time of randomisation, as well as imbalances in management during the first 7 days of hospital admission, there were no significant differences in mortality (OR 0.85; 95% CI 0.58–1.25,  $p = 0.42$ ), or in overall 90-day death and disability (OR 0.85, 95% CI 0.67–1.09,  $p = 0.19$ ), despite a significant decrease in sICH among those with lipid-lowering pretreatment according to the European Cooperative Acute Stroke Study 2 definition (OR 0.49, 95% CI 0.28–0.83,  $p = 0.009$ ). No differences in key efficacy or safety outcomes were seen in patients with and without lipid-lowering pretreatment between low- and standard-dose alteplase arms. **Conclusions:** Lipid-lowering pretreatment is not associated with adverse outcome in AIS patients treated with intravenous alteplase, whether assessed by 90-day death and disability or death alone.

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## Introduction

Intravenous alteplase (recombinant tissue plasminogen activator) is the only approved medical reperfusion treatment in patients with acute ischaemic stroke (AIS); the earlier the treatment is given, the greater the proportional benefit [1]. Concerns over the risk of symptomatic intracerebral haemorrhage (sICH) with intravenous alteplase have led to lower doses being used in many AIS

patient groups, particularly Asians [2], after a dose of 0.6 mg/kg was approved for use in Japan. The Enhanced Control of Hypertension And Thrombolysis stroke study (ENCHANTED) was designed to evaluate the effectiveness of low-dose (0.6 mg/kg body weight) compared to a standard-dose (0.9 mg/kg) of intravenous alteplase in patients with AIS who fulfill guideline-recommended criteria for thrombolysis treatment [3]. While the ENCHANTED trial failed to meet its primary non-inferiority outcome of 90-day death and disability defined by scores of 2–6 on the modified Rankin scale (mRS), low-dose alteplase was non-inferior on the key secondary efficacy outcome of the ordinal analysis of mRS scores [3].

Statins are recommended for both primary and secondary stroke prevention in patients at risk of ischaemic stroke. The 2013 American Heart Association guidelines advise continuation of statin treatment post AIS in those pre-treated with statins based on observational data suggesting improved functional outcomes in AIS patients with statin pretreatment [4]. However, there is significant debate and uncertainty as to the association of lipid-lowering pretreatment with both sICH and functional outcome with intravenous thrombolysis (IVT) [5]. In this study, we report the effects of lipid-lowering pretreatment on functional outcome and sICH in a post hoc secondary analysis of the ENCHANTED trial.

## Methods

### Patients

The ENCHANTED trial is an international, multi-centre, prospective, randomised, open-label, blinded-endpoint trial, which used a  $2 \times 2$  quasi-factorial design to assess the effectiveness of low- versus standard-dose alteplase in the completed arm, and more intensive- versus guideline-recommended control of blood pressure in the ongoing arm, full details of which are outlined elsewhere [3, 6]. Patients with a clinical diagnosis of AIS confirmed on brain imaging and fulfilling local criteria for thrombolysis treatment administered within 4.5 h of symptom onset were randomly assigned to the dose-arm between June 18, 2012 and October 14, 2015. Randomised patients received low-dose (0.6 mg/kg; 15% as bolus, 85% as infusion over 1 h) or standard-dose (0.9 mg/kg; 10% as bolus, 90% as infusion over 1 h) intravenous alteplase. The study protocol was approved by the appropriate ethics committee at each participating centre, and written informed consent was obtained from the patient or an appropriate surrogate.

### Procedures

Key demographic and clinical characteristics were recorded at the time of enrollment, including whether patients were taking statin or other lipid-lowering treatment at hospital admission.

**Table 1.** Major clinical outcomes at 90 days by prior lipid-lowering pretreatment

Outcome	Event, <i>n/n</i> (%)	aOR (95% CI)	<i>p</i> value
Death or disability: mRS score 2–6			
No lipid-lowering pretreatment	344/603 (57.1)	1.0	
Lipid-lowering pretreatment	333/593 (56.2)	0.97 (0.77–1.20)	0.73

aOR, adjusted OR; mRS, modified Rankin Scale.

Stroke severity was measured using the National Institutes of Health stroke scale (NIHSS) at baseline, 24 h, and at day 7 (or earlier, on discharge from hospital). Uncompressed digital images of all baseline and follow-up digital CT, MRI and angiogram images, were collected in the DICOM format on a CD-ROM identified only with the patient's unique study number, and analysed centrally for any intracranial haemorrhage by independent assessors blinded to clinical data, treatment, and date and sequence of scan. Assessors graded any identified haemorrhage as intracerebral, using a range of standard definitions (online suppl. Table; for all online suppl. material, see [www.karger.com/doi/10.1159/000488911](http://www.karger.com/doi/10.1159/000488911)), and subarachnoid, intraventricular, subdural or other.

The primary clinical outcome was the combined endpoint of death or disability at 90 days, defined by scores of 2–6 on the mRS. The secondary (safety) outcome was sICH, defined according to several criteria from other studies (online suppl. Table).

#### Statistical Analysis

The propensity score (PS) method was used to compare lipid pretreatment and no pretreatment groups were given imbalances at baseline (Table 1). On the basis of coefficients from the multivariable logistic regression model, we generated a PS [7, 8] for each patient. Only patients with complete data were included in the analyses to maximize balancing of the PS analysis with the largest number of variables and to avoid the need to impute data. We used optimal matching 1:1 without replacement, with an initial caliper width-matching algorithm that equates to 0.12 (20% of the SD of the logit of the PS) [7]. Generalised estimating equations were used to test the effect of lipid-lowering pretreatment on primary and secondary outcomes, accounting for matching in the PS-matched sub-population [9].

Logistic regression models were used to estimate associations for all the outcomes. Adjustments were made for the baseline covariates, and additionally for aspects of management over the first 7 days following hospital admission. In patients without lipid-lowering pretreatment, the heterogeneity of alteplase treatment effects was tested by adding interaction terms to the statistical models. Two-sided *p* values were reported and *p* < 0.05 was considered statistically significant. The SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for the analysis.

#### Role of the Funding Source

The sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of the report. All authors had full access to the study data. The corresponding author had the final responsibility to make the decision to submit the paper for publication.

## Results

These analyses included 3,284 patients (38% female) with information available on lipid-lowering pretreatment. A total of 615 patients (19%) received statin or other lipid-lowering pretreatment at baseline, and were significantly older and more likely to have a medical history of other vascular co-morbidity, including hypertension, previous stroke, coronary artery disease, diabetes and hypercholesterolaemia, and associated medical therapy, including anti-hypertensive, aspirin or other antiplatelet, and glucose-lowering therapy, with concomitant premorbid mRS score of 1 (Table 2). Other baseline characteristics are shown in Table 2. Overall, patients with lipid-lowering pretreatment were heavier, and accordingly received significantly higher bolus and infusion alteplase doses, even though more patients were randomised to the low-dose arm of the trial in the lipid-lowering pretreatment group (online suppl. Table S1). In addition, patients with lipid-lowering pretreatment were significantly more likely to receive antithrombotic therapy in the first 24 h following thrombolysis, and significantly more likely to be mobilised by a therapist, given rehabilitation, admitted to a stroke unit, and to receive subcutaneous heparin or neurosurgical intervention during the first 7 days (online suppl. Table S1). Full details of management from randomisation over the first 7 days are provided in the online supplement Table S1.

After adjustment for important baseline variables at the time of randomisation, and for imbalances in management during the first 7 days of hospital admission, there were no significant differences in key 90-day outcomes between those patients taking lipid-lowering therapy compared to those not taking lipid-lowering pretreatment: mRS of 2–6 (adjusted OR [aOR] 0.85, 95% CI 0.67–1.09, *p* = 0.19) or mRS of 3–6 (aOR 0.83, 95% CI 0.65–1.06, *p* = 0.13; Fig. 1). In addition, there was no significant difference in 90-day mortality (aOR 0.85, 95% CI 0.58–1.25, *p* = 0.42; Fig. 1). Similarly, no significant differences were seen in sICH rates between patients with and without lipid-lowering pretreatment across a broad

**Table 2.** Baseline characteristics by lipid-lowering pretreatment

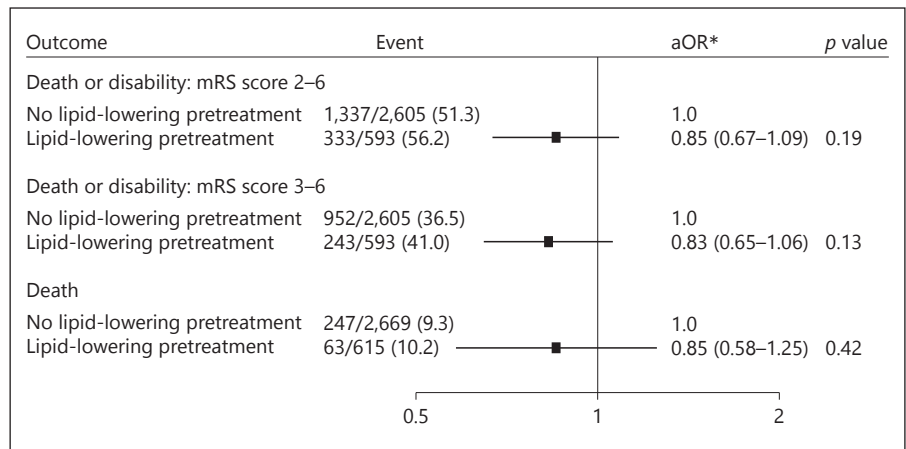
	Lipid-lowering pretreatment		<i>p</i> value
	yes	no	
Time from stroke onset to randomisation, h	2.4 (1.8–3.2)	2.7 (2.1–3.5)	<0.0001
Age, years	70.8 (11.4)	65.6 (12.9)	<0.0001
Gender, female	252/615 (41.0)	993/2,669 (37.2)	0.08
Asian	208/615 (33.8)	1,866/2,669 (69.9)	<0.0001
Clinical features			
Systolic BP, mm Hg	149.5 (20.2)	149.3 (19.7)	0.81
Diastolic BP, mm Hg	81.4 (13.1)	85.4 (12.7)	<0.0001
Heart rate (beats per minute)	79.3 (16.6)	79.0 (15.1)	0.63
Glucose, mg/dL	122.5 (101.0–153.2)	120.7 (102.7–149.0)	0.44
Creatinine, mg/dL	1.0 (0.8–1.2)	0.9 (0.7–1.0)	<0.0001
NIHSS score	7.0 (5.0–13.0)	9.0 (5.0–14.0)	0.005
GCS score	15.0 (14.0–15.0)	15.0 (14.0–15.0)	0.04
Medical History			
Hypertension	498/615 (81.0)	1,563/2,669 (58.6)	<0.0001
Previous stroke	171/615 (27.8)	417/2,669 (15.6)	<0.0001
Coronary artery disease	160/615 (26.0)	318/2,669 (11.9)	<0.0001
Other heart disease (valvular or other)	79/615 (12.8)	155/2,669 (5.8)	<0.0001
Atrial fibrillation	161/615 (26.2)	474/2,666 (17.8)	<0.0001
Diabetes mellitus	195/615 (31.7)	450/2,669 (16.9)	<0.0001
Hypercholesterolaemia	375/615 (61.0)	179/2,669 (6.7)	<0.0001
Current smoker	110/613 (17.9)	659/2,667 (24.7)	0.0004
Pre-stroke function, mRS			
No symptoms	418/615 (68.0)	2,253/2,667 (84.5)	<0.0001
No significant disability	197/615 (32.0)	414/2,667 (15.5)	
Medication at time of admission			
Antihypertensive agents	459/615 (74.6)	1,035/2,669 (38.8)	<0.0001
Warfarin anticoagulation	36/615 (5.9)	46/2,669 (1.7)	<0.0001
Aspirin or other anti-platelet agents	368/615 (59.8)	383/2,669 (14.3)	<0.0001
Glucose-lowering agents	151/615 (24.6)	265/2,669 (9.9)	<0.0001
Brain imaging features			
Visible early ischaemic changes	195/615 (31.7)	575/2,669 (21.5)	<0.0001
Visible cerebral infarction	168/615 (27.3)	574/2,669 (21.5)	0.002
Visible cerebral infarction with mass effect	6/615 (1.0)	41/2,669 (1.5)	0.29
CT or MRI angiogram show proximal occlusion	104/602 (17.3)	400/2,641 (15.1)	0.19
Final diagnosis at time of hospital separation			
Non-stroke	28/611 (4.6)	69/2,619 (2.6)	<0.0001
Large artery occlusion due to significant atheroma	181/611 (29.6)	1,088/2,619 (41.5)	
Small vessel or perforating vessel lacunar disease	89/611 (14.6)	582/2,619 (22.2)	
Cardio-emboli	169/611 (27.7)	471/2,619 (18.0)	
Dissection	2/611 (0.3)	23/2,619 (0.9)	
Other or uncertain aetiology	142/611 (23.2)	386/2,619 (14.7)	

Data are *n/n* (%), mean (SD), or median (interquartile range).

*p* values are based on chi-square, *t* test, or Wilcoxon signed-rank test.

NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; GCS, glasgow coma scale; mRS, modified Rankin scale; CT, computed tomography; MRI, magnetic resonance imaging.

**Fig. 1.** Major clinical outcomes at 90 days by lipid-lowering pretreatment. This figure shows after adjustment for important baseline variables at the time of randomisation, and for imbalances in management during the first 7 days of hospital admission, the differences in key 90-day outcomes between those patients taking lipid-lowering therapy compared to those not taking lipid-lowering pretreatment. aOR, adjusted OR.



**Table 3.** Symptomatic intracerebral haemorrhage outcomes according to standard definitions at 90 days by lipid-lowering pretreatment

	Lipid-lowering pretreatment		OR (95% CI)	p value	aOR (95% CI)	p value
	yes	no				
SITS-MOST criteria	7/615 (1.1)	45/2,669 (1.7)	0.67 (0.3–1.5)	0.33	0.46 (0.2–1.08)	0.07
NINDS criteria	44/615 (7.2)	184/2,669 (6.9)	1.04 (0.74–1.46)	0.82	0.88 (0.61–1.28)	0.51
ECASS2 criteria	18/615 (2.9)	123/2,669 (4.6)	0.62 (0.38–1.03)	0.07	0.49 (0.28–0.83)	0.009
ECASS3 criteria	9/615 (1.5)	52/2,669 (1.9)	0.75 (0.37–1.53)	0.42	0.52 (0.24–1.11)	0.09
IST-3 criteria	14/615 (2.3)	69/2,669 (2.6)	0.88 (0.49–1.57)	0.66	0.65 (0.35–1.21)	0.18
Fatal ICH	3/615 (0.5)	30/2,669 (1.1)	0.43 (0.13–1.42)	0.17	0.34 (0.1–1.15)	0.08
Adjudicated any ICH	122/615 (19.8)	448/2,669 (16.8)	1.23 (0.98–1.53)	0.07	0.99 (0.77–1.27)	0.94

Values are *n/n* (%), or OR (95% CI).

aOR, adjusted OR; SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study; NINDS, National Institute of Neurological Disorders and Stroke; ECASS, European Co-operative Acute Stroke Study; IST, International Stroke Trial.

aOR, adjusted for baseline NIHSS score, time from onset to randomisation (<3 vs. ≥3 h), pre-morbid use of aspirin, atrial fibrillation, and randomised treatment (low-dose vs. standard-dose).

range of definitions except European Co-operative Acute Stroke Study 2 (ECASS), which was significantly lower for patients with lipid-lowering pretreatment (aOR 0.49, 95% CI 0.28–0.83, *p* = 0.009; Table 3).

Finally, there were no significant differences in the main efficacy (Fig. 2 and online suppl. Table S2) and safety (online suppl. Table S3) outcomes between low-dose and standard-dose alteplase in patients with and without lipid-lowering pretreatment.

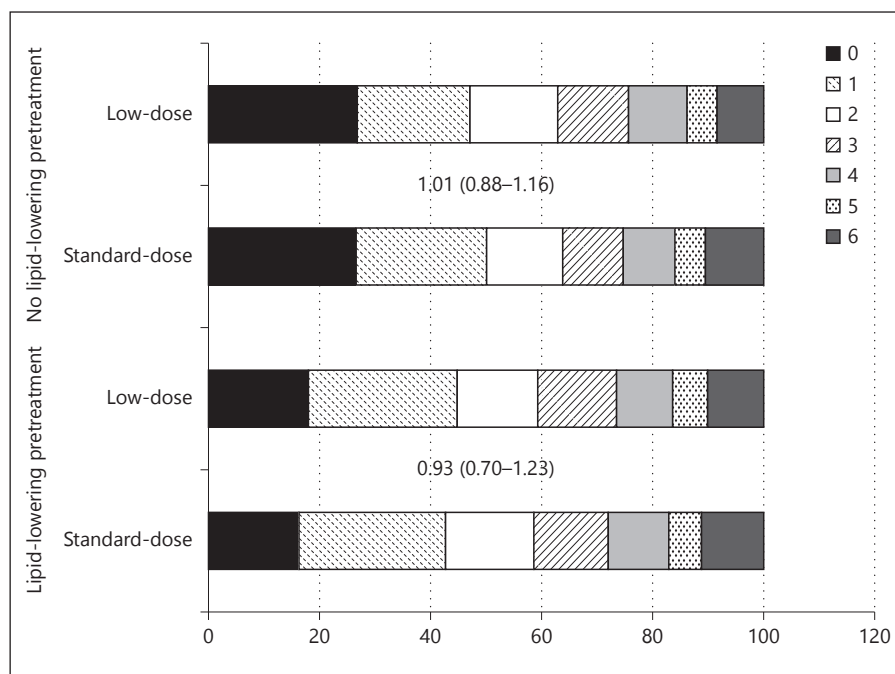
## Discussion

This post hoc subgroup secondary analysis of the ENCHANTED trial has shown that lipid-lowering pretreatment is not associated with adverse outcome in AIS pa-

tients treated with intravenous alteplase, whether assessed by 90-day death and disability, death alone, or sICH. Furthermore, no significant differences were seen in key efficacy and safety outcomes by alteplase dose between patient groups with and without lipid-lowering pretreatment.

Several studies have raised concerns about the risk of statin pretreatment and sICH following IVT for AIS [10], though importantly without an impact on 90-day functional outcomes. However, other retrospective analyses have suggested that statin pretreatment, when continued during the acute phase, may improve both short- and long-term outcome [11, 12]. The most recent study concluded that statin pretreatment was independently associated with higher odds of early clinical recovery (defined as reduction in baseline NIHSS score of ≥10 points) with

**Fig. 2.** Global functional outcome at 90 days in patients with and without lipid-lowering pretreatment by randomised treatment. The figure shows the raw distribution of scores on the mRS at 90 days. Scores on the mRS range from 0 to 6, with 0 indicating no symptoms, 1 symptoms without clinical significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability and 6 death. Unadjusted ORs (and 95% CI) are provided for ordinal shift of mRS between low- and standard-dose intravenous alteplase by patients with and without lipid-lowering pretreatment. mRS, modified Rankin Scale.



no adverse outcomes in AIS patients treated with IVT [12]. To date, the majority of these data arise from registry studies [13], and there is lack of prospective studies to confirm safety concerns or indeed perceived benefits. Therefore, the large, prospective ENCHANTED trial with approximately 20% of patients receiving lipid-lowering pretreatment provides the largest randomised dataset to address these questions alongside a robust propensity analysis to assess baseline differences. In keeping with previous studies, there was no significant difference in mortality or in adjusted overall 90-day death and disability [10, 12]. However, in agreement with some previous studies [10, 14], a significant difference was seen in sICH rates determined using ECASS2 criteria between patients with and without lipid-lowering pretreatment in favour of lipid-lowering pretreatment. Interestingly, the Safe Implementation of Thrombolysis in Stroke Monitoring Study and ECASS3 sICH criteria are also of borderline significance for with and without lipid-lowering pretreatment. Safe Implementation of Thrombolysis in Stroke Monitoring Study, ECASS2 and ECASS3 sICH criteria all relate to an increase of 4 NIHSS points, but National Institute of Neurological Disorders and Stroke sICH criteria are associated with any recorded deterioration in NIHSS and was non-significant in this study. Therefore, lipid-lowering pretreatment might be associated with sICH with change in neurological status beyond a certain NIHSS threshold. However, overall, the ECASS2 findings

should be weighed against the majority of standard definitions for sICH assessed finding no significant association with lipid-lowering pretreatment.

A key limitation of our study is that we recorded whether patients were on statin or other lipid-lowering therapy at baseline but did not distinguish between these lipid-lowering therapies or the duration of treatment. However, it is likely that the majority of patients were treated with statins, and that the prescription had been chronic, given the medical history of vascular co-morbidities. A further limitation of this study is the lack of serum low-density lipoprotein cholesterol (LDL-C) level measurement. It is possible that there were lower LDL-C levels at baseline in the non-lipid lowering group. Lower lipid levels are relevant, as cohort and case-control studies have demonstrated lower serum lipid level and increased risk of ICH [15–17]. Lastly, other limitations include those related to an open-label trial, despite our efforts to minimise reporting bias, concealment of treatment allocation, rigorous assessment of adverse events, and blinded evaluation of clinical outcomes using established criteria. As the ENCHANTED trial included patients with generally milder stroke severity with a slightly longer treatment delay from onset than in previous trials [1] or registries [18], there may be concerns over the generalisability of these data, while imprecision in the estimates of the treatment effect may have arisen from the timing and inter-observer variability in the scoring of the mRS [19].

## Conclusion

In conclusion, our study findings from the largest IVT study to date provide further evidence that lipid-lowering pretreatment is not associated with adverse effects on 90-day death and disability. The potential benefits of statins on early clinical recovery in AIS patients treated with IVT therapy require further exploration.

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